Activity and Health:

Epidemiological studies in older adults

Chantal M. Koolhaas

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	Dr. K. Dhana

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Cepeda M*, **Koolhaas CM***, van Rooij FJA, Tiemeier H, Guxens M, Franco OH, Schoufour JD. Seasonality of physical activity, sedentary behavior, and sleep in a middle-aged and elderly population: The Rotterdam study. *Maturitas*. 2018;110:41-50.

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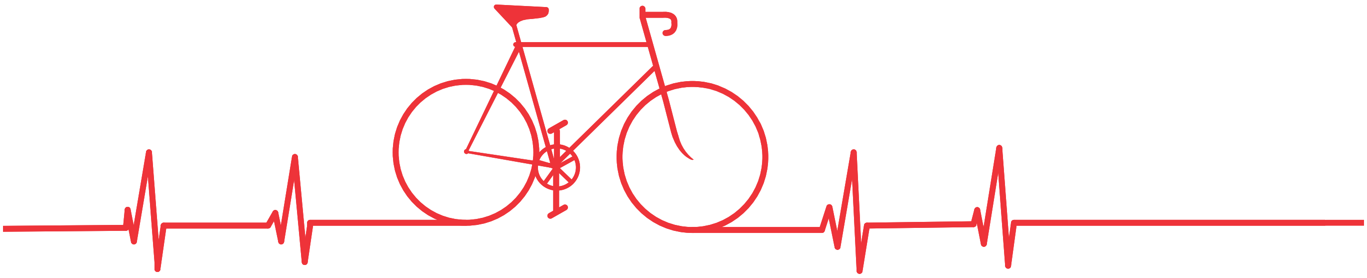
* *Denotes equal contribution within a manuscript*



Chapter 1

General introduction

BACKGROUND

Physical activity, defined as any bodily movement requiring energy expenditure above the resting state,[1] is an important factor associated with health. Worldwide, insufficient levels of physical activity are estimated to cause 6% of the burden of disease, including coronary heart disease, colon cancer and breast cancer, and 9% of the premature mortality.[2] Conversely, engaging in sufficient physical activity can decrease the risk of bone fractures and is related to better cardiovascular health.[3] For adults, it is therefore recommended to be physically active at moderate to vigorous intensity for 30 minutes/day, on most days of the week.[4] However, globally, many individuals do not meet these guidelines[5] and in the Netherlands, around 42% of older adults fail to meet these recommendations.[6] Gaining more insight in the levels of physical activity and the types of physical activity that adults engage in can help to create targeted interventions and recommendations, with the aim to achieve health benefits. This is especially important in older adults, who more often have difficulties in engaging in exercise or sports. For these adults, knowing more about the benefits of other types of activity is of importance. The population of older adults is growing rapidly, which is accompanied by a rise in health care costs associated with diseases in later life.[7] A modifiable lifestyle factor like physical activity could contribute to enhance healthy aging.[8]

In addition to physical activity, the 24-hour cycle of activity consists of sedentary behavior and sleep (Figure 1.1). Sedentary behavior is defined as engaging in sitting, reclining or lying behaviors during the waking hours, which result in little energy expenditure above the basal metabolic rate.[9] Current trends of population ageing, urbanization and automatization of daily activities have contributed to a predominantly sedentary lifestyle, with low levels of physical activity, high levels sedentary behavior and an unhealthy nighttime sleep duration.[10] However, whereas the activity guidelines specifically promote at least 30 minutes of physical activity per day[4] and 7-8 hours of nighttime sleep per day,[11] this leaves approximately 16 hours of unaccounted time, with a vague and non-quantified recommendation to refrain from too much sedentary behavior.[12] Moreover, still little is known about the health effects related to sedentary behavior in older adults. Therefore, more information is required on the determinants associated with inactivity and the health effects associated with all activity domains.

Figure 1.1. 24-hour activity distribution

MEASUREMENT OF ACTIVITY

For practical reasons, physical activity is often measured by questionnaire.[13] In addition, accelerometers are increasingly being used to gain more objective measures of physical activity levels,[13,14] and can provide information on the intensity and duration of physical activity levels.[15] An accelerometer is a small device worn on the body that measures changes in gravitational acceleration. In most previous studies, accelerometers have been worn on the hip and had to be removed for sleeping.[16,17] Wrist-worn devices have the advantage that they can be worn day and night, thereby allowing for collection of 24-hour of activity data.

However, when comparing activity measures obtained by questionnaire with objective methods applied in large populations, major discrepancies emerge.[18,19] The inconsistency might be related to recall-bias, a phenomenon in which information on the variable of interest is reported differently across subgroups of the population.[20] Population characteristics such as age, sex and health status might be related to the extent that the information is reported correctly.[13] In addition, the inconsistency might be derived from the fact that accelerometers cannot measure all physical activity accurately.[21] For example, weight lifting and cycling are generally underestimated by wrist-worn accelerometers.[21] Considering the increased use of accelerometers in current research,[13] it is important to understand and quantify how physical activity assessed using questionnaires and accelerometers differ and how these differences might be related to population characteristics.[22] This is especially relevant in older adults, because the higher likelihood of cognitive impairment[23] might lead to more recall bias and reporting errors.

FACTORS ASSOCIATED WITH ACTIVITY

With the information collected from wrist-worn accelerometers, we can shed more light on the daily distribution of physical activity, sedentary behavior and sleep in older adults, as well as the factors associated with these activities domains. To date, several studies have examined factors associated with objectively assessed physical activity in adults aged 60 years and over,[16,17,24] and showed that physical activity levels decrease with increasing age and across increasing levels of body mass index (BMI). However, it has not yet been investigated what factors are associated with activity in the very old (aged 77 and over), a population with generally lower activity levels and more disability. Moreover, the demographic and health factors associated with sleep and sedentary behavior have not been addressed jointly with physical activity in the elderly. Additionally, it is still unclear which environmental factors are associated with these different activity domains. Physical activity has a seasonal pattern, with higher levels of physical activity in the summer and less physical activity in the winter,[25] but it is unclear whether this is at the expense of sedentary behavior or sleep. It is also still unclear which meteorological factors are related to this seasonal pattern of activity in older adults, and it remains unknown whether the seasonality of activity might have an effect on health outcomes.

ACTIVITY AND MORTALITY

There is extensive literature on the association between physical activity and mortality.[26] However, there is limited information on what type of physical activities are beneficially associated with mortality after retirement in an elderly population, and more specifically if the association between physical activity and mortality differs by cause of death. In particular, information is currently lacking on whether physical activity is associated with reduced mortality related to dementia and chronic lung disease.[27-29]

Furthermore, information on the association between sedentary behavior and mortality currently mostly relies on studies using self-reported measures of sedentary behavior[30] and studies using accelerometers have only a limited follow-up time, up to an average of 4.5 years.[31-33] Self-reported sedentary behavior might be influenced by information and recall bias[34] and the limited follow-up time in studies using accelerometers increases the likelihood of the results being influenced by reverse causation. An underlying disease or disability might be related to both sedentary behavior and a higher mortality risk. Therefore, it is important to examine the association between sedentary behavior and all-cause mortality with longer follow-up, by using objective measures of sedentary behavior.

ACTIVITY AND CARDIOVASCULAR HEALTH

The inverse association between higher physical activity levels and lower risk of cardiovascular diseases (CVDs) has been well documented in literature.[3] According to recent meta-analyses, regular physical activity of moderate to vigorous intensity may contribute to up to 27% reduced risk of coronary heart disease.[35,36] However, it remains unclear whether all cardiovascular conditions, including atrial fibrillation, benefit from physical activity. Atrial fibrillation is the most common chronic cardiac arrhythmia with significant morbidity and mortality.[37] Since known risk factors of atrial fibrillation, such as heart failure and myocardial infarction are directly influenced by the level of physical activity,[38] high levels of physical activity might also reduce the risk of atrial fibrillation.

Previous studies on the association between physical activity and CVDs have mainly focused on the effect of overall leisure time physical activity, whereas it remains unclear what specific physical activity types contribute most to the beneficial effects of physical activity. Only a few studies have addressed the impact of different types of physical activity on CVD[39,40] or specifically coronary heart disease[41] or atrial fibrillation.[42] Several studies documented a beneficial association between walking and risk of coronary heart disease[43] or atrial fibrillation,[44] but evidence of the influence of cycling and domestic work remains scarce among the elderly,[39,45] whereas domestic work is an important domain contributing to the daily physical activity of older adults.[46] Additionally, in order to provide comprehensive information for public and individual health care planning, measures of the lifetime consequences of physical activity, including life expectancy estimates, are most informative. Since individuals with CVD have a lower quality of life,[47] information on the life years with and without CVD is of relevance in this matter.

Furthermore, it has been suggested that physical activity might counterbalance the CVD risk associated with overweight and obesity,[48] but information among the elderly is scarce. In older adults, it has been suggested that the risks of myocardial infarction and stroke associated with overweight and obesity are attenuated,[49] possibly because in older adults BMI is a poor indicator of body composition. Therefore, we examined the role of physical activity in the association of overweight and obesity with CVD in elderly adults.

ACTIVITY AND MENTAL HEALTH AND WELLBEING

Physical activity and sedentary behavior have been associated with health-related quality of life (HRQL) and mental health outcomes such as depression, anxiety and cognitive function. HRQL is defined as an individuals' perspective of well-being in physical, mental and social domains of life.[50] Recent studies have shown a consistent association between physical activity and HRQL.[51,52] However, it remains unclear what specific physical activity types contribute most to the beneficial effects of physical activity in older adults.

Regarding mental health, higher levels of self-reported sedentary behavior have been associated with a higher risk to develop depression[53] and anxiety disorders[54] and with a lower risk to decrease in cognitive functioning.[55] However, most studies performed thus far were cross-sectional, making it impossible to infer temporality. In addition, only a limited number of studies adjusted for disability status, which can be considered an important confounder influencing both the sedentary behavior and the mental health measures. Furthermore, the use of subjective measures of sedentary behavior, which are usually assessed by probing types of sitting behavior (e.g. television viewing, car driving), might have influenced the associations.[56,57] In this regard, the reported associations might be driven more by the social context of sitting than sedentary behavior. Therefore, using objective measures of sedentary behavior, while carefully adjusting the associations for important confounders such as disability, can provide additional information on the association between sedentary behavior and mental health measures.

Furthermore, sleep has received interest as a possible modifiable factor that might influence body weight.[58,59] Short sleep duration has been associated with obesity,[58] giving rise to the idea that chronic sleep deprivation might contribute to the obesity epidemic.[59] However, studies assessing the association between sleep and obesity have mostly been cross-sectional, thus the temporality of the relation between sleep and adiposity could not be explored.[58,60] Second, prospective studies performed thus far have relied on self-reported measures, which are prone to information and recall bias.[61] Moreover, adiposity most probably impacts sleep, but very few studies have examined the hypothesis that the association between sleep and adiposity might be bidirectional.[62-64] Prospective studies using objectively measured sleep and body composition are required.

STUDY DESIGN: THE ROTTERDAM STUDY

The Rotterdam Study (RS) is a prospective population-based cohort, among subjects aged 55 years or older in the well-defined Ommoord neighborhood, in the municipality of Rotterdam, the Netherlands.[65] The Rotterdam Study started in 1990 and was set up to study risk factors of cardiovascular, endocrine, hepatic, neurological, ophthalmic, psychiatric, dermatological, oncological, and respiratory diseases. In the original study cohort, 7,983 participants aged 55 years and older were enrolled, which constituted 78% of all 10,215 invitees. In 2000-2001, the Rotterdam Study was extended with 3,011 participants out of 4,472 invitees who were ≥55 years old or had moved into the study district. In 2006 a third study cohort was initiated, in which 3,932 adults aged 45 years and older were included.[65] Physical activity was assessed for the first time by questionnaire during the third examination of the original cohort (RS-I-3, between 1997 and 1999) and during the baseline examination of the extended cohort (RS-II-1, between 2000 and 2001). Objective measures of activity were obtained for the first time between 2002 and 2008, in a subset of participants from each of the cohorts. From 2012 on forwards, objective data on physical activity has been collected in all participants who agreed to wear a wrist-worn accelerometer.

Data on clinical outcomes, including cardiovascular disease, depression and dementia, were collected through a follow-up system involving digital linkage of the study database to medical records maintained by general practitioners working in the research area. Trained research assistants collected notes, outpatient clinic reports, hospital discharge letters, electrocardiograms, and imaging results from general practitioner records and hospital records. Other health-related measurements were obtained during the home-interview or at the research center.

OVERALL AIM OF THIS THESIS

The overall aim of this thesis was to study the factors associated with activity in older age and to examine the association of activity domains with mortality, cardiovascular disorders and mental health outcomes. In Chapter 2, we discuss differences between objectively and subjectively measured physical activity, as well as provide an overview of the 24-hour activity distribution in an elderly population and report which factors are associated with physical activity, sedentary behavior and sleep. In Chapter 3, we discuss the association between physical activity and sedentary behavior with all-cause and cause-specific mortality. In Chapter 4, we discuss the association of overall physical activity and specific physical activity types with several cardiovascular health outcomes. In Chapter 5, we study the association of physical activity and sedentary behavior with mental health and wellbeing, including health-related quality of life, depression, anxiety and cognition. Last, in the general discussion in Chapter 6, we address methodological considerations, practical implications of our findings and suggestions for future research.

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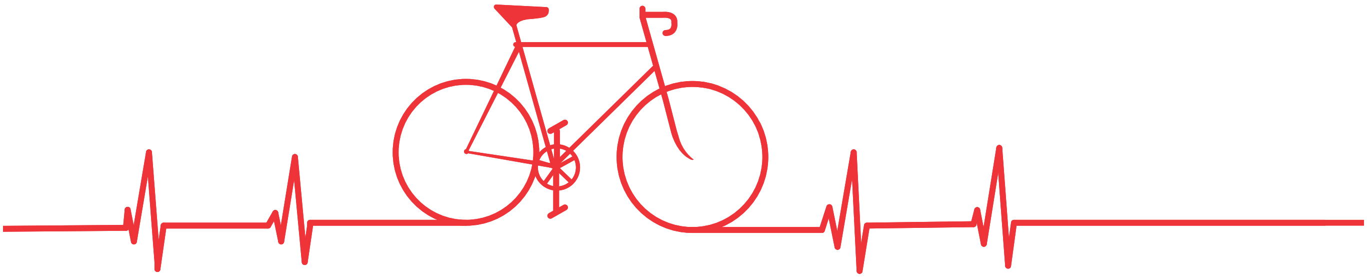
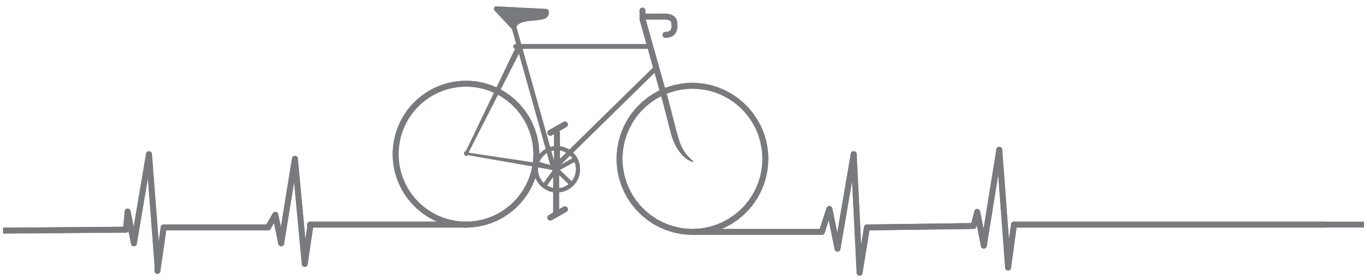


Chapter 2

Activity in the elderly



Chapter 2.1

Comparing physical activity derived from questionnaires and accelerometers

Manuscript based on this chapter:

Koolhaas CM, van Rooij FJA, Cepeda M, Tiemeier H, Franco OH, Schoufour JD. Physical activity derived from questionnaires and wrist-worn accelerometers: comparability and the role of demographic, lifestyle, and health factors among a population-based sample of older adults. *Clinical Epidemiology*. 2018;10:1-16

ABSTRACT

Background: The agreement between questionnaires and accelerometers to measure physical activity (PA) differs between studies and might be related to demographic, lifestyle and health characteristics, including disability and depressive symptoms.

Methods: We included 1,410 individuals aged 51-94 years from the population-based Rotterdam Study. Participants completed the LASA Physical Activity questionnaire (LAPAQ) and wore a wrist-worn accelerometer on the non-dominant wrist for one week thereafter. We compared the Spearman correlation and disagreement (level and direction) for total PA across levels of demographic, lifestyle and health variables. The level of disagreement was defined as the absolute difference between questionnaire- and accelerometer-derived PA, whereas the direction was defined as questionnaire PA minus accelerometer PA. We used linear regression analyses with the level and direction of disagreement as outcome, including all demographic, lifestyle and health variables in the model.

Results: We observed a Spearman correlation of 0.30 between questionnaire- and accelerometer-derived PA in the total population. The level of disagreement (ie absolute difference) was 941.9 (standard deviation [SD]=747.0) minutes/week and the PA reported by questionnaire was on average 529.4 minutes/week (SD=1079.5) lower than PA obtained by the accelerometer. The level of disagreement decreased with higher educational levels. Additionally, participants with obesity and those with higher disability scores and more depressive symptoms underestimated their self-reported PA more than their healthier counterparts.

Conclusion: We observed large differences in PA time as derived from the LAPAQ and the wrist-worn accelerometer. Differences between the methods were related to body mass index, level of disability, and presence of depressive symptoms. Future studies using questionnaires and/or accelerometers should account for of these differences.

INTRODUCTION

Physical activity (PA) is an important modifiable risk factor in the prevention of diseases, including cardiovascular disease, diabetes mellitus and several types of cancer.[1] For practical reasons, PA is often measured subjectively, by questionnaire.[2] However, self-reported PA can suffer from reporting bias, partially attributable to the cognitive challenge of estimating the frequency, intensity and duration of PA.[3] Moreover, activities of light intensity are hard to recall and might not be reported.[4,5] Objective methods, including accelerometers, offer a solution to these problems and can give objective estimates on duration and intensity of PA. Therefore, accelerometers are increasingly being used in current research.[2,6] However, when comparing questionnaire data with objective methods applied in large populations, major discrepancies emerge.[7,8] The inconsistency might be related to recall-bias, which can be influenced by population characteristics, such as age, sex and health status.[2,9] In addition, the inconsistency might stem from the fact that accelerometers cannot measure all PA accurately.[10,11] For example, weight lifting and cycling are generally underestimated by accelerometers worn on the upper body.12 Considering the increased use of accelerometers in current research,[2,6] it is important to understand and quantify how PA assessed with questionnaires and accelerometers differ and how these difference relate to population characteristics.[13]

Previous studies showed that the correlation between self-reported and objectively measured PA differs by age, sex, ethnicity, socio-economic status and level of PA.[8,9] However, results presented refer to correlation coefficients, which are a measure of the extent to which two variables are linearly related, but do not take into account their measurement scales. Hence, these studies do not provide information regarding the level of agreement and the direction of disagreement of the two methods.[14] A study that accounted for the direction of disagreement between objective and subjective measured PA in young adults suggested that overweight adults have the tendency to overestimate the time spent in vigorous PA more than normal weight individuals.[15] Information from older adults, a population with different PA patterns than younger adults,[16] is currently lacking. Moreover, the effect of socioeconomic-status and mental and physical health on the agreement between accelerometer and questionnaire remains unclear.

Therefore we aimed to quantify the level and direction of disagreement between questionnaire-assessed PA and accelerometer-assessed PA and to investigate if differences in agreement are explained by sociodemographic, lifestyle and health factors.

METHODS

Study Population

This paper utilizes data from the Rotterdam Study, a population based cohort designed to examine the onset and risk factors of diseases in older adults.[17] The Rotterdam Study has been approved by the medical ethics committee according to the Wet Bevolkingsonderzoek ERGO

(Population Study Act Rotterdam Study), executed by the Ministry of Health, Welfare and Sport of the Netherlands. Trained research assistants interviewed the participants at home to collect the baseline information and individuals visited the research center twice, where clinical measurements were obtained.

Participants were invited to wear an accelerometer and fill out a PA questionnaire, between June 2011 and June 2014 (wave 1) and between July 2014 and May 2016 (wave 2). Participants were included in the analysis if they had valid accelerometer data (>1200 min/day) for at least 4 days, including one weekend day. Twenty-four cases were excluded because of unreliable high (ie higher than the mean + three times the standard deviation) levels of data on self-reported PA (Figure 2.1.1).

Since the PA questionnaire used in the Rotterdam Study did not cover occupational activity, we also excluded participants with paid occupation (n=389) or without information on occupational status (n=27). Additionally, because 72 participants participated in both waves, we excluded the observation from the second wave of these participants, to avoid clustering of data. In the current analyses, we included 1,410 adults aged 50+ years with data on both objective and subjective PA. All subjects gave written informed consent.

Questionnaire physical activity

After the home interview, participants received the PA questionnaire and were requested to hand in their questionnaire during their first research center visit. Questionnaire PA was assessed with the self-administered LASA Physical Activity Questionnaire (LAPAQ), a validated questionnaire with a reasonably good test-retest reliability (0.65–0.75).[18] The correlations with a pedometer and 7-day diary were 0.56 and 0.68, respectively.[18] The LAPAQ includes questions on the frequency and duration of walking, cycling, sports (including two open-ended questions in which participants could report “other sports” they participated in), gardening, and housework. Participants reported how many hours/week they spent in each activity in the previous two weeks. Detailed information on the assessment of questionnaire-derived PA can be found elsewhere.[19] We used metabolic equivalent of task (MET) to quantify activity intensity. MET-values were assigned to all activities in the questionnaire, using a compendium of activity energy costs.[20] Of all mentioned other activities, 18 (3.2%) were not sports and 28 (5.1%) were not in the compendium (eg ‘physiotherapy training, ‘indoor sports’, ‘revalidation). No MET-values were assigned to these activities and they were not included in the analyses. Duration in total PA was computed by summing time spent in all activities mentioned in the questionnaire.

To be able to evaluate whether differences in total PA were driven by a particular intensity category (ie light, moderate or vigorous PA), we categorized activities in three groups. Activities with MET-values lower than 3 METs, were coded as light intensity PA; for values from 3 to 6 METs, activity was coded as moderate intensity PA; and for values of 6 and higher, the activity was coded as vigorous intensity PA.[21]

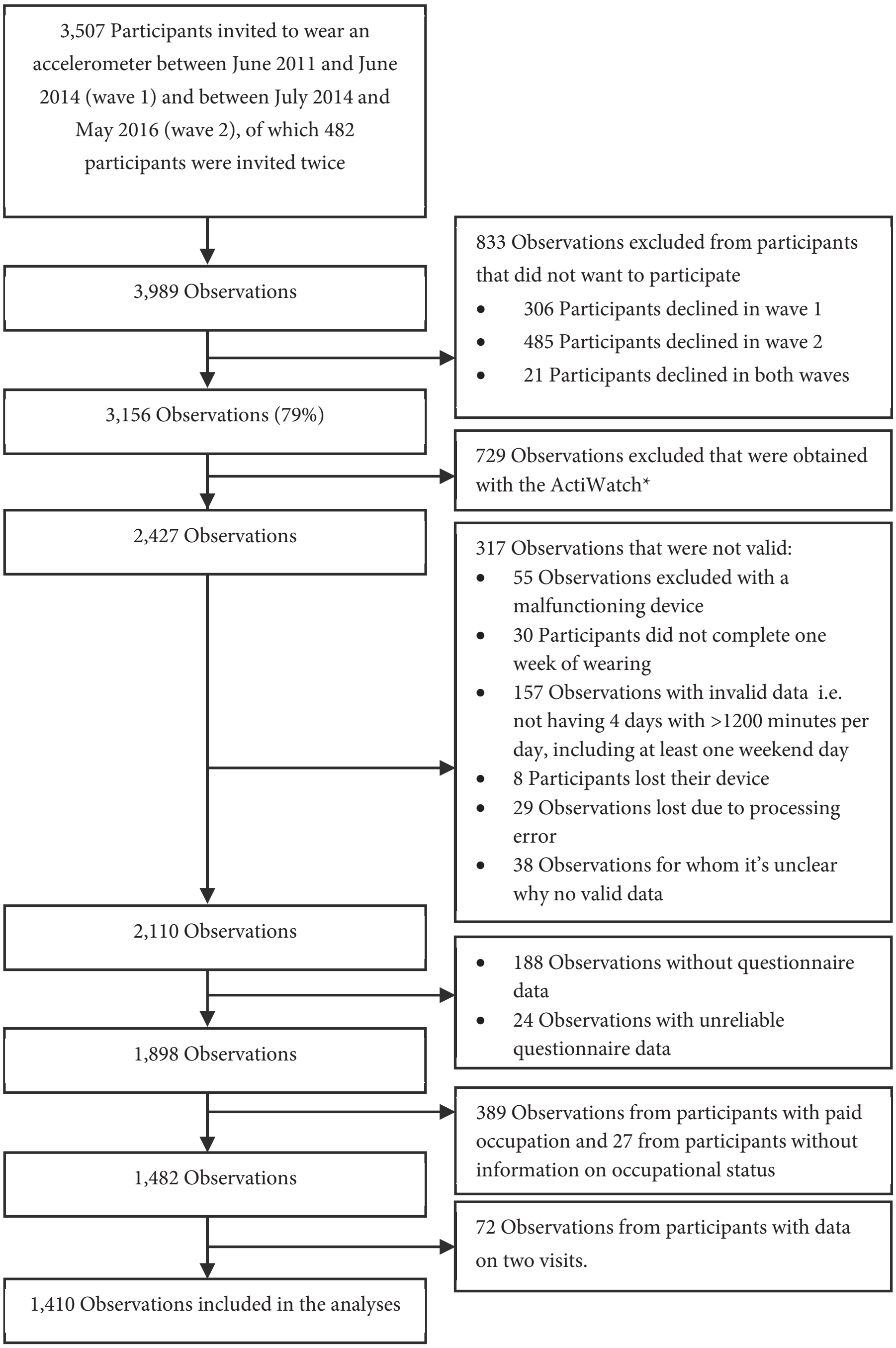


Figure 2.1.1. Flow chart of participant inclusion for the Rotterdam Study

* The ActiWatch (Actiwatch model AW4; Cambridge Technology, Cambridge, UK)) is a one-dimensional device and could not be used to measure physical activity.

Accelerometer-assessed physical activity

At the first center visit, participants were requested to wear a triaxial accelerometer (GeneActiv; Activinsights Ltd, Kimbolton, Cambridgeshire, United Kingdom, http://www.geneactiv.org/) on the non-dominant wrist for 7 consecutive days and nights. Since the GeneActiv device is waterproof, the device could also be worn while bathing and swimming. The accelerometer was sampled at 50 Hz and acceleration was expressed relative to gravity (g units; 1 g =9.81 m/s2).[9,22,23] Data were extracted from the first wearing day up to seven days later and all days with ≥1200 minutes of data were included.

To quantify the acceleration related to the registered movement, we calculated the high-pass filtered vector magnitude (HPFVM). This approach applies a high-pass filter with a cut-off frequency of 0.2 Hertz to the acceleration signal, treating gravity as a low-frequency component that is filtered out.[24]

Accelerometer data were processed in Python (2.6.6), with the open access PAMPRO software, a program for the systematic analysis of PA data collected in epidemiological studies.[25] Non-wear time was defined as all time periods where the standard deviation of acceleration in each of the three axes fell below 13mg for over 1 hour.[24] Any non-wear period was excluded from analyses. The pattern of non-wear time was accounted for by balancing the weighting of the data according to the diurnal profile.[26]

Activity was categorized into sedentary (<48 mg), light (48 < 154 mg), moderate (154 <389 mg) and vigorous activity (>389 mg), based on a recent validation study in 1695 middle-aged adults (mean age: 50 years).[24] Because not all participants wore the watch for 7 days, data were recoded as such that our measures reflected PA over a 1-week course, to match with the questionnaire data. The average duration in light, moderate and vigorous PA was calculated for weekdays and weekend days. Consequently, the weekly accelerometer-assessed total PA was calculated as [(5x mean daily duration in total PA on weekdays) + (2 x mean daily duration in total PA on weekend days)].

Assessment of factors

Self-reported alcohol use was obtained with a food frequency questionnaire, expressed in grams/day and categorized in tertiles. Socioeconomic status was evaluated by education, assessed in consonance with the international standard classification of education and categorized as primary, lower, intermediate and higher education.[27] Smoking was categorized in three categories: current, former and never. Body mass index (BMI) (kg/m^2) was calculated using height and weight and defined as normal weight (<25 kg/m^2), overweight (25–30 kg/m^2) and obese (≥30 kg/m^2). Marital status was defined as living with a partner or not. Disability was assessed by activities of daily living, from the Stanford Health Assessment Questionnaire Disability Index.[28] For descriptive purposes, disability was defined as disability index higher than 0.5 and severe disability as an index higher than 1.0.[29] The presence of coronary heart disease, diabetes, stroke and cancer were determined using medical records up to the year 2012, to define the number of comorbidities. Depressive symptoms were assessed with the Center for Epidemiologic Studies

Depression (CES-D) scale,[30] a self-report scale with 20 items and a maximum score of 60. A score of 16 or greater is traditionally accepted as cut off to define clinical depression[31] and was used for descriptive purposes. Cognitive function was assessed with the Mini Mental State Examination (MMSE).[32] MMSE-scores range from 0-30, with a higher score indicating better cognitive performance. We used a cut-off of 26 to categorize participants as having a cognitive impairment in our descriptive analysis.[33]

Statistical analyses

Descriptive statistics were used to characterize the sample. The difference in time spent in PA according to questionnaire and accelerometer was examined using a paired samples t-test and the Bland-Altman method was used to visualize the level of (dis)agreement between questionnaire- and accelerometer-derived PA levels. We assessed the Spearman correlation between questionnaire- and accelerometer-derived PA in the total population and separately for the following categories: age-group (ie 50-60 years, 60-70 years; 70-80 years, older than 80 years), sex, education, marital status, smoking status, BMI category, alcohol consumption, disability, prevalent chronic disease, cognitive function and prevalent depression. Since the Spearman correlation coefficient is equal to the slope of the regression between the ranked values of the questionnaire and accelerometer, we used linear regression models to obtain the correlation coefficients and corresponding 95% confidence intervals (95%CI) using accelerometer-derived PA as dependent variable.

For our main analyses, we devised two measures of disagreement, in resemblance with previous research.[34] First, we computed the 'level of disagreement', expressed as the absolute time difference between questionnaire- and accelerometer-assessed PA. Second, we computed the 'direction of disagreement', indicating whether an individual had the tendency to overestimate or underestimate PA, by subtracting accelerometer-assessed PA from questionnaire-derived PA levels. To assess the association between assessed factors and the level and direction of disagreement, we used linear regression analyses with the level and direction of disagreement as outcome variables, including all demographic, lifestyle and health variables, total PA measured by the accelerometer, time between interview date and the first accelerometer wear date, cohort and wave. Age, the CES-D score, disability index, MMSE-score and number of comorbidities were used as continuous variables in these analyses. To quantify if the association is dependent on the level of PA, the β (95%CI) for the association of accelerometer-derived PA, expressed in hours/week, with the level and direction of disagreement will also be obtained from these analyses.

We performed several sensitivity analyses. We compared baseline characteristics for those agreeing to wear an accelerometer versus those who rejected, and in those with paid occupation versus those without paid occupation. Next, we examined the level and direction of disagreement in each intensity category of PA (light, moderate and vigorous). Additionally, we repeated the analyses in a population also including participants with paid occupation. In these analyses, we additionally included occupational status as covariate. Moreover, because accelerometers do not to measure cycling accurately, we repeated the analyses in those that did not report any cycling.

Our data contained 49.1% missing data on alcohol use. Other covariates had <2% missing data. We imputed missing data using Markov Chain Monte Carlo multiple imputation (n=20 imputations). All analyses were performed using IBM SPSS Statistics for Windows (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp) and R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was accepted at $p < 0.05$.

RESULTS

Participants who agreed to wear an accelerometer were slightly younger, more often men, and showed a better health profile with regard to the MMSE score, CESD score and disability score, than those who did not agree to wear an accelerometer (Supplement 2.1.1). The participants included in our study had a mean age of 73.8 years (SD: 7.6) and 742 (52.6%) were female (Table 2.1.1).

The mean (SD) daily wear-time of the accelerometer was 23.8 (0.3 hours) and the median time difference between the interview and the first accelerometer wear date was 8.7 weeks (interquartile range: 5.1-13.7). The mean (SD) weekly time spent in PA was 1579.3 (386.1) minutes according accelerometer and 1049.9 (1108.3) minutes according questionnaire ($p<0.001$), indicating that overall, total PA was underestimated in the questionnaire. This is also visualized in the Bland-Altman plot in Supplement 2.1.2.The Spearman correlation was 0.30 (0.25, 0.34) in the total sample and differed as a function of education, disability, smoking status, depressive symptoms and cognitive function (Table 2.1.2).

Per one hour/week more accelerometer-derived PA the level of disagreement was 30.2 minutes/week more (95%CI: 23.6, 36.7; $p < 0.001$). Independent of the PA volume, those with intermediate and higher education showed smaller differences between the questionnaire PA and accelerometer PA than those with primary education (Figure 2.1.2). No other determinants were associated with the level of disagreement.

Per one hour/week more accelerometer-derived PA, questionnaire PA was underestimated more by 29.1 minutes (95%CI: -38.6. -19.6; $p < 0.001$). The results of the regression analyses with the direction of the disagreement are presented in Figure 2.1.3. Independent of the PA volume, obese participants underestimated their self-reported PA levels more than normal weight participants (β= -234.3 minutes/week; 95%CI: -398.2, -70.5; $p = 0.002$). Additionally, the underestimation of self-reported PA in the questionnaire was larger for participants with higher levels of the disability score and CES-D score (Figure 2.1.3).

Table 2.1.1. Characteristics of the study population (n=1,410)

Characteristic	
Demographic factors	
Age (years)	73.8 (7.6)
Female, n (%)	742 (52.6)
Education	
Elementary	86 (6.1)
Lower secondary	571 (40.5)
Higher secondary	434 (30.8)
Tertiary	319 (22.6)
Living with partner, n (%)	989 (70.1)
Lifestyle factors	
Smoking, n (%)	
Never smoker	471 (33.4)
Former smoker	833 (59.1)
Current smoker	106 (7.5)
BMI, n (%)	
Normal weight	418 (29.6)
Overweight	668 (47.4)
Obese	324 (23.0)
Alcohol consumption, n (%)	
Low	502 (35.6)
Medium	464 (32.9)
High	444 (31.5)
Health factors	
Disability score	0.64 (0.68)
Prevalent cancer, CVD or diabetes, n (%)	635 (45.0)
MMSE score	28.1 (1.7)
CESD score	5.0 (6.3)
Physical activity variables	
Total PA according questionnaire (minutes/week)	1049.9 (1108.3)
Total PA according accelerometer (minutes/week)	1579.3 (386.1)
Level of disagreement between questionnaire and accelerometer	941.9 (747.0)
Direction of disagreement between questionnaire and accelerometer	-529.4 (1079.5)
Time between interview and first accelerometer wear date (weeks), median (IQR)	8.7 (5.1-13.7)

Data are presented as mean (SD) unless otherwise stated.

Abbreviations: BMI, body mass index; CESD, Center for Epidemiologic Studies Depression; CVD, cardiovascular disease; IQR, interquartile range; MMSE, mini mental state examination; n, number; PA, physical activity; SD, standard deviation

Sensitivity analyses showed that light and vigorous PA were underestimated by the questionnaire (mean (SD) -708.4 (484.3) minutes/week and -25.6 (338.1) minutes/week, respectively), whereas the level of moderate PA was on average overestimated with 204.6 minutes/week (SD: 780.8) (Supplement 2.1.3). In the analyses with light, moderate and vigorous PA, factors associated with the level and direction of disagreement were similar as in the main analyses (Supplement 2.1.4 – Supplement 2.1.5).

When comparing those with and without paid occupation, we observed that those with paid occupation were younger, higher educated and showed a better health profile regarding the CESD score, MMSE score and disability score (Supplement 2.1.6). In sensitivity analyses including those with paid occupation (n=1823), the level and direction of disagreement were larger compared to the main analyses (mean [SD]= 971.8 [788.0] minutes/week and -589.0 [1104.0] minutes/week, respectively).

Table 2.1.2. Spearman correlation between questionnaire-assessed total physical activity and accelerometer-assessed total physical activity, according to characteristics of the study population

Total population, factors, and physical activity	n	Spearman's r	95% CI
Total population	1,410	0.30	0.25, 0.34
Demographic factors			
Age group			
50-60 years	62	0.24	0.01, 0.48
60-70 years	334	0.26	0.16, 0.37
70-80 years	756	0.28	0.21, 0.34
older than 80 years	258	0.24	0.13, 0.36
Sex			
Male	668	0.32	0.25, 0.39
Female	742	0.27	0.20, 0.33
Education			
Elementary	86	0.46	0.28, 0.64
Lower secondary	571	0.27	0.19, 0.35
Higher secondary	434	0.28	0.19, 0.37
Tertiary	319	0.31	0.21, 0.42
Marital status			
Living alone	421	0.31	0.27, 0.36
Living with someone	989	0.28	0.26, 0.31
Lifestyle factors			
Smoking			
Never smoker	472	0.28	0.22, 0.35
Former smoker	833	0.32	0.29, 0.35
Current smoker	106	0.17	0.08, 0.26

Table 2.1.2 (continued). Spearman correlation between questionnaire-assessed total physical activity and accelerometer-assessed total physical activity, according to characteristics of the study population

Total population, factors, and physical activity	n	Spearman's r	95% CI
BMI			
Normal weight	418	0.27	0.18, 0.36
Overweight	668	0.29	0.21, 0.36
Obese	324	0.26	0.16, 0.36
Alcohol consumption			
Low	502	0.29	0.20, 0.37
Medium	646	0.29	0.19, 0.4
High	444	0.31	0.21, 0.42
Health factors			
Disability			
Not disabled	743	0.27	0.21, 0.34
Disabled	300	0.31	0.26, 0.36
Severely disabled	367	0.23	0.14, 0.33
Prevalent chronic disease			
No prevalent chronic disease	775	0.28	0.21, 0.35
Prevalent cancer, CVD or diabetes	635	0.29	0.22, 0.36
Cognitive function			
MMSE score below 26	97	0.43	0.25, 0.61
MMSE score of 26 or higher	1,313	0.29	0.23, 0.34
Depression			
No depression	1,304	0.29	0.27, 0.32
Depression present	106	0.33	0.15, 0.51
Physical activity			
Self-reported PA[a]			
Low	485	0.16	0.07, 0.25
Medium	445	0.16	0.07, 0.25
High	480	0.10	0.01, 0.19
Accelerometer-derived PA[b]			
Low	514	0.23	0.14, 0.31
Medium	485	0.08	-0.01, 0.16
High	411	0.11	0.02, 0.20

Abbreviations: BMI, body mass index; CESD, Center for Epidemiologic Studies Depression; CI, confidence interval; CVD, cardiovascular disease; MMSE, mini mental state examination; PA, physical activity

[a] The median reported level of physical activity across the low, medium and high category were 210, 765 and 1807 minutes/week.

[b] The median accelerometer-derived level of physical activity across the low, medium and high category were 1229, 1601 and 2003 minutes/week.

In sensitivity analyses including those with paid occupation (n=1,823), the level and direction of disagreement were larger compared to the main analyses (mean [SD]= 971.8 [788.0] minutes/week and -589.0 [1104.0] minutes/week, respectively). The factors associated with the disagreement were similar compared to the sample included in the main analyses (Supplement 2.1.7). In those not reporting cycling (n=692), factors associated with the direction of disagreement were equal compared to the sample included in the study (Supplement 2.1.8), although some associations were no longer significant.

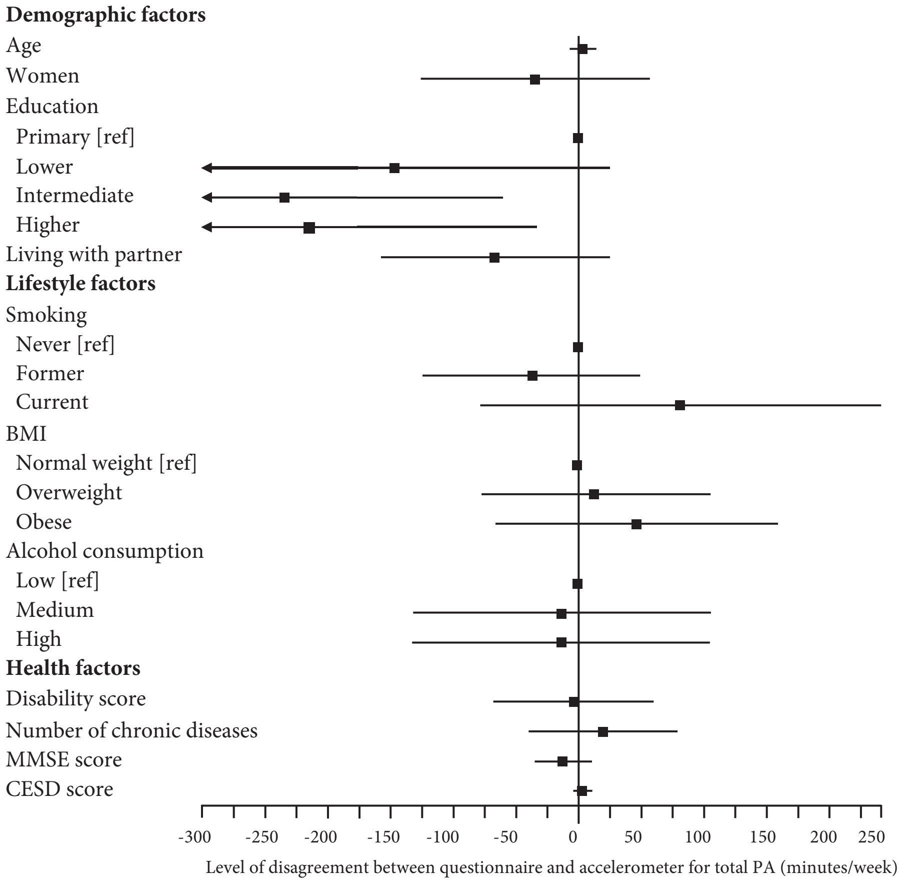


Figure 2.1.2. Factors associated with the level of disagreement (i.e. absolute difference) between accelerometer and questionnaire physical activity

Notes: A positive difference indicates a larger absolute difference between the questionnaire and the accelerometer compared to the reference, whereas a negative difference indicates a smaller difference. Analyses included all demographics: lifestyle and health variables, total accelerometer-derived physical activity, time between interview date and first accelerometer-wear date, cohort, and wave. The coefficient for women was relative to men, and the coefficient for paid occupation relative to those without. For continuous variables (age, disability score, number of chronic diseases, MMSE score, and CESD score), values correspond to a 1-unit increase in the determinant.

Abbreviations: BMI, body-mass index; CESD, Center for Epidemiologic Studies Depression; MMSE, Mini-Mental State Examination; PA: physical activity; ref, reference.

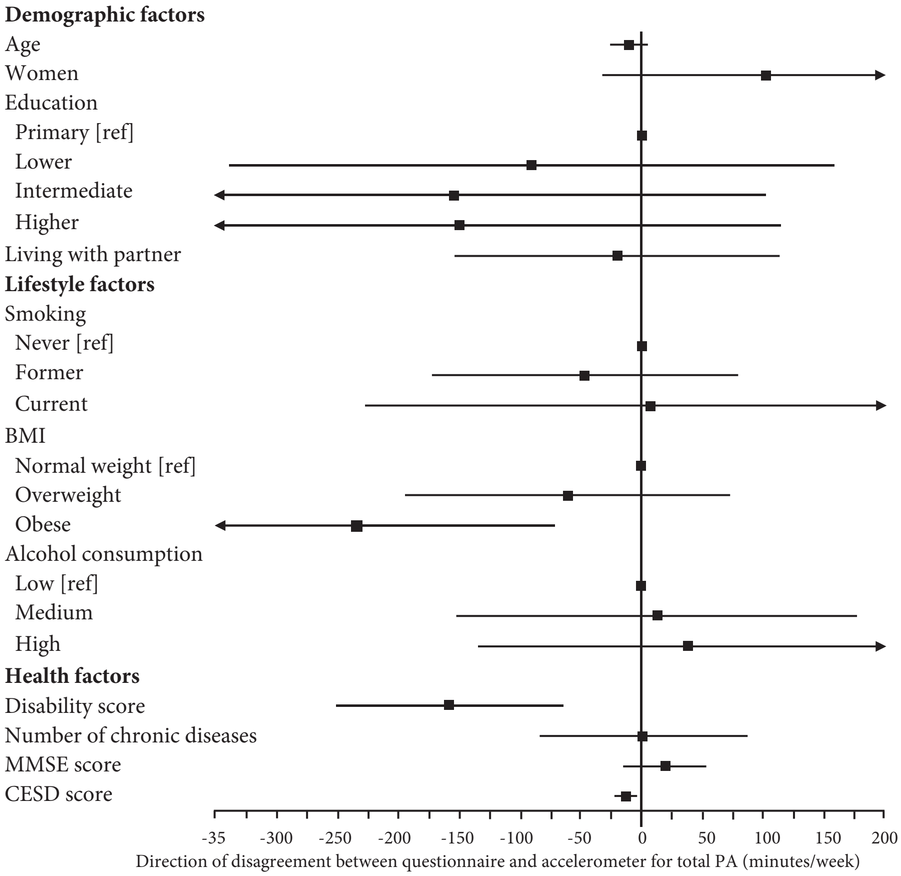


Figure 2.1.3. Factors associated with the direction of disagreement between accelerometer and questionnaire physical activity

Notes: Considering the average direction of disagreement equaled –529.4 minutes/week, positive disagreement indicates less underestimation in the questionnaire. Relative to the accelerometer. Negative disagreement indicates more underestimation in the questionnaire compared to the accelerometer. Analyses included all demographic, lifestyle, and health variables, total accelerometer-derived physical activity, time between interview date and first accelerometer-wear date, cohort, and wave. The coefficient for women was relative to men and the coefficient for paid occupation relative to those without paid occupation. For continuous variables (age, disability score, number of chronic diseases, MMSE-score, and CESD-score), values correspond with a 1-unit increase in the determinant.

Abbreviations: BMI, body-mass index; CESD, Center for Epidemiologic Studies Depression; MMSE, Mini-Mental State Examination; PA, physical activity.

DISCUSSION

The aim of the current study was to quantify the level and direction of disagreement between questionnaire- and accelerometer-assessed PA and to investigate if sociodemographic, lifestyle and health factors could explain differences in agreement. We found that the overall agreement between the LASA Physical Activity Questionnaire and a wrist-worn accelerometer was low and that it differed across lifestyle and health variables. The level of disagreement was higher in less educated individuals. In addition, obese individuals, those with higher disability, and those with more depressive symptoms underreported PA more in the questionnaire compared to the reference group. Moreover, with higher levels of accelerometer-derived PA, the underestimation of PA in the questionnaire was more obvious.

The low correlation between accelerometer- and questionnaire-derived PA observed in the current study (r=0.30) is similar to results reported in previous studies in older adults,[2,9] but lower than another study using the LAPAQ in 439 adults aged 69-92 years (r=0.56).[18] This difference might be related to the study design, as participants in the study of Stel et al. wore a pedometer directly after filling out the LAPAQ,[18] whereas in the current study the time between questionnaire- and accelerometer-assessment had a median value of 8.7 weeks. Moreover, in the study of Stel et al,[18] participants additionally completed a 7-day diary while wearing the pedometer, which might have altered their PA patterns, due to increased awareness. Furthermore, in contrast to most studies, but similar to the study of Sabia et al,[9] our participants wore the accelerometer around the wrist. There is general consensus that a wrist-worn accelerometer is worse in estimating activity during large-muscle, dynamic activities like cycling than a hip-worn device.[35] This could lead to an underestimation of PA performed solely by the legs.[10,11] Moreover, when the wrist is constrained during PA, for example when carrying a briefcase or groceries, the PA level will likely be underestimated.[35] Considering the fact that these activities are usually of light to moderate activity, the agreement between questionnaire and accelerometer might be different for hip-worn accelerometers for these intensity domains.

However, an advantage of the wrist-worn accelerometer is that it allows for 24-hours of data-collection per day, including during water-based activities, leading to a comprehensive overview of daily PA. This is in contrast to hip-worn devices that have to be removed during the night and are usually not waterproof. However, since the correlation between PA derived from questionnaire and accelerometer observed in the current study is similar to the correlation in studies using hip-worn devices,[2,9] the high compliance of the wrist-worn accelerometers is unlikely to enhance the comparability between questionnaire and accelerometer.

In the total population, we found that, compared to the accelerometer, the questionnaire on average underestimated PA levels with 529 minutes/week, equivalent to 76 minutes/day. This difference could be explained by missing items on the questionnaire that are measured by the accelerometer, including climbing stairs, walking within shops, playing with domestic animals and dressing and cleaning oneself. These kinds of activities could add up to over one hour per day. An additional explanation for the underestimation of PA in the questionnaire could be that some activities are of very short duration (<1 minute) and therefore might not be recalled by the participants when filling in the questionnaire, whereas the accelerometer accumulates all these small bouts of activity. These two explanations might be especially important for light activity, for which we found that in the total population, weekly light PA was 708 minutes/week (corresponding to 1 ¾ hour per day) lower according to questionnaire compared to the accelerometer (Supplement 2.1.4), which is in line with previous evidence.[36,37]

To our knowledge, we are the first to report that more depressive symptoms and disability are associated to a larger underestimation in the questionnaire compared to the accelerometer. An explanation could be that those with depressive symptoms or disability have a more pessimistic estimate of their PA levels than their counterparts. In other research domains, depressive symptoms have also been associated with reporting bias[38] and it has been suggested that individuals suffering from depression process information about the self in a maladaptive fashion compared to their healthier counterparts.[39]

In other research domains, depressive symptoms have also been associated with reporting bias[38] and it has been suggested that individuals suffering from depression process information about the self in a maladaptive fashion compared to their healthier counterparts.[39] For example, in a study regarding the agreement between self-reported and actigraphic assessed sleep, participants with more depressive symptoms reported a lower sleep duration than was measured using actigraphy.[34] In the same study, higher levels of functional disability were associated with a larger absolute difference between self-reported and actigraphic sleep, indicating that being disabled might affect self-reported levels in domains other than PA as well.

Furthermore, our findings show that the absolute difference between questionnaire and accelerometer is highest in those with primary education, although there was no difference between educational groups regarding the direction of this disagreement. This indicates that the degree of underreporting differs for participants with a low education, which is cancelled out in the absolute difference between questionnaire and accelerometer. Finally, obese individuals underreported their total PA more than normal weight participants, which is contradictory to previous research showing over reporting of PA in questionnaires.[15,40] However, in line with our observation, a study among 365 young and middle-aged adults found that participants who underestimated their PA levels were more likely to have a higher BMI.[41] In this regard, it's possible that those with obesity perceive their PA levels as inadequate, because of the belief that they could not have been obese with adequate PA levels.[41,42]

The results of our study can have implications for current and future practice on PA measurements. Considering the increase in the use of accelerometers in current research, researchers need to be aware that results between studies using either questionnaire or accelerometer should be compared with caution. Importantly, the disagreement increased with higher levels of accelerometer-derived PA. More detailed instructions in the questionnaire may be needed[43] and questionnaires might need to be improved to better capture the overall PA pattern of older adults. To this aim, future studies should focus on enhancing the agreement between questionnaire- and accelerometer-derived PA levels. Moreover, individuals working in clinical practice should be aware that especially those with worse perceived health might not have a realistic view of their PA levels. Asking more thoroughly about their activities could provide more information than a simple question on whether they perceive their PA as sufficient or not. Furthermore, the large discrepancy between accelerometer- and questionnaire-derived PA in those with paid occupation found in our sensitivity analysis implies that studies using questionnaires in working populations should always include occupational PA.

The use of accelerometers could also be improved in future studies to more accurately measure activities solely performed with the lower extremities. The bias between questionnaire and accelerometer might be reduced by future efforts to develop specified algorithms that can identify these activities, taking into account their specific rhythm when wearing an accelerometer. Moreover, our findings that (perceived) health and educational status can influence reported PA stresses the importance of taking into account these factors in in future studies and analyses. Finally, regardless of the (dis)agreement between questionnaires and accelerometers, both methods should be used simultaneously in research to gain the most information. Whereas accelerometers provide an accurate distribution of intensity and duration, questionnaires might more accurately reflect the perceived PA. In order to be able to influence the PA levels of individuals, both sources of information are important. We would therefore recommend for all individuals, including those with higher BMI, more depressive symptoms and more disability, to measure PA by using both methods whenever possible.

Our study contains several strengths. We are one of the first to examine both the correlation and disagreement between PA as derived from questionnaire and a wrist-worn accelerometer in a large community-based cohort of older adults, using a wide variety of determinants. Moreover, the use of a waterproof wrist-worn accelerometer ensured high compliance. Consequently, the high compliance ensures a low amount of non-wear periods in which assumptions would have to be made on whether this time was spent active or sedentary.[44,45] As a result, PA is generally assessed more precisely.[45]

However, some limitations also have to be acknowledged. First, the PA estimates as derived from accelerometer and questionnaire were not obtained in the same week. This might have contributed to the low agreement in the current study. However, addressing questionnaire and accelerometer simultaneously might make participants more aware of their behavior and could result in larger agreement than otherwise obtained.[43] Second, we did not have up-to-date information on cancer, cardiovascular disease and diabetes. Consequently, some residual confounding might be present which could result in bias towards the null. Third, our results are based on the difference between the LASA Physical Activity Questionnaire and the wrist-worn GeneActiv accelerometer. Our findings might therefore not be generalized to other questionnaires or hip-worn accelerometers. Fourth, using accelerometers providing raw output in milligravity is relatively new and therefore the cut-off points to define activity intensity have not been firmly established. Therefore, the use of different cut-offs might shift the distribution of time spent in light, moderate and vigorous PA according the accelerometer. Furthermore, we measured PA during one week, which might not represent overall engagement in PA. Additionally, participants that agreed to wear an accelerometer were more often men and showed a better health profile regarding the MMSE score, CESD score and disability score. This might affect the generalizability towards the total population of older adults. Finally, the current participants were from a Dutch population, with relatively high levels of PA compared to other Western countries.[46] Considering the fact that the disagreement in the current was higher for higher levels of accelerometer-derived

PA, the disagreement between questionnaire- and accelerometer-derived PA might be lower in countries with generally lower PA levels.

Conclusions

In conclusion, we observed that the correspondence between questionnaire- and accelerometer-derived PA is low. In the total population, the number of minutes per week spent in PA was in general underestimated in the questionnaire. This was a consequence of underreporting light PA, whereas moderate PA was over reported in the questionnaire. These differences were partly explained by BMI, disability and depressive symptoms, as participants with higher BMI and more disability and depressive symptoms underestimated their self-reported PA more than their healthier counterparts. Moreover, the underestimation was larger with higher levels of accelerometer-derived PA. Future studies using questionnaires and/or accelerometers to measure PA should be aware of these differences.

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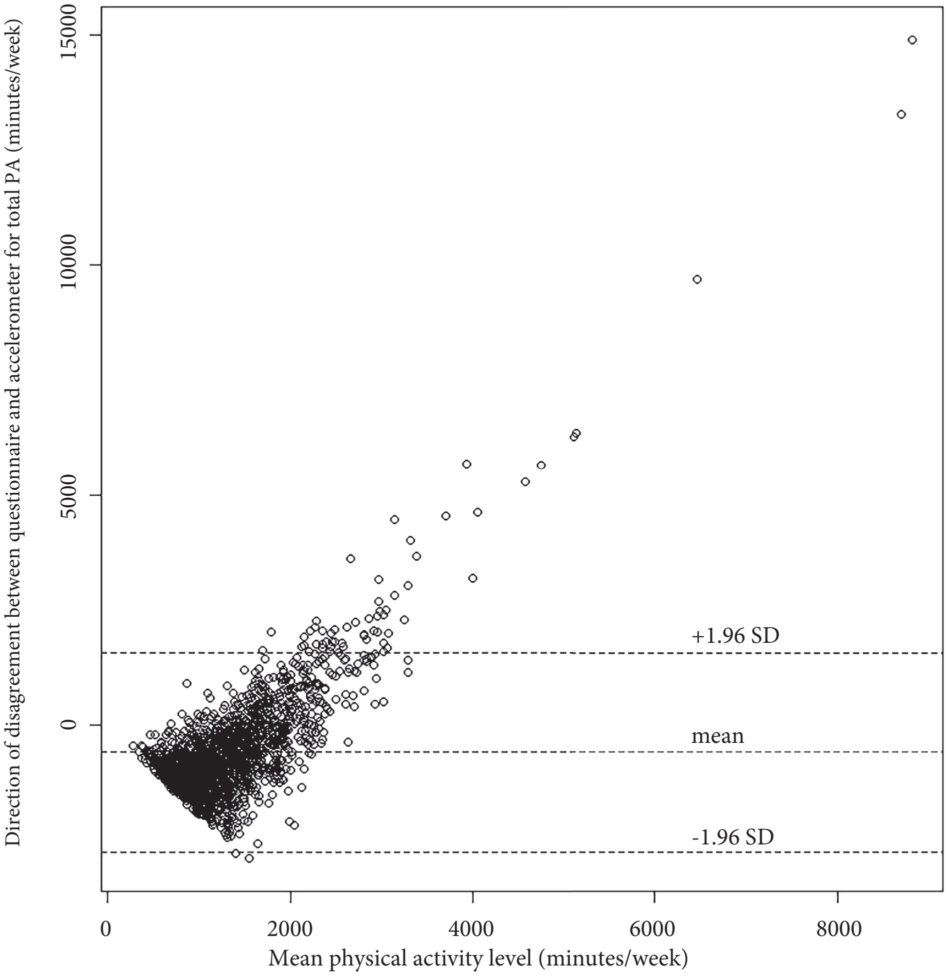
SUPPLEMENT CHAPTER 2.1

Supplement 2.1.1. Characteristics of participants who agreed to participate and those who did not agree to participate

	Did not agree to participate	Agreed to participate*	p
Participants	833	3,156	
Age (years)	72.70 (22.7)	70.78 (9.0)	<0.001
Women, n (%)	528 (63.6)	1,669 (52.9)	<0.001
Education			<0.001
Elementary	66 (8.1)	197 (6.3)	
Lower secondary	374 (46.0)	1,202 (38.5)	
Higher secondary	239 (29.4)	966 (30.9)	
Tertiary	134 (16.5)	757 (24.2)	
BMI, n (%)			0.06
Normal weight	258 (31.3)	880 (27.9)	
Overweight	358 (43.4)	1,507 (47.8)	
Obese	209 (25.3)	768 (24.3)	
Smoking, n (%)			0.002
Non smoker	296 (35.8)	1,048 (33.3)	
Former smoker	424 (51.3)	1,800 (57.2)	
Current smoker	107 (12.9)	301 (9.6)	
Disability score	0.75 (0.87)	0.55 (0.65)	<0.001
Living with partner, n (%)	508 (61.4)	2,261 (71.7)	<0.001
Currently with job, n (%)	120 (16.7)	599 (20.6)	0.02
Prevalent cancer, CVD or diabetes, n (%)	352 (42.3)	1276 (40.4)	0.36
MMSE score	27.51 (2.40)	28.12 (1.74)	<0.001
CESD score	6.44 (7.30)	5.35 (6.79)	<0.001
Total PA according questionnaire (minutes/week),	970.19 (1176.5)	1110.09 (1486.5)	0.02

Data are presented as mean (SD) unless otherwise stated.
Abbreviations: BMI, body mass index; CESD, Center for Epidemiologic Studies Depression; CVD, cardiovascular disease; IQR, interquartile range; MMSE, mini mental state examination; n, number; PA, physical activity; SD, standard deviation.
* The study sample agreeing to participate also includes participants that wore an Actiwatch device.

Supplement 2.1.2. Bland-Altman plot for total physical activity



Abbreviation: SD, standard deviation.

Supplement 2.1.3. Physical activity characteristics of light, moderate and vigorous physical activity in the total population

Characteristic	Mean (SD)
Physical activity according questionnaire	
Light PA (minutes)	316.1 (473.1)
Moderate PA (minutes)	651.8 (800.8)
Vigorous PA (minutes)	82.0 (338.7)
Physical activity according accelerometer	
Light PA (minutes)	1024.4 (218.1)
Moderate PA (minutes)	447.3 (139.2)
Vigorous PA (minutes)	107.6 (53.7)
Level of disagreement between questionnaire and accelerometer	
Light PA (minutes)	781.6 (354.1)
Moderate PA (minutes)	405.8 (697.6)
Vigorous PA (minutes)	131.0 (312.7)
Direction of disagreement between questionnaire and accelerometer	
Light PA (minutes)	-708.4 (484.3)
Moderate PA (minutes)	204.6 (780.8)
Vigorous PA (minutes)	-25.6 (338.1)

*Paired t-tests indicated significant differences between light, moderate and vigorous physical activity as measured by questionnaire and accelerometer.
Abbreviations: PA, physical activity; SD, standard deviation

Supplement 2.1.4. Factors associated with the level of disagreement between accelerometer and questionnaire physical activity, according to PA intensity

	Light PA			Moderate PA			Vigorous PA		
	β	(95%CI)	p	β	(95%CI)	p	β	(95%CI)	p
Demographic factors									
Age	3.9	-0.82, 8.5	0.11	-5.3	-15.2, 4.5	0.29	-3.9	-8.34, 0.47	0.08
Women	-115.0	-156.3, -73.7	<0.001	-20.2	-107.4, 7.0	0.65	-43.4	-82.3, -4.6	0.03
Education									
Primary	Ref			Ref			Ref		
Lower	-18.1	-95.1, 59.0	0.65	-66.6	-228.2, 95.1	0.42	-111.3	-183.5, -39	0.003
Intermediate	-64.4	-143.5, 14.6	0.11	-116.6	-282.7, 49.6	0.17	-121.7	-195.9, -47.5	0.001
Higher	-50.9	-133.4, 31.6	0.23	-113.6	-286.6, 59.5	0.20	-114.3	-191.7, -37.0	0.004
Living with partner	-4.1	-45.7, 37.5	0.85	-64.4	-152.0, 23.3	0.15	-34.0	-73.2, 5.2	0.09
Lifestyle factors									
Smoking									
Never smoker	Ref			Ref			Ref		
Former smoker	-10.6	-49.1, 28.0	0.59	4.2	-77.1, 85.4	0.92	-25.3	-61.6, 11.03	0.17
Current smoker	17.3	-54.8, 89.4	0.64	103.3	-48.6, 255.3	0.18	-51.8	-119.8, 16.2	0.14
BMI									
Normal weight	Ref			Ref			Ref		
Overweight	0.59	-40.6, 41.8	0.98	-42.1	-128.9, 44.6	0.34	15.4	-23.3, 54.2	0.44
Obese	50.0	-0.6, 100.7	0.053	-78.5	-185.2, 28.3	0.15	-16.3	-64.0, 31.5	0.50
Alcohol consumption									
Low	Ref			Ref			Ref		
Medium	0.9	-47.4, 49.2	0.97	48.4	-61.2, 158.0	0.39	-14.9	-58.8, 29.0	0.51
High	7.0	-44.9, 58.9	0.79	27.7	-83.0, 138.4	0.62	-10.0	-55.6, 35.6	0.67
Health factors									
Disability score	29.2	0.6, 57.8	0.05	-41.3	-101.6, 19.0	0.18	-26.9	-53.8, -0.01	0.05
Number of chronic diseases	0.4	-26.3, 27.09	0.98	1.5	-54.7, 57.8	0.96	0.2	-25.0, 25.4	0.99
MMSE score	-7.4	-17.9, 2.99	0.16	11.7	-10.4, 33.8	0.30	-2.0	-11.79, 7.8	0.69
CESD score	2.9	-0.05, 5.76	0.05	-5.3	-11.4, 0.82	0.09	0.7	-2.02, 3.46	0.61

Analyses were adjusted for all included demographic, lifestyle and health variables, total accelerometer-derived PA, time between interview date and the first accelerometer wear date, cohort and wave. **Abbreviations**: BMI, body mass index; CESD, Center for Epidemiologic Studies Depression Scale; MMSE, mini mental state examination; PA, physical activity

Supplement 2.1.5. Factors associated with the direction of disagreement between accelerometer and questionnaire physical activity, according to PA intensity

	Light PA			Moderate PA			Vigorous PA		
	β	(95%CI)	p	β	(95%CI)	p	β	(95%CI)	p
Demographic factors									
Age	3.9	-0.82, 8.5	0.11	-5.3	-15.2, 4.5	0.29	-3.9	-8.34, 0.47	0.08
Women	-115.0	-156.3, -73.7	<0.001	-20.2	-107.4, 7.0	0.65	-43.4	-82.3, -4.6	0.03
Education									
Primary	Ref			Ref			Ref		
Lower	-18.1	-95.1, 59.0	0.65	-66.6	-228.2, 95.1	0.42	-111.3	-183.5, -39	0.003
Intermediate	-64.4	-143.5, 14.6	0.11	-116.6	-282.7, 49.6	0.17	-121.7	-195.9, -47.5	0.001
Higher	-50.9	-133.4, 31.6	0.23	-113.6	-286.6, 59.5	0.20	-114.3	-191.7, -37.0	0.004
Living with partner	-4.1	-45.7, 37.5	0.85	-64.4	-152.0, 23.3	0.15	-34.0	-73.2, 5.2	0.09
Lifestyle factors									
Smoking									
Never smoker	Ref			Ref			Ref		
Former smoker	-10.6	-49.1, 28.0	0.59	4.2	-77.1, 85.4	0.92	-25.3	-61.6, 11.03	0.17
Current smoker	17.3	-54.8, 89.4	0.64	103.3	-48.6, 255.3	0.18	-51.8	-119.8, 16.2	0.14
BMI									
Normal weight	Ref			Ref			Ref		
Overweight	0.59	-40.6, 41.8	0.98	-42.1	-128.9, 44.6	0.34	15.4	-23.3, 54.2	0.44
Obese	50.0	-0.6, 100.7	0.053	-78.5	-185.2, 28.3	0.15	-16.3	-64.0, 31.5	0.50
Alcohol consumption									
Low	Ref			Ref			Ref		
Medium	0.9	-47.4, 49.2	0.97	48.4	-61.2, 158.0	0.39	-14.9	-58.8, 29.0	0.51
High	7.0	-44.9, 58.9	0.79	27.7	-83.0, 138.4	0.62	-10.0	-55.6, 35.6	0.67
Health factors									
Disability score	29.2	0.6, 57.8	0.05	-41.3	-101.6, 19.0	0.18	-26.9	-53.8, -0.01	0.05
Number of chronic diseases	0.4	-26.3, 27.09	0.98	1.5	-54.7, 57.8	0.96	0.2	-25.0, 25.4	0.99
MMSE score	-7.4	-17.9, 2.99	0.16	11.7	-10.4, 33.8	0.30	-2.0	-11.79, 7.8	0.69
CESD score	2.9	-0.05, 5.76	0.05	-5.3	-11.4, 0.82	0.09	0.7	-2.02, 3.46	0.61

Analyses were adjusted for all included demographic, lifestyle and health variables, total accelerometer-derived PA, time between interview date and the first accelerometer wear date, cohort and wave. **Abbreviations**: BMI, body mass index; CESD, Center for Epidemiologic Studies Depression Scale; MMSE, mini mental state examination; PA, physical activity

Supplement 2.1.6. Characteristics of the study population, stratified by occupational status

	Without paid occupation	With paid occupation*	p
Participants	1,410	386	
Age (years)	73.81 (7.61)	60.31 (6.17)	<0.001
Female, n (%)	742 (52.6)	174 (45.1)	0.01
Education			<0.001
Elementary	85 (6.1)	15 (3.9)	
Lower secondary	562 (40.5)	94 (24.5)	
Higher secondary	428 (30.8)	120 (31.2)	
Tertiary	314 (22.6)	155 (40.4)	
BMI, n (%)			0.70
Normal weight	418 (29.6)	111 (28.8)	
Overweight	668 (47.4)	192 (49.7)	
Obese	324 (23.0)	83 (21.5)	
Smoking, n (%)			0.005
Never smoker	471 (33.4)	115 (29.8)	
Former smoker	832 (59.0)	222 (57.5)	
Current smoker	106 (7.5)	49 (12.7)	
Disability score	0.64 (0.68)	0.25 (0.38)	<0.001
Living with partner, n (%)	988 (70.1)	323 (83.7)	<0.001
Prevalent cancer, CVD or diabetes, n (%)	635 (45.0)	79 (20.5)	<0.001
MMSE score	28.10 (1.74)	28.61 (1.28)	<0.001
CESD score	5.04 (6.30)	4.24 (5.74)	0.03
Total PA according questionnaire (minutes/week)	1049.9 (1108.3)	970.9 (1149.9)	0.22
Total PA according accelerometer (minutes/week)	1579.3 (386.1)	1779.2 (396.7)	<0.001

Data are presented as mean (SD) unless otherwise stated.
Abbreviations: BMI, body mass index; CESD, Center for Epidemiologic Studies Depression; CVD, cardiovascular disease; IQR, interquartile range; MMSE, mini mental state examination; n, number; PA, physical activity; SD, standard deviation.
* The fact that the number of participants is different from the number mentioned in the flowchart is related to the fact that a second observation was excluded for 3 additional participants.

Supplement 2.1.7. Factors associated with the level and direction of disagreement between accelerometer and questionnaire physical activity, including participants with paid occupation (n=1,823)

	Level of disagreement			Direction of disagreement		
	β	95%CI	p	β	95%CI	p
Demographic factors						
Age	0.84	-8.8, 10.5	0.86	-8.8	-22.4, 4.8	0.21
Women	-66.4	-149.3, 16.5	0.12	120.0	2.6, 237.4	0.05
Education						
Primary	Ref			Ref		
Lower	-176.1	-340.2, -12.1	0.04	-59.9	-291.8, 171.9	0.61
Intermediate	-268.6	-436.3, -101	0.002	-115.1	-352.0, 121.8	0.34
Higher	-241.5	-413.9, -69.0	0.01	-101.9	-345.4, 141.6	0.41
Paid occupation	185.0	72.7, 297.3	0.001	-312.7	-471.5, -154	<0.001
Living with partner	-44.4	-131.9, 43.1	0.32	1.0	-122.7, 124.8	0.99
Lifestyle factors						
Smoking						
Never smoker	Ref			Ref		
Former smoker	-2.5	-82.2, 77.3	0.95	-18.3	-131.0, 94.5	0.75
Current smoker	88.1	-53.1, 229.4	0.22	-12.6	-212.5, 187.3	0.90
BMI						
Normal weight	Ref			Ref		
Overweight	19.4	-65.6, 104.5	0.65	-109.0	-229.2, 11.1	0.08
Obese	49.2	-55.9, 154.3	0.36	-260.2	-408.9, -111.6	0.001
Alcohol consumption						
Low	Ref			Ref		
Medium	-16.3	-121.5, 89.0	0.76	-46.3	-191.7, 99.2	0.53
High	-14.6	-116.7, 87.6	0.78	-28.4	-176.6, 119.8	0.71
Health factors						
Disability score	-15.6	-79.3, 48.1	0.63	-134.7	-224.7, -44.6	0.003
Number of chronic diseases	19.9	-38.2, 78.0	0.50	-3.4	-85.44, 78.7	0.94
MMSE score	-4.6	-27.0, 17.9	0.69	21.6	-10.3, 53.5	0.18
CESD score	2.4	-3.7, 8.5	0.44	-12.5	-21.1, -3.95	0.004

Analyses were adjusted for all included demographic, lifestyle and health variables, total accelerometer-derived physical activity, time between interview date and the first accelerometer wear date, cohort and wave.

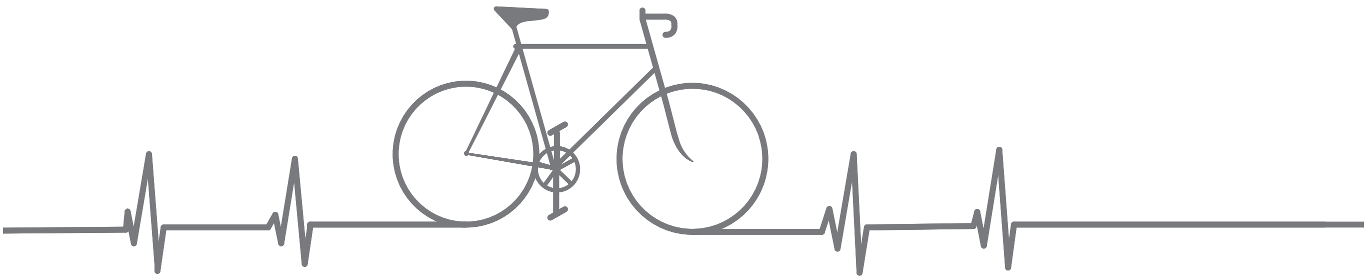
Abbreviations: BMI, body mass index; CESD, Center for Epidemiologic Studies Depression Scale; MMSE, mini mental state examination; PA, physical activity

Supplement 2.1.8. Factors associated with the level and direction of disagreement between accelerometer and questionnaire physical activity, in those not reporting cycling (n=692)

	Level of disagreement			Direction of disagreement		
	β	95%CI	p	β	95%CI	p
Demographic factors						
Age	-0.4	-14.1, 13.3	0.96	-21.2	-40.7, -1.7	0.03
Women	-31.6	-165.1, 101.9	0.64	94.5	-95.1, 284.1	0.33
Education						
Primary	Ref			Ref		
Lower	3.0	-216.2, 222.3	0.98	186.0	-124.8, 496.8	0.24
Intermediate	-89.7	-316.3, 136.9	0.44	10.0	-311.0, 331.1	0.95
Higher	-80.5	-323.1, 162.1	0.52	129.3	-214.2, 472.9	0.46
Living with partner	-77.8	-203.9, 48.3	0.23	-132.5	-311.2, 46.2	0.15
Lifestyle factors						
Smoking						
Never smoker	Ref			Ref		
Former smoker	8.4	-113.8, 130.6	0.89	-15.2	-188.3, 158.0	0.86
Current smoker	162.4	-47.9, 372.7	0.13	83.6	-214.5, 381.7	0.58
BMI						
Normal weight	Ref			Ref		
Overweight	-81.4	-214.0, 51.2	0.23	-149.3	-337.1, 38.6	0.12
Obese	-14.9	-170.0, 140.3	0.85	-283.7	-503.4, -63.9	0.01
Alcohol consumption						
Low	Ref			Ref		
Medium	10.4	-154.7, 175.5	0.90	-27.6	-282.9, 227.7	0.83
High	-42.5	-224.1, 139.1	0.64	-26.9	-287.8, 234.0	0.84
Health factors						
Disability score	5.0	-74.5, 84.4	0.90	-91.9	-204.6, 20.8	0.11
Number of chronic diseases	37.6	-46.6, 121.8	0.38	49.9	-69.5, 169.2	0.41
MMSE score	8.3	-23.3, 39.8	0.61	26.0	-18.7, 70.7	0.25
CESD score	-1.0	-9.5, 7.6	0.83	-15.3	-27.4, -3.19	0.01

Analyses were adjusted for all included demographic, lifestyle and health variables, total accelerometer-derived physical activity, time between interview date and the first accelerometer wear date, cohort and wave.

Abbreviations: BMI, body mass index; CESD, Center for Epidemiologic Studies Depression Scale; MMSE, mini mental state examination; PA, physical activity



Chapter 2.2

Distribution of objective activity measures and associations with demographic and health factors

Manuscript based on this chapter:

Koolhaas CM, van Rooij FJA, Schoufour JD, et al. Objective measures of activity in the elderly: distribution and associations with demographic and health factors. *J Am Med Dir Assoc*. 2017;18(10):838-847.

ABSTRACT

Background: Little is known about the distribution of activity over the full 24-hour spectrum in late old age and its association with demographic and health factors. Therefore, we aimed to evaluate the distribution of physical activity (PA), sedentary behavior, and sleep, and associated factors in the elderly population.

Methods: Our study included 1,210 participants (51.9% women) aged 70-94 years [mean age 77.5 years, standard deviation (SD) 5.0] from the population-based Rotterdam Study. Participants wore a triaxial accelerometer (GENEActiv) around the wrist for 7 days between July 2014 and June 2016. We examined if PA, sedentary behavior, and sleep differed by age, sex, body mass index (BMI), smoking status, alcohol consumption, education, season, disability status, marital status, presence of chronic disease, and use of sleep medication.

Results: Mean total PA, expressed in milli-gravity (mg) units, was slightly higher for women (20.3, SD 5.6) than for men (19.3, SD 5.2, $P < .01$). Mean (SD) daily duration spent in sedentary behavior and light and moderate-to-vigorous PA was 13.3 (1.5) h/d, 147.5 (31.5) min/d, and 75.0 (25.5) min/d, respectively, among women; and 13.8 (1.6) h/d, 140.5 (31.1) min/d, and 71.5 (24.5) min/d, respectively, among men. Women spent on average 6.7 (SD 1.1) h/d sleeping and men 6.6 (1.4) h/d. Across increasing categories of age and BMI and in participants with chronic disease and disability, time spent in light and moderate-to-vigorous PA was decreased. Higher age and BMI were associated with more sedentary time. In addition, obese men spent slightly more time sleeping than their normal weight counterparts and women spent slightly less time sleeping in the summer than in spring.

Conclusion: PA and sedentary behavior in the elderly differed by sex, age, BMI, prevalence of chronic disease, and disability, whereas there were no clear patterns for sleep. On average, our participants spent up to 79.5% of their time awake being sedentary and 7%-8% in moderate-to-vigorous PA. Replacing sedentary behavior with light PA would be a good starting point for those with the lowest level of PA. Older adults, those with high BMI and worse health could benefit from targeted interventions to increase PA.

INTRODUCTION

Physical activity (PA) plays a major role in healthy aging, by preventing disease, reducing disability and improving well-being.[1-3] Given the importance of PA in older adulthood, understanding the levels of PA in elderly adults might provide information for public health institutions to create targeted recommendations. In epidemiological studies, PA is usually assessed by questionnaires.[4] However, these data are known to be prone to reporting errors and recall bias, especially for low intensity behaviors.[5,6] These limitations may be exacerbated in older populations, in whom cognitive impairment is more likely.[7] Therefore, accelerometers are increasingly used to measure PA and sedentary behavior objectively.[8]

To date, several studies objectively assessed PA and sedentary behavior using accelerometers in adults aged 60 years and over[9-19] and examined the associations with demographic and health factors. It has been shown that PA levels decrease with increasing age[9-13,16,19] and across increasing levels of BMI.[9-12,14] Whereas these studies provided useful information, the associations were often obtained from unadjusted analyses. Moreover, there is limited information on the 24-hour activity spectrum in the elderly, including PA, sedentary behavior and sleep. It remains unknown how these factors are interrelated and how they are distributed across age-groups and other demographic and health factors. In previous studies, accelerometers have most often been worn on the hip and had to be removed for sleeping. Wrist-worn devices can be worn day and night, thereby allowing for collection of 24-hour of activity data, recently shown to be valid indicators of activity energy expenditure.[20,21] Additionally, wrist-worn devices have been argued to promote better compliance of device wear.[22]

The Rotterdam Study is one of the first large population studies to objectively assess PA in an elderly population of adults aged 70-94 years using a triaxial accelerometer. The main aim of this study was to provide a description of objectively measured activity in elderly adults from the Rotterdam Study, over the complete 24-hour period. Additionally, we examined the demographic and health factors associated with activity measures in this cohort.

METHODS

Study population

This study was embedded in the Rotterdam Study, a prospective population-based cohort in the Netherlands. The main aim of this study was to examine the incidence of risk factors for neurological, cardiovascular, psychiatric, and other chronic diseases. Details of the study have been published previously.[23] For the current study, 1,900 successive participants of the Rotterdam Study were invited to participate, from July 2014 to May 2016, of which 506 did not consent. For 1,210 participants valid data (>1200 min/day) on at least 4 days was available (See Figure 2.2.1).

All subjects gave written informed consent, and the study protocol was approved by the medical ethics committee of Erasmus University, Rotterdam. Detailed information on the design of the Rotterdam Study can be found elsewhere.[23]

Accelerometer-assessed physical activity

All participants were asked to wear a triaxial accelerometer (GeneActiv; Activinsights Ltd, Kimbolton, Cambridgeshire, UK, http://www.geneactiv.org/) on the non-dominant wrist for 7 consecutive days and nights and to complete a 7-day sleep diary to report overnight sleep periods. The accelerometer sampled at 50 Hz and as in previous studies[18,24,25] acceleration was expressed relative to gravity (g units; 1 g =9.81 m/s^2 at this location in the Netherlands[26]), since the sensors are calibrated relative to gravity. Calibration error was estimated based on static periods in the data and corrected if necessary.[27]

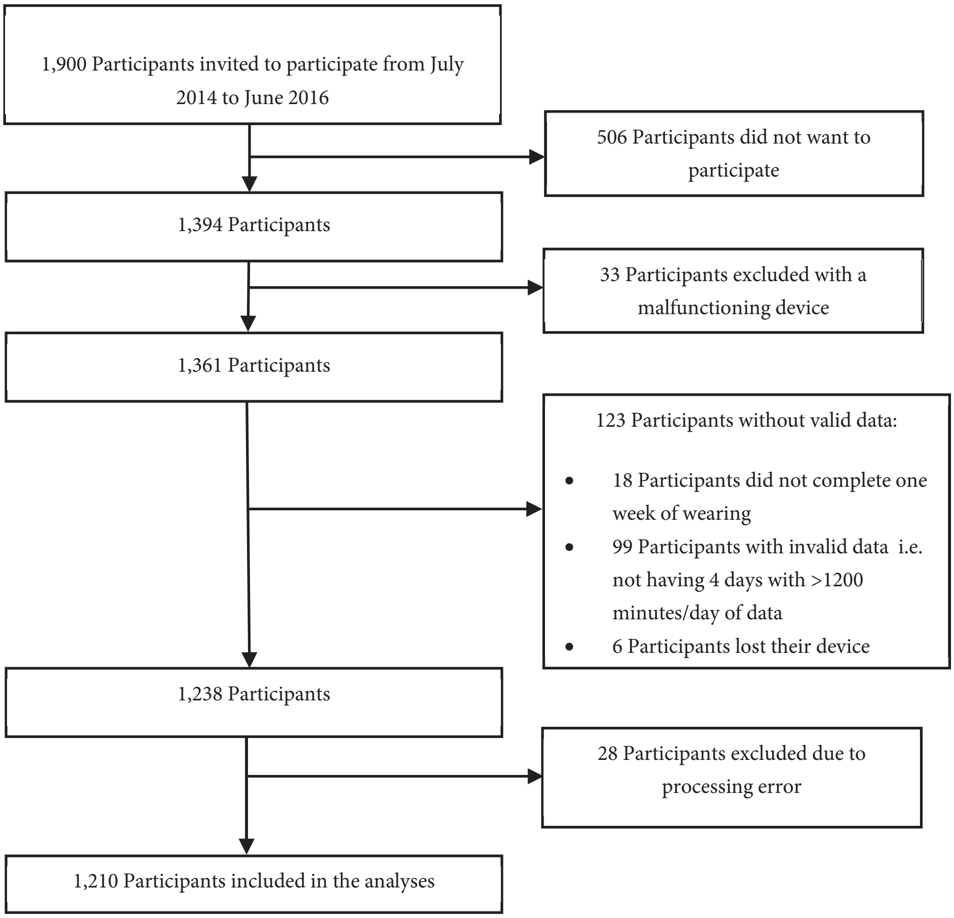


Figure 2.2.1. Flow chart of participant inclusion for the Rotterdam Study.

We used two vector magnitude-based measures to quantify the acceleration related to the movement registered. The first was the Euclidean norm minus 1 g with negative numbers rounded to zero (ENMO).[21] In addition, we calculated the high-pass filtered vector magnitude (HPFVM), which applies a high-pass filter to the acceleration signal with a cut-off frequency of 0.2 Hertz, treating gravity as a low-frequency component to be filtered out.[20]

Accelerometer data were processed in Python (2.6.6) using the open access PAMPRO software. Pampro is a software program for the systematic analysis of physical activity data collected in epidemiological studies.[28] Data was extracted from the first wearing day up to seven days later. Non-wear time was estimated as time periods where the standard deviation of acceleration in all three axes fell below 13mg for longer than 1 hour,[20] and any non-wear period was excluded from analyses. The pattern of non-wear time was accounted for by balancing the weighting of the data according to the diurnal profile.[29]

Assessment of factors

Information on health behaviors was collected through home interviews or measured at the study center, as described previously.[30,31] Alcohol use was defined as the number of times drinking alcohol per time unit (i.e. never drinking alcohol; drinking 1-4 per month; drinking 2-4 per week). Education was assessed in line with the International Standard Classification of Education and categorized as primary, lower, intermediate and higher education.[32] Smoking was divided in three categories: current, former and never. Height and weight were measured to calculate body mass index (BMI) (kg/m2) and categorised as normal weight (<25 kg/m^2), overweight (25–30 kg/m^2) and obese (>30 kg/m^2). Marital status was defined as living with a partner or not. Disability status was assessed by the Activities of Daily Living from the Stanford Health Assessment Questionnaire Disability Index (HAQ-DI).[33] In accordance with literature we used a HAQ-DI 0.5 ≥1.0 to define a participant as disabled and a HAQ-DI ≥ 1.0 to define a participant as severely disabled.[34] Use of sleep medication was obtained from the sleep diary, and used as a binary variable (not in the past 7 days/at least one day in the past 7 days). The presence of cardiovascular disease (CVD), diabetes mellitus (DM) and cancer were determined using medical records, to define presence of chronic disease. The LASA Physical Activity Questionnaire (LAPAQ) was used to determine total self-reported PA and was expressed in MET·hours·week^{-1}. The questionnaire included questions on walking, cycling, housekeeping, sports and gardening. Finally, using the first wearing date of the GeneActiv, we classified the season according to the light definition, centered at equinoxes (winter: November 6 to February 4, spring: February 5 to May 6, summer: May 7 to August 5 and autumn: August 6 to November 5.[35]

Data analysis

Descriptive statistics for continuous PA variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR) if data were not normally distributed. We created 9 intervals, to visually evaluate the distribution of time spent in overall PA, and how it varied by gender and age-group. Additionally, we categorized activity based on HPFVM in sedentary (<48 mg), light (48 < 154 mg), moderate (154 <389 mg) and vigorous activity (>389 mg), based on a recent study.20 For the current study, we combined moderate and vigorous activity in our main analyses. Sleep duration was assessed with a validated algorithm,36 using information on bed time and awake time from the sleep diary, and was subtracted from total sedentary behavior.

To describe our data and test differences in average time per day spent in sedentary behavior, light PA, moderate-to-vigorous PA and sleep across two categories or across three or more categories of the health-related and socio-demographic variables, we used t-tests and Analyses of variance (ANOVA), respectively. We further examined the robustness of the individual associations by mutually adjusting for all demographic and health factors in linear regression analyses. All determinants were entered as categorical variables and the activity variables were the outcome variables in these analyses. To evaluate the explained variance by the determinants, we obtained the adjusted R-squared. We decided a priori to present the results stratified by sex for comparability with previous and future studies. The average time/d in each activity level was plotted as a portion of the 1440 minutes of the day to graphically inspect the distribution of activity levels across age-groups and BMI-groups. The average time across BMI-groups was adjusted for age.

In sensitivity analyses, we tested whether the health-related and socio-demographic characteristics differed between men and women, to be able to explain any gender differences. We also tested whether those participating differed from those not agreeing to participate, in regard to baseline characteristics. Furthermore, we repeated the linear regression analyses stratified by age (older or younger than 80 years), to examine if the associations in the oldest old (i.e. 80 years or older) were different than in those younger than 80 years. We also repeated the linear regression analyses stratified by a BMI of 27 kg/m^2, the median level in the population.

Analyses were conducted using SPSS software version 20 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp), R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria) and Stata version 14.1 SE (StataCorp LP, College Station, Texas).37 A double-sided $p < 0.05$ was considered statistically significant.

RESULTS

Participants who agreed to participate in the study were more often men and less often disabled than those who did not agree to wear an accelerometer (Supplement 2.2.1). In the total sample of 1200 participants, a total of 71,232 valid days were recorded, in accordance with an average of 5.9 (SD: 0.4) days per participant. The proportion of males in the sample was 48.1% and the mean age was 77.5 (SD: 5.0). The median (IQR) accelerometer wear-time was slightly higher in men registering 154.2 hours (152.6, 156.4) than in women registering 153.6 hours (151.6, 156.0), p <0.001. Furthermore, participating women were more often obese or disabled than men, whereas men more often had prevalent chronic disease (Supplement 2.2.2). The proportion of participants who reported engaging in walking, cycling, housework, gardening and sports in the LAPAQ is shown in Supplement 2.2.3. Men participated significantly more in cycling and gardening than women ($p<0.05$).

Total PA, expressed in mg, was slightly higher for women (20.3, SD:5.5) than for men (19.3, SD: 5.2, $p=0.002$). Figure 2.2.2 and Figure 2.2.3 show the acceleration distribution of time spent in 9 systematic intervals (including time spent sleeping), stratified by sex and age category, respectively. Women spent less time in the interval with the lowest acceleration (0-100 mg), and spent more time in each other interval than men. For the age-categories, the oldest age-group (≥ 85 years) spent the most time in the lowest interval (0-100 mg) and spent less time in each other interval.

Mean (SD) time per day spent in sedentary behavior and light and moderate-to-vigorous intensity PA was 13.3 (1.5) hours/d, 147.5 (31.5) minutes/d and 75.0 (25.5) minutes/d, respectively, among women (Table 2.2.1); and 13.8 (1.6) hours/d, 140.5 (31.1) minutes/d and 71.5 (24.5) minutes/d, respectively, among men (Table 2.2.2). Time spent in moderate and vigorous PA separately and in total sedentary behavior (including sleep) is presented in Supplement 2.2.4 (women) and Supplement 2.2.5 (men). Women spent 6.7 hours/d (SD: 1.4) sleeping and men (6.6 hours/d, SD: 1.4), $p = 0.12$. Men spent significant more minutes in sedentary behavior ($p<0.001$) and less time in light ($p<0.001$) and moderate PA ($p<0.004$). The time spent in vigorous PA did not differ significantly between men and women. The percentage of awake time spent sedentary was 79.5% for men and 78.2% for women (Supplement 2.2.6 - Supplement 2.2.7) and 6.9% and 7.4% of the waking time was spent in moderate-to-vigorous PA in men and women, respectively.

Table 2.2.1 (women) and Table 2.2.2 (men) show the results from the univariate analyses (ANOVA and t-test), and show that PA levels decreased across higher strata of age and BMI and with worsening health in both men and women. None of the variables was associated with sleep duration in these analyses. The distribution of the respective activity levels across age-groups and BMI categories is visually presented in Figure 2.2.4 and 2.2.5.

Table 2.2.3 (women) and Table 2.2.4 (men) show the results from the linear regression analyses with mutual adjustment for all demographic and health factors. The explained variance by the determinants was highest for moderate-to-vigorous PA in men (16.6%) and women (22.2%). Factors significantly associated with total PA (expressed in mg) and light and moderate-to-vigorous PA were age, BMI, disability status and prevalent chronic disease. Older participants, those with higher BMI and those with chronic disease or disability were less physically active. Moreover, in women, living with a partner was associated with significant higher levels of total PA and light and moderate-to-vigorous PA and lower time spent sedentary. Sedentary time increased across higher strata of age and BMI and was higher in those with chronic disease (women). Regarding sleep duration, obese men spent more hours sleeping than normal weight men (Table 2.2.4) and women spent slightly less time sleeping in the summer, compared to spring (Table 2.2.3).

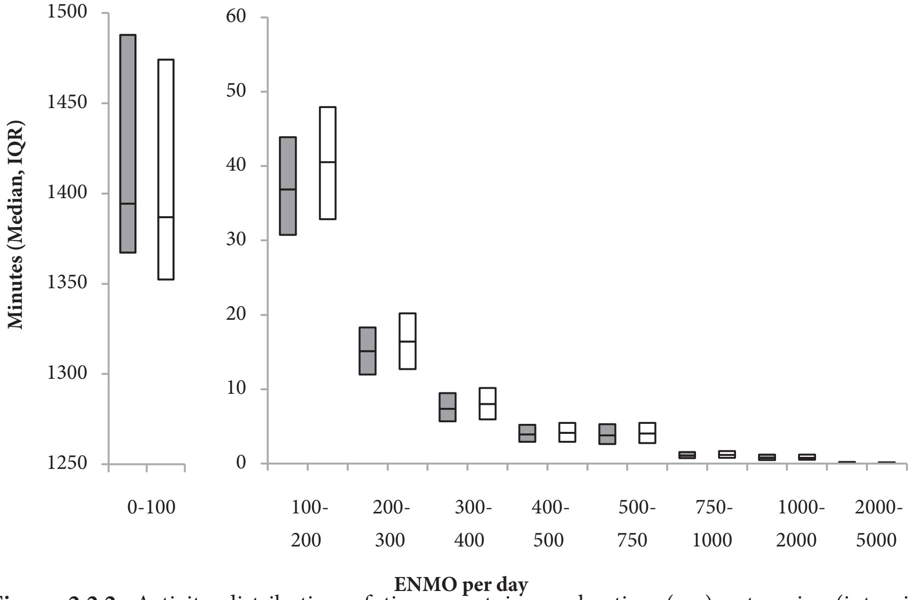


Figure 2.2.2. Activity distribution of time spent in acceleration (mg) categories (intensity) stratified by sex.

ENMO, The Euclidean norm minus 1 g with negative numbers rounded to zero; IQR, interquartile range.
Dark bars represent men and white bars represent women.

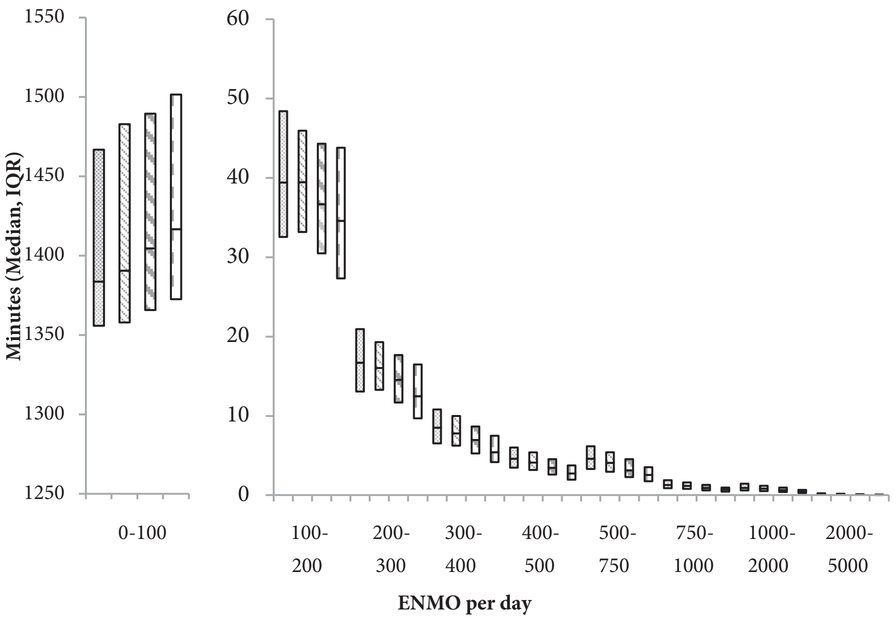


Figure 2.2.3. Activity distribution of time spent in acceleration (mg) categories (intensity) stratified by age-group

ENMO, The Euclidean norm minus 1 g with negative numbers rounded to zero; IQR, interquartile range.
From left to right, bars represent adults aged ≤74 years, 75-79 years, 80-84 years and ≥85 years.

Table 2.2.1. Objectively assessed physical activity subcomponents and sedentary time in women (n=628), according to characteristics of the study population

	n	Acceleration (mg/day)	Sedentary time (h/day)	Light PA (min/day)	Moderate-vigorous PA (min/day)	Sleep time (h/day)
Total	628	20.3 (5.6)	13.3 (1.5)	147.5 (31.5)	75 (25.5)	6.7 (1.4)
Age-group						
70-74	200	22.3 (6.2)	13.3 (1.4)	153.5 (30.7)	85.2 (27.0)	6.6 (1.2)
75-79	226	20.2 (5.1)	13.2 (1.6)	147.7 (31.2)	75.0 (23.3)	6.8 (1.4)
80-84	130	18.9 (4.5)	13.4 (1.4)	144.5 (30.4)	67.7 (21.0)	6.8 (1.4)
≥85	72	17.5 (4.9)	13.6 (1.6)	135.7 (33.1)	59.7 (23.6)	6.9 (1.5)
p		<0.001	0.33	<0.001	<0.001	0.19
Education						
Primary	41	18.1 (5.3)	13.7 (1.8)	135.2 (31.9)	64.8 (25.9)	6.7 (1.6)
Lower	337	20.1 (5.1)	13.3 (1.4)	147.0 (30.7)	74.5 (23.9)	6.8 (1.3)
Intermediate	163	20.3 (5.9)	13.4 (1.5)	146.0 (30.5)	74.3 (26.1)	6.7 (1.3)
Higher	75	21.5 (6.0)	13.3 (1.5)	157.1 (33.8)	82.2 (27.2)	6.5 (1.4)
p		0.02	0.31	0.003	0.004	0.47
Season						
Spring	163	20.2 (5.2)	13.2 (1.6)	146.7 (31.3)	75.0 (24.7)	6.9 (1.4)
Summer	74	21.3 (6.5)	13.4 (1.6)	148.1 (30.9)	78.0 (27.5)	6.6 (1.5)
Autumn	206	19.9 (5.9)	13.3 (1.4)	145.5 (32.6)	73.0 (27.1)	6.7 (1.3)
Winter	182	20.3 (5.0)	13.4 (1.4)	149.4 (30.5)	75.4 (23.3)	6.6 (1.3)
p		0.38	0.56	0.67	0.52	0.44
BMI						
Normal weight	183	22.4 (5.9)	12.8 (1.3)	157.9 (29.9)	84.0 (25.7)	6.9 (1.3)
Overweight	265	20.3 (5.4)	13.3 (1.5)	148.2 (30.7)	75.2 (25.4)	6.7 (1.4)
Obese	179	18.2 (4.6)	13.9 (1.5)	136.1 (30.3)	65.7 (21.7)	6.6 (1.4)
p		<0.001	<0.001	<0.001	<0.001	0.10
Smoking						
Non smoker	282	20.7 (5.6)	13.1 (1.4)	150.8 (31.3)	76.7 (25.5)	6.8 (1.4)
Former smoker	310	20.1 (5.5)	13.5 (1.4)	145.4 (31.4)	74.0 (25.4)	6.6 (1.3)
Current smoker	36	19.0 (5.5)	13.6 (2.0)	139.3 (32.1)	70.1 (25.9)	6.7 (1.7)
p		0.14	0.01	0.03	0.22	0.15
Alcohol consumption						
Never	123	19.7 (4.7)	13.3 (1.5)	145.2 (30.3)	72.1 (22.9)	6.8 (1.4)
1-4 times/month	217	19.5 (5.2)	13.4 (1.4)	142.5 (31.7)	71.5 (24.5)	6.8 (1.4)
2-4 time/week	288	21.2 (6.0)	13.3 (1.6)	152.2 (31.4)	78.8 (26.8)	6.6 (1.3)
p		0.001	0.83	0.002	0.002	0.27
Disability status						
Not disabled	243	21.5 (5.4)	13.2 (1.3)	152.0 (30.3)	81.1 (25.5)	6.7 (1.3)

Table 2.2.1 (continued). Objectively assessed physical activity subcomponents and sedentary time in women (n=628), according to characteristics of the study population

	n	Acceler-ation (mg/day)	Sedentary time (h/day)	Light PA (min/day)	Moderate-vigorous PA (min/day)	Sleep time (h/day)
Disabled	139	20.8 (5.7)	13.1 (1.6)	150.6 (29.2)	77.0 (24.5)	6.9 (1.5)
Severely disabled	245	18.9 (5.4)	13.6 (1.5)	141.2 (33.1)	67.8 (24.4)	6.7 (1.3)
p		<0.001	0.003	<0.001	<0.001	0.40
Prevalent CVD, DM or cancer						
Not present	336	21.3 (5.7)	13.1 (1.4)	151.4 (30.7)	79.3 (25.7)	6.8 (1.3)
Present	292	19.1 (5.1)	13.5 (1.5)	143.0 (31.9)	70.0 (24.3)	6.7 (1.4)
p		<0.001	0.001	0.001	<0.001	0.42
Marital status						
Living alone	309	19.2 (5.4)	13.5 (1.6)	141.1 (31.9)	69.7 (25.0)	6.8 (1.4)
Living with partner	319	21.3 (5.6)	13.2 (1.4)	153.7 (29.9)	80.1 (25.0)	6.7 (1.3)
p		<0.001	0.02	<0.001	<0.001	0.41
Sleep medication						
Not using any	459	20.5 (5.3)	13.5 (1.2)	148.9 (31.6)	76.2 (24.8)	6.6 (1.1)
Using ≥1 day/week	135	19.7 (6.2)	13.7 (1.4)	142.7 (30.1)	71.6 (27.3)	6.5 (1.2)
p		0.16	0.13	0.04	0.06	0.36

Abbreviations: BMI, body mass index; ENMO, The Euclidean norm minus 1 g with negative numbers rounded to zero; n, number; PA, physical activity. Body mass index was calculated as weight in kilograms divided by height in meters squared. Categories were defined as normal weight: 18.5 < 25 kg/m^2, overweight: 25 < 30 kg/m^2 and obese: ≥ 30 kg/m^2. Results are obtained from t-tests for determinants with two categories and analysis of variance (ANOVA) for determinants with 3 or more categories. Data are mean (SD). Total N varies due to variation in the amount of missing data for different covariates.

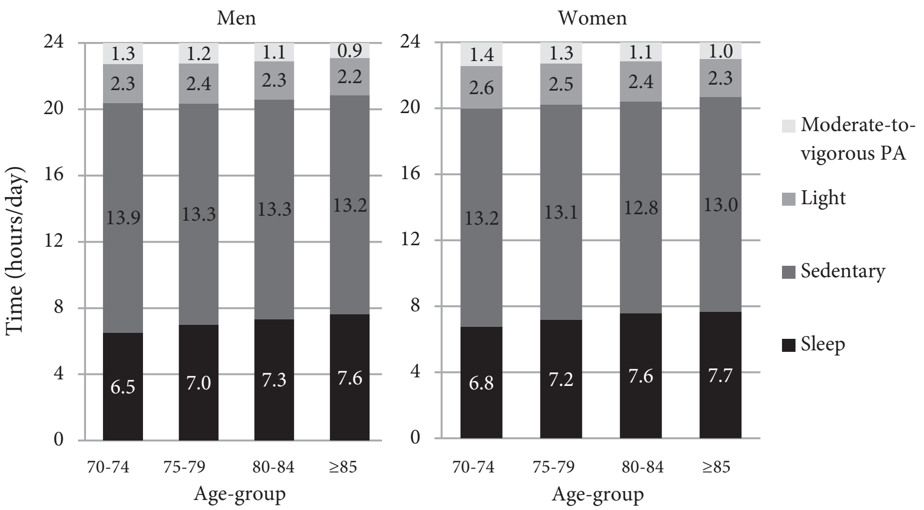


Figure 2.2.4. Distribution of activity across the 24-hour period in men and women, according to age-group.

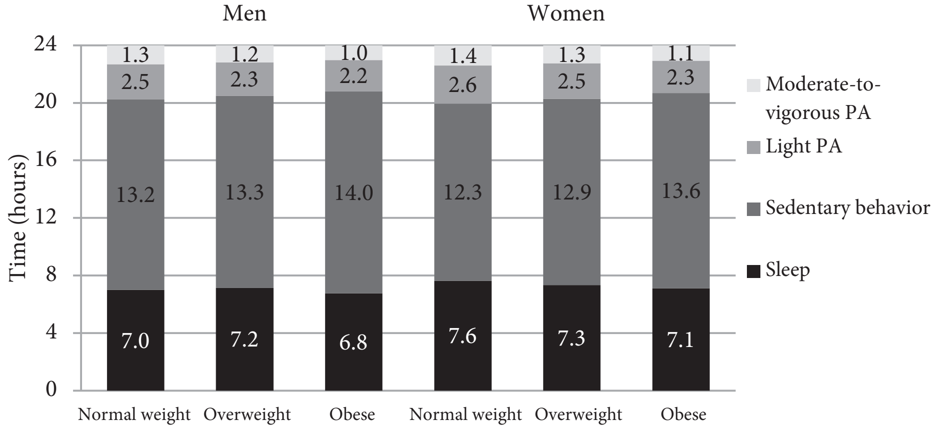


Figure 2.2.5. Distribution of activity across the 24-hour period in men and women, according to normal weight, overweight and obesity

Body mass index was calculated as weight in kilograms divided by height in meters squared. Categories were defined as normal weight: 18.5 < 25 kg/m^2, overweight: 25 < 30 kg/m^2, and obese: ≥30 kg/m2. The average time spent in each activity level was adjusted for age

Sensitivity analyses

In sensitivity analyses split by age, we observed that in the oldest old (i.e. 80 years and older), there were less gender differences and there was no effect of season, compared to those younger than 80 years (Supplement 2.2.8 - Supplement 2.2.9). Moreover, in the oldest old, disability status and marital status were not associated with sedentary behavior or PA, whereas these were associated with activity in participants younger than 80 years.

In the analyses split by BMI, we observed that marital status was not associated with activity in participants with a BMI < 27 kg/m^2, whereas it was associated with activity in those with higher BMI (Supplement 2.2.10 - Supplement 2.2.11). In contrast, smoking status was a determinant of activity in those with BMI< 27 kg/m^2 and not in participants with ≥ 27 kg/m^2.

DISCUSSION

The aim of this study was to provide a comprehensive description of objectively measured activity in old participants from the Rotterdam Study, by socio-demographic characteristics and other health-related variables. We show that sedentary behavior and light and moderate-to-vigorous PA vary by age-group, sex, BMI, prevalence of disease and disability status, whereas we observed no clear differences between categories for sleep duration. Overall, men and women spent 13.8 (79.5%) hours and 13.3 (78.2%) hours of their waking time in sedentary behavior, respectively, and around 70 minutes of their waking time (7-8%) in moderate-to-vigorous PA.

Table 2.2.2. Objectively assessed physical activity subcomponents and sedentary time in men (n=582), according to characteristics of the study population

	n	Acceler-ation (mg/day)	Sedentary time (h/day)	Light PA (min/day)	Moderate-vigorous PA (min/day)	Sleep time (h/day)
Total	582	19.3 (5.2)	13.8 (1.6)	140.5 (31.1)	71.5 (24.5)	6.6 (1.4)
Age-group						
70-74	201	20.2 (5.3)	13.8 (1.5)	140.2 (30.2)	76.0 (25.1)	6.5 (1.3)
75-79	203	20.0 (4.9)	13.5 (1.7)	144.2 (30.3)	74.8 (23.3)	6.8 (1.6)
80-84	130	18.2 (5.0)	13.9 (1.4)	137.2 (32.0)	65.6 (22.8)	6.6 (1.3)
≥85	48	16.0 (4.6)	14.2 (1.6)	134.6 (34.5)	54.5 (21.6)	6.5 (1.4)
p		<0.001	0.01	0.11	<0.001	0.10
Education						
Primary	22	17.2 (4.3)	13.7 (1.4)	133.3 (32.7)	61.8 (19.5)	6.9 (1.6)
Lower	146	19.3 (5.0)	13.8 (1.5)	140.6 (28.7)	71.0 (24.3)	6.6 (1.4)
Intermediate	224	19.1 (5.2)	13.7 (1.7)	139.9 (32.3)	71.0 (24.7)	6.6 (1.5)
Higher	180	19.8 (5.4)	13.9 (1.6)	141.7 (31.7)	73.2 (25.1)	6.5 (1.3)
p		0.16	0.81	0.68	0.22	0.38
Season						
Spring	140	18.4 (5.0)	13.9 (1.6)	136.3 (28.0)	67.7 (23.7)	6.6 (1.5)
Summer	64	20.7 (5.6)	13.1 (1.9)	143.9 (32.8)	77.1 (26.9)	7.0 (1.8)
Autumn	163	19.7 (5.3)	13.8 (1.6)	142.4 (31.8)	72.8 (24.9)	6.5 (1.5)
Winter	213	19.4 (5.0)	13.9 (1.3)	140.7 (31.9)	71.4 (23.9)	6.5 (1.2)
p		0.02	0.01	0.27	0.07	0.06
BMI						
Normal weight	167	20.6 (5.7)	13.5 (1.6)	146.8 (31.3)	77.3 (26.9)	6.6 (1.3)
Overweight	298	19.4 (4.8)	13.7 (1.5)	140.7 (29.7)	71.8 (22.4)	6.7 (1.4)
Obese	117	17.5 (4.9)	14.3 (1.8)	130.6 (32.0)	62.4 (23.8)	6.4 (1.7)
p		<0.001	<0.001	<0.001	<0.001	0.16
Smoking						
Non smoker	127	19.4 (5.2)	13.8 (1.5)	139.6 (27.4)	72.0 (24.2)	6.6 (1.4)
Former smoker	425	19.4 (5.2)	13.7 (1.6)	141.4 (31.7)	71.8 (24.5)	6.6 (1.4)
Current smoker	28	17.4 (5.5)	13.8 (1.6)	129.5 (36.9)	62.0 (25.4)	6.8 (1.4)
p		0.13	0.82	0.14	0.12	0.75
Alcohol consumption						
Never	66	19.7 (6.2)	13.7 (1.8)	145.2 (31.2)	72.4 (30.1)	6.6 (1.5)
1-4 times/month	128	18.7 (4.9)	13.9 (1.7)	134.6 (30.8)	68.9 (23.1)	6.6 (1.5)
2-4 time/week	387	19.5 (5.1)	13.7 (1.5)	141.7 (31.0)	72.1 (24.0)	6.6 (1.4)
p		0.27	0.64	0.04	0.41	0.94
Disability status						
Not disabled	302	20.6 (5.0)	13.6 (1.5)	145.3 (29.7)	77.5 (23.7)	6.6 (1.3)
Disabled	87	18.0 (5.2)	13.8 (1.6)	137.2 (32.5)	65.4 (23.5)	6.8 (1.4)

Table 2.2.2 (continued). Objectively assessed physical activity subcomponents and sedentary time in men (n=582), according to characteristics of the study population

	n	Acceleration (mg/day)	Sedentary time (h/day)	Light PA (min/day)	Moderate-vigorous PA (min/day)	Sleep time (h/day)
Severely disabled	192	18.0 (5.1)	14.0 (1.7)	134.5 (31.6)	64.6 (23.9)	6.6 (1.6)
p		<0.001	0.07	<0.001	<0.001	0.49
Prevalent CVD, DM or cancer						
Not present	232	20.5 (5.1)	13.7 (1.6)	145.3 (29.0)	76.8 (22.9)	6.6 (1.4)
Present	350	18.5 (5.1)	13.8 (1.6)	137.2 (32.0)	67.9 (25.0)	6.6 (1.4)
p		<0.001	0.16	0.002	<0.001	0.53
Marital status						
Living alone	100	18.5 (5.5)	13.8 (1.7)	138.6 (32.1)	66.7 (26.0)	6.6 (1.5)
Living with partner	481	19.5 (5.1)	13.8 (1.6)	140.9 (30.9)	72.4 (24.1)	6.6 (1.4)
p		0.08	0.70	0.51	0.03	0.28
Sleep medication						
Not using any	504	19.3 (5.2)	13.9 (1.4)	140.3 (31.2)	71.4 (24.5)	6.4 (1.1)
Using ≥1 day/week	53	19.7 (4.8)	13.9 (1.6)	144.9 (28.2)	74.0 (22.4)	6.4 (1.3)
p		0.62	0.70	0.30	0.45	0.75

Abbreviations: BMI, body mass index; ENMO, The Euclidean norm minus 1 g with negative numbers rounded to zero; n, number; PA, physical activity. Body mass index was calculated as weight in kilograms divided by height in meters squared. Categories were defined as normal weight: 18.5 < 25 kg/m^2, overweight: 25 < 30 kg/m^2 and obese: ≥ 30 kg/m^2. Results are obtained from t-tests for determinants with two categories and analysis of variance (ANOVA) for determinants with 3 or more categories. Data are mean (SD). Total N varies due to variation in the amount of missing data for different covariates.

When examining differences by age-groups, we found the lowest PA volume in the oldest age-group (aged ≥ 85 years), which is in accordance with literature indicating that PA declines with increasing age.[9,10,12,16,19] In men and women, the time spent in light, moderate and vigorous intensity PA declined with age, whereas the absolute time spent sedentary increased with age. Considering that sleep time was constant across age groups, the increase in sedentary behavior was at the extent of both light and moderate-to-vigorous PA. Since literature indicates that total sleep time decreases with age,[38] it is possible that the algorithm used to detect sleep overestimated sleep time, if participants lay motionless, but awake, in bed at night.[36] If this is the case, older adults were actually sleeping inefficiently during their time in bed. A better understanding of the distribution of activity across the 24-hour time span might benefit public health interventions. Since daily PA might enhance sleep quality,[39,40] replacing sedentary behavior with light or moderate activity might improve PA levels and sleep quality simultaneously. Future studies are required to identify activities in which elderly adults can engage in to improve PA levels.

Table 2.2.3. The association between activity measures and demographic and health factors in women; results from linear regression analyses

Variable	n	Acceleration (mg/day) β ± SE	p	Sedentary time (h/day) β ± SE	p	Light PA (min/day) β ± SE	p	Moderate-vigorous PA (min/day) β ± SE	p	Sleep time (accelerometer) (h/day) β ± SE	p
Age-group											
70-74	187	Referent		Referent		Referent		Referent		Referent	
75-79	201	-1.51 ± 0.52	0.003	0.06 ± 0.13	0.61	-1.78 ± 3.07	0.56	-7.28 ± 2.35	0.002	0.04 ± 0.12	0.71
80-84	124	-2.61 ± 0.61	<0.001	0.13 ± 0.15	0.39	-3.94 ± 3.63	0.28	-13.14 ± 2.78	<0.001	0.08 ± 0.14	0.57
≥85	65	-3.81 ± 0.80	<0.001	0.51 ± 0.20	0.01	-10.13 ± 4.76	0.03	-19.88 ± 3.65	<0.001	-0.04 ± 0.18	0.81
Education											
Primary	39	Referent		Referent		Referent		Referent		Referent	
Lower	313	-0.49 ± 0.87	0.58	-0.14 ± 0.22	0.52	1.31 ± 5.18	0.80	-2.36 ± 3.97	0.55	0.11 ± 0.19	0.58
Intermediate	154	-0.25 ± 0.91	0.79	-0.06 ± 0.23	0.80	-0.18 ± 5.41	0.97	-2.52 ± 4.15	0.54	0.07 ± 0.20	0.74
Higher	71	0.25 ± 1.03	0.81	-0.10 ± 0.26	0.69	8.75 ± 6.15	0.16	2.22 ± 4.71	0.64	-0.08 ± 0.23	0.71
Season											
Spring	142	Referent		Referent		Referent		Referent		Referent	
Summer	63	1.48 ± 0.75	0.05	0.30 ± 0.19	0.11	2.89 ± 4.47	0.52	4.66 ± 3.43	0.17	-0.40 ± 0.17	0.02
Autumn	203	0.58 ± 0.54	0.28	-0.02 ± 0.13	0.85	3.17 ± 3.20	0.32	1.84 ± 2.46	0.45	-0.04 ± 0.12	0.75
Winter	169	0.38 ± 0.56	0.50	0.05 ± 0.14	0.74	3.13 ± 3.35	0.35	1.53 ± 2.57	0.55	-0.10 ± 0.13	0.44
BMI											
Normal weight	164	Referent		Referent		Referent		Referent		Referent	
Overweight	246	-2.06 ± 0.50	<0.001	0.45 ± 0.12	<0.001	-9.29 ± 2.97	0.002	-8.70 ± 2.28	<0.001	-0.10 ± 0.11	0.38
Obese	167	-3.87 ± 0.57	<0.001	0.90 ± 0.14	<0.001	-19.05 ± 3.36	<0.001	-16.79 ± 2.58	<0.001	-0.24 ± 0.13	0.06
Smoking											
Non smoker	261	Referent		Referent		Referent		Referent		Referent	
Former smoker	283	-0.35 ± 0.43	0.42	0.19 ± 0.11	0.08	-2.76 ± 2.57	0.28	-1.35 ± 1.97	0.49	-0.12 ± 0.10	0.22
Current smoker	33	-1.97 ± 0.94	0.04	0.41 ± 0.23	0.08	-9.04 ± 5.58	0.11	-8.51 ± 4.28	0.05	-0.08 ± 0.21	0.70

Table 2.2.3 (continued). The association between activity measures and demographic and health factors in women; results from linear regression analyses

Variable	n	Acceleration (mg/day) β ± SE	p	Sedentary time (h/day) β ± SE	p	Light PA (min/day) β ± SE	p	Moderate-vigorous PA (min/day) β ± SE	p	Sleep time (accelerometer) (h/day) β ± SE	p
Alcohol consumption											
Never	117	Referent		Referent		Referent		Referent		Referent	
1-4 times/month	204	0.50 ± 0.58	0.39	-0.05 ± 0.14	0.71	0.15 ± 3.42	0.96	2.43 ± 2.62	0.35	0.04 ± 0.13	0.74
2-4 time/week	256	0.78 ± 0.56	0.16	0.11 ± 0.14	0.43	3.22 ± 3.33	0.33	3.26 ± 2.55	0.20	-0.17 ± 0.13	0.17
Disability status											
Not disabled	223	Referent		Referent		Referent		Referent		Referent	
Disabled	123	0.04 ± 0.56	0.94	-0.06 ± 0.14	0.69	1.54 ± 3.36	0.65	-0.33 ± 2.57	0.90	0.00 ± 0.13	1.00
Severely disabled	231	-0.93 ± 0.50	0.06	0.06 ± 0.12	0.64	-3.43 ± 2.97	0.25	-5.42 ± 2.28	0.02	0.04 ± 0.11	0.75
Prevalent CVD, DM or cancer											
Not present	308	Referent		Referent		Referent		Referent		Referent	
Present	269	-1.65 ± 0.41	<0.001	0.35 ± 0.10	<0.001	-6.77 ± 2.47	0.01	-6.82 ± 1.89	<0.001	-0.13 ± 0.09	0.18
Marital status											
Living alone	288	Referent		Referent		Referent		Referent		Referent	
Living with partner	289	1.47 ± 0.44	<0.001	-0.18 ± 0.11	0.10	9.66 ± 2.61	<0.001	6.62 ± 2.00	<0.001	-0.10 ± 0.10	0.32
Sleep medication											
Not using any	444	Referent		Referent		Referent		Referent		Referent	
Using ≥1 day/week	133	-0.50 ± 0.49	0.30	0.15 ± 0.12	0.21	-5.15 ± 2.90	0.08	-3.43 ± 2.23	0.12	-0.10 ± 0.11	0.37

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; n, number; PA, physical activity; SE, standard error. Body mass index was calculated as weight in kilograms divided by height in meters squared. Categories were defined as normal weight: 18.5 < 25 kg/m², overweight: 25 < 30 kg/m² and obese: ≥ 30 kg/m².

The explained variance in the models, according the adjusted R-squared, was 21.0%, 11.4%, 13.2%, 22.2% and 0.8% for acceleration, sedentary behavior, light physical activity, moderate-to-vigorous physical activity and sleep, respectively.

Total N is reduced due to variation in the amount of missing data for different covariates.

The multivariate linear regression analysis was adjusted for all variables included in the table.

Table 2.2.4. The association between activity measures and demographic and health factors in men; results from linear regression analyses

Variable	n	Acceleration (mg/day) β ± SE	p	Sedentary time (h/day) β ± SE	p	Light PA (min/day) β ± SE	p	Moderate-vigorous PA (min/day) β ± SE	p	Sleep time (accelerometer) (h/day) β ± SE	p
Age-group											
70-74	191	Referent		Referent		Referent		Referent		Referent	
75-79	181	-0.16 ± 0.51	0.76	-0.13 ± 0.14	0.37	4.70 ± 3.22	0.14	-0.85 ± 2.39	0.72	0.09 ± 0.12	0.49
80-84	127	-1.49 ± 0.58	0.01	0.10 ± 0.16	0.55	-1.1 ± 3.69	0.77	-7.99 ± 2.74	0.004	0.02 ± 0.14	0.90
≥85	44	-3.77 ± 0.88	<0.001	0.64 ± 0.25	0.01	-5.23 ± 5.57	0.35	-19.77 ± 4.14	<0.001	-0.18 ± 0.21	0.40
Education											
Primary	21	Referent		Referent		Referent		Referent		Referent	
Lower	138	1.46 ± 1.13	0.20	0.04 ± 0.32	0.91	4.70 ± 7.12	0.51	6.59 ± 5.29	0.21	-0.18 ± 0.27	0.51
Intermediate	212	0.96 ± 1.10	0.38	0.22 ± 0.31	0.48	1.87 ± 6.95	0.79	4.73 ± 5.16	0.36	-0.28 ± 0.27	0.30
Higher	172	0.90 ± 1.12	0.42	0.41 ± 0.31	0.19	1.21 ± 7.09	0.86	3.80 ± 5.26	0.47	-0.42 ± 0.27	0.12
Season											
Spring	129	Referent		Referent		Referent		Referent		Referent	
Summer	63	1.30 ± 0.79	0.10	-0.13 ± 0.22	0.55	3.74 ± 5.00	0.45	4.07 ± 3.72	0.27	-0.06 ± 0.19	0.77
Autumn	203	1.23 ± 0.57	0.03	-0.05 ± 0.16	0.73	7.20 ± 3.58	0.04	4.47 ± 2.66	0.09	-0.17 ± 0.14	0.22
Winter	169	0.58 ± 0.55	0.29	-0.04 ± 0.15	0.82	3.11 ± 3.48	0.37	1.49 ± 2.58	0.56	-0.06 ± 0.13	0.68
BMI											
Normal weight	156	Referent		Referent		Referent		Referent		Referent	
Overweight	279	-1.26 ± 0.49	0.01	0.26 ± 0.14	0.06	-5.10 ± 3.11	0.10	-5.52 ± 2.31	0.02	-0.11 ± 0.12	0.38
Obese	108	-2.76 ± 0.63	<0.001	0.96 ± 0.18	<0.001	-13.51 ± 4.01	<0.001	-13.12 ± 2.98	<0.001	-0.54 ± 0.15	0.001
Smoking											
Non smoker	119	Referent		Referent		Referent		Referent		Referent	
Former smoker	397	0.67 ± 0.51	0.19	-0.10 ± 0.14	0.51	4.05 ± 3.24	0.21	3.00 ± 2.41	0.21	-0.03 ± 0.12	0.79
Current smoker	27	-2.71 ± 1.05	0.01	0.13 ± 0.30	0.67	-13.34 ± 6.67	0.05	-13.13 ± 4.95	0.01	0.20 ± 0.26	0.44

Table 2.2.4 (continued). The association between activity measures and demographic and health factors in men; results from linear regression analyses

		Acceleration (mg/day)		Sedentary time (h/day)		Light PA (min/day)		Moderate-vigorous PA (min/day)		Sleep time (accelerometer) (h/day)	
Variable	n	β ± SE	p	β ± SE	p	β ± SE	p	β ± SE	p	β ± SE	p
Alcohol consumption											
Never	60	Referent		Referent		Referent		Referent		Referent	
1-4 times/month	121	-1.04 ± 0.77	0.18	0.08 ± 0.22	0.70	-11.33 ± 4.87	0.02	-4.19 ± 3.62	0.25	0.23 ± 0.19	0.23
2-4 time/week	362	-0.47 ± 0.68	0.49	-0.07 ± 0.19	0.71	-4.66 ± 4.29	0.28	-1.84 ± 3.18	0.56	0.25 ± 0.16	0.13
Disability status											
Not disabled	286	Referent		Referent		Referent		Referent		Referent	
Disabled	83	-1.95 ± 0.61	<0.001	0.13 ± 0.17	0.44	-5.82 ± 3.87	0.13	-9.61 ± 2.88	<0.001	0.14 ± 0.15	0.34
Severely disabled	174	-2.11 ± 0.47	<0.001	0.37 ± 0.13	0.01	-9.54 ± 3.00	<0.001	-10.81 ± 2.23	<0.001	-0.04 ± 0.12	0.76
Prevalent CVD, DM or cancer											
Not present	215	Referent		Referent		Referent		Referent		Referent	
Present	328	-1.28 ± 0.44	0.004	-0.03 ± 0.12	0.81	-6.69 ± 2.77	0.02	-4.91 ± 2.06	0.02	0.20 ± 0.11	0.06
Marital status											
Living alone	91	Referent		Referent		Referent		Referent		Referent	
Living with partner	452	0.08 ± 0.58	0.89	0.06 ± 0.16	0.72	0.02 ± 3.68	1.00	1.25 ± 2.73	0.65	-0.05 ± 0.14	0.70
Sleep medication											
Not using any	490	Referent		Referent		Referent		Referent		Referent	
Using ≥1 day/week	53	0.34 ± 0.70	0.62	-0.04 ± 0.20	0.86	4.55 ± 4.41	0.30	2.57 ± 3.27	0.43	-0.09 ± 0.17	0.61

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; n, number; PA, physical activity; SE, standard error. Body mass index was calculated as weight in kilograms divided by height in meters squared. Categories were defined as normal weight: 18.5 < 25 kg/m^2, overweight: 25 < 30 kg/m^2 and obese: ≥ 30 kg/m^2.

The explained variance in the models, according the adjusted R-squared, was 21.0%, 11.4%, 13.2%, 22.2% and 0.8% for acceleration, sedentary behavior, light physical activity, moderate-to-vigorous physical activity and sleep, respectively.

Total N is reduced due to variation in the amount of missing data for different covariates.

The multivariate linear regression analysis was adjusted for all variables included in the table.

In our study, men and women spent around 70 minutes per day in moderate-to vigorous PA. In similar study populations in Iceland,[9] Norway[16] and the United Kingdom[12] these numbers were up to 15, 36 and 23 minutes per day, respectively. Comparisons are hampered by the different study population characteristics (e.g. age), use of different devices and anatomical placements, the use of counts per minute and the stratification into sedentary time and light, moderate and vigorous activity by different cut-offs. Consequently, we cannot be sure whether participants in our study were really more active, or that the different estimates are the result of the different cut-points. Because the Ommoord district in which most participants live is a safe neighborhood with opportunity to walk and cycle in a safe manner, it could be expected that the participants from our study were indeed more active in comparison to other studies.

In our study, we found higher levels of acceleration in women compared to men, in all age-groups. This is in contrast with most studies in older adults,[9,12,14,41] but in agreement with two others.[11,19] In addition, in the total population, we found that women spent more time in moderate PA than men. An explanation for the higher activity in women compared to men might be traditional gender roles, in which women are more involved in household activities than men. Chen et al. indicated that the discrepancies between the studies might be related to cultural lifestyle differences.[11] Nevertheless, they performed their study among Japanese elderly and our participants come from a Western population, in which men often are reported to be more active than women.[9,12,14,41] The results from the current study might be explained by the fact that men more often had chronic disease than women (60.1% vs. 46.5%). However, women were more often disabled and obese than men, both variables associated with lower PA levels.

Another explanation for the difference might be related to the fact that men reported significantly more cycling than women (47.3% in men versus 33.6% in women) in the current study. A wrist-worn accelerometer is known to underestimate activities performed with the lower extremities.[42] Future studies are needed to examine whether the observed results reflect a true difference between sexes. Moreover, more research is needed to be able to identify lower body activities with wrist-worn accelerometers.

Important correlates of sedentary behavior and PA were BMI, age, disability status and the prevalence of chronic disease in both sexes. Obese individuals had a lower acceleration and lower levels of light and moderate-to-vigorous PA, compared to their normal weight counterparts. These results are in agreement with existing data.[9-12,14] Moreover, in women, living with a partner was associated with more time spent in light and moderate-to-vigorous PA. In sensitivity analyses split by age and BMI, we showed that living with a partner was also associated with activity in participants younger than 80 years and in those with BMI ≥27 kg/m^2. These results suggest opportunities for focused intervention, targeting specifically those with higher BMI and age, as well as those suffering from a chronic condition or disability. The fact that women living with a partner were more active than those living alone, might indicate that women are more likely to engage in PA socially. Public health programs might provide opportunities for specific sub-groups with the lowest levels of PA, including organized PA programs. Furthermore, in sensitivity analyses in the oldest old, we observed no gender differences for PA levels. However, in these participants, being obese was associated with larger decreases in light and moderate-to-vigorous PA than in participants younger than 80 years. Possibly, the additional weight is more of a burden in the oldest old. This stresses the importance of a healthy weight, even in old age.

This study has several strengths. It is one of the first studies providing a detailed description of the full intensity distribution of PA in this age-range of participants over the 24-hour period. Additionally, since the accelerometer device was waterproof and was worn day and night, we could collect comprehensive information of all activity performed. However, some limitations also have to be acknowledged. Using raw accelerometer derived data to describe activity is relatively new and therefore the cut-off points to define intensity of behavior have not been firmly established. Moreover, as in other studies using objectively measured PA, not all PA can be accurately captured. For example, cycling or other activities mostly performed with the legs will be underestimated.[42] Additionally, since no method exists for differentiating between the postural allocations of sitting, standing and lying down from triaxial wrist acceleration signals in this population, we were unable to distinguish socializing from driving. Furthermore, we used an algorithm to define sleep, in which we defined sleep as an absence of change in arm angle greater than 5 degrees for 5 minutes or more.[36] Using another sleep definition may influence estimated sleep time and hence the sedentary time observed in our participants. Although van Hees et al[36] made extensive effort to validate their algorithm in the Whitehall II Study using polysomnography, future studies are needed to optimize the used algorithm.

Another limitation is that we did not have up-to-date information on cancer, cardiovascular disease and diabetes. Therefore, some residual confounding might be present and might have resulted in bias towards the null for those comparisons. Additionally, participants that agreed to participate were less often disabled and more often men. This might affect the generalizability towards the total population of older adults. Finally, participants attending these visits of the Rotterdam Study might have a better health-status than the general population, an issue often occurring in cohort studies.

Conclusions

In conclusion, in this population based cohort study of elderly individuals, men spent significantly more time in sedentary behavior and less time in light and moderate-to-vigorous PA compared to women. However, whereas this difference was significant, it was of small numeric value, indicating that both men and women spent a high proportion of their day sedentary. Furthermore, our findings suggest that sedentary behavior and light and moderate-to-vigorous PA patterns differ according to age, BMI, disability status and presence of disease, whereas sleep duration did not differ according demographic factors and health behaviors. Replacing sedentary behavior with light PA would be a good starting point for those with the lowest level of PA. Older adults, those with high BMI and worse health could benefit from targeted interventions to increase PA.

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SUPPLEMENT CHAPTER 2.2

Supplement 2.2.1. Characteristics of participants who agreed to participate and those who did not agree to participate

	Did not agree to participate	Agreed to participate	p
Participants	506	1,394	
Women, n (%)	334 (66.3)	733 (52.6)	<0.001
Age, mean (SD)	77.6 (27.2)	77.7 (5.0)	0.91
Education, n (%)			<0.001
Primary	44 (9.0)	71 (5.2)	
Lower	241 (49.1)	560 (40.9)	
Intermediate	145 (29.5)	447 (32.7)	
Higher	61 (12.4)	291 (21.3)	
BMI, n (%)			0.53
Normal weight	156 (31.3)	409 (29.4)	
Overweight	217 (43.5)	646 (46.4)	
Obese	126 (25.3)	338 (24.3)	
Smoking, n (%)			0.008
Non smoker	195 (38.7)	473 (34.0)	
Former smoker	268 (53.2)	842 (60.5)	
Current smoker	41 (8.1)	77 (5.5)	
Alcohol use, n (%)			0.002
Never	104 (20.6)	213 (15.3)	
1-4 times/month	160 (31.7)	400 (28.7)	
2-4 time/week	240 (47.6)	779 (56.0)	
Health status, n (%)			<0.001
Not disabled	177 (35.1)	632 (45.4)	
Disabled	116 (23.0)	258 (18.5)	
Severely disabled	211 (41.9)	502 (36.1)	
Prevalent CVD, DM or cancer, n (%)	266 (52.6)	734 (52.7)	1.00
Living with partner, n (%)	269 (53.4)	904 (64.9)	<0.001

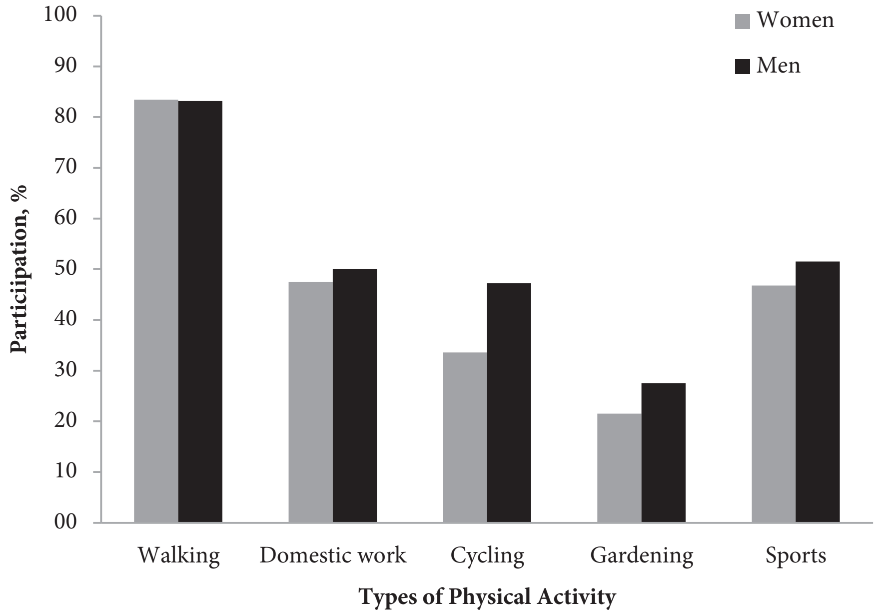
Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; n, number; SD, standard deviation. Body mass index was calculated as weight in kilograms divided by height in meters squared. Categories were defined as normal weight: 18.5 < 25 kg/m^2, overweight: 25 < 30 kg/m^2 and obese: ≥ 30 kg/m^2.
Total N varies due to variation in the amount of missing data for different covariates.

Supplement 2.2.2. Characteristics of men and women included in the study

	Men	Women	p
n	582	628	
Age, mean (SD)	77.4 (4.8)	77.7 (5.1)	0.28
Education, n (%)			<0.001
Primary	22 (3.8)	41 (6.7)	
Lower	46 (25.5)	337 (54.7)	
Intermediate	224 (39.2)	163 (26.5)	
Higher	180 (31.5)	75 (12.2)	
BMI, n (%)			0.001
Normal weight	167 (28.7)	183 (29.2)	
Overweight	298 (51.2)	265 (42.3)	
Obese	117 (20.1)	179 (28.5)	
Smoking, n (%)			<0.001
Non smoker	127 (21.9)	282 (44.9)	
Former smoker	425 (73.3)	310 (49.4)	
Current smoker	28 (4.8)	36 (5.7)	
Alcohol use, n (%)			<0.001
Never	66 (11.4)	123 (19.6)	
1-4 times/month	128 (22.0)	217 (34.6)	
2-4 time/week	387 (66.6)	288 (45.9)	
Health status, n (%)			<0.001
Not disabled	302 (52.0)	243 (38.8)	
Disabled	87 (15.0)	139 (22.2)	
Severely disabled	192 (33.0)	245 (39.1)	
Prevalent CVD, DM or cancer, n (%)	350 (60.1)	292 (46.5)	<0.001
Living with partner, n (%)	481 (82.8)	319 (50.8)	<0.001

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; n, number; SD, standard deviation. Body mass index was calculated as weight in kilograms divided by height in meters squared. Categories were defined as normal weight: 18.5 < 25 kg/m^2, overweight: 25 < 30 kg/m^2 and obese: ≥ 30 kg/m^2.
Total N varies due to variation in the amount of missing data for different covariates.

Supplement 2.2.3. Self-reported proportion of participants by physical activity type



Supplement 2.2.4. Objectively assessed moderate and vigorous intensity physical activity in women

	n	Moderate PA (min/day), mean (SD)	Vigorous PA (min/day), median [interquartile range]	Total sedentary time (h/day)*
Total	628	61.3 (19.2)	8.8 [17.1, 17.1]	20.0 (0.9)
Age group				
70-74	200	68.6 (19.8)	10.9 [20.3, 20.3]	19.8 (0.9)
75-79	226	61.4 (17.8)	9.2 [16.7, 16.7]	20.0 (0.9)
80-84	130	56.2 (16.5)	7.9 [14.4, 14.4]	20.2 (0.9)
≥85	72	49.9 (18.4)	6.2 [11.5, 11.5]	20.5 (1.0)
p		<0.001	<0.001	<0.001
Education				
Primary	41	53.3 (19.8)	7.1 [15.6, 15.6]	20.4 (0.9)
Lower	337	61.0 (18.3)	9.2 [17.1, 17.1]	20.0 (0.9)
Intermediate	163	60.6 (19.1)	8.3 [16.3, 16.3]	20.1 (0.9)
Higher	75	66.9 (20.5)	10.2 [19.0, 19.0]	19.8 (1.0)
p		0.003	0.02	0.006
Season				
Spring	163	61.1 (18.8)	13.0 [9.1, 17.5]	20.0 (1.0)
Summer	74	63.4 (20.4)	13.0 [9.8, 18.2]	20.0 (1.0)
Autumn	206	60.0 (20.5)	11.9 [8.0, 16.1]	20.1 (1.0)
Winter	182	61.7 (17.5)	12.9 [9.0, 16.7]	20.0 (0.9)
p		0.60	0.19	0.73
BMI				
Normal weight	183	68.3 (19.1)	10.9 [19.7, 19.7]	19.7 (0.9)
Overweight	265	61.6 (19.1)	8.7 [17.2, 17.2]	20.0 (1.0)
Obese	179	54.0 (16.6)	8.1 [14.4, 14.4]	20.4 (0.8)
p		<0.001	<0.001	<0.001
Smoking				
Non smoker	282	62.7 (19.1)	8.8 [17.4, 17.4]	20.0 (0.9)
Former smoker	310	60.5 (19.2)	8.8 [16.6, 16.6]	20.1 (0.9)
Current smoker	36	57.5 (20.0)	8.4 [16.6, 16.6]	20.3 (1.0)
p		0.19	0.48	0.05
Alcohol consumption				
Never	123	59.3 (17.7)	8.4 [15.9, 15.9]	20.1 (1.0)
1-4 times/month	217	58.7 (18.8)	8.3 [16.0, 16.0]	20.2 (0.9)
2-4 time/week	288	64.2 (19.8)	9.3 [18.2, 18.2]	19.9 (0.9)
p		0.003	0.02	0.005
Health status				
Not disabled	243	65.9 (19.0)	10.1 [19.4, 19.4]	19.9 (0.9)
Disabled	139	62.9 (18.2)	9.8 [17.3, 17.3]	20.0 (0.9)
Severely disabled	245	55.8 (18.8)	7.7 [15.5, 15.5]	20.2 (1.0)
p		<0.001	<0.001	<0.001

Supplement 2.2.4 (continued). Objectively assessed moderate and vigorous intensity physical activity in women

	n	Moderate PA (min/day), mean (SD)	Vigorous PA (min/day), median [interquartile range]	Total sedentary time (h/day)*
Prevalent CVD, DM or cancer				
Not present	336	64.6 (19.1)	13.5 [9.8, 18.1]	19.9 (0.9)
Present	292	57.5 (18.7)	11.9 [8.1, 15.8]	20.2 (1.0)
p		<0.001	<0.001	<0.001
Marital status				
Living alone	309	57.2 (19.0)	11.6 [7.8, 15.3]	20.2 (1.0)
Living with partner	319	65.3 (18.6)	13.7 [9.9, 18.6]	19.9 (0.9)
p		<0.001	<0.001	<0.001

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; n, number; SD, standard deviation. Body mass index was calculated as weight in kilograms divided by height in meters squared. Categories were defined as normal weight: 18.5 < 25 kg/m^2, overweight: 25 < 30 kg/m^2 and obese: ≥ 30 kg/m^2.
Data are mean (SD) or median (interquartile range).
Total N varies due to variation in the amount of missing data for different covariates.
* Total sedentary time is the sum of sedentary time while awake and sleep time.

Supplement 2.2.5. Objectively assessed moderate and vigorous intensity physical activity in men

	n	Moderate PA (min/day), mean (SD)	Vigorous PA (min/day), median [interquartile range]	Total sedentary time (h/day)*
Total	582	58.3 (18.6)	8.7 [16.8, 16.8]	20.4 (0.9)
Age group				
70-74	201	61.1 (18.9)	10.4 [18.8, 18.8]	20.3 (0.9)
75-79	203	60.9 (17.8)	9.8 [17.0, 17.0]	20.3 (0.9)
80-84	130	54.3 (17.6)	7.5 [13.9, 13.9]	20.5 (0.9)
≥85	48	46.2 (17.4)	5.9 [10.1, 10.1]	20.8 (0.9)
p		<0.001	<0.001	0.001
Education				
Primary	22	51.3 (15.2)	7.5 [12.6, 12.6]	20.6 (0.9)
Lower	146	57.9 (18.2)	8.3 [17.8, 17.8]	20.4 (0.8)
Intermediate	224	58.0 (18.9)	8.5 [16.2, 16.2]	20.4 (0.9)
Higher	180	59.4 (19.1)	9.1 [17.6, 17.6]	20.3 (0.9)
p		0.28	0.13	0.59
Season				
Spring	140	55.4 (17.9)	11.5 [7.6, 15.8]	20.5 (0.8)
Summer	64	62.2 (20.4)	13.8 [10.4, 19.3]	20.2 (1.0)
Autumn	163	59.5 (18.9)	12.4 [8.7, 16.6]	20.3 (0.9)
Winter	213	58.2 (18.2)	11.8 [8.9, 16.9]	20.4 (0.9)
p		0.07	0.06	0.07
BMI				
Normal weight	167	62.7 (20.0)	8.8 [19.5, 19.5]	20.2 (0.9)
Overweight	298	58.5 (17.1)	9.4 [16.5, 16.5]	20.3 (0.9)
Obese	117	51.4 (18.6)	6.8 [14.0, 14.0]	20.7 (0.9)
p		<0.001	<0.001	<0.001
Smoking				
Non smoker	127	58.6 (18.1)	9.4 [16.8, 16.8]	20.4 (0.9)
Former smoker	425	58.6 (18.7)	8.8 [17.0, 17.0]	20.3 (0.9)
Current smoker	28	51.3 (20.0)	6.2 [13.6, 13.6]	20.6 (1.1)
p		0.13	0.11	0.31
Alcohol consumption				
Never	66	59.3 (22.8)	7.4 [15.7, 15.7]	20.2 (1.0)
1-4 times/month	128	56.0 (17.4)	8.9 [16.1, 16.1]	20.5 (0.9)
2-4 time/week	387	58.8 (18.2)	9.0 [17.0, 17.0]	20.3 (0.9)
p		0.30	0.48	0.09
Health status				
Not disabled	302	62.8 (18.0)	10.5 [18.7, 18.7]	20.2 (0.9)
Disabled	87	53.9 (17.5)	7.0 [14.2, 14.2]	20.5 (0.9)
Severely disabled	192	53.1 (18.3)	7.4 [14.5, 14.5]	20.6 (0.9)
p		<0.001	<0.001	<0.001

Supplement 2.2.5 (continued). Objectively assessed moderate and vigorous intensity physical activity in men

	n	Moderate PA (min/day), mean (SD)	Vigorous PA (min/day), median [interquartile range]	Total sedentary time (h/day)*
Prevalent CVD, DM or cancer				
Not present	232	62.1 (17.1)	13.5 [10.3, 18.5]	20.2 (0.8)
Present	350	55.8 (19.2)	11.0 [7.7, 15.4]	20.5 (0.9)
p		<0.001	<0.001	0.001
Marital status				
Living alone	100	55.0 (19.7)	10.5 [7.3, 13.6]	20.4 (0.9)
Living with partner	481	58.9 (18.4)	12.7 [9.1, 17.1]	20.3 (0.9)
p		0.05	0.001	0.36

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; n, number; SD, standard deviation. Body mass index was calculated as weight in kilograms divided by height in meters squared. Categories were defined as normal weight: 18.5 < 25 kg/m^2, overweight: 25 < 30 kg/m^2 and obese: ≥ 30 kg/m^2.
Data are mean (SD) or median (interquartile range).
Total N varies due to variation in the amount of missing data for different covariates.
* Total sedentary time is the sum of sedentary time while awake and sleep time.

Supplement 2.2.6. Objectively assessed physical activity subcomponents and sedentary time in women, expressed in percentages of awake time

	n	Sedentary	Light PA	Moderate PA	Vigorous PA	Moderate-to-vigorous PA
Total	628	77.6 (5.6)	14.9 (3.3)	6.2 (2.0)	1.3 [0.9, 1.7]	7.5 (2.6)
Age group						
70-74	200	76.7 (5.4)	15.0 (3.0)	6.7 (1.9)	1.5 [1.1, 2.0]	8.3 (2.6)
75-79	226	77.6 (5.3)	14.9 (3.2)	6.2 (1.8)	1.3 [0.9, 1.7]	7.6 (2.4)
80-84	130	78.0 (5.4)	15.0 (3.4)	5.8 (1.8)	1.1 [0.8, 1.5]	7.0 (2.3)
≥85	72	79.5 (6.7)	14.2 (4.0)	5.3 (2.2)	0.9 [0.7, 1.2]	6.3 (2.8)
p		0.003	0.37	<0.001	<0.001	<0.001
Education						
Primary	41	79.8 (6.1)	13.7 (3.5)	5.4 (2.2)	0.9 [0.7, 1.4]	6.6 (2.8)
Lower	337	77.6 (5.3)	14.9 (3.2)	6.2 (1.8)	1.3 [0.9, 1.7]	7.5 (2.4)
Intermediate	163	77.7 (5.7)	14.8 (3.3)	6.1 (2.0)	1.2 [0.9, 1.7]	7.5 (2.7)
Higher	75	76.4 (6.0)	15.5 (3.5)	6.6 (2.1)	1.4 [1.0, 1.9]	8.1 (2.7)
p		0.02	0.04	0.02	0.01	0.02
Season						
Spring	163	77.6 (5.7)	14.8 (3.3)	6.2 (2.0)	1.3 [0.9, 1.8]	7.6 (2.6)
Summer	74	77.5 (5.5)	14.8 (3.3)	6.3 (2.0)	1.3 [1.0, 1.7]	7.7 (2.6)
Autumn	206	77.5 (6.1)	15.0 (3.6)	6.2 (2.1)	1.2 [0.8, 1.6]	7.5 (2.8)
Winter	182	77.9 (4.9)	14.7 (2.9)	6.1 (1.7)	1.3 [0.9, 1.7]	7.4 (2.3)
p		0.89	0.80	0.87	0.45	0.82
BMI						
Normal weight	183	75.3 (5.2)	16.2 (3.0)	7.0 (1.9)	1.5 [1.1, 2.0]	8.6 (2.6)
Overweight	265	77.5 (5.6)	14.9 (3.3)	6.2 (2.0)	1.3 [0.9, 1.7]	7.6 (2.6)
Obese	179	80.1 (4.8)	13.5 (3.0)	5.3 (1.6)	1.1 [0.8, 1.4]	6.5 (2.1)
p		<0.001	<0.001	<0.001	<0.001	<0.001
Smoking						
Non smoker	282	76.9 (5.4)	15.3 (3.2)	6.4 (1.9)	1.3 [0.9, 1.8]	7.8 (2.5)
Former smoker	310	78.1 (5.5)	14.5 (3.2)	6.1 (1.9)	1.2 [0.9, 1.7]	7.4 (2.6)
Current smoker	36	79.0 (6.7)	14.0 (3.8)	5.8 (2.3)	1.2 [0.8, 1.7]	7.1 (3.0)
p		0.01	0.004	0.08	0.25	0.12
Alcohol consumption						
Never	123	78.1 (5.3)	14.7 (3.2)	6.0 (1.8)	1.2 [0.9, 1.6]	7.3 (2.3)
1-4 times/month	217	78.4 (5.6)	14.4 (3.3)	5.9 (1.9)	1.2 [0.8, 1.6]	7.2 (2.5)
2-4 time/week	288	76.8 (5.6)	15.3 (3.3)	6.4 (2.0)	1.3 [0.9, 1.8]	7.9 (2.7)
p		0.005	0.009	0.007	0.02	0.006
Health status						
Not disabled	243	76.8 (5.1)	15.2 (3.0)	6.6 (1.8)	1.4 [1.0, 1.9]	8.1 (2.5)
Disabled	139	77.0 (5.2)	15.3 (3.1)	6.4 (1.8)	1.3 [1.0, 1.7]	7.8 (2.5)
Severely disabled	245	78.8 (6.0)	14.3 (3.6)	5.7 (2.0)	1.1 [0.8, 1.6]	6.9 (2.6)

Supplement 2.2.6 (continued). Objectively assessed physical activity subcomponents and sedentary time in women, expressed in percentages of awake time

	n	Sedentary	Light PA	Moderate PA	Vigorous PA	Moderate-to-vigorous PA
p		<0.001	0.006	<0.001	<0.001	<0.001
Prevalent CVD, DM or cancer						
Not present	336	76.8 (5.5)	15.2 (3.2)	6.5 (1.9)	1.4 [1.0, 1.8]	8.0 (2.6)
Present	292	78.5 (5.6)	14.4 (3.3)	5.8 (1.9)	1.2 [0.8, 1.6]	7.1 (2.5)
p		<0.001	0.002	<0.001	<0.001	<0.001
Marital status						
Living alone	309	78.6 (6.0)	14.3 (3.5)	5.8 (2.0)	1.2 [0.8, 1.6]	7.1 (2.7)
Living with partner	319	76.7 (5.0)	15.4 (2.9)	6.5 (1.8)	1.4 [1.0, 1.8]	8.0 (2.4)
p		<0.001	<0.001	<0.001	<0.001	<0.001

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; n, number; SD, standard deviation. Body mass index was calculated as weight in kilograms divided by height in meters squared. Categories were defined as normal weight: 18.5 < 25 kg/m^2, overweight: 25 < 30 kg/m^2 and obese: ≥ 30 kg/m^2.
Data are mean (SD) or median (interquartile range).
Total N varies due to variation in the amount of missing data for different covariates.

Supplement 2.2.7. Objectively assessed physical activity subcomponents and sedentary time in men, expressed in percentages of awake time

	n	Sedentary	Light PA	Moderate PA	Vigorous PA	Moderate-to-vigorous PA
Total	582	79.1 (5.3)	13.9 (3.2)	5.7 (1.8)	1.2 [0.9, 1.7]	7.0 (2.4)
Age group						
70-74	201	79.2 (5.3)	13.5 (3.1)	5.9 (1.9)	1.3 [1.0, 1.8]	7.3 (2.5)
75-79	203	78.4 (5.0)	14.2 (3.0)	6.0 (1.7)	1.2 [1.0, 1.7]	7.4 (2.3)
80-84	130	79.5 (5.2)	13.9 (3.3)	5.5 (1.7)	1.0 [0.8, 1.4]	6.6 (2.2)
≥85	48	80.5 (5.9)	13.9 (3.9)	4.8 (1.9)	0.8 [0.5, 1.0]	5.6 (2.3)
p		0.05	0.15	<0.001	<0.001	<0.001
Education						
Primary	22	79.9 (6.1)	13.8 (4.3)	5.3 (1.7)	1.0 [0.7, 1.3]	6.3 (2.1)
Lower	146	79.2 (4.7)	13.8 (2.8)	5.7 (1.7)	1.1 [0.9, 1.7]	7.0 (2.3)
Intermediate	224	79.1 (5.5)	13.9 (3.4)	5.8 (1.9)	1.2 [0.9, 1.6]	7.0 (2.4)
Higher	180	79.0 (5.3)	13.9 (3.2)	5.8 (1.9)	1.2 [0.9, 1.7]	7.2 (2.5)
p		0.89	1.00	0.61	0.27	0.49
Season						
Spring	140	79.9 (4.9)	13.5 (2.9)	5.5 (1.7)	1.2 [0.8, 1.5]	6.7 (2.3)
Summer	64	77.5 (5.7)	14.7 (3.5)	6.3 (2.0)	1.4 [1.1, 1.8]	7.8 (2.6)
Autumn	163	78.4 (5.6)	14.3 (3.5)	6.0 (1.9)	1.2 [0.9, 1.7]	7.3 (2.5)
Winter	213	79.5 (4.9)	13.6 (3.0)	5.6 (1.7)	1.2 [0.9, 1.6]	6.9 (2.2)
p		0.005	0.01	0.005	0.01	0.006
BMI						
Normal weight	167	77.8 (5.4)	14.5 (3.2)	6.2 (2.0)	1.3 [0.9, 1.9]	7.6 (2.6)
Overweight	298	78.9 (5.0)	14.0 (3.1)	5.8 (1.7)	1.2 [0.9, 1.6]	7.1 (2.2)
Obese	117	81.3 (5.2)	12.7 (3.1)	5.0 (1.8)	1.0 [0.7, 1.4]	6.0 (2.3)
p		<0.001	<0.001	<0.001	<0.001	<0.001
Smoking						
Non smoker	127	79.2 (4.9)	13.7 (2.8)	5.8 (1.8)	1.2 [0.9, 1.7]	7.1 (2.4)
Former smoker	425	78.9 (5.3)	14.0 (3.3)	5.8 (1.8)	1.2 [0.9, 1.7]	7.1 (2.4)
Current smoker	28	81.2 (5.9)	12.7 (3.5)	5.0 (2.0)	1.0 [0.6, 1.4]	6.1 (2.5)
p		0.07	0.07	0.11	0.09	0.10
Alcohol consumption						
Never	66	78.3 (5.9)	14.5 (3.3)	5.9 (2.3)	1.1 [0.7, 1.7]	7.2 (3.0)
1-4 times/month	128	80.1 (4.9)	13.2 (3.1)	5.5 (1.7)	1.2 [0.9, 1.6]	6.7 (2.2)
2-4 time/week	387	78.9 (5.2)	14.0 (3.2)	5.8 (1.8)	1.2 [0.9, 1.7]	7.1 (2.3)
p		0.05	0.02	0.17	0.42	0.26
Health status						
Not disabled	302	78.2 (4.9)	14.2 (2.9)	6.1 (1.7)	1.3 [1.0, 1.8]	7.6 (2.3)
Disabled	87	79.6 (5.7)	13.8 (3.6)	5.4 (1.9)	1.0 [0.7, 1.4]	6.6 (2.4)
Severely disabled	192	80.1 (5.4)	13.4 (3.4)	5.3 (1.8)	1.1 [0.7, 1.4]	6.4 (2.4)

Supplement 2.2.7 (continued) Objectively assessed physical activity subcomponents and sedentary time in men, expressed in percentages of awake time (n=582)

	n	Sedentary	Light PA	Moderate PA	Vigorous PA	Moderate-to-vigorous PA
p		<0.001	0.03	<0.001	<0.001	<0.001
Prevalent CVD, DM or cancer						
Not present	232	78.2 (4.9)	14.3 (2.9)	6.1 (1.7)	1.3 [1.1, 1.8]	7.5 (2.3)
Present	350	79.7 (5.4)	13.6 (3.3)	5.5 (1.9)	1.1 [0.8, 1.5]	6.7 (2.4)
p		0.001	0.02	<0.001	<0.001	<0.001
Marital status						
Living alone	100	79.5 (5.6)	13.9 (3.4)	5.5 (2.0)	1.0 [0.7, 1.5]	6.7 (2.6)
Living with partner	481	79.0 (5.2)	13.9 (3.1)	5.8 (1.8)	1.2 [0.9, 1.7]	7.1 (2.3)
p		0.42	1.00	0.12	0.002	0.07

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; n, number; SD, standard deviation. Body mass index was calculated as weight in kilograms divided by height in meters squared. Categories were defined as normal weight: 18.5 < 25 kg/m^2, overweight: 25 < 30 kg/m^2 and obese: ≥ 30 kg/m^2.
Data are mean (SD) or median (interquartile range).
Total N varies due to variation in the amount of missing data for different covariates.

Supplement 2.2.8. The association between physical activity measures and demographic and health factors in participants aged less than 80 years (n=760)

Variable	n	Acceleration (mg/day) β ± SE	p	Awake sedentary time (h/day) β ± SE	p	Light PA (min/day) β ± SE	p	Moderate-vigorous PA (min/day) β ± SE	p	Sleep time (accelerometer) (h/day) β ± SE	p
Age group											
70-74	378	Referent		Referent		Referent		Referent		Referent	
75-79	382	-0.78 ± 0.38	0.04	-0.04 ± 0.10	0.67	1.81 ± 2.21	0.42	-3.81 ± 1.75	0.03	0.06 ± 0.08	0.44
Sex											
Men	372	Referent		Referent		Referent		Referent		Referent	
Women	388	1.92 ± 0.44	<0.001	-0.49 ± 0.11	<0.001	11.92 ± 2.56	<0.001	8.42 ± 2.02	<0.001	0.03 ± 0.10	0.79
Education											
Primary	27	Referent		Referent		Referent		Referent		Referent	
Lower	310	0.46 ± 1.03	0.66	-0.27 ± 0.26	0.31	3.71 ± 5.98	0.54	3.09 ± 4.73	0.51	0.14 ± 0.22	0.54
Intermediate	238	0.29 ± 1.04	0.78	-0.21 ± 0.27	0.43	1.79 ± 6.07	0.77	1.89 ± 4.80	0.69	0.12 ± 0.23	0.59
Higher	185	0.55 ± 1.07	0.60	-0.10 ± 0.27	0.72	5.26 ± 6.20	0.40	3.78 ± 4.90	0.44	-0.06 ± 0.23	0.78
Season											
Spring	193	Referent		Referent		Referent		Referent		Referent	
Summer	96	1.46 ± 0.64	0.02	0.10 ± 0.16	0.55	2.68 ± 3.70	0.47	4.36 ± 2.93	0.14	-0.24 ± 0.14	0.09
Autumn	241	0.98 ± 0.49	0.046	0.02 ± 0.13	0.86	4.41 ± 2.85	0.12	2.69 ± 2.26	0.23	-0.12 ± 0.11	0.28
Winter	230	0.61 ± 0.50	0.22	0.12 ± 0.13	0.36	2.95 ± 2.88	0.31	1.83 ± 2.28	0.42	-0.19 ± 0.11	0.08
BMI											
Normal weight	198	Referent		Referent		Referent		Referent		Referent	
Overweight	365	-1.54 ± 0.45	<0.001	0.30 ± 0.12	0.01	-5.05 ± 2.64	0.0557	-6.63 ± 2.08	0.002	-0.05 ± 0.10	0.62
Obese	197	-2.95 ± 0.53	<0.001	0.90 ± 0.14	<0.001	-12.37 ± 3.09	<0.001	-13.25 ± 2.45	<0.001	-0.41 ± 0.12	0.001
Smoking											
Non smoker	257	Referent		Referent		Referent		Referent		Referent	

Supplement 2.2.8 (continued). The association between physical activity measures and demographic and health factors in participants aged less than 80 years (n=760)

Variable	n	Acceleration (mg/day) β ± SE	p	Awake sedentary time (h/day) β ± SE	p	Light PA (min/day) β ± SE	p	Moderate-vigorous PA (min/day) β ± SE	p	Sleep time (accelerometer) (h/day) β ± SE	p
Former smoker	455	0.46 ± 0.42	0.27	0.03 ± 0.11	0.78	0.92 ± 2.42	0.70	2.42 ± 1.91	0.21	-0.08 ± 0.09	0.36
Current smoker	48	-1.81 ± 0.82	0.03	0.30 ± 0.21	0.16	-6.48 ± 4.77	0.17	-7.88 ± 3.77	0.04	-0.11 ± 0.18	0.55
Alcohol consumption											
Never	110	Referent		Referent		Referent		Referent		Referent	
1-4 times/month	206	0.24 ± 0.60	0.69	-0.03 ± 0.16	0.83	-2.10 ± 3.5	0.55	1.25 ± 2.77	0.65	0.12 ± 0.13	0.36
2-4 times/week	444	0.61 ± 0.56	0.27	0.03 ± 0.14	0.83	1.38 ± 3.23	0.67	1.92 ± 2.56	0.45	-0.02 ± 0.12	0.89
Health status											
Not disabled	385	Referent		Referent		Referent		Referent		Referent	
Disabled	136	-0.83 ± 0.52	0.11	0.00 ± 0.13	0.99	-3.31 ± 3.01	0.27	-4.52 ± 2.38	0.06	0.13 ± 0.11	0.26
Severely disabled	239	-1.80 ± 0.43	<0.001	0.24 ± 0.11	0.03	-9.43 ± 2.51	<0.001	-10.23 ± 1.98	<0.001	0.05 ± 0.09	0.60
Prevalent CVD, DM or cancer											
Not present	389	Referent		Referent		Referent		Referent		Referent	
Present	371	-1.28 ± 0.38	<0.001	0.18 ± 0.1	0.07	-4.69 ± 2.19	0.03	-4.4 ± 1.73	0.01	-0.05 ± 0.08	0.56
Marital status											
Living alone	199	Referent		Referent		Referent		Referent		Referent	
Living with partner	561	1.64 ± 0.45	<0.001	-0.18 ± 0.12	0.120	9.17 ± 2.62	<0.001	7.23 ± 2.07	<0.001	-0.07 ± 0.10	0.47

Supplement 2.2.8 (continued). The association between physical activity measures and demographic and health factors in participants aged less than 80 years (n=760)

Variable	n	Acceleration (mg/day)		Awake sedentary time (h/day)		Light PA (min/day)		Moderate-vigorous PA (min/day)		Sleep time (accelerometer) (h/day)	
		β ± SE	p	β ± SE	p	β ± SE	p	β ± SE	p	β ± SE	p
Sleep medication											
Not using	636	Referent		Referent		Referent		Referent		Referent	
Using	124	0.00 ± 0.51	1.00	0.02 ± 0.13	0.90	-0.42 ± 2.96	0.89	-0.92 ± 2.34	0.70	-0.07 ± 0.11	0.52

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; n, number; PA, physical activity; SE, standard error. Body mass index was calculated as weight in kilograms divided by height in meters squared. Categories were defined as normal weight: 18.5 < 25 kg/m^2, overweight: 25 < 30 kg/m^2 and obese: ≥ 30 kg/m^2.
The multivariate linear regression analysis was adjusted for all variables included in the table. Total N is reduced due to variation in the amount of missing data for different covariates.
The explained variance in the models, according the adjusted R-squared, was 15.7%, 6.9%, 6.9%, 16.6% and 1.5% for acceleration, sedentary behavior, light physical activity, moderate-to-vigorous physical activity and sleep, respectively.

Supplement 2.2.9. The association between physical activity measures and demographic and health factors in participants aged equal or greater than 80 years (n=360)

Variable	n	Acceleration (mg/day)		Awake sedentary time (h/day)		Light PA (min/day)		Moderate-vigorous PA (min/day)		Sleep time (accelerometer) (h/day)	
		β ± SE	p	β ± SE	p	β ± SE	p	β ± SE	p	β ± SE	p
Age group											
80-84	251	Referent		Referent		Referent		Referent		Referent	
≥85	109	-2.05 ± 0.55	<0.001	0.51 ± 0.16	<0.001	-8.18 ± 3.79	0.03	-10.68 ± 2.57	<0.001	-0.15 ± 0.15	0.30
Sex											
Men	171	Referent		Referent		Referent		Referent		Referent	
Women	189	0.58 ± 0.58	0.31	-0.41 ± 0.16	0.01	4.57 ± 4.00	0.25	2.18 ± 2.70	0.42	0.16 ± 0.16	0.30
Education											
Primary	33	Referent		Referent		Referent		Referent		Referent	
Lower	141	-0.23 ± 0.86	0.79	0.17 ± 0.24	0.48	0.30 ± 5.94	0.96	-2.41 ± 4.02	0.55	-0.17 ± 0.23	0.47
Intermediate	128	0.01 ± 0.87	0.99	0.33 ± 0.25	0.18	-0.21 ± 6.07	0.97	-1.34 ± 4.11	0.74	-0.29 ± 0.24	0.22
Higher	58	-0.05 ± 1.02	0.96	0.59 ± 0.29	0.04	-1.08 ± 7.11	0.88	-2.09 ± 4.81	0.66	-0.47 ± 0.28	0.09
Season											
Spring	78	Referent		Referent		Referent		Referent		Referent	
Summer	20	0.93 ± 1.10	0.40	0.27 ± 0.31	0.39	4.09 ± 7.66	0.59	4.14 ± 5.18	0.42	-0.35 ± 0.30	0.24
Autumn	128	0.60 ± 0.64	0.35	-0.21 ± 0.18	0.26	5.85 ± 4.43	0.19	3.72 ± 3.00	0.22	-0.03 ± 0.17	0.84
Winter	134	0.17 ± 0.64	0.79	-0.19 ± 0.18	0.30	4.30 ± 4.45	0.33	0.90 ± 3.01	0.77	0.07 ± 0.17	0.68
BMI											
Normal weight	122	Referent		Referent		Referent		Referent		Referent	
Overweight	160	-2.22 ± 0.54	<0.001	0.44 ± 0.15	0.005	-12.58 ± 3.75	<0.001	-9.38 ± 2.53	<0.001	-0.16 ± 0.15	0.28
Obese	78	-4.14 ± 0.67	<0.001	0.90 ± 0.19	<0.001	-24.97 ± 4.67	<0.001	-18.58 ± 3.16	<0.001	-0.25 ± 0.18	0.17
Smoking											
Non smoker	123	Referent		Referent		Referent		Referent		Referent	

Supplement 2.2.9 (continued). The association between physical activity measures and demographic and health factors in participants aged equal or greater than 80 years (n=360)

Variable	n	Acceleration (mg/day) β ± SE	p	Awake sedentary time (h/day) β ± SE	p	Light PA (min/day) β ± SE	p	Moderate-vigorous PA (min/day) β ± SE	p	Sleep time (accelerometer) (h/day) β ± SE	p
Former smoker	225	-0.74 ± 0.52	0.16	0.18 ± 0.15	0.23	-2.75 ± 3.62	0.45	-4.10 ± 2.45	0.09	-0.06 ± 0.14	0.69
Current smoker	12	-4.79 ± 1.36	<0.001	0.49 ± 0.39	0.20	-34.4 ± 9.43	<0.001	-23.42 ± 6.38	<0.001	0.53 ± 0.37	0.15
Alcohol consumption											
Never	67	Referent		Referent		Referent		Referent		Referent	
1-4 times/month	119	-0.54 ± 0.69	0.43	0.10 ± 0.19	0.59	-7.69 ± 4.76	0.11	-1.87 ± 3.22	0.56	0.05 ± 0.18	0.78
2-4 times/week	174	-0.20 ± 0.66	0.76	0.04 ± 0.19	0.83	-0.17 ± 4.55	0.97	0.89 ± 3.08	0.77	-0.03 ± 0.18	0.87
Health status											
Not disabled	124	Referent		Referent		Referent		Referent		Referent	
Disabled	70	-1.05 ± 0.67	0.12	0.07 ± 0.19	0.70	2.03 ± 4.66	0.66	-4.81 ± 3.15	0.13	-0.08 ± 0.18	0.67
Severely disabled	166	-1.23 ± 0.57	0.03	0.22 ± 0.16	0.17	-0.45 ± 3.92	0.91	-4.94 ± 2.65	0.06	-0.12 ± 0.15	0.43
Prevalent CVD, DM or cancer											
Not present	134	Referent		Referent		Referent		Referent		Referent	
Present	226	-1.68 ± 0.50	<0.001	0.18 ± 0.14	0.20	-9.14 ± 3.47	0.01	-8.39 ± 2.35	<0.001	0.15 ± 0.13	0.28
Marital status											
Living alone	180	Referent		Referent		Referent		Referent		Referent	
Living with partner	180	-0.24 ± 0.54	0.66	0.06 ± 0.15	0.687	0.36 ± 3.75	0.9237	0.79 ± 2.53	0.75	-0.12 ± 0.15	0.42

Supplement 2.2.9 (continued). The association between physical activity measures and demographic and health factors in participants aged equal or greater than 80 years (n=360)

		Acceleration (mg/day)		Awake sedentary time (h/day)		Light PA (min/day)		Moderate-vigorous PA (min/day)		Sleep time (accelerometer) (h/day)	
Variable	n	β ± SE	p	β ± SE	p	β ± SE	p	β ± SE	p	β ± SE	p
Sleep medication											
Not using	298	Referent		Referent		Referent		Referent		Referent	
Using	62	-0.57 ± 0.63	0.36	0.29 ± 0.18	0.10	-3.90 ± 4.36	0.37	-2.14 ± 2.95	0.47	-0.18 ± 0.17	0.28

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; n, number; PA, physical activity; SE, standard error. Body mass index was calculated as weight in kilograms divided by height in meters squared. Categories were defined as normal weight: 18.5 < 25 kg/m^2, overweight: 25 < 30 kg/m^2 and obese: ≥ 30 kg/m^2.
The multivariate linear regression analysis was adjusted for all variables included in the table. Total N is reduced due to variation in the amount of missing data for different covariates.
The explained variance in the models, according the adjusted R-squared, was 15.7%, 6.9%, 6.9%, 16.6% and 1.5% for acceleration, sedentary behavior, light physical activity, moderate-to-vigorous physical activity and sleep, respectively.

Supplement 2.2.10. The association between physical activity measures and demographic and health factors in participants with body mass index less than 27 (n=554)

Variable	n	Acceleration (mg/day) β ± SE	p	Awake sedentary time (h/day) β ± SE	p	Light PA (min/day) β ± SE	p	Moderate-vigorous PA (min/day) β ± SE	p	Sleep time (accelerometer) (h/day) β ± SE	p
Age group											
70-74	175	Referent		Referent		Referent		Referent		Referent	
75-79	185	-0.97 ± 0.58	0.09	0.07 ± 0.13	0.62	0.84 ± 3.32	0.80	-5.18 ± 2.62	0.048	0.03 ± 0.11	0.80
80-84	130	-1.39 ± 0.65	0.03	0.03 ± 0.15	0.84	0.98 ± 3.74	0.79	-8.36 ± 2.95	0.005	0.11 ± 0.13	0.41
≥85	64	-3.11 ± 0.86	<0.001	0.68 ± 0.20	<0.001	-4.29 ± 4.98	0.39	-17.88 ± 3.93	<0.001	-0.23 ± 0.17	0.18
Sex											
Men	276	Referent		Referent		Referent		Referent		Referent	
Women	278	1.58 ± 0.55	0.005	-0.43 ± 0.13	0.001	9.80 ± 3.19	0.002	6.99 ± 2.52	0.006	0.00 ± 0.11	0.98
Education											
Primary	17	Referent		Referent		Referent		Referent		Referent	
Lower	207	-1.03 ± 1.35	0.45	0.63 ± 0.32	0.05	-1.82 ± 7.78	0.82	-5.29 ± 6.14	0.39	-0.41 ± 0.27	0.12
Intermediate	188	-0.85 ± 1.35	0.53	0.61 ± 0.32	0.05	-1.40 ± 7.79	0.86	-4.67 ± 6.14	0.45	-0.45 ± 0.27	0.09
Higher	142	-0.65 ± 1.38	0.64	0.79 ± 0.32	0.01	0.45 ± 7.98	0.96	-3.89 ± 6.29	0.54	-0.63 ± 0.28	0.02
Season											
Spring	131	Referent		Referent		Referent		Referent		Referent	
Summer	61	1.60 ± 0.82	0.05	0.18 ± 0.19	0.36	1.57 ± 4.74	0.74	4.36 ± 3.74	0.24	-0.25 ± 0.16	0.12
Autumn	171	0.58 ± 0.62	0.34	-0.04 ± 0.14	0.77	5.11 ± 3.55	0.15	2.09 ± 2.80	0.45	-0.09 ± 0.12	0.48
Winter	191	0.04 ± 0.61	0.95	0.22 ± 0.14	0.13	1.51 ± 3.50	0.67	-0.64 ± 2.76	0.82	-0.22 ± 0.12	0.07
Smoking											
Non smoker	206	Referent		Referent		Referent		Referent		Referent	
Former smoker	318	-0.51 ± 0.50	0.31	0.29 ± 0.12	0.01	-4.24 ± 2.89	0.14	-2.52 ± 2.28	0.27	-0.19 ± 0.10	0.06

Supplement 2.2.10 (continued). The association between physical activity measures and demographic and health factors in participants with body mass index less than 27 (n=554)

		Acceleration (mg/day)		Awake sedentary time (h/day)		Light PA (min/day)		Moderate-vigorous PA (min/day)		Sleep time (accelerometer) (h/day)	
Variable	n	β ± SE	p	β ± SE	p	β ± SE	p	β ± SE	p	β ± SE	p
Current smoker	30	-3.93 ± 1.08	<0.001	0.46 ± 0.25	0.07	-19.73 ± 6.24	<0.001	-19.19 ± 4.92	<0.001	0.12 ± 0.22	0.58
Alcohol consumption											
Never	100	Referent		Referent		Referent		Referent		Referent	
1-4 times/month	134	0.05 ± 0.70	0.95	0.00 ± 0.16	1.00	-3.27 ± 4.05	0.42	0.53 ± 3.19	0.87	0.07 ± 0.14	0.62
2-4 times/week	320	0.19 ± 0.62	0.76	-0.05 ± 0.15	0.73	-1.39 ± 3.59	0.70	0.75 ± 2.83	0.79	0.12 ± 0.12	0.35
Health status											
Not disabled	300	Referent		Referent		Referent		Referent		Referent	
Disabled	85	-0.31 ± 0.66	0.64	-0.02 ± 0.15	0.88	-1.21 ± 3.79	0.75	-2.83 ± 2.99	0.34	0.06 ± 0.13	0.62
Severely disabled	169	-1.45 ± 0.53	0.01	0.12 ± 0.12	0.34	-6.69 ± 3.04	0.03	-7.64 ± 2.39	0.002	0.05 ± 0.11	0.62
Prevalent CVD, DM or cancer											
Not present	276	Referent		Referent		Referent		Referent		Referent	
Present	278	-1.78 ± 0.46	<0.001	0.08 ± 0.11	0.48	-8.27 ± 2.66	<0.001	-6.57 ± 2.1	0.002	0.16 ± 0.09	0.08
Marital status											
Living alone	185	Referent		Referent		Referent		Referent		Referent	
Living with partner	369	0.53 ± 0.55	0.34	0.08 ± 0.13	0.53	3.60 ± 3.19	0.26	2.81 ± 2.52	0.26	-0.17 ± 0.11	0.13
Sleep medication											
Not using	457	Referent		Referent		Referent		Referent		Referent	
Using	97	-0.28 ± 0.61	0.65	0.02 ± 0.14	0.87	-2.77 ± 3.49	0.43	-2.51 ± 2.75	0.36	-0.02 ± 0.12	0.84

Abbreviations: CVD, cardiovascular disease; DM, diabetes mellitus; n, number; PA, physical activity; SE, standard error. Body mass index was calculated as weight in kilograms divided by height in meters squared. Categories were defined as normal weight: 18.5 < 25 kg/m^2, overweight: 25 < 30 kg/m^2 and obese: ≥ 30 kg/m^2.

The multivariate linear regression analysis was adjusted for all variables included in the table. Total N is reduced due to variation in the amount of missing data for different covariates.

The explained variance in the models, according the adjusted R-squared, was 15.7%, 6.9%, 6.9%, 16.6% and 1.5% for acceleration, sedentary behavior, light physical activity, moderate-to-vigorous physical activity and sleep, respectively.

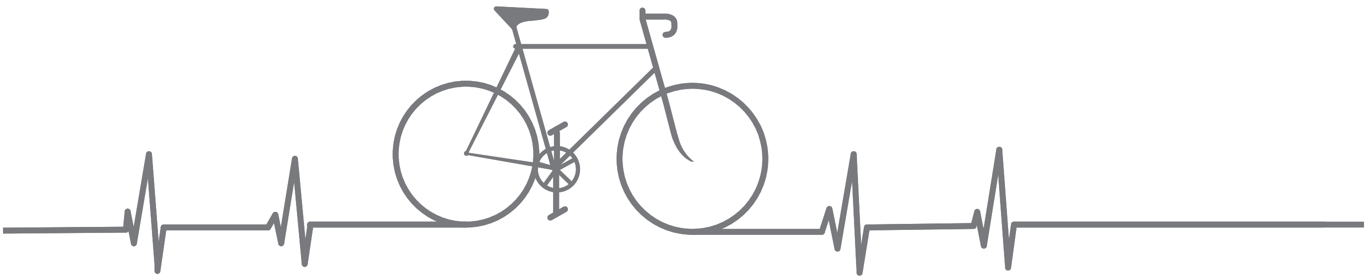
Supplement 2.2.11. The association between physical activity measures and demographic and health factors in participants with body mass index equal or higher than 27 (n=566)

		Acceleration (mg/day)		Awake sedentary time (h/day)		Light PA (min/day)		Moderate-vigorous PA (min/day)		Sleep time (accelerometer) (h/day)	
Variable	n	β ± SE	p	β ± SE	p	β ± SE	p	β ± SE	p	β ± SE	p
Age group											
70-74	203	Referent		Referent		Referent		Referent		Referent	
75-79	197	-0.60 ± 0.46	0.20	-0.16 ± 0.14	0.25	2.10 ± 3.06	0.49	-2.48 ± 2.21	0.26	0.12 ± 0.12	0.33
80-84	121	-2.33 ± 0.55	<0.001	0.06 ± 0.17	0.73	-5.07 ± 3.65	0.16	-11.26 ± 2.63	<0.001	0.08 ± 0.15	0.58
≥85	45	-3.70 ± 0.82	<0.001	0.22 ± 0.24	0.36	-9.40 ± 5.37	0.08	-18.42 ± 3.87	<0.001	0.14 ± 0.22	0.53
Sex											
Men	267	Referent		Referent		Referent		Referent		Referent	
Women	299	1.39 ± 0.46	0.003	-0.44 ± 0.14	0.001	9.6 ± 3.00	0.002	5.92 ± 2.16	0.006	0.08 ± 0.12	0.51
Education											
Primary	43	Referent		Referent		Referent		Referent		Referent	
Lower	244	0.62 ± 0.76	0.42	-0.33 ± 0.23	0.15	3.62 ± 5.04	0.47	2.61 ± 3.64	0.47	0.13 ± 0.20	0.52
Intermediate	178	0.42 ± 0.79	0.60	-0.15 ± 0.24	0.52	0.97 ± 5.21	0.85	1.31 ± 3.76	0.73	0.09 ± 0.21	0.69
Higher	101	0.68 ± 0.87	0.44	-0.16 ± 0.26	0.54	4.66 ± 5.75	0.42	3.46 ± 4.15	0.40	-0.02 ± 0.23	0.93
Season											
Spring	140	Referent		Referent		Referent		Referent		Referent	
Summer	55	0.74 ± 0.73	0.31	0.08 ± 0.22	0.71	2.39 ± 4.81	0.62	2.76 ± 3.47	0.43	-0.22 ± 0.19	0.25
Autumn	198	1.19 ± 0.50	0.02	-0.08 ± 0.15	0.61	4.88 ± 3.31	0.14	4.16 ± 2.39	0.08	-0.07 ± 0.13	0.59
Winter	173	0.67 ± 0.52	0.20	-0.14 ± 0.16	0.36	3.71 ± 3.42	0.28	2.43 ± 2.47	0.33	0.03 ± 0.14	0.81
Smoking											
Non smoker	174	Referent		Referent		Referent		Referent		Referent	
Former smoker	362	0.32 ± 0.44	0.47	-0.02 ± 0.13	0.88	1.98 ± 2.87	0.49	1.79 ± 2.07	0.39	-0.01 ± 0.12	0.91

Supplement 2.2.11 (continued). The association between physical activity measures and demographic and health factors in participants with body mass index equal or higher than 27 (n=566)

		Acceleration (mg/day)		Awake sedentary time (h/day)		Light PA (min/day)		Moderate-vigorous PA (min/day)		Sleep time (accelerometer) (h/day)	
Variable	n	β ± SE	p	β ± SE	p	β ± SE	p	β ± SE	p	β ± SE	p
Current smoker	30	-0.99 ± 0.91	0.28	0.27 ± 0.27	0.32	-4.85 ± 6.01	0.42	-3.56 ± 4.33	0.41	-0.11 ± 0.24	0.65
Alcohol consumption											
Never	77	Referent		Referent		Referent		Referent		Referent	
1-4 times/month	191	-0.09 ± 0.61	0.89	-0.01 ± 0.18	0.94	-3.76 ± 4.02	0.35	0.12 ± 2.90	0.97	0.13 ± 0.16	0.43
2-4 times/week	298	0.51 ± 0.60	0.40	0.06 ± 0.18	0.75	3.25 ± 3.95	0.41	2.48 ± 2.85	0.38	-0.10 ± 0.16	0.53
Health status											
Not disabled	209	Referent		Referent		Referent		Referent		Referent	
Disabled	121	-1.36 ± 0.53	0.01	0.12 ± 0.16	0.45	-2.34 ± 3.49	0.50	-6.24 ± 2.52	0.01	0.05 ± 0.14	0.73
Severely disabled	236	-2.01 ± 0.46	<0.001	0.37 ± 0.14	0.01	-8.04 ± 3.00	0.01	-10.33 ± 2.16	<0.001	-0.04 ± 0.12	0.74
Prevalent CVD, DM or cancer											
Not present	247	Referent		Referent		Referent		Referent		Referent	
Present	319	-1.13 ± 0.40	0.005	0.32 ± 0.12	0.01	-4.94 ± 2.61	0.06	-5.05 ± 1.88	0.008	-0.17 ± 0.11	0.12
Marital status											
Living alone	194	Referent		Referent		Referent		Referent		Referent	
Living with partner	372	1.60 ± 0.44	<0.001	-0.33 ± 0.13	0.012	9.97 ± 2.90	<0.001	7.44 ± 2.09	<0.001	0.03 ± 0.12	0.77
Sleep medication											
Not using	477	Referent		Referent		Referent		Referent		Referent	
Using	89	-0.21 ± 0.53	0.69	0.18 ± 0.16	0.25	-0.32 ± 3.52	0.93	-0.34 ± 2.54	0.89	-0.19 ± 0.14	0.18

Abbreviations: CVD, cardiovascular disease; DM, diabetes mellitus; n, number; PA, physical activity; SE, standard error. Body mass index was calculated as weight in kilograms divided by height in meters squared. Categories were defined as normal weight: 18.5 < 25 kg/m^2, overweight: 25 < 30 kg/m^2 and obese: ≥ 30 kg/m^2.
The multivariate linear regression analysis was adjusted for all variables included in the table. Total N is reduced due to variation in the amount of missing data for different covariates.
The explained variance in the models, according the adjusted R-squared, was 15.7%, 6.9%, 6.9%, 16.6% and 1.5% for acceleration, sedentary behavior, light physical activity, moderate-to-vigorous physical activity and sleep, respectively.



Chapter 2.3

Seasonality of physical activity, sedentary behavior, and sleep

Manuscript based on this chapter:
Cepeda M*, **Koolhaas CM***, van Rooij FJA, Tiemeier H, Guxens M, Franco OH, Schoufour JD. Seasonality of physical activity, sedentary behavior, and sleep in a middle-aged and elderly population: The Rotterdam study. *Maturitas*. 2018;110:41-50.

ABSTRACT

Introduction: Physical activity (PA) and sedentary behavior (SB) have seasonal patterns. It remains unclear how these patterns are associated with sleep, meteorological factors, and health.

Methods: Activity levels were continuously measured with an accelerometer for seven days between July 2011 and May 2016, among middle-aged (50-64 years), young-elderly (65-74 years) and old-elderly (≥75 years) participants of a population-based Dutch cohort study (n=1,116). Meteorological factors (ambient temperature, wind speed, sunlight hours, precipitation, and minimum visibility) were locally recorded. We first examined the seasonality of PA, SB, and nighttime sleep, stratified by age group. Second, we examined the influence of meteorological factors. Third, we modeled the potential seasonality of the all-cause mortality risk due to the seasonality of PA and SB, by using previously published relative risks.

Results: Levels of light and moderate-to-vigorous PA were higher in summer than in winter among middle-aged (seasonal variation=18.1 and 14.8 minutes/day) and young-elderly adults (12.8 and 8.6 minutes/day). The pattern was explained by ambient temperature and sunlight hours. Nighttime sleep was 31.8 minutes/day longer in winter among middle-aged adults. SB did not show a seasonal pattern. No seasonality in activity levels was observed among old-elderly adults. The all-cause mortality risk may be higher in winter than in summer due to the accumulation of low levels of moderate to vigorous PA and high levels of SB.

Conclusion: PA has a larger degree of seasonality than SB and nighttime sleep among middle-aged and young-elderly adults. SB appears strongly ingrained in daily routine. Recommending the interruption of SB with light PA might be a good starting point for public health institutions.

INTRODUCTION

Population ageing, urbanization, and automatization of daily activities have contributed to a predominantly sedentary lifestyle with low levels of physical activity (PA), and high levels of sedentary behavior (SB), but also to suboptimal nighttime sleep duration (i.e. not sleeping 7-8 hours).[1,2] However, although low levels of PA cluster with high SB and suboptimal nighttime sleep duration,[1,3] these are partly independent phenomena. Moreover, the proportions of the various types of daily (in)activity (i.e. PA, SB, sleep) may influence cardio-metabolic health, beyond their independent effects.[4-6] Therefore, there is increasing interest in the factors determining the composition of daily activity levels.

Objective measurements with accelerometers have demonstrated that levels of PA and SB are not constant throughout the year. Studies performed in young and middle-aged populations report that time spent in PA decreases in winter,[7,8] whereas sedentary time increases.[9,10] However, it is unclear whether sleep duration is related to this variation, because previous studies have used sleep diaries[10] rather than objective measures or because sleep was omitted from the daily routine.[9]

Several factors determine the seasonality of activity levels. For example, with increasing age, time spent in PA and nighttime sleep tend to decrease, while sedentary behavior increases.[11,12] Retirement may also explain this pattern, as leisure PA is more sensitive to seasonal changes than occupational PA.[8] Additionally, age interacts with meteorological factors to influence PA levels[13,14] and the seasonality of PA is more marked in geographical regions with more climatic variation.[15,16] However, an age-specific assessment of the impact of meteorological factors on the seasonality of activity levels has not been performed.

The seasonality of activity levels is of relevance to public health, as PA is often prescribed as a first means to improve health, e.g. to reduce dyslipidemia and high blood pressure.[17] Indeed, it is hypothesized that the seasonal pattern of cardio-metabolic risk and mortality can be partly explained by the seasonality of PA.[7,18] Nevertheless, it is not clear whether this seasonality is large enough to influence all-cause mortality on a seasonal basis.

We therefore examined the seasonality of objectively measured daily levels of PA, SB, and nighttime sleep duration according to age, using around-the-clock measurements. Furthermore, we examined to what extent meteorological factors explained the seasonality of activity levels. Finally, we modeled the seasonality of the all-cause mortality risk produced by the seasonal variation in levels of moderate-to-vigorous PA and SB.

METHODS

Study design

We performed a cross-sectional study to analyze the annual seasonal variation in PA, SB and nighttime sleep duration. This study was embedded in the Rotterdam Study (RS), a prospective population-based cohort established in 1989, which has invited all middle-aged and elderly people living in the Ommoord district of Rotterdam, the Netherlands. Baseline invitations sent to all the home addresses within the district, including senior housing facilities, retirement homes and assisted living facilities. The aim of the Rotterdam Study was to examine the incidence of risk factors for neurological, cardiovascular, psychiatric, and other chronic diseases.[19] The study is composed by three cohorts (RS-I, RS-II and RS-III) and follow-up visits are performed every five years.[19] The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (MEC 02.1015) and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study). All participants provided written informed consent to their involvement in the study and to obtain information from their treating physicians.

Between June-2011 and June-2014 (wave 1) and between July-2014 and May-2016 (wave 2), 3,507 participants were invited to wear an accelerometer for seven days, to measure their activity levels; 482 participants were invited in both waves. Along with wearing the accelerometer, participants reported overnight sleep periods in a sleep diary. For the current study, we selected 1,166 sets of observations (48 from participants who participated in both wave 1 and wave 2) obtained from non-disabled participants. Disability was defined as having a disability index > 0.5.[20] The participation flowchart is provided in Supplement 2.3.1.

Physical activity, sedentary behavior and nighttime sleep duration

To measure activity, we used a GENEActiv device (GENEActiv; Activinsights Ltd, Kimbolton, Cambridgeshire, UK, http://www.GENEActiv.org/), a tri-axial accelerometer that can be worn like a watch. The GENEActiv was sampled at 50 Hz and acceleration was expressed relative to gravity (g units; 1 g =9.81 m/s^2).[21-23] To quantify acceleration related to the movement registered, we computed the high-pass filtered vector magnitude (HPFVM).

Participants were instructed to wear the accelerometer on the non-dominant wrist for 7 consecutive days and nights. Accelerometer data were processed in Python (2.6.6) using the open access PAMPRO software.[24] Data were extracted from the first wearing day up to seven days later. Participants were included in the analysis if they wore the watch for >1,200 min/day, for at least 4 days. Activity was categorized into sedentary (<48 mg), light (48 < 154 mg), moderate (154 <389 mg) and vigorous activity (>389 mg), based on a recent validation study.[25] Nighttime sleep duration was detected using a validated algorithm,[26] which combines the accelerometer data and the time when participants reported they went to bed and woke up from the sleep diary. Time-in-bed was also extracted from sleep diaries. Sleep efficiency was calculated as (nighttime sleep duration/time-in-bed)*100.

Meteorological factors

Daily information on meteorological factors in Rotterdam was obtained from the Koninklijk Nederlands Meteorologisch Instituut (KNMI).[27] The monitor is located approximately 8km from the Ommoord district (coordinates: 51° 58' N.B. 04° 27' O.L). The daily meteorological data were linked to the dates on which the accelerometer was worn. In the current study, we included daily average temperature (˚C), average relative humidity (percentage), total number of sunlight hours, accumulated precipitation (mm), average wind speed (m/s), and minimum visibility (km), classified as <1.8km, 1.8-3.9km, 3.9-7km, 7-12km and ≥12km.

Covariates

Data on covariates were collected through home interviews or measured in the Rotterdam Study research center by trained research assistants.[19] Height and weight were measured and were used to calculate body mass index (BMI; calculated as weight divided by height squared). History of cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease (COPD) and cancer at the visit date was obtained from medical records. Smoking behavior was categorized as never, current or former and requested via questionnaires. Housing condition was classified as living independent vs. living in assisted living facilities (i.e., service flat, nursing home). A disability index was calculated using the Stanford Health Assessment Questionnaire.[20] Depression was screened during the home interview using the Center for Epidemiology Studies Depression Scale (CES-D Scale).[28] Alcohol intake was obtained using the AUDIT tool.[29]

Statistical methods

All analyses were stratified by age group: 50–64 years (middle-aged), 65–74 years (young-elderly) and aged 75 years or older (old-elderly). General characteristics of the population are presented as absolute frequencies and percentage for categorical variables and as median and interquartile range (25^{th} and 75^{th} percentile) for continuous variables. Differences in distributions between the age-groups were evaluated using the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables.

In our analysis, we first examined the seasonality of light and moderate-to-vigorous PA, SB, and nighttime sleep duration (in minutes/day) using a linear mixed effects model to account for the correlation within days contributed per participant. We used the participant id as clustering variable. Because 48 participants wore the accelerometer in both waves, we accounted for the correlation between these repeated measurements by adding a second random intercept, using the wave as a clustering variable. The seasonality was evaluated using a cosinor model assuming a sinusoidal pattern with a period of one year,[8] by adding sine and cosine terms of the accelerometer wear-date in the fixed part of the model.[30] All models were adjusted for the covariates listed above, plus the day of the week (weekday or weekend day).

The seasonality is reported as the seasonal variation, corresponding to the peak-to-nadir difference in activity levels throughout the year. Procedures to estimate the seasonal variation are provided elsewhere.[30] A subgroup analysis stratified by sex was performed, including the seasonal variation in time-in-bed (minutes/day) and sleep efficiency (%).

Second, to examine to what extent the meteorological factors explained the seasonality of activity levels, we included one meteorological factor at a time in the fully adjusted model. Then, we calculated the difference of the seasonal variation before and after the inclusion of the meteorological factor. The influence of a meteorological factor on the seasonality of activity levels was considered significant if the seasonal variation became non-significant or was reduced by more than 5%. Average temperature was categorized in quintiles to account for the non-linear association. Wind speed, sunlight hours, precipitation, and humidity were converted to z-scores and added as continuous variables.

Finally, we examined the potential seasonality of the all-cause mortality risk as a function of moderate-to-vigorous PA and SB, as described in detail in Supplement 2.3.2. Briefly, we first multiplied the time/day spent in moderate-to-vigorous PA and in SB with the log transformed relative risk (RR) for the association of moderate-to-vigorous PA (RR=0.72) and SB (RR=1.24) with all-cause mortality, as obtained from published meta-analyses.[31,32] The sum of these products was considered the hypothetical all-cause mortality risk due to moderate-to-vigorous PA and SB combined. Next, we modeled the seasonality of this hypothetical all-cause mortality risk using cosinor analysis, adjusted for the covariates listed above, and stratified by age-group. Using the seasonal variation obtained in the previous step, we calculated the hypothetical all-cause mortality risk at the peak and the nadir of the seasonal variation and, using standard lifetables, we calculated the corresponding life expectancy at each extreme. The difference between the life expectancy at the peak and at the nadir is expressed in months. The analyses were repeated for PA and SB separately and using the lower and upper boundaries of the 95% confidence interval of the RRs.
All analyses were performed in Stata version 14.1 SE (StataCorp LP, College Station, Texas).[33]

RESULTS

General characteristics

A total of 1,166 sets of measurements were made; 34% (n=394) were among middle-aged adults, 39% among young-elderly (n=449), and 28% among old-elderly participants (n=323). Old-elderly adults more often participated in the study during winter than during summer (43.6% vs. 6.2% of the days contributed). The other age-groups did not show this difference in participation across the seasons. Additionally, old-elderly adults were more often living in assisted living facilities and were less often in paid employment than middle-aged and young-elderly adults (Table 2.3.1).

Seasonal variation in activity levels

Among middle-aged participants, levels of light PA were highest in early-August (seasonal variation=18.1 minutes/day (standard error (SE)=4.0)), and levels of moderate-to-vigorous PA were highest in late-July (seasonal variation=14.8 minutes/day (SE=3.8)), whereas nighttime sleep duration was highest mid-January (seasonal variation=31.8 minutes/day (SE=6.6)). No significant seasonal variation in SB was observed (Figure 2.3.1). Among young-elderly adults, levels of light PA and of moderate-to-vigorous PA were highest in late-July (seasonal variation= 12.8 minutes/day (SE=3.9) and 9.9 minutes/day (SE=3.3), respectively), but no significant seasonal variation was observed for nighttime sleep duration. Among old-elderly participants, no significant seasonal variation was observed for any activity level. No large sex differences in the seasonality of activity levels were observed (Supplement 2.3.3).

Table 2.3.1. Characteristics of the population at visit-date, The Rotterdam Study, The Netherlands, 2011-2016

Covariate	Middle-aged (50-64 years, n=394)		Young-elderly (65-74 years, n=449)		Old-elderly (≥75 years, n=323)		P-value
	Median	25th - 75th percentile	Median	25th - 75th percentile	Median	25th - 75th percentile	
Age (years)	59.1	56.1-62.4	71.3	67.3-72.8	78.9	77-81.4	
Waist circumference (cm)	92.2	84.5-101.8	94.9	87.3-102.3	92.5	85.8-101.1	0.014
Body mass index (kg/m^2)	26.7	24.2-29.4	26.7	24.7-28.9	26.1	24-28.5	0.026
Disability index[a]	0.1	0-0.3	0.1	0-0.3	0.3	0.1-0.4	<0.001
Depression	3	0-6	2	0-4	2	0-6	0.004
Activity levels (minutes/day)[b, c]							
Light PA	154.1	154.8-144.5	150.7	151.9-142.1	147.4	147.5-139.5	<0.001
Moderate-to-vigorous PA	99.6	100-90.8	87.7	88-80	76.4	76.3-69.3	<0.001
Sedentary while awake	806.3	808.7-783.7	818.6	815.4-798.2	825.4	826.1-809	<0.001
Nighttime sleep duration	370.4	369.1-354.4	374	373.6-364.7	381.3	381-372.2	<0.001
	n	Percentage	n	Percentage	n	Percentage	
Sex							
Men	203	51.5	256	57	189	58.5	0.127
Women	191	48.5	193	43	134	41.5	
Comorbidities							
Cancer	23	5.8	62	13.8	109	33.8	<0.001
Cardiovascular disease	13	3.3	59	13.1	53	16.4	<0.001
Diabetes	34	8.6	60	13.4	48	14.9	0.022
Chronic obstructive pulmonary disease	47	11.9	71	15.8	46	14.2	0.266
Medication intake [d]							
Antihypertensive	107	27.2	206	46.2	154	48	<0.001
Diabetic medication	24	6.1	29	6.5	27	8.4	0.442
Statin	72	18.3	138	30.9	96	29.9	<0.001
Smoking behavior							
Never	118	29.9	219	48.9	249	77.1	<0.001

Table 2.3.1 (continued). Characteristics of the population at visit-date, The Rotterdam Study, The Netherlands, 2011-2016

Covariate	Middle-aged (50-64 years, n=394)		Young-elderly (65-74 years, n=449)		Old-elderly (≥75 years, n=323)		P-value
	n	Percentage	n	Percentage	n	Percentage	
Currently	68	17.2	48	10.7	16	5	
Previously	209	52.9	181	40.4	58	18	
Housing conditions							
Living independent	392	99.5	440	98	297	92	<0.001
Assisted living facilities	2	0.5	9	2	26	8.1	
Occupation							
Working	340	86.1	136	30.4	17	5.3	<0.001
Not working	55	13.9	312	69.6	306	94.7	
Alcohol intake							
<2.5 glass/day	285	72.3	337	75.1	272	84.2	
2.4-4.4 glass/day	90	22.8	92	20.5	44	13.6	<0.001
≥4.5 glass/day	19	4.8	20	4.5	7	2.2	
Contribution of days							
1-3 days	128	32.4	156	34.8	108	33.4	0.776
4-6 days	197	49.9	222	49.6	168	52	
7 days	70	17.7	70	15.6	47	14.6	
Season[3]							
Winter	480	22.1	651	25.5	805	43.6	<0.001
Spring	638	29.3	661	25.9	398	21.5	
Summer	594	27.3	459	18	114	6.2	
Autumn	465	21.4	781	30.6	531	28.7	
Day of the week[3]							
Weekend	755	34.7	865	33.9	626	33.9	0.817
Weekday	1,422	65.3	1687	66.1	1222	66.1	

PA: Physical activity [a] Measured with Stanford Health Assessment Questionnaire.[20] [b] Adjusted for cosinor terms, age, gender, body mass index, comorbidities (cancer, cardiovascular disease, diabetes, chronic obstructive pulmonary disease), depression, medication intake (antihypertensive, statins, antidiabetic), smoking behavior, housing status, disability index, occupation status, alcohol intake and day of the week (weekend day or weekday). [c] Sample sizes/total are days contributed per participant: 2,171 days (middle-aged), 2,541 days (young-elderly) and 1,836 days (old-elderly). [d] Medication intake information was not available for 1 middle-aged participant, 2 young-elderly and 2 old-elderly.

Impact of meteorological factors on the seasonality of activity levels

Among middle-aged adults, the seasonality of levels of light PA was explained by ambient temperature (seasonal variation change=-16.3%) and sunlight hours (-16.0%). The seasonality of levels of moderate-to-vigorous PA was explained by sunlight hours (-21.5%) and the seasonality of nighttime sleep duration was explained by ambient temperature (-49.4%). Among young-elderly participants, the seasonality of levels of light PA was explained by ambient temperature (-46.7%) and relative humidity (-17.7%), and the seasonality of levels of moderate-to-vigorous PA was explained by ambient temperature (-14.0%), minimal visibility (-12.7%), and relative humidity (-11.0%). The meteorological factors had a large significant association with PA levels among the old-elderly, but none explained the seasonality (Tables 2.3.2 and 2.3.3).

Seasonal variation in the all-cause mortality risk and life expectancy as a function of the seasonality of activity levels

If the all-cause mortality risk depended entirely on the levels of moderate-to-vigorous PA and SB, it would increase by 1.09 (95%CI: 0.99, 1.21) times in winter compared with summer among middle-aged participants, 1.11 (95%CI: 1.01, 1.21) times in winter compared with summer among young-elderly participants, and 1.04 (95%CI: 0.95, 1.15) times in autumn compared to spring among old-elderly participants (Table 2.3.4). The estimates were similar when using the 95%CI of the RR (Supplement 2.3.4).

DISCUSSION

In this population-based cohort, middle-aged and young-elderly participants spent more time in light and moderate-to-vigorous PA in summer than in winter, but no seasonality of PA was observed among old-elderly adults. Also, no seasonality was observed for SB in any age group. Nighttime sleep duration was higher in winter than in summer among middle-aged participants. The seasonality of PA and nighttime sleep duration was mostly explained by ambient temperature and sunlight hours. The modeled all-cause mortality risk might increase in winter because of the accumulation of low levels of moderate-to-vigorous PA and high levels of SB.

The heterogeneous seasonal patterns according to activity levels and age group can be explained by several factors. First, the magnitude of the seasonal variation in PA decreased with age, which can be explained by the age-specific domain composition of PA (i.e. occupational, transportation, leisure, and household). Indeed, while up to 30% of daily PA among middle-aged adults correspond to occupational PA,[11] this domain nearly disappears after retirement, around age 65 (i.e. the young-elderly).[11] Therefore, the summer increase in PA among middle-aged participants, and to a lesser extent among young-elderly participants, likely reflects an increase in leisure, household, and transportation PA, while levels of occupational PA remain constant. In contrast, because old-elderly adults have less structured daily PA (due to absence of occupational PA), they are less sensitive to the variation led by holidays and vacations.

Table 2.3.2. Seasonality in light and moderate-to-vigorous physical activity after accounting for meteorological factors, The Rotterdam Study, The Netherlands, 2011-2016[a]

Meteorological factors	Middle-aged (50-64 years)				Young-elderly (65-74 years)				Old-elderly (≥75 years)			
	SV	% SV change	Co.	95% CI	SV	% SV change	Co.	95%CI	SV	% SV change	Co.	95% CI
(a) Light PA, minutes/day												
Model												
+ temperature (°C)	15.2*	-16.3			6.81	-46.7			4.2	121.5		
-9.8 - 6.6 (Ref)												
6.7 - 10.3			-2.5	(-6.6, 1.7)			-1.0	(-4.8, 2.8)			**-4.5**	**(-8.0, -1.0)**
10.4 - 14.0			0.6	(-5.4, 6.6)			3.7	(-1.1, 8.6)			-3.1	(-7.7, 1.6)
14.1 - 27			2.2	(-5.2, 9.5)			4.5	(-1.3, 10.3)			2.3	(-4.2, 8.8)
+ wind speed (SD m/s)[b]	16.8**	-7.1	-0.3	(-2.0, 1.3)	11.4**	-10.9	-1.0	(-2.5, 0.5)	8	287.2	**-3.3**	**(-5.3, -1.4)**
+ sunlight (SD hrs)[b]	15.2**	-16	**1.8**	**(0.0, 3.6)**	11.2*	-12.1	1.0	(-0.5, 2.6)	10	385.5	**4.2**	**(2.2, 6.3)**
+ precipitation (SD mm)[b]	17.3**	-4.7	-0.9	(-2.6, 0.8)	12.1**	-5.4	**-1.7**	**(-3.2, -0.2)**	5.3	157.1	**-3.4**	**(-5.1, -1.6)**
+ relative humidity (SD %)[b]	16.5**	-9	-1.1	(-2.9, 0.8)	10.5	-17.7	**-2.5**	**(-4.1, -0.8)**	6.3	208.4	**-2.4**	**(-4.5, -0.2)**
+ minimum visibility (km)	18.8**	3.9			10.9*	-15.1			2.2	5.2		
<1.8 (Ref)												
1.8-3.9			0.3	(-3.8, 4.3)			**-3.7**	**(-7.1, -0.2)**			-1.1	(-4.3, 2.2)
3.9-7.0			-1.2	(-5.3, 2.8)			1.4	(-2.1, 4.8)			-0.7	(-4.2, 2.9)
7.0-12.0			-1.2	(-5.2, 2.8)			3.2	(-0.2, 6.6)			0.0	(-3.4, 3.4)
≥12.0			-1.4	(-5.7, 2.8)			4.4	(0.6, 8.2)			0.8	(-3.3, 4.8)
(b) Moderate-to-vigorous PA, minutes/day												
Model												
+ temperature (°C)	14.2**	-4.1			8.5*	-14			4.4	13.2		
-9.8 - 6.6 (Ref)												
6.7 - 10.3			-2.7	(-6.4, 0.9)			-1.9	(-5.0, 1.1)			**-3.6**	**(-6.1, -1.1)**
10.4 - 14.0			0.8	(-4.5, 6.1)			-0.3	(-4.2, 3.6)			-2.5	(-5.8, 0.9)
14.1 - 27			-0.3	(-6.8, 6.2)			0.2	(-4.4, 4.9)			0.4	(-4.3, 5.1)

Table 2.3.2 (continued). Seasonality in light and moderate-to-vigorous physical activity after accounting for meteorological factors, The Rotterdam Study, The Netherlands, 2011-2016[a]

Meteorological factors	Middle-aged (50-64 years)				Young-elderly (65-74 years)				Old-elderly (≥75 years)			
	SV	% SV change	Co.	95% CI	SV	% SV change	Co.	95%CI	SV	% SV change	Co.	95% CI
+ wind speed (SD m/s)[b]	13.5**	-8.9	-1.3	(-2.7, 0.1)	9.8**	-0.9	-0.9	(-2.1, 0.3)	8.3	113.8	**-2.8**	**(-4.3, -1.4)**
+ sunlight (SD hrs)[b]	11.6**	-21.5	**2.2**	**(0.6, 3.8)**	9.3*	-6.1	**1.3**	**(0.0, 2.5)**	9.1	132.2	**3.3**	**(1.8, 4.8)**
+ precipitation (SD mm)[b]	14.6**	-1.4	**-1.9**	**(-3.4, -0.4)**	10.4**	4.6	**-2.3**	**(-3.4, -1.1)**	6.3	60.6	**-3.2**	**(-4.5, -1.9)**
+ relative humidity (SD %)[b]	12.8**	-13.1	**-18.5**	**(-34.5, -2.4)**	8.8	-11	**-22.7**	**(-36.0, -9.4)**	6.2	59.4	-15.2	(-31.3, 0.9)
+ minimum visibility (km)	14.8**	0.5			8.6*	-12.7			4.3	9.1		
<1.8 (Ref)												
1.8-3.9			-1.7	(-5.3, 1.8)			-1.9	(-4.7, 0.9)			-1.9	(-4.3, 0.4)
3.9-7.0			-1.6	(-5.1, 2.0)			2.2	(-0.5, 5.0)			-1.7	(-4.2, 0.9)
7.0-12.0			-0.2	(-3.7, 3.3)			2.2	(-0.5, 4.9)			0.2	(-2.2, 2.7)
≥12.0			-0.4	(-4.1, 3.3)			**4.2**	**(1.2, 7.3)**			1.4	(-1.5, 4.3)

CI = Confidence interval. Co. = Coefficient. SD = Standard deviation. SV = Seasonal variation. ** At least one significant cosinor term at 0.025 confidence level. * At least one significant cosinor term at 0.05 confidence level. [a]All estimates are adjusted for cosinor terms, sex, age, body mass index, prevalent comorbidities (cancer, cardiovascular disease, diabetes, and chronic obstructive pulmonary disease), smoking behavior, housing status, occupation, alcohol intake, disability index and day of the week. [b] Increment in activity levels (minutes/day) per increment of one standard deviation of meteorological factor: wind speed 2.17 m/s, wind chill: 2.06 m/s, sunlight hours: 3.97, precipitation: 4.6mm, relative humidity: 8.5%. Bold coefficients are statistically significant at 95% confidence level.

Table 2.3.3. Seasonality in sedentary behavior and nighttime sleep duration after accounting for meteorological factors, The Rotterdam Study, The Netherlands, 2011-2016[a]

Meteorological factors	Middle-aged (50-64 years)				Young-elderly (65-74 years)				Old-elderly (≥75 years)			
		% SV change	Co.	95% CI		% SV change	Co.	95%CI	SV	% SV change	Co.	95% CI
(a) Sedentary behavior, minutes/day												
Model												
+ temperature (°C)	15.9	33.9			17.3	24.8			7	9.2		
-9.8 - 6.6 (Ref)												
6.7 - 10.3			10.4	(-0.5, 21.4)			6.2	(-4.2, 16.6)			8.2	(-2.5, 19.0)
10.4 - 14.0			10.4	(-5.4, 26.2)			2.7	(-10.5, 15.8)			6.2	(-8.1, 20.6)
14.1 - 27			13.3	(-5.9, 32.6)			8.2	(-7.7, 24.1)			0.3	(-19.5, 20.1)
+ wind speed (SD m/s)[b]	13.3	12	0.5	(-3.6, 4.7)	15.9	14.8	3.3	(-0.8, 7.4)	23.8	269.6	**10.2**	**(4.3, 16.2)**
+ sunlight (SD hrs)[b]	17.4	46.2	-3.4	(-8.0, 1.3)	18	29.9	-0.7	(-4.9, 3.5)	18.7	190.2	**-7.1**	**(-13.6, -0.6)**
+ precipitation (SD mm)[b]	13.6	14.2	1.4	(-3.0, 5.8)	18.3	32.0	3.9	(0.0, 7.9)	20.3	216.4	5.4	(-0.1, 11.0)
+ relative humidity (SD %)[b]	14.1	18.8	6.6	(-40.3, 53.6)	17.1	23.2	17.0	(-28.6, 62.5)	20.9	225.5	1.0	(-67.4, 69.5)
+ minimum visibility (km)	11.3	-4.9			11.4	-17.6			7.91	23.1		
<1.8 (Ref)												
1.8-3.9			3.6	(-7.3, 14.4)			6.2	(-3.5, 15.8)			7.5	(-2.7, 17.6)
3.9-7.0			10.4	(-0.4, 21.2)			-3.5	(-13.2, 6.1)			8.3	(-2.8, 19.3)
7.0-12.0			9.1	(-1.6, 19.7)			-3.1	(-12.6, 6.3)			1.6	(-9.0, 12.2)
≥12.0			2.2	(-9.1, 13.5)			-4.7	(-15.2, 5.9)			5.9	(-6.7, 18.4)
(b) Nighttime sleep duration, minutes/day												
Model												
+ temperature (°C)	16.1	-49.4			2.2	-60.8			6.7	-27.7		
-9.8 - 6.6 (Ref)												
6.7 - 10.3			-4.8	(-13.7, 4.2)			-1.3	(-9.7, 7.2)			-0.4	(-9.5, 8.7)
10.4 - 14.0			-12.5	(-25.4, 0.4)			-3.4	(-14.1, 7.3)			2.1	(-10.1, 14.3)
14.1 - 27			**-16.7**	**(-32.3, -1.0)**			-8.6	(-21.5, 4.4)			-5.4	(-22.1, 11.4)

Table 2.3.3 (continued). Seasonality in sedentary behavior and nighttime sleep duration after accounting for meteorological factors, The Rotterdam Study, The Netherlands, 2011-2016[a]

Meteorological factors	Middle-aged (50-64 years)				Young-elderly (65-74 years)				Old-elderly (≥75 years)			
		% SV change	Co.	95% CI		% SV change	Co.	95%CI	SV	% SV change	Co.	95% CI
+ wind speed (SD m/s)[b]	33.5**	5.6	1.1	(-2.4, 4.5)	2.5	-56.2	-0.7	(-4.1, 2.7)	17.7	90.1	-3.9	(-8.9, 1.1)
+ wind speed (SD m/s)[b]	33.5**	5.6	1.1	(-2.4, 4.5)	2.5	-56.2	-0.7	(-4.1, 2.7)	17.7	90.1	-3.9	(-8.9, 1.1)
+ sunlight (SD hrs)[b]	33.3**	5	-0.6	(-4.4, 3.2)	4.4	-23.5	-1.9	(-5.3, 1.6)	18.2	95.4	0.0	(-5.4, 5.5)
+ precipitation (SD mm)[b]	34.2**	7.6	0.2	(-3.4, 3.8)	2.5	-56	0.2	(-3.0, 3.5)	18.6	99.6	1.6	(-3.0, 6.3)
+ relative humidity (SD %)[b]	32.4**	2.1	1.8	(-2.0, 5.7)	5.5	-4.3	2.2	(-1.5, 6.0)	21	125.5	2.0	(-3.7, 7.7)
+ minimum visibility (km)	32.3**	1.8			5.3	-7.9			10	7.1		
<1.8 (Ref)												
1.8-3.9			-1.2	(-10.2, 7.8)			-1.8	(-9.6, 6.1)			-3.8	(-12.5, 4.8)
3.9-7.0			-5.4	(-14.3, 3.6)			0.0	(-7.8, 7.8)			-3.9	(-13.3, 5.5)
7.0-12.0			-4.4	(-13.2, 4.5)			-1.4	(-9.1, 6.3)			-1.6	(-10.6, 7.4)
≥12.0			0.5	(-8.8, 9.8)			-3.6	(-12.1, 5.0)			-6.9	(-17.6, 3.8)

CI = Confidence interval. Co. = Coefficient. SD = Standard deviation. SV = Seasonal variation. ** At least one significant cosinor term at 0.025 confidence level. * At least one significant cosinor term at 0.05 confidence level. [a] All estimates are adjusted for cosinor terms, sex, age, body mass index, prevalent comorbidities (cancer, cardiovascular disease, diabetes, and chronic obstructive pulmonary disease), smoking behavior, housing status, occupation, alcohol intake, disability index and day of the week. [b] Increment in activity levels (minutes/day) per increment of one standard deviation of meteorological factor: wind speed 2.17 m/s, wind chill: 2.06 m/s, sunlight hours: 3.97, precipitation: 4.6mm, relative humidity: 8.5%. Bold coefficients are statistically significant at 95% confidence level.

Second, the summer reduction in nighttime sleep duration among middle-aged adults suggests its seasonality is led by PA, which appears to replace sleep time in summer. Third, a small and non-statistically significant seasonality of SB was observed in our population (about 10minutes/day), which is in contrast with O'Connell et al., who reported a winter increment of SB of about 30 minutes/day.[10] This difference could be explained by the large proportion of the waking time our population spent in SB (around 77%), and because we classified the non-sleep time-at-bed as SB time. Taken together, our findings suggest that middle-aged and young-elderly participants replaced their nighttime sleep with more light PA and moderate-to-vigorous PA, and that SB is much more ingrained in the daily routine of the population.

We found a discrete influence of meteorological factors on the seasonality of activity levels. Klenk et al.,[34] similarly found a strong association of objectively measured daily walking time with several meteorological factors, but not with season, among elderly German participants.

Table 2.3.4. Variation of life expectancy along with seasonal variation of moderate-to-vigorous PA and SB, The Rotterdam Study, The Netherlands, 2011-2016

Age group [a,b]	Peak-to-nadir all-cause mortality risk ratio [c]		Peak	LE at the peak of the variation (years)	LE at the nadir of the variation (years)	Peak-to-nadir difference of LE[d] (months)
	SV	(95% CI)				
(a) Variation due to both moderate-to-vigorous PA and sedentary behavior combined						
Middle-aged	1.09	(0.99, 1.21)	23-Feb	16.6	17.2	-8.2
Young-elderly	1.11	(1.01, 1.21)	4-Feb	8.1	8.5	-4.5
Old-elderly	1.04	(0.95, 1.15)	13-Sep	2.6	2.7	-1.4
(b) Variation due to moderate-to-vigorous PA alone						
Middle-aged	1.08	(1.04, 1.13)	25-Jan	27.5	28.0	-6.3
Young-elderly	1.06	(1.02, 1.09)	27-Jan	16.1	16.4	-3.7
Old-elderly	1.02	(0.99, 1.06)	18-Sep	9.1	9.3	-2.4
(c) Variation due to sedentary behavior alone						
Middle-aged	1.04	(0.97, 1.12)	27-Apr	19.2	20.0	-9.0
Young-elderly	1.05	(0.98, 1.12)	13-Feb	18.7	19.3	-7.8
Old-elderly	1.02	(0.95, 1.10)	8-Sep	18.6	19.0	-5.3

CI: Confidence interval. LE: Life expectancy. PA: Physical activity. SV: Seasonal variation. Bold estimates are statistically significant at 95% confidence level. [a] Age groups are: middle-aged (40-64 years), young-elderly (65-75 years) and old-elderly (≥76 years). [b]For middle-aged and young-elderly, estimates are calculated at the middle of the range: 57 years and 69.5 years, respectively. For old-elderly, estimates are obtained at 79 years for analysis with moderate-to-vigorous PA component, and at 80 years for analysis with light-to-moderate PA component. [c] Represents the risk ratio of all-cause mortality at the peak of the seasonal variation, compared with its nadir. [d] Life expectancy for Dutch population at each age categories was 24.4, 13.8 and 7.1 years, respectively, using mortality rates from literature.[46]

The domain composition of activity levels could contribute to this finding. For example, while active transportation might be sensitive to meteorological factors, it represents a small proportion of the daily PA. In contrast, indoors occupational PA would be less sensitive to meteorological factors, but corresponds to a larger proportion of daily PA. Leisure PA could also be sensitive to meteorological conditions,[16] but people will remain sedentary if it is ingrained in their daily occupational routine,[35,36] irrespective of favorable weather. Therefore, although meteorological factors have a strong influence on daily activity levels, they may be less relevant than the domain composition of PA and SB to explain the seasonality in activity levels.

Previous evidence suggested that the seasonality of PA plays a role in the well-described seasonality of cardiovascular disease and mortality.[7,18,37] Our results suggest that the all-cause mortality risk will increase in winter among middle-aged and young-elderly adults, due the accumulation of low levels of moderate-to-vigorous PA and high levels of SB. Our results need to be interpreted cautiously, because this approach does not take into account physical fitness, as a measure of functional reserve.[38]

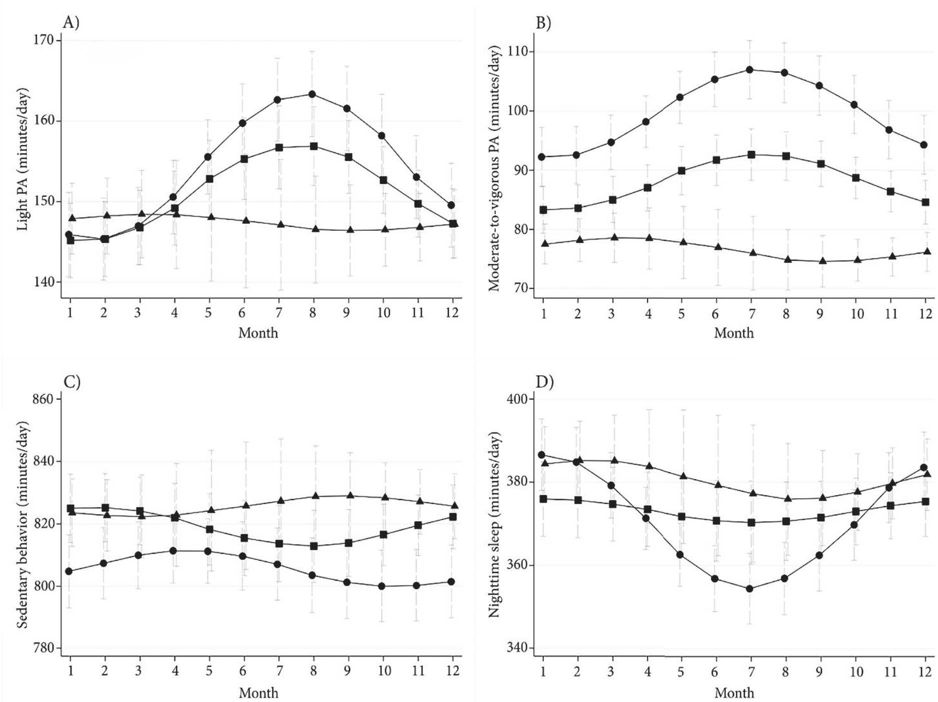


Figure 2.3.1 Seasonal pattern of activity levels according to age group

Monthly averages of A) light physical activity; B) moderate-to-vigorous physical activity; C) Sedentary behavior; D) Nighttime sleep behavior. PA: Physical activity. All estimates are adjusted for cosinor terms, sex, age, body mass index, prevalent comorbidities (cancer, cardiovascular disease, diabetes, chronic obstructive pulmonary disease), smoking behavior, housing status, occupation, alcohol intake, disability index and day of the week. Middle-aged participants (circles) included those aged 50-64 years, young-elderly participants (squares) included those aged 65-74 years and old-elderly (triangles) included adults aged ≥75 years.

We assumed a linear association of PA with all-cause mortality risk, although it is suggested that the association is steeper at lower than at higher PA levels.[32] Nevertheless, this analysis illustrates the potential seasonality of all-cause mortality risk as a function of the seasonal variation in activity levels. Consequently, these findings suggest that season and age should be taken into consideration when interventions are designed to improve activity levels both in clinical practice and in public health. For example, interventions can be designed to avoid people replacing active time with SB. Strategies may include promoting active transportation, by offering facilities to change wet clothes, fans and showers, encouraging people to wear lighter clothes during warm and humid days, and ensuring safe transportation during adverse climate conditions (e.g. snow and high wind speed). People can also be encouraged to exercise (e.g. yoga and strength training) and to undertake regular activities of daily living of light and moderate intensity, such as housework. These interventions could also contribute to interrupting long bouts of SB, since SB is also associated with several adverse health outcomes.[4-6,39]

There is an ongoing discussion regarding the potential of accelerometers and other wearable devices that measure activity levels within interventions aimed to promote PA and reduce SB. Based on our findings, wearable devices could provide feedback regarding the declining levels of PA in winter and could prompt people to interrupt long SB periods, even in real time. The high compliance with accelerometer use in our study showed the relative ease of evaluating activity in a middle-aged and elderly population, using a device with a minimal burden for the participant, as it is worn as a watch and participants did not have to remove it during the measurement week. This improves the precision of the measurements[40] and avoids the need for assumptions to be made about activity levels when the device is not being worn.[40,41] Nevertheless, there is controversy regarding the effectiveness of interventions based on wearable devices to change behavior,[42,43] partly because these changes appear not to be sustained in the longer term.[44] Additionally, it is yet to be examined whether there are differences in the effectiveness of interventions using standard feedback based on average individual data[42] and that of personalized feedback and targets. These issues are sensitive to an elderly population, for whom standard targets for moderate-to-high intensity PA may be less feasible than improving light PA[43] and reducing long SB periods; but also because barriers, either individual (e.g. lack of self-efficacy, frailty, or fear of falling) or environmental (e.g. meteorological conditions and built environment).[45] may hamper the effectiveness of such interventions. Therefore, improving PA and reducing SB through the use of wearable devices may be a promising strategy in clinical practice. Nevertheless, long-term clinical trials are required of interventions with user-friendly, precise, and low-cost devices,[42] with relevant, age-appropriate targets for PA and SB.

The main strength of our study is the objective round-the-clock measurement of activity levels in middle-aged and elderly adults, allowing us to evaluate the seasonality of 24-hour age-specific activity levels. Moreover, we improved the accuracy of SB and nighttime sleep measurements, because our participants were instructed not to remove the accelerometer during the measurement week and because we calculated non-sleep time-in-bed, which seemed to contribute to overall sedentary time. Second, to our knowledge, we are the first to examine the seasonality of the all-cause mortality risk and life expectancy, under the assumption that it will depend solely on levels of moderate-to-vigorous PA and SB. In these analyses, we used RR estimates obtained from comprehensive systematic reviews with meta-analysis,[31,32] thereby enhancing the representativeness of our modeling. Third, all our participants were resident in a single area, the Ommoord district, which reduces the variation in activity levels that can be attributed to other determinants, such as the built environment.

Nevertheless, we acknowledge several limitations. First, we could not test which domains of PA and SB might explain the seasonality. Furthermore, we had repeated sets of measurements of activity in only 48 participants and each participant contributed only one week of data in each wave. Given their uneven participation throughout the year, this might lead to under- or over-representation of certain traits at specific periods of the year. Therefore, some seasonal variation could be explained by residual confounding or selection bias. The lack of detailed information on the type of jobs participants engaged in and the lack of information on community-based seasonal activities (e.g. walking or cycling events) might also have contributed to residual confounding. Second, our all-cause mortality risk estimations are based on a modeled distribution of the all-cause mortality risk, and were assumed to be determined only by the seasonality of activity levels. Moreover, although we adjusted all our estimates by several covariates, the generalizability of our findings is limited to middle-aged and elderly adults with rather high BMI and a high prevalence of comorbidities. Third, we used the same cut-offs to define activity intensity in middle-aged, young-elderly and old-elderly adults, whereas it might be argued that a particular activity would be experienced as vigorous by old-elderly adults, but as moderate activity by middle-aged adults. Consequently, we might have some misclassification of activity. Finally, not all physical activities are captured by the device, as it depends on acceleration of the wrist to detect the movement. Therefore, we may have not captured activities performed mostly by the legs, such as cycling, which is a common mode of transport in the Netherlands.

Conclusions

In conclusion, middle-aged and young-elderly adults spent more time in light and moderate-to-vigorous PA in the summer than in the winter. In the summer, PA appears to replace nighttime sleep, especially among middle-aged adults. The small seasonal variation observed in SB may be explained by the large proportion of the day dedicated to SB, as this is a behavior strongly ingrained in the daily routine. Meteorological factors had a discrete impact on the seasonality of activity levels. However, on a daily basis, the meteorological factors had a strong association with PA and SB, especially among old-elderly individuals. The all-cause mortality risk would increase in winter due to the accumulation of low levels of PA and high levels of SB. The use of wearable devices may contribute to the design of interventions to improve PA and reduce SB, which are relevant targets within clinical practice to improve health. These interventions should be designed to attend to specific needs according to season and age. Since we observed the largest seasonality in levels of light PA, recommending the interruption of SB with light PA might be a good starting point for public health interventions.

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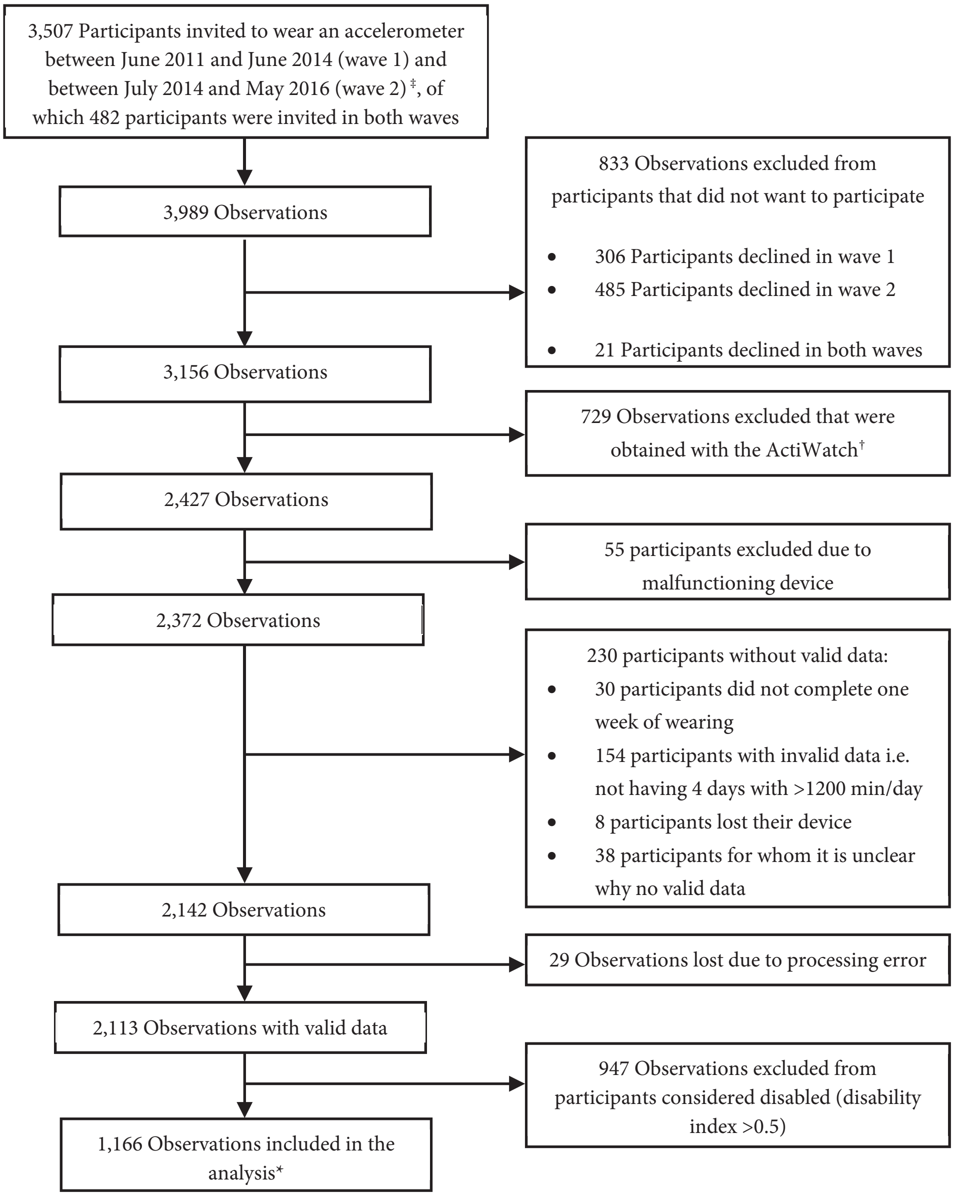
SUPPLEMENT CHAPTER 2.3

Supplement 2.3.1. Flow chart of participant inclusion for the Rotterdam Study



† The ActiWatch is a one-dimensional device and could not be used to measure physical activity.
* The 1,166 observations included 49 participants with two observations.
‡In wave 1, participants from the fifth follow-up visit of RS-I (RS-I-5), the third visit of RS-II (RS-II-3), and the second visit of RS-III (RS-III-2) were invited. In wave 2, participants from the sixth follow-up visit of RS-I (RS-I-6) and the fourth visit of RS-II (RS-II-4) were invited.

Supplement 2.3.2. Procedures for the modeling of the all-cause mortality risk and LE as function of moderate-to-vigorous PA and SB

To examine the potential health impact of the seasonality of moderate-to-vigorous PA and SB, we modeled the all-cause mortality risk using risk ratios (RR) and the estimates for the 95% confidence interval (95%CI) obtained from literature. For moderate-to-vigorous PA, we extracted the RR (95%CI) of 0.72 (0.65, 0.80) from a recently published systematic review with meta-analysis.[1] The RR expresses the all-cause mortality risk of those achieving an equivalent of 150 minutes of moderate-to-vigorous PA per week, compared to those not achieving this equivalent. We assumed the RR was equivalent to achieving 30 minute/day of moderate-to-vigorous PA,[2] to be able to use our daily data.

For SB, we used the RR (95%CI) of 1.24 (1.09, 1.41) reported in a recent review and meta-analysis.[3] It expresses the all-cause mortality risk of people with high SB levels compared to those with low SB. Because no specific cut-off was provided to define high SB, we used the median of the cut-offs indicated in the primary studies included in the review to define high versus low SB (8 hours/day).

Hypothetical all-cause mortality risk due to moderate-to-vigorous PA

For each participant, we modeled the all-cause mortality risk due to moderate-to-vigorous PA. To do so, we multiplied the time/day spent in moderate-to-vigorous PA with the natural log transformed risk ratio of the association of moderate-to-vigorous PA with all-cause mortality, estimated by Hupin et al.[1] (RR=0.72; log transformed = -0.33). Because the RR represents the association between accumulating 150 minutes/week of moderate-to-vigorous PA vs. less than 150 minutes/week, we did two assumptions: 1) that the RR would be equivalent if the person accumulated 30minutes/day of moderate-to-vigorous, 2) that the association is linear, and the RR represents the reduction of the risk when accumulating 150 minutes per day, and could increase or reduce linearly and proportionally to the levels of moderate-to-vigorous PA of the participants. To fulfill these assumptions, we first centered the moderate-to-vigorous variable at 30 minutes/day, by subtracting 30 and then, dividing the difference by 60, to express the difference in hours. To model the lower and upper boundary of the 95% confidence interval (95%CI), we used the lower and upper boundary of the 95%CI of the risk ratio (0.65 and 0.80).

Hypothetical all-cause mortality risk due to SB

For each participant, we modeled the all-cause mortality risk due to SB. To do so, we repeated the previous process but using the SB variable and the natural log transformed risk ratio of the association between SB and all-cause mortality, as estimated by Biswas et al[3] (RR=1.24; log transformed = 0.22). We modeled the 95%CI by using the lower and upper boundary of the 95%CI of the risk obtained risk ratio (1.09 and 1.41). The RR calculated by Biswas et al. represents the increment of the all-cause mortality risk at high levels of SB, compared to low. They meta-analyzed the RR at the levels of high SB as defined by every paper included in the meta-analysis, so the definition of high SB corresponds to a range of categories between >=4hours/day to >=11 hours/day. We defined high SB at the median of the cut-offs of the studies included in the meta-analysis, at 8 hours/day. Therefore, for the calculation of the daily individual mortality risk due to SB, the time was centered at 8 hours/day.

Hypothetical all-cause mortality risk due to PA and SB

The newly generated variables of the modeled all-cause mortality risk per participant and day recorded are summed up between them.

Example: The average middle-aged participant of the study had 99minutes/day of moderate-to-vigorous PA and 805minutes/day of SB. The centered time of moderate-to-vigorous PA would be calculated as (99-30)/60=1.15, and for SB would be (805-480)/60=5.4. Therefore, the all-cause mortality risk due to moderate-to-vigorous PA would be ln(0.72)*1.15=-0.38, and for SB would be ln(1.24)*5.4=1.16. Therefore, the overall all-cause mortality risk would be (-0.38)+1.16=0.78. This procedure was performed for each participant for each day contributed per participant. Also, the procedure was calculated using the lower and upper boundaries of the 95% confidence intervals of the RR for both moderate-to-vigorous PA and SB, for sensitivity analyses.

Seasonality of the hypothetical all-cause mortality risk

The seasonality of the modeled overall (PA and SB) all-cause mortality risk was calculated using the standard cosinor analysis. The seasonal variation (peak-to-nadir difference of the risk) was estimated in this analysis. The difference between the modeled risk at the peak and at the nadir represents the seasonal variation of the modeled all-cause mortality risk. Because the difference is expressed in log units, the exponential of this difference represents the quotient between the risk at the peak and at the nadir of the variation, it means, the risk ratio for the modeled mortality risk. Therefore, a RR higher than one can be interpreted as the number of times the modeled all-cause mortality risk ratio increases at the peak compared to the nadir of the variation. Because the PA seasonal patterns were different for each age group, the seasonality of the modeled all-cause mortality risk was calculated stratified according to age group, the same way the seasonality of the activity levels was calculated.

Seasonality of the life expectancy as a consequence of the hypothetical all-cause mortality risk

To calculate how the variation of the modeled all-cause mortality risk would impact the life expectancy (LE), we created a hypothetical baseline scenario, using the age-specific mortality rates in the Dutch population in 2015, obtained from the Global Burden of Disease (GBD) data. Using these mortality rates, a standard life table was constructed.

Then, to calculate how would be the LE at the peak of the seasonality of the hypothetical mortality risk, we multiplied the mortality rate of each group by the exponential of the sum of the predicted all-cause mortality risk of each age group plus the amplitude of the seasonal variation [mortality rate (expressed in deaths/100,000) * exp(average adjusted all-cause mortality risk+amplitude of the seasonality of all-cause mortality risk)]. The average adjusted all-cause mortality risk was obtained with the Stata postestimation command margins after fitting the cosinor model of the all-cause mortality risk. The amplitude corresponds to the seasonal variation divided by two. The updated mortality rates at the peak of the seasonality of the all-cause mortality risk provided the LE at the peak of the seasonal pattern.

To calculate how would be the LE at the nadir of the seasonality of the hypothetical mortality rsik, we multiplied the mortality rate of each group by the exponential of the difference between the predicted all-cause mortality risk of each age group (same as defined above) and the amplitude of the seasonal variation (same as defined above) [mortality rate (expressed in deaths/100,000) * exp(average adjusted all-cause mortality risk - amplitude of the seasonality of all-cause mortality risk)]. The updated mortality rates were used to calculate the LE at the nadir of the seasonal pattern.

Finally, the difference in months of the LE was calculated as the difference between the peak and the nadir of the seasonal variation of the all-cause mortality risk.

Supplement 2.3.3. Seasonal variation of activity levels (minutes/day) according to age group and sex

Activity level	Middle-aged (50-64 years, n=394)					Young-elderly (65-74 years, n=447)					Old-elderly (≥75 years, n=321)				
Strata	SV	SE	Peak	Ps.	No. days	SV	SE	Peak	Ps.	No. days	SV	SE	Peak	Ps.	No. days
Light, minutes/day															
All	18.1	4**	09-aug	394	2,171	12.8	3.9**	04-aug	447	2,541	1.9	5.6	17-Mar	318	1,818
Men	19.6	5.3**	01-aug	203	1,131	19.9	5.2**	21-aug	254	1,454	7.6	7.5	17-dec	188	1,076
Women	18.6	6**	16-aug	191	1,040	9.5	6	05-jul	193	1,087	11.4	8.3	17-jun	130	742
Moderate-to-vigorous, minutes/day															
All	14.8	3.8**	26-jul	394	2,171	9.9	3.3**	27-jul	447	2,541	3.9	4.3	19-Mar	318	1,818
Men	15	5.2**	20-jul	203	1,131	12	4.4*	10-aug	254	1,454	8	5.7	09-jan	188	1,076
Women	16.3	5.7*	07-aug	191	1,040	9	5	10-jul	193	1,087	12.5	6.6	08-jun	130	742
Sedentary awake, minutes/day															
All	11.9	9.1	27-apr	394	2,171	13.9	9.3	13-feb	447	2,539	6.4	13.7	08-sep	318	1,818
Men	23.9	12.4	30-jun	203	1,131	31.2	12.3*	21-feb	254	1,454	29.2	18	10-aug	188	1,076
Women	21.7	13.3	5-Mar	191	1,040	10.6	14.4	6-Oct	193	1,085	38.8	20.8	17-jan	130	742
Nighttime sleep duration, minutes/day															
All	31.8	6.6**	17-jan	394	2,171	5.7	7.6	17-jan	447	2,539	9.3	11.4	26-feb	318	1,818
Men	51.7	8.3**	17-jan	203	1,131	2.7	10.4	13-May	254	1,454	22.4	14.7	11-Mar	188	1,076
Women	17.7	10.3	25-jan	191	1,040	15.2	11.5	31-jan	193	1,085	6.8	17.9	09-sep	130	742
Time-in-bed, minutes/day															
All	27.5	6.7**	13-jan	394	2,171	4.4	7.3	30-nov	447	2,539	12.3	11	21-apr	318	1,818
Men	45.2	8.4**	18-jan	203	1,131	2.6	9.2	19-nov	254	1,454	24	14*	16-apr	188	1,076
Women	17.3	10.4	08-jan	191	1,040	7.1	12.4	10-feb	193	1,085	5.2	18.1	19-jun	130	742
Sleep efficiency (%)															
All	1.9	0.8*	17-jan	394	2,171	0.8	0.9	28-feb	447	2,537	2.5	1.4	19-dec	318	1,814
Men	3.4	1.1**	11-jan	203	1,131	1.2	1.4	31-May	254	1,454	3.5	2	07-jan	188	1,072
Women	0.8	1.1	24-Mar	191	1,040	2.3	1.1	19-jan	193	1,083	2.1	1.6	17-Oct	130	742

No .: Number. Ps.: Participants. SE: Standard error. SV: Seasonal variation ** At least one significant cosinor term at 0.025 confidence level. * At least one significant cosinor term at 0.05 confidence level. Seasonal variation adjusted for cosinor terms, sex, age, body mass index, prevalent comorbidities (cancer, cardiovascular disease, diabetes, chronic obstructive pulmonary disease), smoking behavior, housing status, occupation, alcohol intake, disability index and day of the week.

Supplement 2.3.4. Potential seasonality of all-cause mortality risk as a function of moderate-to-vigorous PA and SB, sensitivity analyses

Age group [a,b]	Peak-to-nadir all-cause mortality risk ratio [c]		Peak	LE at the peak of the variation (years)	LE at the nadir of the variation (years)	Peak-to-nadir difference of LE[d] (months)
	SV	(95% CI)				
Sensitivity analysis 1: Lower 95%CI boundary of all-cause mortality risk estimates						
(a) Variation due to both moderate-to-vigorous PA and sedentary behavior combined						
Middle-aged	**1.11**	**(1.03, 1.20)**	04-feb	23.3	24.1	-8.6
Young-elderly	**1.09**	**(1.03, 1.17)**	31-jan	12.6	13	-4.9
Old-elderly	1.04	(0.97, 1.11)	15-sep	6.0	6.2	-2.6
(b) Variation due to moderate-to-vigorous PA alone						
Middle-aged	**1.11**	**(1.05, 1.18)**	25-jan	28.5	29.2	-8.2
Young-elderly	**1.07**	**(1.02, 1.12)**	27-jan	16.9	17.3	-5.0
Old-elderly	1.03	(0.98, 1.08)	18-sep	9.8	10.1	-3.4
(c) Variation due to sedentary behavior alone						
Middle-aged	1.02	(0.99, 1.05)	27-apr	39.6	40.2	-6.4
Young-elderly	1.02	(0.99, 1.05)	13-feb	39.4	39.8	-5.6
Old-elderly	1.01	(0.98, 1.04)	08-sep	39.3	39.7	-4.4
Sensitivity analysis 2: Upper 95%CI boundary of all-cause mortality risk estimates						
(a) Variation due to both moderate-to-vigorous PA and sedentary behavior combined						
Middle-aged	1.09	(0.96, 1.24)	18-Mar	10.6	11.2	-7.3
Young-elderly	1.12	(1.00, 1.26)	08-feb	5.1	5.5	-4.3
Old-elderly	1.05	(0.92, 1.20)	11-sep	1.1	1.2	-0.7
(b) Variation due to moderate-to-vigorous PA alone						
Middle-aged	**1.06**	**(1.03, 1.09)**	25-jan	26.5	26.8	-4.3
Young-elderly	**1.04**	**(1.01, 1.06)**	27-jan	15.3	15.5	-2.4
Old-elderly	1.01	(0.99, 1.04)	18-sep	8.4	8.5	-1.5
(c) Variation due to sedentary behavior alone						
Middle-aged	1.07	(0.96, 1.19)	27-apr	9.6	10.2	-7.8
Young-elderly	1.08	(0.98, 1.20)	13-feb	8.9	9.5	-7.3
Old-elderly	1.04	(0.92, 1.17)	08-sep	8.8	9.1	-4.0

CI: Confidence interval. LE: Life expectancy. SV: Seasonal variation. Bold estimates are statistically significant. [1] Age groups are: middle-aged (40-64 years), young-elderly (65-75 years) and old-elderly (>=76 years). [2]For middle-aged and young-elderly, estimates are calculated at the middle of the range: 57 years and 69.5 years, respectively. For old-elderly, estimates are obtained at 79 years for analysis with moderate-to-vigorous PA component, and at 80 years for analysis with light-to-moderate PA component. [3]Represents the risk ratio of all-cause mortality at the peak of the seasonal variation, compared with its nadir. [4] Life expectancy for Dutch population at each age categories was 24.4, 13.8 and 7.1 years, respectively, using mortality rates from.[4]

SUPPLEMENTARY REFERENCES

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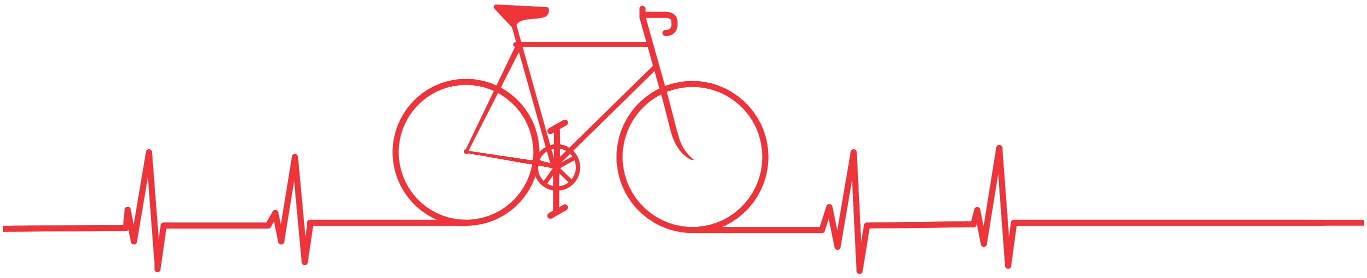
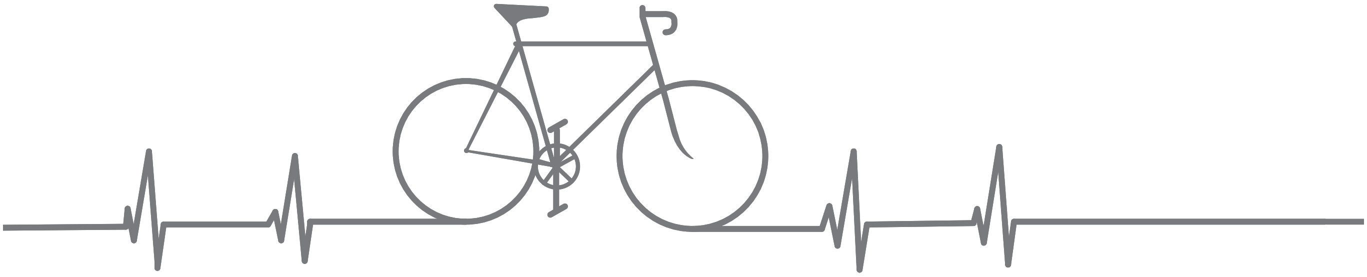


Chapter 3

Activity and mortality



Chapter 3.1

Physical activity and cause-specific mortality

Manuscript based on this chapter:

Koolhaas CM, Dhana K, Schoufour JD, Lahousse L, van Rooij FJA, Ikram MA, Brusselle G, Tiemeier H, Franco OH. Physical activity and cause-specific mortality: The Rotterdam Study. *Submitted for publication.*

ABSTRACT

Background: Physical activity (PA) is associated with lower risk for all-cause mortality. However, in elderly people, it remains unknown which types of PA are associated with mortality and whether the association between PA and mortality differs by cause of death.

Methods: We assessed the association of total PA, walking, cycling, domestic work, sports and gardening with all-cause mortality and the association of total PA with cause-specific mortality using Cox proportional hazard models among 7,225 older adults (mean age: 70 years) from the prospective population-based Rotterdam Study. Deaths were classified as due to cardiovascular diseases (CVDs), cancer, infections, external causes, dementia, chronic lung diseases or other causes. Activities were categorized into tertiles (lowest tertile as reference). To account for the possibility of reverse causation, we excluded the first 5 and 10 years of follow-up.

Results: Over a median of 13.1 years of follow-up (interquartile range: 8.4-14.6 years), 3,261 participants died. The hazard ratios (HRs) and 95% confidence intervals (95%CIs) associated with high total PA compared to low were 0.69 (0.63, 0.75), 0.69 (0.58, 0.81), 0.44 (0.27, 0.71), 0.47 (0.32, 0.71) and 0.56 (0.46, 0.69) for mortality from all-causes, CVDs, chronic lung diseases, infections and other causes, respectively. With longer exclusion times, the strength of these associations was attenuated. All PA types were associated with lower all-cause mortality risk.

Conclusion: Engagement in higher PA levels was associated with lower risk of mortality from CVDs, chronic lung diseases, infections and other causes. Participating in any PA might reduce mortality risk in older adults.

INTRODUCTION

Being physically active at moderate intensity at the recommended level of 150 to 300 minutes/week[1] can reduce the all-cause mortality risk by up to 26%.[2,3] However, most studies have focused on the effect of overall physical activity (PA). Thus, it remains unclear which specific PA types relate to mortality.[4-7] Differences in frequency, intensity, duration and context in which one is engaged in specific PA types[8,9] might lead to different associations with mortality. For older people who are unable to engage in recreational or leisure time PA, information on the health effects of other PA types could help public health institutes create recommendations specially targeted at older adults.

Recently, one study investigated the association between different PA domains and mortality among adults (16-92 years) and found a beneficial association of leisure time PA with all-cause mortality, but not with work-related PA or commuting.[7] In two other studies, cycling to work [4] and walking or cycling for transportation[6] were associated with a lower all-cause mortality risk. The described studies were performed mostly in middle-aged adults and less is known about what kind of activities are beneficially associated with mortality in an elderly population. This is important since PA levels tend to decrease with age and PA types in which older adults engage differ markedly from the activities performed by younger and middle-aged adults.[10] Additionally, information is lacking on whether PA is associated with specific causes of death, including mortality related to dementia and chronic lung diseases.[11-13]

We examined the association of PA with all-cause and cause-specific mortality in a middle-aged and elderly population. Furthermore, we assessed independent associations of walking, cycling, sports, domestic work and gardening with all-cause mortality.

METHODS

Study population

This study was embedded in the Rotterdam Study (RS), a prospective population-based cohort, among subjects aged 55 years or older in the municipality of Rotterdam, the Netherlands. The aim of the study was to examine the incidence of risk factors for neurological, cardiovascular, psychiatric and other chronic diseases. Details of the study have been published previously.[14] Between 1997 and 2001, 7,808 participants were invited for the research examinations, of which 7310 participants completed a PA questionnaire (Figure 3.1.1). Subsequently, 52 subjects were excluded due to not provided or withdrawn informed consent for follow-up data collection, and 33 participants were excluded due to unreliable PA data. Finally, 7,225 subjects were included in the analyses. To collect baseline information, trained research assistants interviewed the participants at home.

All subjects gave written informed consent, and the study was approved by the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center and by the review board of The Netherlands Ministry of Health, Welfare and Sports.

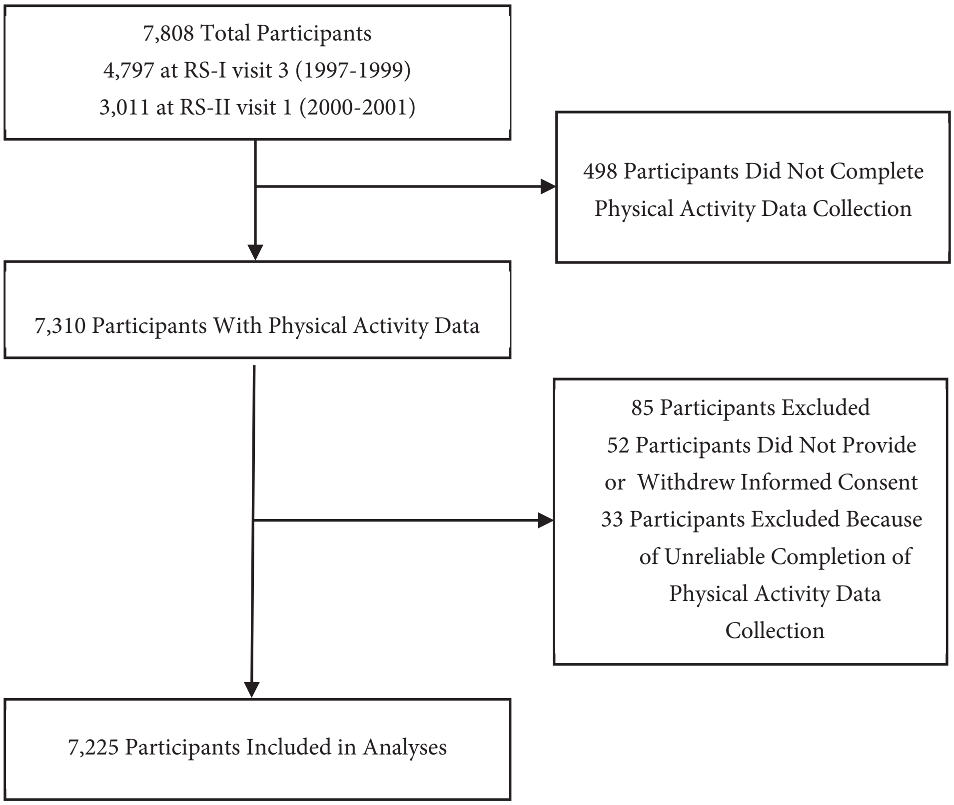


Figure 3.1.1. Flowchart of participant inclusion for the Rotterdam Study (RS), 1997–2012.
RS-I, original cohort; RS-II, extended cohort.

Physical activity assessment

PA levels were assessed at baseline with an adapted version of the Zutphen Physical Activity Questionnaire.[15] This questionnaire has been validated with a test-retest reliability of 0.93. The correlation with doubly labelled water, the golden standard for measuring PA, was 0.61.[16] The original Zutphen questionnaire contains questions on walking, cycling, sports, gardening and hobbies. In the current, study questions on housekeeping activities were added to attain a more complete assessment of PA levels. Detailed information on the collection of PA data has been described previously.[17]

To quantify activity intensity, we used metabolic equivalent of task (MET). We assigned MET-values to all activities mentioned in the questionnaire.[18] Sports that were not in this compendium and to which no MET-value could be assigned (e.g. underwater hockey, roller skiing) were not used in the analyses (n=33; 2.8%).

Finally, we multiplied MET-values of specific activities with time (in hours) per week spent in that activity to calculate MET·hours·week^{-1} in total PA and in every PA type (cycling, walking, sports, domestic work, gardening).

Assessment of covariates

Information on covariates was collected through home interviews or was measured at the study centre visit as described previously.[19,20] Alcohol use was defined as the amount of glasses per day and used as a continuous variable. We assessed marital status as a dichotomous variable describing whether the participant lived alone or not. Education was divided in primary, junior vocational/academic education and higher vocational/academic education. Smoking was divided into three categories: current, former and never. Body mass index (BMI) was calculated using measured height and weight (kg/m^2) and used continuously. Presence of diabetes was determined using medical records and used as binary variable (present/not present). Concentration of serum total cholesterol and high-density lipoprotein cholesterol was determined using an automated enzymatic procedure (Boehringer Mannheid System, Mannheim, Germany), expressed in mmol/L and used as a continuous variable. Two seated blood pressure measurements were obtained at the right brachial artery using a random zero sphygmomanometer and the mean of two consecutive measurements expressed in mmHg was used in analyses as a continuous variable. Activities of daily living (ADL) were measured with the Stanford Health Assessment Questionnaire and used to indicate general health.[21] In accordance with literature, we used a score ≥ 0.5 to define participants as disabled.[22,23] Dietary information was not collected at the same time as PA data collection. Therefore we used diet information measured in the first wave (1989-1993) of the original cohort (RS-I) and in the third wave (2011-2012) of the extended cohort (RS-II). Information on diet was obtained through a 170-item validated semi quantitative food frequency questionnaire.[24] From the questionnaire an overall healthy diet score representing adherence to the Dutch dietary guidelines was calculated, as described previously,[25] which was used as a continuous variable. Medication use was assessed during the home interview, and use of blood pressure lowering medication was used as a binary variable (yes/no).

A history of cardiovascular disease was defined as a history of myocardial infraction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, heart failure or stroke before the date of inclusion, as previously described.[26] Information on cancer prevalence was obtained through the general practitioners and by linkage with a nationwide registry of histo- and cytopathology in the Netherlands (PALGA). Prevalence of chronic obstructive pulmonary disease (COPD) was based on an obstructive spirometry ([forced expiratory volume in 1 second]/[forced vital capacity] < 0.7, assessed by prebronchodilator) during the visit at the research center or on information collected continuously from medical records of general practitioners and lung physicians.[27,28]

Assessment of cause-specific mortality

General practitioners report events of interest by means of a computerized system or notify new events annually. Trained research assistants subsequently collected information from medical records at the general practitioners' offices, hospitals and nursing homes. Two research physicians independently coded the events according to the International Classification of Diseases, Tenth Revision (ICD-10). Thereafter, a senior physician reviewed all coded events. Information on vital status of the participants was obtained from the clinical follow-up data collection described above and from municipal records. Coded information on cause-specific mortality was available until January 1st, 2014.

Cause-specific mortality was recoded according to the ICD-10 codes. We categorized the events as deaths due to cardiovascular diseases (CVDs), cancer, external causes, dementia, infections, chronic lung diseases and other causes[29] The ICD-10 codes associated with each of the 7 causes of death were I05-I30.0, I31, I32, I32.8, I34-I37, I42-I79, I81-I99, G95.1, F01 for cardiovascular diseases (cardio- and cerebrovascular diseases); codes C00-D09.9 for cancer; codes J21.9, J39.9, J40, J42-J84.9, J90-J96 for chronic lung diseases (COPD comprised 56% of this group); codes F00, F02, F03, F05.1, G30 for dementia (81.1% Alzheimer's disease); codes S00-T98 except T82.7, V03.1, V13, W10, W17, W19, X10, X59-X61, X67, X69, X70, X80, X83, X84 for external causes (64.1% fatal fractures); and codes A00-B99, G00-G09, I30.1, I32.0, I32.1, I33.0, J15-J18, J85–86, J41, K35-K38, K57.0, K75.0, I38-I41, I80, M00.9, M86, N71, T82.7 for infectious diseases (pneumonia comprised 63.6% of this group). Other causes (a heterogeneous group including mainly unspecified, unattended and sudden death, as well as a minority of nontumoral renal, gastrointestinal, hematological, and cerebral diseases, cachexia and senility) included codes D10-D48.9, E00-E90, D50-D89.9, G10-G26, G31, G35, G40.3, G41.9, G61, G62.9, G70, G83.9, G91.9, I33, K22-K34, K40-K52, K55-K57, K63.1, K64, K70, K72-K74, K80, K83, K86.1, K92, L12, L51.1, L71, L88 L89, M05, M06, M31, M34, M35, N03, N04, N10, N17-N19, N28, N30, N39.1, R54, R57.9, R64, R96, R98, R99, T99, Y83.

Statistical analysis

Due to non-normal distributions, total PA, walking and domestic work were categorized into three equal sized groups (i.e. tertiles). Since cycling, gardening and sports were not practiced by more than 60% of the population, the reference category for PA levels was no participation and the remaining two categories were divided by using the median.[8] Consequently, the categories of total PA, walking and domestic work were coded as low, medium and high and the categories of cycling, gardening and sports were coded as never, medium and high.

We investigated the associations of total PA and every PA type with all-cause mortality and the association of total PA with cause-specific mortality with Cox proportional hazard analysis, after confirming that the assumption for proportional hazards was met on the basis of Schoenfeld residuals. We adjusted our models for age, sex, smoking, alcohol consumption, education, diet quality (Dutch healthy diet index), marital status and prevalent diseases (i.e. diabetes, CVDs, cancer and chronic obstructive pulmonary disease (COPD)). In the analyses between PA types and all-cause mortality, we additionally adjusted for the other PA types, operationalized as [MET·hours·week^{-1} in total PA] minus [MET·hours·week^{-1} from PA type under investigation]. The decision to include confounders in the multivariable regression models was based on previous literature or a >10%-change of the effect estimate in the crude model.[4,5] PA variables were entered as categorical variables (lowest tertile/no participation as reference) in the separate models. Additionally, we analyzed total PA continuously per 50 MET·hours·week^{-1} increase. The underlying time-scale in all models was follow-up time, defined as the time between PA assessment and death, loss to follow-up or censoring at January 1, 2014.

In sensitivity analyses, to examine the effect of body mass index (BMI) and other biological covariates, we repeated all our analyses in a model adjusted for BMI (model 2a) and a model additionally adjusted for total and high-density (HDL) lipoprotein cholesterol, glucose, systolic blood pressure (SBP) and anti-hypertensive medication (model 2b). We also performed sensitivity analyses with stratified models by age (below/above 65 years) and sex, including descriptive analyses comparing men and women. We investigated the possible effect of reverse causation, by excluding the first five and ten years of follow-up. We also excluded adults with prevalent CVDs, COPD, cancer or diabetes at baseline to examine the possibility that the results would be driven by adults in worse health. Moreover, 11,5% (n=828) was employed at baseline, but we did not collect information on occupational PA. Therefore, we repeated our analyses in participants not in the active labor force. Finally, we examined the association between PA and mortality from the 5 most frequently occurring cancers in the current study: lung cancer, colon cancer, pancreas cancer, breast cancer and prostate cancer.

Data was missing for diet quality (27.0%), HDL cholesterol (14.3%), total cholesterol (13.3%), glucose (13.3%), BMI (10.7%), SBP (10.3%) and diabetes (9.5%). Other covariates had <5% missing data. We imputed missing data using Markov Chain Monte Carlo multiple imputation (n=5 imputations). All analyses were conducted using SPSS software version 20 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp) and R (3.0.1).

RESULTS

Baseline characteristics of the study population are shown in Table 3.1.1 and the proportion of participants who engaged in the different PA types is shown in Supplement 3.1.1. During 15 years of follow-up (median: 13.1 years, interquartile range: 8.4-14.6 years), 3261 participants died. The number of participants and the number of events in each group of every PA type are presented in Supplement 3.1.2 A description and frequency of each cause of death in the total population are presented in Table 3.1.2.

All-cause mortality

In the categorical analysis, high compared to low total PA was associated with a 31% lower risk of all-cause mortality (95%CI:I 0.63, 0.75) (Figure 3.1.2). Additionally, all PA types were associated with a reduction in all-cause mortality (Table 3.1.3). Each 50 MET·hours·week^{-1} increment of total

PA, equivalent to an average 105 minutes/day of PA of 4 METs, was associated with a 19% lower mortality risk (95%CI: 0.78, 0.85) (Figure 3.1.2).

Table 3.1.1. Baseline participant characteristics by tertile of total physical activity

	Tertiles of total PA		
	Low	Medium	High
Total PA, MET·hours·week^{-1}, median (range)	38.5 (<57.6)	74.3 (57.6-94.0)	123.1 (≥94.0)
Participants, no (%)	2,401 (33.0)	2,421 (34.0)	2,403 (33.0)
Female, no (%)	1,045 (43.5)	1,506 (62.2)	1,643 (68.4)
Age, years	72.7 (9.8)	69.5 (7.9)	68.0 (7.2)
Educational level, no (%)			
Primary education	387 (16.1)	328 (13.5)	356 (14.8)
Lower education	901 (37.5)	1,109 (45.8)	1,118 (46.5)
Intermediate education	738 (30.7)	690 (28.5)	690 (28.7)
Higher education	375 (15.6)	294 (12.1)	239 (9.9)
Living with partner, no (%)	1,409 (58.7)	1,525 (63)	1,590 (66.2)
Employed, no (%)	399 (16.6)	252 (10.4)	177 (7.4)
Smoking, no (%)			
Never	991 (41.3)	1,150 (47.5)	1,137 (47.3)
Former	1,048 (43.6)	983 (40.6)	968 (40.3)
Current	362 (15.1)	288 (11.9)	298 (12.4)
Dutch healthy diet index	47.0 (10.6)	48.9 (11.2)	49.3 (11.1)
Alcohol, glasses/day	1.1 (1.5)	1.0 (1.5)	1.0 (1.3)
BMI, kg/m^2	27.3 (4.1)	27.2 (4.1)	26.8 (3.8)
Disabled, no (%)	1,167 (48.6)	778 (32.1)	572 (23.8)
Diabetes, no. (%)	482 (20.1)	365 (15.1)	377 (15.7)
Prevalent cancer, no (%)	290 (12.1)	261 (10.8)	213 (8.9)
Prevalent CVD, no (%)	561 (23.4)	308 (12.7)	252 (10.5)
Prevalent COPD, no (%)	225 (9.4)	173 (7.1)	130 (5.4)
Walking, MET·hours·week^{-1}	12.3 (9.2)	22.9 (13.6)	46.9 (29.7)
Cycling, MET·hours·week^{-1}	2.6 (5.3)	7.7 (10.0)	15.1 (17.3)
Domestic work, MET·hours·week^{-1}	17.9 (12.4)	36.9 (16.6)	52.3 (24.9)
Gardening, MET·hours·week^{-1}	1.4 (3.6)	3.2 (7.0)	6.6 (13.3)
Sports, MET·hours·week^{-1}	2.0 (5.1)	4.2 (8.5)	9.9 (18.1)
Systolic blood pressure, mmHg	145.6 (21.6)	144.1 (22.1)	142.0 (21.1)
Cholesterol, mmol/L	5.7 (1.0)	5.8 (0.9)	5.9 (1.0)
HDL-cholesterol, mmol/L	1.3 (0.4)	1.4 (0.4)	1.4 (0.4)
Glucose, mmol/L	6.2 (1.7)	6.0 (1.6)	5.8 (1.2)

Data are presented as mean (SD), unless otherwise stated.

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; MET, metabolic equivalent of task; no, number; PA, physical activity.

Table 3.1.2. Description and frequencies of cause-specific mortality for participants in the rotterdam study

Cause	Description	Number (%) of deaths
CVD	Cardio- and cerebrovascular pathology	981 (30.1)
Cancer	All cancer-related mortality	843 (25.9)
Chronic lung disease	COPD, respiratory failure	124 (3.8)
Dementia	Dementia as final cause of death	339 (10.4)
Other causes	Unspecified, unattended and sudden death, nontumoral renal, gastrointestinal, hematological, and cerebral diseases, cachexia and senility	662 (20.3)
Infectious	All infection-related mortality	187 (5.7)
External causes	Fractures, accidents and suicides	117 (3.6)
Missing	Cases without ICD-10 codes	8 (0.2)

Abbreviation: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; ICD-10, International Classification of Diseases, Tenth Revision

Table 3.1.3. Association of physical activity types with all-cause mortality

	Walking	Cycling	Domestic work	Gardening	Sports
Tertile of activity	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Low*	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
Medium	0.82 (0.75, 0.89)	0.72 (0.66, 0.79)	0.86 (0.79, 0.94)	0.75 (0.68, 0.83)	0.84 (0.76, 0.93)
High	0.89 (0.81, 0.97)	0.65 (0.58, 0.72)	0.77 (0.70, 0.86)	0.86 (0.77, 0.96)	0.81 (0.73, 0.91)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazards ratio; ref, referent

The models were adjusted for age, sex, smoking, alcohol consumption, education, marital status, diet quality, prevalent CVD, prevalent cancer, prevalent diabetes, chronic obstructive pulmonary disease and the other physical activity types.

* For cycling, gardening and sports, the low category refers to not doing that particular activity.

Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 24, 60 and 141 minutes per day of walking.

Average domestic work is equivalent to 3.5 METs.[18] The median levels of domestic work across categories are therefore equivalent to 28, 83 and 142 minutes per day of domestic work.

Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 51 minutes per day of cycling.

Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 30 minutes per day of gardening.

Average sports is equivalent to 5.5 METs. The median levels of sports across categories are therefore equivalent to 0, 8 and 30 minutes per day of sports.

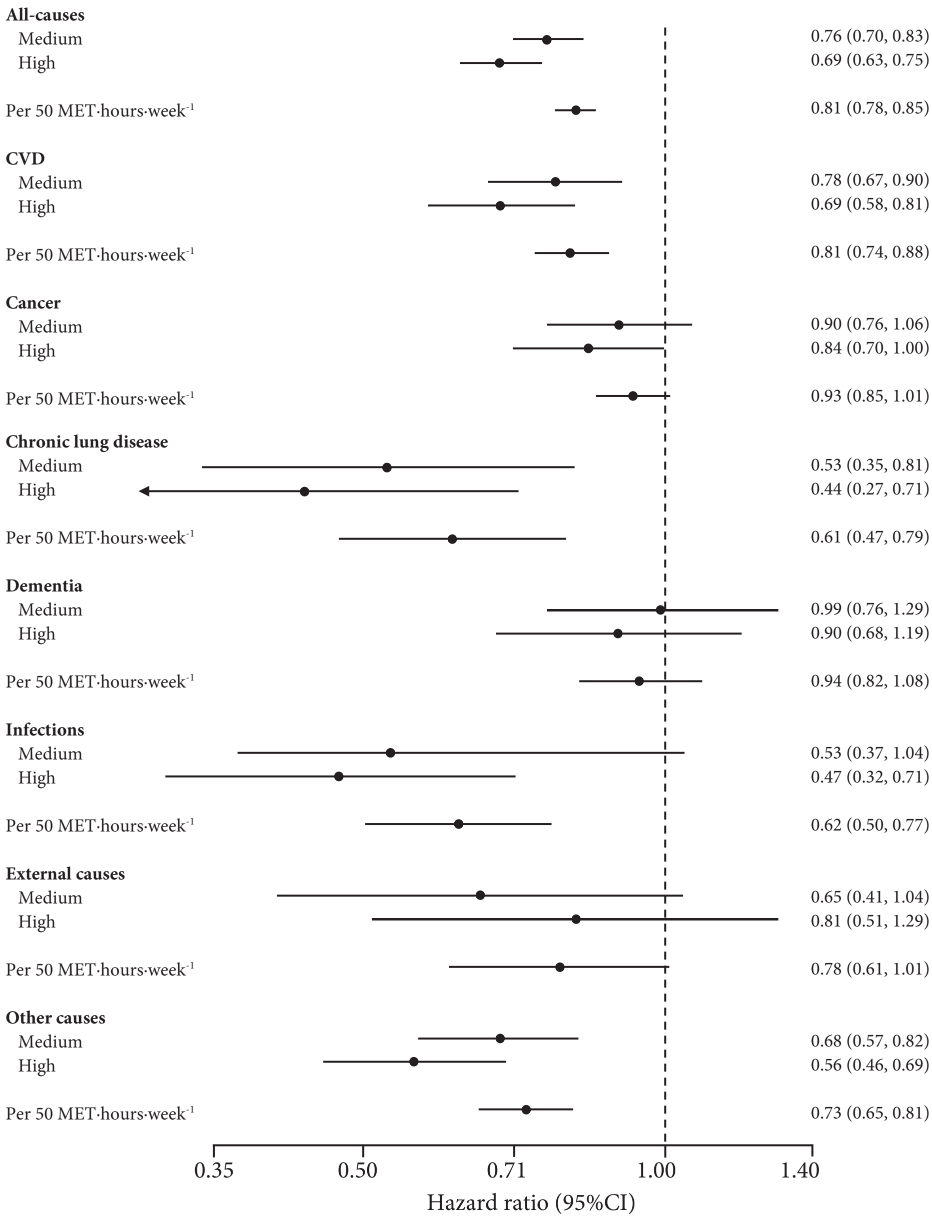


Figure 3.1.2. Association of total physical activity with overall and cause-specific mortality among participants in the Rotterdam Study, 1997–2014.

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

For every medium and high group, the reference is the low category.

The models were adjusted for age, sex, smoking, alcohol consumption, education, prevalent cardiovascular disease, prevalent cancer, prevalent diabetes and prevalent chronic obstructive pulmonary disease.

Total physical activity is composed of all physical activity types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 1.4, 2.7 and 4.4 hours per day of moderate physical activity equivalent of 4 METs.

Cause-specific mortality

Higher levels of total PA were associated with lower risk of mortality from CVDs, chronic lung diseases, infections and death from other causes. Each 50 MET·hours·week^{-1} more of total PA was associated with up to 39% lower risk of mortality from CVDs, chronic lung diseases, other causes and infections (Figure 3.1.2).

Sensitivity analyses

Supplement 3.1.3 and Supplement 3.1.4 show the results from all sensitivity analyses of PA types with all-cause mortality and total PA with cause-specific mortality, respectively. Additional adjustment for BMI in model 2a and for other biological risk factors in model 2b slightly attenuated the associations. In the descriptive analyses stratified by sex, we observed that the mean level of total PA was higher in women than in men, and that domestic work was on average higher in women (46.2 (SD: 21.3) MET·hours·week^{-1}) compared to men (21.2 (SD: 17.7) MET·hours·week^{-1}) (Supplement 3.1.5). The association between domestic work and all-cause mortality seems to be driven by women. After excluding the first 5 years of follow-up our results did not materially change. After excluding the first 10 years, the associations were attenuated. Noteworthy, we observed a reduction in the strength of the association between total PA and cause-specific mortality with longer exclusion times (Supplement 3.1.6). The association in participants without prevalent chronic disease were similar to the main results. Excluding participants in active labor force did not materially change the effect estimates. In our sensitivity analysis stratified by age, we observed that the associations were stronger in adults aged >65 years. The analyses in cancer-specific mortality did not show any associations (Supplement 3.1.7).

DISCUSSION

In this population-based study of older adults aged 55 and over, total PA was associated with a lower risk of mortality due to all-causes, CVDs, chronic lung diseases, infections and other causes. In contrast, we did not observe an association of total PA with mortality from cancer, dementia and external causes. All five PA types were associated with a lower risk of all-cause mortality. Our findings underline that engagement in any PA type may be conducive to reduce mortality risk in older adults.

Existing literature on cause-specific mortality mostly focused on CVD and cancer mortality.[4-6,30,31] Our finding that higher levels of total PA are associated with lower risk of CVD mortality is in agreement with these studies. However, the fact that we did not observe an association with cancer mortality is in contrast to most previous evidence indicating a protective effect from higher PA levels.[5,26,30,32,33] The association between PA and cancer might depend on the cancer site[34,35] and it has been suggested that the association between PA and cancer occurs at least 10 years after the activity has been undertaken.[6] However, in additional analyses stratifying by the 5 most occurring cancers in the current study and in analyses excluding the first 10 years of follow-up, we still observed no association between PA and cancer mortality. The small number of events in the cancer-specific analyses might have led to limited power to detect an association, and the results do suggest a positive association between PA and cancer, which is similar across cancer site. Future studies with larger sample sizes should further evaluate these associations.

There is a paucity on studies regarding mortality related to external causes, dementia, infections and chronic lung diseases. Our finding that PA is associated with reduced mortality related to chronic lung diseases is in agreement with some studies on respiratory disease.[12,13,36] The mechanism for the potential beneficial effects of regular PA are unknown, although improved muscle function, exercise capacity and reduced inflammation can be on the causal pathway.[12] Whereas we adjusted for prevalent COPD, our finding might still be related to reversed causality, as participants with undiagnosed lung disease might not be capable of engaging in high levels of PA to begin with. Future studies with careful adjustments should be performed to examine whether higher levels of PA truly decrease the risk for lung disease mortality.

In our population, engaging in a median of 13 minutes/day of cycling (the medium category) was associated with a 28% lower all-cause mortality risk, which is in line with recent evidence that any PA is better than none.[37] The mortality risk associated with cycling has been studied before, but conflicting results have been found. Several studies found that cycling to work,[4] cycling for commuting[30] or cycling for sports[31] was associated with lower risk of mortality. In contrast, no association between cycling or walking for transportation and all-cause mortality[6] was found among British adults. The way in which cycling was operationalized (commuting to work, any commuting, cycling for sports or all cycling) might contribute to the different findings. Moreover, the age of the participants and the cycling prevalence differed between studies. In studies including younger participants, the lower number of cases might have led to insufficient power to detect an association and in contrast to the United Kingdom, cycling is a common way of transportation in the Netherlands, where our study was performed.

Domestic work is an important contributor of daily PA, especially in the elderly [10], and was associated with a lower all-cause mortality risk. The associations seemed to be driven by the women in our study, who engaged in domestic work more often than men. Our results are in line with previous studies, observing a lower all-cause mortality risk related to light household activity (<3 METS)[5] and activities around the house, including gardening and do-it-yourself activities.[6] However, in another study, housework was not associated with all-cause mortality in 50-64 year old individuals.[38] The differences between the studies might be related to the age group studied. This is supported by our analyses in adults <65 years, in whom we found weaker associations between domestic work and mortality. The inverse relation between domestic work and mortality independent of other PA types is consistent with the recommendations emphasizing the importance of moderate to vigorous-intensity PA performed as part of daily living.

We acknowledge that our study has several limitations. It may be hypothesized that people in poor health participate in PA less than others, creating the possibility for reverse causation. After repeating our analyses in participants without prevalent chronic disease we observed comparable estimates, suggesting that underlying disease did not affect our associations. In contrast, in the analyses excluding the first 5 and 10 years of follow-up, the strength of the association between total PA and cause-specific mortality was attenuated with longer exclusion times. This indicates that we cannot rule out the possibility of reverse causation affecting our results. Additionally, the attenuation of the association observed with increasing exclusion times might be the result of increasing exposure misclassification, as the time span between exposure and outcome classification increases. In the current study, we only measured PA at baseline, which can cause misclassification of PA over time, since levels of adults tend to decline with age.[39] Due to the prospective design, this misclassification is likely to be non-differential. However, future studies with repeated PA measurements are needed to investigate the effect of exposure misclassification on the association between PA and mortality. Furthermore, we collected no information about occupational PA, so we could not adjust for this in our main analyses. However, excluding participants in active labor force (n=828, 11.5%) in our sensitivity analyses revealed comparable estimates. Additionally, our results are based on self-reported PA. Although our questionnaire has shown to be valid and reliable,[16] potential recall bias and social desirability cannot be excluded. This limitation could have resulted in bias either towards or away from the null hypothesis. Finally, our questionnaire did not distinguish between walking and cycling for sports or for means of transportation. Since the intensity might differ between sports and transportation,[18] future studies are needed to examine the association of the two distinct forms with mortality.

Major strengths of the current study are its prospective population-based design, large sample size of adults aged over 55, relatively long follow-up period and the inclusion of seven different causes of death. Furthermore, we adjusted for several factors, thereby minimizing the possibility of the observed associations being explained by confounding. In addition, we included a number of different activities while adjusting for the remaining activities, which enabled us to examine their independent associations with all-cause mortality.

Conclusions

In summary, in this population of older and elderly adults, we found that PA was associated with a lower risk of mortality from all-causes, CVDs, chronic lung diseases, infections and other causes. All the five PA types under investigation contributed to the reduction in the all-cause mortality risk. For public health recommendations, our findings underline that engagement in any type of PA may successfully reduce mortality risk in older adults. Adults incapable of engaging in sports or exercise can engage in any activity that they enjoy and that their health allows them to, including cycling, walking and in- and around-the-house activities.

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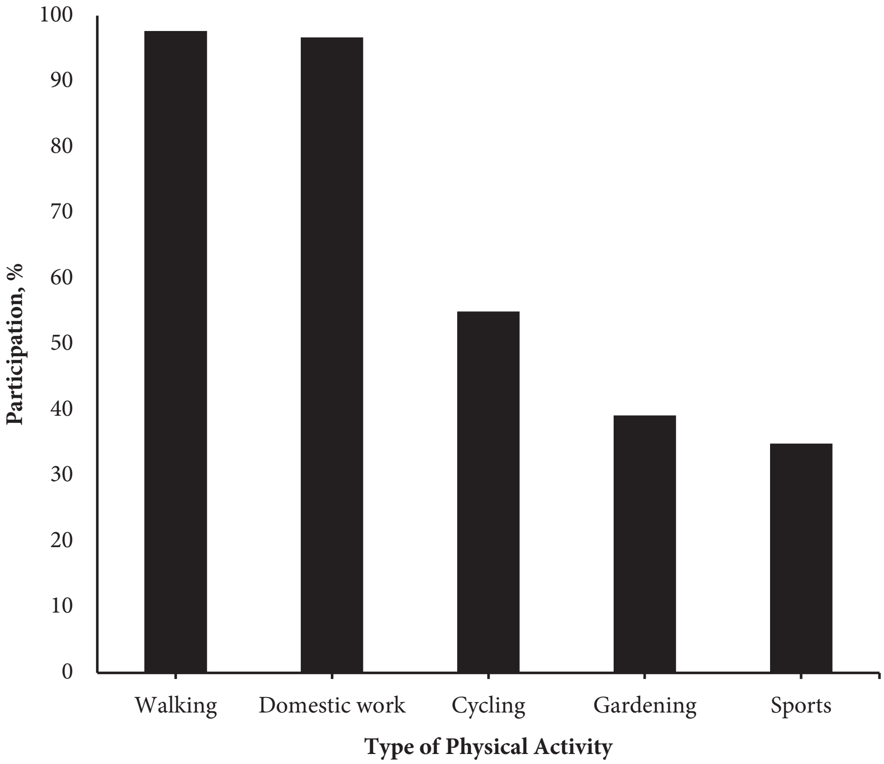
SUPPLEMENT CHAPTER 3.1

Supplement 3.1.1. Proportion of participants by physical activity type



Supplement 3.1.2. Number of participants in each physical activity category

Activity Type and Tertile of Physical Activity	Number of participants	Mortality cause							
		All-causes	CVD	Cancer	CLD	Dementia	Other causes	Infectious	External causes
Total physical activity									
Low	2,401	1,430	449	307	68	122	321	103	56
Medium	2,421	1,006	297	282	33	118	196	48	29
High	2,403	825	235	254	23	99	145	36	32
Walking									
Low	2,440	1,313	418	297	61	128	282	74	50
Medium	2,639	1,009	283	281	42	101	203	63	32
High	2,146	939	280	265	21	110	177	50	35
Domestic work									
Low	2,408	2,035	617	412	78	223	488	136	76
Medium	2,417	736	230	246	27	64	108	34	25
High	2,400	490	134	185	19	52	66	17	16
Cycling									
Low*	3,250	1,239	376	306	60	104	259	81	50
Medium	2,200	1,154	361	300	39	121	231	65	35
High	1,775	868	244	237	25	114	172	41	32
Sports									
Low*	4,702	2,401	742	573	89	252	497	153	91
Medium	1,264	468	131	142	17	48	96	17	14
High	1,259	392	108	128	18	39	69	17	12
Gardening									
Low*	4,390	2,386	710	550	100	248	529	145	98
Medium	1,723	483	152	158	9	47	79	25	11
High	1,112	392	119	135	15	44	54	17	8

Abbreviations: CLD, chronic lung disease; CVD, cardiovascular disease.

* For cycling, gardening and sports, the low category refers to not doing that particular activity.

Supplement 3.1.3. Results from sensitivity analyses on the association between physical activity types and all-cause mortality

	Tertile of PA	total n/ cases	Walking HR (95%CI)	Cycling HR (95%CI)	Domestic work HR (95%CI)	Gardening HR (95%CI)	Sports HR (95%CI)
Original analyses	Low*		1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium	7,225/3,261	0.82 (0.75, 0.89)	0.72 (0.66, 0.79)	0.86 (0.79, 0.94)	0.75 (0.68, 0.83)	0.84 (0.76, 0.93)
	High		0.89 (0.81, 0.97)	0.65 (0.58, 0.72)	0.77 (0.70, 0.86)	0.86 (0.77, 0.96)	0.81 (0.73, 0.91)
Model 2a, after additional adjustment for BMI[a]	Low*		1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium	7,225/3,261	0.81 (0.75, 0.88)	0.71 (0.65, 0.78)	0.85 (0.78, 0.93)	0.75 (0.68, 0.83)	0.84 (0.76, 0.93)
	High		0.88 (0.81, 0.96)	0.64 (0.58, 0.72)	0.76 (0.69, 0.84)	0.86 (0.77, 0.96)	0.81 (0.72, 0.90)
Model 2b, after additional adjustment for biological risk factors[b]	Low*		1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium	7,225/3,261	0.81 (0.74, 0.88)	0.72 (0.66, 0.79)	0.86 (0.78, 0.93)	0.76 (0.69, 0.84)	0.83 (0.75, 0.92)
	High		0.88 (0.81, 0.96)	0.66 (0.59, 0.73)	0.77 (0.69, 0.85)	0.86 (0.77, 0.97)	0.81 (0.73, 0.90)
In women only[c]	Low*		1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium	4,194/1,792	0.79 (0.70, 0.89)	0.70 (0.61, 0.80)	0.78 (0.68, 0.89)	0.78 (0.67, 0.89)	0.89 (0.78, 1.01)
	High		0.94 (0.83, 1.06)	0.64 (0.54, 0.77)	0.67 (0.58, 0.78)	0.92 (0.76, 1.09)	0.80 (0.66, 0.95)
In men only[c]	Low*		1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium	3,031/1,469	0.86 (0.76, 0.97)	0.75 (0.66, 0.85)	0.90 (0.80, 1.02)	0.73 (0.63, 0.84)	0.80 (0.68, 0.93)
	High		0.85 (0.74, 0.97)	0.67 (0.58, 0.77)	0.89 (0.75, 1.07)	0.83 (0.72, 0.96)	0.83 (0.72, 0.95)
Excluding the first 5 years of follow-up	Low*		1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium	6,290/2,346	0.86 (0.78, 0.95)	0.78 (0.70, 0.86)	0.96 (0.87, 1.07)	0.78 (0.69, 0.87)	0.89 (0.79, 1.00)
	High		0.91 (0.82, 1.01)	0.67 (0.59, 0.76)	0.88 (0.78, 1.00)	0.90 (0.79, 1.02)	0.88 (0.78, 1.00)

Supplement 3.1.3 (continued). Results from sensitivity analyses on the association between physical activity types and all-cause mortality

	Tertile of PA	total n/ cases	Walking HR (95%CI)	Cycling HR (95%CI)	Domestic work HR (95%CI)	Gardening HR (95%CI)	Sports HR (95%CI)
Excluding the first 10 years of follow-up	Low*		1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium	5,046/1,121	0.85 (0.73, 0.98)	0.80 (0.69, 0.93)	1.03 (0.87, 1.21)	0.75 (0.64, 0.89)	0.92 (0.78, 1.08)
	High		0.99 (0.85, 1.14)	0.65 (0.54, 0.77)	0.99 (0.83, 1.19)	1.03 (0.87, 1.22)	0.80 (0.67, 0.96)
In adults without prevalent chronic disease[d]	Low*		1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium	4,416/1,561	0.83 (0.73, 0.94)	0.77 (0.68, 0.88)	0.89 (0.78, 1.02)	0.75 (0.65, 0.86)	0.84 (0.73, 0.97)
	High		0.87 (0.77, 0.99)	0.70 (0.60, 0.82)	0.84 (0.72, 0.98)	0.87 (0.74, 1.02)	0.84 (0.72, 0.98)
In unemployed adults	Low*		1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium	6,397/3,131	0.81 (0.75, 0.89)	0.73 (0.66, 0.80)	0.85 (0.78, 0.93)	0.74 (0.67, 0.83)	0.85 (0.76, 0.94)
	High		0.88 (0.80, 0.96)	0.64 (0.57, 0.72)	0.76 (0.69, 0.85)	0.86 (0.76, 0.96)	0.81 (0.73, 0.91)
In adults aged <65 years	Low*		1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium	2,400/342	0.78 (0.60, 1.03)	0.58 (0.45, 0.74)	1.04 (0.78, 1.39)	0.61 (0.47, 0.80)	0.81 (0.60, 1.09)
	High		1.08 (0.83, 1.40)	0.52 (0.39, 0.68)	0.85 (0.60, 1.19)	0.90 (0.68, 1.20)	0.83 (0.63, 1.08)
In adults aged ≥65 years	Low*		1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium	4,825/2,919	0.83 (0.76, 0.90)	0.75 (0.68, 0.82)	0.84 (0.76, 0.92)	0.79 (0.71, 0.88)	0.85 (0.76, 0.94)
	High		0.86 (0.79, 0.95)	0.68 (0.60, 0.76)	0.76 (0.68, 0.85)	0.85 (0.75, 0.96)	0.82 (0.73, 0.92)

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; PA, physical activity; ref, referent.
Analyses were adjusted for age, sex, smoking, alcohol consumption, education, marital status, diet quality, prevalent CVD, prevalent cancer, prevalent diabetes, prevalent chronic obstructive pulmonary disease and the other physical activity types.
* For cycling, gardening and sports, the low category refers to not doing that particular activity. [a] These analyses were additionally adjusted for body mass index.
[b] These analyses were additionally adjusted for body mass index, systolic blood pressure, blood pressure lowering medication, total cholesterol, high-density lipoprotein cholesterol and glucose. [c] These analyses were not adjusted for sex. [d] These analyses were not adjusted for prevalent CVD, prevalent cancer, prevalent diabetes and prevalent chronic obstructive pulmonary disease.

Supplement 3.1.4. Results from sensitivity analyses on the association of total physical activity with all-cause and cause-specific mortality

	Tertile of total PA	total n/ cases	All-causes HR (95%CI)	CVD HR (95%CI)	Cancer HR (95%CI)	Chronic lung disease HR (95%CI)	Dementia HR (95%CI)	Infectious HR (95%CI)	External causes HR (95%CI)	Other HR (95%CI)
Original analyses	Low		1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium	7,225/ 3,261	0.76 (0.70, 0.83)	0.78 (0.67, 0.90)	0.90 (0.76, 1.06)	0.53 (0.35, 0.81)	0.99 (0.76, 1.29)	0.53 (0.37, 0.76)	0.65 (0.41, 1.04)	0.68 (0.57, 0.82)
	High		0.69 (0.63, 0.75)	0.69 (0.58, 0.81)	0.84 (0.70, 1.00)	0.44 (0.27, 0.71)	0.9 (0.68, 1.19)	0.47 (0.32, 0.71)	0.81 (0.51, 1.29)	0.56 (0.46, 0.69)
Model 2a[a]	Low		1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium	7,225/ 3,261	0.76 (0.70, 0.83)	0.77 (0.66, 0.90)	0.90 (0.76, 1.07)	0.51 (0.33, 0.78)	0.98 (0.76, 1.27)	0.53 (0.37, 0.75)	0.65 (0.41, 1.04)	0.68 (0.56, 0.82)
	High		0.68 (0.62, 0.74)	0.68 (0.58, 0.81)	0.84 (0.70, 1.00)	0.41 (0.25, 0.67)	0.87 (0.66, 1.16)	0.46 (0.31, 0.69)	0.80 (0.50, 1.27)	0.55 (0.45, 0.68)
Model 2b[b]	Low		1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium	7,225/ 3,261	0.77 (0.70, 0.83)	0.78 (0.67, 0.90)	0.91 (0.77, 1.08)	0.52 (0.34, 0.80)	0.99 (0.76, 1.28)	0.53 (0.38, 0.76)	0.64 (0.40, 1.02)	0.69 (0.57, 0.83)
	High		0.69 (0.63, 0.75)	0.69 (0.58, 0.82)	0.86 (0.72, 1.03)	0.41 (0.25, 0.67)	0.88 (0.66, 1.17)	0.48 (0.32, 0.71)	0.80 (0.50, 1.28)	0.56 (0.46, 0.69)
In women only[c]	Low		1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium	4,194/ 1,792	0.77 (0.69, 0.87)	0.67 (0.54, 0.83)	1.02 (0.79, 1.32)	0.58 (0.29, 1.16)	0.97 (0.71, 1.34)	0.63 (0.39, 1.04)	0.75 (0.41, 1.35)	0.71 (0.56, 0.90)
	High		0.68 (0.60, 0.76)	0.59 (0.47, 0.75)	0.88 (0.68, 1.16)	0.34 (0.15, 0.77)	0.87 (0.62, 1.21)	0.51 (0.30, 0.88)	0.92 (0.51, 1.65)	0.59 (0.46, 0.77)

Supplement 3.1.4 (continued). Results from sensitivity analyses on the association of total physical activity with all-cause and cause-specific mortality

	Tertile of total PA	total n/ cases	All-causes HR (95%CI)	CVD HR (95%CI)	Cancer HR (95%CI)	Chronic lung disease HR (95%CI)	Dementia HR (95%CI)	Infectious HR (95%CI)	External causes HR (95%CI)	Other HR (95%CI)
In men only[c]	Low	3,031/ 1,469	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium		0.76 (0.67, 0.86)	0.91 (0.73, 1.12)	0.82 (0.65, 1.03)	0.47 (0.27, 0.84)	1.09 (0.69, 1.73)	0.42 (0.25, 0.72)	0.51 (0.23, 1.11)	0.66 (0.49, 0.88)
	High		0.71 (0.62, 0.81)	0.81 (0.64, 1.04)	0.83 (0.65, 1.05)	0.52 (0.28, 0.97)	0.98 (0.59, 1.65)	0.43 (0.24, 0.79)	0.69 (0.31, 1.54)	0.51 (0.36, 0.72)
Excluding the first 5 years of follow-up	Low	6,290/ 2,346	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium		0.87 (0.79, 0.96)	0.91 (0.76, 1.09)	1.03 (0.84, 1.28)	0.59 (0.36, 0.94)	1.04 (0.79, 1.37)	0.60 (0.41, 0.87)	0.69 (0.41, 1.18)	0.84 (0.67, 1.04)
	High		0.78 (0.70, 0.86)	0.79 (0.65, 0.97)	0.98 (0.79, 1.22)	0.48 (0.28, 0.83)	0.95 (0.71, 1.28)	0.43 (0.27, 0.67)	0.84 (0.50, 1.41)	0.73 (0.58, 0.92)
Excluding the first 10 years of follow-up	Low	5,046/ 1,121	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium		0.91 (0.78, 1.05)	0.99 (0.75, 1.30)	1.01 (0.71, 1.43)	0.62 (0.30, 1.28)	1.26 (0.87, 1.81)	0.50 (0.28, 0.89)	0.60 (0.29, 1.23)	0.90 (0.65, 1.24)
	High		0.88 (0.75, 1.02)	0.93 (0.70, 1.23)	1.17 (0.84, 1.65)	0.57 (0.27, 1.22)	1.23 (0.85, 1.79)	0.49 (0.27, 0.90)	0.67 (0.33, 1.36)	0.71 (0.50, 1.01)
In adults without prevalent chronic disease[d]	Low	4,416/ 1,561	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium		0.81 (0.71, 0.91)	0.79 (0.62, 1.01)	0.97 (0.76, 1.23)	0.44 (0.19, 1.01)	1.17 (0.82, 1.66)	0.37 (0.21, 0.66)	0.70 (0.34, 1.43)	0.75 (0.58, 0.98)
	High		0.72 (0.63, 0.82)	0.72 (0.55, 0.93)	0.93 (0.72, 1.19)	0.43 (0.19, 1.01)	0.94 (0.65, 1.37)	0.38 (0.21, 0.69)	0.65 (0.33, 1.31)	0.59 (0.44, 0.78)

Supplement 3.1.4 (continued). Results from sensitivity analyses on the association of total physical activity with all-cause and cause-specific mortality

	Tertile of total PA	total n/ cases	All-causes HR (95%CI)	CVD HR (95%CI)	Cancer HR (95%CI)	Chronic lung disease HR (95%CI)	Dementia HR (95%CI)	Infectious HR (95%CI)	External causes HR (95%CI)	Other HR (95%CI)
In un-employed adults	Low	6,397/ 3,131	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium		0.75 (0.69, 0.82)	0.77 (0.66, 0.90)	0.86 (0.72, 1.02)	0.51 (0.33, 0.78)	1.00 (0.77, 1.31)	0.53 (0.37, 0.76)	0.65 (0.41, 1.04)	0.67 (0.56, 0.81)
	High		0.68 (0.62, 0.75)	0.69 (0.58, 0.82)	0.81 (0.68, 0.98)	0.41 (0.25, 0.68)	0.91 (0.68, 1.21)	0.47 (0.31, 0.70)	0.80 (0.50, 1.28)	0.55 (0.44, 0.68)
In adults aged <65 years	Low	2,400/ 342	1.00 [ref]	1.00 [ref]	1.00 [ref]	NA[e]	NA[e]	NA[e]	NA[e]	1.00 [ref]
	Medium		0.92 (0.69, 1.21)	0.67 (0.39, 1.17)	0.93 (0.61, 1.41)					1.30 (0.69, 2.44)
	High		0.79 (0.59, 1.05)	0.60 (0.34, 1.05)	0.93 (0.62, 1.42)					0.84 (0.42, 1.7)
In adults aged ≥65 years	Low	4,825/ 2,919	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
	Medium		0.74 (0.68, 0.81)	0.78 (0.67, 0.92)	0.85 (0.71, 1.02)	0.47 (0.30, 0.74)	0.95 (0.72, 1.23)	0.53 (0.37, 0.76)	0.65 (0.40, 1.04)	0.66 (0.54, 0.80)
	High		0.68 (0.61, 0.75)	0.70 (0.59, 0.84)	0.78 (0.64, 0.96)	0.44 (0.27, 0.73)	0.86 (0.65, 1.14)	0.46 (0.30, 0.69)	0.85 (0.53, 1.35)	0.56 (0.45, 0.70)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; PA, physical activity; ref, referent.

Analyses were adjusted for age, sex, smoking, alcohol consumption, education, marital status, diet quality, prevalent CVD, prevalent cancer, prevalent diabetes, prevalent chronic obstructive pulmonary disease, the other physical activity types, body mass index, systolic blood pressure, blood pressure lowering medication, total cholesterol, high-density lipoprotein cholesterol and glucose.

a These analyses were additionally adjusted for body mass index. b These analyses were additionally adjusted for body mass index, systolic blood pressure, blood pressure lowering medication, total cholesterol, high-density lipoprotein cholesterol and glucose. c These analyses were not adjusted for sex.

d These analyses were not adjusted for prevalent CVD, prevalent cancer, prevalent diabetes and prevalent chronic obstructive pulmonary disease.

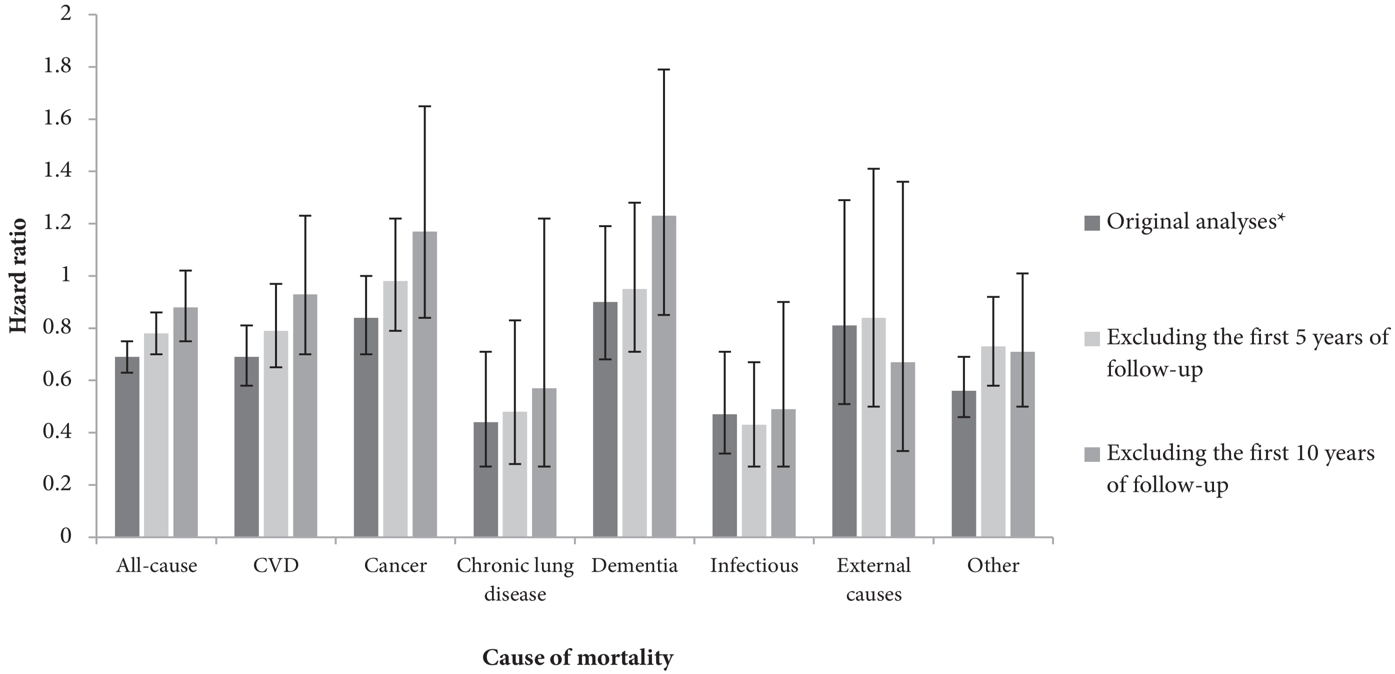
e Due to the small number of mortality cases from chronic lung disease (n=9), dementia (n=14), infections (n=9) and external causes (n=3), no models could be executed for these causes of death.

Supplement 3.1.5. Baseline participant characteristics, stratified by sex

	Men	Women
Participants, no (%)	3,031 (0.4)	4,194 (0.6)
Age, years	69.3 (8.1)	70.7 (8.9)
Educational level, no (%)		
Primary education	293 (9.7)	778 (18.6)
Lower education	926 (30.6)	2,202 (52.5)
Intermediate education	1,177 (38.9)	941 (22.4)
Higher education	635 (20.9)	273 (6.5)
Living with partner	2,391 (78.9)	2,133 (50.9)
Employed, no (%)	532 (17.6)	296 (7.1)
Smoking, no (%)		
Never	736 (24.3)	2,542 (60.6)
Former	1,772 (58.5)	1,227 (29.3)
Current	523 (17.3)	425 (10.1)
Dutch healthy diet index	46.1 (11.2)	50.1 (10.7)
Alcohol, glasses/day	1.6 (1.8)	0.7 (1)
BMI, kg/m^2	26.5 (3.3)	27.4 (4.4)
Disabled, no (%)	706 (23.3)	1,811 (43.2)
Diabetes, no. (%)	512 (16.9)	612 (14.6)
Prevalent cancer, no (%)	366 (12.1)	398 (9.5)
Prevalent CVD, no (%)	665 (21.9)	456 (10.9)
Prevalent COPD, no (%)	288 (0.095)	240 (0.057)
Total PA, MET·hours·week^{-1}	70.9 (43.1)	87.7 (43.3)
Walking, MET·hours·week^{-1}	26.9 (23.3)	27.7 (25)
Cycling, MET·hours·week^{-1}	10.6 (14.5)	7.0 (11.5)
Domestic work, MET·hours·week^{-1}	21.2 (17.7)	46.2 (21.3)
Gardening, MET·hours·week^{-1}	5.1 (11.7)	2.8 (6.6)
Sports, MET·hours·week^{-1}	7.2 (15.2)	4.0 (9.5)
Systolic blood pressure, mmHg	144.1 (21)	143.7 (21.9)
Cholesterol, mmol/L	5.5 (1)	6.0 (1)
HDL-cholesterol, mmol/L	1.2 (0.3)	1.5 (0.4)
Glucose, mmol/L	6.1 (1.7)	6.0 (1.5)

Numbers are mean (SD), unless otherwise stated.
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; MET, metabolic equivalent of task; no, number; PA, physical activity.

Supplement 3.1.6. The association of total physical activity with all-cause and cause-specific mortality for the total follow-up time, and after exclusion of the first 5 and 10 years of follow-up

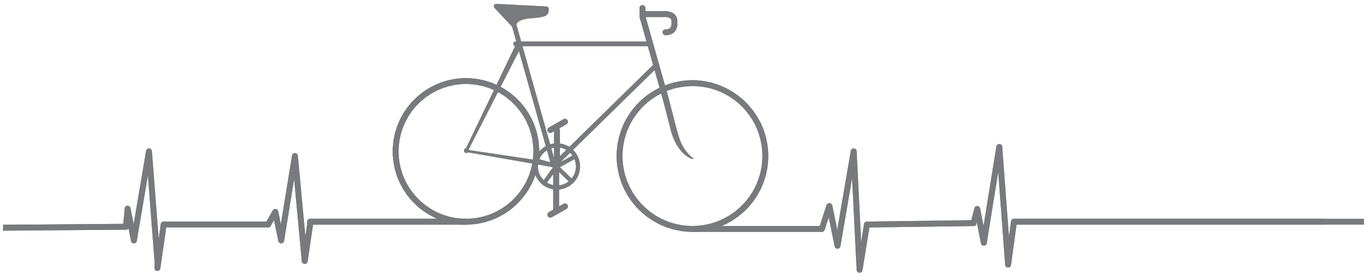


Abbreviations: CVD, cardiovascular disease
Bars indicate the hazard ratio for the high category of total physical activity, compared to the low category.
Error bars indicate the 95% confidence interval of the association.
* In the original analyses, the total follow-up time was included.
Analyses were adjusted for age, sex, smoking, alcohol consumption, education, marital status, diet quality, prevalent CVD, prevalent cancer, prevalent diabetes, prevalent chronic obstructive pulmonary disease, body mass index, systolic blood pressure, blood pressure lowering medication, total cholesterol, high-density lipoprotein cholesterol and glucose.

Supplement 3.1.7. Association of total physical activity and physical activity types with site-specific cancer mortality (n=7,225)

	Tertile of total PA	HR (95%CI)
Bronchus and lung cancer N= 177 cases	Low	1.00 [ref]
	Medium	0.87 (0.60, 1.25)
	High	0.65 (0.43, 0.97)
Colon cancer N=72 cases	Low	1.00 [ref]
	Medium	0.62 (0.35, 1.11)
	High	0.65 (0.35, 1.20)
Pancreas cancer N= 66 cases	Low	1.00 [ref]
	Medium	0.82 (0.44, 1.51)
	High	0.69 (0.35, 1.36)
Breast cancer N=61 cases†	Low	1.00 [ref]
	Medium	0.87 (0.44, 1.73)
	High	0.75 (0.35, 1.59)
Prostate cancer N=50 cases‡	Low	1.00 [ref]
	Medium	1.01 (0.50, 2.04)
	High	0.87 (0.41, 1.86)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; PA, physical activity; ref, referent.
Analyses were adjusted for age, sex, smoking, alcohol consumption, education, marital status, diet quality, prevalent CVD, prevalent cancer, prevalent diabetes, prevalent chronic obstructive pulmonary disease and the other physical activity types.
† The analyses for breast cancer were only run in women (n=4194)
‡ The analyses for prostate cancer were only run in men (n=3031)



Chapter 3.2

Sedentary time assessed by actigraphy and mortality

Manuscript based on this chapter:
Koolhaas CM, Dhana K, van Rooij FJ, Kocevska D, Hofman A, Franco OH, Tiemeier H. Sedentary time assessed by actigraphy and mortality: The Rotterdam Study. *Prev Med* 2017; 95: 59-65.

ABSTRACT

Background: Research suggests that sedentary behavior is a risk factor for mortality. However, most studies rely on questionnaires, which are prone to reporting error.

Methods: We examined the association between sedentary time assessed by actigraphy and mortality among 1,839 participants, aged 45-98 years, from the prospective population-based Rotterdam Study, enrolled between 2004 and 2007. Participants wore an actigraph around the wrist for seven days. Sedentary time was evaluated continuously, per one hour/day increase, and categorically in three groups (<8, 8–11, ≥11 hours/day). The lowest category was used as reference. Mortality risks were examined using Cox proportional hazard models, adjusted for confounders and biological risk factors. We examined the association between sedentary behavior and mortality over and beyond other activity measures (including physical activity (PA) and the disability score in a final model.

Results: During 11 years of follow-up (median:7.5 years, interquartile range: 6.6-8.3 years), 212 participants (11.5%) died. In the multivariable model, the hazard ratio (HR) and 95% confidence interval (95%CI) per 1 more hour/day sedentary time was 1.09 (1.00, 1.18). The HR (95%CI) after adjustment for PA and the disability score was 1.04 (0.96, 1.13). Participants sedentary for ≥11 hours/day had a higher mortality risk (HR:1.80, 95%CI: 1.14, 2.84) than those sedentary <8 hours/day, in the multivariable model. After adjusting for PA and the disability score, this association was clearly attenuated (HR:1.50, 95%CI: 0.93, 2.41).

Conclusion: Our study suggests that sedentary behavior is a risk factor for mortality. Further investigation is needed to examine whether this association is distinct from the effect of other measures of activity.

INTRODUCTION

Over the last decades, the benefits of physical activity (PA) have been well documented. Several studies have shown that people who do not engage in regular moderate physical activity are at increased risk of mortality.[1-3] Other studies documented that sedentary behavior is a risk factor for mortality.[4] Sedentary behavior is defined as engaging in sitting or reclining behaviors during the waking day, which result in little energy expenditure above rest.[5,6] Recent meta-analyses have shown self-reported sedentary behavior to be associated with all-cause mortality, cardiovascular disease mortality and cancer mortality, independent of self-reported PA.[4,7] However, self-reported data is known to be prone to reporting errors and recall bias, especially for low intensity behaviors.[8,9]

To date, few studies examined the association between objectively measured sedentary behavior and mortality.[10-12] Two studies in middle-aged adults, with an average follow up of 2.8 and 2.9 years, showed that objectively measured sedentary time was associated with mortality independent of PA.10,12 This observation is supported by a study in men aged 71 years and older, followed for an average of 4.5 years.[11] Due to the relatively short follow-up, there is a high chance for reverse causation in all of these studies. In this regard, adults could have higher levels of sedentary behavior because of their reduced health status (or underlying disease), and this reduced health could also increase their mortality risk. To minimize the effect of reverse causality, it is warranted to examine the association between sedentary behavior and mortality with longer follow-up and to evaluate the association after excluding the first years of follow-up.

To address the long-term effects of sedentary behavior, we used data from the Rotterdam Study, of adults aged 45 years and older with 11 years of follow-up, and examined the association between sedentary behavior assessed by actigraphy and all-cause mortality.

METHODS

Study population

This study was embedded in the Rotterdam Study, a prospective population-based cohort in the Netherlands which started in 1990. The aim of the study was to examine the incidence of risk factors for neurological, cardiovascular, psychiatric, and other chronic diseases. Details of the study have been published previously.[13]

From December 2004 to April 2007 2,632 consecutive participants of the Rotterdam Study were invited to participate in the actigraphy study. The current study was conducted in the 2,063 participants that agreed to participate (78%). There were no exclusion criteria besides being able to understand the instructions for this study. In accordance with previous studies, 133 days with three or more continuous hours missing were excluded to prevent a time-of-day effect.[14] Subsequently, we excluded 168 recordings that failed because of technical problems or that contained fewer than 4 days (see Supplement 3.2.1). Additionally, data of 54 participants (2.8%) with unusually low (<20% per day) or high (>90% per day) sedentary time was considered unreliable after visual inspection and therefore these participants were excluded. Following, 2 participants were excluded that withdrew consent for the collection of follow-up data. Finally, 1,839 subjects were included in the analyses.

All subjects gave written informed consent, and the study protocol was approved by the medical ethics committee according to the Wet Bevolkingsonderzoek ERGO (Population Study Act Rotterdam Study), executed by the Ministry of Health, Welfare and Sport of The Netherlands.

Measurement of sedentary time

All participants were asked to wear an actigraph around the nondominant wrist (Actiwatch model AW4; Cambridge Technology, Cambridge, UK) for seven consecutive days and nights and to complete a 7-day sleep diary to report overnight sleep periods. The device had to be removed from the wrist for water-based activities only. Recordings were obtained in 30-second intervals during 24-hour periods.[15]

The actigraph devices were initially designed to measure sleep in free-living settings. Since this was also the main interest of the original actigraphy study, the devices were not calibrated to measure the level of PA and thus do not allow comparison across individuals for PA. However, the actigraphy data can be used to estimate sedentary behavior, i.e., to validly measure active versus non-active periods in a person and test across person differences.[16] In this regard, activity refers to all PA that is not sedentary behavior and can include light, moderate and vigorous intensity activity. To quantify sedentary time, only the waking hours were used. Waking hours were defined based on bed time and get up time. These times were derived from the event marker buttons on the device, and if these data were not present for a certain night, we derived them from the sleep diary, to determine sleep start and sleep end.[15] In the current study, 10,852 valid days were recorded. Of these, bed time and get up time were based on the event marker for 11,725 days (88.1%) and on the diary for 1,686 days (11.6%). For 57 days (0.2%), we estimated bed time and get up time based on previous days and actigraphy pattern. The number of minutes per day spent in sedentary behavior was determined using the standard count-based intensity threshold value of <199 counts per minute (cpm).[17]

Clinical outcome

Information on vital status was collected through an automated follow-up system with a digital linkage of the study database to all medical records maintained by general practitioners. Additional information on vital status was obtained from the registry of the municipality of Rotterdam. Follow-up was complete until March 4, 2015.

Covariates

Information on covariates was collected through home interviews or measured at the study center, as described previously.[18,19] Briefly, alcohol use was defined as the amount of glasses per day. Education was assessed in line with the international standard classification of education.[20] Smoking was divided in three categories: current, former and never. Employment status was used as a binary variable (employed/unemployed). Disability was assessed by activities of daily living, from the Stanford Health Assessment Questionnaire, used to indicate general health and expressed as the disability score.[21] The questionnaire included questions on being able to walk outdoors, being able to climb stairs and being able to dress oneself. Height and weight were measured to calculate body mass index (BMI). Serum total cholesterol and high-density lipoprotein (HDL) cholesterol were determined using an automated enzymatic procedure (Cobas, Roche Hitachi 917). Two seated blood pressure measurements were obtained at the right brachial artery using a random zero sphygmomanometer, the mean of two consecutive measurements was used in analyses. The presence of coronary heart disease, diabetes, stroke and cancer were determined using medical records, to define the number of comorbidities.

For part of the study (n=868), PA was assessed at baseline with the validated LASA Physical Activity Questionnaire (LAPAQ).[22] In the remainder (n = 971) the LAPAQ was assessed at follow-up. The LAPAQ included questions on housekeeping activities, walking, cycling, sports and gardening. Time spent in these activities was combined and expressed in MET·hours·week^{-1}. Furthermore, previous research in this cohort revealed that low stability and high fragmentation of the 24-hour activity rhythm, as measured by the actigraph data are associated with higher risk of all-cause mortality.[23] To evaluate whether the association between sedentary behavior and mortality was independent of the 24-hour activity rhythm, we included the following variables in our analyses: interday stability (IS) and intraday variability (IV). Both variables are measures of the 24-hour activity rhythm. Specifically, IS is a measure of how similar the individual 24-hour activity patterns are over time and IV is a variable quantifying the fragmentation of the 24-hour activity profile into brief periods of rest and activity.[24]

Statistical analysis

Sedentary time was analyzed continuously per one hour increase (per day) and categorically. For categories, we created three cut-offs based on the existing literature 1) < 8 hours/day; 2) 8 - 11 hours/day; 3) ≥ 11 hours/day 25-27. In some studies, <4 hours/day was the reference category.[25-27] Since only 6 participants were sedentary for less than 4 hours per day in our study, we chose not to include them in a separate category. Characteristics of participants were compared according to the three categories of sedentary behavior.

To examine the independent associations between sedentary time and all-cause mortality, we used Cox proportional hazard models. The assumption for proportional hazards was tested using Schoenfeld residuals and found to be met for all models. To visualize the survival distribution of the three categories of sedentary behavior, we built Kaplan Meier plots, up to the follow-up time that corresponds to 90-95% of the participants at risk. Furthermore, we applied natural cubic splines to test for non-linearity of the survival models,[28] but we found no evidence for a non-linear association between sedentary behavior and mortality risk.

Covariates were included in the model based on previous research.[4] We created four different models. Model 1 was the crude model, adjusted for age, sex, cohort and time awake. In model 2, we additionally adjusted for smoking, number of comorbidities, alcohol intake and education. To evaluate the independent association between sedentary behavior and mortality, beyond intermediates and proxies of sedentary behavior, we built model 3 and 4. In model 3, we additionally adjusted for biological risk factors, including BMI, total and HDL cholesterol and systolic blood pressure. Disability, PA, IS and IV were considered as proxies of sedentary behavior, and not as pure confounders.[29] Therefore, we additionally adjusted for the disability score, PA, IS and IV in model 4, to evaluate the specificity of the association between sedentary behavior and all-cause mortality.

Statistical interactions of sedentary time with both gender and age on the risk of mortality were tested. None of these interactions reached statistical significance (all p>.05). Therefore results are primarily shown for men and women of all ages combined. Given prior work,[25,30,31] we also present analyses using stratified models by sex. In sensitivity analyses, we investigated the possible effect of reverse causation, by excluding deaths in the first two years. Moreover, we repeated our analyses in non-workers, since 33.8% (n=622) was employed at baseline and we did not collect information on occupational PA. Finally, in literature, sedentary behavior has also been defined as the number of minutes per day spent <100 cpm.[32] Therefore, we repeated our analyses using this cut-off.

Some data was missing for PA (25.6%), the disability score (11.6%), IV (7.9%) and IS (7.9%). Other covariates had <2% missing data only. We used multiple imputation (n=5 imputations) by the Expectation Maximization method to account for uncertainty of missing data. All analyses were conducted using SPSS software version 20 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp) and R (3.0.1).

RESULTS

From the 1,839 participants in the study, 10852 valid days were recorded, for an average of 5.8 (SD: 0.5) days per participant. Baseline characteristics of the study population according to categories of sedentary behavior are shown in Table 3.2.1. Participants sedentary for ≥11 hours were older, more often male and more often had prevalent diabetes or coronary heart disease, compared to participants sedentary <8 hours per day. The average time spent in sedentary behavior was 8.8 hours (SD: 2.0) per day, which corresponds to 55.7% of the time awake. During 11 years of follow-up (median: 7.5 years, interquartile range (IQR): 6.6-8.3 years), 212 participants (11.5%) died.

The Kaplan-Meier survival curves, by categories of sedentary behavior, are presented in Figure 3.2.1. Additional adjustment for biological risk factors in model 3 did not materially affect the associations (see Table 3.2.2). Thus, we focus our discussion on the results presented in model 3.

Table 3.2.1. Baseline participant characteristics by categories of sedentary time, The Rotterdam Study, 2004-2015

	Categories of sedentary behavior, hours/day			Between group differences (p value)[a]
	< 8 hours	8-11 hours	≥ 11 hours	
Participants, n (%)	637 (34.6)	956 (52.0)	246 (13.4)	
Age	60.1 (8.0)	63.7 (9.5)	65.2 (10.6)	<0.001
Female, n (%)	419 (65.8)	478 (50.0)	104 (42.3)	<0.001
Educational level, n (%)				0.06
Primary education	56 (8.8)	71 (7.4)	27 (11.0)	
Lower education	282 (44.3)	387 (40.5)	84 (34.1)	
Intermediate education	183 (28.7)	289 (30.2)	82 (33.3)	
Higher education	116 (18.2)	209 (21.9)	53 (21.5)	
Employed, n (%)	261 (41.0)	293 (30.6)	68 (27.6)	<0.001
Sedentary time (hours/day)	6.7 (1.0)	9.3 (0.8)	12.2 (1.0)	<0.001
Not sedentary time (hours/day)	8.9 (1.3)	6.5 (1.1)	3.9 (1.3)	<0.001
Intraday variability	0.4 (0.1)	0.4 (0.1)	0.5 (0.2)	<0.001
Interday stability	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	<0.001
Smoking, n (%)				
Never	225 (35.3)	294 (30.8)	61 (24.8)	
Former	325 (51.0)	487 (50.9)	127 (51.6)	
Current	87 (13.7)	175 (18.3)	58 (23.6)	
BMI (kg/m^2)	27.3 (4.0)	27.9 (4.1)	29.0 (4.7)	<0.001
Disability score	0.2 (0.3)	0.3 (0.4)	0.4 (0.5)	<0.001
Dutch healthy diet score	57.1 (9.4)	56.2 (9.7)	56.1 (9.7)	0.01
Alcohol (glasses/day)	0.9 (1.1)	1.1 (1.3)	1.1 (1.4)	0.08
Physical activity (METhours/week)	79.7 (54.4)	71.6 (46.7)	66.6 (43.8)	<0.001
Prevalent diabetes, n (%)	65 (10.2)	141 (14.7)	52 (21.1)	<0.001
Cholesterol (mg/dl)	219.7 (39.6)	216.5 (40.3)	210.0 (40.7)	0.002
HDL-cholesterol (mg/dl	58.5 (16.9)	54.4 (15.8)	52.0 (16.2)	<0.001
Glucose (mg/dl)	99.3 (20.4)	102.4 (25.6)	107.4 (28.2)	<0.001
Systolic blood pressure (mm HG)	136.6 (20.2)	139.5 (19.7)	142.7 (23.3)	<0.001
Prevalent CHD, n (%)	25 (3.9)	50 (5.2)	27 (11.0)	<0.001
Prevalent stroke, n (%)	10 (1.6)	31 (3.2)	6 (2.4)	0.12
Prevalent cancer, n (%)	74 (11.6)	105 (11.0)	35 (14.2)	0.37
Deaths, n (%)	39 (6.1)	120 (12.6)	53 (21.5)	<0.001

Data are presented as mean (SD), unless otherwise noted.

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHD, coronary heartdisease; HDL, high-density lipoprotein; M, mean; N, number; SD, standard deviation.

[a] Differences in characteristics across categories were compared using analysis of variance for normally distributed continuous variables, Kruskal–Wallis tests for skewed continuous variables, and chi-square tests for categorical variables.

Results from analyses with continuous sedentary time

In the analysis with continuous sedentary time, every one hour more sedentary time was associated with a higher mortality risk. The hazard ratio (HR) and 95% confidence interval (95%CI) per 1 hour more sedentary time was 1.09 (1.00, 1.18). About half of the observed effect could also be explained by other indicators of activity, that is, PA, the 24-hour activity rhythm (i.e. IS, IV) and the disability score (Table 3.2.2). In particular the disability score and the 24-hour activity rhythm explained half of the observed effect (data not shown).

Results from analyses with categorical sedentary time

Next, we analyzed sedentary time categorically and found that participants sedentary for 8-11 hours/day (median: 9.2 hours, IQR: 8.6-10.0) were not at significantly higher risk of mortality, compared to those sedentary <8 hours/day (median: 6.9 hours/day, IQR: 6.2-7.5). The corresponding HR was 1.24 (0.85, 1.81). However, participants sedentary ≥11 hours/day (median: 12.0 hours/day, IQR: 11.4-12.9) had a 1.80 higher mortality risk (95%CI: 1.14, 2.84). Again, part of the observed effect could be explained with other measures of activity, (see Table 3.2.2, model 4).

In Table 3.2.3 we show the associations between sedentary behavior and mortality, stratified by gender (interaction p-value: 0.77 for model 3 in continuous analysis). Men sedentary for ≥11 hours/day had a higher mortality risk than those sedentary <8 hours/day. The HR (95%CI) was 2.31 (1.19, 4.45), P for trend 0.006, for men and 1.32 (0.66, 2.66), P for trend 0.40, for women. After additional adjustments for indicators of activity, the association in men was attenuated (HR: 1.98, 95%CI: 0.99 ,3.96).

Table 3.2.2. Association between sedentary time and mortality, The Rotterdam Study, 2004-2015

	Continuous analysis	Categorical analysis			
	Per 1 hour more	Low sedentary	Medium sedentary	High sedentary	P for trend
Hours/day sedentary, median (range)		6.9 (<8.0)	9.2 (8.0-11.0)	12.0 (≥11.0)	
No. Participants		637	956	246	
No. deaths		39	120	53	
Confounder adjusted models					
Model 1	1.13 (1.05, 1.23)	1.00 [ref]	1.33 (0.92, 1.94)	2.22 (1.43, 3.45)	<0.001
Model 2	1.08 (1.00, 1.17)	1.00 [ref]	1.23 (0.84, 1.80)	1.74 (1.11, 2.74)	0.01
Model 3	1.09 (1.00, 1.18)	1.00 [ref]	1.24 (0.85, 1.81)	1.80 (1.14, 2.84)	0.01
Additional adjustment for activity scores					
Model 4	1.04 (0.96, 1.13)	1.00 [ref]	1.21 (0.81, 1.81)	1.50 (0.93, 2.41)	0.09

Abbreviations: no, number; ref, reference.
Model 1 is adjusted for age, sex, cohort and time awake.
Model 2 is additionally adjusted for smoking, number of comorbidities, alcohol intake and education
Model 3 is additionally adjusted for body mass index, cholesterol, high-density lipoprotein cholesterol and systolic blood pressure.
Model 4 is model 2 and additionally adjusted for physical activity, the 24h activity rhythm (i.e. interday stability, intraday variability) and the disability score.

In sensitivity analyses excluding events in the first two years, our findings did not materially change, although the associations remained significant in model 1 only (Supplement 3.2.2). Additionally, when we repeated our analyses in non-workers, we found similar results (Supplement 3.2.3). When we repeated the analyses using 100 counts per minute as cut-off for sedentary behavior, the mean time spent in sedentary behavior was 6.8 hour (SD: 2.0), corresponding to 43.0% of the time awake. The distribution of participants across the sedentary behavior categories changed (see Supplement 3.2.4). In these analyses, we found larger HRs in the high category of sedentary behavior, compared to our main analyses (HR: 2.53; 95%CI: 1.31, 4.88 in model 3). However, the HRs in the continuous analyses were very similar to the original analvses (HR: 1.07; 95%CI: 0.99, 1.15 in model 3).

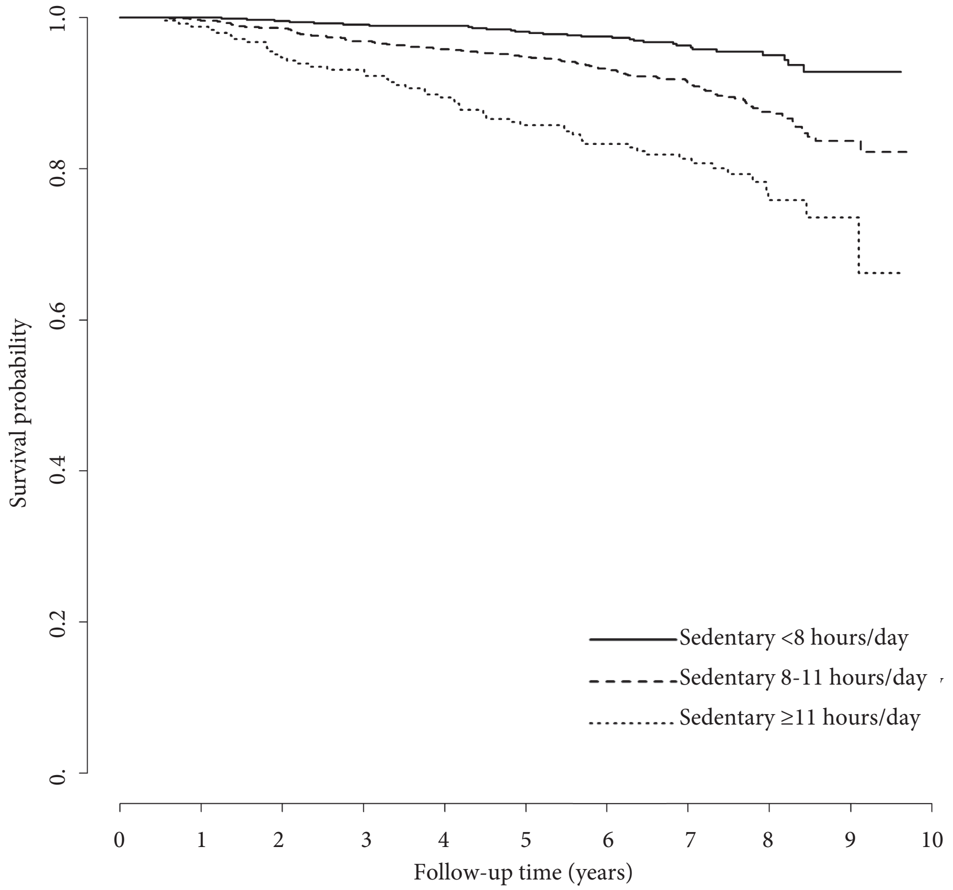


Figure 3.2.1. Kaplan-Meier curve of mortality as a function of follow-up time according to the three categories of sedentary behavior

Table 3.2.3. Association between sedentary time and mortality, stratified by gender, The Rotterdam Study, 2004-2015

	Continuous analysis	Categorical analysis			
	Per 1 hour more	Low sedentary	Medium sedentary	High sedentary	P for trend
Men					
Hours/day sedentary, median (range)		7.0 (<8.0)	9.3 (8.0-11.0)	12.0 (≥11.0)	
No. Participants		218	478	142	
No. deaths		15	66	35	
Confounder adjusted models					
Model 1	1.15 (1.03, 1.29)	1.00 [ref]	1.38 (0.78, 2.46)	2.89 (1.53, 5.46)	<0.001
Model 2	1.09 (0.98, 1.22)	1.00 [ref]	1.21 (0.68, 2.16)	2.20 (1.15, 4.19)	0.007
Model 3	1.10 (0.98, 1.23)	1.00 [ref]	1.26 (0.70, 2.26)	2.31 (1.19, 4.45)	0.006
Additional adjustment for activity scores					
Model 4	1.06 (0.94, 1.20)	1.00 [ref]	1.19 (0.64, 2.21)	1.98 (0.99, 3.96)	0.03
Women					
Hours/day sedentary, median (range)		6.9 (<8.0)	9.1 (8.0-11.0)	12.1 (≥11.0)	
No. Participants		419	478	104	
No. deaths		24	54	18	
Confounder adjusted models					
Model 1	1.12 (1.00, 1.25)	1.00 [ref]	1.34 (0.81, 2.22)	1.59 (0.83, 3.05)	0.15
Model 2	1.08 (0.96, 1.21)	1.00 [ref]	1.25 (0.75, 2.09)	1.27 (0.64, 2.52)	0.44
Model 3	1.08 (0.97, 1.21)	1.00 [ref]	1.23 (0.74, 2.06)	1.32 (0.66, 2.66)	0.34
Additional adjustment for activity scores					
Model 4	1.04 (0.92, 1.17)	1.00 [ref]	1.25 (0.74, 2.11)	1.03 (0.49, 2.16)	0.82

Abbreviations: no, number; ref, reference.
Model 1 is adjusted for age, cohort and time awake.
Model 2 is additionally adjusted for smoking, number of comorbidities, alcohol intake and education.
Model 3 is additionally adjusted for body mass index, cholesterol, high-density lipoprotein cholesterol and systolic blood pressure.
Model 4 is model 2 and additionally adjusted for physical activity, the 24h activity rhythm (i.e. interday stability, intraday variability) and the disability score.

DISCUSSION

In this population-based cohort study, we found that time spent in sedentary behavior, assessed by actigraphy, was associated with a higher mortality risk in middle-aged and elderly adults. Participants sedentary for more than 11 hours a day had a significantly higher mortality risk than participants sedentary for less than 8 hours per day. These associations remained after adjustments for health behaviors and risk factors and after excluding the first two years of follow-up. However, after adjusting for other measures of activity, the association between sedentary behavior and mortality was clearly attenuated.

We found a 1.80 fold increased mortality risk for participants sedentary ≥11 hours per day compared to those sedentary <8 hours per day. This corresponds to a 9% higher mortality risk per every one hour more sedentary time in continuous analyses. A few other studies tested the association between objectively measured sedentary behavior and mortality.[10-12] Schmid et al. found in a study of 1,677 adults aged 50 years and older, that participants sedentary ≥8.6 hours per day had a two times higher risk of mortality than those sedentary less than 8.6 hours per day.[12] In the study of Ensrud et al., in 2918 men aged 71 years and older, sedentary time of more than 15 hours per day was associated with 80% higher mortality risk than being sedentary for less than 12.9 hours per day.[11]

In addition, in a study of 1,906 adults aged 50 years and over, Koster et al. found that adults who were sedentary for more than 10 hours per day, had a 3 times higher relative risk of mortality than those sedentary for 7.6 hours a day.[10] These studies used different ways to categorize sedentary time, included participants from different age ranges and adjustment for potential confounding factors was limited. However, our results are in line with these studies, indicating that sedentary behavior is a risk factor for mortality, independent of the study population. An important limitation of the mentioned studies is that the average follow-up time was less than 5 years. In studies with a relatively short follow-up time, the risk for reversed causation is high. There is a greater probability that sedentary time and mortality risk are both influenced by underlying diseases. Our study has a longer follow-up time of 11 years and is therefore less prone of reverse causation.

To evaluate whether the association between sedentary behavior and mortality could be explained by other measures of activity, we adjusted our analyses for PA and disability as measured by questionnaire and indicators of the 24-hour activity rhythm as measured by actigraphy in our final model. Low PA levels can be the cause of sedentary behavior and may conceptually overlap with sedentary behavior. Our results indicate that the association between sedentary behavior and mortality risk was not independent of PA, which is in contrast to studies with shorter follow-up time.[10,12,25] In contrast to these studies, a study in 5132 adults from the Whitehall II cohort, with over 16 years of follow-up, found no association between self-reported sitting time and mortality, after adjustment for PA.[33] Moreover, a recent meta-analysis concluded that being active at moderate intensity for 60-75 minutes/day can attenuate the risk of death associated with sedentary behavior.[34] One possible explanation for the inconsistent findings between studies might be related to the follow-up, with stronger associations found with shorter follow-up periods. Furthermore, in our analyses, in addition to adjusting for PA, we additionally adjusted for disability, as indicator for health. Importantly, the disability score attenuated the observed association more than PA. The disability score is computed by combining scores from the activities of daily living questionnaire. Activities of daily living reflect physical capabilities, by providing information on being able to walk outdoors, being able to climb stairs and being able to dress oneself.[21] Participants with difficulties in any of the domains of activities of daily living, will not engage in those activities and as a consequence, are more likely to be inactive or sedentary.

Arguably, the information on activities of daily living conceptually overlaps with sedentary behavior and partially provides the same information.

The importance of evaluating the complete 24-hour period in the association with health outcomes has been mentioned recently.[35] In another study with the actigraph data in this cohort, low stability and high fragmentation of the 24-hour activity rhythm predicted all-cause mortality.[23] Therefore, we adjusted for these two measures of the 24-hour activity rhythm (i.e. IV and IS). Our results indicate that the association between sedentary behavior and mortality is not independent of these measures.

Whereas our associations were clearly attenuated after adjustment for other activity measures, our results do not indicate that adults can safely engage in high amounts of sedentary behavior when they meet the PA guidelines. Other activity measures, including activities of daily living or disability, partially provide similar information as sedentary behavior. As a consequence, measuring activities of daily living might be a convenient and accessible tool to evaluate the health status and mortality risk of adults. For public health programs, it remains important to not just focus on increasing population PA levels, but to concomitantly stress reducing sedentary time and improve activities of daily living levels. Encouraging high-risk groups such as individuals with cardiovascular disease, diabetes, overweight or obesity to sit less and to improve their ability to perform activities of daily living should be a public health priority.

In literature, there is no consensus regarding the cut-off to use to define sedentary behavior.[32] Whereas 199 cpm has been used in older adults,[17,36,37] 100 cpm has also been reported.[38] In light of this debate, we have performed our analysis using the cut-off of 199 cpm in our main analyses, and have used the cut-off of 100 cpm in a sensitivity analysis. The results for the analysis using continuous sedentary time were similar, showing the robustness of this association.

Different mechanisms have been proposed to link high sedentariness to an increased mortality risk. The impact of sedentary behavior on survival could reflect changes in metabolic risk factors, including fasting glucose, triglycerides and HDL cholesterol, that accompany sedentary behavior.[39,40] Previous studies documented that metabolic changes in metabolic risk factors appear to be at least partially mediated by changes in lipoprotein lipase activity, a protein important for controlling such metabolic factors.[39] However, when we adjusted for BMI, total cholesterol, HDL cholesterol and systolic blood pressure, the associations did not materially change, indicating only a minor effect of these variables. Other efforts have investigated more distal indicators of potential mechanisms, such as cardiovascular fitness. High sedentariness has been associated with lower cardiovascular fitness,[41] which in turn is associated with increased mortality risk.[42] Low levels of cardiovascular fitness might thus reflect the above pathological processes. However, more research is needed to understand the underlying physiological pathways through which sedentary behavior influences health.

We found no evidence for a statistical interaction between sedentary behavior and gender in our analysis. When we stratified our analysis by gender, the associations between sedentary behavior and mortality risk in men was observed more clearly than in women. One reason for this finding might be that there were more deaths in men (13.8%) than in women (9.6%), resulting in more power to find an association. Additionally, we observed that men spent on average slightly more time in sedentary behavior (9.2, SD 2.0) than women (8.5, SD 2.0), which might have influenced the results.

The strengths of this study are the prospective population-based design, large sample size and a long follow-up period (11 years compared to the average 2.8 and 4.8 in previous publications).[10-12] However, several potential limitations must be discussed. First, persons in poor health engage in sedentary behavior more than others, which could introduce reverse causation and confounding. However, the associations remained after adjusting for comorbidities. Moreover, repeating our analysis after exclusion of the first two years of follow-up showed similar results. Second, a limitation of the actigraph is that it does not allow differentiation between the postural allocations of sitting, standing and lying down and that it cannot distinguishing different types of sedentary behavior. For example, we were unable to distinguish socializing from driving. Moreover, we measured sedentary behavior during one week, which might not represent yearly exposure. Additionally, we did not analyze the length of the sedentary bouts. Therefore, we cannot provide information on the effects of specific patterns of sedentary behavior. Furthermore, we used questionnaire data to estimate PA levels. Although our questionnaire has been shown to be valid and reliable,[22] potential recall bias and socially desired answers cannot be excluded. Another limitation is that for many participants, PA was measured after the actigraph study was conducted. We acknowledge this limitation and used these PA measures as a proxy of prior activities. These last two limitations could have resulted in bias towards the null hypothesis, which means that our findings could be an underestimation of the true effect of sedentary behavior on mortality. Finally, the PA questionnaires did not capture the occupational domain. However, only 33.8% of our population was employed at baseline and only 31 of the 212 events (14.6%) events occurred in this group.

Conclusions

In conclusion, in this population of middle-aged and elderly adults, high levels of sedentary time were associated with mortality risk. After adjustment for other measures of activity, the association was clearly attenuated. Further investigation is needed to examine whether sedentary behavior is a risk factor for mortality, distinct from the effect of other measures of activity.

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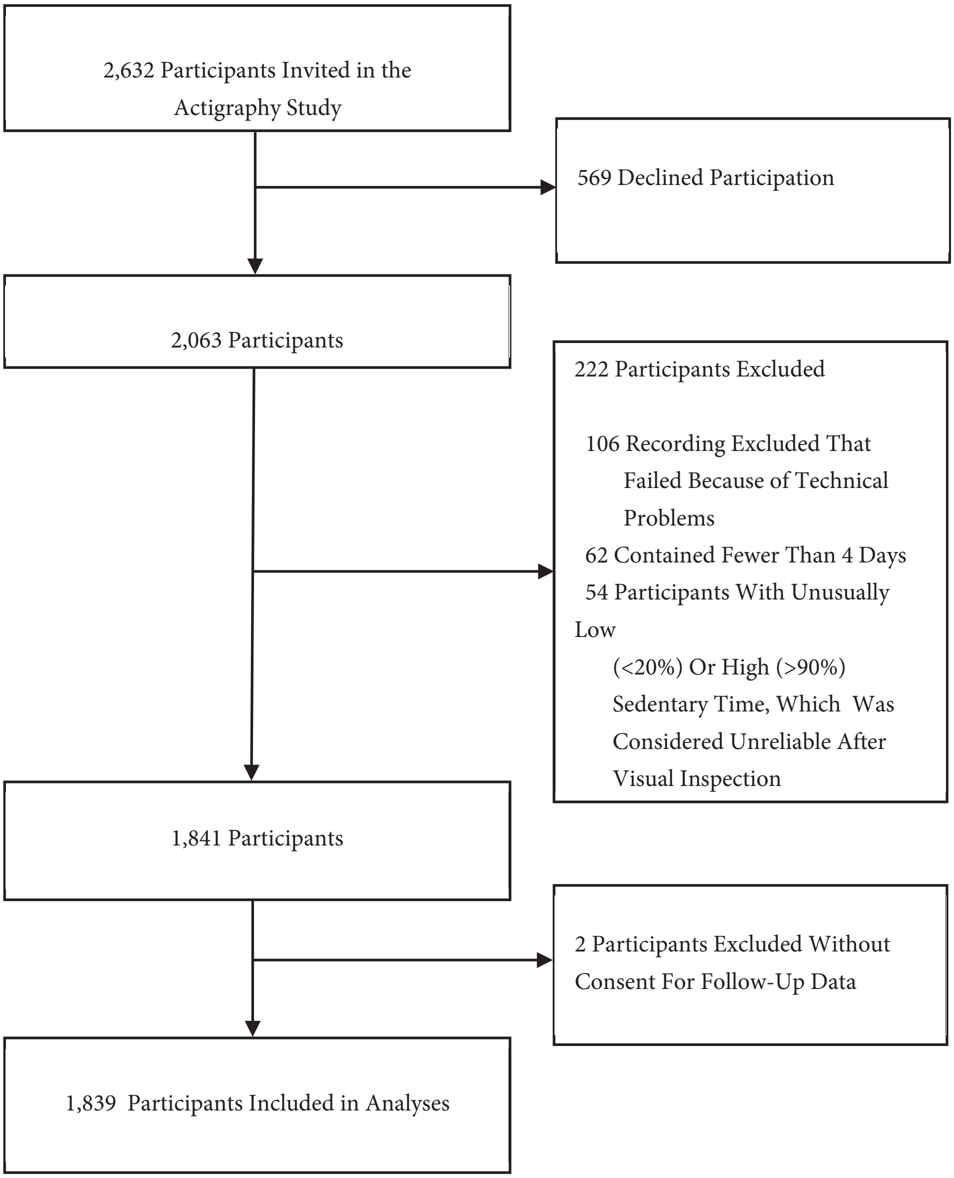
SUPPLEMENT CHAPTER 3.2

Supplement 3.2.1. Flow chart of participant inclusion, the Rotterdam Study, 2004-2015



Supplement 3.2.2. Association between sedentary time and mortality, excluding deaths in the first two years (n=1,808), the Rotterdam Study, 2004-2015

	Continuous analysis	Categorical analysis			
	Per 1 hour more	Low sedentary	Medium sedentary	High sedentary	P for trend
Hours/day sedentary, median (range)		6.9 (<8.0)	9.2 (8.0-11.0)	12.0 (≥11.0)	
No. Participants		633	942	233	
No. deaths		36	107	40	
Confounder adjusted models					
Model 1	1.11 (1.02, 1.20)	1.00 [ref]	1.30 (0.87, 1.93)	1.86 (1.15, 3.01)	0.01
Model 2	1.05 (0.97, 1.15)	1.00 [ref]	1.19 (0.80, 1.77)	1.43 (0.88, 2.34)	0.15
Model 3	1.05 (0.97, 1.15)	1.00 [ref]	1.18 (0.80, 1.76)	1.46 (0.89, 2.39)	0.14
Additional adjustment for activity scores					
Model 4	1.05 (0.97, 1.15)	1.00 [ref]	1.17 (0.77, 1.77)	1.26 (0.75, 2.12)	0.37

Abbreviations: no, number; ref, reference.
Model 1 is adjusted for age, sex, cohort and time awake.
Model 2 is additionally adjusted for smoking, number of comorbidities, alcohol intake and education.
Model 3 is additionally adjusted for body mass index, cholesterol, high-density lipoprotein cholesterol and systolic blood pressure.
Model 4 is model 2 and additionally adjusted for physical activity, the 24h activity rhythm (i.e. interday stability, intraday variability) and the disability score.

Supplement 3.2.3. Association between sedentary time and mortality in non-workers (n=1,217), the Rotterdam Study, 2004-2015

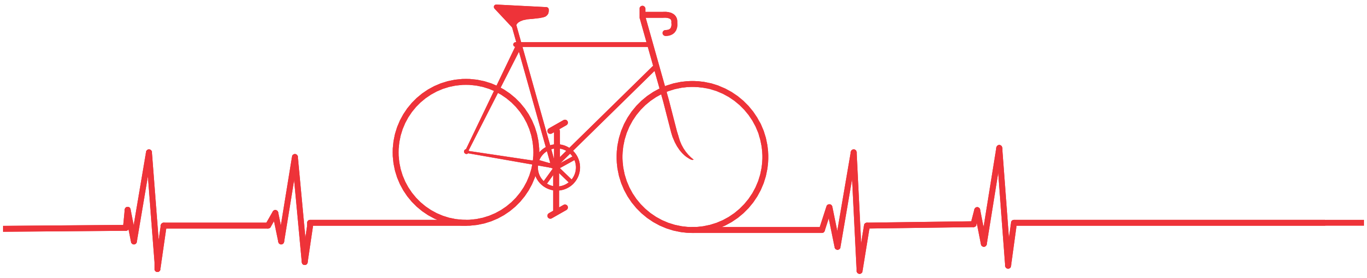
	Continuous analysis	Categorical analysis			
	Per 1 hour more	Low sedentary	Medium sedentary	High sedentary	P for trend
Hours/day sedentary, median (range)		7.0 (<8.0)	9.3 (8.0-11.0)	11.9 (≥11.0)	
No. Participants		376	663	178	
No. deaths		33	98	50	
Confounder adjusted models					
Model 1	1.14 (1.04, 1.25)	1.00 [ref]	1.09 (0.72, 1.65)	2.06 (1.29, 3.29)	0.001
Model 2	1.10 (1.01, 1.20)	1.00 [ref]	1.06 (0.70, 1.61)	1.74 (1.08, 2.81)	0.01
Model 3	1.11 (1.01, 1.21)	1.00 [ref]	1.08 (0.71, 1.64)	1.86 (1.15, 3.03)	0.01
Additional adjustment for activity scores					
Model 4	1.11 (1.01, 1.21)	1.00 [ref]	1.05 (0.68, 1.62)	1.51 (0.92, 2.49)	0.08

Abbreviations: no, number; ref, reference.
Model 1 is adjusted for age, sex, cohort and time awake.
Model 2 is additionally adjusted for smoking, number of comorbidities, alcohol intake and education.
Model 3 is additionally adjusted for body mass index, cholesterol, high-density lipoprotein cholesterol and systolic blood pressure.
Model 4 is model 2 and additionally adjusted for physical activity, the 24h activity rhythm (i.e. interday stability, intraday variability) and the disability score.

Supplement 3.2.4. Association between sedentary time and mortality, using 100 counts per minute as cut off point for sedentary behavior, the Rotterdam Study, 2004-2015

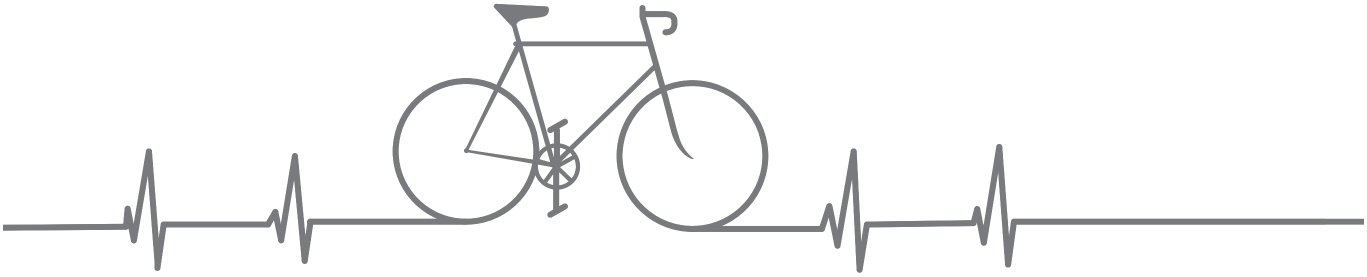
	Continuous analysis	Categorical analysis			
	Per 1 hour more	Low sedentary	Medium sedentary	High sedentary	P for trend
Hours/day sedentary, median (range)		6.0 (<8.0)	8.9 (8.0-11.0)	11.9 (≥11.0)	
No. Participants		1,367	423	49	
No. deaths		125	76	11	
Confounder adjusted models					
Model 1	1.11 (1.03, 1.20)	1.00 [ref]	1.16 (0.86, 1.58)	3.27 (1.73, 6.16)	0.01
Model 2	1.07 (0.99, 1.15)	1.00 [ref]	1.04 (0.76, 1.41)	2.63 (1.37, 5.05)	0.11
Model 3	1.07 (0.99, 1.15)	1.00 [ref]	1.05 (0.77, 1.43)	2.53 (1.31, 4.88)	0.11
Additional adjustment for activity scores					
Model 4	1.03 (0.95, 1.12)	1.00 [ref]	0.93 (0.67, 1.28)	2.02 (1.03, 3.94)	0.50

Abbreviations: no, number; ref, reference.
Model 1 is adjusted for age, sex, cohort and time awake.
Model 2 is additionally adjusted for smoking, number of comorbidities, alcohol intake and education.
Model 3 is additionally adjusted for body mass index, cholesterol, high-density lipoprotein cholesterol and systolic blood pressure.
Model 4 is model 2 and additionally adjusted for physical activity, the 24h activity rhythm (i.e. interday stability, intraday variability) and the disability score.



Chapter 4

Activity and Cardiovascular health



Chapter 4.1

Physical activity types and coronary heart disease risk

Manuscript based on this chapter:
Koolhaas CM, Dhana K, Golubic R, Schoufour JD, Hofman A, van Rooij FJ, Franco OH. Physical activity types and coronary heart disease risk in middle-aged and elderly persons: The Rotterdam Study. *Am J Epidemiol*. 2016 Apr 15;183(8):729-738.

ABSTRACT

Background: Physical activity (PA) is associated with decreased risk of coronary heart disease (CHD). The specific PA types that provide beneficial effects in an older population remain unclear.

Methods: We assessed the association of total PA, walking, cycling, domestic work, sports and gardening with CHD by using Cox proportional hazard models among 5,901 participants aged >55 (median age: 67 years) from the prospective population-based Rotterdam Study, enrolled between 1997 and 2001. Activities were categorized into tertiles and the lowest tertiles were used as reference. In the multivariable model we adjusted for, age, gender, smoking, alcohol consumption, education, diet and other PA types.

Results: During 15 years of follow-up (median:10.3 years, interquartile range: 8.0-11.8 years), 642 participants (10.9%) experienced a CHD event. In the multivariable model, the respective hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the medium and high category compared to the low category were: 0.79 (0.66, 0.96) and 0.71 (0.58, 0.87) for total PA, 0.76 (0.63, 0.92) and 0.70 (0.57, 0.88) for cycling, and 0.81 (0.66, 0.98) and 0.71 (0.56, 0.90) for domestic work. Walking, sports and gardening were not associated with CHD.

Conclusion: In this long-term follow-up study of older adults domestic work and cycling were associated with reduced CHD risk. PA should be promoted in this population with the aim to prevent CHD.

INTRODUCTION

Over the last decades, numerous observational epidemiologic studies have demonstrated that physical activity (PA) is inversely related to cardiovascular morbidity and mortality.[1, 2] According to recent meta-analyses, regular PA of moderate to vigorous intensity may contribute to up to 27% reduced risk of coronary heart disease (CHD).[3, 4] Previous studies have mainly focused on the effect of overall leisure time PA , whereas it remains unclear what specific PA types contribute most to the beneficial effects of PA. Only a few studies have addressed the impact of different types of PA on CHD.[5-7] Moreover, several studies documented a beneficial association between walking and CHD risk,[8, 9] but evidence of the influence of cycling and domestic work remains scarce.[6, 10-12]

Recently, one study[12] investigated the association between different PA types and cardiovascular disease (CVD) in young and middle-aged adults and found a beneficial association with sports and cycling. However, PA levels tend to decrease with age[13] and PA types in which older adults engage differ markedly from the activities performed by younger and middle-aged adults.[14] For example, domestic work contributes to approximately 35% to the PA energy expenditure of elderly adults and only around 27% and 19% in middle-aged and younger adults, respectively.[14] This raises the question what kind of activities are beneficially associated with CHD in an older population. The few studies in older adults showed a beneficial association between walking and CHD risk,[1, 15] but did not focus on other PA. Therefore, we aim to examine the association between PA and CHD incidence in an older population, aged 55 years and over. More specifically, we will assess independent and combined associations between walking, cycling, sports, domestic work and gardening and CHD.

METHODS

Study population

This study was embedded within the Rotterdam Study (RS), a prospective population-based cohort study among subjects aged 55 years or older in the municipality of Rotterdam, the Netherlands. The baseline examination was completed between 1990 and 1993. In 2000-2001, the Rotterdam Study was extended with 3,011 participants who had become ≥ 55 years old or had moved into the study district. For the current study, we used data from the participants attending the third examination of the original cohort (RS-I-3, between 1997 and 1999; n = 4,796) and the participants attending the first examination of the extended cohort (RS-II-1, between 2000 and 2001; n=3,011).[16] Of this combined total, 7,310 participants completed PA collection (see Figure 4.1.1). Following, 52 subjects were excluded due to not provided, or withdrawn, informed consent for collection of follow-up data and 8 were excluded due to missing follow-up data. Subjects with previous CHD (n=622), stroke (n=230), heart failure (n=187) and atrial fibrillation (n=291) were also excluded. Finally, 19 cases were deleted due to unreliable completion of PA data collection. Eventually, 5,901 subjects were included in the analyses. To collect the baseline information, trained research assistants interviewed the participants at home. All subjects gave written informed consent, and the study protocol was approved by the medical ethics committee of Erasmus University, Rotterdam. Detailed information on the design of the Rotterdam Study can be found elsewhere.[16]

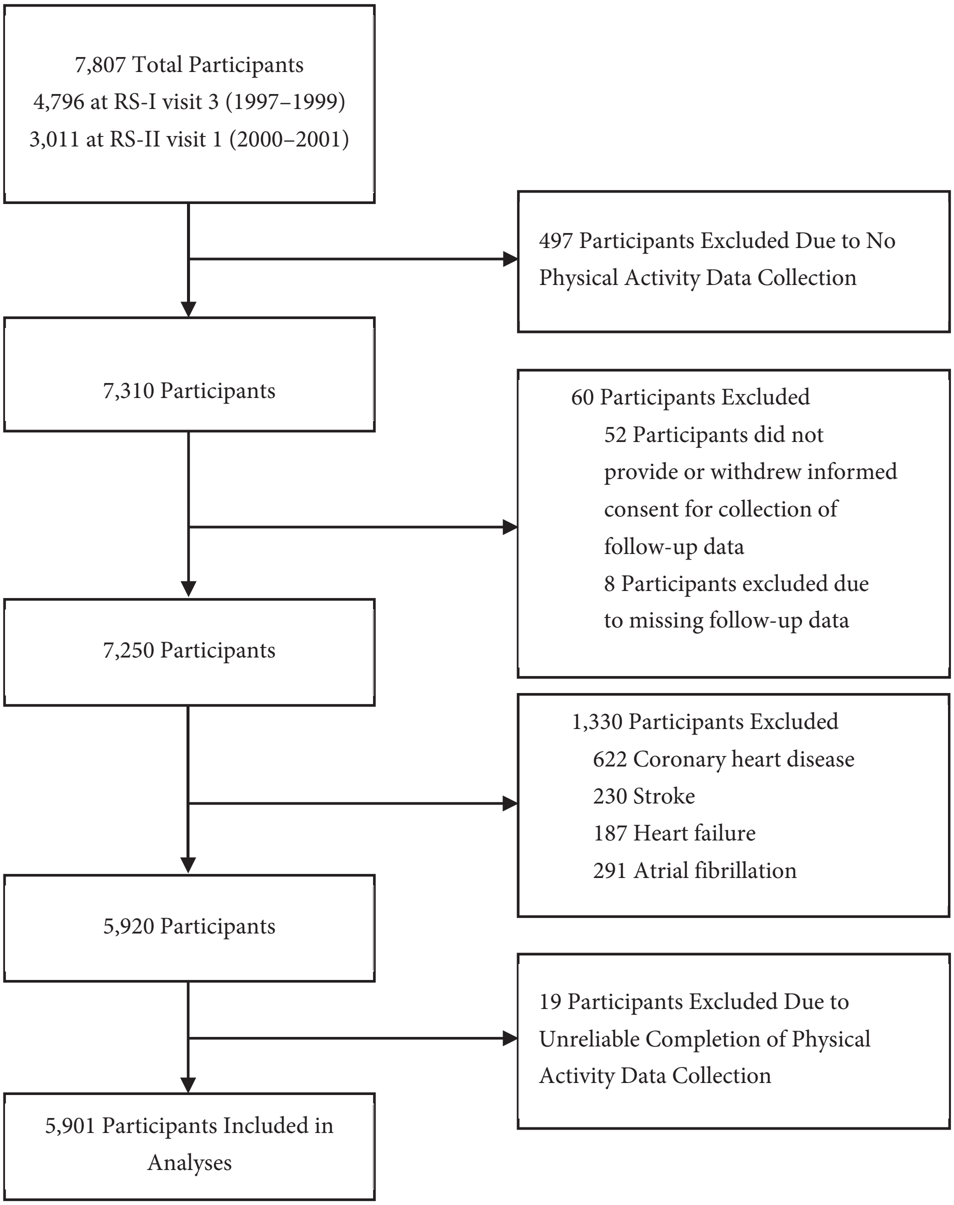


Figure 4.1.1. Flow chart of participant inclusion for the Rotterdam Study, 1997-2012.

Physical activity assessment

PA levels were assessed with an adapted version of the Zutphen Physical Activity Questionnaire.[17] This questionnaire has been validated in which the test-retest reliability was 0.93 and the correlation with doubly labelled water was 0.61.[18] The original Zutphen questionnaire contains questions regarding walking, cycling, sports, gardening and hobbies. In the current study questions on housekeeping activities were added to attain a more complete assessment of PA levels.

Participants were asked how many hours per week they spent in each activity in the past year. To address seasonal variability in PA, participants were asked whether they only participated in a particular activity during summer or winter (e.g. sports, gardening). When answered confirmative, we calculated a weighted estimate by dividing the reported time by two. Furthermore, the questionnaire provided one question in which participants could mention all sports they participated in that were not captured by previous questions. If multiple sports were mentioned, we assumed that time spent in these sports was equally distributed.

To quantify activity intensity, we used metabolic equivalent of task (MET). We assigned MET-values to all activities mentioned in the questionnaire, according to the 2011 updated version of the Compendium of Physical Activities.[19] Sports that were not in this compendium and to which no MET-value could be assigned (e.g. under water hockey, roller skiing) were not used in the analyses (n=33; 2.8%).

Finally, we multiplied MET-values of specific activities with time (in hours) per week spent in that activity to calculate MET·hours·week^{-1} in total PA, defined as the sum of cycling, walking, sports, domestic work and gardening, and in every type of PA (cycling, walking, sports, domestic work, gardening).

Cardiovascular risk factors (covariates)

Information on cardiovascular risk factors was collected through home interviews or was measured at the study centre visit as described previously.[20, 21] Briefly, alcohol use was defined as the amount of glasses per day. Education was divided in primary, junior vocational/academic education and higher vocational/academic education. Smoking was divided into two categories: current and other (former and never). Height and weight were measured, with which body mass index was calculated (kg/m^2). Diabetes mellitus was defined as the use of blood glucose-lowering medication, a random or postload serum glucose level of 11.1 mmol/L or higher[22] or a fasting serum glucose level of 7.0 mmol/L or higher[22] and used as a binary variable (yes/no). Concentration of serum total cholesterol and high-density lipoprotein cholesterol was determined using an automated enzymatic procedure (Boehringer Mannheid System, Mannheim, Germany) and expressed in mg/dl. Two seated blood pressure measurements were obtained at the right brachial artery using a random zero sphygmomanometer and the mean of two consecutive measurements expressed in mmHg was used in analyses as a continuous variable. Hypertension was defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or use of blood pressure–lowering drugs with the indication of hypertension. Medication use was assessed during the home interview. Dietary information was not collected at the same time as PA data collection, therefore we used diet information measured in the first wave (1989-1993) of the original cohort (RS-I) and in the third wave (2011-2012) of the extended cohort (RS-II). Information on diet were obtained through a 170-item validated semi quantitative food frequency questionnaire.[23] From the questionnaire an overall healthy diet score representing adherence to the Dutch dietary guidelines was calculated, as described previously.[24]

Clinical outcome

The main outcome measure under study was CHD, defined as fatal or non-fatal myocardial infarction, surgical or percutaneous coronary revascularization procedure (as a proxy for unstable or incapacitating angina), or death due to CHD.[25] Data on clinical outcomes including CHD were collected through an automated follow-up system involving digital linkage of the study database to medical records maintained by general practitioners working in the research area. Trained research assistants collected notes, outpatient clinic reports, hospital discharge letters, electrocardiograms, and imaging results from general practitioner records and hospital records. Subsequently, research physicians independently adjudicated all data on potential events. Afterwards, medical specialists whose judgments are considered decisive reviewed the potential cases. Information on vital status was additionally obtained from the central registry of the municipality of the city of Rotterdam. Follow-up was complete until January 1, 2012.

Statistical analysis

Total PA and PA types were categorized into tertiles. For activities not practiced by more than 60% of the population (cycling, gardening, sports), the bottom category for PA levels was no participation and the remaining two categories were divided by using the median value.[26] PA types that were significantly associated with CHD were combined to assess the combined association with CHD risk. In this procedure, each tertile of a certain PA type was combined with every tertile of the other PA type, creating 9 groups in total. We investigated the associations between the PA variables and CHD with Cox proportional hazards in three serially adjusted models, after confirming that the assumption for proportional hazards was met on the basis of Schoenfeld residuals. Model 1 was adjusted for age and sex. In model 2 we additionally adjusted for behavioral risk factors, including smoking, alcohol consumption, education, diet and the other PA types. Model 3 was additionally adjusted for biological risk factors, including body mass index, total and high-density lipoprotein high-density lipoprotein cholesterol, diabetes, lipid reducing agents, systolic blood pressure and anti-hypertensive medication. The decision to include confounders in the multivariable regression models was based on previous literature or >10%-change of the effect estimate in the crude model.[6, 7, 12]

Total PA and PA types were entered as categorical variables (tertiles) in the separate models. Additionally, PA variables in which participation was over 60% (i.e. total PA, walking and domestic work) were analyzed continuously per 10 MET·hours·week^{-1} increase. The underlying time-scale in these models was follow-up time, defined as the time between PA assessment and the first fatal or non-fatal CHD event, death, emigration, or censoring at January 1, 2012. There was no interaction for any PA variable with gender or age (p >.05 for all). However, we conducted several sensitivity analyses using stratified models by sex and age (below/above median of 67 years). We investigated the possible effect of reverse causation, by excluding the events in the first two years. Also, we repeated analyses by excluding domestic work, to make sure our results were not driven by that variable. Moreover, 12.9% (n=759) was employed at baseline, but we did not collect information on occupational PA. Therefore, we repeated our analyses in non-workers. Additionally, we repeated the analyses in the original dataset without imputation (n= 4,232). Finally, we stratified our models by fatal and non-fatal outcomes.

Our data contained missing data for diet (26.5%), high-density lipoprotein cholesterol (13.1%), total cholesterol (12.1%) and diabetes (11.4%). Other covariates had <10% missing data. We used multiple imputation (n=5 imputations) by the Expectation Maximization method. All analyses were conducted using SPSS software version 20 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp) and R (3.0.1).

RESULTS

Baseline characteristics of the study population are shown in Table 4.1.1 and the proportion of participants who reported engaging in the considered PA types is shown in Figure 4.1.2. The five most mentioned sports per gender are displayed in Supplement 4.1.1. During 15 years of follow up (median: 10.3 years, interquartile range: 8.0-11.8 years), there were 642 (10.9%) CHD events, of which 284 (44.2%) were fatal.

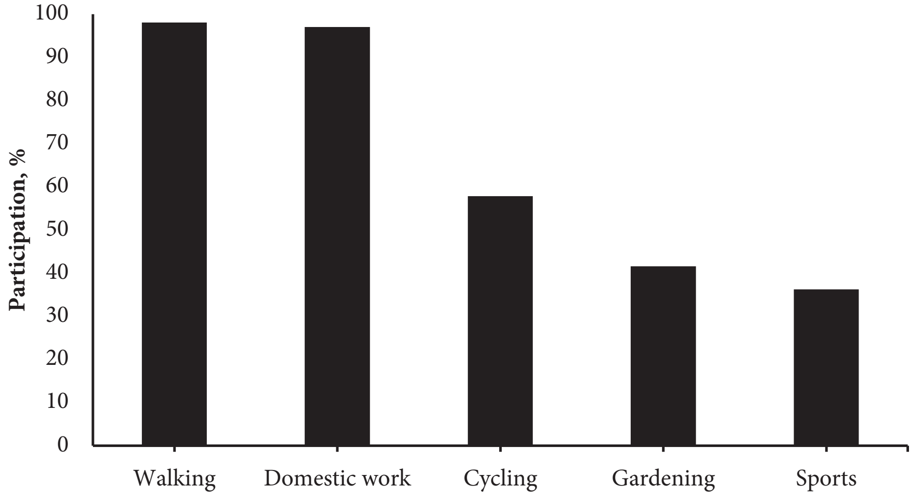


Figure 4.1.2. Proportion of participants by physical activity type for the Rotterdam Study, 1997-2012.

Table 4.1.1. Baseline participant characteristics by tertile of total PA, Rotterdam Study, 1997-2012

	Tertiles of total PA, MET·hours·week[-1]		
Median (range), MET·hours·week[-1]	42.0 (<61.4)	77.5 (61.5-96.9)	126.7 (≥97.0)
Participants, n (%)	1,967 (33.3)	1,968 (33.3)	1,966 (33.3)
Demographic factors			
Age, years	70.7 (9.7)	68.0 (7.7)	66.9 (7.0)
Female, n (%)	916 (46.6)	1,298 (66)	1,413 (71.9)
Primary education, n (%)	754 (38.3)	852 (43.3)	914 (46.5)
Physical activity			
Cycling, hours/week	0.8 (1.5)	2.0 (2.5)	3.9 (4.5)
Gardening, hours/week	0.4 (0.9)	0.8 (1.9)	1.7 (3.3)
Walking, hours/week	4.4 (3.1)	7.8 (4.5)	15.8 (10.2)
Sports, hours/week	0.5 (1.5)	1.1 (2.1)	2.1 (3.7)
Domestic work, hours/week	6.7 (4.6)	12.6 (5.6)	17.6 (8.2)
Lifestyle factors			
Alcohol, glasses/day	1.1 (1.6)	1.0 (1.6)	1.0 (1.2)
Currently smoking	473 (24)	382 (19.4)	374 (19)
Biological risk factors			
BMI[a]	27.2 (4.2)	27.1 (4.1)	26.7 (3.9)
Cholesterol level, mg/dl	222.8 (37.8)	227.0 (35.8)	231.0 (36.8)
HDL-cholesterol level, mg/dl	51.9 (15.1)	55.0 (15.2)	56.1 (15.0)
Systolic blood pressure, mmHg	146.2 (21.0)	143.8 (22,0)	141.9 (20.7)
Having diabetes, n (%)	353 (17.9)	248 (12.6)	201 (10.2)
Using serum lipid reducing agents, n (%)	154 (7.8)	215 (10.9)	180 (9.2)
Using anti-hypertensive medication with the indication of hypertension, n (%)	477 (24.3)	492 (25)	403 (20.5)
Cardiovascular cases			
CHD event, n (%)	272 (13.8)	195 (9.9)	175 (8.9)
Fatal CHD event, no., n (%)	140 (7.1)	73 (3.7)	71 (3.6)
Time to event, years	8.5 (3.7)	9.6 (3.1)	10.2 (3.0)

Abbreviations: BMI, body mass index ; CHD, coronary heart disease; HDL, high-density lipoprotein; MET, metabolic equivalent of task; no, number; PA, physical activity
Data are presented as mean (SD), unless otherwise stated.
[a] Weight (kg)/height (m)^2

Table 4.1.2 presents multivariable-adjusted hazard ratios (HRs) with their 95% confidence interval (CI) for total PA and every PA type. In model 2, total PA, cycling and domestic work were strongly associated with reduced CHD risk. Walking, gardening and sports were not associated with CHD risk in any model. Additional adjustment for biological risk factors in model 3 only slightly attenuated the associations and therefore we will present the results of the second model.

For total PA, the median (interquartile range) levels across categories were 42.0 (29.5-52.5), 77.5 (69.5-86.1) and 126.7 (108.8-150.9) MET·hours·week^{-1}, corresponding to 1.5, 2.8 and 4.5 hours a day of moderate activity of 4 METs. In model 2, compared to the lowest category, the respective HR (95% CI) of the moderate and high category were 0.79 (0.66, 0.96) and 0.71 (0.58, 0.87), with P for trend, <0.001. Each 10 MET·hours·week^{-1} increment of total PA, which is equivalent to an average 21 minutes per day of PA of 4 METs, reduced CHD risk with 4% (HR = 0.96; 95% CI: 0.94, 0.98).

We considered cycling equivalent to 4.0 METs. The median (interquartile range) levels of cycling across categories were 0, 6.0 (3.0-9.0) and 24.0 (16.0-32.0) MET·hours·week^{-1}, which corresponds to 0, 13 and 51 minutes per day. In model 2, compared to the low category, the respective HR (95% CI) of the medium and high category were 0.76 (0.63, 0.92) and 0.70 (0.57, 0.88) respectively (P for trend, <0.001).

For domestic work, we calculated the average intensity to be 3.5 METs.[19,21] The median (interquartile range) levels of domestic work across categories were 12.9 (6.5-19.0), 36.0 (31.0-41.3) and 59.5 (52.6-69.6) MET·hours·week^{-1}, equivalent to 32, 88 and 146 minutes per day. In model 2, compared to the low category, the HR (95% CI) of the medium and high category were 0.81 (0.66, 0.98) and 0.71 (0.56, 0.90), respectively, with P for trend 0.004. Each 10 MET·hours·week^{-1} increment of domestic work, equivalent to an average 25 minutes per day of domestic work, reduced CHD risk with 6% (HR = 0.94; 95% CI: 0.90, 0.99).

In model 2, engaging in both cycling and domestic work revealed a stronger association with CHD risk than these separate activity types (Figure 4.1.3). Compared to the lowest category of combined domestic work and cycling (i.e. low category of domestic work and low category of cycling), the strongest protective association was seen for the combination of the medium category of cycling and the high category of domestic work, reflecting median 146 minutes of domestic work and 13 minutes of cycling a day [HR = 0.46 (95% CI: 0.31, 0.67)].

In our sensitivity analysis split by age, our findings did not materially change (Supplement 4.1.2). Analyses split by gender revealed slightly stronger associations for women than for men, for total PA, cycling and domestic work (Supplement 4.1.3). Excluding events in the first 2 years, excluding domestic work or workers or repeating our analyses in the original dataset without imputation, did not change the results significantly, although some associations were no longer significant (Supplement 4.1.4 – Supplement 4.1.7). Stratifying our analyses by fatal and non-fatal CHD events indicated that the associations were stronger for fatal events (Supplement 4.1.8).

DISCUSSION

In this population-based study of adults aged 55 and over, domestic work and cycling were specific PA types strongly associated with decreased CHD risk. Total PA was also inversely associated with CHD incidence. These associations remained after adjustment for behavioral and biological risk factors and in several sensitivity analyses. The results of our study also suggest that engaging in both cycling and domestic work was strongly related to a reduction in CHD incidence.

We found a linear, inverse association between total PA and CHD risk, which is in agreement with previous studies.[3, 4] Moreover, we found the association to be stronger for fatal events than for non-fatal events, a finding that has been reported before.[27] The plausible biological mechanisms via which PA may reduce CHD risk include reducing blood pressure and body weight, increasing high-density lipoprotein cholesterol and maintaining normal glucose tolerance.[28] However, adjusting for these factors in model 3 did not change our results significantly and it has been reported that only ~35% of the risk reduction can be attributed to this pathway.[28]

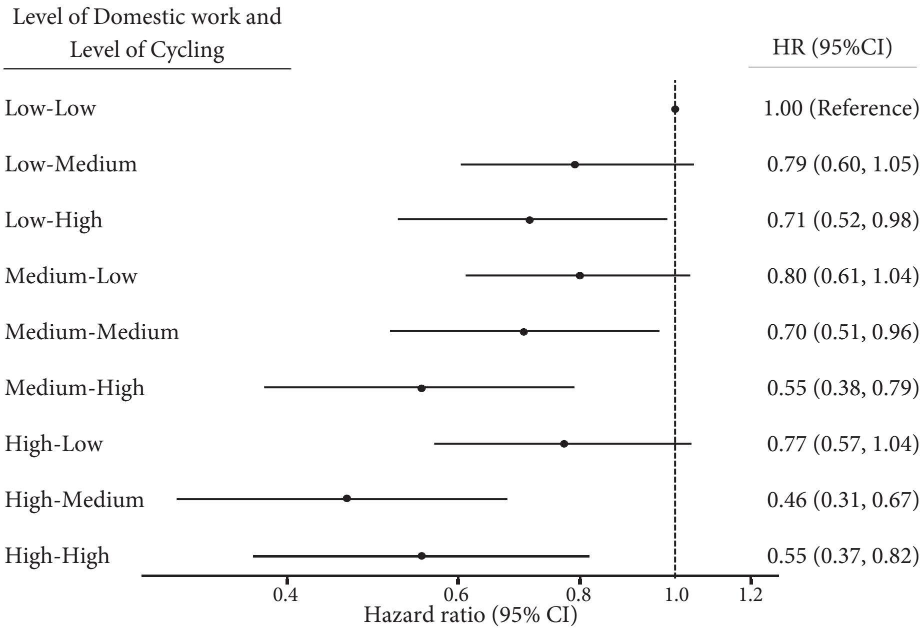


Figure 4.1.3. Hazard ratios and 95% confidence intervals of coronary heart disease for the combined domestic work and cycling variable in multivariable model 2, Rotterdam Study, 1997-2012.

In every combination, the tertile of domestic work is mentioned first and cycling second. Model 2 is adjusted for age, sex, all other physical activity types, smoking, alcohol consumption, diet and education. Circles indicate hazard ratios; horizontal lines indicate 95% confidence interval.
Abbreviations: HR, hazard ratio.

Table 4.1.2. Association between total PA and different types of PA and CHD, Rotterdam Study, 1997-2012

Activity Type and Tertile of Physical Activity	Median MET-hours per week	Range	No. Participants	No. CHD events	Model 1[a]		Model 2[a]		Model 3[a]	
					HR	95% CI	HR	95% CI	HR	95% CI
Total Physical Activity[b]										
1	42.0	<61.4	1,967	272	1.00	Referent	1.00	Referent	1.00	Referent
2	77.5	61.5-96.9	1,968	195	0.76	0.63, 0.92	0.79	0.66, 0.96	0.81	0.67, 0.99
3	126.7	≥97.0	1,966	175	0.69	0.57, 0.84	0.71	0.58, 0.87	0.74	0.61, 0.91
Per 10 MET-hours/week					0.96	0.94, 0.98	0.96	0.94, 0.98	0.97	0.95, 0.99
P for trend					<0.001		<0.001		0.003	
Walking[c]										
1	9.0	<15.0	2,102	223	1.00	Referent	1.00	Referent	1.00	Referent
2	21.0	15.1-30.0	2,009	235	1.10	0.92, 1.32	1.17	0.97, 1.41	1.16	0.96, 1.40
3	49.5	≥30.1	1,790	184	0.89	0.73, 1.08	0.98	0.80, 1.20	0.97	0.79, 1.19
Per 10 MET-hours/week					0.97	0.94, 1.01	0.99	0.96, 1.02	0.99	0.96, 1.02
P for trend					0.28		0.88		0.85	
Domestic work[d]										
1	12.9	<25.0	1,967	280	1.00	Referent	1.00	Referent	1.00	Referent
2	36.0	25.1-46.5	1,970	203	0.78	0.63, 0.95	0.81	0.66, 0.98	0.81	0.66, 0.99
3	59.5	≥46.6	1,964	159	0.67	0.53, 0.84	0.71	0.56, 0.90	0.70	0.55, 0.89
Per 10 MET-hours/week					0.93	0.89, 0.97	0.94	0.90, 0.99	0.94	0.90, 0.98
P for trend					<0.001		0.004		0.003	
Cycling[e]										
1	0.0	0.0	2,488	324	1.00	Referent	1.00	Referent	1.00	Referent
2	6.0	0.0-12.0	1,871	182	0.73	0.60, 0.88	0.76	0.63, 0.92	0.80	0.65, 0.97
3	24.0	≥12.1	1,542	136	0.65	0.53, 0.81	0.70	0.57, 0.88	0.76	0.61, 0.95
P for trend					<0.001		<0.001		0.01	

Table 4.1.2 (continued). Association between total PA and different types of PA and CHD, Rotterdam Study, 1997-2012

Activity Type and Tertile of Physical Activity	Median MET-hours per week	Range	No. Participants	No. CHD events	Model 1[a]		Model 2[a]		Model 3[a]	
					HR	95% CI	HR	95% CI	HR	95% CI
Gardening[f]										
1	0.0	0.0	3,448	401	1.00	Referent	1.00	Referent	1.00	Referent
2	4.0	0.0-6.0	1,514	138	0.86	0.70, 1.05	0.88	0.71, 1.07	0.90	0.74, 1.10
3	14.0	≥6.1	939	103	0.92	0.73, 1.14	0.99	0.79, 1.23	0.99	0.79, 1.24
P for trend					0.26		0.62		0.70	
Sports[g]										
1	0.0	0.0	3,768	439	1.00	Referent	1.00	Referent	1.00	Referent
2	5.5	0.0-7.6	1,073	96	0.80	0.64, 1.00	0.82	0.66, 1.03	0.84	0.67, 1.05
3	19.9	≥7.7	1,060	107	0.90	0.73, 1.12	0.92	0.74, 1.15	0.98	0.79, 1.23
P for trend					0.16		0.25		0.55	

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; NA, not applicable; PA, physical activity; T, tertile.

[a] Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for all other PA types, smoking, alcohol consumption, diet and education. Model 3 was additionally adjusted for BMI, total and HDL-cholesterol, diabetes, lipid reducing agents, systolic blood pressure and hypertension.

[b] Total PA is composed of all PA types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 1.5, 2.8 and 4.5 hours per day of moderate PA equivalent of 4 METs.

[c] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 26, 60 and 141 minutes per day of walking.

[d] Average domestic work is equivalent to 3.5 METs.[19] The median levels of domestic work across categories are therefore equivalent to 32, 88 and 146 minutes per day of domestic work.

[e] Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 51 minutes per day of cycling.

[f] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 30 minutes per day of gardening.

[g] Average sports is equivalent to 5.5 METs. The median levels of sports across categories are therefore equivalent to 0, 9 and 31 minutes per day of sports.

Other plausible mechanisms for decreased CHD risk are improved endothelial function, stabilization of vulnerable plaques preventing plaque rupture and reduced myocardial oxygen demand.[29] Possibly, these adaptations over the years might protect against more severe manifestations of CHD. Since most of the research in this field has been conducted in middle-aged adults,[30] further research is needed to gain more insight in the mechanisms behind the association between PA and CHD risk in older adults.

For cycling, we found a linear decrease of CHD risk for participants in the medium to high category compared with the lowest. The difference in CHD risk between the medium (cycling 13 min/day) and high category (cycling 51 min/day) was 6%, indicating that the largest benefits are achieved by going from no cycling to any level of cycling, a trend that is common for other PA types as well.[4] We found one study in agreement with our findings, reporting an inverse association between cycling and risk of CHD death.[31] Another study[6] did not find an independent association between cycling and CHD risk in 40 to 75-year-old men, which might be because only 7% of their study population spent more than 1 hour per week in cycling. Another possible explanation is that individuals started integrating cycling in their everyday life in an effort to counteract existing disease. In contrast, cycling is a common way of commuting in the Netherlands, and a large proportion of participants in our study participated in cycling on a weekly basis (57.8%).

Domestic work is an important contributor of daily PA, especially in the elderly.[14] For this activity we found a 6% reduced risk for every 2.8 hours per week increment and we found a linear decrease of CHD risk for participants in the medium to high category, compared to the lowest. Increasing from 32 to 88 minutes a day of domestic work decreased CHD risk with 19%. Our results resemble one study in a similar study population,[10] reporting that men and women doing demanding household work had a 22% and 45% reduced risk of having a fatal or non-fatal myocardial infarction, respectively. Another study[11] found no association between intense domestic PA and CVD, which might be explained by the younger age group (mean age 52 years) and the use of only intense domestic PA, whereas domestic work was assessed in a broad sense in the current study.

We did not find an association between walking and CHD, whereas several large prospective investigations[1] and recent meta-analyses[8,32] found inverse associations between walking and CHD. Differences in the findings can be attributed to the different study populations, different methods used to measure walking and the different definitions of walking.[8, 32] Some studies used only walking for transport, whereas other studies assessed walking in a broad sense, as was also done in our study. For example, not only taking a walk, but also walking for transportation and shopping were taken into account.[1, 6] In two studies with walking patterns comparable with the current population,[12, 33] no association with CVD was observed, suggesting that beneficial influence of walking may be limited to relatively inactive populations.[12] Additionally, the fact that we used walking duration instead of walking pace might have influenced our results, since walking pace is a stronger predictor of CHD than walking volume and walking volume does not adequately cover the intensity used during walking.[6, 8]

In the current study, we did not find an association between CHD and gardening or sports. Two studies investigating the independent association between gardening and all-cause mortality[26] or CVD risk,[12] did not report a substantial protective association either. The non-significant association between sports and CHD observed in this study is not in agreement with previous literature.[9, 33-35] Our finding might be explained by the low number of participants engaging in any sport activities and the low duration, leading to insufficient power to detect an association. This low percentage of sports engagement is directly related with the age distribution of our population. In our study, 36.2% of participants engaged in any sporting activities, with a mean duration of 3.5 hours (SD=3.7) per week. This proportion of participants engaging in sports is similar as found in other studies,[36-38] however, a lower rate has also been reported.[14]

When we stratified our analyses by gender, we found the associations for total PA, cycling and domestic work to be stronger in women than in men. This gender difference has been reported before[4, 35] however the specific mechanism remains unclear. Previous evidence does not support more favorable effects of PA on CHD risk factors (including lipid levels, blood pressure, cardiorespiratory fitness, vascular indicators and metabolic syndrome) among women compared with men.[39] The differences may partly be due to differences in PA intensity and PA types in which the men and women engage in[35] and in potential gender differences in ethipathogenesis of cardiovascular disorders. Another explanation might be the difference in perception of the intensity of PA, and therefore a difference in answering the questions between men and women. For example, a recent study has shown men to over-report moderate to vigorous PA more than women.[40]

We acknowledge that our study has limitations. First, it may be hypothesized that people in poor health participate in PA less than others, creating the opportunity for reverse causation. However, repeating our analyses after exclusion of cases that occurred within the first two years of follow up revealed comparable results. Second, we collected no information about occupational PA, so we could not adjust for this in our main analyses. However, excluding these participants (n=759, 12.9%) in our sensitivity analyses also revealed comparable results. Despite this, we cannot rule out the possibility of residual confounding from lifetime exposure to physical activities at work, which can influence CVD risk.[41] Third, we only measured PA at baseline, which can cause misclassification of PA over time, since research showed PA levels of adults to change and decline with age.[42] Moreover, our results are based on self-reported PA. Although our questionnaire has shown to be valid and reliable[18] potential recall bias and social desirability cannot be excluded. These last two limitations could have resulted in bias towards the null hypothesis. Furthermore, diet was measured in the first wave (1989-1993) for the original cohort (RS-I) and in the third wave (2011-2012) of the extended cohort (RS-II). Therefore, we cannot fully exclude the possibility of residual confounding by diet. Finally, we estimated the PA intensity according to the Compendium of Physical Activities,[19] which has a few drawbacks. First, it might not capture the energy expenditure of older adults accurately.[19] However, we carefully took into consideration the age of the participants while assigning METs to activities. Second, there probably was some heterogeneity in the intensity in which participants engaged in the different activity types. This might have led to misclassification of participants with either higher or lower intensity levels than our assigned values. Since this misclassification was non-differential, this could have biased our estimates towards the null hypothesis. Additionally, this heterogeneity might be directly linked to the age and physical fitness of the participants. Therefore, using relative intensity might be more accurate.[43]

Major strengths of the current study are its prospective population-based design, large sample size of adults aged over 55 and relatively long follow-up period. Furthermore, we had an accurate method of outcome ascertainment and were able to adjust for several factors, thereby minimizing the possibility of the observed associations being explained by confounding. In addition, we included a number of different activities while adjusting for the remaining activities, which enabled us to examine their independent associations with CHD.

Conclusions

In summary, in this population of older adults, we found that total PA, and more specifically cycling and domestic work, were associated with lower CHD risk. Engaging in both cycling and domestic work resulted in greater risk reduction than performing either activity alone. Therefore, public health efforts should focus on promoting PA with the aim to prevent CHD.

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SUPPLEMENT CHAPTER 4.1

Supplement 4.1.1. Five most frequent reported sports for men and women in the Rotterdam Study, 1997-2012

	Sport	Ainsworth code[a]	Intensity (MET)[a]	Ainsworth description[a]	No. (%) of men or women	
Men	Billiards	15080	2,5	billiards	236	(10.4)
	Swimming	18240	5,8	swimming laps, freestyle, front crawl, slow, light or moderate effort	208	(9.1)
	Tennis	15675	7,3	tennis, general	158	(6.9)
	Fishing	4001	3,5	fishing, general	136	(6.0)
	Gymnastics	15300	3,8	gymnastics, general	121	(5.3)
Women	Gymnastics	15300	3,8	gymnastics, general	445	(12.3)
	Swimming	18240	5,8	swimming laps, freestyle, slow, light or moderate effort	385	(10.6)
	Yoga	2150	2,5	yoga, hatha	142	(3.9)
	Stretching	2101	2,3	stretching, mild	178	(4.9)
	Tennis	15675	7,3	tennis, general	130	(3.6)

Abbreviations: MET, metabolic equivalent of task; no, number

[a] This information was derived from the Compendium of Physical Activities 2011.[1]

Supplement 4.1.2. Association between total PA and different types of PA and CHD in age above and below 67 years, in the Rotterdam Study, 1997-2012, presented for model 2

Age ≤ 67 years						Age > 67 years					
Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/CHD events	Model 2[a]		Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/CHD events	Model 2[a]	
				HR	95%CI					HR	95%CI
Total Physical Activity[b]						Total Physical Activity[b]					
1	47.4	<67.3	987/108	1.00	Ref	1	38.2	<55.8	980/153	1.00	Ref
2	84.1	67.4-103.0	987/69	0.78	0.57, 1.06	2	71.3	55.9-89.0	981/126	0.78	0.62, 1.00
3	132.5	≥103.1	986/66	0.73	0.52, 1.01	3	119.1	≥89.1	980/120	0.72	0.56, 0.92
Per 10 MET·hours·week^{-1}				0.96	0.93, 0.99	Per 10 MET·hours·week^{-1}				0.96	0.94, 0.99
P for trend				0.05		P for trend				0.01	
Walking[c]						Walking[c]					
1	9.0	<15.0	1,002/83	1.00	Ref	1	9.0	<13.5	1,100/140	1.00	Ref
2	21.0	15.1-30.0	1,025/91	1.16	0.85, 1.57	2	21.0	13.6-28.5	984/144	1.12	0.88, 1.43
3	43.5	≥30.1	933/69	0.89	0.64, 1.25	3	54.0	≥28.6	857/115	0.95	0.74, 1.23
Per 10 MET·hours·week^{-1}				0.97	0.92, 1.03	Per 10 MET·hours·week^{-1}				0.99	0.96, 1.03
P for trend				0.54		P for trend				0.69	
Domestic work[d]						Domestic work[d]					
1	11.6	<24.2	987/119	1.00	Ref	1	14.0	<25.5	957/157	1.00	Ref
2	36.4	24.3-47.8	987/65	0.67	0.48, 0.95	2	36.2	25.6-45.7	1,058/146	0.87	0.68, 1.12
3	61.1	≥47.9	986/59	0.74	0.49, 1.11	3	58.4	≥45.8	926/96	0.72	0.54, 0.96
Per 10 MET·hours·week^{-1}				0.97	0.92, 1.03	Per 10 MET·hours·week^{-1}				0.99	0.96, 1.03
P for trend						P for trend				0.02	
Cycling[e]						Cycling[e]					
1	0.0	0.0	806/80	1.00	Ref	1	0.0	0.0	1,682/244	1.00	Ref
2	6.0	<12.0	1,147/92	0.79	0.58, 1.08	2	6.0	<10.0	724/90	0.79	0.60, 1.02
3	24.0	≥12.1	1,007/71	0.74	0.53, 1.03	3	22.0	≥10.1	535/65	0.66	0.49, 0.88
P for trend				0.08		P for trend				0.003	

Supplement 4.1.2 (continued). Association between total PA and different types of PA and CHD in age above and below 67 years, in the Rotterdam Study, 1997-2012, presented for model 2

Age ≤ 67 years						Age > 67 years					
Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/CHD events	Model 2		Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/CHD events	Model 2	
				HR	95%CI					HR	95%CI
Gardening[f]						Gardening[f]					
1	0.0	0.0	1,387/121	1.00	Ref	1	0.0	0.0	2,061/280	1.00	Ref
2	2.0	<4.0	815/56	0.80	0.58, 1.10	2	4.0	<6.0	503/72	1.00	0.77, 1.31
3	10.0	≥4.1	758/66	1.03	0.76, 1.40	3	14.0	≥6.1	377/47	0.83	0.60, 1.15
P for trend				0.97		P for trend				0.33	
Sports[g]						Sports[g]					
1	0.0	0.0	1,639/134	1.00	Ref	1	0.0	0.0	2,129/305	1.00	Ref
2	5.5	<11.0	600/44	1.04	0.76, 1.43	2	5.3	<7.6	473/52	0.76	0.56, 1.04
3	21.0	≥11.1	721/65	0.96	0.69, 1.33	3	16.5	≥7.7	339/42	0.80	0.59, 1.09
P for trend				0.87		P for trend				0.07	

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; n/a, not applicable; PA, physical activity; Ps, participants; Ref, referent; T, tertile.

[a] Model 2 was adjusted for age, sex, all other PA types, smoking, alcohol consumption, diet and education.

[b] Total PA is composed of all PA types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 1.7, 3.0 and 4.7 hours per day of moderate PA equivalent of 4 METs in the younger age group and equivalent to 1.4, 2.5 and 4.3 hours per day of moderate PA of 4 METs in the older age group

[c] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 26, 60 and 124 minutes per day of walking in the younger age group and equivalent to 26, 60 and 154 minutes per day of walking in the older age group

[d] Average domestic work is equivalent to 3.5 METs .[1] The median levels of domestic work across categories are therefore equivalent to 28, 89 and 150 minutes per day of domestic work in the younger age group and equivalent to 34, 89 and 143 minutes per day of domestic work in the older age group

[e] Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 51 minutes per day of cycling in the younger age group and equivalent to 0, 13 and 47 minutes per day of cycling in the older age group

[f] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 4 and 21 minutes per day of gardening in the younger age group and equivalent to 0, 9 and 30 minutes per day of gardening in the older age group

[g] Average sports is equivalent to 5.5. The median levels of sports across categories are therefore equivalent to 0, 9 and 33 minutes per day of sports in the younger age group and equivalent to 0, 8 and 26 minutes per day of sports in the older age group

Supplement 4.1.3. Association between total PA and different types of PA and CHD in men and women in the Rotterdam Study, 1997-2012, presented for model 2

Men						Women					
Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/CHD events	Model 2[a]		Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/CHD events	Model 2[a]	
				HR	95%CI					HR	95%CI
Total Physical Activity[b]						Total Physical Activity[b]					
1	33.1	<48.9	758/106	1.00	Ref	1	52.1	<69.1	1,209/138	1.00	Ref
2	65.4	49.0-83.8	758/115	0.98	0.75, 1.28	2	84.2	69.2-103.4	1,209/100	0.84	0.65, 1.10
3	111.5	≥83.9	758/104	0.86	0.65, 1.14	3	132.8	≥103.5	1,209/79	0.66	0.49, 0.88
Per 10 MET·hours·week^{-1}				0.98	0.95, 1.00	Per 10 MET·hours·week^{-1}				0.96	0.93, 0.99
P for trend					0.29	P for trend					0.01
Walking[c]						Walking[c]					
1	9.0	<15.0	823/100	1.00	Ref	1	9.0	<15.0	1,279/123	1.00	Ref
2	21.0	15.1-30.0	768/129	1.40	1.07, 1.83	2	21.0	15.1-30.0	1,241/106	1.01	0.79, 1.30
3	45.5	≥30.1	683/96	1.08	0.81, 1.45	3	51.0	≥30.1	1,107/88	0.91	0.68, 1.21
Per 10 MET·hours·week^{-1}				1.00	0.95, 1.05	Per 10 MET·hours·week^{-1}				0.98	0.94, 1.03
P for trend					0.59	P for trend					0.39
Domestic work[d]						Domestic work[d]					
1	5.6	<11.6	775/105	1.00	Ref	1	28.9	<38.2	1,212/130	1.00	Ref
2	17.2	11.7-24.6	747/118	1.07	0.82, 1.41	2	45.9	38.3-54.0	1,206/97	0.83	0.63, 1.09
3	36.2	≥24.7	752/102	0.86	0.65, 1.14	3	64.6	≥54.1	1,209/90	0.79	0.59, 1.05
Per 10 MET·hours·week^{-1}				0.98	0.92, 1.04	Per 10 MET·hours·week^{-1}				0.93	0.88, 0.99
P for trend					0.29	P for trend					0.09
Cycling[e]						Cycling[e]					
1	0.0	0.0	725/117	1.00	Ref	1	0.0	0.0	1,763/207	1.00	Ref
2	6.0	<12.0	834/116	0.83	0.64, 1.09	2	5.0	<11.0	935/60	0.71	0.52, 0.97
3	24.0	≥12.1	715/92	0.75	0.57, 1.00	3	21.0	≥11.1	929/50	0.68	0.49, 0.96
P for trend					0.05	P for trend					0.01

Supplement 4.1.3 (continued). Association between total PA and different types of PA and CHD in men and women in the Rotterdam Study, 1997-2012, presented for model 2

Age ≤ 67 years						Age > 67 years					
Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/CHD events	Model 2		Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/CHD events	Model 2	
				HR	95%CI					HR	95%CI
Gardening[f]						Gardening[f]					
1	0.0	0.0	1,166/181	1.00	Ref	1	0.0	0.0	2,282/220	1.00	Ref
2	4.0	<6.0	639/78	0.79	0.60, 1.04	2	2.0	<4.0	681/50	1.06	0.77, 1.45
3	14.0	≥6.1	469/66	0.89	0.67, 1.19	3	10.0	≥4.1	664/47	1.06	0.76, 1.47
P for trend				0.28		P for trend				0.69	
Sports[g]						Sports[g]					
1	0.0	0.0	1,402/216	1.00	Ref	1	0.0	0.0	2,366/223	1.00	Ref
2	5.8	<13.1	436/51	0.70	0.51, 0.96	2	4.6	<7.6	661/53	1.01	0.74, 1.37
3	26.9	≥13.2	436/58	0.87	0.65, 1.17	3	15.3	≥7.7	600/41	0.97	0.69, 1.36
P for trend				0.15		P for trend				0.90	

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; n/a, not applicable; PA, physical activity; Ps, participants; Ref, referent; T, tertile.

[a] Model 2 was adjusted for age, sex, all other PA types, smoking, alcohol consumption, diet and education.

[b] Total PA is composed of all PA types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 1.2, 2.3 and 4.0 hours per day of moderate PA equivalent of 4 METs in men and equivalent to 1.9, 3,0 and 4.7 hours per day of moderate PA equivalent of 4 METs in women

[c] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 26, 60 and 133 minutes per day of walking in men and equivalent to 26, 60 and 146 minutes per day of walking in women

[d] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 14, 42 and 89 minutes per day of domestic work in men and equivalent to 71, 112 and 158 minutes per day of domestic work in women

[e] Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 51 minutes per day of cycling in men and equivalent to 0, 11 and 45 minutes per day of cycling in women

[f] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 30 minutes per day of gardening in men and equivalent to 0, 4 and 21 minutes per day of gardening in women

[g] Average sports is equivalent to 5.5. The median levels of sports across categories are therefore equivalent to 0, 9 and 42 minutes per day of sports in men and equivalent to 0, 7 and 24 minutes per day of sports in women

Supplement 4.1.4. Association between total PA and different types of PA and CHD, without domestic work, in the Rotterdam Study, 1997-2012, presented for model 2

Activity Type and Tertile of Physical Activity	Median MET-hours per week	Range	No. Ps/CHD events	Model 2[a]	
				HR	95%CI
Total Physical Activity[b]					
1	13.0	<21.0	1,967/272	1.00	Referent
2	31.5	21.1-43.5	1,968/195	0.82	0.74, 0.90
3	68.9	≥43.6	1,966/175	0.75	0.62, 0.91
Per 10 MET·hours·week^{-1}				0.96	0.94, 0.98
P for trend				0.004	
Walking[c]					
1	9.0	<15.0	2,102/223	1.00	Referent
2	21.0	15.1-30.0	2,009/235	1.13	0.94, 1.36
3	49.5	≥30.1	1,790/184	0.93	0.76, 1.13
Per 10 MET·hours·week^{-1}				0.98	0.95, 1.01
P for trend				0.50	
Cycling[d]					
1	0.0	0.0	2,488/324	1.00	Referent
2	6.0	0.0-12.0	1,871/182	0.75	0.61, 0.92
3	24.0	≥12.1	1,542/136	0.69	0.56, 0.86
P for trend				<.001	
Gardening[e]					
1	0.0	0.0	3,448/401	1.00	Referent
2	4.0	0.0-6.0	1,514/138	0.87	0.71, 1.06
3	14.0	≥6.1	939/103	0.97	0.77, 1.21
P for trend				0.50	
Sports[f]					
1	0.0	0.0	3,768/439	1.00	Referent
2	5.5	0.0-7.6	1,073/96	0.82	0.65, 1.02
3	19.9	≥7.7	1,060/107	0.92	0.74, 1.14
P for trend				0.23	

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; n/a, not applicable; PA, physical activity; Ps, participants; Ref, referent; T, tertile.
[a] Model 2 was adjusted for age, sex, all other PA types, smoking, alcohol consumption, diet and education.
[b] Total PA is composed of all PA types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 0.5, 1.1 and 2.5 hours per day of moderate PA equivalent of 4 METs.
[c] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 26, 60 and 141 minutes per day of walking.
[d] Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 51 minutes per day of cycling.
[e] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 30 minutes per day of gardening.
[f] Average sports is equivalent to 5.5. The median levels of sports across categories are therefore equivalent to 0, 9 and 31 minutes per day of sports.

Supplement 4.1.5. Association between total PA and different types of PA and CHD in non-workers, in the Rotterdam Study, 1997-2012, presented for model 2

Activity Type and Tertile of PA	Median MET-hours per week	Range	No. Ps/CHD events	Model 2[a]	
				HR	95%CI
Total Physical Activity[b]					
1	45.5	<64.3	1,715/238	1.00	Referent
2	80.0	64.4-99.8	1,714/174	0.82	0.67, 1.00
3	128.9	≥99.9	1,713/154	0.72	0.58, 0.90
Per 10 MET·hours·week^{-1}					0.95, 0.99
P for trend				0.003	
Walking[c]					
1	9.0	<15.8	1,712/185	1.00	Referent
2	21.0	15.9-30.0	1,782/205	1.23	1.00, 1.51
3	51.0	≥30.1	1,648/176	1.06	0.86, 1.31
Per 10 MET·hours·week^{-1}					0.96, 1.03
P for trend				0.55	
Domestic work[d]					
1	14.1	<28.0	1,520/224	1.00	Referent
2	36.3	28.1-48.2	1,784/192	0.83	0.67, 1.03
3	59.5	≥48.3	1,838/150	0.70	0.55, 0.90
Per 10 MET·hours·week^{-1}					0.89, 0.98
P for trend				0.01	
Cycling[e]					
1	0.0	0.0	2,256/294	1.00	Referent
2	6.0	<12.0	1,543/144	0.73	0.66, 0.82
3	24.0	≥12.1	1,343/128	0.76	0.61, 0.96
P for trend				0.01	
Gardening[f]					
1	0.0	0.0	3,108/371	1.00	Referent
2	4.0	<6.0	1,211/104	0.80	0.64, 1.00
3	14.0	≥6.1	823/91	0.97	0.77, 1.24
P for trend				0.43	
Sports[g]					
1	0.0	0.0	3,334/394	1.00	Referent
2	5.3	<8.4	905/80	0.81	0.64, 1.03
3	18.0	≥8.5	903/92	0.92	0.73, 1.16
P for trend				0.25	

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; n/a, not applicable; PA, physical activity; Ps, participants; Ref, referent; T, tertile.

[a] Model 2 was adjusted for age, sex, all other PA types, smoking, alcohol consumption, diet and education.

[b] Total PA is composed of all PA types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 1.6, 2.9 and 4.6 hours per day of moderate PA equivalent of 4 METs.

[c] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 26, 60 and 146 minutes per day of walking.

[d] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 34, 89 and 146 minutes per day of domestic work.

[e] Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 51 minutes per day of cycling.

[f] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 30 minutes per day of gardening.

[g] Average sports is equivalent to 5.5. The median levels of sports across categories are therefore equivalent to 0, 8 and 28 minutes per day of sports.

Supplement 4.1.6. Association between total PA and different types of PA and CHD, without cases in first two years in the Rotterdam Study, 1997-2012, presented for model 2

Activity Type and Tertile of PA	Median MET-hours per week	Range	No. Ps/CHD events	Model 2[a]	
				HR	95%CI
Total Physical Activity[b]					
1	42.4	<61.7	1,932/217	1.00	Referent
2	77.8	61.8-97.3	1,932/169	0.85	0.69, 1.04
3	126.9	≥97.4	1,932/151	0.74	0.60, 0.92
Per 10 MET·hours·week^{-1}					0.97
P for trend				0.007	
Walking[c]					
1	9.0	<15.0	2,070/191	1.00	Referent
2	21.0	15.1- 30.0	1,967/193	1.10	0.99, 1.22
3	49.5	≥30.1	1,759/153	0.91	0.73, 1.14
Per 10 MET·hours·week^{-1}					0.99
P for trend				0.45	
Domestic work[d]					
1	13.0	<25.3	1,935/227	1.00	Referent
2	36.4	25.4-46.6	1,929/171	0.82	0.71, 0.94
3	59.5	≥46.7	1,932/139	0.72	0.56, 0.93
Per 10 MET·hours·week^{-1}					0.94
P for trend				0.01	
Cycling[e]					
1	0.0	0.0	2,434/270	1.00	Referent
2	6.0	<12.0	1,841/152	0.75	0.61, 0.93
3	24.0	≥12.1	1,521/115	0.71	0.56, 0.90
P for trend				0.003	
Gardening[f]					
1	0.0	0.0	3,385/338	1.00	Referent
2	4.0	<6.0	1,494/118	0.87	0.70, 1.09
3	14.0	≥6.1	917/81	0.90	0.70, 1.16
P for trend				0.29	
Sports[g]					
1	0.0	0.0	3,687/358	1.00	Referent
2	5.5	<9.3	1,062/85	0.88	0.69, 1.12
3	20.0	≥9.4	1,047/94	1.01	0.79, 1.27
P for trend				0.79	

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; n/a, not applicable; PA, physical activity; Ps, participants; Ref, referent; T, tertile.

[a] Model 2 was adjusted for age, sex, all other PA types, smoking, alcohol consumption, diet and education.

[b] Total PA is composed of all PA types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 1.5, 2.8 and 4.5 hours per day of moderate PA equivalent of 4 METs.

[c] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 26, 60 and 141 minutes per day of walking.

[d] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 32, 89 and 146 minutes per day of domestic work.

[e] Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 51 minutes per day of cycling.

[f] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 30 minutes per day of gardening.

[g] Average sports is equivalent to 5.5. The median levels of sports across categories are therefore equivalent to 0, 9 and 31 minutes per day of sports.

Supplement 4.1.7. Association between total PA and different types of PA and CHD in the original dataset without imputation (n=4232), in the Rotterdam Study, 1997-2012, presented for model 2

Activity Type and Tertile of PA	Median MET-hours per week	Range	No. Ps/CHD events	Model 2[a]	
				HR	95%CI
Total Physical Activity[b]					
1	45.7	<64.5	1,411/195	1.00	Referent
2	80.7	64.6-101.0	1,411/128	0.71	0.56, 0.89
3	131.1	≥101.1	1,410/125	0.69	0.55, 0.87
Per 10 MET·hours·week^{-1}					0.97
P for trend				0.004	
Walking[c]					
1	9.0	<15.0	1,422/148	1.00	Referent
2	21.0	15.1-30.0	1,429/162	1.10	0.88, 1.38
3	52.5	≥30.1	1,381/138	0.94	0.74, 1.19
Per 10 MET·hours·week^{-1}					0.99
P for trend				0.61	
Domestic work[d]					
1	14.2	<26.6	1,410/193	1.00	Referent
2	37.6	26.7-47.4	1,412/138	0.84	0.66, 1.08
3	59.8	≥47.5	1,410/117	0.81	0.61, 1.08
Per 10 MET·hours·week^{-1}					0.98
P for trend				0.14	
Cycling[e]					
1	0.0	0.0	1,654/211	1.00	Referent
2	6.0	<12.0	1,392/131	0.74	0.58, 0.93
3	22.0	≥12.1	1,186/106	0.70	0.54, 0.90
P for trend				0.004	
Gardening[f]					
1	0.0	0.0	2,389/270	1.00	Referent
2	4.0	<6.0	1,133/102	0.88	0.70, 1.12
3	14.0	≥6.1	710/76	0.97	0.74, 1.26
P for trend				0.61	
Sports[g]					
1	0.0	0.0	2,683/314	1.00	Referent
2	5.4	<9.1	775/60	0.70	0.53, 0.93
3	19.5	≥9.2	774/74	0.85	0.65, 1.10
P for trend				0.07	

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; n/a, not applicable; PA, physical activity; Ps, participants; Ref, referent; T, tertile.

[a] Model 2 was adjusted for age, sex, all other PA types, smoking, alcohol consumption, diet and education.

[b] Total PA is composed of all PA types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 1.6, 2.9 and 4.7 hours per day of moderate PA equivalent of 4 METs.

[c] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 26, 60 and 150 minutes per day of walking.

[d] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 35, 92 and 146 minutes per day of domestic work.

[e] Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 47 minutes per day of cycling.

[f] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 30 minutes per day of gardening.

[g] Average sports is equivalent to 5.5. The median levels of sports across categories are therefore equivalent to 0, 8 and 30 minutes per day of sports.

Supplement 4.1.8. Association between total PA and different types of PA and fatal and non-fatal CHD events, in the Rotterdam Study, 1997-2012, presented for model 2

Age ≤ 67 years						Age > 67 years					
Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/CHD events	Model 2[a]		Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/CHD events	Model 2[a]	
				HR	95%CI					HR	95%CI
Total Physical Activity[b]						Total Physical Activity[b]					
1	42.0	<61.4	1,967/140	1.00	Ref	1	42.0	<61.4	1,967/132	1.00	Ref
2	77.5	61.5-96.9	1,968/73	0.65	0.48, 0.87	2	77.5	61.5-96.9	1,968/122	0.98	0.76, 1.26
3	126.7	≥97.0	1,966/71	0.66	0.48, 0.89	3	126.7	≥97.0	1,966/104	0.82	0.62, 1.07
Per 10 MET·hours·week^{-1}				0.96	0.93, 0.99	Per 10 MET·hours·week^{-1}				0.98	0.95, 1.00
P for trend					0.004	P for trend					0.14
Walking[c]						Walking[c]					
1	9.0	<15.0	2,102/111	1.00	Ref	1	9.0	<15.0	2,102/112	1.00	Ref
2	21.0	15.1-30.0	2,009/84	1.02	0.76, 1.37	2	21.0	15.1-30.0	2,009/151	1.35	1.05, 1.73
3	49.5	≥30.1	1,790/89	1.14	0.85, 1.52	3	49.5	≥30.1	1,790/95	0.90	0.68, 1.20
Per 10 MET·hours·week^{-1}				1.03	0.98, 1.07	Per 10 MET·hours·week^{-1}				0.96	0.92, 1.01
P for trend					0.40	P for trend					0.56
Domestic work[d]						Domestic work[d]					
1	12.9	<25.0	1,967/122	1.00	Ref	1	12.9	<25.0	1,967/158	1.00	Ref
2	36.0	25.1-46.5	1,970/91	0.71	0.53, 0.96	2	36.0	25.1-46.5	1,970/112	0.93	0.71, 1.23
3	59.5	≥46.6	1,964/71	0.65	0.46, 0.92	3	59.5	≥46.6	1,964/88	0.83	0.60, 1.14
Per 10 MET·hours·week^{-1}				0.93	0.87, 0.99	Per 10 MET·hours·week^{-1}				0.98	0.92, 1.03
P for trend					0.01	P for trend					0.25
Cycling[e]						Cycling[e]					
1	0.0	0.0	2,488/183	1.00	Ref	1	0.0	0.0	2,488/141	1.00	Ref
2	6.0	0.0-12.0	1,871/66	0.68	0.50, 0.93	2	6.0	0.0-12.0	1,871/116	0.86	0.66, 1.11
3	24.0	≥12.1	1,542/35	0.48	0.33, 0.71	3	24.0	≥12.1	1,542/101	0.89	0.68, 1.18
P for trend					<0.001	P for trend					0.41

Supplement 4.1.8 (continued). Association between total PA and different types of PA and fatal and non-fatal CHD events, in the Rotterdam Study, 1997-2012, presented for model 2

Age ≤ 67 years						Age > 67 years					
Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/CHD events	Model 2		Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/CHD events	Model 2	
				HR	95%CI					HR	95%CI
Gardening[f]						Gardening[f]					
1	0.0	0.0	3,448	200	1.00	Ref	1	0.0	0.0	3,448	201
2	4.0	0.0-6.0	1,514	54	0.94	0.68, 1.29	2	4.0	0.0-6.0	1,514	84
3	14.0	≥6.1	939	30	0.76	0.51, 1.14	3	14.0	≥6.1	939	73
P for trend					0.20	P for trend					0.58
Sports[g]						Sports[g]					
1	0.0	0.0	3,768	217	1.00	Ref	1	0.0	0.0	3,768	222
2	5.5	0.0-7.6	1,073	35	0.66	0.45, 0.95	2	5.5	0.0-7.6	1,073	61
3	19.9	≥7.7	1,060	32	0.70	0.47, 1.03	3	19.9	≥7.7	1,060	75
P for trend					<0.05	P for trend					0.73

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; n/a, not applicable; PA, physical activity; Ps, participants; Ref, referent; T, tertile.

[a] Model 2 was adjusted for age, sex, all other PA types, smoking, alcohol consumption, diet and education.

[b] Total PA is composed of all PA types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 1.5, 2.8 and 4.5 hours per day of moderate PA equivalent of 4 METs.

[c] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 26, 60 and 141 minutes per day of walking.

[d] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 32, 88 and 146 minutes per day of domestic work.

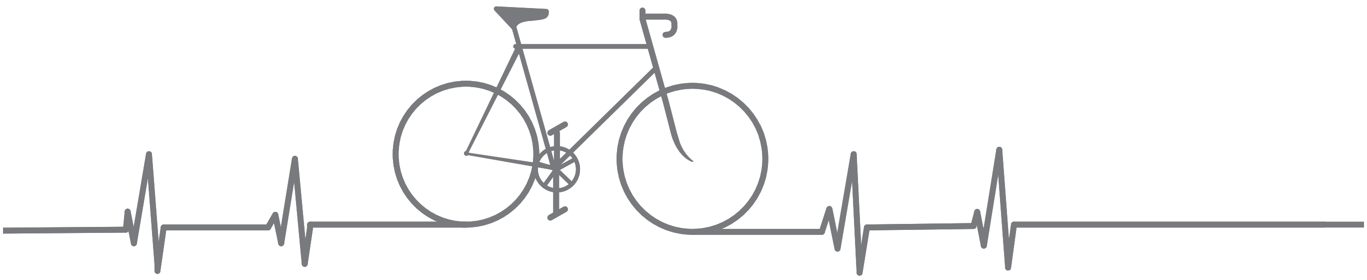
[e] Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 51 minutes per day of cycling.

[f] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 30 minutes per day of gardening.

[g] Average sports is equivalent to 5.5 METs. The median levels of sports across categories are therefore equivalent to 0, 9 and 31 minutes per day of sports.

SUPPLEMENTARY REFERENCES

1. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011;43(8):1575-1581.



Chapter 4.2

Physical activity types and atrial fibrillation risk

Manuscript based on this chapter:
Albrecht M[*], **Koolhaas CM**[*], Schoufour JD, van Rooij FJ, Kavousi M, Ikram MA, Franco OH. Physical activity types and atrial fibrillation risk in the middle-aged and elderly: the Rotterdam Study. *Submitted for publication*.

ABSTRACT

Background: The association between physical activity (PA) and atrial fibrillation(AF) remains controversial. PA has been associated with a higher and lower AF risk. These inconsistent results might be related to the type of PA. We aimed to investigate the association of total and types of PA including walking, cycling, domestic work, gardening and sports, with AF.

Methods: Our study was performed in the Rotterdam Study, a prospective population-based cohort. We included 7,018 participants aged 55 years and older with information on PA between 1997-2001. Cox proportional hazards models were used to examine the association of PA with AF risk. Models were adjusted for biological and behavioural risk factors and the remaining PA types. PA was categorised in tertiles and the low group was used as reference.

Results: During 16.8 years of follow-up (median: 12.3 years, interquartile range: 8.7-15.9 years), 800 AF events occurred (11.4% of the study population). We observed no association between total PA and AF risk in any model. After adjustment for confounders, the hazard ratio and 95%confidence interval for the high PA category compared to the low PA category was: 0.71(0.80,1.14) for total PA. We did not observe a significant association between any of the PA types with AF risk.

Conclusion: Our results suggest no association between PA and a higher or lower risk of incident AF. Neither total PA nor any of the included PA types was associated with AF risk. However, considering the beneficial effect of PA on other health outcomes, PA should still be encouraged for overall health promotion.

INTRODUCTION

Physical activity (PA) has been extensively proven to reduce the risk of cardiovascular disease (CVD) and all-cause mortality.[1,2] However, it remains unclear whether all cardiovascular conditions, including atrial fibrillation (AF), may benefit from PA. AF is the most common chronic cardiac arrhythmia with significant morbidity and mortality.[3] Known risk factors of AF, such as heart failure (HF) and myocardial infarction (MI), are directly influenced by the level of PA.[1,2] Therefore, since increasing PA levels decrease the risk of HF and MI, it might also reduce the risk of AF.

Results regarding the relation between PA an AF remain controversial.[4-6] Meta-analyses of mostly prospective cohort studies with ages of participants ranging from 40 up to 75 years found no significant association between leisure time PA and AF risk in pooled analyses.[4,5] However, it has been hypothesized that the relation between PA and AF is U-shaped, with lower risk when exercising moderately in terms of intensity as well as duration but not when exercising vigorously.[7,8] As intensity is related to the type of PA, this implies that the association between PA and AF risk might be related to the type of PA in which adults engage in. In a study among 5,446 older adults with a mean age of 73 years, higher levels of walking and running were associated with lower AF risk.[7] Furthermore, Drca et al. found cycling and walking among older men (mean age 60 years) to be inversely related to AF risk.[9] In addition to walking and cycling, older people engage in several other PA types, including gardening, domestic work or sports in general. These different PA types vary in intensity, frequency and duration, and might be associated with AF risk in different ways. Furthermore, for older people who cannot engage in certain leisure-time activities or other exercise and perform activities differently from younger and middle-aged adults, health effects of other PA types performed by elderly might by informative and crucial in lowering their AF risk. Since overall PA levels tend to decrease with age this is especially important.[10]

Therefore, we aim to examine the association between total PA and AF incidence in a population of older adults, aged 55 years and over. Furthermore, we will assess the independent association of different types of PA including walking, gardening, domestic work, sports and cycling with AF incidence.

METHODS

Study population

This study was embedded within the Rotterdam Study (RS), a prospective population-based cohort study among subjects aged 55 years or older in the municipality of Rotterdam, the Netherlands. Between 1990 and 1993 the baseline examination of the original cohort was performed (RS-I). The RS was extended in 2000-2001 with 3,011 participants who had either become 55 years old or had moved into the study district (RS-II). For this study, we used data from the participants attending the third examination of the original cohort (RS-I-3, between 1997 and 1999; n = 4,797) and the participants attending the first examination of the extended cohort (RS-II-1, between 2000 and 2001; n = 3,011).[11] 7,310 participants completed PA data collection. Subjects with prevalent AF were excluded (n=205) (See Figure 4.2.1). Following, 54 subjects were excluded due to not provided, or withdrawn, informed consent for collection of follow-up data. 33 cases were removed because of unreliable PA values or missing follow-up data. A total of 7,018 subjects were included in the analyses. Baseline information was collected by trained research assistants who interviewed the participants at home. All subject gave written consent, and the study protocol was approved by the medical ethics committee according to the Wet Bevolkingsonderzoek ERGO (Population Study Act Rotterdam Study), executed by the Ministry of Health, Welfare and Sport of The Netherlands. Detailed information on the design of the Rotterdam Study can be found elsewhere.[11]

Physical activity assessment

PA levels were assessed with an adapted version of the Zutphen Physical Activity Questionnaire.[12] The original questionnaire has been validated with a test-retest reliability of 0.93 and a correlation with doubly labelled water of 0.61.[13] The questionnaire contains questions on walking, cycling, sports, gardening and hobbies. Questions on domestic work were added to obtain a more reliable estimate of the PA level in this age group. Detailed information on the collection of PA can be found elsewhere.[14]

We used metabolic equivalent of task (MET) to quantify the intensity of an activity according to the 2011 updated version of the Compendium of Physical.[15] Sports that were mentioned in the questionnaire that were not in this compendium were not used in the analyses (n=33). Finally, we calculated MET hours per week in total PA (i.e. the sum of cycling, walking, sports, domestic work and gardening) and in every type of PA (cycling, walking, sports, domestic work, gardening).

Assessment of covariates

Covariates were assessed when participants visited the study centre or collected through home interviews as described previously.[14,16,17] Prevalent cardiovascular disease and diabetes was determined using medical records and used as binary variable (present/not present). Alcohol consumption was measured by interview and defined as glasses per day. Smoking was categorized as current, former or never. Height and weight were measured during the centre visit, and body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Blood pressure was measured twice with the participant seated, measuring the right brachial artery using a random zero sphygmomanometer. The mean of the two consecutive measurements in mmHg was used as a continuous variable in our analyses. Hypertension was defined as either a diastolic blood pressure 90 mmHg and above, a systolic blood pressure of 140 mmHg and above or the use of anti-hypertensive medication. Medication use was determined during the home interviews for anti-thrombotic agents and angiotensin converting enzyme (ACE)-inhibitors. With an automated enzymatic procedure (Boehringer Mannheid System, Mannheim, Germany) the serum total cholesterol and high-density lipoprotein (HDL) cholesterol was measured and expressed in mg/dL. As an indication of socio-economic status, educational level was used and divided in primary, junior vocational/academic education and higher vocational/academic education. Dietary information was obtained by a semi-quantitative food frequency questionnaire consisting of 170 items.[18] For part of the study sample (n=4,374 from RS-I-3),

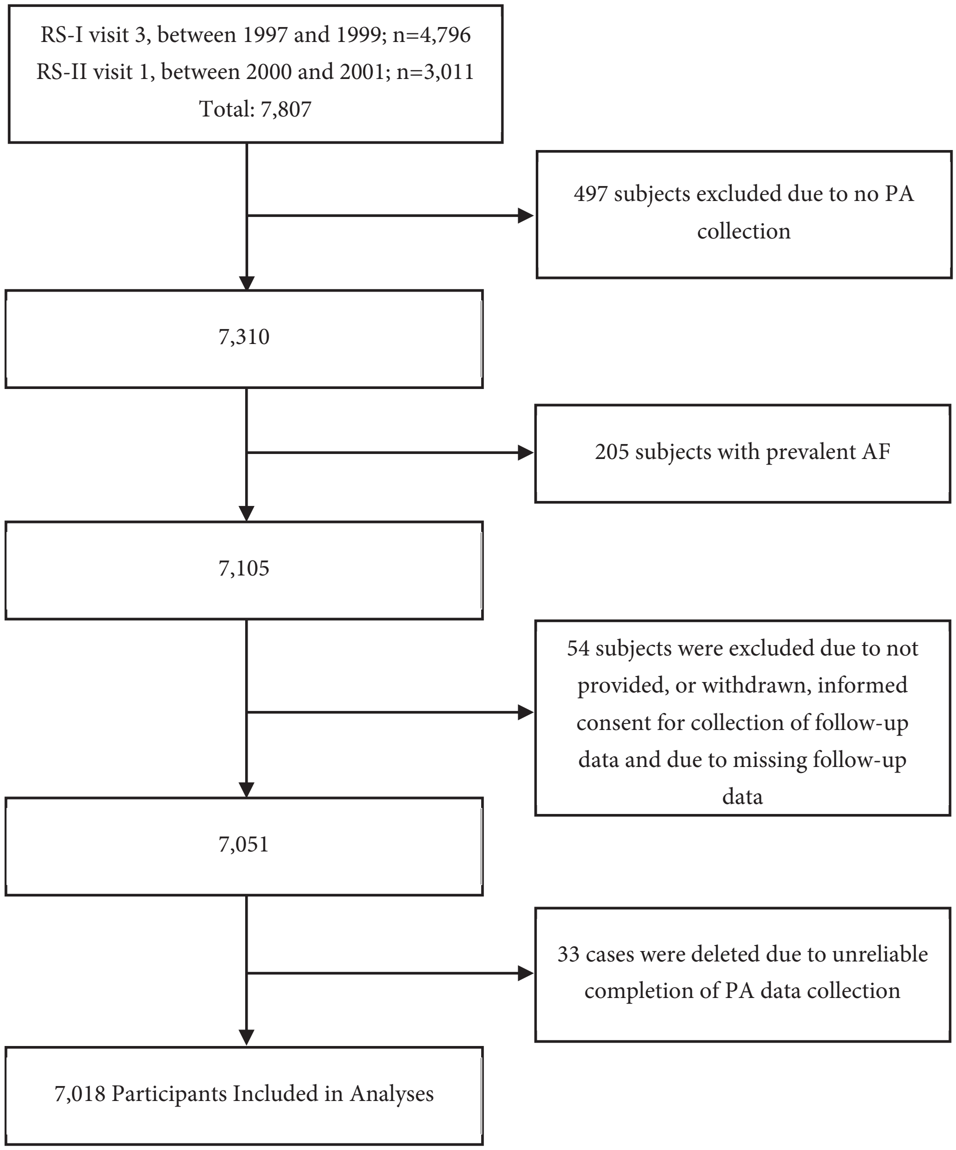


Figure 4.2.1. Flow chart of participant inclusion for the Rotterdam Study, 1997-2012.

Dietary information was not obtained at the same time as the PA data. Therefore, dietary information from the first wave (1989-1993) of the original cohort (RS-I) was used to calculate an overall healthy diet score, based on Dutch dietary guidelines.[19]

Clinical outcome

The main outcome measure under study was AF. Data on clinical outcomes were collected through an automated follow-up system involving digital linkage of the study database to medical records maintained by general practitioners working in the research area. Trained research assistants collected notes, outpatient clinic reports, hospital discharge letters and electrocardiograms (ECG). AF was coded as an event when it had been diagnosed with a 12 lead ECG. Research physicians independently adjudicated all data on potential events. Medical specialists reviewed potential cases as a final decision. Follow-up was complete until January 1, 2014.

Statistical analysis

Due to their non-normal distribution, all five PA types and total PA were categorized into tertiles. Total PA, walking domestic work were divided into three categories of equal size by the 33rd and 66th percentiles of MET·hours·week^{-1}. Since a large proportion of the participants did not participate in sports, gardening and cycling, the bottom category for these types was no participation and the remaining two categories were created by using the median.[14] We assessed the association of total PA and all types of PA with incident AF with Cox proportional hazards, after confirming that the assumption for proportional hazards was met. The underlying timescale in these models was follow-up time, defined as the time between PA assessment and the first fatal or nonfatal AF event, death, or censoring at January 1, 2014.

To minimize confounding, covariates were added separately in different models. Model 1 was adjusted for age and sex. Model 2 was the model additionally adjusted for behavioural risk factors, including smoking, prevalent CVD, alcohol consumption, diet quality and education. For the PA types, model 2 was also adjusted for the MET·hours·week^{-1} in all other PA types. In Model 3 we additionally adjusted for biological risk factors, including BMI, total and HDL-cholesterol, diabetes, lipid reducing agents, systolic and diastolic blood pressure, anti-thrombotic agents and ACE-inhibitor use. The decision to include confounders in the multivariable regression models was based on previous literature or >10% change of the effect estimate in the crude model.[4,5] PA variables were entered as categorical variables (tertiles) in the separate models.

We performed stratified analyses by sex and age (below 65 years and 65 years and above). Furthermore, to see whether our results would be driven by underlying CVD, we performed an additional analysis by excluding participants with prevalent CVD (n=5997). Finally, since we did not obtain occupational PA data, we analysed our data in non-workers (n=6197).

Our data contained missing values for diet (28.7%), systolic and diastolic blood pressure (10.2%), BMI (10.6%), total cholesterol (13.2%) and HDL- cholesterol (14.2%). Other covariates had <10% missing data. Missing variables were calculated by IBM statistics with the multiple imputation (n=5 imputations) function based on the distribution of existing data.

RESULTS

Baseline characteristics of the study population are shown in Table 4.2.1. During 16.8 years of follow up (median: 12.6 years) 800 AF events occurred (11.4% of the study population). Of the 7018 included participants, 4083 (58.2%) were female and the mean (standard deviation (SD)) age among men and women was 69.4 (8.3) years at enrolment. The mean (SD) level of physical activity was 80.9 (44.0) MET·hours·week^{-1}, corresponding to 2.9 hours/day of moderate intensity PA of 4 METs.

Table 4.2.2 shows the multivariable-adjusted hazard ratios (HRs) with their 95% confidence interval (95%CI) for total PA and every PA type. For total PA, the median levels of MET·hours·week^{-1} across the three tertiles were 38.7 MET·hours·week^{-1} in the low group, 74.7 MET·hours·week^{-1} in the medium group and 123.2 MET·hours·week^{-1} in the high group. This corresponds to 1.4 hours/day of moderate intensity PA of 4 METs for the low group, 2.7 hours/day for the medium group and 4.4 hours/day for the high group.

In the model adjusted for behavioural risk factors (model 2) the HR (95% CI) of the medium and high groups, compared to the low group, were 1.05 (0.89-1.24) and 0.71 (0.80-1.14), respectively, with P for trend 0.58.

For all five PA types, we did not observe a significant association with AF risk in the crude model, the model adjusted for behavioural risk factors (model 2), or in the model after adjustment for biological risk factors (model 3). Furthermore, we did not observe a significant trend across categories in any of the analyses. For example, the HR (95% CI) for the high category of walking and cycling were 1.00 (0.84-1.20) and 0.92 (0.76-1.12), respectively, compared to the low categories, with P for trend 0.98 and 0.43, respectively.

Our sensitivity analysis split by age and sex showed some differences in HRs between the groups, but the results remained non-significant (Supplement 4.2.1 – Supplement 4.2.2). Moreover, excluding working people or excluding participants who previously were diagnosed with a CVD did not change the results (Supplement 4.2.3 – Supplement 4.2.4).

Table 4.2.1. Baseline participant characteristics by tertile of total PA, Rotterdam Study, 1997-2012

	Tertiles of total PA, MET·hours·week^{-1}		
Median (range), MET·hours·week^{-1}	40.6 (<58.1)	74.9 (58.1-94.2)	124.8 (≥94.2)
Participants, n (%)	2,340 (33.3)	2,340 (33.3)	2,338 (33.3)
Demographic factors			
Age, years	71.4 (9.6)	68.9 (7.7)	67.6 (7.0)
Female, n (%)	1,016 (43.4)	1,462 (62.4)	1,605 (68.6)
Primary education, n (%)	371 (15.9)	316 (13.5)	336 (14.3)
Physical activity			
Sports, hours/week	2.0 (5.1)	4.3 (8.5)	10.1 (18.3)
Walking, hours/week	12.3 (9.1)	23.0 (13.6)	47.0 (30.0)
Cycling, hours/week	2.7 (5.3)	7.8 (10.1)	15.2 (17.3)
Gardening, hours/week	1.5 (3.6)	3.2 (6.9)	6.6 (13.2)
Domestic work, hours/week	18.0 (12.5)	37.0 (16.6)	52.4 (24.8)
Lifestyle factors			
Alcohol, glasses/day	1.1 (1.6)	1.0 (1.5)	1.0 (1.3)
Currently smoking, n (%)	450 (19.2)	415 (17.7)	401 (17.2)
Diet score	54.7 (10.5)	55.9 (11.0)	56.5 (10.5)
Biological risk factors			
Body mass index[a]	27.1 (4.1)	27.1 (4.1)	26.7 (3.8)
Cholesterol level, mg/dl	219.4 (39.7)	225.1 (36.6)	229.2 (37.4)
HDL-cholesterol level, mg/dl	50.9 (14.5)	54.0 (15.1)	55.7 (15.1)
Systolic blood pressure, mmHg	145.8 (21.3)	144.0 (21.8)	142.1 (20.8)
Having diabetes, n (%)	514 (22)	361 (15.4)	276 (11.8)
Using serum lipid reducing agents, n (%)	300 (12.8)	316 (13.5)	286 (12.2)
Using ACE-inhibitors, n (%)	337 (14.4)	312 (13.3)	238 (10.2)
Using anti-trombotic agents, n (%)	661 (28.2)	456 (19.5)	355 (15.2)
Using anti-hypertensive medication with the indication of hypertension, n (%)	646 (28)	620 (26.5)	500 (21.3)
AF cases			
AF event, n (%)	259 (11.1)	285 (12.2)	256 (10.9)
Time to event, years, n (%)	9.2 (4.8)	11.2 (4.0)	11.9 (3.8)

Abbreviations: AF, atrial fibrillation; HDL, high density lipoprotein; MET, metabolic equivalent of task; SD, standard deviation.

[a] Weight (kg)/height (m)^2

Results are presented as mean (SD) unless otherwise stated.

Table 4.2.2. Association between total PA and different types of PA and AF, Rotterdam Study, 1997-2012

Activity Type and Tertile of Physical Activity	Median MET-hours per week	Range	No. Participants	No. AF events	Model 1[a]		Model 2[a]		Model 3[a]	
					HR	95% CI	HR	95% CI	HR	95% CI
Total Physical Activity[b]										
1	38.7	<58.1	2,340	259	1.00	Reference	1.00	Reference	1.00	Reference
2	74.7	58.1-94.2	2,340	285	1.03	0.87-1.22	1.05	0.89-1.24	1.08	0.91-1.29
3	123.2	≥94.2	2,338	256	0.93	0.78-1.11	0.71	0.80-1.14	1.05	0.87-1.25
P for trend						0.40		0.58		0.65
Walking[c]										
1	8.5	<13.5	2,356	256	1.00	Reference	1.00	Reference	1.00	Reference
2	21.0	13.9-30.0	2,586	283	0.90	0.76-1.06	0.91	0.77-1.07	0.94	0.79-1.11
3	49.5	≥ 30.8	2,076	252	0.94	0.79-1.12	0.96	0.80-1.14	1.00	0.84-1.20
P for trend						0.49		0.64		0.98
Domestic work[d]										
1	11.6	<22.6	2,340	266	1.00	Reference	1.00	Reference	1.00	Reference
2	34.2	22.7-44.7	2,339	277	1.09	0.91-1.31	1.11	0.92-1.33	1.13	0.94-1.36
3	57.8	≥44.7	2,349	257	1.10	0.89-1.35	1.15	0.93-1.42	1.19	0.96-1.46
P for trend						0.40		0.21		0.12
Cycling[e]										
1	0.0	0.0	3,122	360	1.00	Reference	1.00	Reference	1.00	Reference
2	6.0	0.0-12.0	2,154	249	0.93	0.78-1.10	0.92	0.77-1.09	0.98	0.82-1.17
3	24.0	≥12.5	1,742	191	0.87	0.72-1.05	0.70	0.71-1.04	0.92	0.76-1.12
P for trend						0.14		0.12		0.43
Gardening[f]										
1	0.0	0.0	4,245	464	1.00	Reference	1.00	Reference	1.00	Reference
2	4.0	2.0-6.0	1,685	193	0.86	0.70, 1.05	1.09	0.92-1.30	1.13	0.94-1.34
3	14.0	≥8.0	1,088	143	0.92	0.73, 1.14	1.13	0.93-1.37	1.16	0.96-1.41

Table 4.2.2 (continued). Association between total PA and different types of PA and AF, Rotterdam Study, 1997-2012

Activity Type and Tertile of Physical Activity	Median MET-hours per week	Range	No. Participants	No. AF events	Model 1[a]		Model 2[a]		Model 3[a]	
					HR	95% CI	HR	95% CI	HR	95% CI
P for trend					0.16		0.18		0.09	
Sports[g]										
1	0.0	0.0	4,541	514	1.00	Reference	1.00	Reference	1.00	Reference
2	5.5	1.25-9.3	1,250	144	0.80	0.64, 1.00	0.99	0.82-1.19	1.02	0.85-1.23
3	19.8	≥9.5	1,227	142	0.90	0.73, 1.12	0.99	0.82-1.20	1.05	0.87-1.27
P for trend					0.88		0.96		0.61	

Abbreviations: AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; PA, physical activity.; Ps, participants.

[a] Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for all other PA types, smoking, previous cardiovascular disease, alcohol consumption, diet and education. Model 3 was additionally adjusted for BMI, total and HDL-cholesterol, diabetes, lipid reducing agents, systolic and diastolic blood pressure, anti-thrombotic agents and ACE-inhibitor use.

*Sensitivity analysis with model 2 corrected for age, sex, working status and previous cardiovascular disease.

[b] Total PA is composed of all PA types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 1.5, 2.8 and 4.5 hours per day of moderate PA equivalent of 4 METs.

[c] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 26, 60 and 141 minutes per day of walking.

[d] Average domestic work is equivalent to 3.5 METs.[15] The median levels of domestic work across categories are therefore equivalent to 32, 88 and 146 minutes per day of domestic work.

[e] Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 51 minutes per day of cycling.

[f] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 30 minutes per day of gardening.

[g] Average sports is equivalent to 5.5 METs. The median levels of sports across categories are therefore equivalent to 0, 9 and 31 minutes per day of sports.

DISCUSSION

In this population-based study of adults aged 55 years and over, we found no evidence for an association between PA and AF risk over 16.8 years of follow-up. Total PA was not associated with an in- or decreased AF risk and we did not observe an association for any of the PA types with AF.

Our findings are in concordance with two meta-analyses, which do not support an association between leisure-time PA and incidence of AF.[4,5] In these meta-analyses, no association was found for moderate or vigorous PA compared to a sedentary life style. However analysed studies were heterogeneous whether PA was assessed for duration, intensity or life-time exposure or a combination of those three. More recently, a meta-analysis of 13 prospective studies found no association between total life-time PA exposure and AF risk, nor between vigorous intensity PA and risk of AF.[6] However when sex-stratified total physical activity exposure was associated with an increased risk of AF in men. [6]

Our results contradict a number of recent cohort studies, reporting that moderate intensity PA or leisure-time PA is associated with a lower risk of AF.[7,9,20] Between these studies, the shape of the association varies. One study found a J-shaped association with initially lower risk of AF for moderate PA levels of at least 4 hours of exercise per week. The risk of AF however steeply rises when exercising vigorously in terms of intensity and duration.[20] Others observed a U-shaped association, with the lowest risk for participants that exercised at moderate intensity,[21] for example walking at 6.5 kilometers per hour (km/h) or cycling at 16-19 km/h.[7-9] The widely varying categorizing of PA and different cultural patterns of sport seem to limit the comparisons between existing studies.[22] Moreover, only three studies examined the association between PA and AF risk among elderly participants.[7,9,23] One study found that older men (mean age of 60 years) participating in walking and cycling at baseline were at lower risk of AF, compared to individuals almost never engaging in these activities.[9] Additionally, in a study of the same research group in older women, higher levels of leisure time PA were associated with lower risk of AF.[23] In another study among elderly men, Mozaffarian et al. found that higher levels of leisure-time PA and walking were associated with progressively lower AF risk.[7] In this study, both walking distance and walking pace was assessed, whereas only information on walking duration was obtained in the current study. The different results between this study and our study might be explained by this methodological difference. For example, in our study it's possible that two persons both reported 1 hour of walking per week, but that one person walked 4 km within this time frame, whereas another walked 6 km. In this case, the discriminative power of our walking estimate might be too low to find an association with AF. Future studies on the association between walking and AF should therefore collect information on walking duration, walking pace and walking distance, to get a more complete overview of the PA pattern.

The fact that we did not find an association between any PA variable and AF might also be explained by the relatively high PA levels of our population. In the low group of total PA, individuals engaged in a median level of 38.7 MET·hours·week^{-1}of PA, corresponding to 1.4

hours/day of moderate intensity PA of 4 METs. Additionally, more than 98.5% of our study population had higher total PA levels than the recommended 7.5 MET·hours·week^{-1}.[24] Considering the fact that the greatest health effects are usually gained at low levels of PA,[9,25] it is possible that the participants in the low group of PA in the current study were already sufficiently active and where therefore not at increased AF risk. This hypothesis is supported by the relatively low percentage of AF cases in the current study (11.4%), compared to the 19% of AF incidence in a similar study population of the study of Mozaffarian at al.[7] The participants in the current study might also have a relatively high cardiorespiratory fitness, which has been demonstrated to be associated with lower AF risk.[26] Moreover, Kwok et al. hypothesized that a health-consciousness attitude might contribute to non-significant association between PA and AF risk.[5] Athletes or active individuals participating in sports, might be more health conscious and therefore more often evaluated for cardiac arrhythmias.[5] In comparison to individuals who perform less exercise, this subgroup might thus have higher rates of AF diagnoses. Subsequently, this could bias the association between PA and AF.

There have been several proposed mechanisms for the association between PA and either higher or lower AF risk. The proposed mechanism behind the association between PA and lower AF risk is that PA can have a beneficial effect on several AF risk factors, including improving the management of hypertension and diabetes mellitus,[27] assist in weight management[28] and improve cardiac structure and function.[29,30] Hypertension and obesity are linked to interstitial fibrosis, conduction slowing and low atrial voltages due to atrial remodeling.[30] Therefore, PA or exercise could protect against AF. Protection of AF through exercise could lead to harm when PA is done frequently and with high intensity, resulting in an increased risk of AF when exercising 5-7 times a week.[31] Pathophysiological pathways for increased AF risk following vigorous exercise are left atrial enlargement, left ventricular hypertrophy left ventricular dilation, inflammatory changes and an increase in parasympathetic tone.[9,32,33] To add to the complexity, a 12-week physician-led program for increasing exercise activity led to a lower AF recurrence independent of weight changes among AF patients.[34] This shows that PA might have a short-term effect on recurrent AF risk. Only a very limited number of individuals with prevalent AF at baseline in the current study had a second event (Data not shown) and therefore we could not test this effect of PA on the recurrence of AF in the current study. It has also been shown that life-time PA exposure and the intensity of PA that was performed both are related to AF risk.[31] It might be that some participants have been very active in their young-adult and middle-aged life and this might have contributed to a higher AF risk in later life.[31,35] In this case, our associations might be affected by residual confounding by previous PA levels.

Importantly, whereas our study does not show evidence for that higher PA levels are associated with lower AF risk in older age, we do not refute the effect that PA can have on other health outcomes. In no case is the risk of exercising higher than an inactive or sedentary life style.[25] However, with high levels of endurance training especially adults should be made aware of the modest increase in the risk of AF.[31] But most importantly, any type of PA should be encouraged as it reduces risk of mortality and promotes well-being.[25]

Our study contains several strengths, including the large sample size of elderly adults a long follow-up period of almost 17 years and the prospective population-based design. Furthermore, our method of confirming the AF diagnosis by ECG was very accurate. By adding different types of PA, we were able to independently study their association with AF. Moreover, in studying this association, we adjusted for several factors which minimized the chance of finding a confounded result.

However, we also need to acknowledge some limitations. We measured PA with a self-reported questionnaire. Our questionnaire has shown to be valid and reliable,[13] but recall bias and social desirable answers cannot be excluded. However, the use of questionnaire data on PA is essential when examining types of PA. Further, in the current study we used The Compendium of Physical Activities to assign MET-values to activities in the questionnaire.[15] While assigning these values, we carefully considered the age of our study population. However, it might not have captured the energy expenditure of older adults accurately. Furthermore, since only duration of performed PA was obtained, this might also have given rise to heterogeneity with regard to the intensity in which participants engaged in the different PA types. This might have led to misclassification of participants with either higher or lower intensity levels than our assigned values. Since this misclassification was non-differential, this could have biased our estimates towards the null hypothesis. Also, PA was assessed only once in our study, which could have resulted in missing PA changes in participants, which could have altered their AF risk during follow-up as compared to their baseline activity profile. Further, AF has a tendency to be asymptomatic. We cannot rule out that some of our non-cases were in fact 'silent' AF cases leading to an underestimation of total AF cases.

Conclusions

In conclusion, our results suggest that there is no association between PA and risk of increased or decreased incident AF. Neither total PA nor any of the included PA types was associated with AF risk in any of the analyses. However, considering the beneficial effect of PA on other health outcomes, PA should still be promoted.

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SUPPLEMENT CHAPTER 4.2

Supplement 4.2.1. Association between total PA and different types of PA and AF, Rotterdam Study, 1997-2012, stratified by sex.

Women						Men					
Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/AF events	Model 2[a]		Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/AF events	Model 2[a]	
				HR	95%CI					HR	95%CI
Total Physical Activity[b]						Total Physical Activity[b]					
1	40.6	<58.1	1016/106	1.00	Reference	1	37.0	<58.1	1324/153	1.00	Reference
2	74.9	58.1-94.2	1462/158	1.24	0.79-1.32	2	74.3	58.1-94.2	878/127	1.05	0.83-1.34
3	124.8	≥94.2	1605/149	0.86	0.66-1.12	3	120.2	≥94.2	733/107	1.07	0.83-1.38
Walking[c]						Walking[c]					
1	9.0	<13.5	1349/137	1.00	Reference	1	7.9	<13.5	1007/128	1.00	Reference
2	21.0	13.9-30.0	1526/145	0.90	0.66-1.22	2	21.0	14.3-30.0	1060/138	0.91	0.66-1.26
3	51.0	≥ 30.8	1208/131	0.98	0.72-1.33	3	48.0	≥30.8	868/121	0.97	0.70-1.35
Domestic work[d]						Domestic work[d]					
1	15.4	<22.6	468/38	1.00	Reference	1	11.2	<22.6	1872/228	1.00	Reference
2	35.8	22.7-44.7	1570/163	0.78	0.57-1.06	2	31.0	22.6-44.6	769/114	0.92	0.67-1.27
3	58.1	≥44.7	2045/212	0.67	0.45-0.99	3	57.1	≥44.7	294/45	0.84	0.60-1.19
Cycling[e]						Cycling[e]					
1	0.0	0.0	2099/240	1.00	Reference	1	0.0	0.0	1023/120	1.00	Reference
2	6.0	0.0-12.0	1121/110	1.37	0.80-2.34	2	6.0	0.0-12.0	1033/139	1.06	0.80-1.41
3	22.0	≥12.5	863/63	1.46	0.86-2.50	3	24.0	≥12.5	879/128	1.02	0.66-1.57
Gardening[f]						Gardening[f]					
1	0.0	0.0	2642/283	1.00	Reference	1	0.0	0.0	1603/181	1.00	Reference
2	4.0	2.0-6.0	936/84	0.99	0.72-1.36	2	4.0	2.0-6.0	749/109	1.30	0.94-1.80
3	12.0	≥8.0	505/46	0.87	0.57-1.32	3	14.0	≥8.0	583/97	1.17	0.85-1.63
Sports[g]						Sports[g]					

Supplement 4.2.1 (continued). Association between total PA and different types of PA and AF, Rotterdam Study, 1997-2012, stratified by sex.

Women						Men					
Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/AF events	Model 2[a]		Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/AF events	Model 2[a]	
				HR	95%CI					HR	95%CI
1	0.0	0.0	2701/285	1.00	Reference	1	0.0	0.0	1840/229	1.00	Reference
2	5.4	1.25-9.3	821/85	0.98	0.77-1.26	2	5.8	1.5-9.3	429/59	1.02	0.77-1.36
3	16.6	≥9.5	561/43	0.77	0.56-1.07	3	22	≥9.5	666/99	1.14	0.90-1.45

Abbreviations: AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; PA, physical activity; ; Ps, participants.

[a] Model 2 was adjusted for all other PA types, smoking, previous cardiovascular disease, alcohol consumption, diet and education.

*Sensitivity analysis with model 2 stratified for Sex.

[b] Total PA is composed of all PA types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 1.5, 2.8 and 4.5 hours per day of moderate PA equivalent of 4 METs.

[c] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 26, 60 and 141 minutes per day of walking.

[d] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 32, 88 and 146 minutes per day of domestic work.

[e] Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 51 minutes per day of cycling.

[f] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 30 minutes per day of gardening.

[g] Average sports is equivalent to 5.5 METs. The median levels of sports across categories are therefore equivalent to 0, 9 and 31 minutes per day of sports.

Supplement 4.2.2. Association between total PA and different types of PA and AF, Rotterdam Study, 1997-2012, stratified by age.

Below 65 years						65 years and over					
Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/AF events	Model 2[a]		Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/AF events	Model 2[a]	
				HR	95%CI					HR	95%CI
Total Physical Activity[b]						Total Physical Activity[b]					
1	40.1	<57.9	644/58	1.00	Reference	1	38.2	<58.1	1696/201	1.00	Reference
2	76.3	58.1-94.2	813/54	0.87	0.59-1.28	2	73.9	58.1-94.2	1527/231	1.09	0.89-1.32
3	122.4	≥94.3	962/66	0.92	0.62-1.35	3	123.5	≥94.2	1376/190	0.94	0.77-1.16
Walking[c]						Walking[c]					
1	9.0	<13.5	761/66	1.00	Reference	1	7.5	<13.5	1598/199	1.00	Reference
2	21.0	15.0-30.0	939/55	0.7	0.49-1.01	2	21.0	13.9-30.0	1647/228	0.95	0.86-1.05
3	42.0	≥ 30.8	719/57	0.93	0.64-1.36	3	52.5	≥ 30.8	1357/195	0.95	0.77-1.16
Domestic work[d]						Domestic work[d]					
1	10.4	<22.6	815/73	1.00	Reference	1	12.3	<22.6	1525/193	1.00	Reference
2	34.6	22.7-44.7	734/54	1.17	0.78-1.74	2	34.6	22.6-44.7	1605/223	1.1	0.89-1.35
3	59.0	≥44.7	870/51	1.13	0.70-1.82	3	57.5	≥44.7	1469/206	1.15	0.90-1.45
Cycling[e]						Cycling[e]					
1	0.0	0.0	635/51	1.00	Reference	1	0.0	0.0	2487/309	1.00	Reference
2	6.0	0.3-12.0	950/69	0.8	0.56-1.15	2	6.0	0.3-12.0	1204/180	0.94	0.78-1.15
3	24.0	≥12.5	834/58	0.77	0.52-1.13	3	22.0	≥12.7	908/133	0.87	0.71-1.11
Gardening[f]						Gardening[f]					
1	0.0	0.0	1120/74	1.00	Reference	1	0.0	0.0	3125/390	1.00	Reference
2	4.0	2.0-6.0	849/63	1.13	0.81-1.59	2	4.0	2.0-6.0	836/130	1.11	0.91-1.36
3	14.0	≥8.0	450/41	1.37	0.93-2.01	3	14.0	≥8.0	638/102	1.05	0.84-1.31
Sports[g]						Sports[g]					

Supplement 4.2.2 (continued). Association between total PA and different types of PA and AF, Rotterdam Study, 1997-2012, stratified by age.

Below 65 years						65 years and over					
Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/AF events	Model 2[a]		Activity Type and Tertile of PA	Median MET-hours/week	Range	No. Ps/AF events	Model 2[a]	
				HR	95%CI					HR	95%CI
1	0.0	0.0	1326/101	1.00	Reference	1	0.0	0.0	3215/413	1.00	Reference
2	5.5	1.25-9.3	485/32	0.89	0.59-1.33	2	5.5	1.25-9.3	765/112	1.03	0.84-1.27
3	21.6	≥9.6	608/45	0.91	0.64-1.30	3	17.9	≥9.4	619/97	1.06	0.85-1.33

Abbreviations: AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; PA, physical activity; ; Ps, participants.

[a] Model 2 was adjusted for all other PA types, smoking, previous cardiovascular disease, alcohol consumption, diet and education.

*Sensitivity analysis with model 2 stratified for Age.

[b] Total PA is composed of all PA types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 1.5, 2.8 and 4.5 hours per day of moderate PA equivalent of 4 METs.

[c] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 26, 60 and 141 minutes per day of walking.

[d] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 32, 88 and 146 minutes per day of domestic work.

[e] Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 51 minutes per day of cycling.

[f] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 30 minutes per day of gardening.

[g] Average sports is equivalent to 5.5 METs. The median levels of sports across categories are therefore equivalent to 0, 9 and 31 minutes per day of sports.

Supplement 4.2.3. Association between total PA and different types of PA and AF, Rotterdam Study, 1997-2012, in participants without paid employment

Physical Activity Type and Tertile	Median MET-hours per week	Range	No. Ps/AF events	Model 2[a]	
				HR	95% CI
Total Physical Activity[b]					
1	39.3	<58.1	1,940/223	1.00	Reference
2	75.1	58.1-94.2	2,092/270	1.08	0.90-1.30
3	123.4	≥94.2	2,165/239	0.94	0.77-1.14
Walking[c]					
1	8.3	<13.5	1,980/231	1.00	Reference
2	21.0	13.9-30.0	2,291/261	0.92	0.78-1.08
3	51.0	≥30.8	1,926/240	0.97	0.81-1.17
Domestic work[d]					
1	12.5	<22.6	1,870/224	1.00	Reference
2	34.2	22.6-44.7	2,133/263	1.10	0.91-1.33
3	57.7	≥44.7	2,194/245	1.11	0.89-1.39
Cycling[e]					
1	0.0	0.0	2,863/336	1.00	Reference
2	6.0	0.33-12.0	1,805/221	0.94	0.78-1.13
3	24.0	≥12.5	1,529/175	0.87	0.71-1.07
Gardening[f]					
1	0.0	0.0	3,868/444	1.00	Reference
2	4.0	2.0-6.0	1,368/161	1.04	0.86-1.25
3	14.0	≥8.0	961/127	1.06	0.87-1.31
Sports[g]					
1	0.0	0.0	4,071/477	1.00	Reference
2	5.5	1.3-9.3	1,108/133	1.00	0.82-1.21
3	18.6	≥9.4	1,018/122	0.98	0.80-1.20

Abbreviations: AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; PA, physical activity; Ps, participants.

[a] Model 2 was adjusted for all other PA types, smoking, previous cardiovascular disease, alcohol consumption, diet and education.

*Sensitivity analysis with model 2 stratified for Previous CVD.

[b] Total PA is composed of all PA types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 1.5, 2.8 and 4.5 hours per day of moderate PA equivalent of 4 METs.

[c] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 26, 60 and 141 minutes per day of walking.

[d] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 32, 88 and 146 minutes per day of domestic work.

[e] Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 51 minutes per day of cycling.

[f] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 30 minutes per day of gardening.

[g] Average sports is equivalent to 5.5 METs. The median levels of sports across categories are therefore equivalent to 0, 9 and 31 minutes per day of sports.

Supplement 4.2.4. Association between total PA and different types of PA and AF, Rotterdam Study, 1997-2012, in adults without prevalent CVD

Physical Activity Type and Tertile	Median MET-hours per week	Range	No. Ps/AF events	Model 2[a]	
				HR	95% CI
Total Physical Activity[b]					
1	40.0	<58.1	1,830/195	1.00	Reference
2	74.9	58.1-94.2	2,060/229	1.01	0.82-1.23
3	123.5	≥94.2	2,107/219	0.93	0.84-1.04
Walking[c]					
1	9.0	<13.5	1,911/198	1.00	Reference
2	21.0	13.9-30.0	2,277/238	0.96	0.80-1.17
3	49.5	≥30.8	1,809/207	1.00	0.82-1.22
Domestic work[d]					
1	11.9	<22.6	1,835/188	1.00	Reference
2	34.4	22.6-44.7	2,011/230	1.20	0.97-1.48
3	57.8	≥44.7	2,151/225	1.19	0.94-1.52
Cycling[e]					
1	0.0	0.0	2,549/281	1.00	Reference
2	6.0	0.33-12.0	1,895/207	0.96	0.79-1.17
3	24.0	≥12.5	1,553/155	0.87	0.70-1.07
Gardening[f]					
1	0.0	0.0	3,513/364	1.00	Reference
2	4.0	2.0-6.0	1,539/163	1.10	0.91-1.34
3	14.0	≥8.0	945/116	1.14	0.92-1.41
Sports[g]					
1	0.0	0.0	3,831/416	1.00	Reference
2	5.5	1.3-9.3	1,095/119	0.99	0.80-1.21
3	20.0	≥9.4	1,071/108	0.94	0.76-1.17

Abbreviations: AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; PA, physical activity; CVD, cardiovascular disease; Ps, participants.

[a] Model 2 was adjusted for all other PA types, smoking, previous cardiovascular disease, alcohol consumption, diet and education.

*Sensitivity analysis with model 2 stratified for Previous CVD.

[b] Total PA is composed of all PA types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 1.5, 2.8 and 4.5 hours per day of moderate PA equivalent of 4 METs.

[c] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 26, 60 and 141 minutes per day of walking.

[d] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 32, 88 and 146 minutes per day of domestic work.

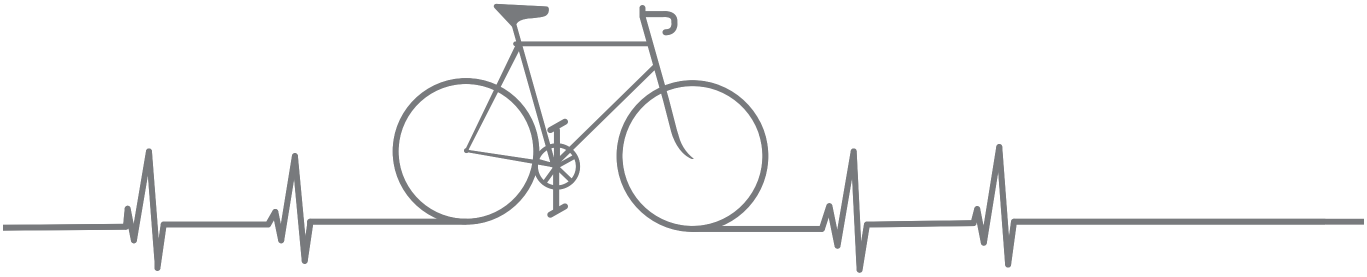
[e] Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 51 minutes per day of cycling.

[f] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 30 minutes per day of gardening.

[g] Average sports is equivalent to 5.5 METs. The median levels of sports across categories are therefore equivalent to 0, 9 and 31 minutes per day of sports.

SUPPLEMENTARY REFERENCES

1. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011;43(8):1575-1581.



Chapter 4.3

Physical activity types and life expectancy with and without cardiovascular disease

Manuscript based on this chapter:

Dhana K*, **Koolhaas CM***, Berghout MA, Peeters A, Ikram MA, Tiemeier H, Hofman A, Nusselder W, Franco OH. Physical activity types and life expectancy with and without cardiovascular disease: the Rotterdam Study. *J Public Health (Oxf)*. 2017;39(4):e209-e218.

ABSTRACT

Background: We aimed to determine the contribution of specific physical activity (PA) types (i.e. walking, cycling, domestic work, sports and gardening) on total life expectancy (LE) and LE with and without cardiovascular disease (CVD).

Methods: We constructed multistate life tables to calculate the effects of total PA and PA types on LE, among individuals older than 55 years from the Rotterdam Study. For the life table calculations, we used sex-specific prevalences, incident rates and hazard ratios for 3-transitions (healthy-to-CVD, healthy-to-death, and CVD-to-death) by levels of PA and adjusted for confounders.

Results: High total PA was associated with gains in total and CVD-free LE. High cycling contributed to higher total LE in men (3.7 years) and women (2.1 years) and higher LE without CVD in men (3.1 years) and women (2.4 years). Total and CVD-free LE were increased by high domestic work in women (2.6 and 2.4 years, respectively) and high gardening in men (2.7 and 2.0 years, respectively).

Conclusions: Higher PA levels are associated with increased LE and more years lived without CVD. Of the different PA types, cycling provided high effects in both men and women. Cycling could be more strongly encouraged in activity guidelines to maximize the population benefits of PA.

INTRODUCTION

The association between physical activity (PA) and reduced risk of mortality and cardiovascular disease (CVD) has been well documented.[1,2] According to a recent meta-analysis, regular PA of moderate to vigorous intensity may contribute to up to 27% reduced risk of CVD and mortality.[3] However, to provide comprehensive information for public and individual health care planning, it could be informative to look beyond hazard ratios and to provide measures of the lifetime consequences of PA. Additionally, since individuals with CVD have a reduced quality of life,[4,5] information on the life years with and without CVD is of relevance.

Previous studies evaluating the association between PA and LE have shown that compared to individuals with low levels of PA, high levels of PA in adulthood are associated with an increase in LE of 1.8-4.2 years.[6-8] Two studies within the Framingham Heart Study both showed that at the age of 50 years, high levels of PA not only increased total LE, but also increased the number of years lived without CVD.[9,10] However, these studies started data collection in the end of the 20th century, whereas treatment for cardiovascular risk factors has improved after 1990, resulting in the reduction of cardiovascular incidence and mortality rates.[11] Additionally, previous studies have evaluated the effect of total or leisure time PA, whereas it remains unclear whether specific PA types contribute most to the beneficial effects of PA in middle-aged and elderly adults. It is important to distinguish and to measure the independent effect of different types of PA (e.g. cycling, walking, domestic work) on LE, to be able to make clear and effective public health recommendations.

Therefore, we aimed to evaluate the impact of total PA and PA types on the average years lived with and without CVD at age 55 years or older. Using data from the Rotterdam study, we constructed multistate life tables from data collected starting in the year 2000 and with over 10 years of follow-up.

METHODS

Study population

This study was embedded within the Rotterdam Study, a prospective population-based cohort study among subjects aged ≥55 years in Rotterdam, the Netherlands. Baseline examinations were completed between 1990 and 1993. In 2000-2001, the Rotterdam Study was extended with 3,011 participants who had become ≥55 years old or had moved into the study district. The objectives and design of the Rotterdam Study have been described in detail elsewhere.[12]

For the current study, we used data from 7,808 participants attending the third examination of the original cohort (RS-I-3, between 1997 and 1999; n =4,797) and the participants attending the first examination of the extended cohort (RS-II-1, between 2000 and 2001; n=3,011). Of this combined total, 7,310 participants completed PA collection (see Supplement 4.3.1). Subsequently, we excluded participants without informed consent (n=52) or without information regarding CVD (n=4). After exclusion, 7,254 participants (4,207 women) were available for the current analysis. Baseline information was collected through home interviews or was measured at the study center visit as described previously.[13,14]

Physical activity assessment

Participants were asked how many hours per week they spent in walking, cycling, sports, gardening and domestic work in the past year, using an adapted version of the Zutphen Physical Activity Questionnaire.[15,16] We used metabolic equivalent of task (MET) to quantify the intensity of activity. MET-values were assigned to every activity, according to the 2011 updated version of the Compendium of Physical Activities.[17] Sports that were not in this compendium and to which we could not assign a MET-value (e.g. under water hockey, "revalidation sports") were not used in the analyses (n=33; 2.8%). MET-values of physical activities were multiplied with time (in hours) per week spent in that specific activity to calculate MET·hours·week^{-1} in total PA and in every type of PA (cycling, walking, sports, domestic work, gardening). Further detail on the assessment of PA can be found elsewhere.[18]

Finally, all PA variables were categorized into tertiles. For activities not practiced by more than 60% of the population (cycling, gardening, sports), the bottom category for PA levels was no participation and the remaining two categories were divided by using the median value.

Assessment of outcome

The main outcome measure under study was incident non-fatal or fatal CVD and overall mortality. CVD is defined as the presence of one or more definite manifestation of coronary heart disease (coronary revascularization or non-fatal or fatal myocardial infarction or death due to coronary heart disease), stroke and heart failure.[19-21] Information about cause and circumstances of death was obtained from general practitioner medical records and from municipal records. The follow-up was complete until January 1, 2010.

Confounding variables

The confounding variables included smoking, education, living situation and alcohol use, which were assessed by questionnaire. Smoking status was accounted for through the states 'current smoker', 'former smoker' and 'never smoker'. Height and weight were measured, with which body mass index (BMI) was calculated (kg/m^2). Education was assessed according to the standard classification of education comparable to the international standard classification of education and was grouped into four categories "elementary education", "lower secondary education", "higher secondary education" and "tertiary education".[22] We assessed living situation as a dichotomous variable describing whether the participant lived alone or not. Based on daily intake of alcohol consumption in glasses per day we created 3 equal groups and added alcohol in the model as categorical variable. Concentration of serum total cholesterol and high-density lipoprotein (HDL) cholesterol was determined using an automated enzymatic procedure (Boehringer Mannheid System, Mannheim, Germany) and expressed in mg/dl. Blood pressure was measured at the right brachial artery with a random-zero sphygmomanometer with the participant in sitting position, and the mean of 2 consecutive measurements was used. Treatment for hypertension was assessed through interview. We classified participants by the presence of hypertension; as defined by systolic and diastolic blood pressure higher than 140/90 mmHg or the use of treatment for hypertension. Diabetes was defined as a fasting serum blood glucose ≥ 7.0 mmol/L, a non-fasting blood glucose ≥ 11.1 mmol/L (when fasting samples were not available), or the use of blood glucose lowering medication.

Data analysis

To calculate LE with and without CVD, we built multistate life tables for participants with low, medium and high levels of total PA and every PA type. We included three health states: "free of CVD", "history of CVD" and "death". The possible transitions were from free of CVD to CVD, from free of CVD to death and from history of CVD to death. Backflows were not allowed, and only the first entry into a state was considered.[9,23]

In order to assess the differences in risk of mortality and CVD among individuals 55 years and older by different categories of PA at baseline, we first calculated the overall sex- and age-specific rates for each transition. Following, we calculated the prevalence of low, medium and high PA, for every PA variable, by sex, 10-year age groups, and for individuals with and without CVD separately. Subsequently, gender-specific hazard ratios (HRs) comparing high and medium PA categories to low PA for each PA variable were calculated using Poisson regression ("Gompertz" distribution) in 3 models.[9,19] Model 1 was adjusted for age; model 2 was additionally adjusted for smoking status, alcohol consumption in tertiles, education, marital status, cancer prevalence and the other PA types; model 3 was additionally adjusted for body mass index, total and high-density lipoprotein cholesterol, diabetes, lipid reducing agents and anti-hypertensive medication. Additionally, we repeated the analyses in the total population, in which we adjusted for sex in model 1-3.

Finally, we calculated three sets of transitions rates for each PA variable separately using the (1) overall sex-specific transition rates, the (2) adjusted HRs (model 2) for CVD and mortality, and the (3) prevalence of PA by gender and absence or presence of CVD. Comparable calculations have been previously described.[9,19] The multistate life table was started at age 55 years and was closed at age 100 years.

Confidence intervals for all life expectancies and differences in LE were calculated using @RISK software (Anonymous 2000; MathSoft Inc, Cambridge, Mass), by Monte Carlo simulation (parametric bootstrapping) 10 000 runs.[23,24]

In a sensitivity analysis, to exclude potential bias caused by disease, we estimated the life expectancy among participants without diabetes, hypertension and dyslipidemia at baseline (n = 4,049) for the three categories of total PA.

Missing values for covariates (less than 15%) were imputed using single imputation with the Expectation Maximization method in SPSS (IBM SPSS Statistical for Windows, Armonk, New York: IBM Corp). We used STATA version 13 for Windows (StataCorp, College Station) and R statistical software (A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) for our analysis.

RESULTS

We observed 1,156 (19.3%) incident CVD events and 2,363 (32.6%) overall deaths over 10 years of follow-up. Compared to women, men were slightly younger, smoked more and showed lower levels of BMI and total PA levels (Table 4.3.1). Individuals not completing PA data collection were slightly older and more often female, compared to individuals included in the study.

HRs of men and women were very similar. Therefore, Table 4.3.2 presents the HRs and 95% confidence interval (95%CI) for the total population, for model 2. Additional adjustment for biological risk factors in model 3 only slightly attenuated the associations. Therefore, the results for model 1 and 3 are presented in Supplement 4.3.2. Sex-specific HRs used for the analyses are presented in Supplement 4.3.3 and Supplement 4.3.4. High total PA was associated with a lower risk of incident CVD (HR:0.73, 95%CI: 0.63, 0.85), compared to low PA, in model 2. Regarding PA types, compared to the low category, the high level of cycling (HR:0.77, 95%CI: 0.65, 0.91) and the medium category of sports (HR:0.80, 95%CI: 0.68, 0.95) were associated with a lower risk of incident CVD.

Among participants without CVD, high total PA was associated with a lower mortality risk (HR:0.66, 95%CI: 0.58, 0.75), compared to low PA. Regarding types, walking, cycling, domestic work, sports and gardening were each associated with 12-35% reduced mortality risk (Table 4.3.2). Compared to the low categories, the largest risk reductions were observed for the high categories of cycling, domestic work and gardening (Table 4.3.2).

Among participants with CVD, high total PA was associated with a lower mortality risk (HR:0.73, 95%CI: 0.62, 0.86), compared to the low category. Regarding types, the medium category of walking (HR:0.85, 95%CI: 0.73, 0.98) and sports (HR:0.76, 95%CI: 0.63, 0.93) and the high category of cycling (HR:0.76, 95%CI: 0.63, 0.93) were associated with reduced mortality risk, compared to the low categories.

The association between total PA and every PA type with the risk of each transition was translated into number of years lived with and without CVD (Table 4.3.3 (men), Table 4.3.4 (women) and Figure 4.3.1).

Compared to men with low total PA, total LE was increased with 2.2 (95%CI: 1.5, 2.9) years in the medium category and 3.5 (95%CI: 2.8, 4.2) years in the high category. For women, these differences were 1.5 (95%CI: 0.8, 2.1) and 3.0 (95%CI: 2.3, 3.5) years, respectively (Table 4.3.3). The LE without CVD associated with total PA was up to 3.3 (95%CI: 2.5, 4.2) years in men and up to 2.8 (95%CI: 2.2, 3.6) years in women. In men, the amount of years lived with CVD was higher in the medium category of total PA.

Regarding types of PA, men and women in the medium and high category of walking, cycling, domestic work, sports and gardening had higher total LE and LE without CVD than participants in the low categories of these PA types, although the magnitude of the effect differed per PA type (Table 4.3.3).

Table 4.3.1. Baseline characteristics of study population (n=7,254)

	Men	Women
Participants	3,047 (42.0)	4,207 (58.0)
Demographic factors		
Age	69.3 (8.1)	70.7 (8.9)
Educational level, n (%)		
Elementary	297 (9.7)	782 (18.6)
Lower secondary	933 (30.6)	2,212 (52.6)
Higher secondary	1,175 (38.6)	938 (22.3)
Tertiary	642 (21.1)	275 (6.5)
Marital status, n (%)		
Single	87 (2.9)	294 (7.0)
Married	2,404 (78.9)	2,142 (50.9)
Widowed	347 (11.4)	1,363 (32.4)
Divorced/separated	209 (6.9)	408 (9.7)
Physical activity		
Total PA, METhours/week	71.0 (43.2)	88.0 (43.8)
Walking, METhours/week	26.9 (23.4)	27.8 (25.3)
Cycling, METhours/week	10.5 (14.5)	7.0 (12.0)
Domestic work, METhours/week	21.2 (17.8)	46.4 (21.7)
Sports, METhours/week	7.2 (15.4)	4.0 (9.5)
Gardening, METhours/week	5.2 (11.9)	2.8 (6.6)
Lifestyle factors		
Smoking, n (%)		
Never	909 (29.8)	2,558 (60.8)
Former	1,569 (51.5)	927 (22.0)
Current	569 (18.7)	722 (17.2)
BMI, kg/m^2	26.5 (3.2)	27.4 (4.2)
Alcohol, n (%)		
Low	618 (20.3)	1,827 (43.4)
Medium	974 (32.0)	1,487 (35.3)
High	1,455 (47.8)	893 (21.2)
Biological risk factors		
Using blood pressure medication, n (%)	707 (23.2)	1,143 (27.2)
Using lipid reducing agents, n (%)	412 (13.5)	486 (11.6)
Cholesterol, mg/dl	5.5 (1.0)	6.0 (1.0)
HDL-cholesterol, mg/dl	1.2 (0.3)	1.5 (0.4)
Glucose, mg/dl	6.2 (1.7)	6.0 (1.6)
Systolic blood pressure, mm HG	144.4 (21.2)	143.8 (21.7)
Prevalent diabetes, n (%)	534 (17.5)	661 (15.7)

Values are mean (SD) or number (percentage).

Table 4.3.2. Hazard ratios for the different transitions for men and women, based on the Rotterdam Study

		No CVD to CVD	No CVD to death	CVD to death
No. events		1156	1569	1136
Person-years		45219	54715	13641
	Median (Range) (MET hours week^{-1})	Model 2[a] HR (95% CI)	Model 2[a] HR (95% CI)	Model 2[a] HR (95% CI)
Total PA[b]				
Low	38.5 (≤57.6)	1 [ref]	1 [ref]	1 [ref]
Moderate	74.3 (57.7-94.0)	0.93 (0.81,1.07)	0.76 (0.68,0.86)	0.86 (0.75,0.99)
High	123.2 (≥94.1)	0.73 (0.63,0.85)	0.66 (0.58,0.75)	0.73 (0.62,0.86)
P for trend		<0.001	<0.001	<0.001
Walking[c]				
Low	8.3 (≤13.5)	1 [ref]	1 [ref]	1 [ref]
Moderate	21.0 (13.6-30.0)	0.89 (0.77,1.02)	0.88 (0.79,1.00)	0.85 (0.73,0.98)
High	49.5 (≥30.1)	0.86 (0.74,1.00)	0.90 (0.79,1.02)	0.87 (0.75,1.01)
P for trend		0.05	0.09	0.05
Cycling[d]				
Low	0.0 (0.0)	1 [ref]	1 [ref]	1 [ref]
Moderate	6.0 (≤12.0)	0.85 (0.74,0.99)	0.71 (0.62,0.81)	0.85 (0.73,1.00)
High	24.0 (≥12.1)	0.77 (0.65,0.91)	0.65 (0.56,0.76)	0.76 (0.63,0.93)
P for trend		0.002	<0.001	0.004
Domestic work[e]				
Low	11.6 (≤22.5)	1 [ref]	1 [ref]	1 [ref]
Moderate	34.1 (22.6-44.7)	0.93 (0.80,1.09)	0.83 (0.73,0.94)	0.94 (0.82,1.09)
High	57.8 (≥44.8)	0.85 (0.71,1.01)	0.73 (0.63,0.85)	0.88 (0.74,1.05)
P for trend		0.06	<0.001	0.15
Sports[f]				
Low	0.0 (0.0)	1 [ref]	1 [ref]	1 [ref]
Moderate	5.4 (≤6.0)	0.80 (0.68,0.95)	0.79 (0.68,0.91)	0.81 (0.67,0.97)
High	19.2 (≥6.1)	1.06 (0.90,1.26)	0.86 (0.73,1.00)	0.85 (0.70,1.03)
P for trend		0.87	0.005	0.02
Gardening[g]				
Low	0.0 (0.0)	1 [ref]	1 [ref]	1 [ref]
Moderate	4.0 (≤9.2)	0.89 (0.76,1.04)	0.75 (0.65,0.87)	0.87 (0.72,1.05)
High	14.0 (≥9.3)	0.98 (0.82,1.18)	0.73 (0.62,0.87)	0.94 (0.77,1.15)
P for trend		0.53	<0.001	0.28

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio, PA, physical activity; ref, referent.

[a] Model 2 was adjusted for age, sex smoking status, alcohol consumption in tertiles, education, marital status and cancer prevalence. For PA types, model 2 was also adjusted for all other PA types.

[b] Total PA is composed of all PA types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 1.4, 2.7 and 4.4 hours per day of moderate PA equivalent of 4 METs.

[c] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 24, 60 and 141 minutes per day of walking.

[d] Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 51 minutes per day of cycling.

[e] Average domestic work is equivalent to 3.5 METs.[17] The median levels of domestic work across categories are therefore equivalent to 28, 83 and 142 minutes per day of domestic work.

[f] Average sports is equivalent to 5.5 METs. The median levels of sports across categories are therefore equivalent to 0, 8 and 30 minutes per day of sports.

[g] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 30 minutes per day of gardening.

In men and women, high cycling increased LE with 3.7 (95%CI: 3.0, 4.4) years and 2.1 (95%CI: 1.1, 3.0) years, respectively. In women, domestic work was also associated with large gains in LE, with up to 2.6 (95%CI: 1.9, 3.3) years for the high category. In men, both sports and gardening were associated with higher LE. The medium category of sports increased LE with 3.1 (95%CI: 2.3, 4.0) years, and the high category of gardening had 2.7 (95%CI: 1.9, 3.5) years higher LE, compared to the low category.

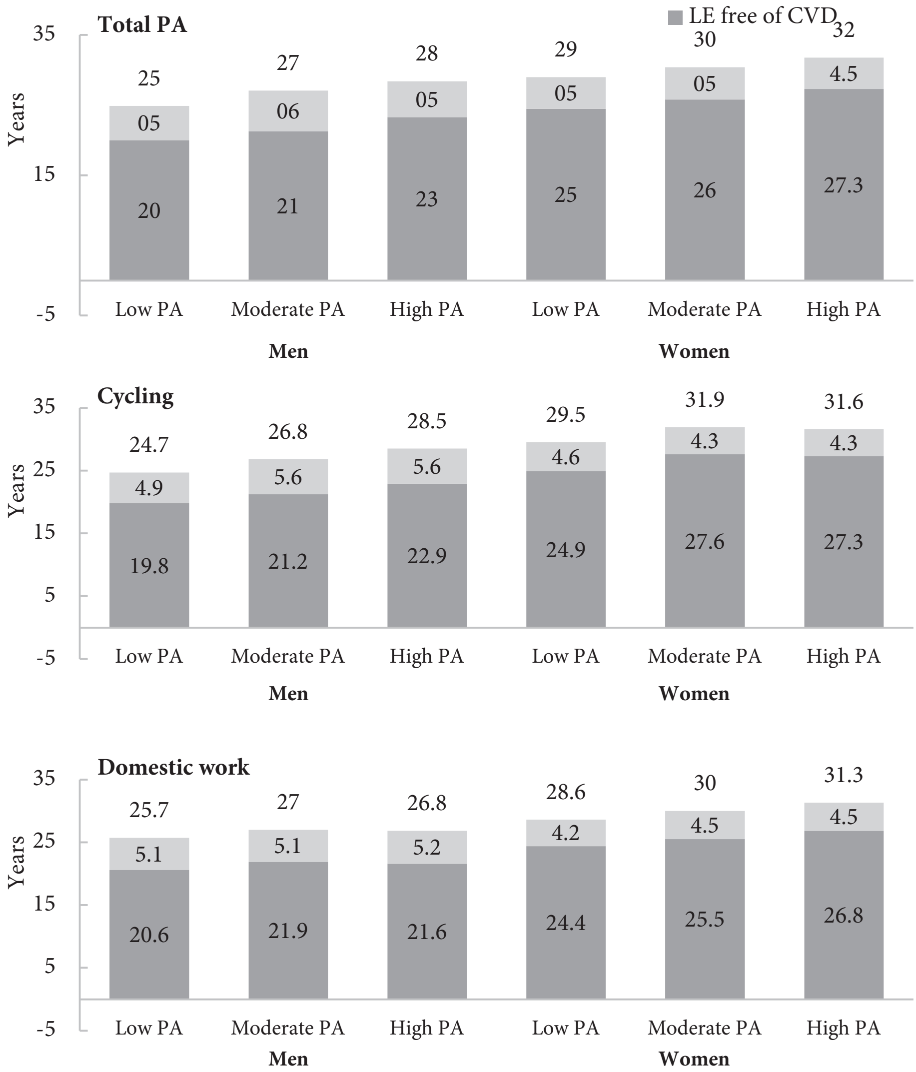


Figure 4.3.1. Effect of physical activity on life expectancy with and without CVD at age 55 years. All life expectancies have been calculated with sex-specific hazard ratios adjusted for age, smoking status, alcohol consumption in tertiles, education, marital status and cancer prevalence. Models with PA types were additionally adjusted for the other PA types. Abbreviations: CVD, cardiovascular disease; LE, life expectancy; PA, physical activity.

The largest gains in LE without CVD were found for cycling, with up to 3.3 (95%CI: 2.5, 4.2) years in men and 2.7 (95%CI: 1.9, 3.5) years in women. In men, the medium category of sports also increased LE without CVD with 2.9 (95%CI: 1.8, 4.0) years and the medium and high category of gardening increased LE with 2.4 (95%CI: 1.5, 3.4) and 2.0 (95%CI: 0.8, 3.1) years, respectively. In women, domestic work was associated with increases in LE in the medium and high category of 1.1 (95%CI: 0.1, 2.0) and 2.4 (95%CI: 1.5, 3.3) years, respectively.

Total LE and the number of years lived with and without CVD for participants without hypertension, diabetes and dyslipidemia are presented in Supplement 4.3.5 for total PA. Compared to the population included in the main analyses, total LE was up to 1.2 year higher for individuals without hypertension, diabetes and dyslipidemia. Moreover, in this population, LE free from CVD was up to 1.6 year higher, whereas LE with CVD was lower.

DISCUSSION

In this prospective cohort study, we found that high total PA at age 55 and over was associated with an increase in total LE and with a greater number of years lived without CVD. Cycling was associated with gains in total LE in both men and women. Additionally, domestic work in women and sports and gardening in men were independently associated with large increases in total LE. Cycling also had a beneficial effect on extending LE without CVD in both men and women. Total PA and types of PA had a small impact on years lived with CVD.

The higher LE free from CVD in individuals with higher PA levels was the result of a lower risk of CVD and mortality. Due to the lower CVD risk, the first CVD event occurs later in the lifespan and consequently, LE without CVD is increased. Furthermore, being free from CVD reduces the mortality risk and therefore increases the number of years lived and consequently the number of years free of CVD. We also found that men with higher levels of total PA, sports and cycling spent slightly more years with CVD, compared to men with low PA. The years lived with CVD are a consequence of the CVD risk in individuals without history of CVD, influencing the age of the first event, and mortality risk in those with CVD, determining the years lived after the CVD event. In our study, men with high PA and a history of CVD had a lower mortality risk and therefore they lived slightly longer with CVD.

The HRs we found in our study support existing evidence that PA reduces the incidence of CVD.[3,25] Moreover the reduction in mortality risk among persons without history of CVD associated with total PA, is in line with previous studies.[26,27] Our results also confirm that total PA reduces mortality in persons with a history of CVD.[26,28,29] The effects of specific types of PA, however, are less well documented in literature. We found one study reporting the association between gardening, sports, walking and cycling with incident CVD, which reported similar HRs as we found.[30] Additionally, a study within the Whitehall population reported similar HRs for all-cause mortality for cycling, sports and gardening.[31] In this study, domestic work did not reduce mortality risk, which might be related to the slightly younger participants (mean age 56 years).

Table 4.3.3. Total life expectancy (total LE), life expectancy without CVD (LE without CVD) and life expectancy with CVD (LE with CVD), and difference, in Years at Age 55, for men*

	Total LE (years)	Dif Total LE (years)†	LE free of CVD (years)	Dif LE free of CVD (years)†	LE with CVD (years)	Dif LE with CVD (years)†
Total PA						
Low	24.9 (24.6, 25.2)	Ref	20.0 (19.6, 20.4)	Ref	4.9 (4.6, 5.2)	Ref
Moderate	27.1 (26.5, 27.7)	2.2 (1.5, 2.9)	21.3 (20.6, 22.1)	1.3 (0.4, 2.3)	5.8 (5.2, 6.5)	0.9 (0.1, 1.7)
High	28.4 (27.7, 29.0)	3.5 (2.8, 4.2)	23.3 (22.5, 24.1)	3.3 (2.5, 4.2)	5.1 (4.5, 5.7)	0.2 (-0.5, 0.8)
Walking						
Low	25.4 (24.9, 25.8)	Ref	20.3 (19.8, 20.8)	Ref	5.1 (4.7, 5.4)	Ref
Moderate	26.7 (26.1, 27.4)	1.3 (0.6, 2.1)	21.3 (20.6, 22.0)	1.0 (0.1, 1.9)	5.5 (4.9, 6.1)	0.4 (-0.4, 1.2)
High	26.7 (26.0, 27.4)	1.3 (0.5, 2.1)	21.8 (21.0, 22.6)	1.5 (0.5, 2.5)	4.9 (4.3, 5.5)	-0.2 (-0.9, 0.6)
Cycling						
Low	24.7 (24.4, 25.0)	Ref	19.8 (19.4, 20.3)	Ref	4.9 (4.6, 5.2)	Ref
Moderate	26.8 (26.3, 27.4)	2.1 (1.4, 2.9)	21.2 (20.5, 21.9)	1.4 (0.4, 2.4)	5.6 (5.1, 6.3)	0.7 (0.0, 1.6)
High	28.4 (27.7, 29.0)	3.7 (3.0, 4.4)	22.9 (22.1, 23.7)	3.1 (2.1, 4.0)	5.5 (4.8, 6.2)	0.6 (-0.2, 1.3)
Domestic work						
Low	25.7 (25.4, 26.0)	Ref	20.6 (20.3, 21.0)	Ref	5.1 (4.8, 5.4)	Ref
Moderate	27.0 (26.4, 27.6)	1.3 (0.5, 2.0)	21.9 (21.2, 22.7)	1.3 (0.4, 2.2)	5.1 (4.5, 5.6)	0.0 (-0.8, 0.7)
High	26.8 (25.7, 27.9)	1.1 (-0.1, 2.2)	21.6 (20.3, 22.9)	1.0 (-0.5, 2.4)	5.2 (4.2, 6.3)	0.1 (-1.0, 1.3)
Sports						
Low	25.6 (25.3, 25.9)	Ref	20.8 (20.4, 21.2)	Ref	4.8 (4.5, 5.1)	Ref
Moderate	28.7 (27.9, 29.5)	3.1 (2.3, 4.0)	23.7 (22.7, 24.7)	2.9 (1.8, 4.0)	5.0 (4.3, 5.8)	0.2 (-0.6, 1.0)
High	26.8 (26.1, 27.6)	1.2 (0.4, 2.1)	20.5 (19.5, 21.5)	-0.3 (-1.6, 0.9)	6.4 (5.5, 7.2)	1.6 (0.5, 2.6)
Gardening						
Low	25.2 (25.0, 25.5)	Ref	20.2 (19.8, 20.5)	Ref	5.1 (4.8, 5.3)	Ref
Moderate	27.9 (27.2, 28.6)	2.7 (1.9, 3.4)	22.6 (21.8, 23.4)	2.4 (1.5, 3.4)	5.3 (4.6, 6.0)	0.2 (-0.5, 1.0)
High	27.9 (27.2, 28.7)	2.7 (1.9, 3.5)	22.2 (21.2, 23.2)	2.0 (0.8, 3.1)	5.8 (5.0, 6.6)	0.7 (-0.2, 1.6)

Abbreviations: CVD, cardiovascular disease; LE, life expectancy; PA, physical activity; ref, referent.

*All life expectancies were calculated with sex-specific hazard ratios adjusted for age, smoking status, alcohol consumption in tertiles, education, marital status and cancer prevalence. For PA types, models were also adjusted for all other PA types. Unless otherwise indicated, data are reported as mean (95% confidence interval) years.

†Differences are calculated using the low physical activity group as the reference: moderate vs low and high vs low

Table 4.3.4. Total life expectancy (total LE), life expectancy without CVD (LE without CVD) and life expectancy with CVD (LE with CVD), and difference, in Years at Age 55, for women*

	Total LE (years)	Dif Total LE (years)†	LE free of CVD (years)	Dif LE free of CVD (years)†	LE with CVD (years)	Dif LE with CVD (years)†
Total PA						
Low	28.9 (28.6, 29.3)	Ref	24.5 (24.1, 24.9)	Ref	4.5 (4.2, 4.8)	Ref
Moderate	30.4 (29.9, 30.9)	1.5 (0.8, 2.1)	25.8 (25.2, 26.4)	1.3 (0.5, 2.1)	4.6 (4.2, 5.1)	0.1 (-0.4, 0.8)
High	31.9 (31.3, 32.4)	3.0 (2.3, 3.5)	27.3 (26.7, 27.9)	2.8 (2.2, 3.6)	4.5 (4.0, 5.0)	0.0 (-0.5, 0.6)
Walking						
Low	29.8 (29.4, 30.1)	Ref	25.3 (24.9, 25.8)	Ref	4.4 (4.2, 4.7)	Ref
Moderate	30.6 (30.1, 31.2)	0.8 (0.2, 1.5)	26.3 (25.7, 26.9)	1.0 (0.2, 1.7)	4.3 (3.9, 4.8)	-0.1 (-0.7, 0.5)
High	30.5 (29.9, 31.2)	0.7 (0.0, 1.5)	26.0 (25.3, 26.7)	0.7 (-0.2, 1.5)	4.6 (4.0, 5.1)	0.2 (-0.5, 0.8)
Cycling						
Low	29.5 (29.3, 29.7)	Ref	24.9 (24.7, 25.2)	Ref	4.6 (4.4, 4.8)	Ref
Moderate	31.9 (31.3, 32.5)	2.4 (1.6, 3.1)	27.6 (27.0, 28.3)	2.7 (1.9, 3.5)	4.3 (3.7, 4.8)	-0.3 (-1.0, 0.3)
High	31.6 (30.7, 32.5)	2.1 (1.1, 3.0)	27.3 (26.4, 28.1)	2.4 (1.4, 3.3)	4.3 (3.5, 5.1)	-0.3 (-1.1, 0.6)
Domestic work						
Low	28.6 (28.2, 29.1)	Ref	24.4 (23.8, 25.0)	Ref	4.2 (3.8, 4.7)	Ref
Moderate	30.0 (29.4, 30.5)	1.4 (0.6, 2.1)	25.5 (24.7, 26.2)	1.1 (0.1, 2.1)	4.5 (3.9, 5.1)	0.3 (-0.5, 1.1)
High	31.2 (30.6, 31.8)	2.6 (1.9, 3.3)	26.8 (26.1, 27.5)	2.4 (1.5, 3.3)	4.5 (3.9, 5.0)	0.3 (-0.5, 0.9)
Sports						
Low	30.0 (29.7, 30.2)	Ref	25.5 (25.3, 25.8)	Ref	4.5 (4.3, 4.6)	Ref
Moderate	31.0 (30.3, 31.7)	1.0 (0.2, 1.8)	26.8 (26.1, 27.6)	1.3 (0.4, 2.1)	4.2 (3.6, 4.7)	-0.3 (-0.9, 0.4)
High	30.9 (30.0, 31.9)	0.9 (-0.1, 2.0)	26.6 (25.6, 27.6)	1.1 (0.0, 2.2)	4.3 (3.5, 5.2)	-0.2 (-1.1, 0.9)
Gardening						
Low	30.0 (29.8, 30.2)	Ref	25.7 (25.4, 25.9)	Ref	4.3 (4.1, 4.5)	Ref
Moderate	31.1 (30.4, 31.9)	1.1 (0.3, 1.9)	26.6 (25.8, 27.4)	0.9 (0.0, 1.9)	4.6 (3.9, 5.3)	0.3 (-0.5, 1.0)
High	30.3 (29.2, 31.4)	0.3 (-0.9, 1.5)	25.9 (24.7, 27.1)	0.2 (-1.1, 1.5)	4.4 (3.5, 5.4)	0.1 (-1.0, 1.1)

Abbreviations: CVD, cardiovascular disease; LE, life expectancy; PA, physical activity; ref, referent.

*All life expectancies were calculated with sex-specific hazard ratios adjusted for age, smoking status, alcohol consumption in tertiles, education, marital status and cancer prevalence. For PA types, models were also adjusted for all other PA types. Unless otherwise indicated, data are reported as mean (95% confidence interval) years.

†Differences are calculated using the low physical activity group as the reference: moderate vs low and high vs low

Our study is the first to report mortality risk for several PA types among participants with and without prevalent CVD. Moreover, we revealed that cycling, sports and walking not only prevented the first cardiovascular event in those without CVD, but also improved the prognosis of CVD in participants with CVD. In our study, compared to low PA, we found increases in LE for high PA which are similar to findings from other studies.[6-10] One study found a slightly higher LE,[7] which could be explained by the fact that they only looked at leisure time PA, whereas we evaluated leisure time, housework and transportation combined. Additionally, compared to low PA, we found increases in LE without CVD for high total PA of 3.3 in men and 2.8 in women, comparable to previous studies.[9,10] In earlier studies comprising participants from the Framingham Heart Study, at age 50, high PA was associated with increases in LE without CVD of 3.0-3.2 years for men and 3.1-3.3 years for women, compared to low PA.[9,10] This study included participants aged 50 years, between 1948 and 1950, and followed them up until the end of the 20th century, whereas we included participants starting from 1999 and followed them until 2010. After 1990, the treatment for cardiovascular risk factors has improved, which resulted in the reduction of cardiovascular incidence and mortality rates.[11] Additionally, it might be expected that our population was less physically active, due to population changes in PA over the years. In spite of these population differences, the relative contribution of high PA compared to low PA has remained stable, indicating that being physically active can protect against CVD, independent of differences in the population.

In our analyses, cycling was an important contributor to the effect of total PA. Furthermore, domestic work was important for women, whereas gardening and sports were important for men. The beneficial effect of several different PA types on LE has not been studied before and we are the first to show that these PA types have independent effects on total LE and LE without CVD. However, previous studies have shown beneficial effects of cycling, domestic work and sports on CVD and mortality risk.[30,32-36] Moreover, whereas the World Health Organization recommends to engage in 30 minutes of PA, 5 days a week, to gain health benefits,[37] our results suggest that 13 minutes of cycling per day (the medium category) can already increase LE with 2.1 years in men and 2.4 years in women. This has also been shown in another study,[38] in which an increase in total LE of 3 years was reported for 15 minutes of leisure time PA per day. Regarding other specific PA types, we only found one study reporting on walking, with increases in LE similar to ours.[39]

This study has some limitations. First, we did not collect information on occupational PA, so we could not adjust for this in our analyses. However, since only 11.5% was employed at baseline, we do not believe this would have significantly influenced our results. Second, although our questionnaire has been validated,[15] some error in self-report is inevitable. Moreover, since PA was measured at baseline only, this could have led to misclassification of PA over time. These last two limitations could have resulted in bias towards the null. Furthermore, people in poor health might participate in PA less than others, creating the opportunity for reverse causation. However, we adjusted for diabetes and hypertension in our third model and observed no major changes in the HRs. Finally, we excluded individuals that did not complete PA data collection. These individuals were slightly older and more often female.

Major strengths of the current study are our relatively long follow-up period in a well-defined prospective population-based cohort study. Furthermore, we had a very accurate method of outcome ascertainment and we were able to adjust for several factors, thereby minimizing the possibility of the observed associations being explained by confounding. Additionally, by including a number of different physical activities, while adjusting for the remaining activities, we could examine their independent associations with CVD and mortality.

Conclusions

We conclude that high levels of PA are associated with a higher LE and prolonged years lived without CVD. Cycling contributed most to the most health benefits in both men and women, whereas domestic work contributed in women and sports and gardening contributed in men. Such activities could be more strongly encouraged in activity guidelines to maximize the population benefits of physical activity.

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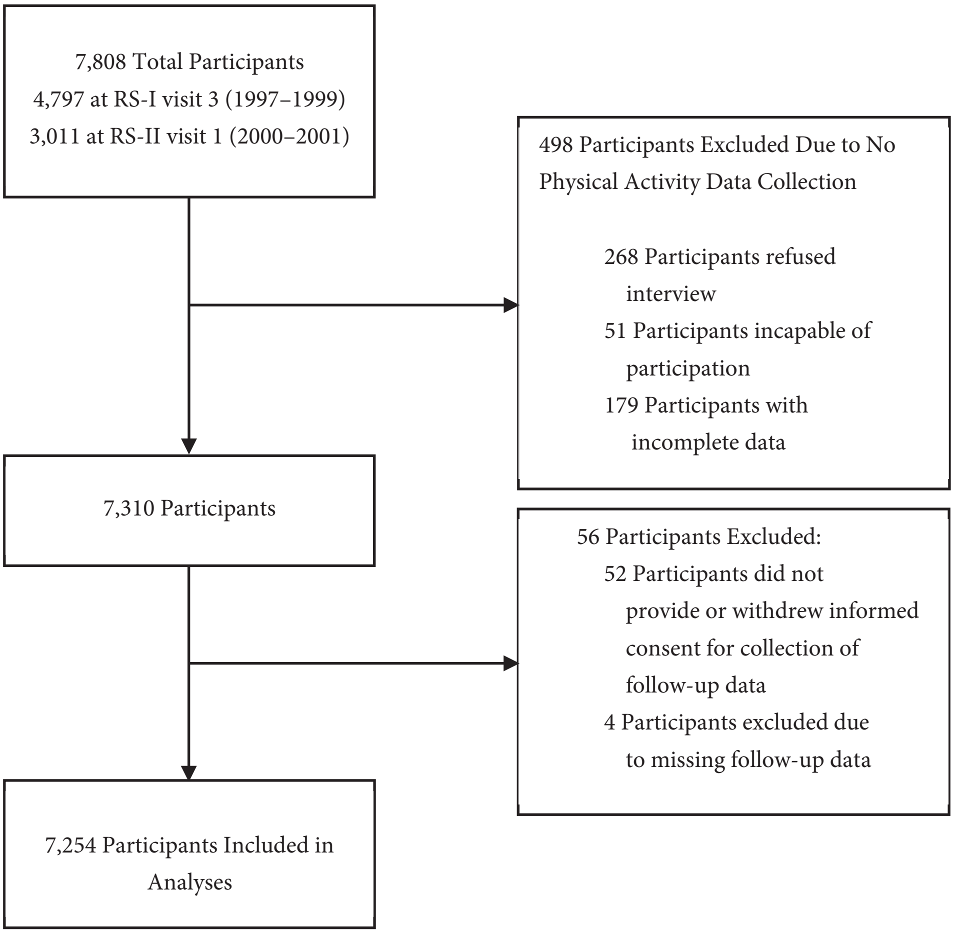
SUPPLEMENT CHAPTER 4.1

Supplement 4.3.1. Flowchart of participant inclusion in the Rotterdam Study.



Supplement 4.3.2. Hazard ratios for the different transitions for men and women, based on the Rotterdam Study, for model 1 and 3

		No CVD to CVD		No CVD to death		CVD to death	
Number of events		1,156		1,569		1,136	
Person-years		45,219		54,715		13,641	
	Median (Range) (MET-hours per week)	Model 1[a] HR (95% CI)	Model 3[b] HR (95% CI)	Model 1[a] HR (95% CI)	Model 3[b] HR (95% CI)	Model 1[a] HR (95% CI)	Model 3[b] HR (95% CI)
Total PA[c]							
Low	38.5 (≤57.6)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	74.3 (57.7-94.0)	0.91 (0.79,1.04)	0.97 (0.84, 1.12)	0.74 (0.66,0.83)	0.79 (0.70, 0.89)	0.86 (0.75,0.99)	0.87 (0.75, 1.00)
High	123.2 (≥94.1)	0.71 (0.61,0.83)	0.80 (0.68, 0.93)	0.63 (0.56,0.72)	0.70 (0.61, 0.81)	0.76 (0.65,0.89)	0.76 (0.64, 0.89)
Walking[d]							
Low	8.3 (≤13.5)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	21.0 (13.6-30.0)	0.88 (0.77,1.01)	0.88 (0.77, 1.02)	0.88 (0.78,0.99)	0.87 (0.77, 0.98)	0.85 (0.74,0.98)	0.84 (0.72, 0.97)
High	49.5 (≥30.1)	0.86 (0.74,1.00)	0.88 (0.75, 1.02)	0.88 (0.78,1.00)	0.91 (0.80, 1.04)	0.88 (0.76,1.02)	0.91 (0.78, 1.06)
Cycling[e]							
Low	0.0 (0.0)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	6.0 (≤12.0)	0.82 (0.71,0.95)	0.88 (0.76, 1.03)	0.68 (0.60,0.78)	0.71 (0.62, 0.82)	0.87 (0.74,1.02)	0.83 (0.70, 0.98)
High	24.0 (≥12.1)	0.73 (0.61,0.86)	0.82 (0.69, 0.98)	0.61 (0.52,0.71)	0.67 (0.57, 0.78)	0.75 (0.62,0.91)	0.77 (0.63, 0.95)
Domestic work[f]							
Low	11.6 (≤22.5)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	34.1 (22.6-44.7)	0.95 (0.81,1.10)	0.92 (0.79, 1.08)	0.86 (0.76,0.98)	0.81 (0.71, 0.93)	0.97 (0.84,1.11)	0.95 (0.82, 1.10)
High	57.8 (≥44.8)	0.85 (0.71,1.01)	0.85 (0.71, 1.02)	0.76 (0.65,0.88)	0.74 (0.63, 0.86)	0.93 (0.78,1.11)	0.88 (0.74, 1.06)
Sports[g]							
Low	0.0 (0.0)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	5.4 (≤6.0)	0.80 (0.67,0.94)	0.86 (0.72, 1.02)	0.77 (0.67,0.90)	0.83 (0.71, 0.97)	0.80 (0.67,0.96)	0.81 (0.67, 0.98)
High	19.2 (≥6.1)	1.05 (0.89,1.23)	1.19 (1.01, 1.41)	0.85 (0.73,1.00)	0.90 (0.77, 1.06)	0.84 (0.70,1.02)	0.84 (0.69, 1.03)

Supplement 4.3.2 (continued). Hazard ratios for the different transitions for men and women, based on the Rotterdam Study, for model 1 and 3

		No CVD to CVD		No CVD to death		CVD to death	
Number of events		1,156		1,569		1,136	
Person-years		45,219		54,715		13,641	
	Median (Range) (MET-hours per week)	Model 1[a] HR (95% CI)	Model 3[b] HR (95% CI)	Model 1[a] HR (95% CI)	Model 3[b] HR (95% CI)	Model 1[a] HR (95% CI)	Model 3[b] HR (95% CI)
Gardening[h]							
Low	0.0 (0.0)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	4.0 (≤9.2)	0.86 (0.74,1.01)	0.90 (0.77, 1.06)	0.72 (0.63,0.83)	0.77 (0.67, 0.89)	0.83 (0.69,1.00)	0.91 (0.76, 1.10)
High	14.0 (≥9.3)	0.95 (0.80,1.13)	1.01 (0.84, 1.21)	0.69 (0.58,0.82)	0.76 (0.63, 0.90)	0.89 (0.73,1.08)	0.92 (0.75, 1.14)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio, PA, physical activity; ref, referent.

[a] Model 1 was adjusted for age and sex.

[b] Model 3 was adjusted for age, sex, smoking status, alcohol consumption in tertiles, education, marital status, cancer prevalence, the other PA types, body mass index, total and high-density lipoprotein cholesterol, diabetes, lipid reducing agents and anti-hypertensive medication.

[c] Total PA is composed of all PA types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 1.4, 2.7 and 4.4 hours per day of moderate PA equivalent of 4 METs.

[d] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 24, 60 and 141 minutes per day of walking.

[e] Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 51 minutes per day of cycling.

[f] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 28, 83 and 142 minutes per day of domestic work.

[g] Average sports is equivalent to 5.5 METs. The median levels of sports across categories are therefore equivalent to 0, 8 and 30 minutes per day of sports.

[h] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 30 minutes per day of gardening.

Supplement 4.3.3. Hazard ratios for the different transitions for men, based on the Rotterdam Study

		No CVD to CVD			No CVD to death			CVD to death		
Number of events		487			678			574		
Person-years		16,881			20,592			7,107		
	Range (MET-hours per week)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)
Total PA[d]										
Low	36.9 (≤57.6)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	74.1 (57.7-94.0)	0.99 (0.80,1.21)	0.99 (0.80,1.21)	1.06 (0.85, 1.31)	0.71 (0.59,0.85)	0.72 (0.60,0.86)	0.75 (0.62, 0.90)	0.82 (0.68,0.99)	0.82 (0.68,1.00)	0.86 (0.70, 1.05)
High	120.6 (≥94.1)	0.75 (0.59,0.94)	0.74 (0.59,0.94)	0.81 (0.64, 1.03)	0.62 (0.51,0.76)	0.63 (0.51,0.77)	0.66 (0.54, 0.82)	0.78 (0.62,0.98)	0.75 (0.60,0.94)	0.77 (0.61, 0.97)
Walking[e]										
Low	7.5 (≤13.5)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	21.0 (13.6-30.0)	0.90 (0.72,1.11)	0.91 (0.73,1.12)	0.88 (0.71, 1.10)	0.86 (0.72,1.03)	0.87 (0.73,1.05)	0.87 (0.72, 1.05)	0.81 (0.67,0.99)	0.80 (0.65,0.97)	0.79 (0.64, 0.97)
High	47.3 (≥30.1)	0.83 (0.66,1.04)	0.84 (0.67,1.06)	0.85 (0.67, 1.07)	0.81 (0.67,0.99)	0.84 (0.69,1.02)	0.85 (0.70, 1.04)	0.92 (0.75,1.13)	0.90 (0.73,1.11)	0.93 (0.75, 1.16)
Cycling[f]										
Low	0.0 (0.0)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	6.0 (≤12.0)	0.94 (0.76,1.16)	0.97 (0.78,1.20)	0.99 (0.79, 1.23)	0.69 (0.58,0.83)	0.73 (0.61,0.88)	0.74 (0.61, 0.9)	0.86 (0.70,1.04)	0.83 (0.68,1.01)	0.80 (0.65, 0.99)
High	24.0 (≥12.1)	0.75 (0.59,0.94)	0.79 (0.62,1.00)	0.83 (0.65, 1.07)	0.57 (0.46,0.69)	0.63 (0.51,0.77)	0.64 (0.52, 0.79)	0.69 (0.55,0.87)	0.70 (0.55,0.88)	0.71 (0.56, 0.91)
Domestic work[g]										
Low	11.1 (≤22.5)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	30.9 (22.6-44.7)	0.92 (0.74,1.13)	0.88 (0.71,1.08)	0.88 (0.71, 1.09)	0.89 (0.75,1.06)	0.83 (0.70,0.99)	0.82 (0.68, 0.99)	0.92 (0.76,1.11)	0.92 (0.76,1.11)	0.95 (0.78, 1.15)

Supplement 4.3.3 (continued). Hazard ratios for the different transitions for men, based on the Rotterdam Study

		No CVD to CVD			No CVD to death			CVD to death		
	Range (MET-hours per week)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)
High	57.2 (≥44.8)	1.08 (0.82,1.43)	0.97 (0.72,1.31)	0.98 (0.72, 1.32)	0.94 (0.74,1.21)	0.80 (0.62,1.03)	0.81 (0.62, 1.06)	1.07 (0.80,1.43)	1.03 (0.76,1.40)	1.03 (0.76, 1.40)
Sports[h]										
Low	0.0 (0.0)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	5.5 (≤6.0)	0.74 (0.56,0.99)	0.75 (0.56,1.00)	0.84 (0.63, 1.13)	0.67 (0.53,0.85)	0.68 (0.53,0.87)	0.76 (0.59, 0.97)	0.71 (0.54,0.94)	0.71 (0.54,0.94)	0.74 (0.56, 0.99)
High	21.9 (≥6.1)	1.16 (0.93,1.44)	1.19 (0.96,1.48)	1.31 (1.05, 1.64)	0.85 (0.69,1.05)	0.86 (0.70,1.06)	0.92 (0.75, 1.14)	0.79 (0.63,0.99)	0.79 (0.63,0.99)	0.77 (0.61, 0.98)
Gardening[i]										
Low	0.0 (0.0)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	4.0 (≤9.2)	0.78 (0.62,0.98)	0.82 (0.65,1.03)	0.86 (0.68, 1.09)	0.65 (0.53,0.80)	0.70 (0.57,0.86)	0.74 (0.60, 0.91)	0.77 (0.60,0.98)	0.80 (0.62,1.02)	0.86 (0.67, 1.11)
High	14.0 (≥9.3)	0.91 (0.72,1.15)	0.95 (0.75,1.20)	0.98 (0.77, 1.24)	0.58 (0.46,0.72)	0.63 (0.50,0.79)	0.65 (0.51, 0.83)	0.84 (0.66,1.06)	0.87 (0.68,1.11)	0.87 (0.68, 1.12)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio, PA, physical activity; ref, referent.

[a] Model 1 was adjusted for age.

[b] Model 2 was adjusted for age, smoking status, alcohol consumption in tertiles, education, marital status and cancer prevalence. For PA types, model 2 was also adjusted for all other PA types.

[c] Model 3 was adjusted for age, smoking status, alcohol consumption in tertiles, education, marital status, cancer prevalence, the other PA types, body mass index, total and high-density lipoprotein cholesterol, diabetes, lipid reducing agents and anti-hypertensive medication.

[d] Total PA is composed of all PA types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 1.3, 2.6 and 4.3 hours per day of moderate PA equivalent of 4 METs.

[e] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 21, 60 and 135 minutes per day of walking.

[f] Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 51 minutes per day of cycling.

[g] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 27, 76 and 140 minutes per day of domestic work.

[h] Average sports is equivalent to 5.5 METs. The median levels of sports across categories are therefore equivalent to 0, 9 and 34 minutes per day of sports.

[i] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 30 minutes per day of gardening.

Supplement 4.3.4. Hazard ratios for the different transitions for women, based on the Rotterdam Study

		No CVD to CVD			No CVD to death			CVD to death		
Number of events		669			891			562		
Person-years		28,338			34,123			6,534		
	Range (MET-hours per week)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)
Total PA[d]										
Low	40.2 (≤57.6)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	74.6 (57.7-94.0)	0.87 (0.72,1.05)	0.91 (0.75,1.10)	0.92 (0.75, 1.12)	0.77 (0.66,0.90)	0.79 (0.67,0.93)	0.81 (0.68, 0.96)	0.91 (0.75,1.11)	0.90 (0.74,1.10)	0.90 (0.74, 1.11)
High	124.7 (≥94.1)	0.71 (0.58,0.87)	0.75 (0.61,0.91)	0.80 (0.65, 0.99)	0.65 (0.54,0.77)	0.67 (0.57,0.80)	0.72 (0.60, 0.86)	0.75 (0.60,0.94)	0.74 (0.59,0.93)	0.78 (0.62, 0.99)
Walking[e]										
Low	9.0 (≤13.5)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	21.0 (13.6-30.0)	0.88 (0.73,1.06)	0.89 (0.74,1.07)	0.90 (0.74, 1.09)	0.89 (0.76,1.04)	0.89 (0.76,1.04)	0.87 (0.74, 1.03)	0.90 (0.73,1.11)	0.93 (0.75,1.15)	0.93 (0.74, 1.15)
High	51.0 (≥30.1)	0.90 (0.74,1.09)	0.91 (0.74,1.10)	0.92 (0.75, 1.13)	0.93 (0.79,1.11)	0.95 (0.80,1.13)	0.97 (0.82, 1.16)	0.83 (0.67,1.04)	0.83 (0.67,1.04)	0.89 (0.71, 1.12)
Cycling[f]										
Low	0.0 (0.0)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	6.0 (≤12.0)	0.74 (0.60,0.92)	0.77 (0.62,0.95)	0.80 (0.64, 0.99)	0.67 (0.55,0.81)	0.68 (0.56,0.82)	0.67 (0.55, 0.82)	0.88 (0.66,1.17)	0.92 (0.69,1.23)	0.92 (0.68, 1.24)
High	22.0 (≥12.1)	0.75 (0.59,0.97)	0.81 (0.63,1.04)	0.86 (0.67, 1.12)	0.67 (0.53,0.86)	0.70 (0.55,0.90)	0.71 (0.56, 0.92)	0.99 (0.68,1.44)	0.97 (0.66,1.42)	0.95 (0.65, 1.39)
Domestic work[g]										
Low	15.1 (≤22.5)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	35.7 (22.6-44.7)	0.97 (0.76,1.24)	0.99 (0.77,1.26)	0.98 (0.76, 1.27)	0.79 (0.65,0.96)	0.77 (0.63,0.93)	0.74 (0.60, 0.90)	1.03 (0.83,1.28)	0.98 (0.79,1.23)	0.96 (0.76, 1.21)

Supplement 4.3.4 (continued). Hazard ratios for the different transitions for women, based on the Rotterdam Study

		No CVD to CVD			No CVD to death			CVD to death		
	Range (MET-hours per week)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)
High	58.1 (≥44.8)	0.82 (0.64,1.06)	0.85 (0.66,1.10)	0.87 (0.66, 1.14)	0.66 (0.54,0.81)	0.65 (0.53,0.80)	0.64 (0.51, 0.80)	0.93 (0.73,1.18)	0.87 (0.68,1.10)	0.86 (0.67, 1.11)
Sports[h]										
Low	0.0 (0.0)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	5.3 (≤6.0)	0.83 (0.67,1.03)	0.84 (0.68,1.04)	0.87 (0.70, 1.09)	0.86 (0.71,1.03)	0.87 (0.72,1.05)	0.88 (0.72, 1.06)	0.88 (0.69,1.12)	0.93 (0.73,1.19)	0.92 (0.71, 1.20)
High	16.5 (≥6.1)	0.90 (0.69,1.16)	0.91 (0.70,1.18)	1.03 (0.79, 1.35)	0.84 (0.66,1.07)	0.83 (0.65,1.05)	0.85 (0.67, 1.09)	0.98 (0.69,1.41)	1.02 (0.71,1.47)	1.00 (0.70, 1.45)
Gardening[i]										
Low	0.0 (0.0)	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	4.0 (≤9.2)	0.94 (0.76,1.16)	0.97 (0.79,1.20)	0.94 (0.76, 1.17)	0.78 (0.64,0.95)	0.81 (0.66,0.99)	0.79 (0.64, 0.96)	0.90 (0.69,1.19)	0.96 (0.72,1.26)	0.98 (0.73, 1.30)
High	12.0 (≥9.3)	1.00 (0.76,1.31)	1.02 (0.78,1.34)	1.05 (0.79, 1.39)	0.88 (0.68,1.14)	0.91 (0.70,1.18)	0.92 (0.71, 1.21)	0.98 (0.68,1.39)	1.06 (0.74,1.53)	1.03 (0.70, 1.49)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio, PA, physical activity; ref, referent.

[a] Model 1 was adjusted for age.

[b] Model 2 was adjusted for age, smoking status, alcohol consumption in tertiles, education, marital status and cancer prevalence. For PA types, model 2 was also adjusted for all other PA types.

[c] Model 3 was adjusted for age, smoking status, alcohol consumption in tertiles, education, marital status, cancer prevalence, the other PA types, body mass index, total and high-density lipoprotein cholesterol, diabetes, lipid reducing agents and anti-hypertensive medication.

[d] Total PA is composed of all PA types and thus of different METs. In this regard, the median levels of total PA across categories are equivalent to 1.4, 2.7 and 4.5 hours per day of moderate PA equivalent of 4 METs.

[e] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 26, 60 and 146 minutes per day of walking.

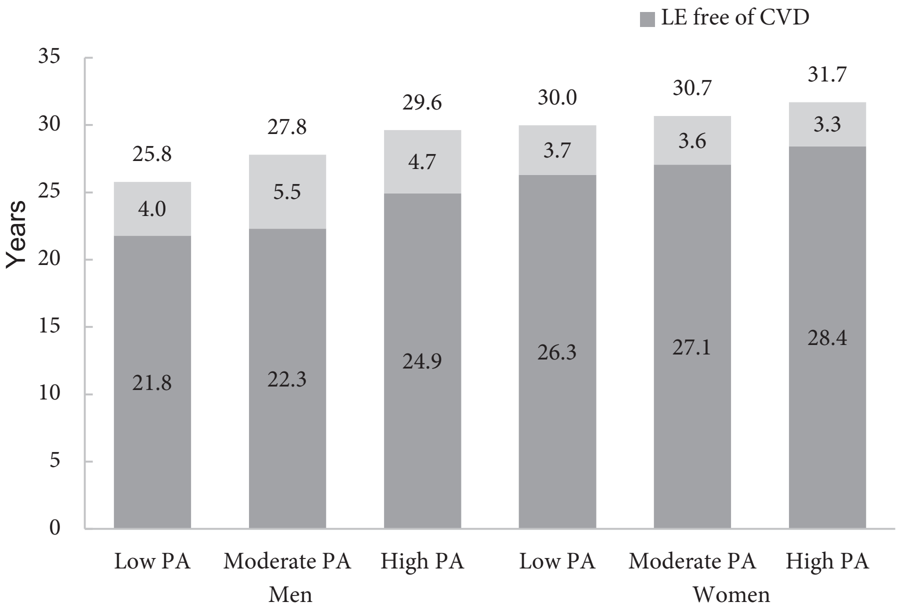
[f] Cycling is equivalent to 4.0 METs. The median levels of cycling across categories are therefore equivalent to 0, 13 and 47 minutes per day of cycling.

[g] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 37, 87 and 142 minutes per day of domestic work.

[h] Average sports is equivalent to 5.5 METs. The median levels of sports across categories are therefore equivalent to 0, 8 and 26 minutes per day of sports.

[i] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 26 minutes per day of gardening.

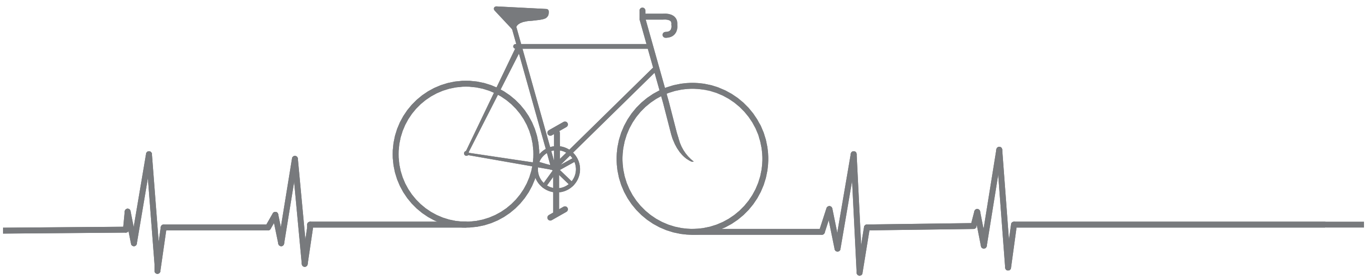
Supplement 4.3.5. Effect of total physical activity on life expectancy with and without cardiovascular disease (CVD) at age 55 years, for participants without hypertension, diabetes and dyslipidemia.



All life expectancies have been calculated with sex-specific hazard ratios adjusted for age, smoking status, alcohol consumption in tertiles, education, marital status and cancer prevalence. CVD indicates cardiovascular disease.

SUPPLEMENTARY REFERENCES

1. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011;43(8):1575-1581.



Chapter 4.4

The impact of physical activity on the association of overweight and obesity with cardiovascular disease

Manuscript based on this chapter:

Koolhaas CM, Dhana K, Schoufour JD, Ikram MA, Kavousi M, Franco OH. Impact of physical activity on the association of overweight and obesity with cardiovascular disease: The Rotterdam Study. *Eur J Prev Cardiol*. 2017;24(9):934-941.

ABSTRACT

Background: Being overweight or obese is associated with increased risk of cardiovascular disease (CVD). Physical activity (PA) might reduce the risk associated with overweight and obesity. We examined the association between overweight and obesity and CVD risk as a function of PA levels in a middle aged and elderly population.

Methods: This study included 5,344 participants aged 55 years or older from the population-based Rotterdam Study. Participants were classified as having high or low PA, based on the median of the population. Subsequently, normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese participants (≥30 kg/m^2) were categorized as having high or low PA, forming 6 categories. We assessed the association of the six categories with CVD risk using Cox proportional hazard models, adjusted for confounders. High PA and normal weight was used as the reference group.

Results: During 15 years of follow-up (median:10.3 years, interquartile range: 8.2-11.7 years), 866 participants (16.2%) experienced a CVD event. Overweight and obese participants with low PA had a higher CVD risk, compared to normal weight individuals with high PA. The hazard ratio (HR) and 95% confidence interval (95%CI) were 1.33 (1.07-1.66) and 1.35 (1.04-1.75), respectively. Overweight and obese individuals with high PA did not show a higher CVD risk: HRs (95%CIs) 1.03 (0.82-1.29) and 1.12 (0.83-1.52), respectively.

Conclusions: Our findings suggest that the beneficial impact of PA on CVD might outweigh the negative impact of BMI among middle-aged and elderly people. This emphasizes the importance of PA for all individuals and across all BMI strata, while highlighting the risk associated with inactivity even among normal-weight persons.

INTRODUCTION

While overweight and obesity are associated with increased risk of cardiovascular disease (CVD),[1-3] higher levels of physical activity are associated with a decreased risk of CVD.[4-6] However, to what extent physical activity can counterbalance the risk associated with overweight and obesity remains unclear.

In recent years, several studies have investigated the combined association of physical activity and body mass index (BMI) with CVD risk in middle-aged adults, but the results are inconsistent.[7-12] A review combining studies that evaluated the risk associated with obesity and physical activity, reported that four out of eight studies favored the hypothesis that the risk for cardiovascular mortality was lower in obese individuals with high physical activity than in normal weight individuals with low levels of physical activity.[13] A study by Weinstein et al. that assessed the joint effect of physical activity and BMI on coronary heart disease in women reported that the risk of coronary heart disease associated with elevated BMI was considerably reduced by higher levels of physical activity8 These results indicate that the CVD risk associated with high BMI might be partly negated by physical activity. However, previous studies included middle-aged participants and information among the elderly remains to be scarce. In older adults, it has been suggested that the risk of myocardial infarction and stroke associated with overweight and obesity are attenuated.[14] This might be because in older adults, BMI is a poor indicator of body fat and distribution and BMI alone might not be a good indicator of CVD risk.[15] Moreover, lean mass and fat mass might act as nutritional preserves during illness. Furthermore, physical activity levels tend to decrease with age.[16] Therefore, the role of physical activity on the association between BMI and CVD could differ between younger, middle-aged and elderly adults.

In the current study, using data from the large population-based Rotterdam Study, we aimed to study the role of physical activity in the association between BMI and CVD among middle-aged and elderly individuals.

METHODS

Study population

This study was embedded within the Rotterdam Study (RS), a prospective population-based cohort study among persons aged 55 years or older in the municipality of Rotterdam, the Netherlands. The baseline examination of the original cohort (RS-1) was completed between 1990 and 1993. In 2000-2001, the Rotterdam Study was extended with 3,011 participants who had become ≥ 55 years old or had moved into the study district (RS-II). For the current study, we used data from participants attending the third examination of the original cohort (RS-I-3, between 1997 and 1999; n = 4,797) and the participants attending the first examination of the extended cohort (RS-II-1, between 2000 and 2001; n=3,011). Of this combined total (n=7,808), 6,510 participants completed data collection for both physical activity and BMI. Furthermore, 1,122 persons with prevalent CVD were excluded and 6 were excluded due to missing follow-up data.

Subjects who were considered being underweight (BMI < 18.5 kg/m^2) were also excluded (n=38). Eventually, 5,344 subjects were included in the current analyses. To collect the baseline information, trained research assistants interviewed the participants at home.

All subjects gave written informed consent, and the study protocol was approved by the medical ethics committee of Erasmus University, Rotterdam. Detailed information on the design of the Rotterdam Study can be found elsewhere.[17]

Assessment of anthropometrics and physical activity

Height and weight were measured with the participants standing without shoes and heavy outer garments. Subsequently, BMI was calculated as weight divided by height squared (kg/m^2). physical activity levels were assessed with an adapted version of the Zutphen Physical Activity Questionnaire,[18] including questions regarding walking, cycling, sports, gardening and housekeeping activities. To quantify activity intensity, we assigned metabolic equivalent of task (MET)-scores to all activities, according to the 2011 updated version of the Compendium of Physical Activities.[19] Finally, we multiplied MET-values of specific activities with time (in hours) per week spent in that activity to calculate MET·hours·week^{-1} in total physical activity. Further detail on the assessment of physical activity can be found elsewhere.[20]

Assessment of confounders

Alcohol use was defined as the amount of glasses per day. Education was assessed according to the standard classification of education comparable to the international standard classification of education and was grouped into four categories "elementary education", "lower secondary education", "higher secondary education" and "tertiary education".[21] Smoking was divided into 2 categories: current and other (former and never). Dietary information was not collected at the same time as physical activity data were collected; therefore, we used the diet information measured in the first examination of the original cohort (RS-I-1, between 1989 and 1993) and in the third examination of the extended cohort (RS-II-3, between 2011 and 2012). Information on diet were obtained through a 170-item validated semiquantitative food frequency questionnaire.[22] From the questionnaire, an overall healthy diet score representing adherence to the Dutch dietary guidelines was calculated, as described previously.[23] A family history of premature myocardial infarction was defined as having a parent, sibling, or child who experienced a myocardial infarction at the age of ≤65 years and used as a binary variable (yes/no). Since 97.6 % of our participants were Caucasian, adjustment for ethnicity was not required

Clinical outcome

The main outcome measure under study was incident hard atherosclerotic CVD, composed of fatal and non-fatal myocardial infarction, other coronary heart disease mortality, and fatal and non-fatal stroke.[24] Data on clinical outcomes including CVD were collected through an automated follow-up system involving digital linkage of the study database to medical records managed by general practitioners working in the research area. Trained research assistants collected notes, outpatient clinic reports, hospital discharge letters, electrocardiograms, and imaging results from general practitioners and hospital records. Subsequently, research physicians adjudicated all data on potential events independently. Following, medical specialists whose judgments are considered decisive reviewed the potential cases. Information on vital status was additionally obtained from the central registry of the municipality of the city of Rotterdam. Follow-up was complete until January 1, 2012.

Statistical analysis

Participants were classified as having a high or low level of total physical activity by using the median. Following, normal weight (<25 kg/m^2), overweight (25-29.9 kg/m^2), and obese participants (≥30 kg/m^2) were categorized as being high or low physically active, forming 6 categories. Baseline characteristics of the study population are presented as mean ± SD (or frequency and percentage when appropriate) for the 6 phenotypes formed by the physical activity levels (lower and higher) across different BMI categories.

In our analysis, we first estimated the CVD risk associated with the BMI categories and with physical activity, using Cox proportional hazard regression analysis. Second, in our main analysis, we used Cox proportional hazard regression analysis to estimate the hazard ratio (HR) and 95% confidence interval (95%CI) for the 6 phenotypes described above in association with CVD, using normal weight with high levels of physical activity as the reference category. Proportional hazards assumptions were confirmed in all Cox models by visually comparing Kaplan-Meier curves of the different groups. The models were adjusted for age, gender, smoking, alcohol use, education, diet quality and family history of premature myocardial infarction. We decided a priori not to adjust for systolic blood pressure, total or high density lipoprotein cholesterol or plasma glucose, as they are all intermediators in the association between BMI and CVD.

Physical activity, BMI and the joint BMI and physical activity phenotypes were entered as categorical variables in the model. Additionally, we assessed whether there was a trend across categories of BMI, by entering the categorical BMI variable as continuous in the model.

We did not observe a significant interaction of gender or age with BMI, physical activity or the joint BMI and physical activity phenotypes. Moreover, no multiplicative or additive interaction between BMI and physical activity was observed.

Sensitivity analyses

Due to high competing risk of non-CVD death among the elderly, we performed a competing risk analysis using the method proposed by Fine and Gray.[25] Additionally, we repeated the main analysis in participants older than 65, to specifically examine the associations in the elderly. We further investigated the possible effect of reverse causation by excluding the events in the first two years. Finally, we repeated the analysis in participants without missing information on diet.

We had 24.6% missing data on the diet quality. For other covariates, we had less than 5% missing data. We used the single imputation by the Expectation Maximization method in SPSS. The analyses were performed using IBM SPSS Statistics for Windows (IBM SPSS Statistics for

Windows, Armonk, NY: IBM Corp) and R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was accepted at $p < 0.05$.

RESULTS

The median level of physical activity by which the two physical activity categories were created was 79.4 MET·hours·week^{-1}. The median and interquartile range (IQR) were 111.3 (93.7-139.6) and 54.6 (39.0-67.5) for the high and low category, respectively. These numbers correspond to 4 hours and 2 hours per day of moderate intensity physical activity (4 METs). Table 4.4.1 shows the characteristics of the participants by the level of physical activity and BMI categories. The participants with low levels of physical activity were more often male, older and more often current smokers compared with participants with a high level of physical activity. The mean age of the population was 68.5 years (standard deviation: 7.9; range: 55-97 years) and 60.1% was female. During a median follow-up of 10.3 years, there were 866 (16.2%) incident CVD events.

Table 4.4.2 presents the association of BMI categories and level of physical activity with incident CVD separately. Compared with normal weight individuals, overweight (HR 1.13, 95%CI 0.97-1.57) and obese (HR 1.20, 95%CI 0.99-1.46) individuals were not at significantly increased CVD risk. In addition, we observed no significant trend across categories of BMI (P for trend 0.05). Compared with the higher level of physical activity (irrespective of obesity), individuals with a low level of physical activity were at higher risk of CVD (HR 1.22, 95%CI 1.06-1.41).

Figure 4.4.1 shows the association between the joint physical activity and BMI phenotypes with incident CVD. Compared to normal weight participants with high levels of physical activity, the risk of CVD was not significantly different in overweight (HR: 1.03, 95%CI: 0.82-1.29) and obese (HR: 1.12, 95%CI: 0.83-1.52) participants with a high level of physical activity. In contrast, overweight and obese participants with a low level of physical activity were at increased risk of CVD, compared to normal weight individuals with high physical activity. The corresponding HRs (95%CIs) were 1.33 (1.07-1.66) and 1.35 (1.04-1.75), respectively.

Sensitivity analyses

Supplement 4.4.1 shows that the HRs (95%CIs) from the competing risk approach were not substantially different from our original analysis. Additionally, when we repeated the main analysis in adults 65 and older, or when we excluded first 2 years of follow-up, we found similar results (Supplement 4.4.2 and Supplement 4.4.3) as in the total population. Finally, the results in the participants with information on diet quality were similar to the main analysis (Supplement 4.4.4).

DISCUSSION

In this population-based study of adults aged 55 and over, overweight and obese individuals with high levels of physical activity were not at increased risk of CVD, compared with their normal weight counterparts. In contrast, among individuals with lower levels of physical activity, being overweight and obese was associated with a higher risk of CVD. Moreover, low physical activity levels increased the risk of CVD in the total population. These findings suggest that the impact of physical activity on CVD might outweigh that of BMI among middle-aged and elderly individuals.

Similar studies regarding the joint association of BMI and physical activity with CVD are consistent with our findings.[7-12] A study comprised of 18,892 Finish men and women aged 25-74 years concluded that physical inactivity has an independent association with CVD risk, whereas obesity increases the risk through modification of other risk factors.[11] In addition, the Women's Health Study found that the risk of coronary heart disease associated with elevated BMI is considerable reduced by higher physical activity levels.[8]

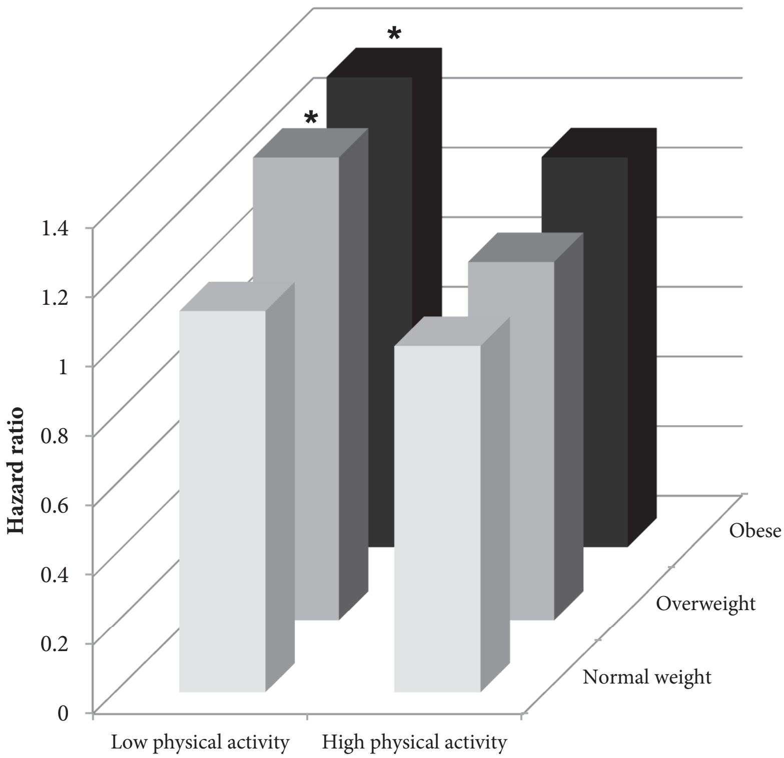


Figure 4.4.1. The association between joint physical activity and body mass index categories with cardiovascular disease

Analyses adjusted for age, gender, education, diet quality, alcohol, smoking and family history of premature myocardial infarction

*p < 0.05 vs. reference group.

Table 4.4.1. Characteristics at baseline as a function of metabolic health status and body mass index

	High levels of physical activity			Low levels of physical activity		
	Normal weight	Overweight	Obese	Normal weight	Overweight	Obese
Participants, n (%)	924	1,279	468	841	1256	576
Age, years	67.3 (6.9)	67.6 (7.0)	66.9 (7.0)	70.0 (8.8)	69.4 (8.6)	69.4 (8.5)
Women, n (%)	645 (69.8)	834 (65.2)	371 (79.3)	416 (49.5)	547 (43.6)	399 (69.3)
Body mass index, kg/m^2	23.1 (1.5)	27.2 (1.4)	33.0 (2.7)	23.1 (1.4)	27.3 (1.4)	33.2 (3.2)
Total physical activity,	112.2	111.3	110.1	54.4	54.9	54.8
MET·hours·week^{-1}, median (IQR)	[95.0, 139.4]	[93.0, 139.6]	[93.5, 139.6]	[39.7, 67.4]	[38.9, 67.4]	[37.3, 68.2]
Participating in walking, n (%)	921 (99.7)	1,277 (99.8)	468 (100.0)	829 (98.6)	1233 (98.2)	555 (96.4)
Participating in cycling, n (%)	696 (75.3)	944 (73.8)	306 (65.4)	433 (51.5)	669 (53.3)	216 (37.5)
Participating in domestic work, n (%)	919 (99.5)	1268 (99.1)	464 (99.1)	809 (96.2)	1177 (93.7)	554 (96.2)
Participating in gardening, n (%)	490 (53.0)	661 (51.7)	216 (46.2)	305 (36.3)	471 (37.5)	165 (28.6)
Participating in sports, n (%)	476 (51.5)	592 (46.3)	196 (41.9)	240 (28.5)	385 (30.7)	149 (25.9)
Current smoking, n (%)	198 (21.4)	202 (15.8)	56 (12.0)	195 (23.2)	209 (16.6)	87 (15.1)
Dutch healthy diet index	49.1 (10.9)	50.3 (11.0)	50.2 (11.0)	47.8 (11.3)	48.4 (11.3)	50.2 (10.3)
Alcohol use, glasses per day, median (IQR)	0.4 [0.1, 1.4]	0.6 [0.1, 1.7]	0.29 [0.0, 1.1]	0.50 [0.0, 1.4]	0.59 [0.1, 2.0]	0.2 [0.0, 1.0]
Education, n (%)						
Elementary	109 (11.8)	161 (12.6)	77 (16.5)	94 (11.2)	149 (11.9)	97 (16.8)
Lower secondary	434 (47.0)	618 (48.3)	229 (48.9)	300 (35.7)	505 (40.2)	272 (47.2)
Higher secondary	253 (27.4)	371 (29.0)	130 (27.8)	299 (35.6)	393 (31.3)	143 (24.8)
Tertiary	128 (13.9)	129 (10.1)	32 (6.8)	148 (17.6)	209 (16.6)	64 (11.1)

Abbreviations: n, number; MET, metabolic equivalent; IQR, interquartile range.

Values are mean (SD), unless otherwise stated.

Body mass index was calculated as weight in kilograms divided by height in meters squared. Categories were defined as normal weight: 18.5 < 25 kg/m^2, overweight: 25 < 30 kg/m^2 and obese: ≥ 30 kg/m^2.

Table 4.4.2. The association of body mass index, and physical activity levels with cardiovascular disease

		n/N	HR (95%CI)
Body mass index	Normal weight	270/1,765	1.00 (reference)
	Overweight	428/2,535	1.13 (0.97-1.32)
	Obese	168/1,044	1.20 (0.99-1.46)
Physical activity	High physical activity	367/2,671	1.00 (reference)
	Low physical activity	499/2,673	1.22 (1.06-1.40)*

Abbreviations: n, number of events; N, number at risk; HR, hazard ratio; CI, confidence interval.
Analyses adjusted for age, gender, education, diet quality, alcohol and smoking.
*$p < 0.05$ vs. reference group.

However, the risk was not completely eliminated, which reinforces the importance of being lean and physically active.8 Similarly, the analysis from the Nurse's Health Study of 88,393 women aged 34 to 59 older showed that being moderately physically active attenuated, but did not eliminate, the adverse effect of obesity on coronary heart disease risk.[7] Furthermore, they also showed that being lean did not counteract the increased risk associated with physical inactivity.[7] In the current study, we extended the evidence to the middle-aged and elderly individuals. We showed that once analyzed separately, the magnitude of the association between reduced physical activity with CVD was roughly similar to the one between obesity and CVD, although the latter did not reach statistical significance. However, once analyzed jointly, overweight and obese individuals with high levels of physical activity were not at significantly increased risk of CVD, whereas being overweight and obese was associated with increased risk of CVD among physically inactive individuals. Our results, while not refuting the cardiovascular risk associated with overweight and obesity, suggest that the impact of physical activity on CVD might outweigh that of BMI among middle-age and elderly adults.

In addition to leisure time physical activity, we included transportation and housework in the assessment of total physical activity in the current study. Therefore, our results extend the previous findings and indicate that overall higher levels of physical activity (irrespective and beyond leisure time) can be beneficial to reduce CVD risk. Moreover, our study has been conducted in an older population. Elderly individuals might have more difficulties in engaging in sports or exercise (leisure time physical activity) and spend a relatively large proportion of their time on housework, compared to younger individuals.[26] Our study emphasizes the importance of the beneficial effects of physical activity as part of our daily life, as supported in the recent recommendations.[27]

In the current study, overweight and obese individuals with a low level of physical activity had a 1.33 and 1.35 times higher risk of CVD, compared to normal weight individuals with a high level of physical activity. Other studies,[7,8,11,12] reported a up to 3 times higher CHD risk[7,8] and up to 2.36 times higher CVD risk[11,12] for obese individuals with low physical activity, compared to normal weight individuals with high activity. The lower risk in the current study might be explained by the relatively high levels of physical activity in the low physical activity group. The median level of physical activity for the low group was 54.6 MET·hours·week^{-1}, corresponding to 2 hours per day of moderate intensity physical activity. This is a higher physical activity level than reported in the low group of other studies.[7,8,11,12] Whereas our risk estimates were relatively low, our results do not indicate that the risk associated with inactivity should be neglected. For public health programs, it remains important to focus on increasing population physical activity levels, and to concomitantly stress body weight management. The mechanism underlying the harmful effect of overweight and obesity on CVD risk has been well investigated. Adipose tissue releases free fatty acids, interleukins, and cytokines that influence cardiac function by acceleration of atherosclerosis processes, inflammation, endothelial and coagulation dysfunction.[28,29] The plausible mechanisms through which physical activity has been suggested to improve CVD risk are improved endothelial function, stabilization of vulnerable plaques preventing plaque rupture and reduced myocardial oxygen demand.[30] This indicates that physical activity directly reduces and combats the harmful effect of the prothrombotic factors released by adipose tissue.[8,31]

In our study, obese individuals with high levels of physical activity conferred a similar risk of CVD as normal weight individuals with low level of physical activity when we compared both groups to normal weight individuals with a high level of physical activity. Notably, both groups were at high risk of CVD, although the associations did not reach the significance threshold. These findings suggest that being lean does not counteract the increased risk associated with physical inactivity, but also being physically active does not offset the increased risk of being obese. Therefore, our study confirms previous findings that physically active and lean individuals are at low risk of CVD[7,11] and extends these findings to middle-aged and elderly individuals.

Major strengths of the current study are its prospective population-based design, large sample size of adults aged 55 years and older and relatively long follow-up period. Furthermore, we had a reliable assessment of CVD events and were able to adjust for several lifestyle factors, thereby minimizing the possibility of the observed associations being explained by confounding. However, several limitations should be considered. First, our conclusions are drawn from baseline measurements. Therefore some misclassification, due to the changes in BMI or physical activity levels during follow-up, could have occurred. However, weight gain tends to be linear over time and therefore the difference between the groups is likely to remain constant, even with weight change.[8] Additionally, our results are based on self-reported physical activity. Although our questionnaire has shown to be valid and reliable[32] potential recall bias and social desirability cannot be excluded. These last two limitations could have resulted in bias towards the null hypothesis. Furthermore, information on diet quality was not collected at the same time as BMI and physical activity. We acknowledge this limitation and used this information as a proxy of diet quality. Additionally, information on diet quality was missing for 24.6% of participants and was therefore imputed. Although we cannot fully exclude the possibility of residual confounding by diet quality, restricting the analysis to participants with diet information revealed comparable results. Finally, it may be hypothesized that participants with poor health engage in physical activity less than others, thereby creating the opportunity for reverse causation. However, in our analyses exclusion events that occurred within the first two years of follow up revealed comparable results.

Conclusions

In summary, in this long-term follow-up study of older adults the risk associated with overweight and obesity was attenuated in individuals with high physical activity levels. This suggests that regular physical activity reduces the CVD risk in older adults and that further benefits can be gained from maintaining a healthy weight.

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SUPPLEMENT CHAPTER 4.4

Supplement 4.4.1. The association between joint physical activity and body mass index phenotypes with cardiovascular disease after taking in account competing risk

		n/N	HR (95%CI)
High physical activity	Normal weight	125/924	1.00 (reference)
	Overweight	179/1,279	1.05 (0.84, 1.32)
	Obese	63/468	1.12 (0.83, 1.51)
Low physical activity	Normal weight	145/841	1.02 (0.79, 1.30)
	Overweight	249/1,256	1.27 (1.02, 1.58)*
	Obese	105/576	1.30 (1.01, 1.69)*

Analyses adjusted for age, gender, education, diet, alcohol, smoking and family history of premature myocardial infarction.
Abbreviations: CI, confidence interval; HR, hazard ratio; n, number of events; N, number at risk.
*$p < 0.05$ vs. reference group.

Supplement 4.4.2. The association between joint physical activity and body mass index phenotypes with cardiovascular disease in elderly, aged 65+ (n=3,238)

		n/N	HR (95%CI)
High physical activity	Normal weight	96/524	1.00 (reference)
	Overweight	142/737	1.05 (0.81, 1.36)
	Obese	54/259	1.24 (0.89, 1.74)
Low physical activity	Normal weight	115/545	1.08 (0.82, 1.42)
	Overweight	201/800	1.34 (1.05, 1.72)*
	Obese	88/373	1.36 (1.02, 1.83)*

Analyses adjusted for age, gender, education, diet, alcohol, smoking and family history of premature myocardial infarction.
Abbreviations: CI, confidence interval; HR, hazard ratio; n, number of events; N, number at risk.
*$p < 0.05$ vs. reference group.

Supplement 4.4.3. The association between joint physical activity and body mass index phenotypes with cardiovascular disease, excluding events in the first 2 years (n=5,150)

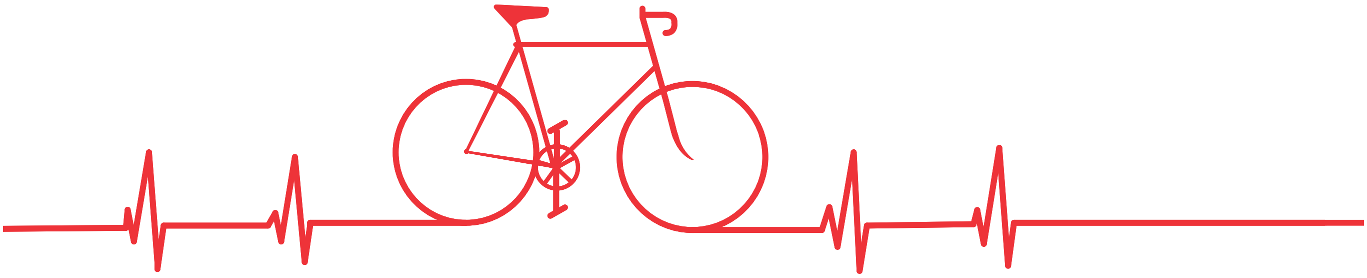
		n/N	HR (95%CI)
High physical activity	Normal weight	101/900	1.00 (reference)
	Overweight	136/1,236	0.96 (0.74, 1.25)
	Obese	52/457	1.12 (0.80, 1.57)
Low physical activity	Normal weight	114/810	1.13 (0.86, 1.49)
	Overweight	187/1,194	1.30 (1.02, 1.67)*
	Obese	82/553	1.33 (0.99, 1.79)

Analyses adjusted for age, gender, education, diet, alcohol, smoking and family history of premature myocardial infarction.
Abbreviations: CI, confidence interval; HR, hazard ratio; n, number of events; N, number at risk.
*$p < 0.05$ vs. reference group.

Supplement 4.4.4. The association between joint physical activity and body mass index phenotypes with cardiovascular disease, in those without missing dietary quality information (n=4,030)

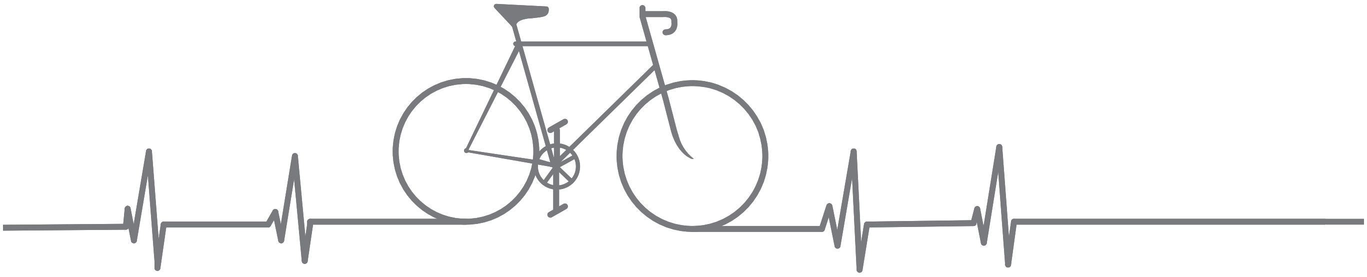
		n/N	HR (95%CI)
High physical activity	Normal weight	102/752	1.00 (reference)
	Overweight	133/991	0.99 (0.76, 1.28)
	Obese	43/372	0.94 (0.66, 1.35)
Low physical activity	Normal weight	103/612	1.11 (0.84, 1.47)
	Overweight	176/903	1.37 (1.07, 1.76)*
	Obese	68/400	1.31 (0.96, 1.79)

Analyses adjusted for age, gender, education, diet, alcohol, smoking and family history of premature myocardial infarction.
Abbreviations: CI, confidence interval; HR, hazard ratio; n, number of events; N, number at risk.
*$p < 0.05$ vs. reference group.



Chapter 5

Activity and mental health and wellbeing



Chapter 5.1

Physical activity types and health-related quality of life

Manuscript based on this chapter:

Koolhaas CM, Dhana K, van Rooij FJA, Schoufour JD, Hofman A, Franco OH. Physical activity types and health-related quality of life among middle-aged and elderly adults: The Rotterdam Study. *The journal of nutrition, health & aging*. 2018;22(2):246-253.

ABSTRACT

Background: Physical activity (PA) is associated with health-related quality of life (HRQL). The specific PA types that provide beneficial effects in an older population remain unclear. We assessed the association of total PA, walking, cycling, domestic work, sports and gardening with HRQL in middle-aged and elderly adults.

Methods: Our cross-sectional study included 5,554 individuals from the population-based Rotterdam Study. Total PA was categorized in five groups to evaluate the dose-response effect of PA and specific PA types were categorized in tertiles. HRQL was measured with the EuroQoL 5-dimension. The outcome of every HRQL domain (i.e. mobility, self-care, daily activities, pain and mood) was expressed as having any problems versus not having problems. Logistic and linear regression analyses were used, adjusting for confounders, to examine associations of total PA and PA types with HRQL domains.

Results: In both middle-aged (<65 years) and elderly adults (>65 years), we found a dose-response association between total PA and better HRQL (i.e. lower odds of having problems in HRQL domains). In the middle-aged, sports was the only PA type associated with lower odds of having problems with all HRQL domains. In the elderly, all PA types were associated with less problems with HRQL domains, but cycling contributed most to the beneficial effect.

Conclusion: Total PA was associated with better HRQL. Sports and cycling were the activity types that contributed most to this association in the middle-aged and elderly, respectively. Since PA levels tend to decline with aging, cycling and sports should be promoted with the aim to improve HRQL.

INTRODUCTION

Recent studies have shown a consistent association between physical activity (PA) and health-related quality of life (HRQL).[1,2] HRQL is defined as an individuals' perspective of well-being in physical, mental and social domains of life.[3] Previous studies have mainly focused on the effect of overall PA,[1,2] whereas it remains unclear how specific PA types affect quality of life. To be able to make clear and effective public health recommendations, It is important to distinguish between different types of PA (e.g. cycling, walking) and HRQL.

In young adults, performing sports was reported to be associated with better HRQL in 20-70 year old adults4 and domestic work was positively associated to general health in male university students.[5] In men aged 18-55 years old, cycling frequency was associated with higher physical and psychological quality of life.[6] However, information among older adults remains scarce. With increasing age, PA levels tend to decrease[7] and PA types in which older adults engage differ markedly from the activities performed by younger adults.[8] This raises the question what kind of activities are beneficially associated with HRQL in the middle-aged and elderly. Additionally, because 65 years of age is considered the retirement age in many countries, it is interesting to explore whether different PA types are associated with HRQL before and after retirement age. Moreover, only a few studies have investigated the nature of the dose-response relation between PA and HRQL, with conflicting results and limited information among the elderly.[2,9-11] The Rotterdam study includes adults aged 45 years and older and has previously shown to be a relatively active population,[12] which makes it an interesting population to study.

Therefore, we aimed to examine the association between PA, PA types (walking, cycling, sports, domestic work, and gardening) and HRQL in a middle-aged and elderly population. In addition, we aimed to describe the dose-response relationship between PA and HRQL.

METHODS

Study population

This study was embedded within the Rotterdam Study, a prospective population-based cohort in the Netherlands.[13] The cohort was initially defined in 1990 (RS-I) and expanded in 2000 (RS-II) and 2005 (RS-III). In 1990 and 2000, all inhabitants aged 55 years and older of Ommoord, a suburb of Rotterdam, were invited to participate. In 2005, all inhabitants aged 45 years and older were invited. For the current study, we used data from participants attending the fifth examination of the original cohort (RS-I-5, between 2009 and 2011; n =2,147; aged 72 to 97 years), participants attending the third examination of the extended cohort (RS-II-3, between 2011 and 2012; n=1,893; aged 64 to 97 years) and participants attending the second examination of the third cohort (RS-III-2, between 2012 and 2014; n=3,122; aged 51 to 92 years).[13,14] Of this combined total, 5,573 completed both PA and HRQL collection (See Supplement 5.1.1). We did not exclude any participants based on their health status. However, 19 cases were excluded because their PA data was considered unreliable. After exclusion, 5,554 participants were available for the current analysis.

All subjects gave written informed consent, and the study protocol was approved by the medical ethics committee according to the Wet Bevolkingsonderzoek ERGO (Population Study Act Rotterdam Study), executed by the Ministry of Health, Welfare and Sport of The Netherlands. Detailed information on the design of the Rotterdam Study can be found elsewhere.[13,14]

Physical activity assessment

PA levels were assessed with the self-administered LASA Physical Activity Questionnaire (LAPAQ). This questionnaire has been validated in 439 participants from the Longitudinal Aging Study Amsterdam (LASA), in which the LAPAQ was completed twice and participants completed a 7-day activity diary and wore a pedometer for 7 days. The test-retest reliability was reasonably good (0.65–0.75) and the correlations with the pedometer and 7-day diary were 0.56 and 0.68, respectively.[15] The LAPAQ contains questions regarding the frequency and duration of walking, cycling, sports, gardening, and housework. Participants were asked how many hours per week they spent in each activity in the past two weeks. Furthermore, the questionnaire provided two questions in which participants could mention other sports they participated in that were not captured by previous questions. Missing values for specific PA questions were imputed using age- and sex-specific means. For example, if participants indicated they participated in walking two times per week, but they did not fill in the walking duration, the age- and sex-specific mean was imputed.

To quantify activity intensity, we used metabolic equivalent of task (MET). MET-values were assigned to all activities in the questionnaire, according to the 2011 updated version of the Compendium of Physical Activities.[16] Of all mentioned other activities, 14 (3.8%) were not sports and 16 (4,4%) were not in the compendium (e.g. ‘treadmill’, ‘indoor sports’, ‘power plate’). For these activities, no MET-values were assigned and they were not used in the analyses.

Finally, we multiplied MET-values of specific activities with time (in hours) per week spent in that activity to calculate MET·hours·week^{-1} in total PA, defined as the sum of cycling, walking, sports, domestic work and gardening, and in every type of PA.

Covariates

Information on covariates was collected through home interviews, using an extensive questionnaire, or obtained at the study center visit, as described previously.[17,18] Briefly, alcohol use was defined as alcohol intake in grams per day. Smoking was divided in three categories: current, former and never. Education was assessed according to the standard classification of education, comparable to the international standard classification of education.[19] We assessed living situation as a dichotomous variable describing whether the participant lived alone or not. Information on job status was categorized in employed/unemployed. Height and weight were measured and body mass index (BMI) was calculated (kg/m^2). Finally, comorbidity was defined as the presence of cancer, diabetes, stroke, or coronary heart disease in 2012 and used as a binary variable (yes/no).

Health-related quality of life (HRQL) assessment (Outcome)

HRQL was evaluated using the Dutch version of the EuroQoL, during the home interview. This questionnaire has been validated in 90 participants who completed the questionnaire at baseline and after six months,[20] in which the Spearman retest correlation was 0.67. The EuroQoL consists of five dimensions: mobility, self-care, daily activities, pain/discomfort, and mood (i.e. anxiety/depression)[21,22] and each of the dimensions is assessed based on a single question with three response levels (no problem, some or moderate problems, and extreme problems). For the current study, each dimension was recoded in two levels: no problems versus any problems. Furthermore, the EuroQoL includes a standard vertical 20 cm visual analogue scale (VAS), for recording an individual's rating for their current HRQL.

Statistical analysis

For all PA types, we categorized participants into tertiles based on MET·hours·week^{-1}, because of the non-normal distribution of all PA types. For activities not practiced by more than 60% of the population (cycling, gardening, sports, domestic work), the bottom category for PA levels was no participation and the remaining two categories were divided by using the median.23 The median levels were 6.0, 26.9, 8.0 and 14.9 MET·hours·week^{-1} for cycling, domestic work, gardening and sports, respectively. For total PA, we created five categories, based on percentiles, to examine the dose-response association between total PA and HRQL. The values on which the categories were based are 12.0, 27.5, 53.0 and 88.8 MET·hours·week^{-1}.

Logistic regression models were used to analyze associations between PA (total and per type) with binary HRQL outcomes and linear regression models were used to evaluate the association with the VAS. A lower odds ratio (OR) indicates lower odds of having problems in a particular HRQL domain. We performed separate analyses for middle-aged (≤65 years) and elderly adults (>65 years) because PA might have a different association with HRQL in both age groups.9 Analyses were adjusted for age, sex, living situation, smoking, alcohol consumption, education, job status and comorbidity. For PA types, models were additionally adjusted for the other PA types. The decision to include confounders in the multivariable regression models was based on previous literature or >10%-change of the effect estimate in the crude model.[9,10] Total PA and PA types were entered as categorical variables in the separate models.

Given prior work, we conducted a sensitivity analysis using stratified models by sex.[11] Moreover, 24.6% (n=1,364) was employed at baseline, but we did not collect information on occupational PA. Therefore, we repeated our analyses in non-workers. Finally, we repeated the analysis in participants with and without comorbidity to evaluate whether the association is driven by individuals who are less healthy.

Our data contained 15.2% missing data for alcohol consumption and all other covariates had less than 5% missing data. We used multiple imputation (n=5 imputations) by the Expectation Maximization method. All analyses were conducted using SPSS software version 20 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp) and R (3.0.1).

RESULTS

Middle-aged adults participated more often in cycling, domestic work, gardening and sports than elderly adults (Figure 5.1.1). Additionally, middle-aged adults reported fewer problems with mobility, self-care and daily activities (Table 5.1.1). The number of participants in each group of every PA type is presented in Supplement 5.1.2. The median (range) of the 5 categories of total PA are 1) 6.0 (<12.0) MET·hours·week^{-1}; 2) 18.8 (12.1-27.5) MET·hours·week^{-1}; 3) 39.3 (27.6-53.0) MET·hours·week^{-1}; 4) 68.2 (53.1-88.8) MET·hours·week^{-1}; 5) 119.9 (>88.8) MET·hours·week^{-1}. The median levels of total PA across categories are therefore equivalent to 13, 40, 84, 146 and 257 minutes per day of total physical activity of 4 METs. There were no associations found with the VAS for any PA variable (Supplement 5.1.3).

In both middle-aged and elderly adults, higher total PA was associated with lower odds of having problems with mobility, daily activities and mood (i.e. being anxious or depressed) and with lower odds of having pain (Figure 5.1.2). Additionally, total PA was associated with lower odds of having problems with self-care in the elderly. The ORs (95%CI) of the associations between the highest level of total PA, compared to the lowest level of total PA, and having mobility problems were 0.54 (0.35, 0.83) and 0.33 (0.26, 0.43) in middle-aged and elderly adults, respectively. For problems with mood the ORs (95%CI) for the highest level of total PA were 0.59 (0.36, 0.96) and 0.57 (0.41, 0.8) for the middle-aged and elderly, respectively.

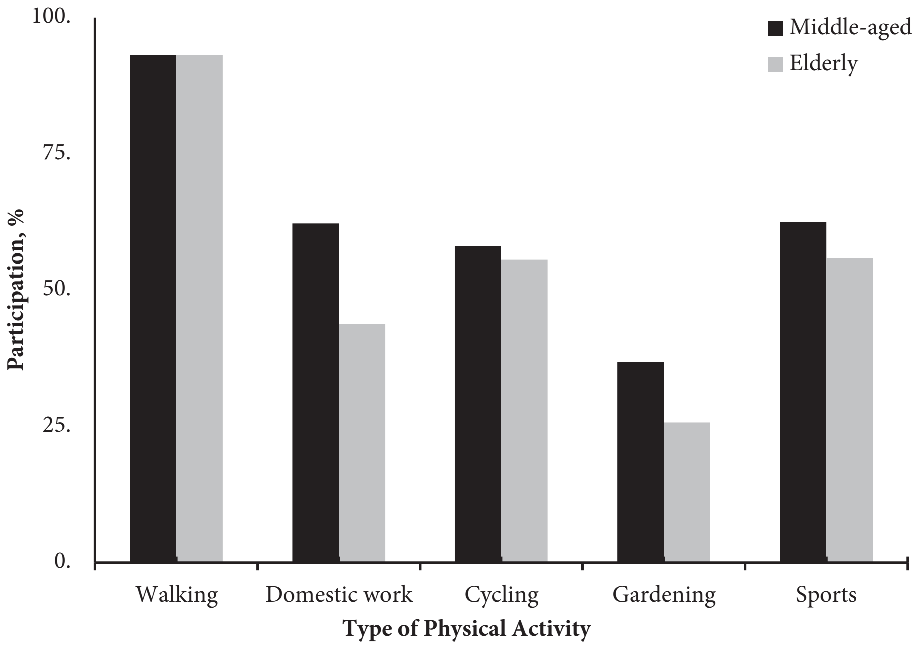


Figure 5.1.1. Proportion of participants by physical activity type for the Rotterdam Study.

Table 5.1.1. Baseline participant characteristics per age group (n=5,554)

	Middle-aged (≤ 65 years)	Elderly (>65 years)
Participants, no.	1,819	3,735
Female, no. (%)	1,055 (58.0)	2,143 (57.4)
Age	59.2 (3.7)	74.0 (6.4)
Educational level, no. (%)		
Primary education	122 (6.7)	323 (8.6)
Lower education	573 (31.5)	1,635 (43.8)
Intermediate education,	553 (30.4)	1,112 (29.8)
Higher education,	571 (31.4)	665 (17.8)
Living with partner, no. (%)	1,455 (80.0)	2,489 (66.6)
Employed, no. (%)	1,134 (62.3)	232 (6.2)
Smoking, no. (%)		
Never	637 (35.0)	1,297 (34.7)
Former	886 (48.7)	2,095 (56.1)
Current	296 (16.3)	343 (9.2)
Alcohol, grams/day	13.3 (14.7)	11.1 (14.1)
BMI, no. (%)		
Underweight (<18.5 kg/m^2)	49 (2.7)	60 (1.6)
Normal weight (18.5 – 25.0 kg/m^2)	539 (29.6)	980 (26.2)
Overweight (25 – 30 kg/m^2)	822 (45.2)	1,825 (48.9)
Obese (≥30 kg/m^2)	409 (22.5)	870 (23.3)
Diabetes, no. (%)	166 (9.1)	649 (17.4)
Cancer, no. (%)	166 (9.1)	818 (21.9)
CHD, no. (%)	65 (3.6)	400 (10.7)
Stroke, no. (%)	17 (0.9)	148 (4.0)
Groups of physical activity, no. (%)		
Very low	305 (16.8)	822 (22.0)
Low	350 (19.2)	740 (19.8)
Medium	417 (22.9)	698 (18.7)
High	393 (21.6)	719 (19.3)
Very high	354 (19.5)	756 (20.2)
Total PA, MET·hours·week^{-1}	55.9 (52.1)	54.1 (55.0)
Walking, MET·hours·week^{-1}	11.3 (15.0)	12.2 (14.1)
Cycling, MET·hours·week^{-1}	5.5 (10.5)	4.2 (9.0)
Domestic work, MET·hours·week^{-1}	20.8 (31.3)	20.0 (28.9)
Gardening, MET·hours·week^{-1}	3.7 (10.7)	3.8 (11.5)
Sports, MET·hours·week^{-1}	14.6 (23.8)	14.0 (28.9)
Any problems with mobility, no. (%)	278 (15.3)	967 (25.9)
Any problems with self-care, no. (%)	33 (1.8)	196 (5.2)
Any problems with daily activities, no. (%)	174 (9.6)	526 (14.1)
Any problems with pain, no. (%)	825 (45.4)	1,657 (44.4)
Any problems with mood, no. (%)	223 (12.3)	424 (11.4)
Visual analogue scale	82.1 (53.1)	80.4 (40.1)

Abbreviations: BMI, body mass index; CHD, coronary heart disease; no, number; PA, physical activity
Numbers are mean (SD), unless otherwise stated.

Regarding PA types, walking was not associated with any HRQL domain in middle-aged adults (Table 5.1.2), but with mobility, self-care, daily activities and pain in the elderly (Table 5.1.3). For example, in the elderly, the high walking category was associated with 43% lower odds of having problems with mobility (95%CI: 0.47, 0.69), compared to the low category.
Cycling was associated with HRQL in the elderly only (Table 5.1.3). Moreover, cycling was the PA type associated with the lowest ORs overall in elderly adults. Compared to low cycling, high cycling was associated with 37% (95%CI: 0.50, 0.78), 57% (95%CI: 0.24, 0.77), 58% (95%CI: 0.30, 0.59) and 33% (95%CI: 0.56, 0.80) lower odds of having problems with mobility, self-care, daily activities and pain, respectively.

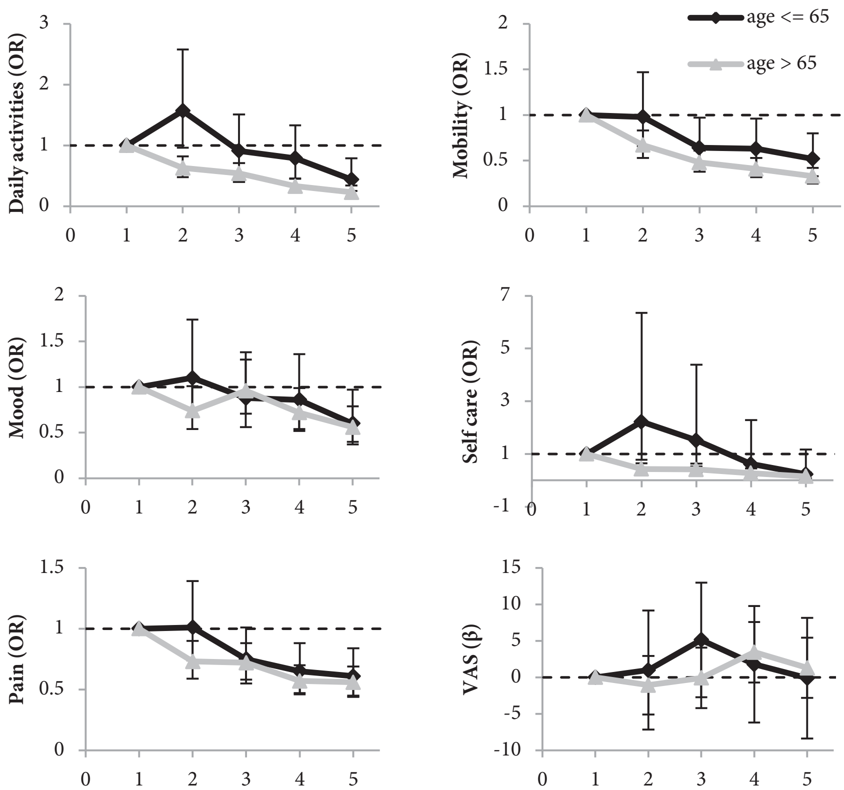


Figure 5.1.2. Associations between total physical activity groups with quality of life measures in middle aged (≤65 years) and elderly adults (age >65 years).

Abbreviations: OR, odds ratio; VAS, visual analogue scale.
Association between five total PA categories and six measures of health-related quality of life. The x-axis represents the 5 levels of total physical activity The median (range) are 1) 6.0 (<12.0) MET·hours·week^{-1}; 2) 18.8 (12.1-27.5) MET·hours·week^{-1}; 3) 39.3 (27.6-53.0) MET·hours·week^{-1}; 4) 68.2 (53.1-88.8) MET·hours·week^{-1}; 5) 119.9 (>88.8) MET·hours·week^{-1}. The median levels of total physical activity across categories are therefore equivalent to 13, 40, 84, 146 and 257minutes per day of total physical activity of 4 metabolic equivalents. The y-axis represents odds ratios (OR) and 95% confidence intervals (95%CIs) of having problems with a quality of life domain, and beta coefficients and their 95%CI for the visual analogue scale. The first total physical activity category is the reference category (i.e. OR = 1 and β=0). Models are adjusted for age, sex, marital status, smoking, alcohol consumption, education, job status, and comorbidity.

We found domestic work to be associated with pain in middle-aged adults (Table 5.1.2) and with mobility, self-care, daily activities and pain in the elderly (Table 5.1.3). For example, in the middle-aged, medium domestic work was associated with 27% lower odds of having pain (95%CI: 0.57, 0.93), compared to the low category.

For gardening we found significant associations with HRQL domains in both middle-aged and elderly adults (Table 5.1.2-5.1.3). For example, high gardening was associated with 57% (95%CI: 0.21, 0.88) and 38% (95%CI: 0.41-0.92) lower odds of having problems with daily activities in middle-aged and elderly adults, respectively.

We found sports to be associated with better mobility and less pain in both age groups and with better self-care, daily activities and mood in middle-aged adults (Table 5.1.2). Moreover, it was the PA type with the most associations with HRQL domains in the middle-aged. In this age group, compared to low sports, high sports was associated with 41% (95%CI: 0.41, 0.85), 82% (95%CI: 0.04, 0.84), 60% (95%CI: 0.24, 0.66), 44% (95%CI: 0.43, 0.72) and 34% (95%CI: 0.45, 0.99) lower odds of having problems with mobility, self-care, daily activities, pain and mood, respectively (Table 5.1.2).

In our sensitivity analyses by gender, employment status and presence of comorbidity, our findings did not materially change (Supplement 5.1.4 – Supplement 5.1.13).

DISCUSSION

In this population-based cohort of middle-aged and elderly adults, we found a dose-response relation between total PA and better HRQL. Additionally, we found that sport was associated with better mobility, self-care, daily activities, mood and less pain in middle-aged adults, whereas cycling was associated strongest with these HRQL domains in the elderly.

Only a few studies have investigated the nature of the dose-response relation between PA and HRQL, and have reported conflicting results.[2,9-11] A systematic review among adults aged <65 years suggested that there might be optimal levels of PA, and any PA below or above this threshold might not have additional benefits on HRQL.[2] In contrast, two studies in middle-aged adults found a linear trend between PA and HRQL.[10,11] Finally, a study from the Australian Longitudinal Study on Women's Health, in middle-aged and elderly women (aged 50-81 years), found that improvements in HRQL were observed at very low levels of PA and continued up to higher levels, after which increases were less marked for some outcomes, like the physical component summary and physical functioning.[9] In agreement with this study, we found that the odds of having problems with HRQL domains decreased with increasing total PA levels in both middle-aged and elderly adults. In the elderly, the decreases were observed at the lowest PA levels and continued up to the highest level, but were less marked. In middle-aged participants, the odds of having problems with HRQL domains declined less rapidly with increasing total PA levels.

Table 5.1.2. Odds ratios and their 95% confidence intervals for quality of life scores in middle-aged adults (≤ 65 years) for all physical activity types, the Rotterdam Study, 2009-2014 (n= 1,819).

		Mobility		Self-care		Daily activities		Pain		Mood	
	Median MET·hours·week^{-1} (range)	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Walking[a]											
Low	2.3 (<4.5)	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Moderate	7.9 (4.5-12.0)	0.91	0.66, 1.25	1.38	0.61, 3.1	0.95	0.64, 1.41	1.02	0.82, 1.28	0.95	0.68, 1.33
High	21.0 (≥12.1)	1.00	0.72, 1.38	0.55	0.2, 1.54	1.04	0.69, 1.56	0.88	0.69, 1.12	0.76	0.53, 1.11
Cycling[b]											
Low	0 (0)	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Moderate	3.0 (0-6.0)	1.03	0.76, 1.40	1.11	0.47, 2.63	1.06	0.73, 1.53	1.03	0.82, 1.29	1.00	0.71, 1.40
High	12.0 (≥6.1)	0.81	0.57, 1.14	1.63	0.65, 4.05	0.68	0.44, 1.06	0.82	0.64, 1.04	0.93	0.65, 1.35
Domestic work[c]											
Low	0 (0)	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Moderate	12.3 (0-26.9)	0.75	0.53, 1.05	0.99	0.41, 2.39	0.99	0.65, 1.50	0.73	0.57, 0.93	0.82	0.56, 1.18
High	45.9 (≥27.0)	0.74	0.52, 1.05	0.67	0.24, 1.90	1.15	0.75, 1.77	0.81	0.63, 1.05	0.81	0.56, 1.18
Gardening[d]											
Low	0 (0)	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Moderate	4.0 (0-8.0)	0.63	0.44, 0.89	1.14	0.48, 2.70	0.80	0.54, 1.20	0.90	0.72, 1.14	1.05	0.74, 1.49
High	16.0 (≥8.1)	0.84	0.54, 1.31	0.31	0.04, 2.36	0.43	0.21, 0.88	1.08	0.79, 1.48	1.25	0.79, 1.97
Sports[e]											
Low	0 (0)	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Moderate	7.6 (0-14.9)	0.94	0.67, 1.31	1.32	0.56, 3.11	1.15	0.77, 1.72	0.82	0.64, 1.05	0.96	0.67, 1.39
High	29.0 (≥15.0)	0.59	0.41, 0.85	0.18	0.04, 0.84	0.40	0.24, 0.66	0.56	0.43, 0.72	0.66	0.45, 0.99

Abbreviations: CI, confidence interval; OR, odds ratio; Ref, referent. Odds ratios below 1 indicate lower odds of having problems in that domain. Models are adjusted for age, sex, marital status, smoking, alcohol consumption, education, job status, comorbidity and the other physical activity types.

[a] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 6, 23 and 60 minutes per day of walking.

[b] Cycling is equivalent to 4.0 METs. The median levels of walking across categories are therefore equivalent to 0, 6 and 26 minutes per day of walking.

[c] Average domestic work is equivalent to 3.5 METs.[16] The median levels of domestic work across categories are therefore equivalent to 0, 30 and 111 minutes per day of domestic work.

[d] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 34 minutes per day of gardening.

[e] Sports can consist of different intensities. The median levels of sports across categories are therefore equivalent to 0, 13 and 50 minutes per day of sports of 5 METs.

Table 5.1.3. Odds ratios and their 95% confidence intervals for quality of life scores in elderly adults (> 65 years) for all physical activity types, the Rotterdam Study, 2009-2014 (n= 3,735).

	Median MET·hours·week^{-1}	Mobility		Self-care		Daily activities		Pain		Mood	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Walking[a]	(range)										
Low	2.3 (<4.5)	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Moderate	7.9 (4.5-12.0)	0.74	0.61, 0.89	0.48	0.34, 0.69	0.61	0.48, 0.77	0.87	0.74, 1.03	0.81	0.63, 1.04
High	21.0 (≥12.1)	0.57	0.47, 0.69	0.44	0.31, 0.64	0.55	0.43, 0.70	0.81	0.69, 0.96	0.83	0.65, 1.06
Cycling[b]											
Low	0 (0)	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Moderate	3.0 (0-6.0)	0.61	0.49, 0.76	0.34	0.19, 0.60	0.4	0.29, 0.54	0.71	0.60, 0.85	0.82	0.62, 1.08
High	12.0 (≥6.1)	0.63	0.50, 0.78	0.43	0.24, 0.77	0.42	0.30, 0.59	0.67	0.56, 0.80	0.80	0.60, 1.08
Domestic work[c]											
Low	0 (0)	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Moderate	14.5 (0-26.9)	0.84	0.68, 1.02	0.93	0.63, 1.37	0.99	0.76, 1.27	0.82	0.69, 0.98	0.94	0.71, 1.22
High	47.2 (≥27.0)	0.65	0.53, 0.80	0.60	0.38, 0.96	0.61	0.46, 0.81	0.79	0.67, 0.94	0.80	0.61, 1.04
Gardening[d]											
Low	0 (0)	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Moderate	4.0 (0-8.0)	0.81	0.62, 1.05	0.57	0.30, 1.08	0.58	0.40, 0.85	0.78	0.64, 0.97	1.16	0.85, 1.58
High	17.8 (≥8.1)	0.86	0.66, 1.13	0.46	0.21, 1.00	0.62	0.41, 0.92	1.13	0.92, 1.40	0.77	0.53, 1.11
Sports[e]											
Low	0 (0)	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Moderate	6.8 (0-14.9)	0.97	0.79, 1.18	1.09	0.73, 1.64	1.17	0.91, 1.51	0.89	0.75, 1.06	0.91	0.70, 1.19
High	30.5 (≥15.0)	0.68	0.54, 0.87	1.10	0.64, 1.89	0.75	0.53, 1.05	0.71	0.59, 0.86	0.77	0.56, 1.04

Abbreviations: CI, confidence interval; OR, odds ratio; Ref, referent. Odds ratios below 1 indicate lower odds of having problems in that domain.

Models are adjusted for age, sex, marital status, smoking, alcohol consumption, education, job status, comorbidity and the other physical activity types.

[a] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 6, 23 and 60 minutes per day of walking.

[b] Cycling is equivalent to 4.0 METs. The median levels of walking across categories are therefore equivalent to 0, 6 and 26 minutes per day of walking.

[c] Average domestic work is equivalent to 3.5 METs.[16] The median levels of domestic work across categories are therefore equivalent to 0, 35 and 114 minutes per day of domestic work.

[d] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 38 minutes per day of gardening.

[e] Sports can consist of different intensities. The median levels of sports across categories are therefore equivalent to 0, 12 and 52 minutes per day of sports of 5 METs.

Due to the cross-sectional nature of the studies, we cannot comment on the direction of the association between PA and HRQL. It is unclear whether physically active individuals experience a better HRQL or that people with a better HRQL are more likely to be physically active. In this regard, it is plausible that lower odds of having pain lead to higher levels of sports participation, but it could also be that higher sports participation leads to lower odds of having pain problems.

Data from randomized controlled trials indicate that exercise has a positive effect on quality of life in older adults with insomnia[24] and minor depression[25] and can reduce pain among individuals with osteoarthritis.[26,27] In addition, a recent randomized controlled trial in frail elderly adults indicated that an activity oriented intervention program (e.g. training of functions and skills) could aid in improving physical functioning and vitality, although these results did not reach significance.[28] Moreover, longitudinal studies suggest that increases in PA levels are associated with improvements in physical functioning and vitality scores,[9,29] indicating that PA patterns are an important determinant of HRQL.

Our study included both middle-aged (≤65 years) and elderly adults (>65 years). In the Netherlands, 65 years is considered retirement age, and different PA patterns for these groups are therefore expected We found that walking was associated with lower odds of having problems with mobility, self-care, daily activities and pain in elderly participants, but not in the middle-aged. This resembles results from a recent study, that found stronger associations of walking with the mental component summary, physical functioning, mental health and vitality in older compared to middle-aged women.[9] Another study in adults aged 75 years and older reported that older persons who attained recommended levels of walking had better results in most aspects of HRQL.[30] Moreover, a walking intervention among older individuals has shown beneficial effects on physical and mental HRQL.[31] The fact that in the current study walking was only associated with HRQL in the elderly participants might be explained by the relative importance of this activity type among the elderly, whereas they participate less in other PA types.[32]

We found that a high level of cycling was associated with fewer problems with daily activities, mobility, self-care and pain in the elderly, but we not in middle-aged adults. We are not aware of another study evaluating the association between cycling and HRQL in elderly adults. Even so, a study in Australian men, aged 18-55 years, found a beneficial association between cycling frequency and psychological well-being.[6] The fact that we found no association between cycling and HRQL in middle-aged adults might be explained by the fact that in contrast to Australia, cycling is a common way of commuting in the Netherlands, instead of a solely a form of sports. Indeed, a large proportion of participants in our study participated in cycling on a weekly basis (57.5% of middle-aged and 39.8% of elderly).

We found an association between gardening and HRQL that has not been reported before. Since gardening can be considered a relaxing activity, this might explain the positive association. Moreover, being outside might contribute to the effect as well. It is possible that sunlight exposure during gardening increased vitamin D levels, which consequently improved quality of life.[33] Furthermore, in literature, the association between domestic work and HRQL remains unclear. A study in younger adults reported an inverse association,[34] whereas domestic work was positively related to HRQL in university students.[5] Our study indicates that domestic work is associated with better HRQL in middle-aged and elderly adults.

Sports is an activity type that has been reported to be associated with HRQL in middle-aged adults.[4] In our study, we found that it was associated with lower odds of having problems with all HRQL-aspects in middle-aged adults, whereas it was only associated with better mobility and less pain in elderly adults. Probably, elderly adults engage in different kinds of sports than their middle-aged counterparts. Indeed, we found that younger adults engage more in high intensity activities like tennis and jogging, whereas elderly participated more in gymnastics, bowls and billiards (data not shown). Additionally, sports made up 20% of the total MET·hours·week^{-1} in middle-aged adults and 15% of the MET·hours·week^{-1} in the elderly.

Major strengths of our study were the use of a large community-based cohort and the categorization of participants into broad range of PA categories, to facilitate the examination of dose-response relationships. Furthermore, we included a number of different activities while adjusting for the remaining activities, which enabled us to examine their independent associations with HRQL. However, our study has some limitations worth mentioning: because of the cross-sectional design, the influence of PA on HRQL could not be determined. It is possible that PA influenced HRQL, but it is also possible that people with lower HRQL are less likely to engage in PA. Second, it may be hypothesized that people in poor health participate in PA less than others, creating the opportunity for reverse causation. Although we did not find that results were influenced by comorbidity. Furthermore, we had data on cancer, cardiovascular disease and diabetes up to 2012, whereas we collected data on PA and HRQL for RS-III (n=1,893) between 2012 and 2014. It is possible that part of the observed associations might be explained presence of comorbidities that presented after 2012. Therefore, we cannot fully exclude the possibility of residual confounding by comorbidities. Another limitation is that our results are based on self-reported PA and HRQL. Although our questionnaires have shown to be valid and reliable[15,35] potential recall bias and social desirability cannot be excluded.

Conclusions

In summary, sport was the PA type with most associations with HRQL in middle-aged adults, whereas activities with lower intensity, like walking, cycling and domestic work, were more important in elderly adults. These results suggest that different activities could be promoted to different age groups, to improve HRQL. Future research, involving trials or studies with longitudinal designs, could provide more insight about the characteristics of specific PA types beneficially related with HRQL in different populations.

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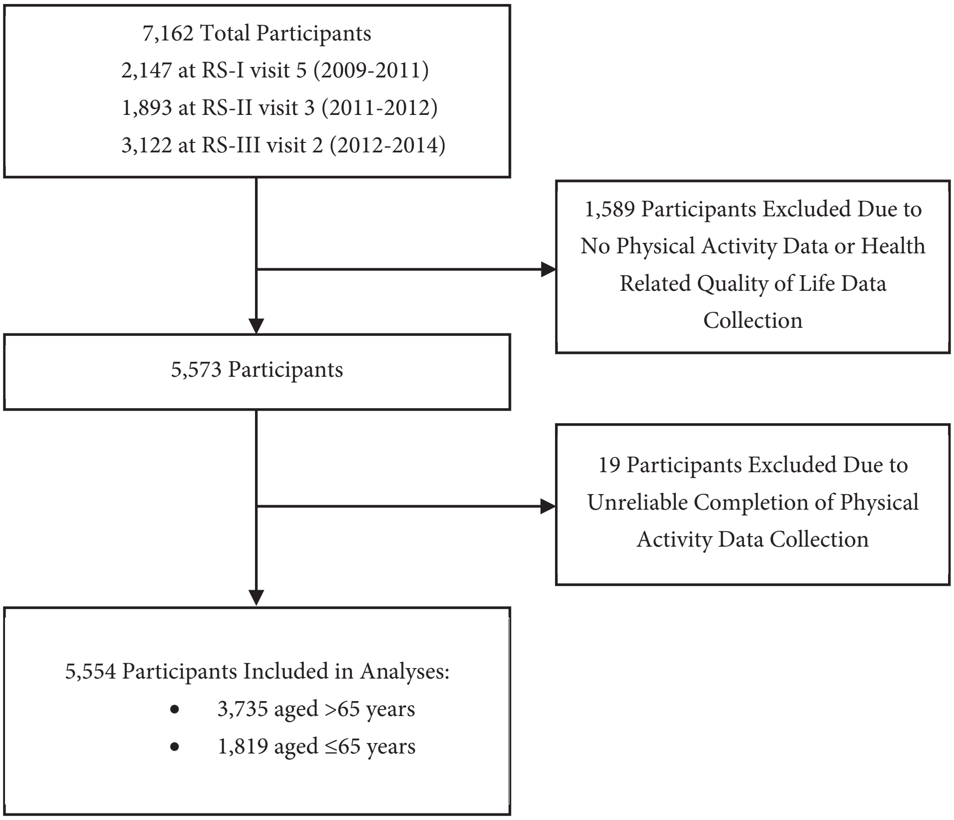
SUPPLEMENT CHAPTER 5.1

Supplement 5.1.1. Flow chart of participant inclusion for the Rotterdam Study.



Supplement 5.1.2. Number of middle-aged (≤65 years) and elderly adults (>65 years) in each physical activity group

Activity Type and Tertile of Physical Activity	Number of participants	
	Middle-aged participants (age ≤65 years)	Elderly participants (age > 65 years)
Total Physical Activity		
1	520	1,335
2	690	1,159
3	609	1,241
Walking		
1	704	1,201
2	605	1,242
3	510	1,292
Domestic work		
1	762	2,103
2	576	846
3	481	786
Cycling		
1	687	1,658
2	610	997
3	522	1,080
Sports		
1	1,150	2,775
2	468	498
3	201	462
Gardening		
1	683	1,649
2	559	1,054
3	577	1,032

Supplement 5.1.3. Beta coefficients and their 95% confidence intervals for the visual analogue scale in middle-aged (≤65 years) and elderly adults (> 65 years) for all physical activity types, the Rotterdam Study, 2009-2014.

	Middle-aged adults			Elderly adults		
	Median METhours/ week (range)	β	95% CI	Median METhours /week (range)	β	95% CI
Walking						
Low	2.3 (<4.5)		Ref	2.3 <4.5		Ref
Moderate	7.9 (4.5-12.0)	-5.69	-11.46, 0.08	7.9 4.5-12.0	-0.64	-3.83, 2.55
High	21.0 (≥12.1)	-3.08	-9.28, 3.11	21.0 ≥12.1	2.10	1.06, 5.27
Cycling						
Low	0 (0)		Ref	0 0		Ref
Moderate	3.0 (0-6.0)	1.66	-4.18, 7.49	3.0 0-6.0	1.73	-1.61, 5.08
High	12.0 (≥6.1)	7.63	1.47, 13.78	12.0 ≥6.1	-0.06	-3.52, 3.40
Domestic work						
Low	0 (0)		Ref	0 0		Ref
Moderate	12.3 (0-26.9)	-1.88	-7.98, 4.23	14.5 0-26.9	-1.16	-4.5, 2.19
High	45.9 (≥27.0)	-4.53	-11.15, 2.09	47.2 ≥27.0	-1.24	-4.57, 2.09
Gardening						
Low	0 (0)		Ref	0 0		Ref
Moderate	4.0 (0-8.0)	0.64	-5.19, 6.47	4.0 0-8.0	-1.56	-5.51, 2.39
High	16.0 (≥8.1)	2.66	-5.36, 10.68	17.8 ≥8.1	1.76	-2.31, 5.82
Sports						
Low	0 (0)		Ref	0 0		Ref
Moderate	7.6 (0-14.9)	-4.21	-10.57, 2.16	6.8 0-14.9	-0.81	-4.19, 2.58
High	29.0 (≥15.0)	-0.72	-7.11, 5.68	30.5 ≥15.0	0.05	-3.59, 3.69

Abbreviations: Ref, referent; VAS, visual analogue scale.
Models are adjusted for age, sex, marital status, smoking, alcohol consumption, education, job status, comorbidity and the other physical activity types

Supplement 5.1.4. Odds ratios and beta coefficients and their 95% confidence intervals for quality of life scores in male adults aged 65 years and younger all physical activity types (n=764)

	Median MET·hours·week^{-1} (range)	Mobility		Self-care		Daily activities		Pain		Mood		VAS	
		OR	95% CI	OR	95% CI	OR	β	β	95% CI	OR	95% CI	β	95% CI
Walking[a]													
Low	2.3 (<4.5)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	7.5 (4.5-12.0)	0.83	0.48, 1.43	1.00	0.29, 3.44	0.70	0.34, 1.45	0.97	0.68, 1.37	0.82	0.43, 1.57	-3.54	-12.92, 5.85
High	21.0 (≥12.1)	0.79	0.43, 1.44	0.50	0.10, 2.60	0.71	0.33, 1.54	0.81	0.55, 1.20	0.84	0.42, 1.67	4.08	-6.35, 14.51
Cycling[b]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	2.7 (0-6.0)	0.91	0.52, 1.61	1.46	0.35, 6.12	0.95	0.46, 1.94	1.12	0.78, 1.60	0.87	0.45, 1.67	2.22	-7.5, 11.94
High	12.0 (≥6.1)	0.94	0.50, 1.74	4.00	0.91, 17.61	0.70	0.31, 1.61	0.7	0.47, 1.04	0.79	0.39, 1.60	7.02	-3.32, 17.37
Domestic work[c]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	9.9 (0-26.9)	0.51	0.30, 0.89	0.82	0.23, 2.88	1.11	0.54, 2.29	0.91	0.64, 1.29	0.59	0.30, 1.16	-7.31	-16.58, 1.95
High	40.3 (≥27.0)	0.53	0.24, 1.16	No events in 3rd tertile		1.52	0.57, 4.09	1.28	0.78, 2.08	1.61	0.76, 3.40	-8.02	-21.3, 5.27
Gardening[d]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	4.0 (0-8.0)	0.65	0.35, 1.22	1.69	0.51, 5.62	0.87	0.41, 1.87	0.81	0.56, 1.16	0.74	0.35, 1.54	2.33	-7.32, 11.97
High	17.0 (≥8.1)	0.79	0.36, 1.74	No events in 3rd tertile		0.69	0.23, 2.08	1.04	0.64, 1.69	1.79	0.85, 3.77	9.47	-3.62, 22.56
Sports[e]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	8.2 (0-14.9)	0.91	0.51, 1.64	0.6	0.15, 2.50	1.00	0.49, 2.03	1.01	0.68, 1.49	1.25	0.65, 2.43	-5.00	-15.52, 5.53
High	30.6 (≥15.0)	0.46	0.24, 0.86	0.13	0.01, 1.16	0.23	0.09, 0.61	0.7	0.48, 1.02	0.55	0.27, 1.14	-2.02	-12.02, 7.97

Abbreviations: CI, confidence interval; OR, odds ratio; T, tertile; VAS, visual analogue scale.

[a] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 6, 21 and 60 minutes per day of walking.

[b] Cycling is equivalent to 4.0 METs. The median levels of walking across categories are therefore equivalent to 0, 6 and 26 minutes per day of walking.

[c] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 0, 24 and 97 minutes per day of domestic work.

[d] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 36 minutes per day of gardening.

[e] Sports can consist of different intensities. The median levels of sports across categories are therefore equivalent to 0, 14 and 52 minutes per day of sports of 5 METs

Supplement 5.1.5. Odds ratios and beta coefficients and their 95% confidence intervals for quality of life scores in male adults older than 65 years for all physical activity types (n=1,592).

	Median MET·hours·week^{-1} (range)	Mobility		Self-care		Daily activities		Pain		Mood		VAS	
		OR	95% CI	OR	95% CI	OR	β	β	95% CI	OR	95% CI	β	95% CI
Walking[a]													
Low	2.3 (<4.5)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	7.5 (4.5-12.0)	0.72	0.53, 0.97	0.30	0.15, 0.62	0.50	0.31, 0.79	0.75	0.58, 0.97	0.71	0.45, 1.13	-2.68	-8.41, 3.05
High	21.0 (≥12.1)	0.60	0.44, 0.83	0.58	0.31, 1.09	0.53	0.33, 0.87	0.87	0.67, 1.13	0.79	0.50, 1.25	1.49	-4.33, 7.31
Cycling[b]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	3.0 (0-6.0)	0.71	0.51, 0.99	0.18	0.05, 0.58	0.49	0.28, 0.86	0.80	0.61, 1.04	0.58	0.35, 0.97	0.91	-4.98, 6.8
High	12.0 (≥6.1)	0.58	0.41, 0.84	0.62	0.28, 1.37	0.48	0.26, 0.89	0.80	0.6, 1.05	0.58	0.34, 0.98	-3.16	-9.29, 2.97
Domestic work[c]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	12.6 (0-26.9)	0.85	0.63, 1.15	0.68	0.34, 1.34	0.96	0.6, 1.54	0.87	0.67, 1.12	1.14	0.72, 1.79	-1.53	-7.17, 4.11
High	41.4 (≥27.0)	0.78	0.53, 1.15	0.68	0.28, 1.65	0.81	0.42, 1.54	0.91	0.67, 1.24	1.2	0.69, 2.07	-3.69	-10.54, 3.15
Gardening[d]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	4.0 (0-8.0)	0.93	0.64, 1.36	0.90	0.39, 2.09	0.84	0.46, 1.53	1.02	0.75, 1.37	1.20	0.71, 2.01	-3.54	-10.16, 3.08
High	17.0 (≥8.1)	0.69	0.45, 1.04	0.39	0.12, 1.29	0.45	0.20, 0.99	1.24	0.91, 1.68	0.77	0.42, 1.43	3.13	-3.72, 9.99
Sports[e]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	7.6 (0-14.9)	1.14	0.82, 1.58	0.79	0.39, 1.62	1.21	0.74, 1.96	0.96	0.73, 1.27	0.96	0.58, 1.58	0.08	-6.15, 6.30
High	32.3 (≥15.0)	0.69	0.48, 0.99	0.66	0.28, 1.54	0.60	0.32, 1.13	0.68	0.51, 0.90	0.91	0.55, 1.51	-0.17	-6.32, 5.99

Abbreviations: CI, confidence interval; OR, odds ratio; T, tertile; VAS, visual analogue scale.

[a] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 6, 21 and 60 minutes per day of walking.

[b] Cycling is equivalent to 4.0 METs. The median levels of walking across categories are therefore equivalent to 0, 6 and 26 minutes per day of walking.

[c] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 0, 30 and 100 minutes per day of domestic work.

[d] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 36 minutes per day of gardening.

[e] Sports can consist of different intensities. The median levels of sports across categories are therefore equivalent to 0, 13 and 55 minutes per day of sports of 5 METs.

Supplement 5.1.6. Odds ratios and beta coefficients and their 95% confidence intervals for quality of life scores in female adults aged 65 years and younger all physical activity types (n=1,055)

	Median MET·hours·week⁻¹ (range)	Mobility		Self-care		Daily activities		Pain		Mood		VAS	
		OR	95% CI	OR	95% CI	OR	β	β	95% CI	OR	95% CI	β	95% CI
Walking[a]													
Low	2.3 (<4.5)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	8.8 (4.5-12.0)	0.94	0.64, 1.40	1.57	0.49, 5.01	1.11	0.69, 1.79	1.04	0.77, 1.40	1.02	0.68, 1.52	-7.60	-14.9, -0.30
High	21.0 (≥12.1)	1.11	0.74, 1.65	0.56	0.14, 2.23	1.24	0.77, 2.01	0.91	0.67, 1.24	0.75	0.48, 1.16	-8.06	-15.71, -0.41
Cycling[b]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	3.0 (0-6.0)	1.07	0.73, 1.55	0.96	0.31, 2.94	1.08	0.70, 1.68	0.97	0.72, 1.31	1.05	0.70, 1.56	1.40	-5.86, 8.67
High	12.0 (≥6.1)	0.77	0.51, 1.17	1.21	0.34, 4.31	0.67	0.40, 1.13	0.90	0.66, 1.22	0.98	0.63, 1.51	7.91	0.25, 15.57
Domestic work[c]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	15.0 (0-26.7)	0.99	0.64, 1.52	1.07	0.29, 3.96	0.95	0.56, 1.60	0.59	0.42, 0.83	0.97	0.62, 1.51	3.14	-5.15, 11.43
High	47.8 (≥26.8)	0.83	0.55, 1.24	1.11	0.34, 3.64	1.07	0.66, 1.72	0.67	0.49, 0.92	0.70	0.46, 1.08	-1.96	-9.56, 5.64
Gardening[d]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	4.0 (0-8.0)	0.60	0.39, 0.91	0.79	0.21, 2.95	0.76	0.47, 1.23	0.97	0.72, 1.30	1.17	0.78, 1.77	-0.56	-7.88, 6.76
High	16.0 (≥8.1)	0.84	0.48, 1.45	0.60	0.07, 4.89	0.33	0.13, 0.84	1.09	0.72, 1.64	1.02	0.57, 1.83	-2.44	-12.58, 7.69
Sports[e]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	7.3 (0-14.8)	1.01	0.67, 1.52	2.50	0.76, 8.15	1.26	0.77, 2.04	0.70	0.50, 0.97	0.87	0.56, 1.36	-3.97	-11.98, 4.03
High	27.7 (≥14.9)	0.70	0.44, 1.11	0.25	0.03, 2.29	0.51	0.28, 0.92	0.45	0.32, 0.64	0.71	0.44, 1.15	0.20	-8.17, 8.57

Abbreviations: CI, confidence interval; OR, odds ratio; T, tertile; VAS, visual analogue scale.

[a] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 6, 25 and 60 minutes per day of walking.

[b] Cycling is equivalent to 4.0 METs. The median levels of walking across categories are therefore equivalent to 0, 6 and 26 minutes per day of walking.

[c] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 0, 36 and 115 minutes per day of domestic work.

[d] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 34 minutes per day of gardening.

[e] Sports can consist of different intensities. The median levels of sports across categories are therefore equivalent to 0, 12 and 47 minutes per day of sports of 5 METs.

Supplement 5.1.7. Odds ratios and beta coefficients and their 95% confidence intervals for quality of life scores in female adults older than 65 years for all physical activity types (n=2,143).

	Median MET·hours·week^{-1} (range)	Mobility		Self-care		Daily activities		Pain		Mood		VAS	
		OR	95% CI	OR	95% CI	OR	β	β	95% CI	OR	95% CI	β	95% CI
Walking[a]													
Low	2.5 (<4.5)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	8.9 (4.5-12.0)	0.77	0.61, 0.98	0.58	0.38, 0.88	0.65	0.49, 0.86	0.97	0.78, 1.21	0.87	0.64, 1.18	1.21	-2.33, 4.74
High	21.0 (≥12.1)	0.57	0.45, 0.73	0.41	0.26, 0.65	0.56	0.43, 0.74	0.80	0.64, 0.99	0.86	0.64, 1.15	3.09	-0.37, 6.55
Cycling[b]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	3.0 (0-6.0)	0.55	0.41, 0.74	0.46	0.24, 0.90	0.35	0.24, 0.52	0.66	0.52, 0.83	0.96	0.69, 1.34	2.57	-1.20, 6.34
High	12.0 (≥6.1)	0.66	0.49, 0.89	0.31	0.13, 0.74	0.41	0.27, 0.61	0.60	0.48, 0.77	0.92	0.65, 1.31	3.14	-0.76, 7.04
Domestic work[c]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	18.1 (0-26.9)	0.86	0.65, 1.13	1.09	0.67, 1.76	1.06	0.78, 1.44	0.79	0.62, 1.01	0.90	0.64, 1.26	-1.60	-5.58, 2.37
High	49.7 (≥27.0)	0.59	0.46, 0.76	0.58	0.34, 1.00	0.56	0.41, 0.76	0.74	0.6, 0.91	0.69	0.50, 0.93	0.28	-3.13, 3.69
Gardening[d]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	4.0 (0-8.0)	0.71	0.49, 1.03	0.35	0.13, 0.99	0.46	0.28, 0.76	0.63	0.47, 0.84	1.13	0.76, 1.69	1.02	-3.63, 5.68
High	17.8 (≥8.1)	1.00	0.70, 1.44	0.48	0.17, 1.36	0.70	0.43, 1.12	1.05	0.78, 1.40	0.75	0.47, 1.20	-0.05	-4.8, 4.7
Sports[e]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	6.3 (0-14.8)	0.87	0.67, 1.13	1.32	0.80, 2.18	1.18	0.87, 1.60	0.85	0.68, 1.06	0.9	0.65, 1.25	-1.68	-5.38, 2.01
High	28.4 (≥14.9)	0.68	0.49, 0.95	1.68	0.82, 3.44	0.85	0.56, 1.28	0.71	0.55, 0.93	0.71	0.48, 1.05	0.09	-4.18, 4.35

Abbreviations: CI, confidence interval; OR, odds ratio; T, tertile; VAS, visual analogue scale.

[a] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 7, 25 and 60 minutes per day of walking.

[b] Cycling is equivalent to 4.0 METs. The median levels of walking across categories are therefore equivalent to 0, 6 and 26 minutes per day of walking.

[c] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 0, 44 and 120 minutes per day of domestic work.

[d] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 38 minutes per day of gardening.

[e] Sports can consist of different intensities. The median levels of sports across categories are therefore equivalent to 0, 11 and 49 minutes per day of sports of 5 METs.

Supplement 5.1.8. Odds ratios and beta coefficients and their 95% confidence intervals for quality of life scores in non-working adults aged 65 years and younger all physical activity types (n=686)

	Median MET·hours·week^{-1} (range)	Mobility		Self-care		Daily activities		Pain		Mood		VAS	
		OR	95% CI	OR	95% CI	OR	β	β	95% CI	OR	95% CI	β	95% CI
Walking[a]													
Low	2.9 (<4.5)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	9.0 (4.5-12.0)	0.63	0.39, 1.02	1.46	0.57, 3.74	0.94	0.55, 1.61	0.87	0.59, 1.29	0.67	0.40, 1.12	-12.29	-24.4, -0.17
High	21.0 (≥12.1)	0.96	0.61, 1.51	0.68	0.23, 2.03	1.02	0.59, 1.74	0.85	0.57, 1.25	0.63	0.38, 1.04	-10.5	-22.55, 1.56
Cycling[b]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	3.0 (0-6.0)	1.07	0.70, 1.65	1.31	0.53, 3.26	1.10	0.67, 1.80	1.05	0.72, 1.53	1.13	0.70, 1.84	0.75	-10.38, 11.88
High	12.0 (≥6.1)	0.71	0.43, 1.18	1.06	0.34, 3.30	0.70	0.39, 1.26	0.74	0.49, 1.10	1.07	0.62, 1.85	13.95	1.20, 26.71
Domestic work[c]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	14.1 (0-26.9)	0.67	0.40, 1.12	0.99	0.36, 2.68	0.96	0.53, 1.75	0.55	0.35, 0.85	1.15	0.67, 1.98	2.58	-10.44, 15.6
High	52.0 (≥27.0)	0.75	0.47, 1.21	0.61	0.19, 1.93	1.21	0.69, 2.11	0.69	0.46, 1.04	0.74	0.43, 1.26	-5.84	-17.84, 6.17
Gardening[d]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	4.0 (0-8.0)	0.54	0.32, 0.91	1.10	0.40, 3.00	0.85	0.48, 1.50	0.89	0.59, 1.33	0.94	0.55, 1.61	4.81	-7.27, 16.89
High	18.0 (≥8.1)	0.76	0.41, 1.41	0.40	0.05, 3.12	0.55	0.24, 1.27	1.06	0.65, 1.74	1.04	0.53, 2.07	-2.29	-16.95, 12.36
Sports[e]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	7.9 (0-14.9)	1.03	0.63, 1.70	1.44	0.54, 3.80	1.23	0.70, 2.13	0.79	0.51, 1.23	1.26	0.74, 2.17	-7.99	-20.97, 4.99
High	31.5 (≥15.0)	0.54	0.32, 0.91	0.12	0.01, 0.97	0.35	0.18, 0.68	0.41	0.27, 0.63	0.60	0.33, 1.10	-2.45	-15.00, 10.11

Abbreviations: CI, confidence interval; OR, odds ratio; T, tertile; VAS, visual analogue scale.

[a] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 8, 26 and 60 minutes per day of walking.

[b] Cycling is equivalent to 4.0 METs. The median levels of walking across categories are therefore equivalent to 0, 6 and 26 minutes per day of walking.

[c] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 0, 34 and 126 minutes per day of domestic work.

[d] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 39 minutes per day of gardening.

[e] Sports can consist of different intensities. The median levels of sports across categories are therefore equivalent to 0, 14 and 54 minutes per day of sports of 5 METs.

Supplement 5.1.9. Odds ratios and beta coefficients and their 95% confidence intervals for quality of life scores in non-working adults older than 65 years for all physical activity types (n=3,504).

	Median MET·hours·week^{-1} (range)	Mobility		Self-care		Daily activities		Pain		Mood		VAS	
		OR	95% CI	OR	95% CI	OR	β	β	95% CI	OR	95% CI	β	95% CI
Walking[a]													
Low	2.3 (<4.5)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	7.9 (4.5-12.0)	0.76	0.63, 0.93	0.50	0.35, 0.72	0.62	0.49, 0.79	0.91	0.77, 1.08	0.81	0.62, 1.04	-0.87	-4.27, 2.53
High	21.0 (≥12.1)	0.58	0.48, 0.71	0.46	0.32, 0.67	0.56	0.44, 0.72	0.83	0.70, 0.98	0.81	0.63, 1.05	2.22	-1.14, 5.59
Cycling[b]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	3.0 (0-6.0)	0.61	0.49, 0.76	0.35	0.20, 0.61	0.39	0.28, 0.54	0.70	0.58, 0.83	0.82	0.62, 1.09	1.69	-1.88, 5.26
High	12.0 (≥6.1)	0.61	0.48, 0.77	0.41	0.23, 0.75	0.42	0.30, 0.59	0.65	0.54, 0.79	0.77	0.57, 1.04	0.07	-3.63, 3.76
Domestic work[c]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	14.7 (0-26.9)	0.85	0.69, 1.04	0.95	0.64, 1.41	1.00	0.77, 1.30	0.82	0.69, 0.99	0.98	0.74, 1.29	-1.46	-5.04, 2.11
High	47.8 (≥27.0)	0.66	0.53, 0.81	0.59	0.37, 0.95	0.60	0.45, 0.80	0.79	0.67, 0.95	0.84	0.64, 1.10	-1.57	-5.09, 1.96
Gardening[d]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	4.0 (0-8.0)	0.81	0.62, 1.06	0.59	0.31, 1.12	0.56	0.38, 0.84	0.78	0.63, 0.97	1.24	0.90, 1.71	-1.60	-5.85, 2.64
High	18.0 (≥8.1)	0.84	0.64, 1.11	0.33	0.13, 0.83	0.57	0.37, 0.87	1.15	0.93, 1.43	0.81	0.56, 1.18	2.00	-2.37, 6.37
Sports[e]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	6.7 (0-14.9)	0.98	0.80, 1.21	1.12	0.75, 1.69	1.19	0.92, 1.55	0.88	0.74, 1.06	0.98	0.74, 1.28	-1.07	-4.67, 2.53
High	30.6 (≥15.0)	0.70	0.55, 0.89	1.11	0.64, 1.92	0.77	0.54, 1.08	0.70	0.58, 0.85	0.80	0.59, 1.10	-0.27	-4.17, 3.63

Abbreviations: CI, confidence interval; OR, odds ratio; T, tertile; VAS, visual analogue scale.

[a] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 6, 23 and 60 minutes per day of walking.

[b] Cycling is equivalent to 4.0 METs. The median levels of walking across categories are therefore equivalent to 0, 6 and 26 minutes per day of walking.

[c] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 0, 35 and 115 minutes per day of domestic work.

[d] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 39 minutes per day of gardening.

[e] Sports can consist of different intensities. The median levels of sports across categories are therefore equivalent to 0, 11 and 52 minutes per day of sports of 5 METs.

Supplement 5.1.10. Odds ratios and beta coefficients and their 95% confidence intervals for quality of life scores in adults aged 65 years and younger without comorbidities for all physical activity types (n=1,454)

	Median MET·hours·week^{-1} (range)	Mobility		Self-care		Daily activities		Pain		Mood		VAS	
		OR	95% CI	OR	95% CI	OR	β	β	95% CI	OR	95% CI	β	95% CI
Walking[a]													
Low	2.3 (<4.5)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	8.0 (4.5-12)	0.85	0.58, 1.23	1.39	0.52, 3.68	0.92	0.59, 1.46	1.13	0.88, 1.45	0.94	0.65, 1.36	-3.89	-9.91, 2.13
High	21.0 (≥12.1)	0.99	0.67, 1.46	0.53	0.15, 1.84	1.09	0.68, 1.74	0.89	0.68, 1.17	0.65	0.42, 0.98	-2.16	-8.73, 4.41
Cycling[b]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	3.0 (0-6)	0.95	0.67, 1.36	0.63	0.20, 1.97	0.98	0.64, 1.50	0.93	0.72, 1.20	0.99	0.68, 1.43	1.84	-4.26, 7.94
High	12.0 (≥6.1)	0.70	0.47, 1.06	1.96	0.70, 5.44	0.63	0.38, 1.05	0.76	0.58, 0.99	0.85	0.56, 1.28	5.62	-0.89, 12.13
Domestic work[c]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	12.1 (0-26.9)	0.81	0.55, 1.20	1.04	0.36, 3.07	1.01	0.62, 1.65	0.71	0.54, 0.93	0.92	0.61, 1.38	-2.48	-8.9, 3.94
High	45.9 (≥27.0)	0.75	0.5, 1.13	0.74	0.23, 2.41	1.08	0.66, 1.76	0.79	0.59, 1.05	0.97	0.64, 1.46	-4.76	-11.67, 2.14
Gardening[d]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	4.0 (0-8.0)	0.64	0.43, 0.96	1.33	0.47, 3.70	0.67	0.42, 1.09	0.99	0.77, 1.27	0.98	0.66, 1.45	1.56	-4.52, 7.64
High	16.3 (≥8.1)	0.84	0.50, 1.38	0.41	0.05, 3.22	0.46	0.22, 0.98	1.16	0.82, 1.63	1.14	0.69, 1.88	3.82	-4.41, 12.05
Sports[e]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	7.6 (0-14.8)	0.99	0.67, 1.47	1.25	0.45, 3.52	1.08	0.68, 1.71	0.77	0.58, 1.02	1.17	0.78, 1.75	-2.26	-8.96, 4.44
High	28.8 (≥14.9)	0.62	0.40, 0.94	0.24	0.05, 1.19	0.38	0.21, 0.67	0.54	0.41, 0.72	0.69	0.45, 1.08	1.37	-5.32, 8.05

Abbreviations: CI, confidence interval; OR, odds ratio; T, tertile; VAS, visual analogue scale.

[a] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 6, 23 and 60 minutes per day of walking.

[b] Cycling is equivalent to 4.0 METs. The median levels of walking across categories are therefore equivalent to 0, 6 and 26 minutes per day of walking.

[c] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 0, 29 and 111 minutes per day of domestic work.

[d] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 35 minutes per day of gardening.

[e] Sports can consist of different intensities. The median levels of sports across categories are therefore equivalent to 0, 13 and 49 minutes per day of sports of 5 METs.

Supplement 5.1.11. Odds ratios and beta coefficients and their 95% confidence intervals for quality of life scores in adults aged 65 years and younger, with comorbidities, for all physical activity types (n=365).

	Median MET·hours·week^{-1} (range)	Mobility		Self-care		Daily activities		Pain		Mood		VAS	
		OR	95% CI	OR	95% CI	OR	β	β	95% CI	OR	95% CI	β	95% CI
Walking[a]													
Low	2.3 (<4.5)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	7.5 (4.5-12.0)	1.11	0.59, 2.06	1.99	0.34, 11.72	1.06	0.48, 2.34	0.66	0.39, 1.11	1.05	0.43, 2.55	-13.09	-29.21, 3.02
High	21.0 (≥12.1)	1.08	0.57, 2.04	0.68	0.09, 5.37	0.92	0.40, 2.12	0.85	0.50, 1.45	1.48	0.63, 3.44	-6.20	-22.53, 10.14
Cycling[b]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	3.0 (0-6.0)	1.19	0.64, 2.21	6.39	1.03, 39.84	1.23	0.56, 2.67	1.45	0.85, 2.48	0.98	0.41, 2.35	-0.50	-16.71, 15.71
High	12.0 (≥6.1)	1.11	0.58, 2.12	0.85	0.05, 13.45	0.77	0.31, 1.90	0.98	0.57, 1.67	1.44	0.62, 3.36	18.18	1.66, 34.7
Domestic work[c]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	12.8 (0-26.9)	0.57	0.29, 1.09	0.88	0.14, 5.31	0.95	0.39, 2.28	0.78	0.45, 1.33	0.53	0.21, 1.30	-1.29	-17.89, 15.31
High	46.1 (≥27.0)	0.66	0.32, 1.37	0.46	0.04, 5.34	1.42	0.55, 3.67	0.93	0.5, 1.73	0.32	0.12, 0.88	-5.27	-24.13, 13.58
Gardening[d]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	4.0 (0-8.0)	0.55	0.27, 1.12	0.86	0.15, 5.01	1.23	0.56, 2.70	0.59	0.35, 1.00	1.45	0.63, 3.34	-5.25	-21.64, 11.14
High	16.0 (≥8.1)	0.85	0.32, 2.24	No cases in 3[rd] tertile		0.21	0.03, 1.71	0.75	0.34, 1.62	1.92	0.64, 5.78	-0.84	-25.05, 23.37
Sports[e]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	7.5 (0-14.9)	0.78	0.41, 1.51	2.14	0.34, 13.44	1.57	0.67, 3.69	1.07	0.61, 1.88	0.42	0.16, 1.13	-14.99	-32.15, 2.17
High	29.6 (≥15.0)	0.52	0.25, 1.08	No cases in 3[rd] tertile		0.51	0.17, 1.49	0.62	0.35, 1.11	0.61	0.24, 1.56	-12.09	-29.86, 5.69

Abbreviations: CI, confidence interval; OR, odds ratio; T, tertile; VAS, visual analogue scale.

[a] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 6, 21 and 60 minutes per day of walking.

[b] Cycling is equivalent to 4.0 METs. The median levels of walking across categories are therefore equivalent to 0, 6 and 26 minutes per day of walking.

[c] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 0, 31 and 111 minutes per day of domestic work.

[d] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 34 minutes per day of gardening.

[e] Sports can consist of different intensities. The median levels of sports across categories are therefore equivalent to 0, 13 and 51 minutes per day of sports of 5 METs.

Supplement 5.1.12. Odds ratios and beta coefficients and their 95% confidence intervals for quality of life scores in adults older than 65 years, without comorbidities, for all physical activity types (n=2,120).

	Median MET·hours·week⁻¹ (range)	Mobility		Self-care		Daily activities		Pain		Mood		VAS	
		OR	95% CI	OR	95% CI	OR	β	β	95% CI	OR	95% CI	β	95% CI
Walking[a]													
Low	2.5 (<4.5)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	8.0 (4.5-12.0)	0.92	0.70, 1.20	0.56	0.32, 0.99	0.62	0.44, 0.86	1.03	0.83, 1.29	1.00	0.72, 1.40	-1.13	-5.29, 3.03
High	21.0 (≥12.1)	0.80	0.61, 1.04	0.64	0.36, 1.13	0.57	0.40, 0.80	0.91	0.73, 1.13	0.79	0.56, 1.12	-0.37	-4.52, 3.77
Cycling[b]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	3.0 (0-6.0)	0.60	0.44, 0.81	0.52	0.24, 1.14	0.45	0.30, 0.70	0.71	0.56, 0.89	0.75	0.51, 1.09	0.72	-3.56, 4.99
High	12.0 (≥6.1)	0.64	0.47, 0.88	0.33	0.12, 0.94	0.51	0.33, 0.79	0.64	0.50, 0.81	0.79	0.54, 1.17	-0.25	-4.69, 4.19
Domestic work[c]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	16.2 (0-26.9)	0.73	0.54, 0.97	0.98	0.52, 1.85	0.78	0.53, 1.14	0.81	0.64, 1.03	1.13	0.79, 1.62	-4.59	-9.04, -0.13
High	49.0 (≥27.0)	0.51	0.38, 0.68	0.43	0.2, 0.93	0.53	0.36, 0.77	0.74	0.59, 0.93	0.63	0.43, 0.92	-3.39	-7.65, 0.87
Gardening[d]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	4.0 (0-8.0)	0.67	0.46, 0.98	0.23	0.05, 0.95	0.50	0.29, 0.87	0.74	0.56, 0.97	0.89	0.57, 1.37	-1.13	-6.06, 3.81
High	18.0 (≥8.1)	1.03	0.72, 1.47	0.48	0.14, 1.56	0.61	0.35, 1.05	1.06	0.81, 1.4	0.73	0.45, 1.19	3.92	-1.21, 9.04
Sports[e]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	6.9 (0-14.9)	0.8	0.6, 1.07	1.32	0.68, 2.57	0.95	0.66, 1.38	0.88	0.69, 1.11	1.07	0.74, 1.54	-2.34	-6.78, 2.11
High	31.4 (≥15.0)	0.58	0.41, 0.82	1.43	0.59, 3.51	0.73	0.46, 1.17	0.62	0.48, 0.81	0.68	0.44, 1.05	-3.05	-7.79, 1.69

Abbreviations: CI, confidence interval; OR, odds ratio; T, tertile; VAS, visual analogue scale.

[a] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 7, 23 and 60 minutes per day of walking.

[b] Cycling is equivalent to 4.0 METs. The median levels of walking across categories are therefore equivalent to 0, 6 and 26 minutes per day of walking.

[c] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 0, 39 and 118 minutes per day of domestic work.

[d] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 39 minutes per day of gardening.

[e] Sports can consist of different intensities. The median levels of sports across categories are therefore equivalent to 0, 12 and 54 minutes per day of sports of 5 METs.

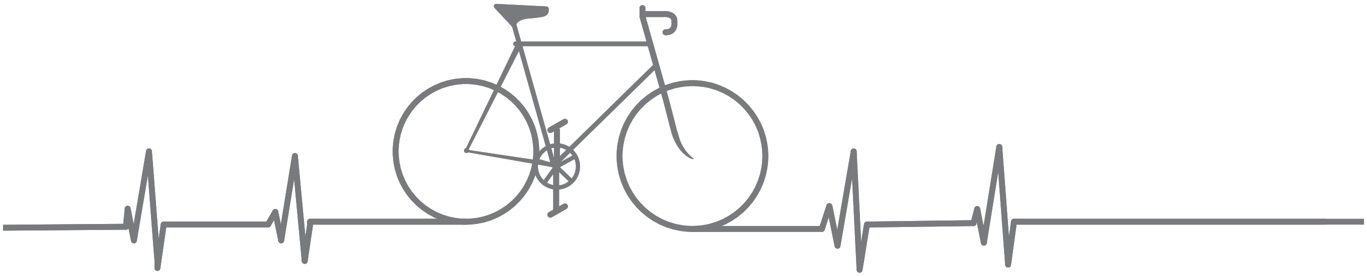
Supplement 5.1.13. Odds ratios and beta coefficients and their 95% confidence intervals for quality of life scores in adults older than 65 years, with comorbidities, for all physical activity types (n=1,615).

	Median MET·hours·week^{-1} (range)	Mobility		Self-care		Daily activities		Pain		Mood		VAS	
		OR	95% CI	OR	95% CI	OR	β	β	95% CI	OR	95% CI	β	95% CI
Walking[a]													
Low	2.3 (<4.5)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	7.5 (4.5-12.0)	0.60	0.46, 0.78	0.42	0.26, 0.67	0.58	0.42, 0.82	0.71	0.55, 0.90	0.60	0.41, 0.89	-0.10	-5.06, 4.86
High	21.0 (≥12.1)	0.41	0.31, 0.54	0.33	0.20, 0.55	0.52	0.37, 0.74	0.71	0.56, 0.91	0.86	0.60, 1.23	5.53	0.62, 10.44
Cycling[b]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	3.0 (0-6.0)	0.64	0.47, 0.87	0.24	0.10, 0.56	0.34	0.21, 0.55	0.72	0.55, 0.95	0.93	0.62, 1.41	3.02	-2.34, 8.38
High	12.0 (≥6.1)	0.60	0.43, 0.84	0.52	0.26, 1.03	0.35	0.21, 0.59	0.73	0.55, 0.96	0.79	0.51, 1.23	-0.22	-5.77, 5.32
Domestic work[c]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	13.1 (0-26.9)	0.96	0.73, 1.28	0.9	0.55, 1.49	1.24	0.87, 1.76	0.84	0.65, 1.08	0.76	0.50, 1.15	2.62	-2.45, 7.69
High	45.2 (≥27.0)	0.86	0.63, 1.16	0.78	0.44, 1.39	0.72	0.48, 1.08	0.85	0.65, 1.10	1.06	0.72, 1.56	1.10	-4.25, 6.45
Gardening[d]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	4.0 (0-8.0)	0.98	0.68, 1.42	0.87	0.42, 1.80	0.68	0.39, 1.17	0.86	0.62, 1.20	1.62	1.02, 2.56	-2.48	-9.01, 4.05
High	16.0 (≥8.1)	0.68	0.45, 1.04	0.45	0.16, 1.28	0.62	0.34, 1.14	1.23	0.88, 1.71	0.81	0.45, 1.44	-1.46	-8.08, 5.16
Sports[e]													
Low	0 (0)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent		Referent
Moderate	6.5 (0-14.9)	1.17	0.88, 1.55	1.01	0.60, 1.71	1.45	1.02, 2.08	0.90	0.69, 1.16	0.77	0.51, 1.15	0.69	-4.53, 5.92
High	29.2 (≥15.0)	0.78	0.55, 1.09	0.94	0.47, 1.87	0.74	0.45, 1.22	0.83	0.62, 1.10	0.91	0.59, 1.41	3.87	-1.83, 9.56

Abbreviations: CI, confidence interval; OR, odds ratio; T, tertile; VAS, visual analogue scale.
Abbreviations: CI, confidence interval; OR, odds ratio; T, tertile; VAS, visual analogue scale.
[a] Walking is equivalent to 3.0 METs. The median levels of walking across categories are therefore equivalent to 6, 21 and 60 minutes per day of walking.
[b] Cycling is equivalent to 4.0 METs. The median levels of walking across categories are therefore equivalent to 0, 6 and 26 minutes per day of walking.
[c] Average domestic work is equivalent to 3.5 METs.[1] The median levels of domestic work across categories are therefore equivalent to 0, 32 and 109 minutes per day of domestic work.
[d] Gardening is equivalent to 4.0 METs. The median levels of gardening across categories are therefore equivalent to 0, 9 and 34 minutes per day of gardening.
[e] Sports can consist of different intensities. The median levels of sports across categories are therefore equivalent to 0, 11 and 50 minutes per day of sports of 5 METs.

SUPPLEMENTARY REFERENCES

1. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011;43(8):1575-1581.



Chapter 5.2

Sedentary behavior measured by actigraphy and mental and cognitive health

Manuscript based on this chapter:
Koolhaas CM. van Rooij FJA, Kocevska D, Luik AI, Franco OH, Tiemeier H. Objectively measured sedentary time and mental and cognitive health: cross-sectional and longitudinal associations in The Rotterdam Study. *Submitted for publication*.

ABSTRACT

Introduction Based on studies using self-reported sitting time, sedentary behavior has been suggested as a risk factor for poor mental health and cognition. However, it remains unclear whether objectively measured sedentary behavior is longitudinally associated with depression, anxiety disorders or cognition.

Methods In the population-based Rotterdam Study, cross-sectional and longitudinal associations of objectively assessed sedentary time with depressive symptoms, anxiety disorders and cognition were assessed among 1,841 participants (mean follow-up: 5.7 years). Participants wore a wrist actigraph for seven days between 2004 and 2007 to assess sedentary time (hours/day). Depression, anxiety disorders and cognition were assessed twice between 2004 and 2014. Depressive symptoms were continuously measured with the Centre for Epidemiologic Studies-Depression scale (CES-D) and diagnoses of anxiety disorders (n=147) were obtained by interviews. Cognition was assessed using a test battery. Analyses were adjusted for age, sex, smoking, education, body mass index, occupational status, marital status, functional disability score, and physical activity.

Results One hour/day more sedentary time was cross-sectionally associated with 0.25 (95% confidence interval (95%CI): 0.08, 0.41) higher CES-D score, 1.11 (95%CI: 1.01, 1.21) higher odds of anxiety disorder, and 0.03 (95%CI: -0.05, -0.01) lower global cognition score. After adjustment for confounders, these associations no longer remained. Sedentary time at baseline was not associated longitudinally with changes in depressive symptoms, anxiety disorders and cognition.

Conclusions We found no support for an association between objectively measured sedentary behavior and impaired mental health or cognition. All observed associations were explained by confounders, in particular, disability, occupational status and smoking. The previously reported association between sitting time and mental health might reflect residual confounding, bias of subjective measures, or the social context of sedentary behavior.

INTRODUCTION

Sedentary behavior has been suggested as a risk factor for several chronic diseases, including cardiovascular disease, diabetes, poor mental health and low cognitive performance.[1] However, reviews of the effect of sedentary behavior on mental health and cognitive performance conclude this association is less conclusive, even though several studies have related higher levels of sedentary behavior to an increased likelihood of depression[2-4] anxiety disorders,[5,6] and worse cognition.[7,8]

There are important limitations to the studies included in these reviews and meta-analyses. First, most studies were cross-sectional,[3,4,6,8-10] making it impossible to determine whether high sedentary behavior leads to impaired mental health and cognition or the converse. Second, only a few studies adjusted for a measure of disability, which can be considered an important confounder in the association of sedentary behavior with mental health and cognition, certainly in a middle-aged or elderly population. Third, the majority of the studies included self-reported measures of sedentary behavior, which might be subject to the influence of perception, particularly in persons with problems related to depression, anxiety or cognition.[11] Moreover, these subjective measures of sedentary behavior typically address television viewing, computer use or occupational sitting as proxies of sedentary behavior. This practice, however, can influence the results,[12-15] as associations might be driven more by the social context than the sedentary behavior itself.[16] In summary, it remains unclear whether objectively measured sedentary behavior is longitudinally associated with depression, anxiety, and cognition.

In this population-based study, we examined the cross-sectional and longitudinal association of objectively measured sedentary behavior with depression, anxiety, and cognition, in older persons. Depression, anxiety and cognition were assessed twice over an average follow-up period of 5.7 years.

METHODS

Study population

This study was embedded in the Rotterdam Study, a prospective population-based cohort in the Netherlands, started in 1990. The aim of the study was to examine the incidence of psychiatric, neurological, cardiovascular, and other chronic diseases. Details of the study have been published elsewhere.[17]

From December 2004 to April 2007, 2,632 successive participants of the Rotterdam Study were invited to participate in the actigraphy study. The current study was conducted in 2,063 participants who agreed to participate (78%). The only requirement for participation was being able to understand the instructions for this study. To prevent missing data diluting our estimated hours of sedentary behavior per day, days with more than 3 hours of continuous missing data (133 days) were excluded.[18,19] We excluded 168 recordings with technical problems or that contained fewer than 4 days (see Figure 5.2.1). Additionally, sedentary data of 54 participants

(2.8%) with unusually low (<20% per day) or high (>90% per day) sedentary time was considered unreliable after visual inspection and therefore excluded. The 1,841 participants with data on sedentary behavior all had information on at least one of the 5 outcomes relating to mental health or cognition (Figure 5.2.1). More specifically, 1,488 participants (80.8%) had information on all 5 measures, 321 (17.4%) on 4 measures, 25 (1.4%) on 3 measures and 7 (0.4%) on 2 measures. The number (%) of individuals with an anxiety disorder at baseline was 147 (8.0%) and 22 (1.2%) were diagnosed with prevalent major depressive disorder (MDD). Since a diagnosis of MDD was conditional on information on depressive symptoms, MDD was not included in the flowchart.

All subjects provided written informed consent, and the study protocol was approved by the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center and by the review board of The Netherlands Ministry of Health, Welfare and Sports.

Measurement of sedentary time

Participants were asked to wear an actigraph around the non-dominant wrist (Actiwatch model AW4; Cambridge Technology, Cambridge, UK) for seven consecutive days and nights and to additionally complete a 7-day sleep diary to report overnight sleep periods. The actigraph had to be removed from the wrist for water-based activities only. Recordings were collected in 30-second intervals, during 24-hour periods.[20] Initially, the actigraph devices were introduced to the Rotterdam study to measure sleep in everyday life. The devices were therefore not calibrated to measure the level of physical activity and do not allow for comparison across individuals regarding physical activity. However, the actigraph device can validly measure active versus non-active intervals within a person. We can use these data as a proxy of sedentary behavior and test between person differences.[21]

To quantify sedentary time, we only used waking hours, based on bedtime and get up time. Bedtime and get up time were obtained from the event marker button on the actigraph for 9575 (88.1%) days. If these data were not present for a night, we obtained the information from the sleep diary (n=1265 days, 11.6%) or we estimated bedtime and get up time based on the previous days and the actigraphy pattern (n=24 days, 0.2%).[20] The time (hours/day) spent in sedentary behavior was determined using the standard count-based intensity threshold value of <199 counts per minute (cpm).[22]

Measurement of clinical outcomes

Depressive symptoms

At baseline (2004-2007) and the next follow-up measurement (2009-2014) depressive symptoms were assessed with the Dutch version of the Centre for Epidemiologic Studies Depression scale (CES-D),[23] a scale designed to assess presence and severity of self-reported depressive symptoms.[24] During the home interview, participants were asked 20 questions that correspond with criterion-based symptoms associated with depression and the summative scale ranges from score 0 to 60. A score of 16 or greater is traditionally accepted as cut-off to define clinical depression.[25]

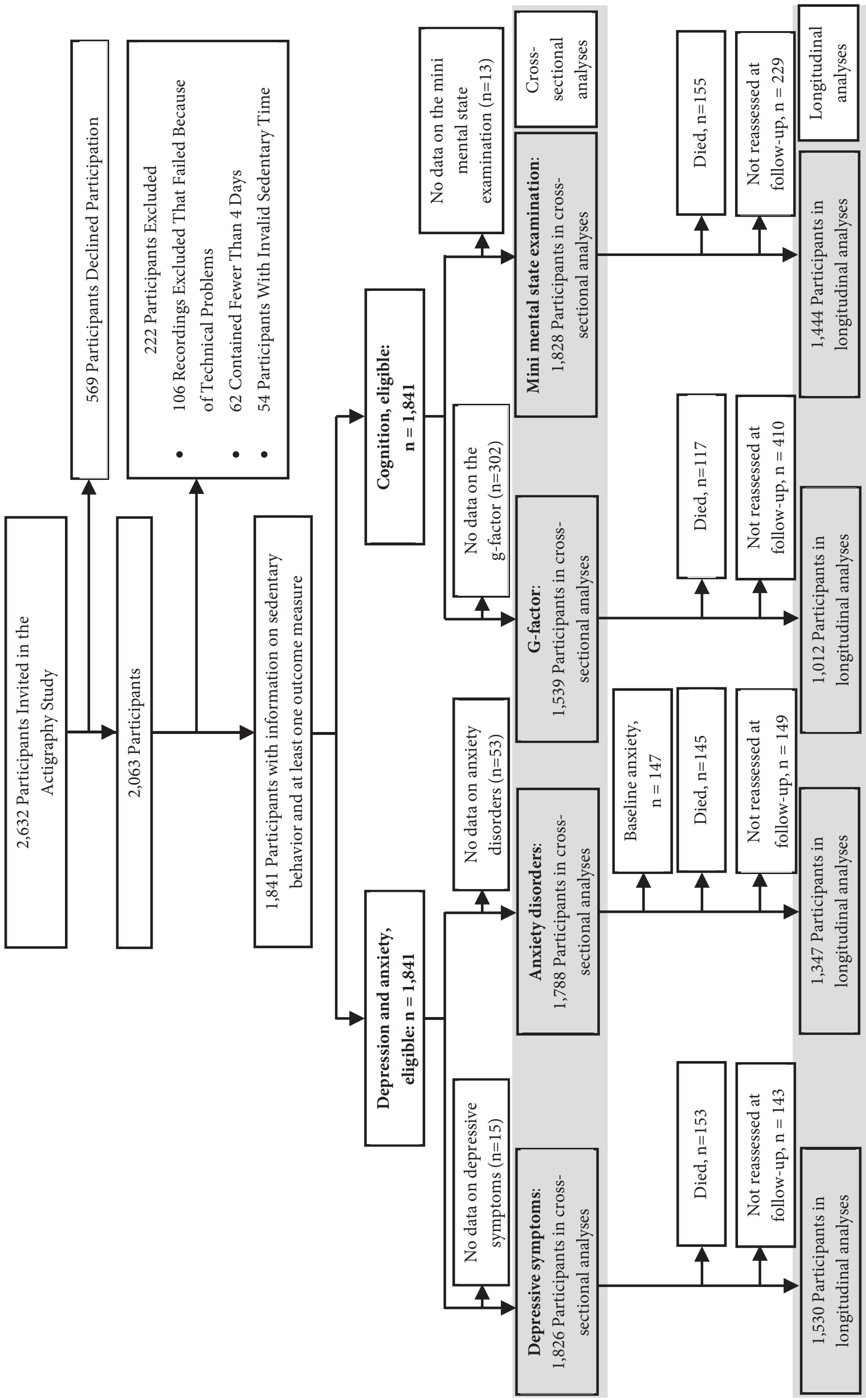


Figure 5.2.1. Flow chart of participant inclusion, the Rotterdam Study, 2004-2015

Depression diagnosis

Participants with a CES-D score of 16 or higher were invited for a semi-structured clinical interview with the Schedules for Clinical Assessment of Neuropsychiatry (SCAN),[26] an instrument commonly used to diagnose depression in older adults of the Dutch population.[27] The SCAN interview was conducted by a trained clinician at the participant's home. Using a digitalized algorithm of the DSM-IV, we considered a participant having an MDD when they met the condition for MDD according to the DSM-IV.

Anxiety disorders

The 12-month prevalence of 5 different anxiety disorders according to the DSM-IV-TR (Text Revision) Criteria[28] was assessed during the home interview, using an adapted version of the Munich version of the Composite International Diagnostic Interview (M-CIDI). The anxiety disorders under consideration were generalized anxiety disorder, panic disorder, agoraphobia, social phobia, and specific phobia as described previously.[29] Participants were classified as having an anxiety disorder if they had at least one of these anxiety disorders. The M-CIDI was designed specifically to obtain DSM-IV diagnoses of mental disorders. The test-retest reliability of using the M-CIDI for anxiety disorders is satisfactory.[30]

Cognitive function

A detailed assessment of cognitive function was obtained using a test battery during the research center visit. The tests included the mini mental state examination (MMSE), Stroop test (time in seconds taken for completing each of the following 3 tasks: word reading, color naming, and a reading/color naming interference task), the letter-digit substitution task (scored as the number of correct digits in 1 minute), the verbal fluency test (scored as the number of mentioned animal species within 1 minute), the 15-word learning test (recall and recognition of visually presented words), and the Purdue pegboard test for fine motor skills.[31] For the Purdue pegboard test, the scores from the right hand, left hand, and both hands were summed.

We calculated a general cognitive factor (g-factor) by performing principal component analyses incorporating the letter-digit substitution task, the verbal fluency test, 15-word learning delayed recall subtask, the inverse value of the Stroop color–word interference subtask and the sum of the Purdue pegboard scores. A higher g-factor indicates better performance. The g-factor explained 52.3% of all variance in cognitive tests at baseline and 51.6% at the follow-up measurement, which is in accordance with literature.[31]

Measurement of covariates

Information on covariates was collected through home interviews or measured at the study center, as described elsewhere.[32,33] For the current study, alcohol consumption was defined as the amount of glasses per day. Education was assessed in line with the international standard classification of education and classified as primary, lower, intermediate and higher education.[34] Smoking was categorized in three groups: current, former and never. Marital status was defined as living with a partner or not. Occupational status was used as a binary variable (employed/unemployed). Activities of daily living were measured with the Stanford Health Assessment Questionnaire and used to indicate the level of disability (i.e. disability score).[35] Height and weight were measured to calculate body mass index (BMI). The presence of coronary heart disease, diabetes, stroke and cancer were determined using medical records, to define the number of comorbidities. For part of the study population (n=870), physical activity was assessed at baseline with the validated LASA Physical Activity Questionnaire (LAPAQ).[36] In the remainder (n = 971) the LAPAQ was assessed in the next round of measurements and this assessment was used as a proxy for current physical activity levels at baseline. The LAPAQ included questions on housekeeping activities, walking, cycling, sports and gardening. Time spent in these activities was combined and expressed in MET·hours·week^{-1}.

Statistical analysis

Sedentary time was analyzed continuously (per one hour/day). Additionally, baseline characteristics were compared across three categories of sedentary behavior: 1) < 8 hours/day; 2) 8 - 11 hours/day; 3) ≥ 11 hours/day.[19]

To examine the cross-sectional and longitudinal associations of sedentary time with depressive symptoms, the g-factor and MMSE score, we used linear regression models. To examine the association of sedentary time with anxiety disorders and MDD, we used logistic regression models. We applied natural cubic splines to test for non-linearity of each of the models,[37] but found no evidence for a non-linear association of sedentary behavior with any outcome in any model. Covariates were included in the models based on previous research[2,5,7] or a 10% change in the effect estimate.[38] Based on these results, we did not include alcohol consumption and the number of comorbidities in our models.

For our cross-sectional analyses, we first created a basic model for all the outcomes (i.e. depressive symptoms, MDD, anxiety disorders, g-factor, MMSE score), including age, sex, cohort and time awake. In model 2, we additionally included sociodemographic and lifestyle factors, i.e. education, occupational status, marital status, smoking and BMI. In model 3, to examine the effect of sedentary behavior beyond physical activity and disability measures, we additionally adjusted for physical activity and the disability score. We examined the effect of adding each of these factors in the models, by computing the percentage change in the effect estimate for sedentary behavior after including the specific factor.

For the longitudinal analyses we also created 3 separate models in line with the cross-sectional analyses. To account for the longitudinal design, we additionally adjusted model 1 for the time between the baseline and the follow-up measurement and the baseline value of the outcome (for the analyses of depressive symptoms, g-factor or MMSE score). For our longitudinal analyses of anxiety disorders, we excluded prevalent cases at baseline from our analyses. Because incidence of MDD in participants without MDD at baseline was limited (n=7), we did not conduct the longitudinal analyses of MDD.

In sensitivity analyses, we examined the associations stratified by age (younger or older than 65 years old) and sex. We also repeated the analyses for depressive symptoms, g-factor and

MMSE-score with change (e.g. depressive symptoms at time point 2 - depressive symptoms at time point 1) as the outcome variable while not adjusting for baseline scores of the outcome variable. Finally, we performed cross-sectional analyses of the cognitive tests included in the g-factor.

Substantial data was missing for physical activity (24.5%) and the disability score (25.5%), other covariates had <2% missing data. We performed multiple imputations (n=20 imputations) using a Markov Monte Carlo imputation method. All analyses were conducted using SPSS software version 21 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp) and R (3.4.1).

Non-response analysis

When we compared participants who agreed to those who refused to wear an actigraph, we observed that the former were slightly older, more often men, had better scores for the g-factor and MMSE and had a lower disability score (Supplement 5.2.1).

RESULTS

Table 5.2.1 shows the baseline characteristics of the 1,841 participants included in the study according to categories of sedentary behavior. Mean age was 62.6 years (standard deviation (SD): 9.3), 54.4% of the sample was female, and the mean daily sedentary time was 8.8 hours (SD: 2.0), corresponding to 55.7% of the waking time. The mean (SD) follow-up time was 5.7 (0.6) years.

Sedentary behavior in association with depressive symptoms and MDD

In our cross-sectional analyses adjusted for age, sex, cohort and time awake (model 1), one hour more sedentary time was associated with 0.25 point higher CES-D score (95%CI: 0.08, 0.41) (Table 5.2.2). After additional adjustment for confounders in model 2, the effect estimate was slightly reduced (β: 0.18; 95%CI: 0.006, 0.34). The association was clearly attenuated after additional adjustment for activity variables in model 3 (β: 0.08; 95%CI: -0.09, 0.24). The change in the effect estimate was particularly large (54%) after adding the disability score to the model (Supplement 5.2.2A). Additionally, occupational status, marital status, and smoking were associated with changes in the effect estimate of more than 10%.

In our longitudinal analyses, we observed no association between sedentary time and the CES-D score in any model (Table 5.2.3). We also observed no cross-sectional association of sedentary behavior with MDD in any model (Table 5.2.2).

Table 5.2.1. Baseline participant characteristics by categories of sedentary time, the Rotterdam Study

	Categories of sedentary behavior, hours/day		
	< 8 hours	8-11 hours	≥ 11 hours
Demographics			
Participants, n (%)	637 (34.6)	958 (52)	246 (13.4)
Age	60.1 (8)	63.7 (9.5)	65.2 (10.6)
Female	419 (65.8)	478 (49.9)	104 (42.3)
Educational level, n (%)			
Primary education	56 (8.7)	71 (7.4)	27 (11)
Lower education	282 (44.3)	387 (40.3)	84 (34.1)
Intermediate education	182 (28.6)	291 (30.3)	82 (33.3)
Higher education	117 (18.4)	210 (21.9)	53 (21.5)
Employed, n (%)	262 (41.1)	293 (30.6)	68 (27.7)
Living with partner, n (%)	513 (80.5)	753 (78.6)	170 (69.1)
Lifestyle factors			
Smoking, n (%)			
Never	224 (35.2)	294 (30.7)	61 (24.8)
Former	327 (51.3)	489 (51.0)	127 (51.5)
Current	86 (13.5)	176 (18.3)	58 (23.7)
BMI (kg/m^2)	27.3 (4.0)	27.9 (4.1)	29.0 (4.8)
Disability score	0.3 (0.3)	0.3 (0.4)	0.4 (0.4)
Alcohol (glasses/day)	0.9 (1.1)	1.1 (1.3)	1.1 (1.4)
Physical activity (METhours/week)	68.8 (66.5)	57.3 (64.7)	50.2 (52.4)
Mental Health			
Baseline CESD score	5.2 (6.8)	5.5 (6.9)	5.7 (7.2)
Prevalent MDD, n (%)	6 (1.0)	13 (1.4)	3 (1.3)
Prevalent anxiety disorder, n (%)	50 (8.1)	77 (8.2)	20 (8.5)
Baseline g-factor	0.2 (0.9)	-0.1 (1.0)	-0.4 (1.1)
MMSE score	28.0 (1.8)	27.9 (2.0)	27.9 (1.8)
Prevalent diseases			
Prevalent diabetes, n (%)	65 (10.2)	142 (14.8)	52 (21.1)
Prevalent CHD, n (%)	25 (3.9)	52 (5.4)	27 (11)
Prevalent stroke, n (%)	10 (1.6)	31 (3.2)	6 (2.4)
Prevalent cancer, n (%)	74 (11.6)	105 (11.0)	35 (14.2)

Data are presented as means (SD), unless otherwise stated.
Abbreviations: BMI, body mass index; CESD, Center for Epidemiologic Studies Depression; CHD, coronary heart disease; MET, metabolic equivalent of task; MDD, major depressive disorder; MMSE, mini mental state examination

Sedentary behavior in association with anxiety disorders

Per one hour more sedentary time, the odds of having an anxiety disorder were 1.11 times higher (95%CI: 1.01, 1.21) when adjusted for age, sex, cohort and time awake only. However, after additional adjustment for lifestyle factors, the association did not remain (Table 5.2.2). Again, the change in the effect estimate was largest (26.9%) after inclusion of the disability score to the model. Additionally, physical activity, smoking, and BMI were associated with changes in the effect estimate of more than 10% (Supplement 5.2.2B).

We observed no longitudinal association between sedentary time and anxiety disorders (Table 5.2.3).

Table 5.2.2. Cross-sectional associations of objectively assessed sedentary time with depressive symptoms and anxiety disorders

	Depressive symptoms score (n=1,826)		Major depressive disorder* (n=1,817)		Anxiety disorders* (n=1,788)	
	β (95%CI)	p	β (95%CI)	p	OR (95%CI)	p
Per 1 hour/day more sedentary time						
Model 1	0.25 (0.08, 0.41)	0.004	1.17 (0.96, 1.44)	0.12	1.11 (1.01, 1.21)	0.03
Model 2	0.18 (0.01, 0.34)	0.04	1.14 (0.92, 1.41)	0.23	1.07 (0.98, 1.17)	0.15
Model 3	0.08 (-0.09, 0.24)	0.37	1.10 (0.88, 1.38)	0.41	1.04 (0.95, 1.14)	0.40

Abbreviations: CI, confidence interval; OR, odds ratio; ref, reference

* There were 22 participants with a major depressive disorder and 147 participants with an anxiety disorder.

Model 1 is adjusted for age, sex, cohort and time awake.

Model 2 is additionally adjusted for education, occupational status, marital status, smoking and body mass index.

Model 3 is additionally adjusted for physical activity and the disability score.

Table 5.2.3. Longitudinal associations of objectively assessed sedentary time with depressive symptoms and anxiety disorders

	Depressive symptoms score (n=1,530)		Anxiety disorders* (n=1,347)	
	β (95%CI)	p	OR (95%CI)	p
Per 1 hour/day more sedentary time				
Model 1	0.13 (-0.04, 0.31)	0.13	1.13 (0.99, 1.28)	0.08
Model 2	0.08 (-0.09, 0.26)	0.36	1.07 (0.93, 1.23)	0.33
Model 3	0.05 (-0.13, 0.23)	0.57	1.06 (0.92, 1.22)	0.42

Abbreviations: CI, confidence interval; OR, odds ratio; ref, reference

* There were 59 incident cases of anxiety disorders.

Model 1 is adjusted for age, sex, cohort and time awake, the time between the baseline and follow-up measurement and the baseline measurement of depression symptoms

Model 2 is additionally adjusted for smoking, education, body mass index, occupational status and marital status.

Model 3 is additionally adjusted for physical activity and the disability score.

Sedentary behavior in association with cognition: g-factor and MMSE score

In our cross-sectional analyses adjusted for age, sex, cohort and time awake, one hour more sedentary time was associated with 0.03 lower score for the g-factor (95%CI: -0.05, -0.01). Again, the association disappeared with additional adjustment for sociodemographic and lifestyle factors in model 2 and 3 (Table 5.2.4). Smoking, BMI and the disability score were all associated with large changes in the effect estimate (Supplement 5.2.2C).

In longitudinal analyses, we observed no association between sedentary time and the g-factor in any model (Table 5.2.5). We also observed no cross-sectional or longitudinal association between sedentary behavior and the MMSE-score (Table 5.2.4 – Table 5.2.5).

The cross-sectional analyses with the separate components of the g-factor showed a similar trend as the overall g-factor (Supplement 5.2.3).

Table 5.2.4. Cross-sectional associations of objectively assessed sedentary time with cognition

	G-factor, Z-score (n=1,539)		MMSE score (n=1,828)	
	β (95%CI)	p	β (95%CI)	p
Per 1 hour/day more sedentary time				
Model 1	-0.03 (-0.05, -0.01)	0.005	-0.01 (-0.06, 0.04)	0.66
Model 2	-0.02 (-0.04, 0.004)	0.12	-0.0017 (-0.05, 0.04)	0.94
Model 3	-0.01 (-0.03, 0.01)	0.23	-0.0004 (-0.05, 0.05)	0.98

Abbreviations: CI, confidence interval; MMSE, mini mental state examination; OR, odds ratio; ref, reference
Model 1 is adjusted for age, sex, cohort and time awake.
Model 2 is additionally adjusted for education, occupational status, marital status, smoking and body mass index.
Model 3 is additionally adjusted for physical activity and the disability score.

Table 5.2.5. Longitudinal associations of objectively assessed sedentary time with cognition

	G-factor, Z-score (n=1,012)		MMSE score (n=1,444)	
	β (95%CI)	p	β (95%CI)	p
Per 1 hour/day more sedentary time				
Model 1	-0.01 (-0.02, 0.01)	0.37	0.02 (-0.03, 0.06)	0.46
Model 2	-0.01 (-0.02, 0.01)	0.44	0.02 (-0.03, 0.06)	0.46
Model 3	-0.004 (-0.02, 0.01)	0.61	0.02 (-0.02, 0.07)	0.31

Abbreviations: CI, confidence interval; MMSE, mini mental state examination; OR, odds ratio; ref, reference
Model 1 is adjusted for age, sex, cohort and time awake, the time between the baseline and follow-up measurement and the baseline measurement of the g-factor or MSSE score.
Model 2 is additionally adjusted for smoking, education, body mass index, occupational status and marital status.
Model 3 is additionally adjusted for physical activity and the disability score.

Sensitivity analyses

In our sensitivity analyses stratified by age, we observed that the cross-sectional associations were driven by the oldest participants (> 65 years), but there were no apparent differences in the longitudinal analyses (Supplement 5.2.4 – Supplement 5.2.7). Furthermore, the sex-stratified analyses showed similar associations for men and women (Supplement 5.2.8 – Supplement 5.2.11). The analyses of sedentary behavior with change in depressive symptoms, the g-factor and MMSE-score also did not provide any support to reject the null hypothesis (Data not shown).

DISCUSSION

In this population-based cohort study, we found no evidence for a cross-sectional or longitudinal association of actigraphically assessed sedentary time with depressive symptoms, anxiety disorders or cognition. The observed cross-sectional associations between sedentary behavior and the mental health or cognitive outcome measures were explained by external factors. and were not observed longitudinally.

In several cross-sectional studies, associations of higher self-reported or objectively measured sedentary time with depression.[3,4] and anxiety,[6] and with impaired cognitive function[8] have been reported. In the current study, we also found that high levels of sedentary time were cross-sectionally associated with more depressive symptoms, worse cognitive performance, and higher odds for anxiety disorders. However, the associations were largely explained by other variables, including disability, smoking and occupational status.

In the associations between sedentary behavior and mental and cognitive health, the effect estimate for sedentary behavior changed notably after inclusion of the disability score. Having a disability increases the risk of worse mental health and cognition,[39-41] and higher levels of disability are associated with higher levels of sedentary behavior,[42] making disability an important factor to consider. In the association between sedentary behavior and mental health and cognition, we considered disability as a confounder; an antecedent of the exposure and the outcome, and not on the causal pathway.[43] However, it might be argued that prior sedentary behavior had led to disabilities, which in turn led to poor mental health and impaired cognition. Many scientists, such as Schisterman et al.,[44] have warned for overadjustment bias when analyses are adjusted for an intermediate variable that is on a causal pathway from the exposure to the outcome. However, we argue that it is more likely that in the elderly having physical disabilities will lead to more sedentary behavior than the converse. It is certainly important to understand the effect of sedentary tome above the effect of disease, thus it is important to include a measure of disability or functional limitations. However, only a few other studies have adjusted for a measure of disability in the association between sedentary behavior and mental health and cognition. In the recent meta-analysis of Zhai et al., which summarizes the association between sedentary behavior and depression, only 4 out of 20 studies adjusted for physical disability or perceived physical health.[2] In the meta-analysis of Falck et al.,[7] only 2 out of 8 studies adjusted for disability in the association between sedentary behavior and cognitive function. None of the studies in the meta-analyses of sedentary behavior and anxiety adjusted for disability.[5] We can only speculate whether previous studies might have been affected by (residual) confounding, but future studies examining the association between sedentary behavior and mental health should be aware of the possibility of residual confounding if not adjusting for by disability.

Other important confounders in the cross-sectional analyses were smoking and occupational status. Whereas most previous studies adjusted for these variables, others did not consider these factors in their analyses.[2,5,7] Unhealthy behaviors tend to cluster together,[45] and participants with higher levels of sedentary behavior were more often smokers in the current study. Since adults with poor mental health tend to smoke more than adults with better mental health status,[46] this makes smoking an important confounding factor in the association between sedentary behavior and mental health and cognition. Regarding employment, adults with paid occupation had lower levels of sedentary behavior in the current study and having employment is generally associated with having better mental health and cognition.[47]

In the longitudinal analyses, we observed no association between objectively measured sedentary behavior and depressive symptoms, anxiety or cognitive performance after a follow-up period of 5.7 years, whether disability and other confounders were accounted for or not. In contrast, previous longitudinal studies using self-reports provided support for effects of high sedentary time on poor mental health and cognitive performance,[2,5,7] next to the detrimental effects of prolonged sitting on cardio-metabolic features.[1] The follow-up time in previous studies ranged from 1 to 10 years, with most studies including 6 years of follow-up, similar to the current study.[12,48-56] Furthermore, the age-range of participants in previous studies is similar to the population in the current study. Therefore, it seems unlikely that these factors contribute to the inconsistent findings between studies. Instead, the explanation for these inconsistencies might be related to the measure of sedentary behavior. For self-report, there is a possibility of shared method variance bias or reporter bias.[57] In previous studies based on self-reported sedentary behavior, the information on the dependent and independent variable were both obtained from the same individual with subjective measures. Furthermore, with more objective methods, like actigraphy, all sedentary behavior during the day is captured, whereas questionnaires typically do not address sitting during breakfast, lunch or dinner.

Possibly, overall sedentary behavior does not underlie the observed association between self-reported sedentary behavior and mental health and cognition, rather the context of sedentary behavior. All of the studies observing a longitudinal association between sedentary behavior and mental health or cognition included watching television in their measure, whereas the studies using computer or internet use as a proxy for sitting time more often observed no association with mental health.[2,5,58,59] This suggests that not all types of sedentary behaviors are related to poor mental health and cognition. In contrast to the (socially) interactive character of computer/internet use, television viewing is a passive form of sedentary behavior. We cannot rule out that viewing television is an independent risk factor for poor mental health over and above sitting.

Taken together, the results of the current study suggest that sedentary behavior per se might not be related to impaired mental health and cognition and we found no support for a pathway from sedentary behavior to depression, anxiety or cognitive performance. However, since there is evidence that high levels of sedentary behavior are associated with worse cardiometabolic health,[1] public health efforts should continue encouraging adults to be active. Future studies using comprehensive questionnaires in addition to objective measures to capture sedentary behavior are recommended to better understand the association of sedentary behavior with mental health and cognition.

The strengths of this study are the objective measurement of sedentary behavior, the prospective population-based design and the relatively large sample size over a follow-up period of six years. However, several potential limitations must be acknowledged. Participants that agreed to wear an Actiwatch were more often men, showed a lower disability score and better cognitive performance than individuals not participating in the current study. This might affect the generalizability towards the total population of older adults. Furthermore, we did not analyze the length of the sitting bouts in the current study. Therefore, we were unable to provide information on the association of specific patterns of sedentary behavior with mental health. Moreover, in our longitudinal analyses, there might be some survival effect, since only those alive at follow-up could complete the next measurements of the mental health factors. Finally, other selection biases may have occurred, since participants with missing information on any of the outcome measures might be in worse health than those with complete information. For example, we could only compute the g-factor if all the cognitive tests were completed. Those with missing test scores for the cognitive test battery might be cognitively more compromised than those who completed all tests. However similar associations were seen when the respective cognitive tests were analyzed individually.

In conclusion, in this population of middle-aged and elderly adults, high levels of sedentary time were not associated with depressive symptoms, anxiety or cognition. Previously observed longitudinal associations might be driven by specific types of sedentary behavior or the subjective assessment of sedentary behavior.

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SUPPLEMENT CHAPTER 5.2

Supplement 5.2.1. Characteristics of participants who agreed to participate in the study compared to those who rejected participation

	Participants agreeing to participate	Participants not agreeing to participate	P value
Demographics			
Participants, n (%)	2,086	546	
Age	61.9 (9.4)	53.6 (4.4)	0.049
Female	1,146 (54.9)	328 (60.1)	0.04
Educational level, n (%)			0.07
Primary education	174 (8.4)	63 (11.6)	
Lower education	843 (40.7)	229 (42.2)	
Intermediate education	622 (30)	153 (28.2)	
Higher education	431 (20.8)	98 (18)	
Employed, n (%)	719 (34.8)	123 (23)	<0.001
Marital status, n (%)	1,598 (77.3)	346 (64.7)	<0.001
Lifestyle factors			
Smoking, n (%)			0.90
Never	649 (31.4)	170 (31.8)	
Former	1,037 (50.2)	263 (49.2)	
Current	380 (18.4)	102 (19.1)	
BMI (kg/m^2)	27.9 (4.3)	27.6 (4.2)	0.16
Disability score	0.35 (0.43)	0.49 (0.53)	<0.001
Alcohol (glasses/day)	1.1 (1.3)	1.2 (1.5)	0.14
Physical activity (METhours/week)	60.3 (61.7)	49.5 (45.7)	0.004
Mental Health			
Baseline CESD score	5.6 (7.1)	6.1 (7.5)	0.11
Prevalent MDD, n (%)	29 (1.4)	9 (1.7)	0.76
Prevalent anxiety disorder, n (%)	173 (8.6)	44 (8.5)	1.00
Baseline g-factor	0.06 (0.98)	-0.25 (1.05)	<0.001
MMSE score	27.9 (2.0)	27.4 (2.5)	<0.001
Prevalent diseases			
Prevalent diabetes, n (%)	285 (13.8)	89 (16.9)	0.09
Prevalent CHD, n (%)	112 (5.4)	47 (8.7)	0.005
Prevalent stroke, n (%)	54 (2.6)	30 (5.5)	0.001
Prevalent cancer, n (%)	245 (11.7)	90 (16.5)	0.004

Data are presented as mean (SD), unless otherwise stated.

Abbreviations: BMI, body mass index; CESD, Center for Epidemiologic Studies Depression; CHD, coronary heart disease; MET, metabolic equivalent of task; MDD, major depressive disorder; MMSE, mini mental state examination

Supplement 5.2.2A. The effect of adding covariates to the cross-sectional model between sedentary time and the CESD score

Factor added to the model*	β per 1 hour/day more sedentary time	(95%CI)	p	% Change from former to current β
NA (Model 1)	0.25	(0.08, 0.41)	0.004	na
+ Education	0.24	(0.08, 0.41)	0.004	1.0
+ Occupational status	0.22	(0.05, 0.38)	0.011	10.3
+ Marital status	0.19	(0.03, 0.36)	0.023	11.2
+ Smoking	0.17	(0.01, 0.34)	0.043	10.7
+ BMI	0.18	(0.01, 0.34)	0.043	-1.5
+ Physical activity	0.16	(-0.01, 0.33)	0.06	6.4
+ Disability score	0.08	(-0.09, 0.24)	0.37	53.6

Abbreviations: BMI, body mass index; CESD, Center for Epidemiologic Studies Depression; CI, confidence interval; na, not applicable

Model 1 is adjusted for age, sex, cohort and time awake.

* Each of the factors is added to the models in addition to the previous factors, so that the final model includes age, cohort, time awake, education, occupational status, marital status, smoking, BMI, physical activity and the disability score.

Supplement 5.2.2B. The effect of adding covariates to the cross-sectional model between sedentary time and anxiety disorders

Factor added to the model*	β per 1 hour/day more sedentary time	(95%CI)	p	% Change from former to current β
NA (Model 1)	0.10	(0.01, 0.19)	0.026	na
+ Education	0.10	(0.01, 0.19)	0.025	-0.3
+ Occupational status	0.09	(0.01, 0.18)	0.038	6.3
+ Marital status	0.09	(-0.002, 0.18)	0.06	7.8
+ Smoking	0.07	(-0.02, 0.16)	0.11	14.5
+ BMI	0.07	(-0.02, 0.16)	0.15	10.2
+ Physical activity	0.05	(-0.04, 0.15)	0.24	17.8
+ Disability score	0.04	(-0.05, 0.13)	0.40	26.9

Abbreviations: BMI, body mass index; CI, confidence interval; na, not applicable; OR, odds ratio

Model 1 is adjusted for age, sex, cohort and time awake.

* Each of the factors is added to the models in addition to the previous factors, so that the final model includes age, cohort, time awake, education, occupational status, marital status, smoking, BMI, physical activity and the disability score.

Supplement 5.2.2C. The effect of adding covariates to the cross-sectional model between sedentary time and the g-factor

Factor added to the model	β per 1 hour/day more sedentary time	(95%CI)	p	% Change from former to current β
NA (Model 1)	-0.031	(-0.05, -0.01)	0.005	na
+ Education	-0.034	(-0.05, -0.01)	0.002	-7.7
+ Occupational status	-0.03	(-0.05, -0.01)	0.005	10.3
+ Marital status	-0.029	(-0.05, -0.01)	0.007	4.5
+ Smoking	-0.022	(-0.04, -0.001)	0.043	25.4
+ BMI	-0.017	(-0.04, 0.004)	0.12	22.5
+ Physical activity	-0.017	(-0.04, 0.004)	0.12	-0.4
+ Disability score	-0.013	(-0.03, 0.01)	0.23	22.3

Abbreviations: BMI, body mass index; CI, confidence interval; na, not applicable
Model 1 is adjusted for age, sex, cohort and time awake.
* Each of the factors is added to the models in addition to the previous factors, so that the final model includes age, cohort, time awake, education, occupational status, marital status, smoking, BMI, physical activity and the disability score.

Supplement 5.2.3. Cross-sectional associations of objectively assessed sedentary time with g-factor sub-components

	Model 1			Model 2			Model 3		
	β (95% CI) associated with 1 hour/day more sedentary time		p	β (95% CI) associated with 1 hour/day more sedentary time		p	β (95% CI) associated with 1 hour/day more sedentary time		p
Outcome variable									
Stroop test	-0.0002	(-0.0003, -0.0001)	0.004	-0.0001	(-0.0003, 0.00002)	0.09	-0.0001	(-0.0003, 0.00002)	0.11
Letter-digit substitution task	-0.14	(-0.30, 0.01)	0.06	-0.09	(-0.23, 0.06)	0.26	-0.05	(-0.20, 0.10)	0.51
Verbal fluency test	-0.15	(-0.29, -0.02)	0.03	-0.12	(-0.25, 0.02)	0.09	-0.09	(-0.23, 0.05)	0.19
15-word learning test	-0.06	(-0.13, 0.01)	0.08	-0.05	(-0.12, 0.02)	0.18	-0.04	(-0.11, 0.03)	0.23
Purdue pegboard test	-0.10	(-0.21, -0.002)	0.05	-0.05	(-0.15, 0.06)	0.38	-0.01	(-0.11, 0.10)	0.87

Abbreviations: CI, confidence interval; MMSE, mini mental state examination; OR, odds ratio; ref, reference
Model 1 is adjusted for age, cohort and time awake.
Model 2 is additionally adjusted for education, occupational status, marital status, smoking and body mass index.
Model 3 is additionally adjusted for physical activity and the disability score.

Supplement 5.2.4. Cross-sectional associations of objectively assessed sedentary time with depressive symptoms and anxiety disorders, stratified by age

Adults < 65 years	Depressive symptoms score (n=1,184)			Anxiety disorders* (n=1,163)		
	β	(95%CI)	p	OR	(95%CI)	p
Per 1 hour/day more sedentary time						
Model 1	0.18	(-0.03, 0.40)	0.09	1.09	(0.98, 1.21)	0.10
Model 2	0.10	(-0.12, 0.31)	0.37	1.04	(0.94, 1.16)	0.43
Model 3	0.05	(-0.16, 0.26)	0.62	1.03	(0.92, 1.15)	0.62

Adults ≥ 65 years	Depressive symptoms score (n=642)			Anxiety disorders* (n=625)		
	β	(95%CI)	p	OR	(95%CI)	p
Per 1 hour/day more sedentary time						
Model 1	0.35	(0.08, 0.62)	0.01	1.15	(0.97, 1.36)	0.12
Model 2	0.27	(-0.004, 0.55)	0.05	1.13	(0.94, 1.35)	0.20
Model 3	0.13	(-0.14, 0.40)	0.33	1.08	(0.90, 1.31)	0.40

Abbreviations: CI, confidence interval; OR, odds ratio; ref, reference
There were 103 prevalent cases with an anxiety disorder in adults < 65 years and 44 in adults ≥ 65 years.
Model 1 is adjusted for age, sex, cohort and time awake.
Model 2 is additionally adjusted for education, occupational status, marital status, smoking and body mass index.
Model 3 is additionally adjusted for physical activity and the disability score.

Supplement 5.2.5. Longitudinal associations of objectively assessed sedentary time with depressive symptoms and anxiety disorders, stratified by age

Adults < 65 years	Depressive symptoms score (n=1,044)			Anxiety disorders* (n=923)		
	β	(95%CI)	p	OR	(95%CI)	p
Per 1 hour/day more sedentary time						
Model 1	0.12	(-0.08, 0.32)	0.24	1.12	(0.97, 1.29)	0.13
Model 2	0.06	(-0.15, 0.27)	0.57	1.07	(0.92, 1.24)	0.37
Model 3	0.04	(-0.17, 0.25)	0.68	1.07	(0.92, 1.24)	0.40

Adults ≥ 65 years	Depressive symptoms score (n=486)			Anxiety disorders* (n=424)		
	β	(95%CI)	p	OR	(95%CI)	p
Per 1 hour/day more sedentary time						
Model 1	0.09	(-0.23, 0.42)	0.57	NA		
Model 2	0.02	(-0.31, 0.36)	0.90	NA		
Model 3	-0.01	(-0.35, 0.32)	0.95	NA		

Abbreviations: CI, confidence interval; NA, not applicable due to limited number of cases; OR, odds ratio; ref, reference
*There were 51 incident cases of anxiety disorders in adults <65 years and 8 cases in adults ≥ 65 years.
Model 1 is adjusted for age, sex, cohort and time awake, the time between the baseline and follow-up measurement and the baseline measurement of depression symptoms
Model 2 is additionally adjusted for smoking, education, body mass index, occupational status and marital status.
Model 3 is additionally adjusted for physical activity and the disability score.

Supplement 5.2.6. Cross-sectional associations of objectively assessed sedentary time with cognition, stratified by age

Adults < 65 years	G-factor, Z-score (n=1,013)			MMSE score (n=1,182)		
	β	(95%CI)	p	β	(95%CI)	p
Per 1 hour/day more sedentary time						
Model 1	-0.02	(-0.04, 0.01)	0.21	0.002	(-0.05, 0.05)	0.94
Model 2	-0.01	(-0.03, 0.02)	0.52	0.001	(-0.05, 0.05)	0.98
Model 3	-0.01	(-0.03, 0.02)	0.57	-0.003	(-0.05, 0.05)	0.92

Adults ≥ 65 years	G-factor, Z-score (n=526)			MMSE score (n=646)		
	β	(95%CI)	p	β	(95%CI)	p
Per 1 hour/day more sedentary time						
Model 1	-0.06	(-0.10, -0.02)	0.001	-0.04	(-0.13, 0.05)	0.42
Model 2	-0.03	(-0.07, 0.01)	0.11	0.004	(-0.09, 0.10)	0.94
Model 3	-0.02	(-0.06, 0.01)	0.21	0.01	(-0.08, 0.11)	0.77

Abbreviations: CI, confidence interval; MMSE, mini mental state examination; OR, odds ratio; ref, reference
Model 1 is adjusted for age, sex, cohort and time awake.
Model 2 is additionally adjusted for education, occupational status, marital status, smoking and body mass index.
Model 3 is additionally adjusted for physical activity and the disability score.

Supplement 5.2.7. Longitudinal associations of objectively assessed sedentary time with cognition, stratified by age

Adults < 65 years	G-factor, Z-score (n=740)			MMSE score (n=999)		
	β	(95%CI)	p	β	(95%CI)	p
Per 1 hour/day more sedentary time						
Model 1	-0.01	(-0.03, 0.01)	0.33	0.01	(-0.03, 0.06)	0.52
Model 2	-0.01	(-0.03, 0.01)	0.33	0.01	(-0.03, 0.06)	0.54
Model 3	-0.01	(-0.03, 0.01)	0.48	0.02	(-0.03, 0.06)	0.47

Adults ≥ 65 years	G-factor, Z-score (n=272)			MMSE score (n=445)		
	β	(95%CI)	p	β	(95%CI)	p
Per 1 hour/day more sedentary time						
Model 1	0.01	(-0.03, 0.04)	0.63	0.06	(-0.05, 0.18)	0.28
Model 2	0.01	(-0.02, 0.05)	0.50	0.08	(-0.04, 0.20)	0.18
Model 3	0.01	(-0.02, 0.05)	0.50	0.09	(-0.03, 0.22)	0.13

Abbreviations: CI, confidence interval; MMSE, mini mental state examination; OR, odds ratio; ref, reference
Model 1 is adjusted for age, sex, cohort and time awake, the time between the baseline and follow-up measurement and the baseline measurement of the g-factor or MSSE score.
Model 2 is additionally adjusted for smoking, education, body mass index, occupational status and marital status.
Model 3 is additionally adjusted for physical activity and the disability score.

Supplement 5.2.8. Cross-sectional associations of objectively assessed sedentary time with depressive symptoms and anxiety disorders, stratified by sex

Men	Depressive symptoms score (n=832)			Anxiety disorders* (n=826)		
	β	(95%CI)	p	OR	(95%CI)	p
Per 1 hour/day more sedentary time						
Model 1	0.26	(0.05, 0.48)	0.02	1.01	(0.84, 1.22)	0.89
Model 2	0.26	(0.04, 0.48)	0.02	0.98	(0.80, 1.19)	0.82
Model 3	0.16	(-0.06, 0.39)	0.15	0.93	(0.76, 1.15)	0.52

Women	Depressive symptoms score (n=994)			Anxiety disorders* (n=962)		
	β	(95%CI)	p	OR	(95%CI)	p
Per 1 hour/day more sedentary time						
Model 1	0.24	(-0.01, 0.48)	0.06	1.13	(1.02, 1.25)	0.02
Model 2	0.12	(-0.13, 0.37)	0.34	1.09	(0.98, 1.21)	0.11
Model 3	0.01	(-0.23, 0.26)	0.91	1.06	(0.96, 1.18)	0.26

Abbreviations: CI, confidence interval; OR, odds ratio; ref, reference
There were 33 men with a prevalent anxiety disorder and 114 women with a prevalent anxiety disorder.
Model 1 is adjusted for age, cohort and time awake.
Model 2 is additionally adjusted for education, occupational status, marital status, smoking and body mass index.
Model 3 is additionally adjusted for physical activity and the disability score.

Supplement 5.2.9. Longitudinal associations of objectively assessed sedentary time with depressive symptoms and anxiety disorders, stratified by sex

Men	Depressive symptoms score (n=692)			Anxiety disorders* (n=652)		
	β	(95%CI)	p	OR	(95%CI)	p
Per 1 hour/day more sedentary time						
Model 1	0.09	(-0.12, 0.30)	0.39	1.09	(0.80, 1.49)	0.58
Model 2	0.06	(-0.16, 0.27)	0.60	1.07	(0.76, 1.51)	0.68
Model 3	0.04	(-0.18, 0.26)	0.72	1.06	(0.75, 1.51)	0.73

Women	Depressive symptoms score (n=838)			Anxiety disorders* (n=696)		
	β	(95%CI)	p	OR	(95%CI)	p
Per 1 hour/day more sedentary time						
Model 1	0.17	(-0.09, 0.43)	0.21	1.14	(0.99, 1.32)	0.07
Model 2	0.11	(-0.16, 0.38)	0.43	1.09	(0.94, 1.27)	0.25
Model 3	0.07	(-0.20, 0.34)	0.61	1.08	(0.93, 1.26)	0.32

Abbreviations: CI, confidence interval; NA, not applicable due to limited number of cases; OR, odds ratio; ref, reference
There were 11 men with an incident anxiety disorder and 48 women with an incident anxiety disorder.
Model 1 is adjusted for age, cohort and time awake, the time between the baseline and follow-up measurement and the baseline measurement of depression symptoms
Model 2 is additionally adjusted for smoking, education, body mass index, occupational status and marital status.
Model 3 is additionally adjusted for physical activity and the disability score.

Supplement 5.2.10. Cross-sectional associations of objectively assessed sedentary time with cognition, stratified by sex

Men	G-factor, Z-score (n=686)			MMSE score (n=834)		
	β	95%CI	p	β	95%CI	p
Per 1 hour/day more sedentary time						
Model 1	-0.03	(-0.06, 0.001)	0.06	-0.04	(-0.111, 0.03)	0.24
Model 2	-0.02	(-0.05, 0.01)	0.25	-0.03	(-0.10, 0.03)	0.33
Model 3	-0.02	(-0.05, 0.01)	0.23	-0.03	(-0.10, 0.04)	0.42

Women	G-factor, Z-score (n=853)			MMSE score (n=994)		
	β	95%CI	p	β	95%CI	p
Per 1 hour/day more sedentary time						
Model 1	-0.03	(-0.06, -0.001)	0.045	0.01	(-0.05, 0.07)	0.65
Model 2	-0.02	(-0.05, 0.01)	0.26	0.03	(-0.03, 0.09)	0.41
Model 3	-0.01	(-0.04, 0.02)	0.49	0.03	(-0.04, 0.09)	0.41

Abbreviations: CI, confidence interval; MMSE, mini mental state examination; OR, odds ratio; ref, reference

Model 1 is adjusted for age, cohort and time awake.

Model 2 is additionally adjusted for education, occupational status, marital status, smoking and body mass index.

Model 3 is additionally adjusted for physical activity and the disability score.

Supplement 5.2.11. Longitudinal associations of objectively assessed sedentary time with cognition, stratified by sex

Men	G-factor, Z-score (n=451)			MMSE score (n=658)		
	β	(95%CI)	p	β	(95%CI)	p
Per 1 hour/day more sedentary time						
Model 1	-0.01	(-0.04, 0.01)	0.35	0.01	(-0.06, 0.09)	0.71
Model 2	-0.01	(-0.04, 0.01)	0.32	0.01	(-0.07, 0.08)	0.81
Model 3	-0.01	(-0.03, 0.02)	0.54	0.02	(-0.06, 0.09)	0.65

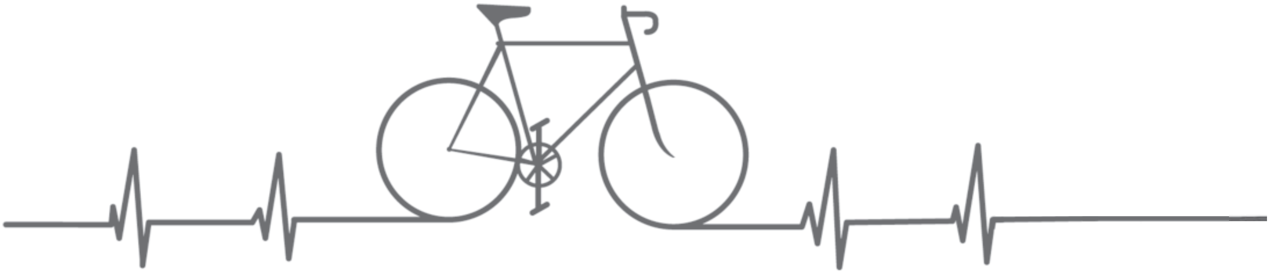
Women	G-factor, Z-score (n=561)			MMSE score (n=786)		
	β	(95%CI)	p	β	(95%CI)	p
Per 1 hour/day more sedentary time						
Model 1	-0.003	(-0.02, 0.02)	0.80	0.02	(-0.04, 0.07)	0.56
Model 2	-0.001	(-0.02, 0.02)	0.90	0.02	(-0.04, 0.07)	0.61
Model 3	-0.001	(-0.02, 0.02)	0.96	0.02	(-0.04, 0.08)	0.46

Abbreviations: CI, confidence interval; MMSE, mini mental state examination; OR, odds ratio; ref, reference

Model 1 is adjusted for age, cohort and time awake, the time between the baseline and follow-up measurement and the baseline measurement of the g-factor or MSSE score.

Model 2 is additionally adjusted for smoking, education, body mass index, occupational status and marital status.

Model 3 is additionally adjusted for physical activity and the disability score.



Chapter 5.3

The bidirectional association between objectively measured sleep and body mass index

Manuscript based on this chapter:

Koolhaas CM*, Kocevska D*, te Lindert BHW, Erler NS, Franco OH, Tiemeier H, Luik AI. The bidirectional association between objectively measured sleep and body mass index: The Rotterdam Study. *Submitted for publication.*

ABSTRACT

Background: Based on cross-sectional and longitudinal studies using self-reports , short sleep is considered a risk factor for obesity. It remains unknown whether the association is bidirectional.

Methods: We studied the bidirectional association between sleep measured by a wrist-worn actigraph, and body size in the population-based Rotterdam Study. Body mass index (BMI), actigraphic total sleep time (TST), sleep onset latency (SOL), sleep efficiency (SE) and wake after sleep onset (WASO) were measured twice between 2004 and 2014 (n=1,031, age: 45-91 years, median follow-up: 6 years). Cross-sectional associations of sleep with BMI were examined with linear regressions adjusted for lifestyle and health parameters. Longitudinal associations were explored with linear mixed models.

Results: Cross-sectionally, each hour shorter TST was associated with approximately 0.5kg/m^2 higher BMI. Longitudinally, average longer sleep duration and higher sleep efficiency were associated with lower BMI, and a slower decrease in BMI across time. Conversely, one point higher average BMI was associated with a 0.02 hours (95% confidence interval: -0.03,-0.01) shorter TST, reduced the yearly increase in TST by 0.002 hours, and reduced the yearly increase in SE by 0.02%. A 1 kg/m^2 increase in BMI across the follow-up was associated with 0.23 hours longer TST (95%CI: 0.04,0.41).

Conclusion: In this population of older adults there was a clear bidirectional association between sleep and BMI over a follow-up of 6 years. Although sleep has been implied as an important determinant of body size, a healthy BMI also relates to better sleep indices in an age group with increasing sleep problems.

INTRODUCTION

Sleep has been identified as a potentially modifiable factor related to mental and physical health.[1,2] Short sleep duration has been associated with higher body weight and obesity.[3] This has given rise to the idea that chronic sleep curtailment contributes to the developing obesity epidemic.[4]

Systematic reviews of observational studies examining the association between sleep duration and adiposity[3,5] concluded that short sleep is associated with an increased risk of obesity.[3] Based on these findings, the hypothesis that short and disturbed sleep has a direct influence on energy metabolism leading to weight gain has been postulated.[6] However, studies assessing the association between sleep and obesity have important methodological limitations. First, studies have mostly been cross-sectional, thus the temporality of the relation cannot be explored.[3,5] Second, prospective studies have relied on self-reported measures, prone to information and recall bias.[7]

Adiposity might also influence sleep. Few studies have examined the hypothesis that the association between sleep and adiposity is bidirectional.[8-10] One study using self-reports concluded that higher a BMI predicts a decrease in sleep duration over time, but not vice versa.[11] To overcome these limitations, prospective studies using objectively measured sleep and body composition are required.

We evaluated the direction of the association of actigraphic sleep patterns with BMI, in a population-based prospective cohort of older persons. Objective measures of sleep and BMI were assessed twice over a follow-up of 6 years.

METHODS

Study population

This study was embedded in the Rotterdam Study, an ongoing prospective population-based cohort in the Netherlands.[12] Participants undergo extensive follow-up examinations approximately every 5 years.[13,14]

For the baseline of our study (T1: December 2004 to April 2007), 2,632 participants were invited to participate in the actigraphy study, 2,063 (78%) agreed to participate.[15,16] Due to technical issues (n=125), valid data was available for 1,938 participants at baseline. Of the 1,431 participants invited for a follow-up measurement (T2: March 2009 to June 2014), valid sleep data on at least 4 consecutive days and BMI data in both waves was available for 1,031 individuals (details in Supplement 5.3.1). There were no exclusion criteria besides being able to understand the instructions for this study. All subjects gave written informed consent, and the study protocol was approved by the medical ethics committee according to the Wet Bevolkingsonderzoek ERGO (Population Study Act Rotterdam Study), executed by the Ministry of Health, Welfare and Sport of The Netherlands.

Measurement of sleep

At baseline, all participants wore an actigraph around the non-dominant wrist (Actiwatch model AW4; Cambridge Technology, Cambridge, UK) for seven consecutive days and nights. The device had to be removed for water-based activities. At follow-up, participants wore either the Actiwatch (n=592), or a GeneActiv triaxial accelerometer (Activinsights Ltd, Kimbolton, Cambridgeshire, UK) (n= 439). Recordings were sampled at 32Hz (Actiwatch) and 50Hz (GeneActiv), and were averaged into a score for each 30-second interval, taking into account weighted values of previous and following epochs. To ensure comparability between the estimates of the two devices, we used a validated algorithm to convert the triaxial GeneActiv to one-dimensional 30s epoch data (using the z-axis), that was thereafter calibrated to Actiwatch counts using Passing-Bablok regression.[17]

To estimate sleep, we used an algorithm validated against polysomnography at the highest sensitivity (sleep threshold <20 counts).[7,18] Sleep diaries were used to determine sleep-wake schedules (bedtime, wake-time and get-up time), and were used as an event marker by the sleep algorithm. A night's data was considered invalid if recording had failed due to technical issues, the participant had discontinued wearing the actigraph, or if the information on bedtime and get-up time from the sleep diary were invalid or missing. The assumed sleep period was defined as the time between sleep onset and final wake-time estimated by the algorithm,[7,17,18] and the following sleep parameters were calculated: 1) Total sleep time (TST, hours): the sum of the number of epochs in the assumed sleep period scored as sleep, multiplied by the epoch length; 2) Sleep onset latency (SOL, minutes): time between bed time according to the sleep diary and the estimated sleep onset; 3) Sleep efficiency (SE, %): ratio of TST to time in bed (time between bedtime and wake-time) multiplied by 100; and 4) Wake after sleep onset (WASO, minutes), defined as the number of epochs within the assumed sleep period scored as wake multiplied by the epoch length.

Anthropometric measurements

Height and weight were measured by trained staff in the research center with the participants standing without shoes and heavy outer garments on a calibrated scale. BMI was calculated as weight divided by height squared (kg/m^2).

Measurement of covariates

Education was assessed in line with the international standard classification of education [19] and grouped into primary education, lower education, intermediate education and higher education. Employment status was used as a binary variable (employed/unemployed). Smoking was categorized as: current, former and never. Physical activity was assessed with the validated LASA Physical Activity Questionnaire,[20] including questions on housekeeping activities, walking, cycling, sports and gardening. Time spent in these activities was combined and expressed in MET·hours·week^{-1}.[21] The presence of cardiovascular disease, diabetes and cancer were determined using medical records. We defined a binary variable for the presence of any of these chronic diseases. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression (CES-D) scale,[22] excluding the question on restless sleep in the score. Frequency of napping was defined as the number of days the participant had napped during the actigraphy assessment, as reported in the sleep diary.[15]. As a proxy of sleep disordered breathing (SDB), one item of the Pittsburgh Sleep Quality Questionnaire[23] was used to assess the frequency of respiratory pauses during sleep.

Statistical Analyses

Missing values on covariates were less than 10%, except for frequency of SDB at T1 (19%) and frequency of SDB at T2 (17.9%). We imputed missing data using fully conditional specification multiple imputation (m=20 imputations). Statistical analyses were performed on each imputed data set, and results were pooled.[24]

Cross-sectional associations between sleep parameters (TST, SOL, SE and WASO) and BMI were tested using linear regression at baseline and at follow-up in a model correcting for several covariates (see tables). The decision to include covariates was based on previous literature[16,25,26] or >10%-change of the effect estimate in the crude model.[27]

We used linear mixed models to examine whether sleep parameters were associated with BMI across time, and vice versa, whether BMI was associated with sleep parameters across time, corrected for covariates. All models included the time between the baseline and follow-up measurement of the outcome variable in years, the average of the determinant across the two measurements (i.e., $(TST_{T2}+TST_{T1})/2$ and $(BMI_{T2}+BMI_{T1})/2$), the yearly change in the determinant (i.e., $(TST_{T2}-TST_{T1})$/follow-up time and $(BMI_{T2}-BMI_{T1})$/follow-up time), and interaction terms between the average and the change in the determinant and follow-up time (e.g. [average TST]*time and [ΔTST]*time or [average BMI]*time and [ΔBMI]*time). To account for the correlation between measurements of the same individual we included a random intercept based on (adapted) likelihood ratio tests. The final linear mixed model equations are presented in Supplement 5.3.2.

In the linear mixed models, the effect estimate of the average captures how average levels of the determinant influence the trajectory of the outcome across time. The effect estimate of the change captures how changes in levels of the determinant influence the trajectory of the outcome across time. The interaction terms capture changes of the observed associations with time.

Analyses were conducted using SPSS software version 21.0 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp) and R (Version 3.4.1).[28]

Sensitivity analyses.

We repeated all longitudinal analyses stratified by sex.[29,30] Since we included information from two different devices in our study, we stratified the analyses by device at follow-up (GeneActiv or Actiwatch). For nonresponse analyses, participants included in the analyses were compared to those who refused to participate or were lost to follow up (n=754), based on several demographic and health characteristics (i.e. age, sex, depressive symptom score, sleep parameters and BMI) using chi-squared, Mann-Whitney U tests, or independent sample t-tests.

RESULTS

Characteristics of the study population are shown in Table 5.3.1. At baseline, mean age was 60.6 years (standard deviation (SD): 7.7) and 52.0% were women. Mean (SD) BMI was 27.9 (4.3) kg/m^2 at T1, and 27.6 (4.3) kg/m^2 at T2. The median time difference between the two visits was 6 years (range 5 to 9 years).

Table 5.3.1. Characteristics of the study population, Rotterdam Study, 2004-2014

	T1: December 2004 - April 2007	T2: March 2009 – June 2014
Participants, n (%)	1,031	1,031
Age (years)	60.6 (7.7)	66.8 (7.9)
Female, n (%)	535 (52.0)	555 (52.0)
BMI (kg/m^2)	27.9 (4.3)	27.6 (4.3)
Total sleep time (hours)	6.0 (0.9)	6.2 (0.9)
Sleep onset latency (minutes)	20.8 (17.7)	18.3 (16.8)
Sleep efficiency (%)	74.8 (8.6)	75.5 (8.6)
Education, n (%)*		
Primary education	71 (6.9)	NA
Lower education	403 (39.1)	NA
Intermediate education	311 (30.2)	NA
Higher education	246 (23.9)	NA
Employed, n (%)	385 (37.3)	284 (27.5)
Prevalent chronic disease, n (%)	289 (28.0)	383 (37.2)
Smoking, n (%)		
Non smoker	328 (31.8)	345 (33.5)
Former smoker	538 (52.2)	564 (54.7)
Current smoker	165 (16.0)	121 (11.7)
Physical activity (METhours/week)*	NA	64.6 (65.4)
CES-D score†	4.3 (6.2)	4.7 (6.6)
Self-reported frequency of sleep disordered breathing , n (%)		
Not in the past month	845 (82.0)	837 (81.2)
Less than once per week	63 (6.1)	76 (7.4)
Once or twice per week	67 (6.5)	56 (5.4)
More than twice per week	56 (5.4)	62 (6.0)
Number of days with a nap, n (%)	1.5 (1.9)	1.6 (1.9)

Data are presented as mean (SD), unless otherwise stated.
Abbreviations: BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression; MET, metabolic equivalent of task; NA, not applicable; T, time point; WC, waist circumference.
*Education was only assessed at baseline and physical activity only at follow-up.
† The CES-D score did not include the question on restless sleep.

Cross-sectional analyses

In cross-sectional analyses, one hour longer TST was associated with approximately 0.5 kg/m^2 lower BMI at T1 and T2 (see Table 5.3.2). At T2, one percent higher SE was associated with 0.04 kg/m^2 (95%CI: -0.07, -0.01) lower BMI (Table 5.3.2). We observed no associations for SOL and WASO.

Longitudinal analyses: sleep parameters predicting BMI across time

In longitudinal analyses with sleep indices as the exposure variables, we found that on average longer sleep duration and higher sleep efficiency are associated with lower BMI (main effects for average sleep parameters in Table 5.3.3 and Figure 5.3.1a and 5.3.1b). We also observed that the average yearly decrease in BMI of 0.20 kg/m^2 in the elderly (Figure 5.3.1; and effect of time in Table 5.3.3) is reduced by 0.02 kg/m^2 (95%CI: 0.003, 0.05) with every hour longer average sleep duration, and by 0.002 kg/m^2 (95% CI: 0.00002, 0.005) with every 1% higher sleep efficiency. In other words, habitually longer and more efficient sleep is associated with a slower decrease in BMI across time (less steep slopes of dotted lines compared to solid lines in Figure 5.3.1).

In addition, a yearly 1% decrease in sleep efficiency was associated with 0.22 (95%CI: -0.40, -0.03) kg/m^2 higher BMI across time (effect of ΔSE in Table 5.3.3). An increase in WASO over time reversed the slope of BMI, resulting in an increase in BMI across time (dotted lines versus solid lines in Figure 5.3.1d). Changes in TST and SOL across the follow up were not associated with BMI.

Table 5.3.2. Cross-sectional associations of objective sleep with body mass index (kg/m^2) at two time points, Rotterdam Study, 2004-2014

N=1031	Associations at T1 (December 2004 - April 2007)			Associations at T2* (March 2009 - June 2014)		
	B	95% CI	*P*-value	B	95% CI	*P*-value
TST, hours	-0.51	-0.81, -0.21	0.001	-0.58	-0.87, -0.29	<0.001
SOL†, min	0.01	-0.01, 0.02	0.25	0.01	-0.003, 0.03	0.11
SE, %	-0.01	-0.04, 0.02	0.36	-0.04	-0.07, -0.01	0.008
WASO, min	0.002	-0.008; 0.012	0.70	0.005	-0.005; 0.015	0.34

Abbreviations: BMI, body mass index; SE, sleep efficiency; SOL, sleep onset latency; T, time point; TST, total sleep time, WASO, wake after sleep onset.

Models are adjusted for sex, age, cohort, smoking, education, employment, prevalent chronic disease(s), CES-Depression score, self-reported frequency of sleep disordered breathing, and frequency of napping

*Additionally adjusted for physical activity and actigraphy device (Actiwatch or GeneActiv)

† SOL was log-transformed for analyses

Longitudinal analyses: BMI predicting sleep parameters across time

Longitudinal analyses with BMI as exposure variable are shown in Table 5.3.4. One point higher average BMI was associated with a 0.02 hours (95%CI: -0.03, -0.01) shorter TST. However, an increase in BMI across the follow-up was associated with 0.23 hours longer TST (95%CI: 0.04, 0.41) per kg/m^2, but was not related to the other sleep parameters.

Table 5.3.3. Actigraphically measured sleep parameters predicting BMI

	BMI (kg/m^2)Total Sleep Time (hours)	
	β	95% CI
1. Total sleep time (TST), hours		
Average TST	-0.75	-1.08, -0.42
Δ TST	-1.63	-3.57, 0.30
Time, years	-0.20	-0.34, -0.07
Average TST & Time Interaction	0.03	0.003, 0.05
Δ TST & Time Interaction	-0.05	-0.18, 0.08
2. Sleep efficiency (SE), %		
Average SE	-0.04	-0.08, -0.01
Δ SE	-0.22	-0.41, -0.03
Time, years	-0.22	-0.40, -0.05
Average SE & Time Interaction	0.002	0.00002, 0.005
Δ SE & Time Interaction	-0.008	-0.02, 0.005
3. Sleep onset latency (SOL), minutes		
Average SOL	0.40	-0.02, 0.82
Δ SOL	0.08	-1.81, 1.98
Time, years	-0.03	-0.12, 0.05
Average SOL & Time Interaction	-0.01	-0.03, 0.02
Δ SOL & Time Interaction	-0.02	-0.15, 0.11
4. Wake after sleep onset (WASO), minutes		
Average WASO	0.004	-0.01, 0.02
Δ WASO	0.01	-0.05, 0.08
Time, years	-0.03	-0.08, 0.02
Average WASO & Time Interaction	-0.0004	-0.001, 0.0004
Δ WASO & Time Interaction	0.005	0.00003, 0.01

β's are derived from linear mixed models. Time is expressed as 0=baseline and $Date_{BMI\_T2}$ – $Date_{BMI\_T1}$=follow-up, average BMI is expressed as (BMI_{T2} + BMI_{T1})/2, Delta BMI is expressed as (BMI_{T2} - BMI_{T1})/follow-up time.

The interaction term estimates how the effects of the average of the sleep parameter and time depend on each other.

Models are adjusted for sex, age, cohort, actigraphy device at follow-up, smoking, education, employment, prevalent chronic disease(s), depressive symptoms, self-reported frequency of sleep disordered breathing, and frequency of napping

† SOL was log-transformed in analyses.

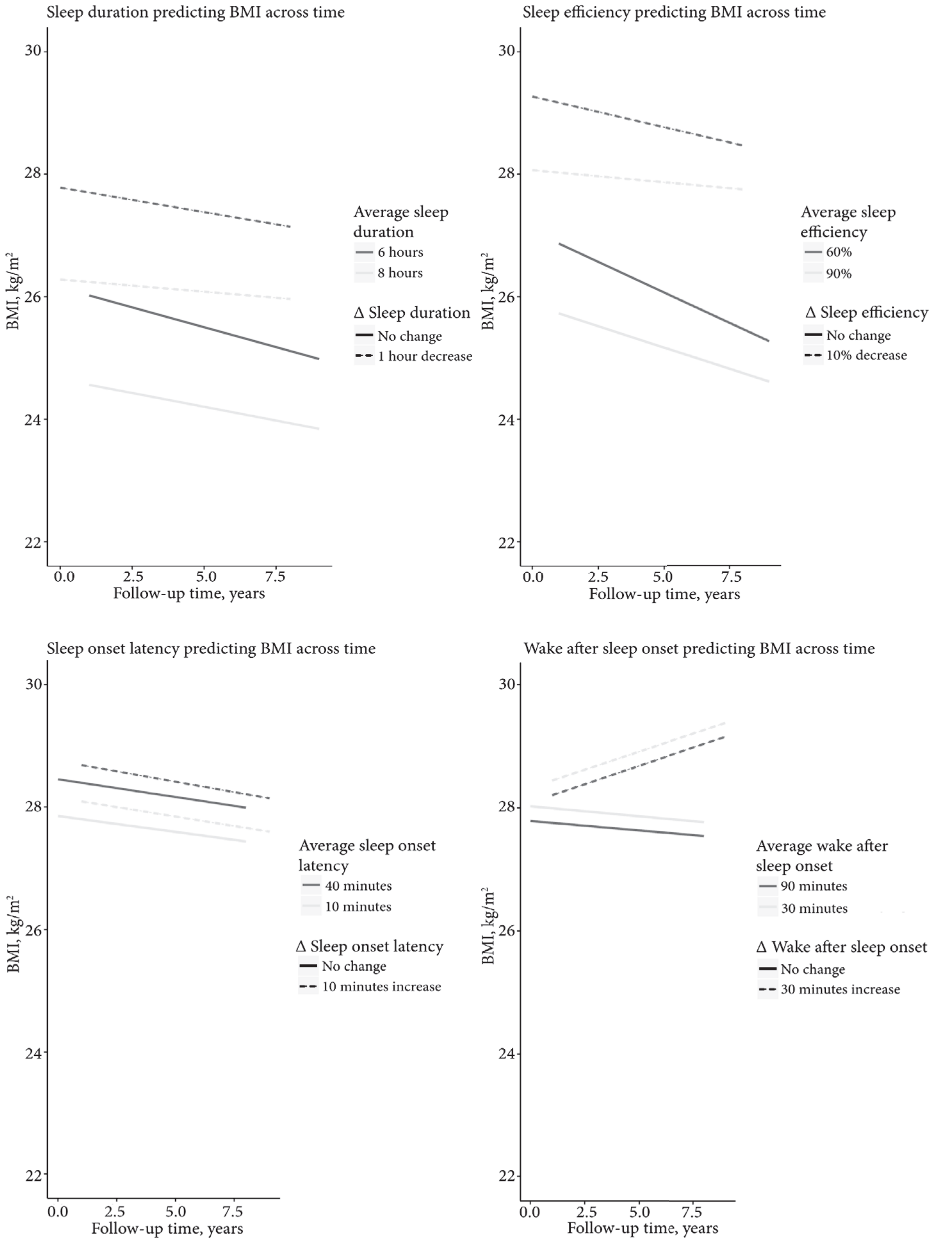


Figure 5.3.1. Actigraphically measured sleep parameters predicting body mass index across time

Abbreviations: BMI, body mass index; TST, total sleep time in hours; SE, sleep efficiency in %; WASO, wake after sleep onset in minutes; SOL, sleep after onset latency in minutes.

Light grey indicates "poor sleep" (e.g. TST=6 hours, SE=60%, SOL=40minutes, WASO=90minutes), Dark grey indicates "good sleep" (e.g. TST=8 hours, SE=90%, SOL=10minutes, WASO=30minutes). Dotted lines indicate a worsening of sleep parameters relative to the respective color (e.g. ↓1 hour TST, ↓ 10% SE, ↑10minutes SOL, ↑30minutes WASO). Estimates are representative for a non-smoking, high-educated male of 61 years old, with no sleep disordered breathing or other comorbidities, and average level of physical activity and depressive symptoms.

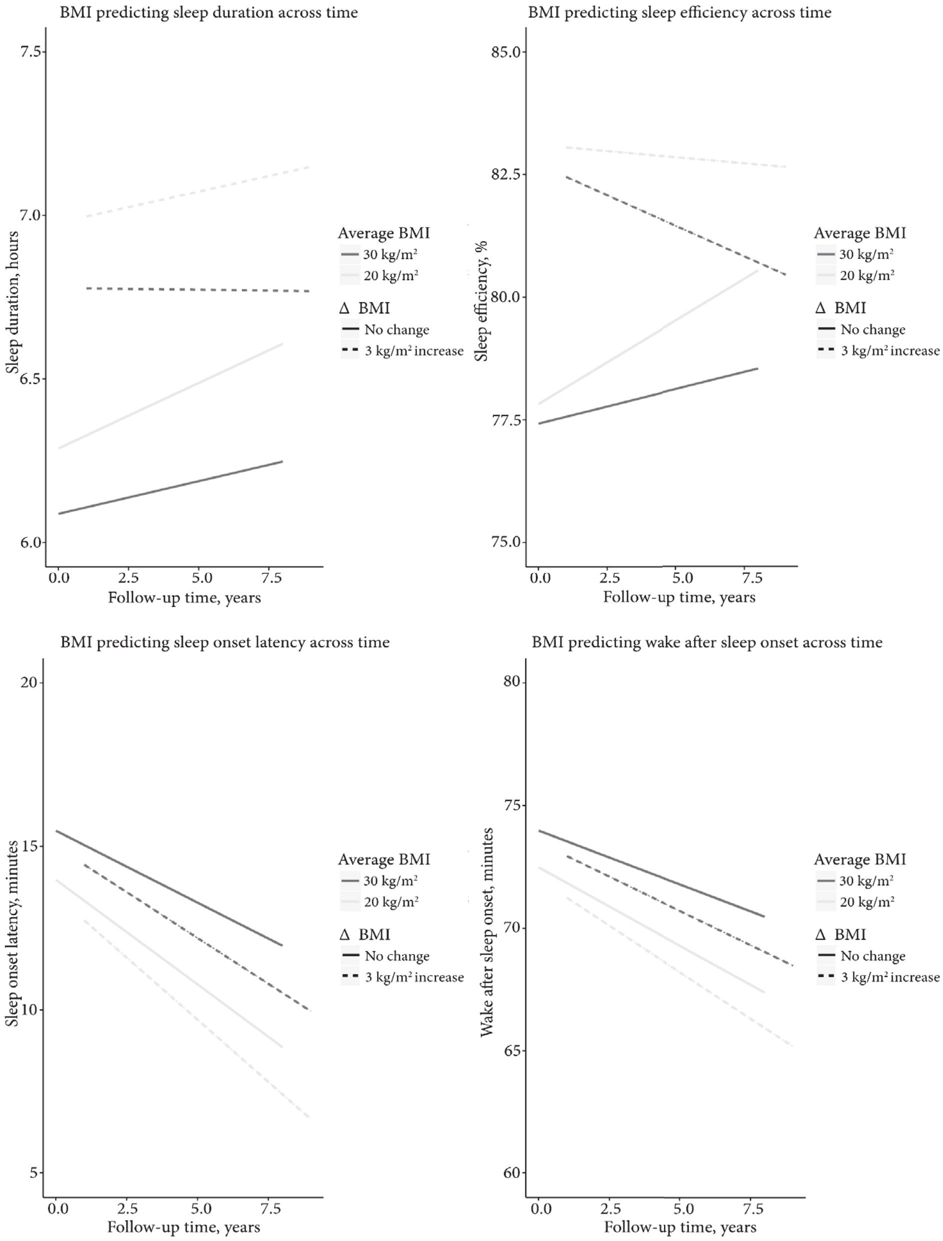


Figure 5.3.2. Body mass index predicting actigraphically measured sleep parameters across time

Abbreviations: BMI, body mass index; TST, total sleep time in hours; SE, sleep efficiency in %; WASO, wake after sleep onset in minutes; SOL, sleep after onset latency in minutes.

Light grey represents the estimates for a BMI of 30 kg/m^2, dark grey represents the estimates of 20 kg/m^2, and dotted lines indicate 3 points decrease from the respective color. Estimates are for a non-smoking, high-educated male of 61 years old, with no sleep disordered breathing or other comorbidities, average physical activity and depressive symptoms level.

In our elderly population, actigraphically assessed sleep duration and efficiency increased over the follow-up (effect of time; Table 5.3.4). However, a high average BMI had a negative effect on this relation. That is, a one point higher average BMI reduced the yearly increase in TST by 0.002 hours, and SE by 0.02% (interaction between average BMI and time; Table 5.3.4). In other words, the negative effect that average BMI has on sleep parameters becomes more pronounced over time ($\beta_{TST*TIME}$=-0.002, (95%CI: -0.004, -0.00002) and $\beta_{SE*TIME}$=-0.02, (95%CI: -0.04, -0.004)). Sleep patterns across time for normal weight and obese person are visually presented in Figure 5.3.2. Interestingly, an increase in 3 points for a person with BMI of 30 kg/m^2 (a shift from overweight to obese) resulted in a decrease in SE over time (Figure 5.3.2b).

Sensitivity analyses

Results were similar across the sexes (Supplement 5.3.3 – Supplement 5.3.4), and across the two actigraphy devices (Supplement 5.3.5 – Supplement 5.3.7). The nonresponse analysis indicated that participants included in the study were more likely to be highly educated (χ^2=12.855, *P*=0.005), but did not differ from those lost to follow up regarding age, sex, depressive symptom score, any of the sleep parameters or baseline BMI.

Table 5.3.4. BMI predicting actigraphically measured sleep parameters

	Total sleep time (TST), hours		Sleep efficiency (SE), %		Sleep onset latency (SOL), minutes		Wake after sleep onset (WASO), minutes	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Average BMI (kg/m^2)	-0.02	-0.03, -0.005	-0.04	-0.17, 0.08	0.01	-0.003, 0.02	0.02	-0.36, 0.40
Δ BMI (kg/m^2)	0.23	0.04, 0.41	1.76	-0.05, 3.58	0.002	-0.15, 0.16	-4.01	-9.44, 1.41
Time (years)	0.08	0.03, 0.14	0.74	0.20, 1.29	-0.02	-0.08, 0.03	-1.14	-2.70, 0.42
Average BMI & Time Interaction	-0.002	-0.004, -0.0002	-0.02	-0.04, -0.004	0.00002	-0.002, 0.002	0.03	-0.03, 0.08
Δ BMI & Time Interaction	-0.007	-0.03, 0.02	-0.13	-0.42, 0.15	-0.003	-0.03, 0.03	0.69	-0.12, 1.50

β's are derived from linear mixed models. Time is expressed as 0=baseline and $Date_{BMI\_T2}$ – $Date_{BMI\_T1}$=follow-up, average BMI is expressed as (BMI_{T2} + BMI_{T1})/2, Delta BMI is expressed as (BMI_{T2} - BMI_{T1})/follow-up time. The interaction term estimates how the effects of average BMI and time depend on each other.
Models are adjusted for sex, age, cohort, actigraphy device at follow-up, smoking, education, employment, prevalent chronic disease(s), depressive symptoms, self-reported frequency of sleep disordered breathing, and frequency of napping
† SOL was log-transformed in analyses.

DISCUSSION

In this population-based cohort, we replicated the strong cross-sectional associations of short and disturbed sleep with higher BMI found in previous studies. In longitudinal analyses, we found evidence for a complex bidirectional association between sleep and body size in the elderly. Actigraphic indices of good sleep (e.g. longer average sleep duration and higher average sleep efficiency), predicted a lower BMI across time. Additionally, a longer sleep duration and higher sleep efficiency slowed down the decrease in BMI across time observed in our elderly population. Converesly, a high average BMI was associated with shorter sleep duration over time. Higher BMI also had a negative effect on the changes in sleep duration and efficiency observed in our elderly population (e.g. obese participants had a decrease in sleep efficiency, as opposed to normal weight who had an increase over the follow-up).

Multiple cross-sectional studies reported that short and fragmented sleep is associated with high BMI and obesity.[16,29,31-33] Supported by evidence from longitudinal studies using subjective measures of sleep, short sleep is increasingly recognized as a potential risk factor for obesity.[34] Previous studies have also reported both short and long self-reported sleep duration to be associated with higher BMI.[35,36] However, in a study among 612 older adults, Lauderdale et al. observed no association of objectively measured sleep duration and fragmentation with changes in BMI.[25] Our prospective findings show that actigraphic indices of good sleep (e.g. longer average sleep duration and higher average sleep efficiency), as well as an increase in sleep efficiency over the follow-up, predicted a lower BMI across time. Additionally, indices of good sleep also slowed down the general decrease in BMI in the elderly over time. One of the factors that might contribute to the differences between studies is the age of the participants. It has been reported that the association between sleep and BMI differs with age,[31] and very few studies in elderly populations have been performed.[37,38] Compared to younger adults, older adults often have more difficulties sleeping,[39] and might have more chronic diseases or different body composition.[40] Our observation that longer sleep duration slows down the decrease in BMI might be specific to older adults. Longer sleep duration and a slightly higher BMI might be proxies for good health in the elderly, since weight loss at older age is often associated with disease. Other factors related to long sleep and high BMI, such as reduced physical activity or depression might also contribute to this association.[41] Longer sleep measured with actigraphy may be a proxy of or associated with long periods of inactivity (i.e. awake in bed or sedentary time) leading to a slower decrease in BMI. However, our results could not be explained by controlling for these variables. Further, we cannot rule out that a residual confounder leads to higher BMI and longer sleep duration (e.g. genetic predisposition, stress, sleep disorders etc.).

Many studies focused on the effect of sleep on weight or BMI, whereas the converse association has gained less attention. Only one previous study explored the direction of this association using subjective sleep measures.[11] The authors reported that a higher BMI predicted a decrease in sleep duration over time, but not vice versa.[11] We demonstrated that high BMI was associated with shorter objectively measured sleep duration, and vice versa short and inefficient sleep was related to higher BMI across time. This indicates that previous cross-sectional studies reporting strong relations between short or disturbed sleep and higher BMI might have been affected by reverse causality (e.g. high BMI might lead to short sleep). Importantly, we showed that high BMI reduces any increase in sleep duration and efficiency over time. For example, if a 61 year old overweight (30kg/m^2) became obese (33 kg/m^2), a steep reduction in sleep efficiency was observed over the follow-up. In contrast, a person of the same age with normal weight (20kg/m^2) a 3 kg/m^2 increase in BMI was paralleled with a slight increase in sleep efficiency over time.

The mechanisms underlying the association between obesity and sleep might be related to health status, as chronically ill people are more likely to experience sleep difficulties or disturbances.[42] However, adjustments for chronic diseases and other health-related variables did not meaningfully change our results. Finally, people with higher BMI are also more likely to snore or experience symptoms of SDB symptoms, which in turn can result in shorter and more fragmented sleep.[43] Almost 20% of our sample reported they have experienced long breathing pauses during sleep. Some of these persons may suffer from sleep apnea, which is likely to partly explain the longitudinal associations between high BMI and short or disturbed sleep.

To the best of our knowledge, there are no other observational studies exploring how changes in sleep parameters influence BMI, or vice versa, how changes in body size influence sleep. Some intervention studies examined the effect of weight loss on sleep,[8-10,44] reporting that weight loss programs result in an increase self-reported sleep duration.[8,10] In our study, an increase in BMI across the follow-up was related to longer sleep duration, but not with other sleep parameters. In the converse relation, only an increase in sleep efficiency was related to lower BMI across time. We measured sleep objectively in a general population of older persons. These associations confirm that the relation between sleep and body size is bidirectional, and regardless of the unestablished causality changes in either sleep or BMI are likely influence health through multiple pathways.

Major strengths of our study are the prospective design with repeated measures of sleep and BMI across a follow-up of 6 years in a large sample of older adults from the general population. In contrast to the only previous longitudinal BMI study which measured sleep objectively,[25] next to repeated anthropometric measures, we also had repeated measures of sleep, allowing us to accurately estimate average between-subject differences in both directions of the association. The longitudinal design of the study allowed us to explore changes over time, and to explore reverse causality, which may influence associations observed in cross-sectional studies.

We acknowledge that our study has some methodological limitations. First, we did not have an objective measure of SDB, but relied on self-report. Furthermore, we only had information on the presence and not on the severity of chronic diseases. These two limitations might give rise to some degree of residual confounding. In our follow-up measurement we used two different devices to measure sleep, which might result in increased measurement error. In addition, our nonresponse analysis indicated that participants included in the study were more likely to highly educated, and this association might differ in populations with different socio-demographic characteristics. Furthermore, BMI does not indicate how the fat is distributed across the body. Nevertheless, BMI has been shown to be a reasonably good measure to assess adiposity.[45]

Conclusions

In conclusion, in this population of older adults there was a clear bidirectional association between sleep and body size across a follow-up of 6 years. Good sleep (e.g. longer sleep duration, higher sleep efficiency) predicted a lower BMI across time. Conversely, high BMI was associated with shorter sleep duration across time. We also observed that long and efficient sleep slowed down the decrease in BMI in the elderly. Vice versa, a high BMI had a negative influence on sleep parameters across time (e.g. obese older adults show a decrease in sleep efficiency over time, whereas older adults with normal weight have an increase). Furthermore, an increase in sleep efficiency was related to lower BMI, whereas an increase in BMI was related to a longer sleep duration. The findings from our general population sample suggest that sleep and body size have a complex intertwined relation to health in older adults. Although sleep has been implied as an important determinant of body size, a healthy BMI is also associated with better sleep indices in an age group with increasing sleep problems and disturbances.

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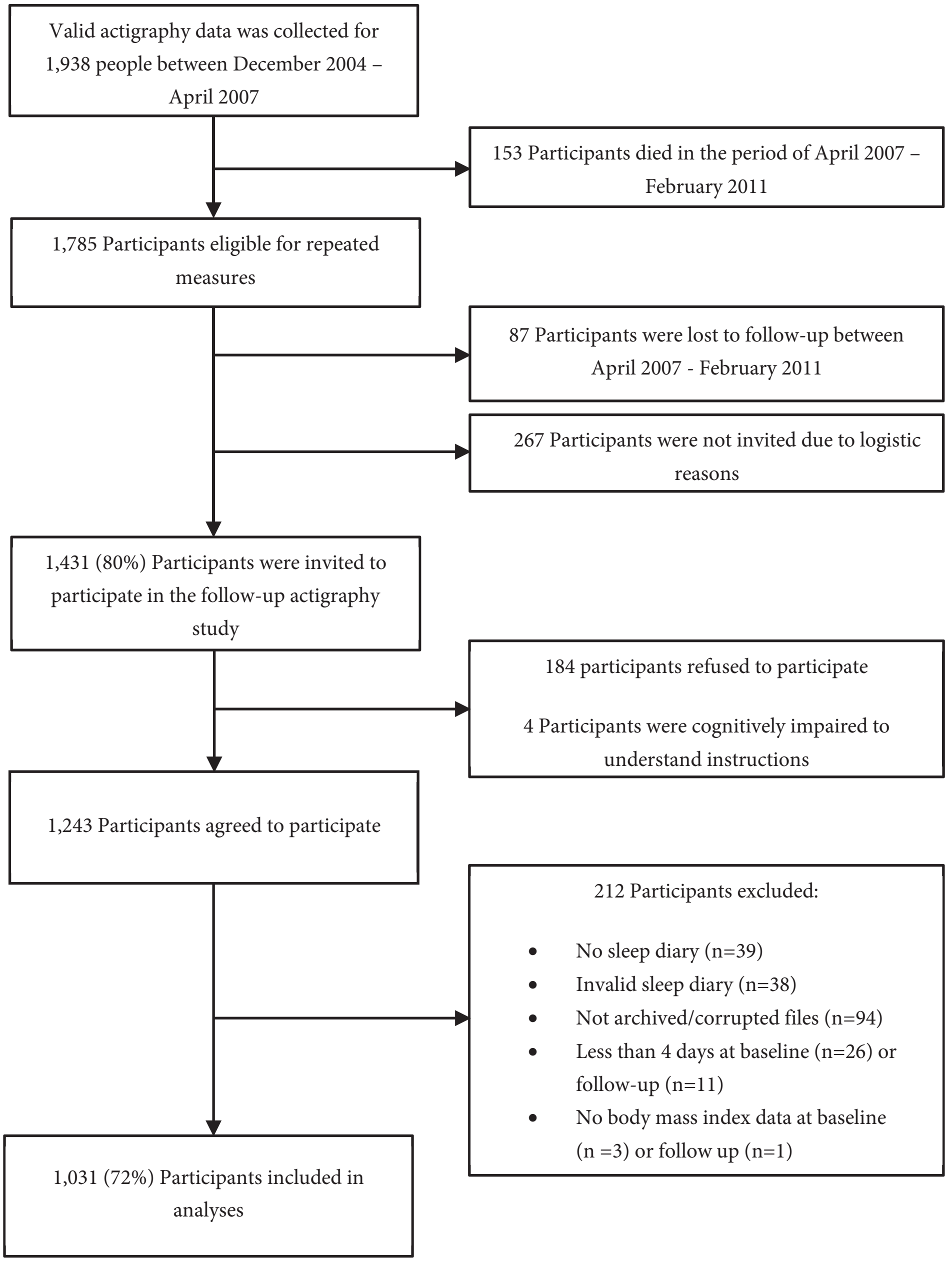
SUPPLEMENT CHAPTER 5.3

Supplement 5.3.1. Flow chart of repeated sleep measures in the Rotterdam Study, 2004-2014



Supplement 5.3.2. Linear Mixed Models equations

Association	**Equation**
TST predicts BMI	$BMI_{ij}= (\beta_0 + b_{i0}) + \beta_1 TST\_delta_i + \beta_2 TST\_avg_i + \beta_3 TIME_{ij} + \beta_4 (TST\_avg_i * TIME_{ij}) + \beta_5 X_i + \varepsilon_{ij}$
SE predicts BMI	$BMI_{ij}= (\beta_0 + b_{i0}) + \beta_1 SE\_delta_i + \beta_2 SE\_avg_i + \beta_3 TIME_{ij} + \beta_4 (SE\_avg_i * TIME_{ij}) + \beta_5 X_i + \varepsilon^{ij}$
WASO predicts BMI	$BMI_{ij}= (\beta_0 + b_{i0}) + \beta_1 WASO\_delta_i + \beta_2 WASO\_avg_i + \beta_3 TIME_{ij} + \beta_4 Xi + \varepsilon ij$
SOL predicts BMI	$BMI_{ij}= (\beta_0 + b_{i0}) + \beta_1 SOL\_delta_i + \beta_2 SOL\_avg_i + \beta_3 TIME_{ij} + \beta_4 Xi + \varepsilon_{ij}$
BMI predicts TST	$TST_{ij}= (\beta_0 + b_{i0}) + \beta_1 BMI\_delta_i + \beta_2 BMI\_avg_i + \beta_3 TIME_{ij} + b_{i1} TIME_{ij} + \beta_4 (BMI\_avg_i * TIME_{ij}) + \beta_5 X_i + \varepsilon_{ij}$
BMI predicts SE	$SE_{jj}= (\beta_0 + b_{i0}) + \beta_1 BMI\_delta_i + \beta_2 BMI\_avg_i + \beta_3 TIME_{ij} + \beta_4 (BMI\_avg_i * TIME_{ij}) + \beta_5 X_i + \varepsilon_{ij}$
BMI predicts WASO	$WASO_{ij}= (\beta_0 + b_{i0}) + \beta_1 BMI\_delta_i + \beta_2 BMI\_avg_i + \beta_3 TIME_{ij} + \beta_5 X_i + \varepsilon_{ij}$
BMI predicts SOL	$SOL_{ij}= (\beta_0 + b_{i0}) + \beta_1 BMI\_delta_i + \beta_2 BMI\_avg_i + \beta_3 TIME_{ij} + b_{i1} TIME_{ij} + \beta_5 X_i + \varepsilon_{ij}$

Abbreviations: BMI, body mass index; SE, sleep efficiency; SOL, sleep onset latency; TST, total sleep time; WASO, wake after sleep onset

$y_{ij} = (\beta_0 + b_{i0}) + (\beta_1 + b_{i1})t_{ij} + \varepsilon_{ij}$;

where

- *i* denotes the individual
- *j* refers to the j-th assessment of the outcome
- β's are the *fixed effects*
- *b*'s are the *random effects*
- X_i is the design matrix of the fixed effects, containing covariates assessed at baseline (see Methods)
- ε_{ij}, *where* $\varepsilon_{ij} \sim N(0; V_i)$; denote the error terms
- Final models were estimated using restricted maximum likelihood (REML) *TST is total sleep time in hours*
- *SE is sleep efficiency in %*
- *WASO is wake after sleep onset*

Supplement 5.3.3. Longitudinal association between BMI and actigraphically measured sleep parameters, stratified by sex

	Total sleep time (TST), hours		Sleep efficiency (SE), %		Sleep onset latency (SOL)†, minutes		Wake after sleep onset (WASO), minutes	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Men (n=496)								
Average BMI (kg/m²)	-0.03	-0.05, -0.005	0.01	-0.23, 0.26	0.005	-0.01, 0.02	-0.78	-1.52, -0.05
Delta BMI (kg/m²)	0.21	-0.11, 0.52	1.75	-1.41, 4.91	0.10	-0.15, 0.35	-6.25	-15.69, 3.19
Time (years)	0.09	-0.01, 0.20	1.22	0.15, 2.28	-0.09	-0.19, 0.003	-3.82	-6.59, -1.05
Average BMI & Time Interaction	-0.002	-0.006, 0.001	-0.04	-0.08, -0.002	0.002	-0.001, 0.006	0.13	0.03, 0.23
Δ BMI & Time Interaction	-0.018	-0.07, 0.03	-0.11	-0.61, 0.38	-0.023	-0.07, 0.02	0.56	-0.75, 1.86
Women (n=535)								
Average BMI (kg/m²)	-0.01	-0.03, 0.003	-0.07	-0.22, 0.08	0.01	-0.005, 0.02	0.34	-0.1, 0.78
Delta BMI (kg/m²)	0.21	-0.02, 0.44	1.83	-0.37, 4.03	-0.06	-0.27, 0.14	-3.25	-9.79, 3.28
Time (years)	0.08	0.01, 0.14	0.54	-0.07, 1.15	0.01	-0.06, 0.08	-0.02	-1.94, 1.91
Average BMI & Time Interaction	-0.002	-0.004, 0.0003	-0.02	-0.04, 0.006	-0.001	-0.003, 0.001	-0.02	-0.09, 0.05
Δ BMI & Time Interaction	0.0004	-0.03, 0.03	-0.15	-0.48, 0.18	0.009	-0.03, 0.04	0.77	-0.27, 1.82

β's are derived from linear mixed models. Time is expressed as 0=baseline and $Date_{BMI\_T2}$ – $Date_{BMI\_T1}$=follow-up, average BMI is expressed as (BMI_{T2} + BMI_{T1})/2, Delta BMI is expressed as (BMI_{T2} - BMI_{T1})/follow-up time. The interaction term estimates how the effects of average BMI and time depend on each other.

Models are adjusted for age, cohort, actigraphy device at follow-up, smoking, education, employment, prevalent chronic disease(s), depressive symptoms, self-reported frequency of sleep disordered breathing, and frequency of napping

† SOL was log-transformed for analyses.

Supplement 5.3.4. Longitudinal association between actigraphically measured sleep parameters and BMI, stratified by sex

	BMI (kg/m^2)Total Sleep Time (hours)			
	Men (n=496)		**Women (n=535)**	
	β	95% CI	β	95% CI
Total sleep time (TST), hours				
Average TST	-0.69	-1.07, -0.31	-0.81	-1.35, -0.27
Δ TST	-1.03	-3.25, 1.19	-2.71	-5.87, 0.45
Time, years	-0.13	-0.30, 0.04	-0.28	-0.49, -0.06
Average TST & Time Interaction	0.01	-0.02, 0.04	0.04	0.003, 0.07
Δ TST & Time Interaction	-0.08	-0.24, 0.08	-0.02	-0.23, 0.18
Sleep efficiency (SE), %				
Average SE	-0.02	-0.06, 0.01	-0.06	-0.12, -0.01
Δ SE	-0.18	-0.39, 0.03	-0.35	-0.68, -0.02
Time, years	-0.16	-0.37, 0.06	-0.30	-0.58, -0.02
Average SE & Time Interaction	0.001	-0.001, 0.004	0.003	-0.0004, 0.007
Δ SE & Time Interaction	-0.005	-0.02, 0.011	-0.012	-0.03, 0.01
Sleep onset latency (SOL)†, minutes				
Average SOL†	0.32	-0.19, 0.83	0.41	-0.25, 1.08
Δ SOL†	0.97	-1.29, 3.24	-0.25	-3.25, 2.76
Time, years	-0.09	-0.20, 0.01	0.01	-0.11, 0.13
Average SOL & Time Interaction	0.01	-0.02, 0.05	-0.02	-0.06, 0.02
Δ SOL & Time Interaction	-0.10	-0.27, 0.07	0.04	-0.16, 0.23
Wake after sleep onset (WASO), minutes				
Average WASO	-0.006	-0.02, 0.01	0.015	-0.004, 0.04
Δ WASO	0.08	-0.002, 0.16	-0.02	-0.14, 0.09
Time, years	-0.02	-0.08, 0.03	-0.03	-0.11, 0.05
Average WASO & Time Interaction	-0.001	-0.001, 0.0004	-0.0002	-0.001, 0.001
Δ WASO & Time Interaction	0.003	-0.003, 0.01	0.006	-0.0007, 0.01

β's are derived from linear mixed models. Time is expressed as 0=baseline and $Date_{BMI\_T2}$ – $Date_{BMI\_T1}$=follow-up, average BMI is expressed as (BMI_{T2} + BMI_{T1})/2, Delta BMI is expressed as (BMI_{T2} - BMI_{T1})/follow-up time.

The interaction term estimates how the effects of the average of the sleep parameter and time depend on each other.

Models are adjusted for age, cohort, actigraphy device at follow-up, smoking, education, employment, prevalent chronic disease(s), depressive symptoms, self-reported frequency of sleep disordered breathing, and frequency of napping

† SOL was log-transformed for analyses

Supplement 5.3.5. Cross-Sectional Associations Between Objective Sleep and Body Mass Index (kg/m^2) at Two Time Points, Stratified by Device at Follow-Up, Rotterdam Study, 2004-2014

Actiwatch						
N=592	Associations at T1			Associations at T2		
	B	95% CI	*P*-value	B	95% CI	*P*-value
TST, hours	-0.35	-0.73, 0.03	0.07	-0.49	-0.86, -0.11	0.011
SOL†, min	0.02	0.005, 0.04	0.014	0.01	-0.01, 0.03	0.21
SE, %	-0.03	-0.07, 0.01	0.17	-0.04	-0.07, 0.003	0.07
WASO, min	0.01	-0.003; 0.023	0.15	0.005	-0.008; 0.017	0.46

GeneActiv						
N=439	Associations at T1			Associations at T2		
	B	95% CI	*P*-value	B	95% CI	*P*-value
TST, hours	-0.69	-1.18, -0.20	0.005	-0.69	-1.15, -0.23	0.004
SOL†, min	-0.01	-0.03, 0.01	0.44	0.02	-0.01, 0.05	0.27
SE, %	0.003	-0.05, 0.05	0.91	-0.05	-0.10, 0.001	0.053
WASO, min	-0.007	-0.02; 0.009	0.40	0.004	-0.01; 0.02	0.68

Abbreviations: BMI, body mass index; SE, sleep efficiency; SOL, sleep onset latency; T, time point; TST, total sleep time; WC, waist circumference.

Models are adjusted for sex, age, cohort, smoking, education, employment, physical activity (at T2 only), prevalent chronic disease(s), CES-Depression score, self-reported frequency of sleep disordered breathing, and frequency of napping

† SOL was log-transformed for analyses

Supplement 5.3.6. Longitudinal association between BMI and actigraphically measured sleep parameters, stratified by actigraphy device at follow-up

	Total sleep time (TST), hours		Sleep efficiency (SE), %		Sleep onset latency (SOL)†, minutes		Wake after sleep onset (WASO), minutes	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Actiwatch (n=592)								
Average BMI (kg/m^2)	-0.01	-0.03, 0.005	-0.09	-0.27, 0.08	0.02	0.0002, 0.03	0.3	-0.21, 0.82
Delta BMI (kg/m^2)	0.29	0.04, 0.55	3.78	1.3, 6.25	-0.216	-0.44, 0.004	-8.79	-16.09, -1.50
Time (years)	0.07	-0.002, 0.14	0.45	-0.3, 1.2	0.0002	-0.07, 0.07	-0.1	-2.23, 2.02
Average BMI & Time Interaction	-0.002	-0.005, 0.0002	-0.02	-0.05, 0.007	-0.0008	-0.003, 0.002	0.02	-0.06, 0.09
Δ BMI & Time Interaction	-0.01	-0.05, 0.03	-0.08	-0.46, 0.3	-0.0004	-0.04, 0.04	0.14	-0.95, 1.22
GeneActiv (n=439)								
Average BMI (kg/m^2)	-0.02	-0.04, -0.005	-0.02	-0.21, 0.17	0.004	-0.012, 0.02	-0.22	-0.77, 0.34
Delta BMI (kg/m^2)	0.12	-0.16, 0.40	-0.15	-2.87, 2.57	0.22	-0.01, 0.45	-0.25	-8.22, 7.72
Time (years)	0.10	0.01, 0.18	1.13	0.35, 1.91	-0.06	-0.14, 0.03	-2.61	-4.79, -0.42
Average BMI & Time Interaction	-0.001	-0.004, 0.001	-0.03	-0.05, 0.001	0.001	-0.002, 0.004	0.04	-0.04, 0.12
Δ BMI & Time Interaction	0.002	-0.04, 0.04	-0.23	-0.64, 0.19	-0.0003	-0.04, 0.04	1.42	0.26, 2.58

β's are derived from linear mixed models. Time is expressed as 0=baseline and $Date_{BMI\_T2}$ – $Date_{BMI\_T1}$=follow-up, average BMI is expressed as (BMI_{T2} + BMI_{T1})/2, Delta BMI is expressed as (BMI_{T2} - BMI_{T1})/follow-up time,. The interaction term estimates how the effects of average BMI and time depend on each other.

Models are adjusted for sex, age, cohort, smoking, education, employment, prevalent chronic disease(s), CES-Depression score, self-reported frequency of sleep disordered breathing, and frequency of napping

Supplement 5.3.7. Longitudinal association between actigraphically measured sleep parameters and BMI, stratified by actigraphy device at follow-up

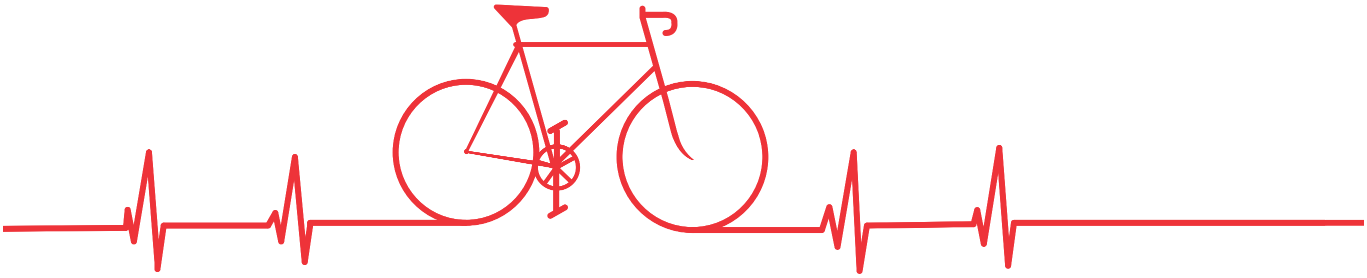
	BMI (kg/m²)Total Sleep Time (hours)			
	Actiwatch (n=592)		**GeneActiv (n=439)**	
	β	95% CI	β	95% CI
Total sleep time (TST), hours				
Average TST	-0.57	-1.00, -0.14	-0.98	-1.51, -0.45
Δ TST	-1.73	-4.23, 0.77	-1.69	-4.78, 1.39
Time, years	-0.21	-0.38, -0.04	-0.21	-0.42, 0.01
Average TST & Time Interaction	0.03	-0.002, 0.05	0.02	-0.01, 0.06
Δ TST & Time Interaction	-0.12	-0.29, 0.05	0.04	-0.17, 0.25
Sleep efficiency (SE), %				
Average SE	-0.05	-0.10, -0.01	-0.03	-0.09, 0.02
Δ SE	-0.16	-0.40, 0.08	-0.31	-0.64, 0.01
Time, years	-0.39	-0.61, -0.17	-0.001	-0.29, 0.28
Average SE & Time Interaction	0.005	0.002, 0.008	-0.001	-0.004, 0.003
Δ SE & Time Interaction	-0.01	-0.03, 0.007	-0.008	-0.03, 0.014
Sleep onset latency (SOL)†, minutes				
Average SOL†	0.62	0.09, 1.15	0.18	-0.54, 0.89
Δ SOL†	-1.52	-4.00, 0.96	1.85	-1.15, 4.85
Time, years	0.04	-0.06, 0.15	-0.16	-0.29, -0.02
Average SOL & Time Interaction	-0.03	-0.07, 0.002	0.04	-0.01, 0.09
Δ SOL & Time Interaction	-0.01	-0.18, 0.16	-0.01	-0.21, 0.19
Wake after sleep onset (WASO), minutes				
Average WASO	0.012	-0.002, 0.03	-0.007	-0.03, 0.01
Δ WASO	0.003	-0.08, 0.09	0.010	-0.10, 0.13
Time, years	0.020	-0.04, 0.09	-0.09	-0.17, -0.02
Average WASO & Time Interaction	-0.001	-0.002, -0.0002	0.001	-0.003, 0.002
Δ WASO & Time Interaction	0.003	-0.003, 0.01	0.009	0.002, 0.02

β's are derived from linear mixed models. Time is expressed as 0=baseline and $Date_{BMI\_T2}$ – $Date_{BMI\_T1}$=follow-up, average BMI is expressed as $(BMI_{T2} + BMI_{T1})/2$, Delta BMI is expressed as $(BMI_{T2} - BMI_{T1})$/follow-up time,.

The interaction term estimates how the effects of the average of the sleep parameter and time depend on each other.

Models are adjusted for sex, age, cohort, smoking, education, employment, prevalent chronic disease(s), CES-Depression score, self-reported frequency of sleep disordered breathing, and frequency of napping

† SOL was log-transformed for analyses



Chapter 6

General discussion

The main aim of this thesis was to study factors associated with activity in older age and to examine the association of activity domains with mortality, cardiovascular disorders and mental health outcomes. The activity domains of interest were physical activity, sedentary behavior, and sleep. Together complete the daily 24-hour activity cycle. Specific findings and discussion points from these analyses are described in the previous chapters. In this general discussion, the findings of this thesis will be summarized, and a general discussion of the major methodological considerations will be provided. Thereafter, public health implications and directions for future research will be discussed.

Factors associated with activity

Until a decade ago, physical activity was most often measured by questionnaires, which are subject to reporting bias and social desirable answers.[1] More recently, the use of accelerometers to measure physical activity has increased.[2,3] Accelerometers have the advantage that they can measure intensity and duration of activity without biases that are associated with self-report. However, questionnaires are currently still needed to gain more insight in the type and context of activity. The different measurement characteristics between questionnaire and accelerometer are reflected in the generally low agreement between the two measurement techniques. Therefore, to gain more knowledge on the disagreement, we studied the agreement between physical activity derived from questionnaires and the wrist-worn GeneActiv accelerometers, and whether the disagreement was related to health and lifestyle factors in Chapter 2.1. We observed that for every hour more physical activity measured by the accelerometer, the questionnaire underestimated physical activity levels more by 29 minutes. This might reflect that questionnaires do not capture all activities that are measured by the accelerometer. For example, climbing stairs and walking within shops were not included in the questionnaire used in this study. Furthermore, participants with more depressive symptoms, more disability and with a higher body mass index underestimated their self-reported physical activity levels more than the reference groups, indicating that perceived health might also affect the judgement of physical activity levels.

The low agreement between the questionnaire and accelerometer indicates that people classified as highly active by the questionnaire, are not necessarily categorized as highly active by the accelerometer. Consequently, the factors associated with objectively measured activity in older age might slightly differ from the known factors associated with questionnaire-derived physical activity.[4,5] Therefore, in Chapter 2.2, we examined the activity distribution of objectively measured physical activity, sedentary behavior and sleep in older adults, and we examined the demographic and health factors associated with these activity measures. Similar to the factors related to the disagreement, we observed that body mass index and disability were related to activity levels. Sedentary behavior was higher across higher levels of body mass index and across increasing age-categories, which was at the expense of light and moderate-to-vigorous physical activity. Additionally, in contrast to previous literature using questionnaires,[4,5] objectively measured physical activity levels were higher in women compared to men.

Next, we examined which external factors are related to activity, by examining the seasonal patterns of objective measures of physical activity, sedentary behavior, and sleep according to an age-specific approach in Chapter 2.3. In adults up to 75 years, we observed a seasonal pattern for physical activity, with higher levels in the summer, at the expense of sleep duration. The seasonal patterns were mostly explained by ambient temperature and sunlight hours. In contrast, sedentary behavior showed no seasonal pattern, suggesting that this is a behavior that is ingrained in daily life and not easily influenced by whether conditions. We observed no seasonal pattern for adults aged 75 and over, which might be because most of their physical activity takes place indoors.

Taken together, these results suggest that body mass index and disability are important factors to consider when examining activity patterns, since both were independently related to a larger underestimation of physical activity levels in the questionnaire, and with lower objectively measured activity levels in older adults. Furthermore, the fact that we observed higher objectively measured physical activity levels for women compared to men might reflect the traditional household pattern, in which women do more domestic chores than men. We did not observe any sex-differences on the disagreement between questionnaire and accelerometer, indicating that questionnaires and accelerometers capture the physical activity levels of men and women similarly. However, considering the increase in the use of accelerometers in current research, researchers need to be aware that results between studies using either questionnaire or accelerometer should be compared with caution. Furthermore, the observation that light physical activity had the largest seasonality suggests that this is behavior that is easily adapted to external conditions. Breaking up sedentary behavior with light physical activity might be a good starting point for public health institutions.

Activity and mortality

Low levels of physical activity and high levels of sedentary behavior have both been related to a higher mortality risk.[6,7] In this thesis, we extended the knowledge on these topics by examining specific causes of death related to physical activity, as well as examining the physical activity types associated with all-cause mortality in Chapter 3.1. Furthermore, we examined the association between objectively measured sedentary behavior and mortality with a longer follow-op than previously reported in literature, and by carefully adjusting for confounders in Chapter 3.2. We found physical activity to be associated with lower risk of mortality related to all-causes, cardiovascular diseases, chronic lung diseases, infections and mortality from other causes. All physical activity types contributed to the lower all-cause mortality risk, supporting that engagement in any physical activity, including physical activity as part of a daily living, might be conducive to reduce mortality risk in older adults. Furthermore, we found higher levels of sedentary behavior to be associated with a higher all-cause mortality risk. However, this association was clearly attenuated after adjusting for other measures of activity, including disability and physical activity. In this study, we again showed the importance of disability in the analyses of an activity measure. The reason not to adjust for a measure of disability in the analyses between physical activity and mortality is related to the overlap between the physical activity questionnaire and the activities of daily living questionnaire used to quantify disability status. Both questionnaires include questions on walking, cycling, and doing household work. Therefore, adjusting for activities of daily living in the analyses between physical activity and mortality was considered over adjustment. In future studies using activity measures, adjustment for a measure for disability should be carefully considered.

Together, the findings from the studies in Chapter 3.1 and Chapter 3.2 illustrate the complicated relation between physical activity and sedentary behavior; persons with a low level of sedentary behavior do not necessarily have high levels of physical activity. Recently, a large meta-analysis including more than 1 million men and women indicated that physical activity can eliminate the higher mortality risk associated with high sedentary time.[8] However, the mortality risk associated with television viewing was not eliminated by adjusting for physical activity.[8] This suggests that not all types of sedentary behavior are similarly related to mortality and that watching television might carry risks above and beyond overall sedentary behavior. This is in contrast to physical activity, for which we observed a risk reduction in all-cause mortality for all physical activity types. Therefore, further investigation is needed to examine whether overall sedentary behavior and several types of sedentary behavior are a risk factor for mortality, distinct from the effect of other measures of activity.

Activity and cardiovascular health

Many epidemiological studies have examined the association between physical activity and cardiovascular diseases.[9,10] However, only few examined the association between specific physical activity types and cardiovascular health outcomes.[11-13] Since older adults do not engage in sports an exercise as much as younger adults,[14] the health effects of other physical activity types are of importance. Therefore, we explored the association of total physical activity, and of walking, cycling, domestic work, gardening and sports with coronary heart disease in Chapter 4.1, with atrial fibrillation in Chapter 4.2, and with the average years lived with and without cardiovascular disease in Chapter 4.3. We observed that specifically domestic work and cycling were independently associated with a reduction in the risk of coronary heart disease, and with large increases in total life expectancy, and extending life expectancy without cardiovascular disease. However, we observed no association between physical activity and risk of atrial fibrillation. Since active individuals might be more health conscious, they might visit their general practitioner more frequently and could therefore more often be evaluated by- and diagnosed with cardiac arrhythmias,[15] and this might have influenced the results.

The fact that specifically domestic work and cycling were associated with cardiovascular outcomes might be related to the intensity, frequency, and duration in which is engaged in these physical activity types. For example, almost all participants (96.7%) engaged in domestic work (see Figure 6.1), and it contributed up to 44% of the total physical activity level (expressed in MET·hours·week^{-1}). For cycling, the relatively high intensity might contribute to better cardiorespiratory fitness, which is related to lower incidence of cardiovascular disease and mortality.[16,17] The fact that we did not observe an association between walking and cardiovascular events might be related to the heterogeneity regarding the intensity in which is engaged in walking. For example, it is possible that two participants both reported 1 hour of walking per week, with one participants walking 4 km within this time frame, whereas another walked 6 km. Consequently, the participants had a different walking pace, and this has been shown to be more strongly associated with cardiovascular disease than frequency and duration.[18]

Furthermore, it has been suggested that physical activity might reduce risk of cardiovascular disease associated with overweight and obesity.[19] In Chapter 4.4 we evaluated the joint effects of physical activity and body mass index with cardiovascular disease risk. We showed that individuals who engaged in higher levels of total physical activity were not at increased risk of cardiovascular disease, regardless of being overweight or obese. In contrast, overweight and obese individuals with lower total physical activity levels were at significantly higher risk of cardiovascular disease. Additionally, the cardiovascular disease risk between normal weight participants with low levels of physical activity was comparable to the risk of obese adults with high levels of physical activity. These findings highlight the importance of promoting physical activity levels across all normal weight, overweight and obese individuals. Moreover, since domestic work and cycling are activities which are accessible for most older adults, our findings indicate that these activities could be promoted in the elderly, with the aim to prevent cardiovascular disease and improve life expectancy.

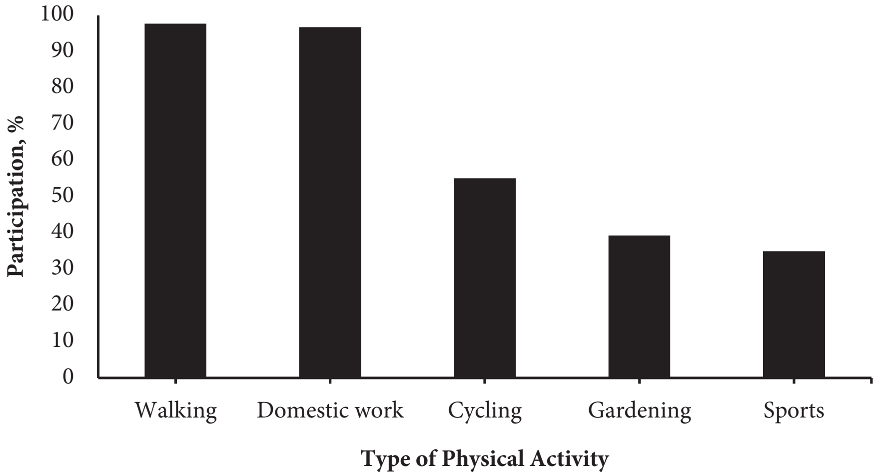


Figure 6.1 Participation in physical activity types

Activity and mental health and wellbeing

Sedentary behavior and physical activity have also been associated with health-related quality of life[20,21] and mental health outcomes as depression, anxiety and cognitive function.[22-24] In Chapter 5.1, we examined the age-specific association between physical activity types and health-related quality of life. Because 65 years of age is considered the retirement age in many countries, we explored whether different types of physical activity are associated with health-related quality of life before and after retirement age. We observed a dose-response relation between total physical activity and better health-related quality of life. Additionally, we found that sport was associated with better mobility, self-care, daily activities and mood, and less pain in middle-aged adults, whereas cycling was associated strongest with these health-related quality of life domains in the elderly. These results suggest that different activities should be promoted to different age groups, to improve health-related quality of life.

In Chapter 5.2, we examined the association between actigraphically measured sedentary behavior and several measures of mental health and cognition. We observed that higher levels of sedentary behavior were associated with more depressive symptoms, higher odds of having a prevalent anxiety disorder and with worse cognitive function. However, these associations were explained by other factors, including disability, occupational status and smoking. Furthermore, we observed no association between sedentary behavior and changes in depressive symptoms or cognitive function over time, nor did we find an association between sedentary behavior and incident anxiety disorders. Previous studies using self-reported measures that do report an association might be explained by residual confounding, because most of these did not adjust for disability status. It is also possible that the associations were driven by the context in which the sedentary behavior takes place.[25] In this case, not sedentary behavior itself, but the situation in which is engaged in sedentary behavior might be related to mental health measures. For example all the studies observing a longitudinal association between sedentary behavior and mental health or cognition included watching television in their measure, whereas the studies using computer or internet use as a proxy for sitting time more often observed null associations with mental health.[22,23,26,27] In line with the finding that television viewing might carry risks over and beyond sitting in the association with mortality,[8] this might also be the case for mental health.

In Chapter 5.3, we used actigraphy to obtain an objective measure of sleep. Sleep has been identified as a possible modifiable behavior that can influence body weight.[28,29] However, the possibility that the association is bidirectional – sleep influencing body weight and body weight influencing sleep – has gained less attention.[30-32] We observed a bidirectional association between objectively measured sleep indices and body mass index, indicating that sleep can influence body mass index and vice versa. A higher average body mass index was associated with a decline in sleep duration over time. Conversely, longer sleep duration and higher sleep efficiency slowed down the decrease in body mass index across time over a period of 6 years. The findings from this general population sample of older adults suggest that among other health benefits, a healthy body mass index is associated with better sleep indices in an age group with increasing sleep problems and disturbances.

METHODOLOGICAL CONSIDERATIONS

Strengths and limitations of the specific studies included in this thesis have been discussed in the corresponding chapters. This section addresses some general methodological issues related to study design, assessment of activity, assessment of cardiovascular disease and mortality, reverse causation and confounding.

Study design

All the studies included in this thesis were performed in the Rotterdam Study, a prospective population-based cohort in Rotterdam. A prospective cohort design is particularly useful to examine potential risk factors for common diseases, although the observational nature challenges any direct conclusion regarding the temporality of the association. However, the fact that exposure variables, including physical activity, sedentary behavior and sleep, can be measured before the outcomes of interest have developed, minimizes recall bias and allows to determine whether the exposure of interest precedes the outcome.[33]

A specific strength of the Rotterdam Study lies in the assessment of the disease outcomes. Information on many common diseases were collected by an automated follow-up system with digital linkage of the study database to medical records maintained by general practitioners in the research area. Trained research assistants collected outpatient clinic reports, hospital discharge letters, electrocardiograms, imaging results and notes from general practitioners and hospitals. In a next step, research physicians independently adjudicated all data on potential events. Finally, medical specialists whose judgments are considered definitive reviewed the potential cases. For information on vital status, information was additionally obtained from the central registry of the municipality of the city of Rotterdam.

Assessment of activity by questionnaire

For practical reasons, physical activity is often measured subjectively by questionnaire.[3] Specific questionnaires have been developed for target populations, including children, young adults and elderly adults. These questionnaires usually measure the duration and frequency of several types of physical activity through self-report or interview. Subsequently, an intensity score can be attributed to each of these activities, by using the Compendium of Physical Activities.[34] The activity is usually expressed in metabolic equivalent of task (MET) or calories.[35] The hours per week spent in each activity is then multiplied by the intensity score (e.g. $\text{MET·hours·week}^{-1}$) and the different physical activity types in the questionnaire can be summed to create an overall physical activity score. The advantages of questionnaires include cost effectiveness and ease of administration.[36] Currently questionnaires are still needed to obtain information on the types of physical activity that adults engage in. However, self-reported physical activity can suffer from reporting bias, partially attributable to the cognitive challenge of estimating the frequency, intensity and duration of physical activity.[1] Moreover, activities of light intensity are hard to recall and might not be reported.[37,38] This is especially relevant in older adults, because the higher likelihood of cognitive impairment might lead to more recall bias and reporting errors.[34]

Furthermore, the use of the Compendium of Physical Activities[34] has a few drawbacks. First, it might not capture the energy expenditure of older adults accurately.[34] Second, there probably is some heterogeneity in the intensity in which participants engage in different activity types, which can lead to misclassification of participants with either higher or lower intensity levels than the assigned values. In longitudinal studies, this misclassification would likely be non-differential, and could bias estimates of particular associations towards the null hypothesis.

In the Rotterdam Study, we assessed physical activity by an adapted version of the Zutphen Physical Activity Questionnaire[39] and in later years by the LASA physical activity questionnaire (LAPAQ).[40] The Zutphen questionnaire has been validated in which the test-retest reliability was 0.93 and the correlation with doubly labelled water was 0.61.[2] The original questionnaire contains questions regarding walking, cycling, sports, gardening and hobbies. For the Rotterdam Study questions on housekeeping activities were added to attain a more complete assessment of physical activity levels of older adults. Participants were asked how many hours per week they spent in each activity in the past year. To address seasonal variability in physical activity, participants were asked whether they only participated in a particular activity during summer or winter (e.g. for sports and gardening). When answered confirmative, we calculated a weighted estimate by dividing the reported time by two. Furthermore, the questionnaire provided two questions in which participants could mention sports that were not captured by previous questions.

In 2006, with the start of an additional cohort (RS-III), the LAPAQ was introduced in the Rotterdam Study; this measure has also been used in the subsequent measurement waves. The LAPAQ was developed and validated in the Longitudinal Aging Study Amsterdam (LASA); the test-retest reliability was reasonably good (0.65–0.75) and the correlations with the pedometer and 7-day diary were 0.56 and 0.68, respectively.[40] Similar to the Zutphen questionnaire, the LAPAQ consists of questions on the frequency and duration of walking, cycling, sports, gardening and housework, and participants are asked how many hours per week they spend on average in each of these activities in the past two weeks. Furthermore, the LAPAQ also provided two questions where participants could mention other sports they participated in that were not captured by previous questions.

For both questionnaires, we assigned MET-values to all activities mentioned in the questionnaires, according to the 2011 updated version of the Compendium of Physical Activities.[35] There are, however, also some differences between the questionnaires. We observed generally higher levels of physical activity measured by the Zutphen Physical Activity Questionnaire compared to the LAPAQ. This might be related to several characteristics of these questionnaires. The Zutphen Physical Activity Questionnaire requires participants to indicate the average time spent in physical activity in the past year and addresses seasonal variation. A limitation of the long time span is the higher likelihood for bias when information is remembered inaccurately. In contrast, the LAPAQ infers about the past two weeks and does not take into account the fact that physical activity levels might be different in the summer compared to the winter. In longitudinal analyses, when the outcome is measured after the exposure, it can be expected that those with disease did not only complete the questionnaire in the winter, where generally lower physical activity levels are observed.[41,42] Therefore, it's unlikely that the differences between the questionnaires have influenced the associations. Another difference between the questionnaires is the way in which questions regarding walking and cycling were phrased. In the Zutphen Physical Activity Questionnaire, all walking and cycling is combined and no differentiation is made between walking for cycling for commuting or for sports. In the LAPAQ, this differentiation is made and consequently, a more accurate picture of physical activity levels can be created. Due to these differences, we were unable to track questionnaire-assessed physical activity levels through time.

Assessment of activity by accelerometer

Accelerometers offer a solution to problems associated with self-report and can give objective estimates on duration and intensity of physical activity. Therefore, they are increasingly being used in research.[2,3] An accelerometer is a small device worn on the body that measures changes in gravitational acceleration. Common methods to place an accelerometer are the hip and the wrist.

However, the placement of the accelerometer will likely lead to the problem that not all physical activity can be measured accurately.[43,44] For example, compared to a hip-worn device, accelerometer placement on the wrist provides only a poor estimate of lower-body activity during dynamic activities like cycling. Consequently, physical activity performed solely by the legs might be underestimated with these accelerometers.[43-45] Additionally, physical activity levels might also be underestimated while the wrist is constrained during physical activity, for example while pushing a wheelchair.[46] On the other hand, a wrist-worn accelerometer also has advantages over a hip-worn accelerometer, because it allows for 24-hours of data-collection per day, including times of water-based activities. Consequently, this can lead to a comprehensive overview of daily activity. Moreover, the use of a waterproof wrist-worn accelerometer ensured high compliance in our study population. In consequence, this high compliance led to few non-wear periods, thus minimizing the times for which assumptions had to be made on whether this time was spent active or sedentary.[47,48] As a result, activity is generally assessed more precisely.[48] This is in contrast with hip-worn devices, which usually have to be removed during the night and are not waterproof.

Some general limitations association with physical activity assessment by accelerometry should also be mentioned. First, the activity levels observed by the accelerometer are only a snapshot and might not accurately reflect the general activity level. During the wearing week, participants might have a higher or lower activity level than their usual pattern. Since it is unlikely that this pattern would be related to the outcome, this bias would be non-differential. Furthermore, upon wearing the device, participants might show social desirable behavior, since most adults know that being physically active is beneficial for health. In the data used for Chapter 2.1 in the current thesis, we observed subtle changes from the first 24-hour wearing day up to the last 24-hour wearing day. For example, time spent in light and moderate intensity physical activity was up to 6 minutes more on the first day compared to the last, and sedentary behavior was up to 30 minutes less on the first wearing day (Data not shown). Since these differences were relatively small, and we used the mean time spent in activity in most analyses, it is unlikely that this would have influenced our associations.

In the studies included in this thesis, we used two different wrist-worn devices to measure activity objectively, which is due to the moment of introduction of objective measurements in the Rotterdam Study. Initially, the Actiwatch was introduced in the Rotterdam Study in 2004 to obtain objective measurements of sleep. The Actiwatch is a one-dimensional device, which measures acceleration and transforms these to counts per 30 seconds on the device. There is currently limited knowledge on the ability of the Actiwatch to measure physical activity. However, since sedentary behavior is a form of inactivity similar to sleep, the Actiwatch can also be used to measure inactivity during day-time. Therefore we used the information from the Actiwatch to obtain a proxy of sedentary behavior. In later years, the GeneActiv device became available and was introduced in the Rotterdam Study in 2011. The GeneActiv measures acceleration in three axes and stores the raw signal on the device. The advantage of the GeneActiv over the Actiwatch is the use of raw signal in three axes, and the validated use of the device to measure physical activity.

For both devices, we used cut-offs based on previous literature to categorize activity as sleep and sedentary behavior, and for the data obtained from the GeneActiv, we additionally categorized activity into light, moderate, and vigorous intensity physical activity. For the Actiwatch, time spent awake and in bed was defined based on sleep start and sleep end. These times were derived from the event marker buttons on the Actiwatch device, and if these data were not available, these data were derived from the sleep diary.[49] Subsequently, we used a cut-off of <20 counts per minute to classify activity as sleep, based on an algorithm validated against polysomnography, the golden standard of measuring sleep, at the highest sensitivity.[49,50] For sedentary behavior, we used the standard count-based intensity cut-off of <199 counts per minute.[51] Whereas actigraphy has been recognized as a valid method to measure sleep,[52] it can also overestimate sleep if participants lie motionless but awake in bed. Moreover, by using actigraphy, no information on posture can be obtained and we can thus not infer whether a participant was sitting, standing, or lying down when sedentary.

To analyze the GeneActiv data, we used two analysis methods. First, we used the Pampro software, a program for the systematic analysis of physical activity data collected in epidemiological studies.[53] This software includes cut-offs to define sedentary behavior and light, moderate and vigorous intensity physical activity. These cut-offs were derived from a validation study, in which participants wore a GeneActiv device around the wrist and performed a treadmill test to provide a signal of individually calibrated physical activity energy expenditure. In addition to wearing the GeneActiv wrist-worn accelerometer, participants wore a heart rate monitor and trunk acceleration was measured. With the combined measurements an equation was developed from which cut-points were derived to estimate physical activity intensity by the GeneActiv. The obtained cut-offs were applied to the data from all participants in the Rotterdam Study. However, using uniform cut-off values to define physical activity intensity in all individuals is less accurate than using individually calibrated cut-off values,[54] especially when the age-range is large. However, we were unable to perform individual calibration procedures in the participants in the studies included in the current thesis. Therefore, there might be some misclassification of time spent in light, moderate and vigorous physical activity.

A limitation of the sedentary time as obtained by the Pampro software, is that is does not differentiate between daytime and nighttime, and hence sleep is also categorized as sedentary behavior. To be able to distinguish between sleep and sedentary behavior, we additionally used an algorithm from the GGIR package to obtain information on sleep duration.[55] In the GGIR package, diary estimates of bed time and waking time are used to define the night period. Subsequently, sleep duration is estimated based on a specific time of inactivity, in combination with a specified wrist angle. According to a validation study in which the algorithm was validated against polysomnography, an inactive time of 10 minutes in combination with a wrist angle of 5 degrees is most sensitive to estimate sleep duration,[55] and these are also the parameters used in the research in this thesis. However, estimating sleep by using this algorithm is relatively new and the parameters have not been firmly established. Therefore, we might have over- or underestimated sleep duration. Subsequently, we cannot be completely certain about the observed seasonal pattern for sleep in Chapter 2.3, and we cannot be entirely certain that there were no demographic and lifestyle factors associated with sleep duration in Chapter 2.2. Future developments in accelerometry might provide more accurate estimates of sleep duration as measured by the GeneActiv. Moreover, if algorithms to estimate sedentary behavior would also make use of the wrist angle, more information on posture might also be obtained from triaxial accelerometers, such as the GeneActiv. This could provide additional information on the association of sedentary behavior with mortality and mental health.

Confounding

One of the main limitations of observational research is the high risk of bias due to confounding. Confounding can occur when variables are associated with both the outcome and the exposure, and are not on the causal pathway between the exposure and outcome variable.[56,57] This can particularly be a problem for lifestyle variables as physical activity, since they often cluster together with other lifestyle factors, including diet and smoking habits. Furthermore, underlying diseases or disabilities can both affect the level of physical activity, as well as several health outcomes. Therefore, these lifestyle and health variables and sociodemographic factors are considered potential confounders in the association between activity and health outcomes. Importantly, a potential confounder should not be on the causal pathway between the exposure and the outcome.[58] In this case, the variable is an intermediate and adjusting for such variable in the analysis would attenuate the true association.[59] This can become problematic, when it is not completely clear what the position of a particular variable is. If a variable is strongly related to the exposure, and less strong to the outcome, then the variable might be midway between an intermediate and a confounder. As an illustration from this thesis, disability is considered a confounder in the association between sedentary behavior and mental health in Chapter 5.2, because it is associated with both sedentary behavior and mental health (See Figure 6.2a).[60-63] However, if the association between disability and mental health would be very weak, then disability could be considered an antecedent of sedentary behavior and in that situation the analyses should not have been adjusted for disability status (See Figure 6.2b). In a final example, it could even be argued that sedentary behavior might lead to disability, which in turn might influence mental health (See Figure 6.2c). In this example, disability could be considered an intermediate and adjusting for this variable would be over adjustment. However, considering the literature on disability, sedentary behavior and mental health, we carefully evaluated the position of disability in these analyses and considered it a confounding factor.

In the work present in this thesis, the possibility of confounding is reduced as much as possible, by adjusting for relevant factors. However, some potential relevant factors have not always been measured. For example, there was no information on the type of occupation participants engaged in, whereas this can be a major contributor to overall physical activity levels, and it can also be associated with health. Additionally, for some studies included in this thesis, information on diet quality and recent information on the status of the presence of chronic disease was not available at the time of the study. These factors might also be associated with both activity levels and health. The fact that we did not have information on these factors might have led to residual confounding. Residual confounding takes place when a confounder is not considered in the analysis, or when it cannot directly or accurately be measured in the study.[56] Although extensive efforts are made within the Rotterdam Study to collect the most relevant information that might contribute as confounders in the association between an exposure and outcome, residual confounding might still be present in the observed associations presented in the work in this thesis.

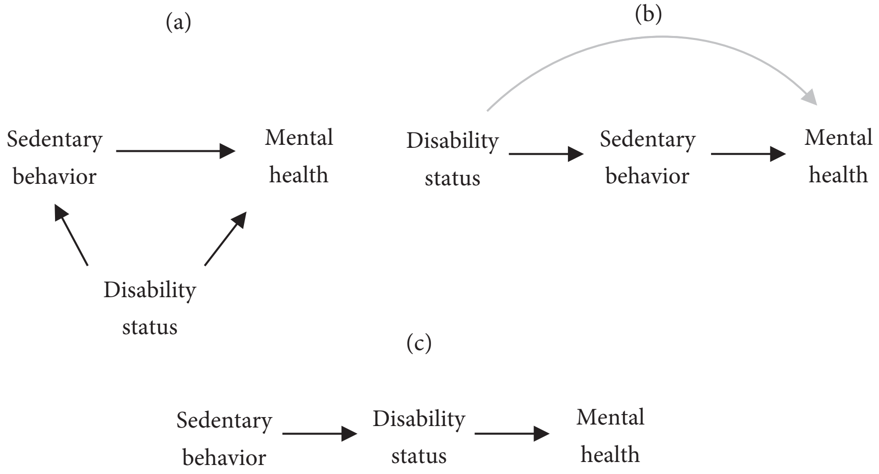


Figure 6.2 Causal diagrams showing three possible underlying associations connecting sedentary behavior, disability status and mental health.

Reverse causation

Another limitation of observational research is the possibility for reverse causation. Reverse causation refers to the phenomenon that two factors are associated, but not in the direction that was expected. In cross-sectional studies this is an issue when the inferred direction of the association is opposite to the true direction of the association. In longitudinal studies, reverse causation is present when the disease or subclinical forms of disease occur before the measurement of the exposure, and influences the exposure. As an example from this thesis, poor cardiovascular health might reduce physical activity levels and simultaneously increase the risk for cardiovascular disease. As a consequence, the observed association between low physical activity levels and a higher risk of cardiovascular disease might be the result of the underlying – but not yet diagnosed – disease. To minimize the possibility of longitudinal associations being influenced by reversed causation, it is warranted to examine the association between exposure and outcome over a longer follow-up period. Moreover, in several chapters of this thesis, we have excluded the first 2 years of follow-up to account for the possibility of reversed causation. We have also tried to reduce the possibility of reverse causation by repeating analyses in those without disease at baseline.

On the other hand, physical activity levels might also increase once a person is diagnosed with (higher risk of) disease. For example, if an individual has a high blood pressure or dyslipidemia, the first advice is to improve physical activity levels and diet quality.[64] Moreover, physical activity is also recommended when trying to lose weight.[65] Subsequently, individuals in relatively poor health might show high physical activity levels when physical activity is assessed after the initiation of a healthier lifestyle. In this case, the high physical activity group includes individuals with higher and lower risk of disease and this might make it more difficult to observe an association.

Selective participation and survival bias

Another source of bias might be selective participation of participants in the study, which occurs when there is a difference between characteristics for people included in the study and those who were not.[66] In the studies with objectively measured activity included in this thesis, participants were asked to wear an accelerometer for one week and to complete a sleep diary. In all studies, we observed that those that agreed to participate were more often male and showed better health characteristics than those who refused to participate. Therefore, the information on objective activity is derived from the healthiest participants in the Rotterdam Study and might not be generalizable to the general population. Selection can also have occurred for outcome measures, such as cognitive function. Only the healthiest participants completed all tests in the test battery to obtain an overall cognitive factor. This might also affect the generalizability of the findings.

Survival bias is another form of selective participations, and occurs when it is ignored that a person had to survive to be able to have an assessment of the exposure of interest,[67] for example physical activity. In the Rotterdam Study, participants were included in the original cohort if they were 55 years or older. In this case, only persons that survived up to that age could participate in the study. Although the response rate was 72% (14,926 of 20,744 invited individuals), which is considered quite good, the included participants might not be a good representation of the general population. It has been shown that cohort studies tend to represent a healthier population than the underlying general population that was eligible for inclusion in the study.[68] In the Rotterdam Study, participants had a slightly lower cardiovascular risk compared to all individuals that were invited, and nonparticipation was associated with mortality risk.[68] The selective participation of healthier individuals might have resulted in higher estimated physical activity levels among the included participants compared to the general population.

The problem of survival bias is most important in cross-sectional studies, in which healthy individuals are compared to individuals with prevalent diseases who survived this disease. In these studies, individuals who die soon after the onset of disease are never included. In longitudinal studies, participants with prevalent diseases are excluded at baseline. Subsequently, statistical methods as Cox proportional hazard models are used to estimate the risk of incident disease over time.[69] In the majority of this thesis, we conducted longitudinal analyses to examine the association with health outcomes. However, some chapters, including Chapter 5.1 on the association between physical activity types and health-related quality of life, we cannot rule out the possibility of survival bias.

Selective participation can also occur due to loss to follow-up.[70] Participants might refuse to participate in subsequent visits, might not be in sufficiently good health to participate, or might have moved across the country. If the loss to follow-up or withdrawal to participation is different for different exposure categories (i.e. levels of physical activity, sedentary behavior or sleep), this might introduce a significant bias in the study. If the tendency to attend a research visit is different across different levels of exposure, this can result in an over- or under-estimation of the true effect. For example, in the study on the association of sedentary behavior with mental health and cognition, we observed that participants with a follow-up measurement on depression, anxiety, or cognition had on average lower levels of sedentary behavior at baseline. In this regard, only the healthiest participants had follow-up measurements and could be included in the longitudinal analyses. The lack of heterogeneity in levels of sedentary behavior might also have made it more difficult to observe an association. We can therefore not completely rule out the possibility that the null finding in this study is related to this selective participation.

IMPLICATIONS FOR PUBLIC HEALTH AND FUTURE RESEARCH

Physical activity

With our results, we ultimately hope to reach the general public directly or indirectly, e.g. by improving guidelines and recommendations. For physical activity it is currently recommended to engage in 30 minutes of moderate-to-vigorous physical activity on most days of the week.[71] Depending on the specific guideline, this might also include work in and around the house, and physical activity by active transportation. In this thesis we provided evidence that in addition to exercise, domestic work and cycling were strongly associated with several health outcomes, including coronary heart disease, cardiovascular disease, all-cause mortality and health-related quality of life. Importantly, already low levels of cycling were associated with better health outcomes. One of the benefits of cycling is that it does not put weight stress on the joints, which makes it an activity easily accessible for heavier adults. Moreover, the current increase in the use of electric-bikes, which are bicycles that are moved forward by human pedaling, complemented by electrical power from a storage battery, makes cycling more accessible for those in poorer health.[72] In several countries, cycling is a common way of commuting and the infrastructure invites individuals to engage in cycling in the Netherlands, Denmark and Germany.[73] Since all individuals have to engage in some form of transportation to go from one place to another, recommending cycling as a way of active transportation, but also as a form of leisure time activity or exercise, could be an important step to increase physical activity levels. Indeed, already in 1996, the US surgeon general specifically recommended cycling for practical, daily travels as an ideal approach to improve physical activity levels.[74] Although the estimated inhaled doses of air pollution and the risk of dying from a traffic accident were higher when cycling compared to driving a car,[75] a review reported that the beneficial effect of increased physical activity due to cycling resulted in approximately 9 times more gains in life-years than the losses in years due to more inhaled doses of air pollution and traffic accidents. Additionally, the fact that domestic work was also associated with several health outcomes indicates that activities that are part of daily living can also contribute to health benefits. We do recognize that the physical activity levels of the participants of the studies included in the current thesis were quite high, and almost all participants engaged in 150 minutes of moderate to vigorous physical activity per week. If future studies consistently find health benefits associated with all forms of physical activity, it might be that the current guidelines recommending 150 minutes of moderate to vigorous physical activity per week might need to be re-evaluated. By a combination of active transportation, sports and work in and around the house 150 minutes per week could easily be accumulated. Therefore, if these different physical activity types contribute to beneficial health effects, this should be specifically mentioned in the guidelines and the limit of 150 minutes might be set to a higher value. The use of objective measurement methods of activity might also be useful to this aim, since this can provide information beyond the perceived time spent in physical activity. It can also provide information on the absolute time and intensity in which is engaged in physical activity.

In Chapter 2.1 in the current thesis, we showed a large discrepancy between objective and subjective measures of physical activity. Therefore, since the use of accelerometers is increasing, researchers and policy makers need to be aware that the results obtained from questionnaire and accelerometers should be combined and/or compared with caution. Moreover, future meta-analyses and reviews need to address objective and subjective methods separately. To improve the agreement between the two measurement methods, more detailed instructions in the questionnaire may be required[76] and questionnaires could be improved to better capture the overall physical activity pattern of older adults. In the current thesis, individuals with a higher disability score, more depressive symptoms and a higher body mass index more often underestimated their physical activity levels compared to their counterparts. Future studies might examine other factors, such as anxiety, pain perception and medication use, that might also be relevant in this association. More information on this topic could help health care providers working in clinical practice to be aware that those individuals might not have a realistic view of their physical activity levels. Additionally, information obtained from accelerometers could also be improved in future studies. Specified algorithms could be identified and used to recognize the type of physical activity in which participants engage (e.g. walking, cycling), taking into account their specific rhythm when wearing an accelerometer. On the other hand, the differences in physical activity levels obtained from questionnaire and accelerometer can also be a source of information. Whereas accelerometers provide an accurate distribution of intensity and duration, questionnaires might more accurately reflect the perceived levels and intensity of physical activity, as well as the types of physical activity in which adults engage in. In order to be able to influence the physical activity levels of individuals, both sources of information are important. We would therefore currently recommend to use questionnaires and accelerometers to gain the most information.

Sedentary behavior

For sedentary behavior, there currently are no clear recommendations, other than 'not to engage in too much sitting'.[77] In one of our studies we showed that engaging in more than 11 hours of sedentary behavior per day was associated with 64% higher risk of mortality. Moreover, other work in this thesis indicated that the levels of sedentary behavior in older adults were high (up to 80% of the waking day) and that they were ingrained in daily life. Since we did not examine the number or duration of the sedentary bouts, we cannot make clear recommendations on what would be the best method to reduce sedentary behavior. However, in one of our studies, we showed a large seasonal variation for light physical activity, indicating that this is a behavior that is easily changed. Therefore, interrupting sedentary behavior with short bouts of light physical activity (e.g. housework, walking) might be a first step to reducing sedentary behavior in older adults. To be able to work towards a concrete recommendation regarding sedentary behavior, future studies should put more focus on the association between patterns of sedentary behavior and health. Moreover, with the advancement of algorithms for accelerometers, the posture might also be obtained from the accelerometer-signal, thereby providing more information on the sedentary activity in which the individual is engaged (e.g. passively standing, sitting or lying down). However, as with physical activity, we also stress the importance of measuring sedentary behavior by questionnaire, since this provides information on the context of the sedentary behavior. In this thesis, we observed no association between objectively measured of sedentary behavior with depression, anxiety or cognition, whereas previous studies using self-report did observe associations.[22-24] The studies in which more sitting was associated with poor mental health and cognition all included television watching in their proxy of sedentary behavior, indicating that the context might be of importance.[78] Therefore, we also recommend to use both subjective and objective methods to obtain the most detailed information on sedentary behavior. Moreover, the agreement between objectively and subjectively sedentary behavior should also be evaluated. Nevertheless, one thing that is currently clear, is that interrupting sedentary time with short bouts of activity on a regular basis is unlikely to induce harm and can be encouraged in older adults.

Sleep

There is currently extensive evidence that a sleep duration between 7-8 hours is associated with health benefits.[79,80] In the current thesis, we observed a seasonal pattern for sleep duration, with lower levels in the summer compared to the winter, which was mostly related to the ambient temperature. This indicates that ensuring an optimal thermal sleep environment might be beneficial to increasing sleep duration in warm summer months. Policies aimed to address the reduction in sleep duration in the summer should therefore account for sleep hygiene.[79,81] Furthermore, in the current thesis we observed a bidirectional association between objectively measured sleep indices and body mass index, indicating that sleep can influence body mass index and vice versa. A higher average body mass index was associated with a decline in sleep duration over time. Conversely, longer sleep duration and higher sleep efficiency slowed down the decrease in body mass index across time. Together, these results highlight a complicated relation. In older adults, the balance between fat and muscle changes and body mass index might not accurately reflect that.[82] Consequently, a reduction in body mass index might also be a proxy of the loss of muscle mass.[83] Future studies should evaluate whether sleep duration and sleep efficiency are association with a slower decline in fat or fat free mas. Additionally, the fact that higher body mass index is associated with a decline in sleep duration, emphasizes the importance of maintaining a healthy body weight across all ages. This health consequence could be highlighted in addition to the benefits of a healthy weight associated with cardiovascular disease and mortality.[84,85]

The results from this thesis show that in older adults, several physical activity types are associated with health benefits. Older adults can be encouraged to engage in physical activity that they enjoy and that they are capable of doing. In the future, the use of objective measures of activity will enhance the current knowledge on patterns of physical activity, sedentary behavior, and sleep. With advancing technology, more information can be obtained by accelerometers, including information on types of physical activity. However, the use of questionnaires remains important, to be able to gain information on the types of activity in which adults engage that cannot be captured by accelerometer (e.g. sitting in front of the television versus sitting in front of the computer), as well as how the activity is perceived. Future efforts should examine to what extent the associations of objective and subjective activity measures with health are similar. Together, this information can aid public health instances in creating targeted recommendations to enhance health in older adults.

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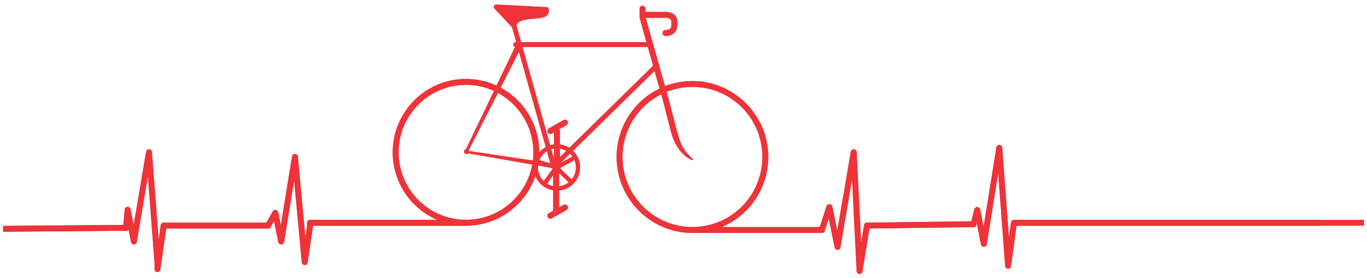

Chapter 7

Appendices

Summary

The aim of this thesis, described in Chapter 1, was to extend the existing knowledge on the association of sedentary behavior, physical activity and sleep with a broad spectrum of health outcomes in older adults. These activity domains were measured subjectively by questionnaire, or objectively by actigraphy and accelerometry.

In the second chapter, we focused on factors associated with objective and subjective measures of activity. In Chapter 2.1, we observed that physical activity levels assessed by questionnaire were generally underestimated compared to a wrist-worn accelerometer. We also showed that adults with more depressive symptoms, more disability and individuals with a higher body mass index underestimated their self-reported physical activity levels more than the reference groups, indicating that perceived health might also affect the judgement of physical activity levels.

Further, in Chapter 2.2 we examined the activity distribution of objectively measured physical activity, sedentary behavior and sleep in elderly adults and examined with which demographic and health factors these activity domains were associated. We showed that sedentary behavior increased across increasing age-categories and across higher levels of body mass index, at the expense of light and moderate-to-vigorous physical activity, but we observed no clear differences between categories for sleep duration. Moreover, individuals with prevalent chronic disease and those with disability showed higher levels of sedentary behavior and lower levels of physical activity than their healthier counterparts. We also observed that women have higher levels of physical activity than men.

In Chapter 2.3, we examined the seasonal pattern of objective measures of physical activity, sedentary behavior and sleep according to an age-specific approach. Moreover, we examined which meteorological factors were related to these seasonal patterns and we modeled the all-cause mortality related to the seasonality. In adults up to 75 years, physical activity levels were highest in the summer, at the extent of sleep duration. Sedentary behavior showed no seasonal pattern, suggesting that this is a behavior very ingrained in daily life. The seasonality of physical activity and nighttime sleep duration was mostly explained by ambient temperature and sunlight hours. Moreover, we demonstrated that the accumulation of low levels of physical activity and high levels of sedentary behavior might lead to a higher all-cause mortality risk in winter.

In Chapter 3, we examined the association of physical activity and sedentary behavior with mortality. First, we assessed the association of total physical activity and physical activity types with all-cause and cause-specific mortality in Chapter 3.1. We observed that total physical activity was associated with lower mortality risk related to all-causes, cardiovascular diseases, chronic lung diseases, infections and mortality from other causes. All activity types were associated with a reduction in all-cause mortality.

Next, we examined the association between actigraphically measured sedentary behavior and all-cause mortality in Chapter 3.2 and observed a higher all-cause mortality risk for participants with the highest levels of sedentary behavior. However, after adjusting for other

measures of activity, including disability and physical activity, the association between sedentary behavior and mortality was clearly attenuated.

In the fourth chapter, we focused on physical activity and cardiovascular health outcomes. We explored the association of total physical activity, and of walking, cycling, domestic work, gardening and sports with coronary heart disease in Chapter 4.1, with atrial fibrillation in Chapter 4.2 and with life expectancy with and without cardiovascular disease in Chapter 4.3. We showed that cycling and domestic work were activity types most strongly related to a reduction in coronary heart disease incidence and with increases in total life expectancy, and extending life expectancy without cardiovascular disease. In contrast, we observed no association of total physical activity or any of the physical activity types with atrial fibrillation incidence.

In Chapter 4.4 we evaluated the joint effects of physical activity and body mass index with cardiovascular disease risk. We showed that individuals who engaged in higher levels of total physical activity were not at increased risk of cardiovascular disease, regardless of being overweight or obese. In contrast, overweight and obese individuals with lower total physical activity levels were at significantly higher risk of cardiovascular disease. Additionally, the cardiovascular disease risk between normal weight participants with low levels of physical activity was comparable to the risk of obese adults with high levels of physical activity.

In the fifth chapter of this thesis, we examined associations between activity and mental health and wellbeing. In Chapter 5.1, we examined the association between physical activity types and health-related quality of life according to an age-specific approach. We observed a dose-response relation between total physical activity and better health-related quality of life. Additionally, we found that sport was associated with better mobility, self-care, daily activities, mood and less pain in middle-aged adults, whereas cycling was associated strongest with these health-related quality of life domains in elderly people.

In Chapter 5.2, we examined the association of actigraphically measured sedentary behavior with depression, anxiety and cognition. We observed that higher levels of sedentary behavior were associated with more depressive symptoms, higher odds of having a prevalent anxiety disorder and with worse cognitive function. However, these associations were completely explained by other factors, including disability, occupational status and smoking. Furthermore, we observed no association between sedentary behavior and changes in depressive symptoms or cognitive function over time, nor did we find an association between sedentary behavior and incident anxiety disorders.

In Chapter 5.3, we examined the bidirectionality of the association between actigraphically measured sleep with body mass index. We observed that long and efficient sleep slow down the general decrease in body mass index over time. Additionally, we observed that higher baseline body mass index had a negative influence on sleep duration and quality over a period of 6 years.

In Chapter 6, we discussed the results of the studies described in this thesis in a broader perspective. Moreover, relevant methodological consideration, clinical implications and directions for future research are discussed.

Samenvatting

Het doel van deze scriptie, beschreven in hoofdstuk 1, was om de bestaande kennis over de associatie tussen sedentair gedrag, lichamelijke activiteit en slaap en een brede range van gezondheidsuitkomsten onder ouderen uit te breiden. Deze verschillende soorten activiteit zijn gemeten met een vragenlijst, of objectief door middel van actigrafie of een accelerometer.

In het tweede hoofdstuk hebben we gefocust op factoren die gerelateerd zijn aan objectief en subjectief gemeten activiteit. In hoofdstuk 2.1, laten we zien dat de gerapporteerde hoeveelheid lichamelijke activiteit zoals gemeten door middel van vragenlijst over het algemeen lager is dan die gemeten door een om de pols gedragen accelerometer. Verder vinden we dat volwassenen met meer depressieve klachten, lichamelijke beperkingen of een hoger body mass index (BMI) hun lichamelijke activiteit nog meer onderschatten dan de referentie groep. Dit impliceert dat de perceptie van eigen gezondheid invloed heeft op het schatten van de hoeveelheid lichamelijke activiteit.

In hoofdstuk 2.2, hebben we de distributie van objectief gemeten lichamelijke activiteit, sedentair gedrag en slaap onderzocht. Daarnaast hebben we onderzocht met welke demografische en gezondheidsfactoren deze domeinen gerelateerd waren. We vinden dat de hoeveelheid sedentair gedrag toeneemt met de leeftijd en BMI, ten koste van lichamelijke activiteit. We laten ook zien dat er geen duidelijke verschillen zijn voor slaapduur tussen de verschillende demografische en gezondheidsfactoren. Verder vinden we dat ouderen met een bestaande chronische ziekte, of met meer lichamelijke beperkingen een hogere hoeveelheid sedentair gedrag hebben, en een lagere hoeveelheid lichamelijke activiteit dan de referentie groep. Tot slot viel ons op dat vrouwen meer lichamelijk actief zijn dan mannen.

In hoofdstuk 2.3 onderzochten we het patroon van objectieve maten van lichamelijke activiteit, sedentair gedrag en slaap gedurende het jaar. Hierbij keken we ook naar welke meteorologische factoren gerelateerd waren aan dit seizoensgebonden patroon en modelleerden we hoe dit de kans op overlijden kan beïnvloeden. Ouderen tot de leeftijd van 75 jaar hadden de grootste hoeveelheid lichamelijke activiteit in de zomer, terwijl de slaapduur toen juist lager was. Voor sedentair gedrag vonden we geen seizoensgebonden patroon. Dit suggereert dat sedentair gedrag is ingebakken in het dagelijkse leven. De fluctuaties van fysieke activiteit en slaap gedurende het jaar werden vooral verklaard door de buitentemperatuur en de hoeveelheid zonlicht. De combinatie van lage hoeveelheid lichamelijke activiteit en hoge hoeveelheid sedentair gedrag kan zorgen voor een hogere kans op overlijden in de winter.

In het derde hoofdstuk hebben we de associatie tussen lichamelijke activiteit en sedentair gedrag met het risico op overlijden onderzocht. In hoofdstuk 3.1 onderzochten we allereerst de associatie tussen totale lichamelijke activiteit en verschillende typen activiteit met sterfte door alle oorzaken en sterfte door specifieke oorzaken. Een hogere hoeveelheid totale lichamelijke activiteit was gerelateerd aan een kleinere kans op sterfte door alle oorzaken, en een kleinere kans op overlijden veroorzaakt door hart- en vaatziekten (HVZ), chronische longziekten, infecties of andere oorzaken. Alle typen lichamelijke activiteit waren geassocieerd met een vermindering in de kans op sterfte door alle oorzaken.

Vervolgens onderzochten we de associatie tussen sedentair gedrag, objectief gemeten met actigrafie, en het risico op overlijden in hoofdstuk 3.2. We laten zien dat grotere hoeveelheden sedentair gedrag gerelateerd zijn aan een grotere kans op overlijden. Echter, na het corrigeren voor andere vormen van activiteit, zoals activiteiten van het dagelijks leven en lichamelijke activiteit, was de associatie duidelijk afgezwakt.

In het vierde hoofdstuk hebben wij ons gericht op lichamelijke activiteit en HVZ. We bestudeerden de relatie tussen totale fysieke activiteit, en specifiek met lopen, fietsen, huishoudelijk werk, tuinieren en sport met coronaire hartziekten in hoofdstuk 4.1, met atrium fibrilleren in hoofdstuk 4.2 en met de levensverwachting met en zonder HVZ in hoofdstuk 4.3. We laten zien dat fietsen en huishoudelijk werk sterk geassocieerd zijn met een lagere kans op coronaire hartziekten, en met een grotere totale levensverwachting, en levensverwachting zonder HVZ. Echter vonden we geen relatie tussen totale lichamelijke activiteit of één van de types lichamelijke activiteit en atrium fibrilleren.

In hoofdstuk 4.4 hebben we het gezamenlijke effect van lichamelijke activiteit en BMI op het risico op HVZ geëvalueerd. Uit ons onderzoek blijkt dat ouderen die veel bewegen geen verhoogde kans hebben op HVZ, ongeacht of ze overgewicht of obesitas hebben. Echter, ouderen met overgewicht en obesitas en met een lage hoeveelheid lichamelijke activiteit hebben wel een hogere kans hebben op HVZ. We laten ook zien dat de kans op HVZ voor mensen met een normaal gewicht en een lage hoeveelheid lichamelijke activiteit vergelijkbaar was met die voor ouderen met obesitas en een hoge hoeveelheid lichamelijke activiteit.

In het vijfde hoofdstuk hebben we de associatie tussen verschillende vormen van activiteit en maten van mentale gezondheid en welzijn onderzocht. In hoofdstuk 5.1 kijken we naar de relatie tussen lichamelijke activiteit en gezondheid-gerelateerde kwaliteit van leven, volgens een leeftijdsspecifieke benadering. We vinden een dosis-responsrelatie tussen de hoeveelheid totale lichamelijke activiteit en een betere gezondheid-gerelateerde kwaliteit van leven. Tevens was sport gerelateerd aan betere mobiliteit, zelfzorg, dagelijkse activiteit, stemming en minder pijn in volwassenen van middelbare leeftijd, terwijl fietsen het sterkst gerelateerd was aan deze factoren in ouderen.

In hoofdstuk 5.2 onderzochten we de relatie tussen actigrafisch gemeten sedentair gedrag met depressie, angst en cognitie. Wanneer deze factoren op hetzelfde tijdstip (cross-sectioneel) werden gemeten, vonden we dat sedentair gedrag gerelateerd was aan meer depressieve symptomen, een grotere kans op een angststoornis en slechtere cognitieve prestatie. Deze associaties konden echter allemaal worden verklaard door andere factoren, zoals lichamelijke beperkingen, werkstatus en rookgedrag. We laten ook zien dat er geen longitudinaal verband is tussen sedentair gedrag en veranderingen in depressieve symptomen of cognitieve prestatie, en dat sedentair gedrag niet gerelateerd is aan het ontwikkelen van een angststoornis.

In hoofdstuk 5.3 onderzochten we of de associatie tussen actigrafische maten van slaap en BMI mogelijk twee kanten op gaat; dat slaap BMI beïnvloedt en dat BMI slaap beïnvloedt. We vinden dat een langere en efficiëntere slaapduur was geassocieerd met een langzamere daling in

BMI over de tijd. Ook laten we zien dat een hogere BMI op baseline is geassocieerd met een vermindering van slaapduur en slaapkwaliteit gedurende een periode van 6 jaar.

In hoofdstuk 6 bespreken we de resultaten van de studies in deze thesis in een breder perspectief. Relevante methodologische overwegingen, klinische implicaties en mogelijkheden tot vervolgonderzoek worden ook besproken.

Author affiliations

Department of Epidemiology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
Marijn Albrecht, Mathilde Berghout, Guy Brusselle, Magda Cepeda, Klodian Dhana, Nicole S. Erler, Oscar H. Franco, Albert Hofman, M. Arfan Ikram, Maryam Kavousi, Desana Kocevska, Chantal M. Koolhaas, Lies Lahousse, Annemarie I. Luik, Frank J.A. van Rooij, Josje D. Schoufour, Henning Tiemeier

Department of Child and Adolescenet Psychiatry/Psychology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
Desana Kocevska, Henning Tiemeier

Department of Psychiatry, Erasmus MC, Rotterdam, The Netherlands
Henning Tiemeier

MRC Epidemiology Unit, University of Cambridge, School of Clinical Medicine, Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, the United Kingdom
Soren Brage

ISGlobal, Center for Research in Environmental Epidemiology, Barcelona, Spain, Pompeu Fabra University, Barcelona, Spain
Monica Guxens

Department of Nutrition, Harvard School of Public Health, Boston, MA, United States
Klodian Dhana

Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium
Lies Lahousse, Guy Brusselle

Department of Respiratory Medicine, Erasmus MC, Rotterdam, the Netherlands
Guy Brusselle

Department of Neurology, Erasmus MC, Rotterdam, The Netherlands
M. Arfan Ikram

Department of Radiology, Erasmus MC, Rotterdam, The Netherlands
M. Arfan Ikram

West Suffolk Hospital, University of Cambridge Associate Teaching Hospital, United Kingdom
Rajna Golubic

Public Health Erasmus MC, University Medical Center Rotterdam, the Netherlands
Wilma Nusselder

Obesity and Population Health, Deakin University, Burwood HWY, Australia
Anna Peeters

Department of Biostatistics, Erasmus MC, University Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, the Netherlands
Nicole S. Erler

Department of Sleep and Cognition, Netherlands Institute for Neuroscience (NIN), an institute of the Royal Netherlands Academy of Arts and Sciences, Amsterdam, The Netherlands
Bart te Lindert

Sleep and Circadian Neuroscience Institute, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK (AIL)
Annemarie I. Luik

About the author

Chantal Koolhaas was born on June 3rd 1989, and grew up in Enkhuizen, the Netherlands. Because of her interest in sports and her affinity with physics, she decided to study Movement Sciences. She completed her Bachelor of Science degree in Movement Sciences in 2011 at the Vrije Universiteit in Amsterdam. At the same university, she continued with a master program in Human Movement Sciences. The original program duration was one year, but in addition to the obligatory research internship, Chantal extended the program with a year by doing an additional research internship and graduated in 2013. Both research projects were performed within the EMGO Institute for Health and Care Research at the Vrije Universiteit. After the second internship, she worked for a research assistant for half a year, after which that project ended.

In 2014, Chantal began her PhD program at the Department of Epidemiology at the Erasmus Medical Center in Rotterdam, by enrolling and successfully completing the Master of Science in Epidemiology at the Netherland Insitute for Health Sciences (NIHES). Additionally, during the PhD program, she participated in the Doctor of Science program in Epidemiology and received the degree in 2017. Chantal performed her research within ErasmusAGE, a research center focusing on the role of lifestyle and nutrition in health throughout the life course. The results of these projects are presented in this thesis. In June 2017, she was awarded for the best oral presentation during the congress of the European Menopause and Andropause Society. In the future Chantal aims to pursue a career in academia.

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Koolhaas CM, Dhana K, Golubic R, Schoufour JD, Hofman A, van Rooij FJ, Franco OH. Physical activity types and coronary heart disease risk in middle-aged and elderly persons: The Rotterdam Study. *Am J Epidemiol*. 2016 Apr 15;183(8):729-738.

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Koolhaas CM, Dhana K, Schoufour JD, Lahousse L, van Rooij FJA, Ikram MA, Brusselle G, Tiemeier H, Franco OH. Physical activity and cause-specific mortality: The Rotterdam Study. *Submitted for publication.*

Albrecht M*, **Koolhaas CM***, Schoufour JD, van Rooij FJ, Kavousi M, Ikram MA, Franco OH. Physical activity types and atrial fibrillation risk in the middle-aged and elderly: the Rotterdam Study. *Submitted for publication.*

Koolhaas CM. van Rooij FJA, Kocevska D, Luik AI, Franco OH, Tiemeier H. Objectively measured sedentary time and mental and cognitive health: cross-sectional and longitudinal associations in The Rotterdam Study. *Submitted for publication.*

Koolhaas CM*, Kocevska D*, te Lindert BHW, Erler, NS, Franco OH, Tiemeier H, Luik AI. The bidirectional association between objectively measured sleep and body mass index: The Rotterdam Study. *Submitted for publication.*

** Denotes equal contribution within a manuscript*

PhD Portfolio summary

Name of PhD Student	Chantal Mireille Koolhaas
Erasmus MC Department	Epidemiology
PhD Period	June 2014-March 2018
Promotors	Prof. dr. Oscar H. Franco
	Prof. dr. Henning Tiemeier
Co-promotors	Dr. Klodian Dhana
	Dr. Josje D. Schoufour

Training	**Year**	**ECTS**
Courses and workshops		
Master of Science, Epidemiology, NIHES	2014-'15	70
Doctor of Science, Epidemiology, NIHES	2015-'17	70
Integrity in Scientific Research, Erasmus MC	2017	2.0
Endnote, Medical Library, Erasmus MC	2014	0.3
Systematic Literature Search, Medical Library, Erasmus MC	2014	0.6
Attended Erasmus MC meetings		
Seminars at the department of Epidemiology	2014-'18	1.0
ErasmusAGE research meetings	2014-'18	1.0
2020 Epidemiology meetings	2014-'18	1.0
Cardiovascular group meetings	2014-'18	1.0

Meeting and conferences

Koninklijke Nederlandse Akademie van Wetenschappen/Dutch Society for Research on Ageing (KNAW/DuSRA)meeting in Leiden, The Netherlands	2017	0.5
European Menopause and Andr opause Society in Amsterdam, The Netherlands	2017	1.5
Congress of the European College of Sport Science in Essen, Germany	2017	1.5
Vereniging van Beweging PhD-day, Rotterdam, The Netherlands	2017	1.0

Presentations

Koninklijke Nederlandse Akademie van Wetenschappen/Dutch Society for Research on Ageing (KNAW/DuSRA)meeting in Leiden, The Netherlands Objective measures of activity in the elderly: Distribution and associations with demographic and health factors – poster presentation	2017	0.2
European Menopause and Andropause Society in Amsterdam, The Netherlands Objective measures of activity in the elderly: Distribution and associations with demographic and health factors – oral presentation	2017	0.2
Congress of the European College of Sport Science in Essen, Germany Seasonality of physical activity, sedentary behavior, and nighttime sleep duration in a middle-aged and elderly population of the Rotterdam Study – oral presentation	2017	0.2

Teaching activities- Supervising master students

Teaching assistant, Biostatistical Methods I: basic principles	2017	0.3
Marijn Albrecht, Physical activity types and atrial fibrillation risk in the middle-aged and elderly	2016-‘17	2
Maria Giulia Loffreda, Self-rated health and cardiovascular disease	2017	2

Other

Peer review of articles for scientific journals	2015-‘17	2
Rotterdam Study general tasks and coding	2014-‘17	2