Obesity, Physical Activity, and Cardio-metabolic Disorders in Older Adults

Klodian Dhana

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Obesity, Physical Activity, and Cardio-metabolic Disorders in Older Adults

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cardio-metabolica aandoeningen bij oudere volwassenen

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Contents

MANUSCRIPTS BASED ON THE STUDIES DESCRIBED IN THIS THESIS

Chapter 2

Dhana K, Kavousi M, Ikram MA, Tiemeier HW, Hofman A, Franco OH. Body shape index in comparison with other anthropometric measures in prediction of total and cause-specific mortality. *J Epidemiol Community Health 2016; 70(1): 90-6.*

Dhana K, Ikram MA, Hofman A, Franco OH, Kavousi M. Anthropometric measures in cardiovascular disease prediction: comparison of laboratory-based versus non-laboratory-based model. *Heart 2015; 101(5): 377-83.*

Dhana K, Koolhaas CM, Schoufour J, Rivadeneira F, Hofman A, Kavousi M, Franco OH. Association of anthropometric measures with fat and fat-free mass in the elderly: The Rotterdam study. *Maturitas 2016; 88: 96-100.*

Chapter 3

Dhana K, Koolhaas CM, van Rossum EF, Ikram MA, Hofman A, Kavousi M, Franco OH. Metabolically healthy obesity and the risk of cardiovascular disease in the rlderly population. *PLoS One 2016; 11(4): e0154273.*

Dhana K, Ligthart S, Hofman A, Dehghan A, Franco OH, Kavousi M. Timing and duration of overweight in association with metabolic syndrome and diabetes among middle-aged and elderly. *Submitted for publication.*

Chapter 4

Dhana K, Berghout MA, Peeters A, Ikram MA, Tiemeier H, Hofman A, Nusselder W, Kavousi M, Franco OH. Obesity in older adults and life expectancy with and without cardiovascular disease. *Int J Obes (Lond) 2016.*

Dhana K, van Rosmalen J, Vistisen D, Ikram MA, Hofman A, Franco OH, Kavousi M. Trajectories of body mass index before the diagnosis of cardiovascular disease: a latent class trajectory analysis. *Eur J Epidemiol 2016.*

Chapter 5

Dhana K, Koolhaas CM, Ikram MA, Hofman A, Franco OH, Kavousi M. The impact of physical activity on the association between overweight, obesity and cardiovascular disease. *Submitted for publication.*

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.*

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. *Submitted for publication*

** Denotes equal contribution within a manuscript*

Chapter 1

General Introduction

The World Health Organization (WHO) defines overweight and obesity as abnormal or excessive fat accumulation that presents a risk to an individual's health.[1] Physical activity is defined by WHO as any bodily movement produced by skeletal muscles that requires energy expenditure.[2] Both obesity and physical inactivity constitute important public health problems because of the association with increased risk of numerous chronic conditions including diabetes, cardiovascular disease, cancer, and disability at older age.[3] The increase in life expectancy due to improvement in health care over the last century has been accompanied by an increase in the prevalence of obesity and disability among the elderly.[4]

Novel and traditional anthropometric measures

Body mass index (BMI) is the most common method of measuring overweight and obesity. For calculation of BMI, a person's body weight (kilograms) is divided by the height (meters) squared.[3] According to the WHO, an individual with a BMI of 30 or more is considered obese, and having a BMI equal to or more than 25 is considered overweight.[5] To assess general adiposity, BMI is a reasonably good measure and is used commonly in clinical practice. Increased BMI is an established risk factor for diabetes, cardiovascular disease (CVD) and some cancers and consequently for mortality.[6,7] However, the association between BMI and mortality is not consistent among young, middle aged and elderly adults and is prone to contradictory conclusions.[8] To overcome limitations of BMI, current national and international guidelines advocate for the routine measurement of waist circumference (WC) and waist to hip ratio (WHR) in the assessment of adiposity.[9] WC and WHR are measures of waist and hip circumference and provide information about distribution of body fat. Recently, a new anthropometric measure, a body shape index (ABSI), has been developed.[10] ABSI has been derived from WC and is independent of height and weight. The added value of ABSI, next to BMI, WC and WHR, has not been addressed in association with total, CVD and cancer mortality among an elderly population.

Considering the value of anthropometric measures as a predictive marker for CVD and mortality, these measures can potentially be used in risk prediction models.[11] To simplify the traditional cardiovascular risk prediction models, BMI has been proposed to substitute lipids in prediction of CVD risk.[12] The simplified cardiovascular risk prediction model is called the non-laboratory based model. This model has similar risk factors (i.e. age, sex, hypertension, smoking status, diabetes mellitus) as the traditional cardiovascular risk prediction model, termed the laboratory-based model, but uses BMI instead of lipids.[13] Evidence shows that BMI becomes a less accurate reflection of fat mass in middle-aged and elderly adults and its role in CVD risk prediction seems to diminish with advancing age.[14,15] Compared to BMI, assessment of other anthropometric measures, such as WC, WHR and ABSI, could provide better information on CVD risk among the elderly population. Therefore, these measures might be better tools for CVD risk assessment to replace lipids in a non-laboratory based model.

Anthropometric measures have also been suggested to assist in identifying individuals at high risk of sarcopenic obesity, a condition defined as a decrease in fat-free mass (FFM) associated with an increase in fat mass (FM).[16,17] However, previous research has shown limited evidence for the value of traditional anthropometric measures, such as BMI, in highlighting individuals at high risk for sarcopenic obesity.[18] Traditional anthropometric measures, such as BMI and WC, could be attributed to an increase in both FM and FFM.[18] The newly developed anthropometric

measure, ABSI, is correlated with WC but is independent of height and weight.[10] Therefore, ABSI could have a differential association with FM and FFM that cannot be distinguished by BMI and WC alone. This might highlight ABSI as a good candidate in identifying individuals at high risk of sarcopenic obesity.

Metabolic health among the elderly

Obesity is often accompanied by the metabolic syndrome, a cluster of dyslipidemia, hyperglycemia, and hypertension.[19] However, not all obese individuals develop metabolic syndrome.[20] In this context, recent interest has focused on a subgroup of obese individuals who have a healthy metabolic profile. Evidence suggests that among the obese population, around 20-30% might present with a healthy metabolic profile.[21] So far, evidence regarding the risk of CVD among obese individuals with a healthy metabolic profile, mostly based on studies among younger or middle-aged individuals, is inconclusive.[20, 22-24] Particularly among the elderly such evidence is lacking. In the elderly, the relation between body weight, body composition, and health behaviors is different than in younger adults.[25] Therefore, the impact of being obese but having a healthy metabolic profile could differ between younger, middle-aged and elderly adults.

Furthermore, to identify obese individuals with healthy metabolic profile, most research has traditionally focused on one time point to assess the BMI status and the presence of metabolic syndrome.[22,24] However, weight history might explain why some overweight individuals appear to be resistant to the adverse metabolic effects of excess body fat.[26,27] Moreover, the pattern of elevation in body weight might also be an important parameter in developing adverse metabolic effects of overweight. These concepts have not yet been addressed in large population-based settings.

Obesity, cardiovascular disease and mortality

Epidemiologic studies suggest that overweight and obesity are associated with an increased risk of CVD and mortality.[6,7] These studies, however, are mostly performed among the young and middle-aged populations. As yet, there is no clear consensus regarding the association of overweight and obesity with the risk for CVD and mortality among the elderly.[8,15,28,29] A few studies have quantified the years lost due to obesity, and estimated that being obese will shorten the life expectancy approximately 3 to 7 years, compared to being normal weight.[30,31] Moreover, while obesity is associated with an increased risk of CVD, it remains unknown whether obese individuals would live fewer or more years suffering from CVD, compared with those of normal weight. Notably, from the public health prospective, it is important to provide information beyond measures of relative risk but of the lifetime consequences of excess weight such as years lived with and without CVD. This would facilitate conveying results to the general public and further understanding the public health implications of obesity on a population level.

Although obese individuals are at higher risk for developing CVD during their lifespan, CVD is not limited to obese individuals.[32] Instead, patients with CVD comprise a heterogeneous group with regard to their BMI levels at the time of diagnosis. Understanding the heterogeneity of CVD by exploring the distinct patterns of change in BMI levels prior to the diagnosis of CVD might carry important implications for improving disease prevention or treatment. For instance, each

trajectory of BMI change prior to CVD could be accompanied by different trajectories of change in other cardio-metabolic risk factors. One way of exploring this heterogeneity is to group individuals with similar patterns of change in BMI over time, through data-driven statistical methods, such as latent class trajectory analysis.[33,34] Likewise, the application of this approach to understanding the progression of cardiovascular risk factors reveals novel pathways on disease development which will open new windows into understanding the complex nature of CVD.

Obesity, physical activity and cardiovascular disease

While overweight and obese individuals have a greater risk for CVD compared to normal weight individuals, this could be partly explained by their reduced physical activity levels.[35,36] Higher levels of physical activity are associated with lower risk of CVD.[37,38] Hence, physical activity might reduce the risk associated with overweight and obesity. These findings have led to the identification of the "fat but fit" phenomenon and raised the question to what extent physical activity can counterbalance the risk associated with overweight and obesity.[39]

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.[40] However, previous studies 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.[41] To date, studies have generally assessed the associations between physical activity and cardiovascular disease only in terms of hazard ratios.[38,40] These measures of association do not allow for translation of the results for public and individual health care planning. Complementing current knowledge with absolute measures such as life expectancy has been extensively recommended. This would facilitate conveying the results to the general public and further understanding the public health implications of physical activity on a population level.

Outline of this thesis

In this thesis, I attempt to provide additional evidence regarding the role of traditional and novel anthropometric measures in prediction of CVD and mortality. Furthermore, I evaluate the metabolic health among older adults in association with CVD and additionally explore how duration of overweight could impact the metabolic risk. I also focus on the impact of obesity on life expectancy with and without CVD, and explore the trajectories of obesity development before the diagnosis of CVD. Finally, I evaluate the impact of physical activity in the association between overweight, obesity and CVD and further explore the types of physical activity in association with coronary heart disease, CVD and life expectancy.

The second chapter of this thesis is dedicated to the evaluation of novel and traditional anthropometric measures in association with CVD and mortality. Chapter 2.1 examines the predictive ability of ABSI in association with total and cause-specific mortality and additionally compares the predictive performance of ABSI with traditional anthropometric measures. The aim of chapter 2.2 is to assess which anthropometric measure is the best predictor for CVD risk in a middle-aged and elderly population to subsequently develop a non-laboratory-based model. In this chapter I compare the performance of this non-laboratory-based model with the laboratory-

based model among an elderly population. Finally, chapter 2.3 evaluates the cross-sectional associations between several anthropometric measures with fat and fat-free mass.

The third chapter focuses on overweight, obesity and cardio-metabolic risk. Chapter 3.1 examines the impact of metabolically healthy obesity on CVD risk. Further, the association of metabolic syndrome with CVD across different BMI categories and the contribution of metabolic syndrome to the association between BMI and CVD among the elderly are addressed. In chapter 3.2 I go one step further and evaluate whether timing and duration of overweight, independent of current BMI status, is associated with metabolic syndrome and with diabetes.

In the fourth chapter of this thesis, I calculate total life expectancy and life expectancy with and without CVD for older adults with obesity, by comparing them to normal weight individuals (chapter 4.1). Also, in this chapter different trajectories of change in BMI prior to a cardiovascular event are identified. I further explore the trajectories of concurrent cardio-metabolic risk factors, including blood pressure, lipids and glucose, within each identified BMI subgroup (chapter 4.2).

The fifth chapter focuses on physical activity. The goal of Chapter 5.1 is to evaluate the role of physical activity in the association between overweight, obesity and cardiovascular disease. Also, in chapter 5, I specifically assess the association between different types of physical activity with coronary heart disease (chapter 5.2) and with life expectancy and life expectancy lived with and without CVD (chapter 5.3).

Finally, the general discussion (chapter 6) summarizes the key findings of the studies included in this thesis, places the results in the context of current literature, elaborates on their potential clinical implications and discusses the directions for future research.

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Chapter 2

Novel versus traditional anthropometric measures of general and central obesity in the middle-age and elderly

2.1 Body shape index in comparison with other anthropometric measures in prediction of total and cause-specific mortality

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Abstract

Background: The association of body mass index (BMI) with mortality remains controversial among middle-aged and elderly. Moreover, the contribution of other anthropometric measures to predict mortality is unclear.

Methods: We assessed the association of BMI, waist circumference (WC), waist-to-height ratio (WHtR), waist-to-hip ratio (WHR) and a body shape index (ABSI) [ABSI=WC/(BMI2/3*Height1/2)] with total, cardiovascular and cancer mortality by using Cox proportion hazard models among 2626 men and 3740 women from the prospective population-based Rotterdam Study. Predictive performance was assessed through informativeness, c-statistic, integrated discrimination improvement (IDI), and continuous net reclassification improvement (cNRI).

Results: During 22-years of follow-up, 3675 deaths from all-causes, 1195 from cardiovascular disease, and 873 from cancer occurred. In multivariable model, ABSI showed a stronger association with mortality compared to BMI, WC, WHtR and WHR. Hazard ratios (HRs) and confidence intervals (95%CIs) for total mortality per 1-standard deviation increase in ABSI were 1.15 (1.09, 1.21) for men and 1.09 (1.04, 1.14) for women. For cardiovascular and cancer mortality, these HRs (95%CI) were 1.18 (1.08, 1.29) and 1.10 (0.99, 1.22) for men, 1.04 (0.96, 1.12) and 1.18 (1.07, 1.30) for women. The models including ABSI did not increase the c-statistics. Among men, in prediction of total mortality the model including ABSI was more informative (X2=26.4) and provided improvement in risk stratification (IDI 0.003, 95%CI 0.001, 0.005; cNRI 0.13, 95%CI 0.06, 0.21).

Conclusion: In our population-based study, among different anthropometric measures, ABSI showed a stronger association with total, cardiovascular and cancer mortality. However, the added predictive value of ABSI in prediction of mortality was limited.

INTRODUCTION

Obesity is increasing globally and the association between body weight, morbidity and mortality has received widespread attention.[1] Among different anthropometric measures, most of the studies have focused on body mass index (BMI) in association with morbidity and mortality.[2,3] While BMI is a widely accepted and an easily applicable measure of obesity, its use has limitations. BMI depends only on height and weight and does not distinguish the distribution of adipose tissue and muscle mass.[4] Furthermore, focusing on BMI in relation to mortality has led to contradictory conclusions.[5,6] A number of studies examined waist circumference (WC), waist to height ratio (WHtR), and waist to hip ratio (WHR) separately in relation to morbidity and mortality.[7-9] While WC is sensitive to height, WHtR is indifferent to body weight and fat distribution.[10] In the measurement of WHR, a disproportionately large hip circumference can hide the status of abdominal obesity.[10]

Recently, a new anthropometric measure, a body shape index (ABSI), has been introduced.[11] ABSI is based on WC, but is independent of height, weight and BMI. Therefore, being independent of BMI, ABSI could shed light on elucidating the predictive ability of abdominal obesity that cannot be attributed to BMI alone. This new measure has been suggested by Krakauer et al. to predict mortality independently from BMI in the US population,[11] and recently in a European population.[12] However, use of ABSI as a predictor of total and cause-specific mortality has not yet been validated in an elderly population, where the predictive ability of traditional risk factors in prediction declines.[13,14] We therefore sought to examine the predictive ability of ABSI in association with total and cause-specific (including cardiovascular disease and cancer) mortality in the population-based Rotterdam Study. We also aimed to compare the predictive performance of ABSI in association with total and cause-specific mortality with those from BMI, WC, WHtR and WHR.

METHODS

Study Population

The Rotterdam Study (RS) is a prospective population-based cohort study in the city of Rotterdam in The Netherlands. The original RS cohort (RS-I) started in 1990 when all inhabitants aged 55 and over residing in the Ommoord district of Rotterdam were invited to participate and 7983 (78.1%) were enrolled. For the present analysis, we excluded all participants without data for weight, height, waist or hip circumference and those who did not provide informed consent for follow-up data collection. This left a total of 6366 persons (2626 men and 3740 women) eligible for the analysis. The Rotterdam Study has been approved by the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center and by the medical ethics committee according to the Wet Bevolkingsonderzoek ERGO (Population Study Act Rotterdam Study), executed by the Ministry of Health, Welfare and Sports of the Netherlands. A more detailed description of the Rotterdam Study can be found elsewhere.[15]

Assessment of anthropometric measurements

Anthropometrics were measured in the research center by trained staff. Height and weight were measured with the participants standing without shoes and heavy outer garments. WC was measured at the level midway between the lower rib margin and the iliac crest with participants in standing position without heavy outer garments and with emptied pockets, breathing out gently. Hip circumference was recorded as the maximum circumference over the buttocks. BMI was calculated as weight divided by height squared (kg/m^2), whereas WHtR and WHR were calculated as WC divided by height, and as WC divided by hip circumference, respectively. ABSI was defined as WC/(BMI 2/3*height1/2) expressing WC and height in meter.[11]

Covariates

Information on covariates was collected through home interviews or was measured at the study center visit. Based on questionnaire, subjects were categorized in groups of current smoker and other (former and ever smokers). Education was assessed according to the standard classification of education comparable to the international standard classification of education (Unesco, Paris, 1976). The information about the marital status (living with partner or not) was obtained from the questionnaires. Basic activities of daily living was assessed with the disability index from the Stanford Health Assessment Questionnaire, consisting of 20 items constituting 8 components: dressing and grooming, arising, eating, walking, hygiene, grip, reach, and activities. Weight loss variable was measured by asking participants if they lost unintentionally more than 3 kg in the last 12 months. Systolic blood pressure was measured on the right arm using a random-zero sphygmomanometer. Serum total cholesterol and high-density lipoprotein (HDL) cholesterol values were measured using standard laboratory techniques. Diabetes mellitus was considered to be present when non-fasting glucose exceeded 200 mg/dL, or when anti-diabetic medication was used. Treatment for hypertension was defined as taking anti-hypertensive medication due to hypertension. 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.

Assessment of Mortality

Data on total and cause-specific mortality were collected using an automated follow-up system until 1st January 2011. Cardiovascular mortality was defined as mortality as a consequence of coronary heart disease, cerebrovascular disease, or other atherosclerotic disease.[16] Cancer mortality was defined as mortality attributed to malignant neoplasms (ICD-10: C00–C97). The median follow up for the analyses was 15.93 years (interquartile range: 8.74-18.01).

Statistical Analysis

Correlation between anthropometric variables was evaluated with Pearson correlation analysis. Cox proportional hazards regression models were used to estimate the Hazard ratios (HR) and 95% confidence intervals (CI) for the association between anthropometric measures and mortality, separately in men and women.[17] We initially adjusted the models for age among men and women. For the main analysis, all models were adjusted for traditional risk factors including age, total and high density lipoprotein (HDL) cholesterol, systolic blood pressure, treatment for

hypertension, current smoking, and diabetes mellitus. Adjustments for confounders were performed based on prior knowledge in published literature.[11] We additionally adjusted the models for education, activity daily living (as a proxy for physical activity), and marital status (living or not living with a partner).

To assess the performance of anthropometric measures in prediction of mortality, we developed several prediction models. Our base model included traditional risk factors. We then developed several extended models by adding each anthropometric measure to the base model (base model + ABSI, base model + BMI, base model + WC, base model + WHR, base model + WHtR) for prediction of different mortality outcomes. First, we computed the informativeness for each model. The informativeness of an anthropometric measure is meant to capture how well it predicts the outcome. Informativeness is calculated as the difference in twice the log-likelihood of a Cox model with and without that anthropometric measure. This difference between these log-likelihoods follows a chi-square-distribution, and the greater the difference, the more "informative" that anthropometric measure is. We then test whether this difference is statistically significant which is similar to the likelihood ratio test between the two models.[18] Second, we calculated the c-statistic based on the Cox proportional hazard regression models to assess discrimination.[19] Discrimination is the ability of a prediction model to assign a higher risk to the individuals who will develop an event compared with those who will not develop an event. The c-statistic was calculated independently for the base model and for each extended model. The comparison between c-statistic of the base and each extended model was based on their respective estimates and confidence intervals. Third, to assess the change in the predictive power of the base model in prediction of different mortality outcomes upon addition of the anthropometric measures, we calculated the 15 year risk for all cause and cause-specific mortality for each participant first based on the base model and then using each extended model. To compare the predicted probabilities from the base model and each extended model, we computed the integrated discrimination improvement (IDI),[20] and the net reclassification improvement (NRI).[21] Since well-established cut-off points for calculation of NRI across different risk categories for mortality are lacking, we calculated the continuous NRI (cNRI) for each participant. The cNRI only takes into account the correct upward and downward reclassifications for individuals with and without an event (i.e. mortality) and does not require risk stratification into categories.

Sensitivity analysis

In a sensitivity analysis, we examined the association of anthropometric measures with mortality stratified by age groups (younger than 65 years vs. at least 65). We did the homogeneity test, which is a Wald test analysis to test the null hypothesis that the hazard ratios (effect size) are similar across the age groups. Also, we additionally adjusted for level of education, daily activity living and marital status (living or not living with a partner). For women we performed an additional analysis by adjusting for the use of hormone therapy. When we analyzed the association between anthropometric measurements and cardiovascular mortality, we additionally adjusted for prevalent cardiovascular disease at baseline. Since detailed information on life-threatening diseases (i.e. cancer prevalence) at baseline was not available, as a sensitivity analysis, we repeated all the analyses by excluding deaths during the first 5 years of follow-up based on the assumption that such deaths are most likely due to diseases present at baseline. We also repeated

the analyses after excluding subjects who had unintentionally lost more than 3 kg in the last 12 months prior to inclusion in the study.

To deal with missing values for the covariates, we used multiple imputation (n=5 imputations) by the Expectation Maximization method in SPSS. For the informativeness, c-statistic, IDI and NRI we used single imputed dataset. Analyses were conducted with using SPSS software version 20 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp) and the R statistical software (http://www.r-project.org), version 3.0.1 and its libraries "survcomp", "nricens", and "Hmisc".

RESULTS

Baseline characteristics

Table 2.1.1 presents the baseline characteristics of the study population. Compared to men, women were slightly older, had higher mean values of total and HDL cholesterol, BMI and WHtR, whereas the mean values for ABSI, WC and WHR were lower among women. A larger proportion of women were receiving antihypertensive treatment whereas a smaller proportion was current smokers. In our study ABSI was not significantly correlated with BMI but strongly correlated with WC, WHrR, and WHR. The correlation coefficients of ABSI with BMI, WC, WHtR, and WHR were: 0.002 ($p = 0.9$), 0.600 ($p < 0.01$), 0.600 ($p <0.01$), and 0.650 ($p < 0.01$) in men and -0.018 ($p = 0.268$), 0.637 ($p < 0.01$), 0.630 ($p < 0.01$), and 0.804 ($p < 0.01$) in women respectively.

Associations with total mortality

Table 2.1.2 shows the association between anthropometric measures and all cause and cause-specific mortality for men and women in multivariable adjusted models. Per one standard deviation increase in ABSI, the risk for total mortality increased by 15% [HR 1.15 (95%CI 1.09, 1.21)] among men and by 9% [HR 1.09 (95%CI 1.04, 1.14)] among women. Among men, BMI and WHR were significantly associated with total mortality, HRs and (95%CI) were 0.93 (0.89, 0.99) and 1.07 (1.01, 1.12), respectively. These results were not significant among women. The association between WC and WHtR with total mortality did not reach statistical significance.

Associations with cardiovascular disease mortality

Among men, the HRs and (95%CI) were 1.18 (1.08, 1.29) and 0.90 (0.82, 0.99) per 1 SD increases in ABSI and BMI, respectively. In women, the associations between anthropometric measures and CVD mortality did not reach statistical significance (Table 2.1.2).

Associations with cancer mortality

Among men, none of anthropometric measures were associated with cancer mortality, whereas in women only ABSI [HR 1.18, (95%CI 1.07, 1.30) per 1 SD increase] was associated with cancer mortality (Table 2.1.2).

Supplement 2.1.1 and 2.1.2 show the associations of anthropometric measures with total and cause-specific mortality in models adjusted only for age, and per tertiles in the multivariable adjusted models, respectively. Associations between anthropometric measures and total and cause-specific mortality in age-adjusted models were generally similar with multivariable models. Compared to the first tertile, the third tertile of ABSI clearly showed a significant association with total and CVD mortality among men. The graded significant associations were less evident among women and confidence intervals largely overlapped. We additionally adjusted the models for education, activity daily living (as a proxy for physical activity), and marital status (living or not living with a partner). This additional adjustment did not substantially change the effect estimates (supplement 2.1.3). All women in our study were post-menopausal. In an additional analysis, we further adjusted the multivariable models for hormone replacement therapy among women. The results for this analysis were not substantially different from the original analysis (data not shown).

Sensitivity analysis

Supplement 2.1.3 shows multivariable adjusted hazard ratios for anthropometric measures and the risk for total and cause-specific mortality stratified by age group. By using homogeneity statistical test, we observed that WHR had a stronger association with total and CVD mortality in men aged 55 to 65 years old, whereas the association of other anthropometric measures with the mortality outcomes were generally similar across the age subgroups. The results for the analyses excluding events during the first five years of follow-up [798 (407 men and 391 women) of all cause deaths] or excluding the participants who lost more than 3kg weight in the last 12 months prior to the study [664 (252 men and 412 women)] did not deviate substantially from our original analysis regarding the associations of ABSI with total and cause-specific mortality. For BMI, the associations with total mortality did not change substantially but some associations were no longer statistically significant.

To show the independence of ABSI over BMI, we conducted a multivariable model that included both ABSI and BMI. When additionally adjusted for each other, the HRs for ABSI and BMI did not change; i.e. the direction and the magnitude of association for both ABSI and BMI were comparable to the multivariate adjusted models containing each measure alone. This pattern was the same for cause-specific mortality (supplement 2.1.4). When we included both BMI and WC in the same multivariable model, the HRs for both BMI and WC in association with total mortality became stronger. After controlling for WC, the HR of BMI in association with total mortality decreased by 11% for men and 8% for women; new HRs (95%CIs) for BMI were 0.82 (0.75, 0.89) and 0.88 (0.83, 0.95) respectively for men and women. After controlling for BMI, the HR of WC in relation to total mortality became significant and increased by 17% for men and 9% for women; new HRs (95%CIs) for WC were 1.19 (1.10, 1.28) and 1.11 (1.04, 1.19) respectively for men and women. We observed the same pattern with the cause-specific mortality (supplement 2.1.4).

Informativeness, Discrimination and Reclassification

Table 2.1.3 shows the informativeness which is the difference in twice the log-likelihood between the base multivariable model and the extended models for each anthropometric measure as continuous variable. Among all anthropometric measures, ABSI was the most informative

measure for predicting total and cause-specific mortality for both men and women. The X2 of likelihood ratio test for ABSI in association with total, CVD and cancer mortality were 26.4, 12.2 and 3.9 in men, and 15.1, 0.9 and 10.6 in women, respectively. BMI and WHR offered a small improvement in model fit. The X2 of likelihood ratio test for BMI in association with total mortality was 6.5 in men and 3.9 in women, and with CVD mortality was 5.1 in men. The X2 of likelihood ratio test for WHR in association with total mortality was 6.0 in men.

Table 2.1.4 shows the c-statistic for the models containing different anthropometric measures in prediction of total and cause-specific mortality. The c-statistics of the models including ABSI were higher compared to the models including other anthropometric measures in prediction of total and cause-specific mortality. However, considering the large overlap in the confidence intervals of the c-statistics, the increase of c-statistic were not statistically significant. In prediction of total mortality, the c-statistic (95%CI) for ABSI: was 0.746 (0.734, 0.757) for men and 0.784 (0.774, 0.794) for women. In prediction of CVD mortality, the c-statistic (95%CI) for ABSI was 0.792 (0.775, 0.810) for men and 0.819 (0.803, 0.835) for women. In prediction of cancer mortality, the c-statistic for ABSI (95%CI) was 0.668 (0.643, 0.692) for men and 0.644 (0.618, 0.670) for women (Table 2.1.4).

Table 2.1.5 shows the IDI and cNRI in prediction of total and cause-specific mortality. Among men, ABSI offered most improvement in model performance compared to other anthropometric measures for prediction of total mortality; IDI 0.003 (95%CI 0.001, 0.005) and cNRI 0.13 (95%CI 0.06, 0.21), followed by WHR [cNRI 0.09 (95%CI 0.01, 0.16)]. ABSI also lead to a cNRI of 0.16 (95%CI 0.06, 0.25) in prediction of CVD mortality among men. However, among women, none of the anthropometric measures led to improvements in risk predictions for total and cause-specific mortality.

DISCUSSION

In this population-based cohort study, among the presented anthropometric measures, ABSI had a stronger association with death from any cause in men and women, from cardiovascular disease in men, and from cancer in women. However, addition of ABSI to the traditional risk factors did not improve the c-statistic and provided only a modest improvement in model fit and had a small impact on risk stratification in prediction of total mortality among men.

ABSI is a new anthropometric measure, recently introduced by Krakauer, et al, which takes into consideration WC and BMI concurrently and is therefore considered to be more comprehensive than other traditional anthropometric measures.[11] Our findings regarding the association of ABSI with total mortality confirm the previous results.[11,12,22] Furthermore, we showed that increase in ABSI was associated with a higher risk for cardiovascular mortality in men and cancer mortality in women in populations over age 55 and irrespective of age.[23] In line with the previous findings, we observed a linear associations between ABSI with total and cause-specific mortality, however, these linear associations in our study were more clearly demonstrated among men.[22] The association of ABSI with the risk of mortality can be addressed through its components. At a given height and weight, high ABSI may correspond to a greater fraction of visceral fat compared to peripheral tissue,[11] to a smaller fraction of limb muscle mass,[11] and to a lower fat-free mass index.[24] Excess visceral fat is associated with a variety of adverse metabolic outcomes. Similarly,

lean tissue mass and limb circumference[25,26] as well as fat-free mass index[27] have been shown to be negatively associated with mortality risk. Therefore, lifestyle interventions that lead to a reduction in ABSI, such as exercise to increase skeletal muscle mass or weight loss to reduce WC and BMI, could potentially yield favorable health effects followed by an increase in the quality of life. However, to this end, replication of ABSI in different population-based settings to establish appropriate cut off values followed by large randomized controlled trials would be necessary.

In our study, the association of ABSI with mortality was not attenuated when BMI was added in the multivariable model and therefore confirms the independence of ABSI over BMI in the association with mortality.[11] Our results indicate that the association of ABSI with total mortality does not differ between the younger and the older age groups, as reported previously.[11] In our study ABSI continued to be a significant predictor for mortality when deaths during the first 5 years of follow-up were excluded. This finding suggests that the association of ABSI with mortality is not confounded by the presence of life-threatening disease at baseline.[11]

The present study demonstrated that increase in BMI was associated with a lower risk for total and cardiovascular mortality among men. While most prospective studies indicate overweight and obesity as risk factors for mortality, the inverse relationship between BMI and total mortality has been reported in studies comprising elderly subjects (e.g above age 65) with acute or chronic illnesses.[17,28] In our study, when we excluded subjects who died during the first 5 years of follow-up, the inverse association of BMI with total mortality did not change substantially but was no longer statistically significant. Although the loss of statistical significance might be due to lower power after excluding deaths during the first five years of follow-up, such an observation might suggest that the association of BMI with mortality might be distorted by presence of group of subjects with life-threatening diseases at baseline for whom an increase in BMI actually improves the outcome.

The positive association between abdominal obesity assessed by WC or WHtR, and abdominal girth, assessed by WHR, with total and cause specific mortality has been well described before.[8,9,17,23] In the current paper, we complement the evidence by comparing these three measures with ABSI. We showed that ABSI is strongly associated with total mortality among both men and women and with cancer mortality among women. Moreover, in contrast to a previous study,[23] we found that ABSI had a stronger association with CVD mortality among men compared to WC, WHtR and WHR. The inconsistency between the previous study with our results may be explained by different age groups of the two study populations. Our study comprises an older population (55+) compared to the previous study (29+),[23] and WC and WHR seem to be more strongly associated with cardiovascular mortality in younger adults compared to the elderly.[29] Moreover, in our population the association of WHR with total and CVD mortality was stronger in individuals aged 55-65 years compared to the elderly (aged 65+). Although it has been suggested that waist circumference, due to its correlation with abdominal fat, may be informative for CVD mortality,[7] we found it less informative than other anthropometric measures. While we did not find an association between WC and WHtR with total mortality in our multivariable analysis, increase in WHR was associated with higher total mortality among men.

Although BMI and WC are strongly correlated, it has recently been recommended to use both of these anthropometric measures in clinical practice simultaneously, as these two measures reflect

different aspects of obesity.[30] While BMI is an indication for non-abdominal fat and abdominal subcutaneous fat, WC is a reflection of the visceral fat.[30] When we included both BMI and WC in one multivariable model in association with total and cause-specific mortality, the associations of both BMI and WC with the outcome became stronger, compared to using each of these anthropometric measures alone. Our results therefore provide further evidence regarding simultaneous use of BMI and WC in assessing the risk of total and cause-specific mortality.[31-33]

The strengths of our study include availability of a long follow-up time with detailed and validated information on cause-specific mortality, access to comprehensive data on a number of anthropometric measures (height, weight, waist circumference and hip circumference) that allowed for head-to-head comparisons of these measures, and availability of data to control for possible confounders. Nevertheless, our study has limitations. We did not have detailed data on life-threatening conditions at baseline (i.e. cancer prevalence). However, as a proxy, we additionally adjusted our multivariable models for unintended weight loss over the last year before subjects entered the study. Moreover, as a sensitivity analyses, we repeated the analyses after excluding subjects who died during the first 5 years of follow-up. Although we developed several models where we adjusted for a wide range of potential confounders, residual confounding cannot be completely ruled out. Moreover, it should be noted that differences in the studies regarding the study population and its characteristics, definition of outcomes, and inclusion of different confounders might lead to discrepancy in the results between the studies. The mean age of our study population was 69 years and our study might therefore not be generalizable to younger populations. We examined the anthropometric measures only once, at the start of the study, for each subject. Thus, no conclusions can be drawn regarding the changes in the anthropometric measures over time.

To conclude, in our population-based study, ABSI as measure of body shape had a stronger association with mortality compared to other presented anthropometric measures. However, the added predictive value of ABSI in prediction of mortality was limited.

Table 2.1.1 Baseline characteristics of the study population (N=6366)

	Values *	
	Men (n=2626)	**Women (n=3740)**
Age (years)	68.2 (8.2) †	69.5 (9.2)
Systolic blood pressure (mm Hg)	139 (21.9)	140 (23)
Treatment for hypertension (N, %)	393 (15) †	734 (20)
Diabetes mellitus (N, %)	262 (10)	385 (10)
Total cholesterol (mg/dL)	244.0 (45.6) †	264.5 (46.7)
HDL cholesterol (mg/dL)	47.1 (12.7) †	55.6 (14.3)
Use of serum lipid reducing agents (N, %)	70 (2.7)	84 (2.2)
Current smoking (N, %)	762 (29) †	699 (19)
Weight loss (N, %)	253 (9.6)	416 (11)
ABSI ($m^{11/6}/kg^{2/3}$)	0.0821 (0.0050) †	0.0776 (0.0068)
BMI (m/kg^2)	25.7 (3.0) †	26.7 (4.1)
WC (m)	0.94 (0.09) †	0.88 (0.11)
WHR	0.96 (0.07) †	0.87 (0.09)
WHtR	0.54 (0.06) †	0.55 (0.07)

Abbreviations: ABSI, a body shape index; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio; WHtR, waist to height ratio; N, numbers.

* Values are means (standard deviations) or numbers (percentages).

† The difference between men and women is significant at $P \leq 0.05$ at 2 sides.

Table 2.1.2 Multivariable adjusted hazard ratios* for the association of anthropometric measures with total and cause-specific mortality

	Total mortality		**CVD mortality†**		**Cancer mortality**	
	Men n=1679/2626	**Women n=1996/3740**	**Men n=564/2626**	**Women n=631/3740**	**Men n=450/2626**	**Women n=423/3740**
ABSI	1.15 (1.09, 1.21)	1.09 (1.04, 1.14)	1.18 (1.08, 1.29)	1.04 (0.96, 1.12)	1.10 (0.99, 1.22)	1.18 (1.07, 1.30)
BMI	0.93 (0.89, 0.99)	0.96 (0.92, 1.01)	0.90 (0.82, 0.99)	1.01 (0.94, 1.09)	0.99 (0.90, 1.10)	0.96 (0.86, 1.06)
WC	1.02 (0.97, 1.07)	1.02 (0.98, 1.07)	1.02 (0.93, 1.10)	1.03 (0.95, 1.12)	1.05 (0.95, 1.16)	1.10 (0.99, 1.21)
WHR	1.07 (1.01, 1.12)	1.02 (0.98, 1.07)	1.04 (0.95, 1.13)	1.00 (0.92, 1.09)	1.08 (0.98, 1.19)	1.07 (0.99, 1.18)
WHtR	1.03 (0.98, 1.08)	1.02 (0.98, 1.06)	1.00 (0.91, 1.08)	1.03 (0.97, 1.10)	1.03 (0.94, 1.14)	1.06 (0.98, 1.14)

Abbreviations: N, number; CVD, Cardiovascular Disease; ABSI, a body shape index; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio; WHtR waist to height ratio.

[a] Hazard Ratios (95% Confidence intervals) are presented per 1 unit standard deviation increase in each anthropometric measure and are adjusted for age, current smoking, systolic blood pressure, medication for hypertension, diabetes mellitus, total cholesterol and high-density lipoprotein cholesterol.

[a] Hazard Ratios (95% Confidence intervals) are presented per 1 unit standard deviation increase in each anthropometric measure and are adjusted for age, current smoking, systolic blood pressure, medication for hypertension, diabetes mellitus, total cholesterol and high-density lipoprotein cholesterol.
† Additionally adjusted for prevalent CVD at baseline.

Table 2.1.3 Informativeness of different models in association with total and specific cause mortality among men and women

	Total mortality		**CVD mortality***		**Cancer mortality**	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**
ABSI	26.4 †	15.1 †	12.2 †	0.9	3.9	10.6 †
BMI	6.5 †	3.9 †	5.1 †	0.2	0.2	1.2
WC	0.6	0.7	0.1	0.6	0.5	2.8
WHR	6.0 †	1.0	0.7	0.02	1.9	1.6
WHtR	1.3	1.3	0.1	1.3	0.8	1.0

Abbreviations: CVD, cardiovascular disease; ABSI, a body shape index; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio.
The presented values are X2 which is the difference in twice log-likelihood of a multivariate model (base model) including age, current smoking, systolic blood pressure, medication for hypertension, diabetes mellitus, total cholesterol and high-density lipoprotein cholesterol, with multivariable models additionally including each anthropometric measure (i.e. base model + ABSI, base model + BMI, base model + WC, base model + WHR, base model + WHtR) in prediction of different mortality outcomes.
* Additionally adjusted for prevalent CVD at baseline
† Significant at $P \leq 0.05$

Table 2.1.4 C-statistic for the models containing different anthropometric measures in prediction of total and cause-specific mortality

	Total mortality		CVD mortality †		Cancer mortality	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**
Base model*	0.744	0.783	0.789	0.819	0.667	0.637
	(0.732, 0.755)	(0.773, 0.793)	(0.771, 0.807)	(0.803, 0.834)	(0.643, 0.691)	(0.610, 0.663)
+ ABSI	0.746	0.784	0.792	0.819	0.668	0.644
	(0.734, 0.757)	(0.774, 0.794)	(0.775, 0.810)	(0.803, 0.835)	(0.643, 0.692)	(0.618, 0.670)
+ BMI	0.744	0.783	0.790	0.819	0.667	0.637
	(0.733, 0.755)	(0.773, 0.793)	(0.773, 0.808)	(0.803, 0.834)	(0.643, 0.692)	(0.611, 0.663)
+ WC	0.744	0.783	0.789	0.819	0.667	0.638
	(0.732, 0.755)	(0.773, 0.794)	(0.772, 0.807)	(0.803, 0.834)	(0.642, 0.691)	(0.612, 0.664)
+ WHR	0.745	0.784	0.790	0.819	0.668	0.638
	(0.733, 0.756)	(0.773, 0.794)	(0.772, 0.807)	(0.803, 0.834)	(0.644, 0.692)	(0.612, 0.665)
+ WHtR	0.743	0.784	0.789	0.819	0.670	0.642
	(0.732, 0.755)	(0.773,0.793)	(0.772, 0.807)	(0.803, 0.834)	(0.646, 0.694)	(0.616, 0.668)

Abbreviations: CVD, cardiovascular disease; ABSI, a body shape index; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio.

* Base model includes age, current smoking, systolic blood pressure, medication for hypertension, diabetes mellitus, total cholesterol and high-density lipoprotein cholesterol. Each anthropometric measure was added alone to the base model (i.e. base model + ABSI, base model + BMI, base model + WC and base model + WHR)

† Additionally adjusted for prevalent CVD at baseline.

Table 2.1.5 Risk reclassification improvement * for total and cause-specific mortality with addition of anthropometric measures to the base model

	Total mortality				**CVD mortality †**				**Cancer mortality**			
	Men		**Women**		**Men**		**Women**		**Men**		**Women**	
	IDI	**NRI**	**IDI**	**NRI**	**IDI**	**NRI**	**IDI**	**NRI**	**IDI**	**NRI**	**IDI**	**NRI**
ABSI	0.003 (0.001, 0.005)	0.13 (0.06, 0.21)	0.001 (-0.001, 0.001)	0.05 (-0.01, 0.12)	0.000 (-0.003, 0.003)	0.16 (0.06, 0.25)	0.000 (0.000, 0.000)	0.05 (-0.04, 0.14)	0.000 (-0.001, 0.000)	-0.02 (-0.13, 0.09)	0.002 (0.000 0.004)	0.06 (-0.05, 0.17)
BMI	0.001 (-0.001, 0.003)	0.04 (-0.04, 0.12)	0.000 (0.000, 0.000)	-0.02 (-0.09, 0.04)	0.003 (0.000, 0.007)	0.07 (-0.03, 0.16)	0.000 (0.000, 0.000)	-0.10 (-0.19, -0.01)	0.000 (-0.001, 0.001)	0.01 (-0.09, 0.12)	0.000 (0.000, 0.000)	0.07 (-0.05, 0.18)
WC	0.000 (0.000, 0.000)	-0.04 (-0.12, 0.04)	0.000 (0.000, 0.000)	0.05 (-0.02, 0.11)	0.000 (-0.000, 0.001)	-0.09 (-0.19, 0.01)	0.000 (0.000, 0.000)	0.05 (-0.04, 0.14)	0.000 (0.000, 0.000)	0.09 (-0.01, 0.20)	0.001 (-0.001, 0.002)	0.07 (-0.04, 0.18)
WHR	0.001 (0.000, 0.001)	0.09 (0.01, 0.16)	0.000 (0.000, 0.000)	0.03 (-0.04, 0.09)	0.000 (0.000, 0.001)	-0.04 (-0.14, 0.06)	0.000 (0.000, 0.000)	-0.01 (-0.10, 0.085)	0.000 (0.000, 0.000)	-0.05 (-0.15, 0.06)	0.000 (-0.001, 0.002)	0.07 (-0.05, 0.19)
WHtR	0.000 (0.000, 0.000)	0.04 (-0.03 0.11)	0.000 (0.000, 0.000)	0.04 (-0.02, 0.10)	0.001 (-0.001, 0.002)	-0.03 (-0.13 0.06)	0.000 (0.000, 0.000)	0.07 (-0.01 0.17)	0.000 (0.000, 0.000)	0.02 (-0.08 0.13)	0.000 (-0.001, 0.002)	0.03 (-0.08, 0.14

Abbreviations: CVD, cardiovascular disease; IDI, integrated discrimination improvement, NRI, continues net reclassification improvement; ABSI, a body shape index; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio.

* NRI and IDI present improvement in risk predictions between the based model: including age, current smoking, systolic blood pressure, medication for hypertension, diabetes mellitus, total cholesterol and high-density lipoprotein cholesterol, and the extended models additionally including each anthropometric measure.

† Base model additionally includes prevalent CVD at baseline.

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SUPPLEMENT CHAPTER 2.1

Supplement 2.1.1 Age adjusted hazard ratios* for the association of anthropometric measures with total and cause-specific mortality

	Total mortality		**CVD mortality†**		**Cancer mortality**	
	Men (n=1679/2626)	**Women (n=1996/3740)**	**Men (n=564/2626)**	**Women (n=631/3740)**	**Men (n=450/2626)**	**Women (n=423/3740)**
ABSI	1.16 (1.11, 1.22)	1.11 (1.06, 1.16)	1.20 (1.10, 1.30)	1.06 (0.98, 1.15)	1.12 (1.01, 1.23)	1.19 (1.07, 1.31)
BMI	0.93 (0.88, 0.97)	0.97 (0.93, 1.02)	0.93 (0.85, 1.01)	1.04 (0.96, 1.13)	0.96 (0.87, 1.06)	0.97 (0.88, 1.07)
WC	1.02 (0.97, 1.07)	1.04 (0.99, 1.09)	1.04 (0.96, 1.14)	1.07 (0.98, 1.16)	1.03 (0.94, 1.13)	1.11 (1.01, 1.23)
WHR	1.08 (1.03, 1.13)	1.05 (1.01, 1.09)	1.08 (0.99, 1.18)	1.05 (0.97, 1.14)	1.07 (0.98, 1.18)	1.09 (0.99, 1.19)
WHtR	1.03 (0.98, 1.08)	1.03 (0.99, 1.07)	1.04 (0.95, 1.13)	1.06 (0.99, 1.12)	1.03 (0.93, 1.13)	1.05 (0.97, 1.13)

Abbreviations: N, number; CVD, Cardiovascular Disease; ABSI, a body shape index; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio; WHtR, waist to height ratio.

[a] Hazard Ratios (95% Confidence intervals) are presented per 1 unit standard deviation increase in each anthropometric measure.

[†] Additionally adjusted for prevalent CVD at baseline.

Supplement 2.1.2 Multivariable adjusted hazard ratios* per tertiles of anthropometric measures for total and cause-specific mortality

		All-cause mortality		CVD mortality†		Cancer mortality	
		Men (n=1679/2626)	Women (n=1996/3740)	Men (n=564/2626)	Women (n=631/3740)	Men (n=450/2626)	Women (n=423/3740)
	1st ref	1	1	1	1	1	1
ABSI	2nd	1.12 (0.99, 1.27)	1.22 (1.09, 1.38)	1.11 (0.88, 1.39)	1.12 (0.91, 1.38)	1.10 (0.87, 1.39)	1.75 (1.36, 2.24)
	3rd	1.26 (1.11, 1.44)	1.26 (1.12, 1.41)	1.39 (1.11, 1.73)	1.11 (0.91, 1.37)	1.16 (0.91, 1.47)	1.60 (1.23, 2.07)
	p-trend	< 0.01	< 0.01	<0.01	0.35	0.24	< 0.01
	1st ref	1	1	1	1	1	1
BMI	2nd	0.85 (0.75, 0.96)	0.90 (0.80, 1.01)	0.81 (0.66, 0.99)	0.82 (0.67, 1.01)	1.01 (0.80, 1.27)	1.01 (0.79, 1.27)
	3rd	0.87 (0.77, 0.99)	0.88 (0.79, 0.98)	0.80 (0.65, 0.99)	0.95 (0.79, 1.15)	0.98 (0.77, 1.24)	0.92 (0.79, 1.17)
	p-trend	0.03	0.02	0.04	0.71	0.84	0.49
	1st ref	1	1	1	1	1	1
WC	2nd	0.94 (0.84, 1.07)	0.95 (0.85, 1.07)	0.90 (0.73, 1.12)	0.87 (0.71, 1.08)	1.01 (0.80, 1.26)	1.24 (0.97, 1.58)
	3rd	1.04 (0.92, 1.18)	0.99 (0.88, 1.11)	1.11 (0.89, 1.37)	0.92 (0.75, 1.13)	1.01 (0.80, 1.28)	1.20 (0.94, 1.55)
	p-trend	0.45	0.91	0.26	0.51	0.92	0.16
	1st ref	1	1	1	1	1	1
WHR	2nd	1.02 (0.90, 1.15)	1.02 (0.91, 1.15)	0.96 (0.78, 1.20)	1.07 (0.87, 1.31)	1.17 (0.93, 1.47)	1.08 (0.85, 1.37)
	3rd	1.14 (1.01, 1.15)	1.04 (0.93, 1.16)	1.06 (0.86, 1.31)	0.98 (0.80, 1.21)	1.09 (0.86, 1.38)	1.13 (0.89, 1.45)
	p-trend	0.03	0.53	0.54	0.78	0.47	0.32
WHtR	1st ref	1	1	1	1	1	1
	2nd	0.96 (0.86, 1.09)	0.98 (0.87, 1.11)	0.99 (0.79, 1.22)	0.92 (0.74, 1.14)	1.03 (0.82, 1.30)	1.12 (0.88, 1.42)
	3rd	1.07 (0.95, 1.20)	1.03 (0.92, 1.16)	1.00 (0.80, 1.23)	1.00 (0.81, 1.23)	1.16 (0.92, 1.46)	1.06 (0.82, 1.36)
	p-trend	0.24	0.52	0.98	0.86	0.21	0.67

ABSI, a body shape index; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio; WHtR, waist to height ratio; CVD, cardiovascular disease.

*

adjusted for prevalent CVD at baseline.

Supplement 2.1.3 Multivariable adjusted hazard ratios* for total and cause-specific mortality, stratified by subgroups.

Total mortality

	Men						Women				
		ABSI	**BMI**	**WC**	**WHR**	**WHtR**		**ABSI**	**BMI**	**WC**	**WHR**	**WHtR**
Original analyses	n=2626	1.15 (1.09, 1.21)	0.93 (0.89, 0.99)	1.02 (0.97, 1.07)	1.07 (1.01, 1.12)	1.03 (0.98, 1.08)	n=3740	1.09 (1.04, 1.14)	0.96 (0.92, 1.01)	1.02 (0.98, 1.07)	1.02 (0.98, 1.07)	1.02 (0.98, 1.06)
Age	< 65 n= 1045	1.20 (1.07-1.35)	0.95 (0.84, 1.06)	1.06 (0.95, 1.18)	1.23 (1.10, 1.37) §	1.05 (0.94, 1.18)	< 65 (n=1404)	1.22 (1.09, 1.38)	1.00 (0.89, 1.12)	1.14 (1.01, 1.28)	1.13 (1.01, 1.27)	1.07 (0.98 1.18)
	≥ 65 n= 1581	1.13 (1.07, 1.20)	0.93 (0.88, 0.98)	1.01 (0.95, 1.07)	1.02 (0.97, 1.08)	1.02 (0.96, 1.08)	≥ 65 (n=2336)	1.08 (1.02, 1.13)	0.95 (0.91, 1.01)	1.02 (0.95, 1.05)	1.01 (0.96, 1.06)	1.01 (0.97, 1.05)
Excluding the first 5years of follow up	n=2216	1.11 (1.05, 1.18)	0.96 (0.91, 1.02)	1.03 (0.97, 1.09)	1.07 (1.01, 1.13)	1.04 (0.98, 1.10)	n=3342	1.08 (1.03, 1.14)	0.98 (0.93, 1.03)	1.03 (0.98, 1.09)	1.02 (0.97, 1.07)	1.03 (0.99, 1.06)
Excluding subjects with weight loss	n=2374	1.13 (1.07, 1.19)	0.97 (0.92, 1.03)	1.05 (0.99, 1.11)	1.08 (1.02, 1.14)	1.06 (1.01, 1.12)	n=3328	1.09 (1.04, 1.15)	0.98 (0.93, 1.03)	1.04 (0.99, 1.09)	1.04 (0.99, 1.09)	1.04 (0.99, 1.07)
Additionally adjusted for education level, marital status and activity daily living	n=2626	1.15 (1.09, 1.21)	0.93 (0.88, 0.98)	1.02 (0.97, 1.07)	1.06 (1.01, 1.12)	1.04 (0.97, 1.09)	n=3740	1.08 (1.03, 1.13)	0.94 (0.90, 0.99)	1.01 (0.96, 1.05)	1.01 (0.97, 1.06)	1.01 (0.91 1.04)

ABSI, a body shape index; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio; WHtR, waist to height ratio; CVD, cardiovascular disease.
* Hazard ratios (95% confidence intervals) are expressed per 1 standard deviation increase in each anthropometric measure and are based on multivariate models adjusted for age, smoking, systolic blood pressure, medication for hypertension, diabetes mellitus, total cholesterol and high-density lipoprotein cholesterol.
† Additionally adjusted for prevalent CVD at baseline.
§ Homogeneity test showed significance differences across age-groups.

Supplement 2.1.3 (continued) Multivariable adjusted hazard ratios* for total and cause-specific mortality, stratified by subgroups.

CVD mortality												
	Men						**Women**					
		ABSI	**BMI**	**WC**	**WHR**	**WHtR**		**ABSI**	**BMI**	**WC**	**WHR**	**WHtR**
Original analyses	n=2626	1.18 (1.08, 1.29)	0.90 (0.82, 0.99)	1.02 (0.93, 1.10)	1.04 (0.95, 1.13)	1.00 (0.91, 1.09	n=3740	1.04 (0.96, 1.12)	1.01 (0.94, 1.09)	1.03 (0.95, 1.12)	1.00 (0.92, 1.09)	1.03 (0.97, 1.10)
Age	< 65 n= 1045	1.40 (1.18, 1.79)	0.86 (0.71, 1.05)	1.03 (0.85, 1.25)	1.32 (1.10, 1.59) §	1.08 (0.89, 1.31)	< 65 (n=1404)	1.06 (0.83, 1.35)	1.04 (0.84, 1.28)	1.08 (0.85, 1.37)	1.04 (0.83, 1.30)	1.04 (0.87, 1.24)
	≥ 65 n= 1581	1.13 (1.02, 1.25)	0.91 (0.81, 1.01)	1.01 (0.91, 1.11)	0.97 (0.88, 1.07)	0.96 (0.88, 1.07)	≥ 65 (n=2336)	1.04 (0.95, 1.13)	1.02 (0.94, 1.11)	1.02 (0.95, 1.13)	1.00 (0.92, 1.09)	1.03 (0.97, 1.11)
Excluding the first 5years of follow up	n=2216	1.13 (1.02, 1.26)	0.94 (0.85, 1.04)	1.02 (0.92, 1.14)	1.07 (0.96, 1.19)	1.01 (0.91, 1.12)	n=3342	1.03 (0.94, 1.13)	1.05 (0.96, 1.15)	1.05 (0.96, 1.16)	0.98 (0.89, 1.07)	1.04 (0.97, 1.12)
Excluding subjects with weight loss	n=2374	1.15 (1.04, 1.26)	0.95 (0.86, 1.05)	1.05 (0.95, 1.15)	1.06 (0.97, 1.16)	1.02 (0.93, 1.12)	n=3328	1.04 (0.95, 1.13)	1.01 (0.92, 1.11)	1.03 (0.94, 1.13)	0.99 (0.91, 1.09)	1.03 (0.96, 1.10)
Additionally adjusted for education level, marital status and activity daily living	n=2626	1.17 (1.07, 1.28)	0.90 (0.82, 0.99)	1.01 (0.93, 1.10)	1.03 (0.95, 1.13)	1.01 (0.91, 1.09	n=3740	1.03 (0.95, 1.12)	0.99 (0.92, 1.08)	1.01 (0.93, 1.10)	1.00 (0.92, 1.08)	1.01 (0.95, 1.08)

ABSI, a body shape index; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio; WHtR, waist to height ratio; CVD, cardiovascular disease.

* Hazard ratios (95% confidence intervals) are expressed per 1 standard deviation increase in each anthropometric measure and are based on multivariate models adjusted for age, smoking, systolic blood pressure, medication for hypertension, diabetes mellitus, total cholesterol and high-density lipoprotein cholesterol.

† Additionally adjusted for prevalent CVD at baseline.

§ Homogeneity test showed significance differences across age-groups.

Supplement 2.1.3 (continued). Multivariable adjusted hazard ratios* for total and cause-specific mortality, stratified by subgroups.

Cancer mortality

	Men						Women					
		ABSI	**BMI**	**WC**	**WHR**	**WHtR**		**ABSI**	**BMI**	**WC**	**WHR**	**WHtR**
Original analyses	n=2626	1.10 (0.99, 1.22)	0.99 (0.90, 1.10)	1.05 (0.95, 1.16)	1.08 (0.98, 1.19)	1.03 (0.94, 1.14)	n=3740	1.18 (1.07, 1.30)	0.96 (0.86, 1.06)	1.10 (0.99, 1.21)	1.07 (0.99, 1.18)	1.06 (0.98, 1.14)
Age	< 65 n= 1045	1.06 (0.88, 1.28)	1.07 (0.89, 1.28)	1.10 (0.91, 1.31)	1.21 (1.01, 1.45)	1.07 (0.89, 1.28)	< 65 (n=1404)	1.25 (1.04, 1.50)	0.91 (0.75, 1.11)	1.11 (0.92, 1.33)	1.10 (0.91, 1.31)	1.04 (0.89, 1.18)
	≥ 65 n= 1581	1.11 (0.99, 1.24)	0.95 (0.84, 1.07)	1.02 (0.91, 1.15)	1.02 (0.91, 1.14)	1.03 (0.92, 1.15)	≥ 65 (n=2336)	1.15 (1.02, 1.29)	0.97 (0.86, 1.10)	1.09 (0.97, 1.23)	1.06 (0.94, 1.20)	1.07 (0.95, 1.14)
Excluding the first 5years of follow up	n=2216	1.08 (0.97, 1.21)	0.99 (0.89, 1.12)	1.05 (0.93, 1.17)	1.07 (0.96, 1.20)	1.05 (0.94, 1.16)	n=3342	1.19 (1.07, 1.33)	0.99 (0.88, 1.11)	1.14 (1.02, 1.27)	1.10 (0.98, 1.22)	1.07 (0.98, 1.13)
Excluding subjects with weight loss	n=2374	1.11 (1.01, 1.23)	1.03 (0.92, 1.14)	1.09 (0.98, 1.20)	1.09 (0.99, 1.21)	1.05 (0.96, 1.16)	n=3328	1.18 (1.06, 1.31)	0.99 (0.89, 1.11)	1.13 (1.02, 1.26)	1.09 (0.98, 1.20)	1.06 (0.98, 1.11)
Additionally adjusted for education level, marital status and activity daily living	n=2626	1.11 (1.01, 1.23)	0.98 (0.89, 1.09)	1.05 (0.95, 1.16)	1.07 (0.97, 1.18)	1.04 (0.94, 1.15)	n=3740	1.17 (1.06, 1.29)	0.95 (0.86, 1.06)	1.09 (0.99, 1.21)	1.06 (0.96, 1.17)	1.01 (0.96, 1.12)

ABSI, a body shape index; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio; WHtR, waist to height ratio; CVD, cardiovascular disease.

* Hazard ratios (95% confidence intervals) are expressed per 1 standard deviation increase in each anthropometric measure and are based on multivariate models adjusted for age, smoking, systolic blood pressure, medication for hypertension, diabetes mellitus, total cholesterol and high-density lipoprotein cholesterol.

† Additionally adjusted for prevalent CVD at baseline.

Supplement 2.1.4 Multivariable adjusted hazard ratios for total and cause-specific mortality based on the models with ABSI alone, BMI alone, WC alone or both ABSI and BMI or BMI and WC.

		ABSI, BMI and WC alone*		**ABSI and BMI†**		**BMI and WC‡**	
		Men	**Women**	**Men**	**Women**	**Men**	**Women**
Total mortality	ABSI	1.15 (1.09, 1.21)	1.09 (1.04, 1.14)	1.15 (1.09, 1.21)	1.09 (1.04, 1.14)	-	-
	BMI	0.93 (0.89, 0.99)	0.96 (0.92, 1.01)	0.93 (0.89, 0.99)	0.96 (0.92, 1.01)	0.82 (0.75, 0.89)	0.88 (0.83, 0.95)
	WC	1.02 (0.97, 1.07)	1.02 (0.98, 1.07)	-	-	1.19 (1.10, 1.28)	1.11 (1.04, 1.19)
CVD mortality §	ABSI	1.18 (1.08, 1.29)	1.04 (0.96, 1.12)	1.18 (1.08, 1.29)	1.04 (0.96, 1.13)	-	-
	BMI	0.90 (0.82, 0.99)	1.01 (0.94, 1.09)	0.90 (0.82, 0.99)	1.02 (0.94, 1.11)	0.75 (0.65, 0.86)	0.99 (0.88, 1.11)
	WC	1.02 (0.93, 1.10)	1.03 (0.95, 1.12)	-	-	1.27 (1.11, 1.45)	1.04 (0.93, 1.17)
Cancer Mortality	ABSI	1.10 (0.99, 1.22)	1.18 (1.07, 1.30)	1.10 (0.99, 1.22)	1.18 (1.07, 1.30)	-	-
	BMI	0.99 (0.90, 1.10)	0.96 (0.86, 1.06)	0.99 (0.90, 1.10)	0.96 (0.86, 1.06)	0.89 (0.76, 1.04)	0.79 (0.68, 0.92)
	WC	1.05 (0.95, 1.16)	1.10 (0.99, 1.21)	-	-	1.14 (0.99, 1.33)	1.30 (1.13, 1.50)

ABSI, a body shape index; BMI, body mass index; WC, waist circumference; CVD, cardiovascular disease. Hazard ratios (95% confidence intervals) are expressed per 1 standard deviation increase in each anthropometric measure and are based on multivariate models adjusted for age, smoking, systolic blood pressure, medication for hypertension, diabetes mellitus, total cholesterol and high-density lipoprotein cholesterol.

* Hazard ratios for total and cause-specific mortality based on the multivariate models with ABSI alone, BMI alone, WC alone (original analysis).

† Hazard ratios for total and cause-specific mortality based on the multivariate models with both ABSI and BMI.

‡ Hazard ratios for total and cause-specific mortality based on the multivariate models with both BMI and WC.

§ Additionally adjusted for prevalent CVD at baseline.

2.2 Anthropometric measures in cardiovascular disease prediction: comparison of laboratory-based versus non-laboratory-based model

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ABSTRACT

Background: Body mass index (BMI) has been used to simplify cardiovascular risk prediction models by substituting total and high-density lipoprotein cholesterol. In elderly, the ability of BMI as a predictor of cardiovascular disease (CVD) declines. We aimed to find the most predictive anthropometric measure for CVD risk to construct a non-laboratory-based model and to compare it with the model including laboratory measurements.

Methods: The study included 2675 women and 1902 men aged 55-79 years from the prospective population-based Rotterdam Study. We used Cox proportional hazard regression analysis to evaluate the association of BMI, waist circumference (WC), waist to hip ratio (WHR) and body shape index (ABSI) with CVD; including coronary heart disease and stroke. Performance of the laboratory-based and non-laboratory-based models were evaluated by studying the discrimination, calibration, correlation, and risk agreement.

Results: Among men, ABSI was the most informative measure associated with CVD, therefore ABSI was used to construct the non-laboratory-based model. Discrimination of the non-laboratory-based model was not different than laboratory-based model (c-statistic: 0.680-vs.-0.683,p=0.71); both models were well-calibrated (15.3% observed CVD risk vs 16.9% and 17.0% predicted CVD risks by the non-laboratory-based and laboratory-based models, respectively); Spearman rank correlation and the agreement between non-laboratory-based and laboratory-based model was 0.89 and 91.7%, respectively. Among women, none of the anthropometric measures were independently associated with CVD.

Conclusion: Among middle-aged and elderly where the ability of BMI to predict CVD declines, the non-laboratory-based model, based on ABSI, could predict CVD risk as accurately as the laboratory-based model among men.

INTRODUCTION

Targeting individuals at high risk of developing cardiovascular disease (CVD) for lifestyle modification or drug treatment is the basis of primary prevention programs.[1] To identify people at high CVD risk, different risk prediction models exist.[2-4] The conventional risk prediction models contain information on traditional cardiovascular risk factors (i.e. age, sex, blood pressure, smoking status, history of diabetes mellitus and lipid profile).[5] However, measurement of blood biomarkers such as total cholesterol may not always be feasible in a clinical setting since results might not be available at the time of a patient's visit or the assays may not be accessible due to scarcity of resources. Therefore, simplified risk prediction models that include only non-laboratory traditional cardiovascular risk factors and substitute total and high-density lipoprotein (HDL) cholesterol with body mass index (BMI) have been proposed.[5] Recently, it has been shown that a model based on non-laboratory risk factors could predict CVD as accurately as the one using laboratory-based risk markers.[6] However, use of non-laboratory based model has not yet been validated in older populations. With advancing age, BMI might become a less accurate reflection of fat mass and its role on CVD risk prediction seems to diminish.[7-11] Moreover, compared to BMI, other anthropometric measures such as waist circumference (WC) and waist to hip ratio (WHR) could be considered better predictors for cardiovascular risk among the elderly.[12-14] Additionally, combination of BMI and WC has been shown to explain a greater variance in non-abdominal, abdominal subcutaneous, and visceral fat than either BMI or WC alone.[15] Recently a new anthropometric measure, a body shape index (ABSI), which combines WC, weight and height, has shown to predict total mortality better than BMI and WC.[16]

Therefore, it is not clear whether a non-laboratory model could predict future CVD risk accurately among the elderly. Nor is it evaluated whether inclusion of other anthropometric measures (WC, WHR, ABSI or combined BMI with WC) instead of BMI in a non-laboratory-based model will improve the CVD risk prediction among the elderly.

In this study we aimed to examine which anthropometric measure is the best predictor for CVD risk in middle-aged and elderly population. We then sought to construct a non-laboratory-based model, using the most predictive anthropometric measure, and to compare the performance of this non-laboratory-based model to the laboratory-based model in our population.

METHODS

Study Population

This study was embedded within the Rotterdam Study, a prospective population-based cohort study among subjects aged 55 years or older in the municipality of Rotterdam, the Netherlands. The objectives and design of the Rotterdam Study have been described in detail elsewhere.[17] In response to the demographic changes leading to an increase in the proportion of elderly, the Rotterdam Study was originally designed to study risk factors of frequent diseases among the elderly people. The baseline examination was completed between 1990 and 1993 (RS-I). In 2000-2001, the Rotterdam Study was extended with 3,011 participants who had become ≥ 55 years of age or had moved into the study district (RS-II). For the current study, we used data from the participants attending the third examination of the original cohort (RS-I-visit 3, 1997-1999;

n=4797) and the participants attending the first examination of the extended cohort (RS-II-visit 1, 2000-2001; n=3011). We excluded participants with missing data on anthropometric measures or lipids (n=1614; 533 men, 1081 women), with prevalent CVD at baseline (n=1052; 639 men, 413 women) [including prevalent coronary heart disease (CHD), stroke, heart failure or atrial fibrillation], and older than 79 years at baseline (risk prediction models are designed for individuals up to age 79 years) (n=565; 169 men, 396 women). After exclusions, 4577 participants (1902 men and 2675 women) were available for the analysis (Figure 2.2.1). The Rotterdam Study has been approved by the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center and by the medical ethics committee according to the Wet Bevolkingsonderzoek ERGO (Population Study Act Rotterdam Study), executed by the Ministry of Health, Welfare and Sports of the Netherlands.

Anthropometric Measurements

Anthropometrics were measured in the research center by trained staff. Height and weight were measured with the participants standing without shoes and heavy outer garments. BMI was calculated as weight divided by height squared (kg/m^2). WC was measured at the level midway between the lower rib margin and the iliac crest with participants in standing position without heavy outer garments and with emptied pockets, breathing out gently. ABSI was calculated as WC divided by BMI in power of 2/3 multiplied by height in power 1/2 ($WC / (BMI^{2/3} * height^{1/2})$).[16] Hip circumference was recorded as the maximum circumference over the buttocks. WHR was consequently calculated as the ratio of WC over the hip circumference. Information regarding the measurement of cardiovascular risk factors is provided in the online supplement.

Measurement of Cardiovascular Risk Factors

Information on cardiovascular risk factors was collected through home interviews or was measured at the study center visit as described previously. Serum total cholesterol and HDL cholesterol values were measured using standard laboratory techniques. Smoking status was classified as current smoking or others (former and never). Diabetes mellitus was considered to be present when participants reported that they were diagnosed with diabetes mellitus. 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 automated linkage to pharmacies with computerized records.

Clinical Outcome

The main outcome measures under study were incident CVD, composed of CHD and stroke.[18,19] CHD was composed of fatal and nonfatal myocardial infarction, other CHD mortality, and stroke was composed of fatal and nonfatal stroke. Data on incident CVD were collected through an automated follow-up system until 1st January 2011.

Statistical Analysis

Anthropometric Measurements and Risk of CVD

We used Cox proportional hazard regression analysis to estimate the hazard ratio (HR) of a 1-standard deviation increase in each anthropometric measures (ABSI, BMI, WC, WHR and combination of BMI with WC) in association with CVD over 10-year follow-up. Each model was adjusted for traditional non-laboratory cardiovascular risk factors (age, current smoking, history of diabetes mellitus, systolic blood pressure and treatment for hypertension). Since the predictive performance of anthropometric measures among the elderly is debatable, we also performed a sensitivity analysis among the subgroup of participants older than 65 years. Moreover, due to the high competing risk of non-CVD death among the elderly, we also performed competing risk analysis using the method proposed by Fine and Gray.[20]

For each anthropometric measure, we assessed the "informativeness" as described by Peto at al.[21] Informativeness was calculated as the difference in twice the log-likelihood between a Cox proportional hazard model including both non-laboratory traditional cardiovascular risk factors and the anthropometric measure, with a model that only included non-laboratory traditional cardiovascular risk factors. The greater the difference, the more "informative" that anthropometric measure is.[21]

Risk Prediction Models

We constructed two risk prediction models, a laboratory-based model and a non-laboratory-based model. The laboratory-based model included similar risk factors as those used in the Framingham risk score 4 (age, current smoking, history of diabetes mellitus, systolic blood pressure, treatment for hypertension, total and HDL cholesterol). The non-laboratory based model included similar risk factors but replaced, total and HDL cholesterol with the most "informative" anthropometric measurement.

The predictive performance of the two models was assessed by studying discrimination and calibration. Discrimination is the ability of a prediction model to assign a higher risk to the individuals who will develop an event compared to those who will not develop an event. We quantified discrimination for both models by calculating the c-statistic based on the Cox proportional hazard regression models.[22] We also assessed the performance of the two models by calculating the sensitivity, specificity, positive and negative predicted values. Calibration is the agreement between the predicted probabilities of the disease, based on the risk prediction models (laboratory-based and non-laboratory-based models), and the actual incidence of events in the population. To assess the calibration of each risk prediction model, the average predicted 10-year risks for each risk function were compared with the average 10-year observed risks (ie, cumulative incidence of the event). The mean predicted probability, based on the risk prediction model, was plotted against the observed CVD incidence in each decile of the predicted risk.

To evaluate how the risk predictions by the laboratory-based model and by the non-laboratory-based model correspond to each other, we assessed the agreement. Using the newly introduced threshold of 7.5% 10-year CVD risk based on the recent ACC/AHA guidelines[23], we categorized individuals into two categories of "high" and "low" risk for each model (alternatively we checked the threshold of 10% and 20% 10-year CVD risk). Percentage agreement between the two models was calculated by dividing the total number of participants that were equivalently characterized as "high" or "low" risk by both models by the total number of individuals in the analysis. In

addition, we assessed the correlation of risk predictions between the two models by calculating the Spearman correlation (risk predictions were not normally distributed).

All the analyses were performed for men and women separately. Co-variables were missing in less than 5% of participants. We used 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 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics of men and women are shown in Table 2.2.1. During median follow up of 10 years (interquartile range: 8.4-10), there were 291 (165 CHD, 126 stroke) and 277 (126 CHD, 151 stroke) CVD events among men and women respectively (Figure 2.2.1). Compared with women, men had lower levels of HDL cholesterol, use of lipid-lowering medication and BMI. However, the levels of WC, WHR, ABSI, and the prevalence of hypertension, current smoking, type 2 diabetes mellitus were significantly higher among men.

Table 2.2.2 presents gender-specific multivariable-adjusted hazard ratios with their 95% confidence intervals (HRs, 95% CI) and the corresponding p value per 1-standard deviation increase in each anthropometric measure in association with incident CVD events. Among men, the anthropometric measures significantly associated with incident CVD were ABSI [HR:1.18 (95%CI:1.05-1.32)] and combined BMI with WC [HR:0.80 (95%CI:0.64-1.00) for BMI and 1.31 (95%CI:1.05-1.64) for WC] in multivariable model. Compared to other anthropometric measures, BMI had a weaker association (p=0.866) with incident CVD. The model containing ABSI [X2ABSI =7.25 (p=0.007)] was more informative than the model including BMI and WC together [X2 BMI_WC =6.08 (p=0.047)] (Supplement 2.2.1). Therefore, we constructed a non-laboratory-based model in men by replacing total and HDL cholesterol levels with ABSI, and compared its performance with the laboratory-based model. Among women, none of the anthropometric measures were significantly associated with incident CVD after adjustment for non-laboratory traditional cardiovascular risk factors (Table 2.2.2 and Supplement 2.2.1). Therefore, we didn't proceed with a non-laboratory model in women.

In our sensitivity analysis, the predictive ability of anthropometric measures (HR, 95% CI) among participants older than 65 years was not substantially different from our original analysis including all participants aged 55-79 years (Supplement 2.2.2). Similarly, the HRs (95% CIs) from the competing risk approach were not substantially different from our original analysis (Supplement 2.2.3).

Table 2.2.3 presents HRs (95% CI) and p values for the variables included in the laboratory-based and non-laboratory-based models among men.

Both models provided comparable and reasonable discrimination. Among men, the c-statistic (95%CI) was 0.683 (0.653-0.715) for the laboratory-based model, and 0.680 (0.650-0.710) for the non-laboratory-based model. The c-statistic for the two models were not significantly different (p=0.71). Overall the sensitivity, specificity and predictive discrimination values were similar for both models at each risk threshold (Table 2.2.4). As expected, the sensitivity declined and the

specificity increased for both models when risk threshold increased from 7.5% to 10% and to 20%. Using the newly introduced threshold of 10-year CVD predicted risk > 7.5% 23, the laboratory-based model correctly classified 95% of men who developed CVD event during follow-up at high-risk (sensitivity). Only 14% of men who remained event-free during follow-up were correctly classified at low risk (specificity) by the laboratory-based model. For the non-laboratory-based model, the sensitivity and specificity were 99% and 10% respectively. From all men categorized as high-risk by the laboratory-based model only 17% developed CVD event during follow-up (positive predicted value), whereas from men categorized at low-risk group 94% remained event-free during the follow-up (negative predicted value). For the non-laboratory-based model the positive and negative predicted values were 17% and 98% respectively. Results for the alternative analyses using the threshold of 10% and 20% 10-year CVD risk are shown in Table 2.2.4.

The 10-year risk estimates based on the laboratory-based and non-laboratory-based models were on average well calibrated. The average predicted risks were 17% by the laboratory-based model and 16.9% by the non-laboratory-based model, compared with the observed cumulative CVD incidence of 15.3%, among men. The overall calibration Chi-square test was not significant ($p = 0.25$ for the laboratory-based model and $p=0.24$ for the non-laboratory-based model). Calibration plots for both models are presented in Figure 2.2.2.

Figure 2.2.3 plots individuals based on their predicted risk using the non-laboratory-based model (vertical axis) and the laboratory-based model (horizontal axis). Using the 7.5% 10-year CVD risk threshold by the ACC/AHA guidelines23, there was 91.6% agreement in risk predictions between the laboratory-based and the non-laboratory-based models. This is interpreted as 91.6% of men would be categorized at "high" or "low" risk groups based on both the laboratory-based and the non-laboratory-based models. The agreement was 87.9% using the 10% and 89.2% using the 20% as the threshold for 10-year CVD risk. In line with the large agreement between the models, the Spearman rank correlation for the risk predictions based on the laboratory-based and the non-laboratory based models was 0.89 ($p < 0.001$).

DISCUSSION

In this population-based study of adults aged 55-79 years, ABSI was the most informative anthropometric measure in prediction of cardiovascular disease. Among men, a non-laboratory-based model substituting ABSI for total and HDL cholesterol, could predict cardiovascular disease as accurately as the laboratory based model including the lipid profile. Furthermore, the predicted cardiovascular risk based on the non-laboratory model containing ABSI showed an excellent agreement with the predicted risk by the laboratory-based model. Among women, none of the anthropometric measures was associated independently with cardiovascular disease.

Cardiovascular risk prediction models often require measurement of laboratory-based predictors such as total and HDL cholesterol.[2,5] Recently, the traditional laboratory-based CVD risk prediction approach has been challenged by the observations that the non-laboratory based models, including BMI instead of lipid measures, could predict CVD with similar accuracy.[5,6] At older ages, the ability of BMI in prediction of CVD decreases.[7-11] Therefore the non-laboratory CVD risk prediction models including BMI might not provide as accurate CVD risk predictions among the elderly as they do among younger individuals. Other anthropometric measures such as

WC, WHR, or BMI in combination with WC, might be able to better predict cardiovascular risk among the elderly. It is also possible that none of the anthropometric measures should be considered for CVD risk prediction among this group of individuals.[12-15] We therefore first examined which anthropometric measure would be most informative in CVD risk prediction in older individuals.

Among all anthropometric measures, a newly introduced measure; ABSI, was most informative for CVD risk prediction among the middle-age and elderly population. ABSI combines information from WC, weight and height. High ABSI is an indication of a higher WC than expected for a given height and weight and corresponds to a more central concentration of body volume, suggesting more visceral fat.[16] Considerable amount of evidence suggests that abdominal fat distribution might be more closely tied to metabolic risks than BMI.[24-26] This might explain why ABSI is a better predictor for cardiovascular risk compared to BMI. Additionally, while in our study BMI and WC alone were not associated with CVD risk, combining both BMI and WC in a multivariable model resulted in strengthening of the association of both anthropometric measures with CVD. These findings, support the evidence that among the elderly BMI is a reflection of lean mass for subjects with the same WC, whereas WC is a reflection of fat mass for subjects with the same BMI.[15] Our findings do not support use of BMI as a proxy for lipid measures in cardiovascular risk prediction models among the elderly. Instead, our results suggest use of ABSI, which includes information on WC, weight and height, as a proxy for lipid measures in CVD risk prediction at older ages in men.

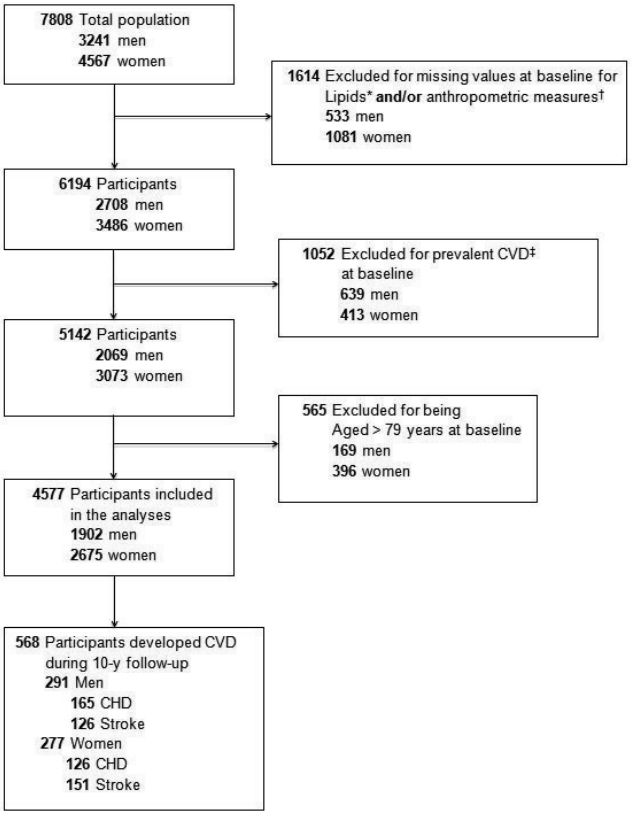
In our study the association of anthropometric measures with CVD risk differed by gender. Unlike in men, none of the anthropometric measures in our study were independently associated with cardiovascular risk in women. This could be explained by the fact that men in our study had higher baseline levels of ABSI, WC, and WHR, higher prevalence of diabetes mellitus, lower plasma HDL-cholesterol concentrations and lower frequency of lipid-lowering treatment. Alternatively, the lower incidence of CVD in women (10.3%) compared to men (15.3%) and the subsequent lower statistical power might explain lack of the associations among women. However, our results are in line with a previous study indicating the comparable performance of both models among men.[27]

Strengths of the current study include detailed follow-up data and availability of all anthropometric measures as well as the traditional cardiovascular risk factors. We therefore could compare different anthropometric measures independently to identify the best measure associated with CVD. There are also limitations. In our study, the c-statistics of both laboratory-based and non-laboratory-based models in prediction of CVD was <0.70. The strength of associations of traditional risk factors diminishes with increasing age. Therefore, it might be expected that traditional cardiovascular risk factors or anthropometric measures provide a lower discrimination in CVD risk prediction among the elderly.[7,28] Since we aimed to evaluate the performance of the non-laboratory-based model among the middle-aged and elderly, it should be noted that our findings could not be generalizable to a younger population (age < 55 years). Further research is required to evaluate the predictive performance of ABSI in association with CVD among other and younger populations.

In summary, we found that among middle-aged and elderly men, the non-laboratory-based model using ABSI could predict cardiovascular risk as accurately as the laboratory-based model

including information on lipid profile. Our results do not support use of BMI instead of lipid measures in risk prediction models among the elderly but give further support to simplify the risk prediction models by substituting lipid levels with ABSI at older ages in men.

Figure 2.2.1 - Flow chart describing the study population



Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease

* Including total and high-density lipoprotein (HDL) cholesterol

† Including weight, height, waist circumference and hip circumference

‡ Including CHD, stroke, heart failure or atrial fibrillation

Table 2.2.1 Characteristics of the study population at baseline (N=4,577)

	Values*	
	Men (n=1902)	**Women (n=2675)**
Age (years)	66.2 ± 6.1	66.8 ± 6.3
Current smoker (N, %)	486 (25.4)	497 (18.6)
Diabetes Mellitus (N, %)	128 (6.7)	161 (6.0)
Systolic blood pressure (mm Hg)	144 ± 21	141 ± 21
Treatment for hypertension (N, %)	362 (19.0)	649 (24.3)
Total cholesterol (mg/dL)	218.2 ± 36.2	234.1 ± 35.7
HDL cholesterol (mg/dL)	48.3 ± 12.4	58.2 ± 15.2
Use of serum lipid reducing agents (N, %)	176 (9.3)	300 (11.2)
ABSI ($m^{11/6}$ / $kg^{2/3}$)	0.083 ± 0.004	0.078 ± 0.006
BMI (m/kg^2)	26.6 ± 3.3	27.3 ± 4.4
WC (m)	0.976 ± 0.095	0.900 ± 0.120
WHR	0.969 ± 0.067	0.871 ± 0.090

Abbreviations: HDL, high-density lipoprotein; ABSI, a body shape index; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio.

* Values are mean ± SD or numbers (percentages).

Table 2.2.2 Multivariable adjusted* Hazard Ratio of anthropometric measures for incident CVD over 10 year follow-up

		Men		**Women**	
		HR † (95% CI)	**p value**	**HR † (95% CI)**	**p value**
ABSI		1.18 (1.05-1.32)	0.007	1.09 (0.97-1.22)	0.141
BMI		1.01 (0.90-1.14)	0.866	0.96 (0.85-1.10)	0.624
WC		1.10 (0.97-1.24)	0.135	1.02 (0.90-1.16)	0.711
WHR		1.11 (0.99-1.25)	0.076	1.09 (0.97-1.23)	0.136
BMI WC ‡	BMI	0.80 (0.64-1.00)	0.050	0.89 (0.73-1.07)	0.229
	WC	1.31 (1.05-1.64)	0.013	1.12 (0.93-1.35)	0.244

Abbreviations: HR, hazard ratios; CI, confidence interval; CVD, cardiovascular disease; ABSI, a body shape index; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio.

* Adjusted for age, current smoking, history of diabetes mellitus, systolic blood pressure and treatment for hypertension).

† Hazard Ratio for 1 standard deviation increase in each anthropometric measure.

‡ BMI and WC are combined (i.e. added simultaneously) in the same multivariate model.

Table 2.2.3 Hazard ratios for the variables included in the laboratory-based and non-laboratory-based models in association with incident CVD over 10 year follow-up among men

Men (N=1902)	Laboratory-based Model		Non-laboratory-based Model	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.07 (1.05-1.10)	0.001	1.06 (1.03-1.08)	0.001
Current smoker	1.56 (1.21-2.01)	0.001	1.54 (1.19-1.98)	0.001
History of diabetes mellitus	1.71 (1.18-2.47)	0.004	1.64 (1.14-2.35)	0.008
SBP	1.01 (1.01-1.02)	0.001	1.01 (1.01-1.02)	0.001
Treatment for hypertension	0.96 (0.72-1.27)	0.775	0.97 (0.73-1.29)	0.869
Total Cholesterol	1.19 (1.05-1.35)	0.005	NA	NA
HDL Cholesterol	0.52 (0.36-0.77)	0.001	NA	NA
ABSI*	NA	NA	1.18 (1.05-1.32)	0.007

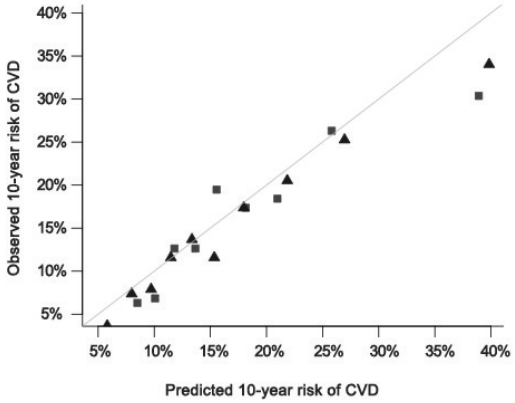
Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval; p, p-value; SBP, systolic blood pressure; HDL, High-density lipoprotein; ABSI, a body shape index; NA, not applicable.
* Hazard ratio for 1 standard deviation increase in ABSI (SD=0.004).

Table 2.2.4 Discriminative ability of models at different 10-year CVD risk thresholds

		Risk thresholds		
Men (N=1902)		**7.5%**	**10%**	**20%**
Sensitivity 95%CI (%)	Laboratory-based model	95% (92%-97%)	89% (85%-93%)	51% (45%-57%)
	Non-laboratory-based model	99% (97%-100%)	92% (88%-95%)	47% (41%-53%)
Specificity 95%CI (%)	Laboratory-based model	14% (12%-15%)	29% (27%-32%)	75% (74%-78%)
	Non-laboratory-based model	10% (9%-12%)	28% (26%-30%)	75% (73%-77%)
Positive predicted value 95%CI (%)	Laboratory-based model	17% (15%-19%)	19% (17%-21%)	27% (23%-31%)
	Non-laboratory-based model	17% (15%-18%)	19% (17%-21%)	26% (22%-29%)
Negative predicted value 95%CI (%)	Laboratory-based model	94% (90%-96%)	94% (91%-96%)	89% (88%-91%)
	Non-laboratory-based model	98% (94%-99%)	95% (93%-97%)	89% (87%-90%)

Abbreviations: CVD, cardiovascular disease; CI, confidence interval.

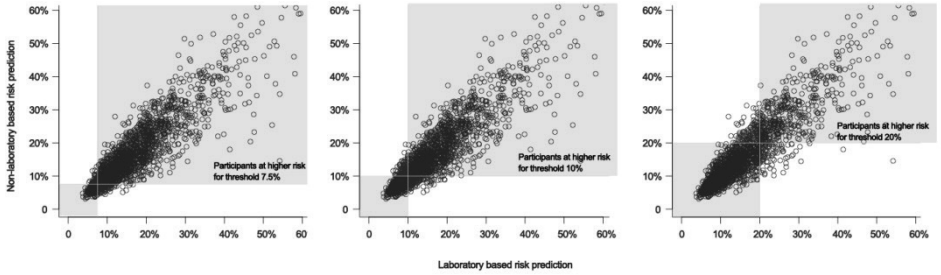
Figure 2.2.2 Observed 10-year risks of CVD by deciles of predicted 10-year risk by the laboratory-based and non-laboratory based models among men (N=1902)



Abbreviations: CVD, cardiovascular disease; Triangle for the laboratory-based model; Square for the non-laboratory-based model.

Calibration is the agreement between the predicted probabilities of disease, based on the risk prediction models (triangle for laboratory-based and square for non-laboratory-based model), and the actual incidence of events in the population. To assess the calibration of each risk prediction model, the average predicted 10-year risks for each risk function were compared with the average 10-year observed risks (i.e. cumulative incidence of the event). The mean of predicted probability based on the risk prediction model was plotted against the observed incidence in each decile of the predicted risk. For the laboratory-based model each triangle correspondents to the (predicted risk; observed risk) for each decile as follows: (5.8; 3.7), (8.0; 7.4), (9.7; 7.9), (11.5; 11.6), (13.4; 13.7), (15.3; 11.6), (18.0; 17.4), (21.8; 20.5), (27.0; 25.3), (39.8; 34.0). For the non-laboratory-based model the square correspondents to the (predicted risk; observed risk) for each decile as follows: (6.4; 2.6), (8.5; 6.3), (10.1; 6.8), (11.8; 12.6), (13.7; 12.6), (15.6; 19.5), (18.1; 17.4), (21.0; 18.4), (25.8; 26.3), (38.9; 30.4).

Figure 2.2.3 Agreement in CVD risk prediction between the laboratory-based and non-laboratory-based models among men (N=1902)



Individual predicted risk of CVD by laboratory-based and non-laboratory-based model are plotted against each other. Based on a risk threshold that corresponds to 10-year CVD risk 7.5% (figure on the left), 10.0% (figure in the middle), and 20% (figure on the right) 91.6% (on the left), 87.9 (in the middle), and 89.2% (on right) of men would be similarly characterized as high or low risk by the laboratory-based and non-laboratory-based model.
Abbreviations: CVD, cardiovascular disease.

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SUPPLEMENTAL FOR CHAPTER 2.2

Supplement 2.2.1 Informativeness* of different anthropometric measures in association with CVD over 10 year follow up

	Men		Women	
	Likelihood ratio test statistic (chi-square)	**p value**	**Likelihood ratio test statistic (chi-square)**	**p value**
ABSI	7.25	0.007	2.15	0.143
BMI	0.03	0.866	0.25	0.620
WC	2.22	0.137	0.14	0.712
WHR	3.10	0.078	2.14	0.144
BMI WC†	6.08	0.047	1.59	0.451

Abbreviations: CVD, cardiovascular disease; ABSI, a body shape index; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio.

* Informativeness was calculated as the difference in twice the log-likelihood between a Cox proportional hazard model including both non-laboratory traditional cardiovascular risk factors (i.e. age, current smoking, history of diabetes mellitus, systolic blood pressure and treatment for hypertension) + each anthropometric measure, with a model that only included non-laboratory traditional cardiovascular risk factors. The greater the difference, the more "informative" that anthropometric measure is.

† BMI and WC are combined (i.e. added simultaneously) in the same multivariate model

Supplement 2.2.2 Multivariable adjusted * Hazard Ratios of anthropometric measures for incident CVD over 10 year follow-up among men and women aged 65+ years (N=2535)

		Men (N=1021)		**Women (N=1514)**	
		HR † (95% CI)	**p value**	**HR † (95% CI)**	**p value**
ABSI		1.15 (1.01-1.32)	0.048	1.10 (0.97-1.24)	0.117
BMI		1.04 (0.90-1.20)	0.598	0.96 (0.85-1.09)	0.564
WC		1.12 (0.96-1.29)	0.139	1.10 (0.96-1.26)	0.152
WHR		1.09 (0.95-1.25)	0.212	1.12 (0.99-1.26)	0.058
BMI WC ‡	BMI	0.85 (0.66-1.10)	0.232	0.93 (0.76-1.15)	0.160
	WC	1.27 (0.98-1.64)	0.068	1.15 (0.94-1.41)	0.777

Abbreviations: HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; ABSI, a body shape index; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio.

* Hazard ratios are adjusted for age, current smoking, history of diabetes mellitus, systolic blood pressure and treatment for hypertension.

† Hazard Ratio for 1 standard deviation increase in each anthropometric measure.

‡ BMI and WC are combined (i.e. added simultaneously) in the same multivariate model.

Supplement 2.2.3 Multivariable adjusted* Hazard Ratios of anthropometric measures for incident CVD over 10 year follow-up, from the competing risk model†

		Men		Women	
		HR † (95% CI)	**p value**	**HR † (95% CI)**	**p value**
ABSI		1.14 (1.03-1.26)	0.014	1.08 (0.96-1.21)	0.19
BMI		1.02 (0.89-1.16)	0.790	0.97 (0.85-1.10)	0.62
WC		1.09 (0.96-1.23)	0.180	1.02 (0.90-1.15)	0.78
WHR		1.09 (0.98-1.22)	0.120	1.08 (0.97-1.21)	0.17
BMI WC ‡	BMI	0.84 (0.68-1.05)	0.120	0.90 (0.73-1.10)	0.29
	WC	1.26 (1.02-1.54)	0.029	1.10 (0.91-1.34)	0.31

Abbreviations: HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; ABSI, a body shape index; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio.

* Hazard ratios are adjusted for age, current smoking, history of diabetes mellitus, systolic blood pressure and treatment for hypertension.

† We quantified the association of anthropometric measures with the sub-distribution hazard of the cumulative incidence of CVD and non-cardiovascular death using the method proposed by Fine and Gray.[3] HRs obtained from these models allow for direct inference of the effect of anthropometric measures on cardiovascular disease in the presence of competing risks of non-CVD death.

‡ BMI and WC are combined (i.e. added simultaneously) in the same multivariate model.

2.3 Association of anthropometric measures with fat and fat-free mass in the elderly

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Abstract

Background: In elderly, the decrease in fat-free mass (FFM) is usually associated with an increase in fat mass (FM), a state referred to as sarcopenic obesity. The use of anthropometric measures to identify sarcopenic obesity is still unclear. We evaluated which anthropometric measures are differentially associated with FM and FFM.

Methods: Anthropometric measures used were body mass index (BMI), waist circumference (WC), and a body shape index (ABSI=WC/(BMI2/3*Height1/2)). FM and FFM were estimated by dual-energy X-ray absorptiometry. An index-score was calculated for both FM (FMI) and FFM (FFMI) dividing FM and FFM by body height. Multivariable linear regression models were used to assess the associations of BMI, WC and ABSI with FMI and FFMI among 3612 participants (2092 women) from the prospective population-based Rotterdam Study.

Results: In multivariate models adjusted for confounders, BMI and WC were positively associated with both FMI and FFMI in men and women. ABSI was positively associated with FMI (β 1.01, 95% confidence interval (95%CI) 0.85, 1.17) and negatively associated with FFMI (β -0.28, 95%CI -0.38, -0.17) in men. In women, ABSI was not associated with FMI and was positively associated with FFMI (β 0.18, 95%CI 0.10, 0.26).

Conclusions: While BMI and WC were both positively associated with FM and FFM, ABSI showed a differential association with FM and FFM in men, but not in women. Since sarcopenic obesity is associated with decreased FFM and increased FM, ABSI could be a useful tool for identifying men at higher risk for sarcopenic obesity.

INTRODUCTION

Aging is associated with physiological modifications, including changes in body composition.1 In elderly individuals, changes in body composition could often result in an increase in body fat accompanied with a decrease of muscle mass and strength;[1,2] this status is often referred to as sarcopenic obesity.[3-5] Sarcopenic obesity is associated with reduced quality of life and increased mortality.[4,6]

The value of traditional anthropometric measures in identifying individuals at high risk for sarcopenic obesity is limited. Body mass index (BMI) is considered an imperfect measure of adiposity. An increase in BMI could be attributed to an increase in both fat mass (FM) and fat-free mass (FFM) and therefore BMI is not able to discriminate FM and FFM.[7-10] Waist circumference (WC), a marker of abdominal adiposity, is also positively associated with both FM,[8,11,12] and FFM12 but is insensitive to height. Therefore, these traditional anthropometric measures (BMI and WC) are not suited to identify individuals at higher risk for sarcopenic obesity.[3] Recently, a new composite anthropometric measure, a body shape index (ABSI), has been introduced (ABSI=WC/(BMI2/3*Height1/2)).[13] This new measure has been suggested to predict mortality independently from BMI in the US population,[13] and recently in a European [14] population. ABSI has been derived from WC and is independent of weight and height. Therefore, being correlated with WC, but independent of weight and height, ABSI could have a differential association with FM and FFM that cannot be distinguished by BMI and WC alone. So far, only one study has reported a negative association between ABSI and FFM.[15] However, this study included only overweight and obese patients recruited by hospital outpatient obesity clinics, and these results can therefore not be generalized to other populations.

In our population-based study of elderly individuals, using the gold standard dual-energy X-ray absorptiometry, we aimed to assess which anthropometric measures are differentially associated with FM and FFM. More specifically, we aimed to assess the association of ABSI with FM and FFM in comparison with BMI and WC among men and women.

METHODS

Study Design, Setting, and Population

These analyses were performed within the Rotterdam Study, a prospective population-based cohort study. Information on the study design and the selection criteria for the ongoing prospective study have been reported previously.[16] For the current study, we used data from the participants attending the fourth examination of the original cohort (RS-I-visit 4, 2002–2004; n=3558) and the participants attending the second examination of the extended cohort (RS-II-visit 2, 2004–2005; n=2506), because body composition was measured during this cycle. Among the total 3713 participants that underwent dual-energy X-ray absorptiometry (DXA) measurements we excluded 65 participants who did not have information on anthropometric measures, 22 participants who were underweight at baseline and 14 participants who did not gave informant consent. After excluding a total of 101 participants, 3612 (1520 men and 2092 women) participants were available for the analysis. The Rotterdam Study has been approved by the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center and by the

medical ethics committee according to the Wet Bevolkingsonderzoek ERGO (Population Study Act Rotterdam Study), executed by the Ministry of Health, Welfare and Sports of the Netherlands. All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Anthropometric measurements

Anthropometric measures considered for this study were BMI, WC and ABSI. Anthropometrics were measured at the research center by trained research staff. Height and weight were measured with the participants standing without shoes and heavy outer garments. BMI was calculated as weight divided by height squared (kg/m^2). Waist circumference was measured at the level midway between the lower rib margin and the iliac crest with participants in standing position without heavy outer garments and with emptied pockets, breathing out gently. ABSI was calculated as WC divided by the product of BMI to the power of 2/3 and the square root of height (WC / (BMI 2/3 * height 1/2)).[13]

Determination of body composition

Total body composition was assessed by DXA using a Prodigy TM total body-fan beam densitometer (GE Lunar Corp, Madison, WI, USA) following manufacturer protocols, with scans analyzed with enCORE software V13.6 using pre-determined regions of interest. We calculated a fat mass index (FMI) by dividing total fat mass by height squared in meters (m^2). Fat-free mass was calculated as the sum of total lean mass and bone mineral content. Similar to FMI, the fat-free mass index (FFMI) was calculated dividing fat-free mass (kg) by the height squared in meters (m^2). Consequently we calculated the ratio between FM/FFM dividing FM by FFM. Additionally, we calculated the total lean mass index (LMI) by dividing lean mass by height squared in meters.

Definitions of covariates

Information on smoking status (never, former, current), and physical activity (total METhours per week) were obtained through interviews in the Rotterdam Study.[16] Blood samples were obtained in the research center of the Rotterdam Study for assays of plasma glucose and insulin, high-sensitivity C-reactive protein (CRP). A homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated as fasting serum insulin (pmol/L) × fasting plasma glucose (mmol/L) / 135. Measures of physical activity, glucose, insulin and CRP were obtained in the third visit of original cohort (RS-I) and first visit of extended cohort (RS-II) of the Rotterdam Study. Information for prevalent chronic disease at the baseline was obtained through general practitioners in the research area. Chronic diseases included in the current study were cardiovascular disease (i.e. coronary heart disease, stroke and heart failure), diabetes mellitus and cancer.[17,18]

Statistical analysis

Analyses were stratified by gender, because it is well established that fat distribution differs by gender.[19] Baseline measures of clinical relevant variables were expressed as means ± standard

deviations for continuous variables or as number and percentages for categorical variables. Correlations between anthropometric measures (i.e. ABSI, BMI, WC) and body composition (i.e. FMI, FFMI, FM/FFM) were evaluated with Pearson correlation analysis. To determine if ABSI, BMI and WC were independently associated with FMI and FFMI, multivariate linear regression analyses adjusted for age, physical activity, smoking and chronic diseases were developed. In addition, multivariate linear regression analyses were performed to assess the association of ABSI with FFMI and FMI within each BMI category (i.e. normal weight, overweight and obese).

Sensitivity analysis

To understand the possible pathways of the association between fat and fat-free mass, we assessed the association of CRP and HOMA-IR with FMI and FFMI in multivariable models in sensitivity analyses. CRP and HOMA-IR were used after logarithmic transformation. In these analyses, we additionally adjusted for weight and excluded patients with prevalent diabetes mellitus. Additionally, although fat free mass is a proxy of lean mass, we analyzed the direct correlation and performed a multivariate linear regression between lean mass and ABSI, WC and BMI. Finally, recognizing the gender differences between the association of gynoid fat mass and metabolic disorders we did a multivariate linear regression to assess the association of gynoid fat mass index (GFI) with CRP and HOMA-IR in our study.

Co-variables were missing in less than 5% of participants, and we used single imputation by the Expectation Maximization method in SPSS for Windows (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp). Statistical analyses were performed using R statistical software (R version 3.1.3). P values less than 0.05 were considered statistically significant.

RESULTS

Compared to women, men had higher mean values of ABSI, WC and FFMI, whereas the mean values for FM, FM/FFM and physical activity were higher among women (Table 2.3.1). The mean values of age and BMI were comparable between men and women.

The Pearson's correlation between anthropometric measures and body composition are shown in Table 2.3.2. ABSI was positively correlated with FMI (0.30) and FM/FFM (0.37) in men but not in women (FMI: 0.01, FM/FFM: -0.02). FFMI was negatively correlated with ABSI in men (-0.19) and positively in women (0.09). BMI and WC were positively correlated with FMI, FFMI and FM/FFM both in men and women (Table 2.3.2).

Multivariable adjusted analyses showed that higher ABSI was associated with higher FMI (β 1.01, 95%CI 0.85, 1.17) and lower FFMI (β -0.28, 95%CI -0.38, -0.17) in men. In contrast, among women higher ABSI was not associated with FMI, but was associated with higher FFMI (β 0.18 95%CI 0.10, 0.26). Higher BMI and WC were associated with higher FMI and FFMI in men and women (Table 2.3.3). The β's (95%CI) of the association of BMI with FMI and FFMI were 2.60 (2.54, 2.67) and 1.23 (1.16, 1.30), respectively in men; and 2.86 (2.82, 2.89) and 1.03 (0.99, 1.07), respectively in women. Similarly, the β (95%CI) of the association of WC with FMI and FFMI were 2.38 (2.30, 2.45) and 0.80 (0.72, 0.88), respectively in men; and 2.83 (2.75, 2.92) and 1.07 (1.02, 1.12), respectively in women. The FM/FFM ratio was positively associated with ABSI in

men, but not in women. A positive association of FM/FFM ratio with BMI and WC were observed in men and women (Table 2.3.3).

The associations of ABSI with FMI and FFMI across different categories of BMI are shown in Table 2.3.4. In men, we observed an association of ABSI with FMI and FFMI in each category of BMI, whereas in women the associations were observed in the overweight and obese category only. In men, higher ABSI was associated with lower FFMI in normal weight (β -0.37, 95%CI -0.50, -0.25), overweight (β -0.51, 95%CI -0.62, -0.40) and obese (β -0.52, 95%CI -0.78, -0.26) individuals. In women these βs (95%CI) were -0.05 (-0.16, 0.06), 0.13 (0.05, 0.21) and 0.26 (0.12, 0.41), respectively. The strength of the association between ABSI and FFMI increased with increasing BMI category in both men and women.

As sensitivity analysis we assessed the associations of CRP and HOMA-IR with FMI and FFMI (Table 2.3.5). In men, higher CRP was associated with the greater FMI (β 0.26, 95%CI 0.18, 0.35) and lower FFMI (β -0.12, 95%CI -0.19, -0.05). In women higher CRP was associated with both higher FMI (β 0.26, 95%CI 0.18, 0.33) and FFMI (β 0.06, 95%CI 0.01, 0.13). Additionally, in men higher HOMA-IR was associated with increased FMI (β 0.51, 95%CI 0.41, 0.62), and not with FFMI (β -0.05, 95%CI -0.14, 0.05). In women higher HOMA-IR was positively associated with FMI (β 0.21, 95%CI 0.11, 0.31) and FFMI (β 0.14, 95%CI 0.07, 0.21).

In Supplement 2.3.1-2.3.2, we observed that the correlation and associations between lean mass and WC, BMI and ABSI were very similar to the correlations and associations between these anthropometric measures and FFMI. Additionally, in women, we observed no association between CRP and GFI and a negative association between HOMA-IR and GFI (Supplement 2.3.3).

DISCUSSION

In this population-based study of elderly individuals we investigated the association between anthropometric measurements and FMI and FFMI. In men, we found a positive association between ABSI and FMI, but an inverse association with FFMI. The inverse association of ABSI with FFMI remained significant across strata of BMI (i.e. normal weight, overweight and obese), and the strength of the association increased with increasing BMI category. In women, higher ABSI was associated with higher FFMI. BMI and WC showed positive associations with both FMI and FFMI among men and women.

Among the elderly, the percentage of fat mass increases, along with a decrease in fat-free mass, a change mainly attributed to an accelerated decrease in lean mass.[1] It has been demonstrated that reduced lean mass and increased fat mass contribute independently to mobility impairment and increased mortality risk.[20] The role of anthropometric measures to assess the FM and FFM has been challenged.[3] An increase (or decrease) in BMI or WC levels could be associated with an increase (or decrease) in both fat and fat-free mass. Therefore, BMI and WC cannot discriminate between fat and fat-free mass and are not capable of identifying sarcopenic obesity.[2] Using DXA as a gold standard measure of fat and fat-free mass, we examined the association of a new anthropometric measure, ABSI, as well as the traditional measures BMI and WC, with FM and FFM.

Among the different anthropometric measures, ABSI was the only measure that was positively associated with fat mass and negatively associated with fat-free mass in men, whereas BMI and WC were positively associated with both FM and FFM. The advantage of ABSI is that it combines information from WC, height and weight. A high ABSI is an indication of a higher WC than expected for a given height and weight and corresponds to a more central concentration of body volume, suggesting more abdominal fat.[13] Abdominal fat deposition leads to systemic inflammation [21] and insulin resistance,[22] and accompanies systemic loss of skeletal muscle mass, as reported previously.[23,24] This could explain the association between higher ABSI and lower fat-free mass in men. This notion is supported in our study, in which we found that higher CRP, a marker of systemic inflammation, was strongly associated with higher fat mass and lower fat-free mass. Additionally, higher levels of HOMA-IR, an insulin resistance index, were associated with higher total fat mass, whereas no association was found with fat-free mass. Furthermore, our study extends previous findings in overweight and obese patients recruited by hospital outpatient obesity clinics, that showed an inverse association between ABSI and FFMI,[15] to a large population-based cohort. Additionally, we showed that the association of ABSI with fat mass and fat-free mass was present across categories of BMI in men, indicating that ABSI could predict sarcopenic obesity independent of BMI status. Moreover, our study supports the findings from the previous study, indicating that ABSI may not be just a marker of visceral obesity, but also represent an index of lower muscle mass.[15]

In our study, the association of ABSI with FM and FFM differed by gender. Unlike in men, who showed an inverse association between ABSI and fat-free mass, there was a positive association in women. This discrepancy in the findings between men and women could be explained by the differences in body fat distribution.[25,26] In men, adipose tissue tends to be more centrally deposited, suggesting increased WC for a given fat mass, whereas in women adipose tissue is mainly deposited in the lower body gynoid (gluteal-femoral), suggesting lower WC for a given fat mass.[27] This notion is supported by our data, in which we found that men had higher WC than women and consequently higher ABSI, whereas their BMI levels were comparable to women's. Additionally, women have more adipose tissue in the lower gynoid, compared to men. This tissue acts as a 'protective' depot, and is associated with lower metabolic risk, including insulin resistance and inflammation.[28,29] Therefore, the increased fat mass in women has relatively lower adverse effects in muscle mass. This is also supported in our study, in which we found a negative association between gynoid fat mass index and HOMA-IR in women, indicating lower levels of insulin resistance for an increase in gynoid adipose tissue. Taken together, these findings could explain in part the mechanism behind the inverse association of ABSI with FFMI in men and the positive association in women.

Because of their simplicity, BMI and WC remain the most commonly used measurements of adiposity in epidemiologic studies. In our study, BMI and WC were both positively associated with FM and FFM and were not able to distinguish between these two measures in either men or women. This finding is in agreement with other studies, in which they found BMI to be positively associated with both FM and FMM.[8-10] Moreover, as in other studies, the correlation was strongest between BMI and FM, compared to FFM.[8,9] Additionally, WC has also been shown to be positively associated with FM[8,11,12] and FFM,[12] similar as in our study. However, these anthropometric measures cannot distinguish between fat mass and lean mass, and therefore their validity in measuring sarcopenic obesity has been questioned.[7]

Strengths of our study include the large sample size from a population-based cohort and the use of DXA as an accurate method to determine fat mass and fat-free mass. Nevertheless, several limitations should be mentioned. First, ABSI is relatively new measure and there are no available cut-off points yet to assign individuals at higher and lower risk for obesity related metabolic risk. Second, to evaluate the association of fat mass with insulin resistance and inflammation as potential mechanisms that contribute to both reduced muscle mass and fat gain we used measures of HOMA-IR and CRP. However, CRP and HOMA-IR, as well as physical activity, were measured in a different wave than the anthropometric and DXA measurements. Therefore, we cannot fully exclude the possibility of residual confounding by these variables. Finally, we only included individuals which were still alive at the fourth follow-up visit of first cohort and second follow-up visit of second cohort of the Rotterdam Study. Thereby, the included participants can be considered survivors and might not reflect the total elderly population.

In conclusion, our study demonstrated that while BMI and WC could not distinguish between FM and FFM, ABSI provided a differential association with FM and FFM in men. Since sarcopenic obesity is associated with decreased FFM and increased FM, ABSI could be a useful tool for identifying males at higher risk for sarcopenic obesity. Nevertheless the observed correlations were small, and the results need to be confirmed in other study populations.

Table 2.3.1 Characteristics of study population (N=3612)

		Men (n=1520)	**Women (n=2092)**
Age (years)		72.8 ± 6.7	72.9 ± 7.1
Body shape index (m $^{11/6}$ kg $^{-2/3}$)		0.083 ± 0.0040	0.077 ± 0.005
Body mass index (kg/m^2)		27.2 ± 3.3	27.8 ± 4.4
Waist circumference (cm)		100.0 ± 9.9	89.4 ± 10.9
Fat mass index (kg/m^2)		7.7 ± 2.4	11.1 ± 3.3
Fat free mass index (kg/m^2)		19.4 ± 1.6	16.5 ± 1.5
Fat mass / fat free mass		0.40 ± 0.11	0.66 ± 0.17
Lean mass index (kg/m^2)		18.4 ± 1.5	15.6 ± 1.4
Gynoid fat mass (kg/m^2)		1.08 ± 0.33	1.77 ± 0.51
Physical activity (METs)		76.4 ± 42.8	97.4 ± 42.2
Smoking (%)	Never smokers	206 (13.6)	893 (42.7)
	Former smokers	1116 (73.4)	925 (44.2)
	Current smokers	198 (13.0)	274 (13.1)
Prevalence of chronic diseases* (%)		714 (46.8)	690 (32.5)
CRP (mmol/L)		1.83 (0.76, 3.91)	1.99 (0.81, 3.90)
HOMA-IR		2.89 (1.92, 4.39)	2.80 (1.88, 4.53)

Mean (SD) or number and (%), or median and (low, high quartile)

* Chronic disease include: cardiovascular disease, diabetes, and cancer.

Table 2.3.2 Pearson's rank correlation in men and women

	ABSI	**BMI**	**WC**
Men (n=1520)			
FMI	0.30 (<0.001)	0.89 (<0.001)	0.85 (<0.001)
FFMI	-0.19 (<0.001)	0.66 (<0.001)	0.43 (<0.001)
FM/FFM	0.37 (<0.001)	0.74 (<0.001)	0.76 (<0.001)
Women (n=2092)			
FMI	0.01 (0.613)	0.95 (<0.001)	0.81 (<0.001)
FFMI	0.09 (<0.001)	0.73 (<0.001)	0.65 (<0.001)
FM/FFM	-0.02 (0.375)	0.81 (<0.001)	0.68 (<0.001)

Abbreviations: ABSI, a body shape index; BMI, body mass index; WC, waist circumference; FMI, fat mas index; FFMI, fat free mass index

Pearson correlation (p value)

Table 2.3.3 Multivariable linear regression analysis between anthropometric measures FFMI, FMI and FM/FFM.

	Men (n=1520)	**Women (n=2092)**
	β coefficients* (95%CI)	**β coefficients* (95%CI)**
FMI (dependent variable)		
ABSI ($m^{11/6}$ $kg^{-2/3}$)	1.01 (0.85, 1.17)	0.04 (-0.13, 0.21)
BMI (kg/m^2)	2.60 (2.54, 2.67)	2.86 (2.82, 2.89)
WC (cm)	2.38 (2.30, 2.45)	2.83 (2.75, 2.92)
FFMI (dependent variable)		
ABSI ($m^{11/6}$ $kg^{-2/3}$)	-0.28 (-0.38, -0.17)	0.18 (0.10, 0.26)
BMI (kg/m^2)	1.23 (1.16, 1.30)	1.03 (0.99, 1.07)
WC (cm)	0.80 (0.72, 0.88)	1.07 (1.02, 1.12)
FM/FFM (dependent variable)		
ABSI ($m^{11/6}$ $kg^{-2/3}$)	0.06 (0.05, 0.07)	-0.01 (-0.01, 0.01)
BMI (kg/m^2)	0.11 (0.10, 0.12)	0.13 (0.12, 0.13)
WC (cm)	0.11 (0.10, 0.11)	0.12 (0.12, 0.13)

Abbreviations: ABSI, a body shape index; BMI, body mass index; WC, waist circumference; FFMI, fat free mass index; FMI, fat mass index; FM, fat mass; FFM, fat free mass.
* β (95%CI) are presented for one standard deviation increase in anthropometric measures, adjusted for age, physical activity, smoking and chronic diseases (cardiovascular disease, diabetes, and cancer).

Table 2.3.4 Multivariable linear regression analysis of ABSI with FFMI and FMI among categories of BMI.

		Men (n=1520)	**Women (n=2092)**
		β coefficients* (95%CI)	**β coefficients* (95%CI)**
FMI (dependent variable)			
ABSI ($m^{11/6}$ $kg^{-2/3}$)	Normal weight	0.60 (0.44, 0.74)	0.10 (-0.05, 0.26)
	Overweight	0.74 (0.61, 0.87)	-0.11 (-0.21, -0.01)
	Obese	0.48 (0.14, 0.83)	-0.48 (-0.71, -0.26)
FFMI (dependent variable)			
ABSI ($m^{11/6}$ $kg^{-2/3}$)	Normal weight	-0.37 (-0.50, -0.25)	-0.05 (-0.16, 0.06)
	Overweight	-0.51 (-0.62, -0.40)	0.13 (0.06, 0.21)
	Obese	-0.52 (-0.78, -0.26)	0.26 (0.12, 0.41)

Abbreviation: ABSI, a body shape index; BMI, body mass index; FFMI, fat free mass index; FMI, fat mass index;
*β (95%CI) are for standard deviation increase in anthropometric measures, adjusted for age, physical activity, smoking and chronic diseases (cardiovascular disease, diabetes, and cancer).

Table 2.3.5 Multivariable linear regression analysis for the association of FFMI and FMI with CRP and HOMA-IR.

	Men (n=1520)	**Women (n=2092)**
	β coefficients* (95%CI)	**β coefficients* (95%CI)**
FMI (dependent variable)		
CRP	0.26 (0.18, 0.35)	0.26 (0.18, 0.33)
HOMA-IR[§]	0.51 (0.41, 0.62)	0.21 (0.11, 0.31)
FFMI (dependent variable)		
CRP	-0.12 (-0.19, -0.05)	0.06 (0.01, 0.13)
HOMA-IR[§]	-0.05 (-0.14, 0.05)	0.14 (0.07, 0.21)

Abbreviation: FFMI, fat free mass index; CRP, C-reactive protein; FFMI, fat free mass index; FMI, fat mass index; HOMA-IR, homeostatic model assessment for insulin resistance.

β coefficients (95%CI) are per 1 SD increase in CRP and HOMA-IR, adjusted for age, physical activity, smoking, weight and chronic diseases (cardiovascular disease, diabetes, and cancer).

[§] Patients with diabetes mellitus at baseline was excluded from analysis. (men, n=1233 and women n=1757)

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SUPPLEMETANTAL FOR CHAPTER 3.2

Supplement 2.3.1 Pearson's rank correlation between lean mass and anthropometric measurements in men and women

	ABSI	**BMI**	**WC**
Men (n=1520)			
Lean mass	-0.19 (<0.001)	0.65 (<0.001)	0.42 (<0.001)
Women (n=2092)			
Lean mass	0.11 (<0.001)	0.71 (<0.001)	0.64 (<0.001)

ABSI, a body shape index; BMI, body mass index; WC, waist circumference.
All correlations are significant ($p < 0.05$).
Pearson correlation (p value)

Supplement 2.3.2 Multivariable linear regression analysis between anthropometric measures with lean mass.

	Men (n=1520)	**Women (n=2092)**
	β coefficients* (95%CI)	**β coefficients* (95%CI)**
Lean mass (dependent variable)		
ABSI ($m^{11/6}$ $kg^{-2/3}$)	-0.26 (-0.36, -0.16)	0.20 (0.12, 0.27)
BMI (kg/m^2)	1.16 (1.09, 1.23)	0.96 (0.92, 1.00)
WC (cm)	0.75 (0.68, 0.83)	1.01 (0.95, 1.06)

Abbreviations: ABSI, a body shape index; BMI, body mass index; WC, waist circumference.
* β (95%CI) are presented for one standard deviation increase in anthropometric measures, adjusted for age, physical activity, smoking and chronic diseases (diabetes, cardiovascular disease and cancer).

Supplement 2.3.3 Multivariable linear regression analysis for the association of GFI with CRP and HOMA-IR.

	Men (n=1520)	**Women (n=2092)**
	β coefficients* (95%CI)	**β coefficients* (95%CI)**
GFI (dependent variable)		
CRP	0.03 (0.02, 0.04)	0.01 (-0.01, 0.02)
HOMA-IR[§]	0.05 (0.04, 0.07)	-0.02 (-0.04, -0.01)

Abbreviation: GFI, gynoid fat mass index; CRP, C-reactive protein; HOMA-IR, homeostatic model assessment-insulin resistance.
β coefficients (95%CI) are per one standard deviation increase in CRP and HOMA-IR, adjusted for age, physical activity, smoking, weight and chronic diseases (diabetes and cardiovascular disease).
[§] Patients with diabetes mellitus at baseline was excluded from analysis and additionally adjusted by weight. (men, n=1233 and women n=1757)

Chapter 3

Overweight, obesity and metabolic risk

3.1 Metabolically healthy obesity and the risk of cardiovascular disease in the elderly

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ABSTRACT

Background: Whether being metabolically healthy obese (MHO) - defined by the presence of obesity in the absence of metabolic syndrome - is associated with subsequent cardiovascular disease (CVD) remains unclear and may depend on the participants' age. We examined the association of being MHO with CVD risk in the elderly.

Methods: This study included 5,314 individuals (mean age 68 years) from the prospective population-based Rotterdam Study. We categorized our population in groups according to body mass index (BMI) and presence and absence of metabolic syndrome, and estimated the hazard ratio (HR) and 95% confidence interval (95%CI) for every group by using Cox proportional hazard models.

Results: Among 1048 (19.7%) obese individuals we identified 260 (24.8%) MHO subjects. Over 14 years of follow-up there were 861 incident CVD cases. In the multivariable adjusted analysis, we did not observe an increased CVD risk in MHO individuals (HR 1.07, 95%CI 0.75-1.53), compared to normal weight individuals without metabolic syndrome. CVD risk was increased by the presence of metabolic syndrome in normal weight (HR 1.35, 95%CI 1.02-1.80), overweight (HR 1.32, 95%CI 1.09-1.60) and obese (HR 1.33, 95%CI 1.07-1.66) individuals, compared to those with normal weight without metabolic syndrome. In a mediation analysis, 71.3% of the association between BMI and CVD was explained by the presence of metabolic syndrome.

Conclusions: In our elderly population, we found that the presence of obesity without metabolic syndrome did not confer a higher CVD risk. However, metabolic syndrome was strongly associated with CVD risk, and was associated with an increased risk in all BMI categories. Therefore, preventive interventions targeting cardiometabolic risk factors could be considered in elderly, regardless of weight status.

INTRODUCTION

Although obesity in young individuals is an established risk factor for cardiovascular disease (CVD), the effect of obesity in the elderly seems to dilute with advancing age, rising towards controversial discussions.[1,2] The discrepancy between the findings at younger versus older ages suggests that additional factors may alter the effect of obesity on risk of CVD. It is well known that the presence of metabolic syndrome (a cluster of cardiovascular risk factors including hypertension, dyslipidemia, hyperglycemia and abdominal obesity) differs among individuals with similar body mass index (BMI), which indicates that the risk of CVD within specific categories of BMI could be heterogeneous.[3,4] In this context, recent interest has focused on a subgroup of obese individuals, termed the metabolically healthy obese (MHO), who despite their increased BMI (BMI≥30kg/m^2) seem to have an adequate metabolic profile and do not have metabolic syndrome.[3, 5, 6]

The effect of being MHO on health outcomes remains controversial. While some studies have reported no increased risk of CVD among MHO individuals,4, 6-8 several other studies have shown an increased risk of CVD in this group.[9-12] For example, a 17 year follow-up study of adults aged 39-63 years found an increased CVD risk for MHO individuals.[9] In contrast, another study in women of 45 years and older, with 10 years follow-up, found no increased CVD risk for obese individuals without metabolic syndrome.[8] It is important to note that in these studies the mean age was below 65 years, indicating that information among the elderly is scarce. In the elderly, the relation between body weight, body composition, and health behaviors is different than in younger adults.[13,14] Therefore, the impact of being MHO could differ between younger, middle-aged and elderly adults.

In the current study, we aimed to study the role of being MHO in association with risk of CVD in middle-aged and elderly individuals. We sought to examine the association of metabolic syndrome with CVD among different BMI categories and to examine the contribution of metabolic syndrome to the association between BMI and CVD.

METHODS

Study design, setting, and 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.[15] The baseline examination of the initial cohort (RS-I) was completed between 1990 and 1993. In 2000-2001, the Rotterdam Study was extended (RS-II) 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 visit 3, between 1997 and 1999; n = 4,797) and the participants attending the first examination of the second cohort (RS-II visit 1, between 2000 and 2001; n = 3,011). We excluded all participants with a history of CVD (coronary heart disease, cerebrovascular disease, or heart failure) at baseline (n = 1,505), those who did not visit the research center at baseline for assessment of cardiovascular risk factors or BMI (n = 660), those who did not have fasting plasma measurements (n = 289), and finally those who were underweight (BMI <18.5 kg/m^2) at baseline (n = 40). This left a total of

5,314 individuals eligible for the present analyses. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC 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 participate in the study and to obtain information from their treating physicians. Detailed information on the design of the Rotterdam Study can be found elsewhere.[15]

Assessment of anthropometric, lifestyle exposures, and laboratory measurements

Height and weight were measured with the participants standing without shoes and heavy outer garments. BMI was calculated as weight divided by height squared (kg/m^2). Waist circumference was measured at the level midway between the lower rib margin and the iliac crest with participants in standing position without heavy outer garments and with emptied pockets, breathing out gently. Information on education (≥ high school, < high school), smoking status (current or former/never), alcohol use (drinking alcohol or not), and physical activity[16] were obtained through interview. Blood pressure was measured in seated position and averaged across two measures. Fasting triglycerides, total cholesterol and high-density lipoprotein (HDL) cholesterol and glucose levels were measured using standard laboratory techniques.[17,18] To assess kidney function we estimated the glomerular filtration rate (GFR), using the Chronic Kidney Disease Epidemiology Collaboration CKD-EPI equation.[19]

Metabolic syndrome and body mass index

Normal weight (18.5-25 kg/m^2), overweight (25-29.9 kg/m^2), and obese participants (≥ 30 kg/m^2) were categorized as either with or without metabolic syndrome based on the "Harmonized metabolic syndrome definition".[20] Participants were considered to have metabolic syndrome if they had ≥ 3 of the following five components: (1) waist circumference ≥ 102 cm in men and ≥ 88 cm in women; (2) systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg or use of antihypertensive treatment; (3) fasting plasma triglycerides ≥ 150 mg/dL; (4) HDL cholesterol level < 40 mg/dL in men and < 50 mg/dL in women; (5) elevated fasting glucose ≥ 100 mg/dL or treatment for diabetes mellitus. Consequently, this information was used to create six phenotypes: normal weight, overweight and obese with or without metabolic syndrome. MHO was defined as obesity without metabolic syndrome (i.e. BMI ≥ 30kg/m^2 and having ≤ 2 components of metabolic syndrome).

Definition of 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.[21] Definite and possible fatal coronary heart disease events are coded by using the definitions applied within the Cardiovascular Health Study and Atherosclerosis Risk in the Communities Study.[22] Stroke is defined as a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent origin other than vascular.[23] Data on incident CVD is collected using an automated follow-up system, through gathering information from general practitioners in the

study area and subsequent collection of information from letters of medical specialists and discharge reports in case of hospitalization. A consensus panel, led by a physician with expertise in field, adjudicated the diagnosis using standardized definitions. The follow-up was complete until January 1, 2012.

Statistical analysis

Baseline characteristics of the study population are presented as mean ± SD (or frequency and percentage when appropriate) for the 6 phenotypes formed by the metabolic syndrome across different BMI categories. 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 six phenotypes described above in association with CVD, using normal weight without metabolic syndrome as the reference category. Additionally, we separately estimated the HR and 95%CI for the associations of the BMI categories and metabolic syndrome with CVD. Proportional hazards assumptions were confirmed in all Cox models, by visually comparing the Kaplan-Meier curves of the different groups. The models were adjusted for age, gender, smoking, cholesterol level, lipid-lowering medication use, GFR, alcohol use, education and physical activity . We decided a priori not to adjust for systolic blood pressure, triglycerides, HDL cholesterol, glucose, diabetes mellitus, and waist circumference, as they are all part of the definition of metabolic syndrome.[10] Kaplan Meier analyses and log rank tests were used to build plots for CVD incidence trends among the BMI categories, metabolic syndrome status and the joint BMI and metabolic syndrome phenotypes. We did not observe a significant association of gender with either BMI, metabolic syndrome or the joint BMI and metabolic syndrome phenotypes. Moreover, we did not find an interaction between BMI and metabolic syndrome.

In a mediation analysis, we examined whether metabolic syndrome could be considered a mediator in the association between BMI and CVD risk. The percentage of excess risk mediated was calculated as $[(\text{HRcon adj} - \text{HRcon + med adj})/(\text{HRcon adj} - 1)] \times 100\%$, where HRcon adj is the confounder-adjusted HR for CVD and HRcon + med adj is the confounder and mediator–adjusted HR.[24]

Sensitivity analyses

Due to the 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. Although there was no interaction between BMI or metabolic syndrome with gender, we repeated our main analysis in men and women, because of gender-differences in body fat distribution. Moreover, to show the independence of metabolic syndrome over BMI, we adjusted for BMI (continuously and categorical) in the association of metabolic status with CVD. Finally, to investigate the dose-response relation between metabolic syndrome and CVD, we evaluated the risk of CVD according to the presence of one, two, three, four, or five components of the metabolic syndrome.

Co-variables were missing in less than 5% of the participants, with the exception of treatment for hypertension, which had 7.7% missing. 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 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of the study participants, stratified by BMI and metabolic syndrome, are shown in Table 3.1.1. Among all participants, 57.2% (n=3,038) were without metabolic syndrome and 19.7% (n=1,048) were obese. The MHO phenotype represented 4.9% (n=260) of the total study population and 24.8% of the obese population. MHO subjects were more often women and reported more physical activity compared to obese individuals with metabolic syndrome. During a median follow-up of 10.3 years (interquartile range: 8.1-11.7 years), there were 861 (16.2%) incident CVD events.

In the association between BMI categories and CVD, we found that being overweight (HR 1.12, 95%CI: 0.96-1.30) or obese (HR 1.18, 95% CI: 0.97-1.44) was not significantly associated with risk of CVD, compared to being normal weight. In contrast, individuals with metabolic syndrome had an increased risk of CVD (HR: 1.27, 95% CI: 1.11-1.46), compared to individuals without metabolic syndrome.

In Table 3.1.2, we present the HRs (95% CIs) for the association between the joint BMI and metabolic syndrome phenotypes with incident CVD. Compared to normal weight subjects without metabolic syndrome, the HRs (95%CIs) were 1.08 (0.89-1.32) in overweight and 1.07 (0.75-1.53) in obese subjects without metabolic syndrome and 1.35 (95%CI, 1.02-1.80) in normal weight, 1.32 (1.09-1.60) in overweight and 1.33 (1.07-1.66) in obese subjects with metabolic syndrome. Figure 3.1.1 presents the Kaplan-Meier survival curves of the cumulative incidence of CVD by categories of BMI (Figure 3.1.1 A), by presence of metabolic syndrome (Figure 3.1.1 B) and as a function of the joint BMI and metabolic status phenotypes (Figure 3.1.1 C). The cumulative incidences of CVD were not different among categories of BMI (log-rank trend P=0.395). However, the cumulative incidence was higher in individuals with metabolic syndrome compared to those without (log-rank trend P<0.001). As expected, the cumulative incidence of CVD was higher in normal weight, overweight and obese individuals with metabolic syndrome, than in individuals without metabolic syndrome (log-rank trend P < 0.001). In the mediation analysis (Table 3.1.3), the percentage of excess risk mediated by metabolic syndrome in the association between BMI (as a continuous variable) and CVD was 71.3%; that is, 71.3% of the association between BMI and CVD could be explained by metabolic syndrome. By categorizing BMI, this proportion increased up to 73.1%.

Sensitivity analyses

Supplement 3.1.1 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 in men and women separately, we found similar results (Supplement 3.1.2 and 3.1.3). Moreover, the association of metabolic status with CVD did not largely change after we further adjusted for BMI (Supplement 3.1.4). The new HR (95%CI) of the presence of metabolic syndrome was 1.25 (1.08-1.46), when we adjusted for BMI continuously. Finally, when we examined the dose-response relation between metabolic syndrome components

and CVD, we observed that the risk of CVD increased stepwise according to the presence of one, two, three, four, or five components of metabolic syndrome (Supplement 3.1.5).

DISCUSSION

In this population-based study of 5,314 middle-aged and elderly individuals, 19.7% of the population was obese, of which 24.8% were without metabolic syndrome (i.e. MHO). Our study yields three key findings. First, compared to normal weight individuals without metabolic syndrome, MHO subjects were not at significant increased risk of CVD. Second, regardless of being normal weight, overweight or obese, the presence of metabolic syndrome consistently increased CVD risk. Third, 71.3% of the association between BMI and CVD was explained by metabolic syndrome. These findings highlight the importance of assessing CVD risk irrespective of BMI in an older population, and stress the importance of metabolic syndrome in the elderly.

Previous studies evaluating the association between metabolically healthy obesity and CVD risk have shown inconsistent results.[4,6-12] While some studies reported no increased risk of CVD among MHO individuals,[4,6-8] several other studies have shown an increased CVD risk in this group.[9-12] In agreement with our study, Meigs et al., in an 11-year follow-up study of 2,902 men and women (mean age of 53 years), reported that MHO individuals do not have an increased risk of CVD in the Framingham Offspring Study.[6] Similarly, a report from the Women's Ischemia Syndrome Evaluation (WISE) study showed that the presence of metabolic syndrome, but not BMI, predicted 3-year risk of cardiovascular death, in 21 to 86-year-old women referred for angiography.[4] Moreover, a large prospective study of 25,626 women aged 45 years and older, followed up to 10 years, found that MHO individuals were not at increased risk of CVD.[8] Additionally, this study showed that the presence of metabolic syndrome conferred a higher risk of developing CVD than BMI.[8] In contrast with these studies, Hinnouho et al., in a 17 year follow-up study, including men and women aged 35–55 years, found that MHO individuals were at increased risk of incident CVD, compared with normal weight individuals without metabolic syndrome.[9] Moreover, in contrast to our findings, these authors revealed a gradual increased CVD risk for overweight and obese individuals, compared to normal weight persons, both in individuals with and without metabolic syndrome. Similarly to Hinnouho et al, Thomsen et al reported that MHO individuals are at higher risk of developing myocardial infarction and ischemic heart disease.[10] Additionally, this short follow-up (median 3.6 years) study of 71,527 men and women aged 20-100 years showed that both in individuals with and without metabolic syndrome, there were increasing cumulative incidences of myocardial infarction and ischemic heart disease going from normal weight through overweight to obesity. Furthermore, in their study, metabolic syndrome explained only 12% of the risk attributed to BMI in the association with myocardial infarction and ischemic heart disease, whereas in our study metabolic syndrome explained 71.3% of the risk attributed to BMI in association with CVD.

The different findings regarding the association between metabolically healthy obesity and CVD risk in the studies mentioned above could reflect differences in the age range of the participants included in the different studies. To explain the importance of age in the association between BMI, metabolic syndrome and CVD, two possibilities could be considered. First, studies have shown that the magnitude of the relation between BMI and CVD risk weakens with age.[26-28] Indeed, in our study there was no evidence for a dose-response increase in CVD risk within BMI

categories in individuals with or without metabolic syndrome, whereas other studies conducted in younger populations showed a progressive increase in CVD risk, going from normal weight through overweight to obesity.[9,10] Although body weight and BMI may remain relatively unchanged with advancing age, there is a change in body composition, followed by visceral fat increases and muscle mass decreases.[29] Hereby, elderly individuals can be considered overweight by body fat standards, without having a BMI above 25. Consequently, BMI becomes a less accurate reflection of fat mass 30 and BMI alone may therefore not be a precise predictor of cardiovascular risk in elderly. On the other hand, metabolic syndrome is an established predictor of future CVD, and as we also showed in our study, the increased risk of CVD starts with the presence of just one component of the metabolic syndrome.[33] Moreover, the prevalence of metabolic syndrome increases in older individuals[31] and was 42.8% in our population. Consequently, the metabolic syndrome becomes a more relevant condition in the elderly. Taken together, these findings stress the importance of metabolic syndrome over BMI in the development of future CVD among older adults, compared to young adults.

The mechanisms underlying the healthy metabolic profile of metabolically healthy obesity are still unclear. It has been suggested that the location, metabolic activity and histological characteristics of adipose tissue may determine metabolic health among obese individuals, whereas the amount of adipose tissue is less crucial.[32] In addition, the amount of years that an individual has been obese might play a role.[33] Moreover, studies have shown that MHO individuals have lower levels of C-reactive protein [34] and higher levels of insulin sensitivity, compared to obese individuals with metabolic syndrome.[35] Additionally, there is some evidence that obese individuals with metabolic syndrome are less fit than MHO individuals.[36] In our study, MHO participants had higher levels of physical activity than their obese counterparts with metabolic syndrome, which supports this last statement. However, a previous study has proposed that MHO is not a permanent state of the healthy metabolic profile, but rather a transient phase, moving toward glucose-metabolic abnormalities.[9] Therefore, it might be wise to re-evaluate the metabolic status of MHO individuals on a regular basis.

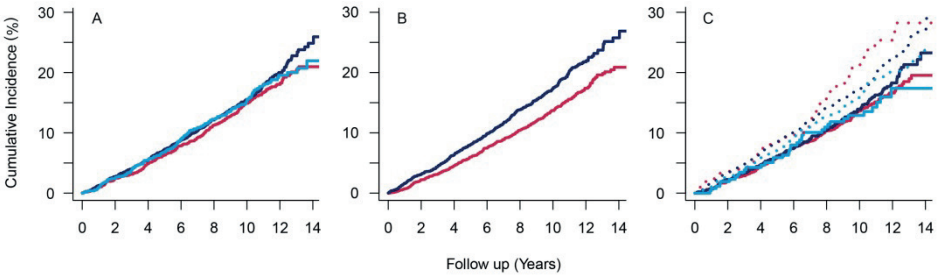
In our study, the presence of metabolic syndrome in normal weight individuals conferred a higher risk of CVD compared to obese individuals without metabolic syndrome, when we compared both groups to normal weight individuals without metabolic syndrome. Moreover, normal weight individuals with metabolic syndrome had a higher cumulative incidence of CVD than obese individuals with metabolic syndrome. Our study showed that the presence of metabolic syndrome in normal weight individuals was accompanied by a higher smoking prevalence and lower levels of physical activity, compared to obese individuals without metabolic syndrome. This finding is in accordance with a previous study,[3] that showed that MHO individuals were more often nonsmokers and met the current physical activity guidelines more frequently than normal weight individuals with metabolic syndrome. Our observation that the cumulative incidence of CVD was higher in normal weight subjects with metabolic syndrome, compared to their obese counterparts, could be explained by the fact that normal weight individuals with metabolic syndrome were older and more often smokers than obese individuals with metabolic syndrome. Moreover, we found that normal weight individuals with metabolic syndrome had a lower proportion of treatment for hypertension at the baseline compared to obese individuals with metabolic syndrome. Remarkably, the baseline systolic blood pressure in

both groups was similar. This may suggest that the obese individuals are more likely to be screened for CVD and subsequently receive medication.

Strengths of the current study include the prospective study design, large sample size, long follow-up, high follow-up rate, reliable assessment of CVD events and detailed assessment of lifestyle factors, components of the metabolic syndrome and cardiovascular risk factors. However, several limitations should be considered. First, our conclusions are drawn from the baseline measurements. In our analyses, we were not able to account for changes in BMI and metabolic factors during follow-up. Therefore, a degree of misclassification, due to changes in these risk factors over time might have occurred. Second, our study population included only Caucasian men and women above 55 years. Therefore, results from the present study cannot be generalized to other age-groups or ethnics groups.

To conclude, in our population-based study of middle-aged and elderly adults, MHO individuals were not at increased risk of CVD. However, the presence of the metabolic syndrome was associated with future cardiovascular risk similarly in normal weight, overweight and obese individuals Additionally, we showed that the association between BMI and CVD was largely (73.1%) explained by the presence of metabolic syndrome. Although it remains prudent to recommend weight loss in overweight and obese individuals and the benefits that these interventions can achieve expand beyond cardiovascular events, our results suggest that preventive interventions targeting cardiometabolic risk factors in older individuals should be considered regardless of weight status.

Figure 3.1.1 Cumulative incidence of cardiovascular disease as a function of follow-up time according to body mass index categories (A), metabolic syndrome (B) and the joint body mass index and metabolic syndrome phenotypes (C).



(A) Red: "normal weight" (1,750 individuals), dark blue: "overweight" (2,516 individuals), light blue: "obese" (1,048 individuals).These incident curves do not differ significantly from each other over the follow-up (log-rank test, P = 0.395). (B) Red: "without metabolic syndrome" (3,038 individuals), dark blue: "with metabolic syndrome" (2276 individuals).These incident curves differ significantly from each other over the follow-up (log-rank test, P = 0.001). (C) Solid lines indicate individuals without metabolic syndrome and dotted lines individuals with metabolic syndrome. Red: "normal weight" (including 1444 without metabolic syndrome and 306 with metabolic syndrome); dark blue: "overweight" (including 1334 without metabolic syndrome and 1182 with metabolic syndrome); light blue: "obese" (including 260 without metabolic syndrome and 788 with metabolic syndrome). These incident curves differ significantly from each other over the follow-up (log-rank test, P = 0.001).

Table 3.1.1 Baseline characteristics of study population across the categories of metabolic health status and body mass index.

	No metabolic syndrome (n=3038)			**Metabolic syndrome (n=2276)**		
	Normal weight	**Overweight**	**Obese**	**Normal weight**	**Overweight**	**Obese**
n, %	1444 (47.5)	1334 (43.9)	260 (8.6)	306 (13.4)	1182 (51.9)	788 (34.7)
Women, %	859 (59.5)	686 (51.4)	203 (78.1)	197 (64.4)	689 (58.3)	568 (72.1)
Age, years	68.2 ± 8.0	68.1 ± 8.0	68.3 ± 8.1	70.1 ± 8.5	68.8 ± 8.1	68.1 ± 7.9
High education, %	520 (36.1)	552 (41.3)	132 (50.7)	124 (40.5)	498 (42.1)	381 (48.3)
Current smokers, %	346 (24.0)	226 (16.9)	40 (15.4)	92 (30.1)	254 (21.5)	117 (14.8)
Alcohol use, %	868 (60.1)	721 (54.0)	177 (68.1)	194 (63.4)	690 (58.4)	554 (70.3)
Physical activity, METHour/week	86.6 ± 42.9	87.1 ± 45.5	85.3 ± 44.1	81.7 ± 43.4	82.0 ± 40.7	80.4 ± 44.0
Estimated glomerular filtration rate, GFR	77.2 ± 13.6	76.3 ± 13.5	76.4 ± 15.7	73.1 ± 15.4	74.1 ± 14.7	75.4 ± 15.2
Waist circumference, cm	83.2 ± 8.3	92.1 ± 8.0	100.3 ± 9.4	89.1 ± 8.2	97.3 ± 7.5	107 ± 10.0
BMI, kg/m^2	23.0 ± 1.5	26.9 ± 1.3	32.3 ± 2.3	23.6 ± 1.2	27.6 ± 1.4	33.4 ± 3.1
Triglycerides, mg/dl	103.1 ± 39.2	109.1 ± 42.3	107.6 ± 30.7	181.1 ± 79.3	173.2 ± 77.0	172.4 ± 86.2
Fasting glucose, mg/dl	97.5 ± 14.7	100.0 ± 16.7	98.6 ± 15.1	115.8 ± 34.5	114.5 ± 28.6	120.3 ± 33.5
HDL cholesterol, mg/dl	61.2 ± 14.7	57.5 ± 13.4	59.7 ± 13.8	46.1 ± 15.1	46.7 ± 12.1	48.2 ± 14.0
Systolic blood pressure, mmHg	137.1 ± 21.3	139.9 ± 20.6	140.3 ± 23.1	150 ± 19.7	149.4 ± 19.8	149.4 ±18.8
Diastolic blood pressure, mmHg	74.2 ± 10.7	76.4 ± 10.6	77.2 ± 10.5	77.1 ± 10.5	79.2 ± 10.9	79.9 ± 10.9
Treatment for hypertension, n (%)	154 (10.7)	231 (17.3)	73 (28.1)	64 (20.9)	376 (31.8)	325 (41.2)
Total cholesterol, mg/dl	224.4 ± 36.0	227.4 ± 36.4	228.3 ± 35.9	232.8 ± 39.2	229.7 ± 37.8	226.6 ± 37.0
Treatment for hyperlipidemia, n (%)	82 (5.7)	93 (7.0)	16 (6.2)	50 (16.3)	158 (13.4)	111 (14.1)

n, number; MET, metabolic equivalent of task; BMI, body mass index; HDL, high-density lipoprotein. Values are means ± standard deviation or numbers (percentages)

Table 3.1.2 Association of the joint body mass index and metabolic syndrome phenotypes with cardiovascular disease

		N	Events	HR (95%CI)
No metabolic syndrome	normal weight	1444	203	1 (Reference)
	overweight	1334	205	1.08 (0.89-1.32)
	obese	260	36	1.07 (0.75-1.53)
Metabolic syndrome	normal weight	306	63	1.35 (1.02-1.80)
	overweight	1182	219	1.32 (1.09-1.60)
	obese	788	135	1.33 (1.07-1.66)

N, number; HR, hazard ratio; CI, confidence interval.
Hazard ratios and 95%CI are for the multivariable model adjusted for age, gender, smoking, total cholesterol, treatment for hyperlipidemia, estimated glomerular filtration rate (GFR), alcohol, physical activity and education.

Table 3.1.3 Percentage of excess risk mediated by metabolic syndrome in association between body mass index and cardiovascular disease

Exposure	Mediator	HR confounder adjusted	HR confounder and mediator adjusted	PERM, %
BMI (continuously)	Metabolic syndrome	1.0174	1.0053	71.3
BMI (categorically)	Metabolic syndrome	1.0901	1.0242	73.1

HR, hazard ratio; PERM, percentage of excess risk mediated; BMI, body mass index
Percentage of excess risk mediated (PERM) was calucalted as $((HR_{confounder\ adjusted} - HR_{confounder+mediator\ adjusted})/(HR_{confounder\ adjusted} -1))*100\%$. Hazard ratios are for the multivariable model adjusted for age, gender, smoking, cholesterol, treatment for hyperlipidemia, estimated glomerular filtration rate (GFR), alcohol, physical activity and education. Body mass index was categorized as normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30kg/m^2).

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SUPPLEMENT CHAPTER 3.1

Supplement 3.1.1 Association of the joint BMI and metabolic syndrome phenotypes with cardiovascular disease, adjusted for competing risk of mortality.

		N	Event	HR (95%CI)
No metabolic syndrome	normal weight	1481	208	1 [Reference]
	overweight	1334	205	1.12 (0.92-1.37)
	obese	260	36	1.08 (0.76-1.55)
Metabolic syndrome	normal weight	309	64	1.28 (0.96-1.72)
	overweight	1182	219	1.31 (1.08-1.60)
	obese	788	135	1.37 (1.09-1.71)

Hazard ratios and 95%CI are for the multivariable model adjusted for age, gender, smoking, cholesterol, treatment for hyperlipidemia, estimated glomerular filtration rate (GFR), alcohol, physical activity and education.

Supplement 3.1.2 Association of the joint BMI and metabolic syndrome phenotypes with cardiovascular disease in adults older than 65 years (n=3174)

		N	Event	HR (95%CI)
No metabolic syndrome	normal weight	846	157	1 [Reference]
	overweight	770	168	1.14 (0.92-1.42)
	obese	158	32	1.15 (0.78-1.68)
Metabolic syndrome	normal weight	203	51	1.32 (0.96-1.82)
	overweight	732	171	1.30 (1.05-1.63)
	obese	465	108	1.34 (1.04-1.72)

Hazard ratios and 95%CI are for the multivariable model adjusted for age, gender, smoking, cholesterol, treatment for hyperlipidemia, estimated glomerular filtration rate (GFR), alcohol, physical activity and education.

Supplement 3.1.3 Association of the joint BMI and metabolic syndrome phenotypes with cardiovascular disease in men and women

Men (n=2112)		**N**	**Events**	**HR (95%CI)**
No metabolic syndrome	normal weight	585	98	1 (Reference)
	overweight	648	111	1.10 (0.83-1.44)
	obese	57	7	1.09 (0.50-2.35)
Metabolic syndrome	normal weight	109	22	1.22 (0.76-1.94)
	overweight	493	106	1.42 (1.07-1.87)
	obese	220	40	1.33 (0.91-1.94)
Women (n=3202)		**N**	**Events**	**HR (95%CI)**
No metabolic syndrome	normal weight	859	105	1 (Reference)
	overweight	686	94	1.07 (0.81-1.42)
	obese	203	29	1.02 (0.68-1.55)
Metabolic syndrome	normal weight	197	41	1.41 (0.98-2.03)
	overweight	689	113	1.23 (0.94-1.61)
	obese	568	95	1.29 (0.97-1.70)

N, number; HR, hazard ratio; CI, confidence interval. Hazard ratios and 95%CI are for the multivariable model adjusted for age, gender, smoking, total cholesterol, treatment for hyperlipidemia, estimated glomerular filtration rate (GFR), alcohol, physical activity and education.

Supplement 3.1.4 Association of metabolic syndrome with cardiovascular disease after adjusting for BMI.

	Adjustment	**N**	**Event**	**HR (95%CI)**
No metabolic syndrome		3038	444	1 [Reference]
Metabolic syndrome	BMI, continuous	2276	417	1.25 (1.08-1.46)
	BMI, categorical	2276	417	1.26 (1.08-1.46)

Hazard ratios and 95%CI are for the multivariable model adjusted for age, gender, smoking, cholesterol, treatment for hyperlipidemia, estimated glomerular filtration rate (GFR), alcohol, physical activity, education and BMI.

Supplement 3.1.5 Risk of cardiovascular disease according to the presence of one, two, three, four, or five components of the metabolic syndrome

		N	Events	HR (95%CI)
Number of metabolic syndrome components	None	433	32	1 (Reference)
	One	1153	175	1.87 (1.28-2.72)
	Two	1452	237	1.94 (1.34-2.82)
	Three	1171	200	2.08 (1.43-3.02)
	Four	732	134	2.35 (1.59-3.46)
	Five	373	83	2.99 (1.97-4.51)

N, number; HR, hazard ratio; CI, confidence interval. Hazard ratios and 95%CI are for the multivariable model adjusted for age, gender, smoking, total cholesterol, treatment for hyperlipidemia, estimated glomerular filtration rate (GFR), alcohol, physical activity and education

3.2 Timing and duration of overweight in association with metabolic syndrome and diabetes among middle-aged and elderly

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ABSTRACT

Background: To investigate the association between timing and duration of overweight, independent of the current body mass index (BMI), with metabolic syndrome and diabetes.

Methods: This study included 3408 individuals from the prospective population-based Rotterdam Study. We studied the BMI measurements in three examinations (1990-2000). Compared to individuals that were never overweight, logistic regression models were used to examine the associations of overweight timing and overweight duration over the course of follow-up with the prevalence of metabolic syndrome and diabetes.

Results: Prevalence of metabolic syndrome and diabetes was 42.9% and 12.5%, respectively. In multivariable analysis, middle-age onset overweight was more strongly associated with prevalence of metabolic syndrome (OR 1.50, 95%CI 1.14-1.98) than elderly onset overweight (OR 1.31, 95%CI 1.00-1.70). The association of diabetes with timing of overweight was similar in middle-age (OR 1.77 (95%CI 1.17-2.71) and elderly (OR 1.81, 95% CI 1.24-2.67) onset overweight. Regarding overweight duration, incident and persistent overweight were associated with metabolic syndrome (OR 1.40, 95%CI 1.03-1.91 and 1.53, 95%CI 1.15-2.04) and fluctuating overweight had the strongest association with diabetes (OR 2.09, 95%CI 1.34-3.26).

Conclusions: Our findings underscore the importance of information regarding weight history, beyond the current BMI levels, to identify individuals at higher risk for metabolic syndrome and diabetes.

INTRODUCTION

Overweight and obesity are often accompanied by the presence of metabolic syndrome, a cluster of central obesity, hypertension, hyperglycemia and dyslipidemia;[1,2] and are established risk factors for diabetes and cardiovascular disease.[3,4] However, many overweight and obese individuals have an adequate metabolic profile without any evidence of metabolic syndrome or diabetes.[5,6] Therefore, the differential adverse metabolic effects of excess body fat remains unclear.

To develop metabolic syndrome or diabetes later in life, duration of overweight in an individual (i.e. being persistently overweight) might be important as it reflects the length of exposure to body fat through life. However, the few studies investigating the association between duration of overweight and the risk of metabolic syndrome and diabetes[7,8,9,10] have been performed among younger and middle-aged adults and have mostly been based on a self-reported weight history.[8,10] Additionally, the age at which individuals start to gain weight (i.e. timing of weight gain) might play a role in increasing the metabolic risk. Notably, the effect of timing of weight gain on the risk of metabolic syndrome or diabetes has not been yet investigated in elderly populations. Therefore, it remains unknown whether the differential and cumulative effects of overweight during late middle-age and elderly periods are still pertinent to the risk of development of metabolic syndrome or diabetes. Due to increased life expectancy and the growing prevalence of obesity, older adults are progressively living more years with overweight.[11,12] Therefore, the impact of overweight on the risk of metabolic syndrome and diabetes becomes increasingly more relevant among the elderly.

In our prospective population-based study of middle-aged and elderly, we aimed to examine whether timing and duration of overweight, independent of current body mass index (BMI) status, is a risk factor for metabolic syndrome and diabetes.

METHODS

Study Design, Setting, and Population

This study was performed within the frame work of the prospective population-based Rotterdam Study (RS). Details regarding the objectives and design of the Rotterdam Study have been reported previously.[13] Shortly, for the original cohort (RS-I), all inhabitants aged 55 and over from a well-defined suburb in the city of Rotterdam, the Netherlands, were invited to participate and 7,983 (78.1%) were enrolled. For the current study, we used data from the participants attending the third examination of the original cohort (RS-I visit 3, between 1997-1999; n = 4797). We then used the information on BMI and age from the two previous visits (RS-I visit 1, between 1989-1993 and RS-I visit 2, between 1993-1995). We excluded all participants who did not give informed consent (n=36), with missing information on BMI at first, second and third visit (n = 1067), who were underweight (BMI < 18.5) in each visit (n = 10), who did not visit the research center at the third visit (RS-I visit 3) for assessment of cardiovascular risk factors or did not have fasting plasma measures or other information for ascertainment of diabetes (n = 275). This left a total of 3408 individuals eligible for the present analysis.

Assessment of anthropometrics, lifestyle factors, laboratory measurements and comorbidities

Height and weight were measured with the participants standing without shoes and heavy outer garments. BMI was calculated as weight divided by height squared (kg/m^2). Waist circumference was measured at the level midway between the lower rib margin and the iliac crest with participants in standing position without heavy outer garments and with emptied pockets, breathing out gently. Information on education (a. primary to low level vocational education, b. secondary education, c. higher vocational education to university; based on international standard classification of education by UNESCO),[14] tobacco smoking status (never, former, current), alcohol use (less than 1 glass per day, 1-4 glasses/day for men and 1-2 glasses/day for women, > 4 glasses/day for men and > 2 glasses/day for women), and physical activity [15] (vigorous vs others) were obtained through home interview. Dietary information was not collected at the third visit (RS-I-3), therefore we used diet information measured in the first visit (RS-I-3). Information on diet were obtained through a 170-item validated semi-quantitative food frequency questionnaire (SFFQ).16 From the SFFQ an overall healthy diet score representing adherence to the Dutch dietary guidelines was calculated, as described previously.[17] Blood pressure (mmHg) was measured twice in seated position and averaged across the two measures. Fasting triglycerides (TG), total cholesterol and high-density lipoprotein (HDL) cholesterol values were measured using standard laboratory techniques.[18,19] Fasting serum glucose levels were determined by using the glucose hexokinase method within 1 week after sampling. The comorbidities included in the study were coronary heart disease, stroke, and cancer and were coded as having none versus one or more comorbidities.

Definition of exposure

Based on BMI, individuals were classified as normal weight (18.5–24.9 kg/m^2) or overweight and obese (>25.0 kg/m^2), in accordance with the World Health Organization guidelines.[20] Overweight timing was determined using age at the visit at which the individual was for the first time classified as being overweight or obese (BMI>25.0 kg/m^2). The individual was categorized as (1) middle-age onset overweight if the first time classification of overweight was before the age of 65 years and (2) elderly onset overweight if the first time classification of overweight was after 65 years of age. Duration of overweight was based on overweight status at visits 1, 2, and 3 and categorized as follows: (1) never overweight; (2) fluctuating overweight (any shift in classification from overweight to non-overweight or vice versa at different visits); (3) incident overweight (from non-overweight at one visit to overweight at the following visit); and (4) persistent overweight (overweight at all 3 visits) (See Table 3.3.2 for more details and examples).[9]

Definition of outcome

The main outcomes were metabolic syndrome and diabetes mellitus. Metabolic syndrome was defined based on the definition of "Harmonized metabolic syndrome".[21] Participants were considered as having metabolic syndrome if they had >= 3 of the following five components: (1) waist circumference >= 102 cm in men and >= 88 cm in women; (2) systolic blood pressure >= 130 mmHg and/or diastolic blood pressure >=85 mmHg or use of antihypertensive treatment; (3) fasting plasma triglyceride >= 1.69 mmol/L; (4) HDL cholesterol level < 1.03 mmol/L in men and < 1.29 mmol/L in women; (5) fasting glucose > 5.6 mmol/L. Type 2 diabetes mellitus was defined as fasting plasma glucose level >= 7.0 mmol/L or the documented use of blood glucose lowering

medication. Additionally, we formed different outcomes for each component of metabolic syndrome including abdominal obesity, hypertension, hypertriglyceridemia, and low HDL cholesterol. Impaired glucose tolerance (fasting glucose > 5.6 mmol/L) was not analyzed separately since diabetes mellitus was analyzed as a separate outcome in the main analysis.

Statistical analysis

Participant characteristics for the overall population and separately for participants with and without metabolic syndrome and diabetes were described using means (SD) and proportions. We ascertained the prevalence of metabolic syndrome and diabetes at the third visit (RS-I-3). Logistic regression analyses were used to estimate odds ratios (OR) and 95% confidence intervals (95%CI) for the presence of metabolic syndrome and diabetes in association with the timing and duration of overweight. We developed two multivariable logistic regression models. The first model was adjusted for age, gender, smoking, education, physical activity, alcohol consumption, diet and comorbidities. The second model was additionally adjusted for current BMI status (i.e. BMI at the third visit, RS-I-3). Adjustments for confounders were performed based on prior knowledge in the published literature.[8] We assessed independently the interaction between timing or duration of overweight with gender in age adjusted and multivariable adjusted models and the interaction terms were not significant ($p>0.3$). Considering the multiple exposures and outcomes in our analysis, and no interaction between gender and our exposure we performed analysis in the overall population.

Since the exact onset of overweight for participants who were already overweight at the start of the study (RS-I-1) was not known, we performed a sensitivity analysis in which we included only normal weight participants at the first visit of the study (RS-I-1).

Covariates were missing in up to 5% of participants. We used single imputation by Chained Equations with R package MICE.[22] The analyses were performed using R software (version 3.1.3) a language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria). Tests of statistical significance were two-tailed, at 0.05 significant level.

RESULTS

Table 3.2.1 present the descriptive characteristics of total population. Of 3408 participants, 1463 (42.9%) had metabolic syndrome and 426 (12.5%) had diabetes. The mean age of the study population was 72.1 (SD 6.8) and 1942 (60%) were women.

Table 3.2.2 details the classification method used for defining different categories regarding the timing and duration of overweight. Of 3408 participants, 931 (37.3%) were never overweight, 1176 (34.5%) were overweight before age of 65 and 1301 (38.2%) were overweight after age of 65. Regarding duration of overweight categories, 329 (9.6%) were fluctuating overweight, 315 (9.2%) were incident overweight and 1833 (53.8%) were persistent overweight.

Figure 3.2.1 shows the prevalence of metabolic syndrome and diabetes according to overweight timing and duration. Prevalence of metabolic syndrome was higher for middle-age onset of overweight (53.4%), and elderly onset of overweight (51.7%) than never overweight (17.3%). Prevalence of diabetes increased from never overweight (5.3%) to middle-age onset of overweight

(12.9%) and elderly onset of overweight (17.3%) (Figure 3.2.1 A). Regarding overweight duration, the prevalence of metabolic syndrome and diabetes was the highest among persistently overweight individuals, 58.9% and 16.9%, respectively. Also, an increased prevalence of diabetes (13.1%) was observed among individuals in the fluctuating overweight group (Figure 3.2.1 B).

Results of the logistic regression analyses for the association between timing and duration of overweight with metabolic syndrome and diabetes are presented in Table 3.2.3. In the multivariable model adjusted for age, gender, education, comorbidities and health behaviors (Model 1), the risk of metabolic syndrome and diabetes increased for all categories of timing and duration of overweight ($p<0.001$).

To determine if the associations between the timing and duration of overweight with metabolic syndrome and diabetes were independent of current BMI level, the odds ratios were additionally adjusted for current BMI status (at the third visit of the Rotterdam Study) (Model 2 in Table 3.2.3). After adjustment for current BMI levels, the risk of metabolic syndrome remained significantly increased for middle-age onset (OR 1.50, 95%CI 1.14-1.99) and elderly onset (OR 1.31, 95%CI 1.00-1.70) overweight compared to never overweight individuals. For diabetes, these ORs (95%CI) were: 1.77 (1.18-2.71) for middle-age onset and 1.81 (1.24-2.66) for elderly onset of overweight.

Regarding overweight duration, after adjusting for current BMI levels, the risk of metabolic syndrome was increased only among individuals who become incident overweight (OR 1.40, 95%CI 1.03-1.71) and were persistent overweight (OR 1.52, 95%CI 1.14-2.03) compared to never overweight individuals. The risk of diabetes was increased in the fluctuating (OR 2.24, 95%CI 1.41-3.53) and persistent (OR 1.98, 95%CI 1.33-2.98) overweight category (Table 3.2.3).

Sensitivity analyses

Supplement 3.2.1 summarizes the association of timing and duration of overweight with components of metabolic syndrome (i.e. hypertension, hypertriglyceridemia, abdominal obesity and low HDL cholesterol). In multivariable model adjusted for age, education, comorbidities and health behaviors (Model 1), all categories of timing and duration of overweight were associated with risk of all components of metabolic syndrome ($p<0.001$). After adjustment for current BMI levels (Model 2), middle-age and elderly onset overweight remained a risk factor for low HDL cholesterol (OR 1.44, 95%CI 1.10-1.89 and 1.62, 95%CI 1.25-2.10, respectively) and hypertriglyceridemia (OR 1.33, 95%CI 1.02-1.74 and 1.31 95%CI 1.01-1.69, respectively). Regarding duration of overweight, incident and persistent overweight were associated with risk of low HDL cholesterol (OR 1.70, 95%CI 1.24-2.31 and 1.66, 95%CI 1.26-2.19 respectively) and hyperglycemia (OR 1.54, 95%CI 1.14-2.09 and 1.37, 95%CI 1.04-1.80, respectively).

Since the exact onset of overweight for participants who were already overweight at the start of the study (RS-I-1) was not known, we performed a sensitivity analysis in which we included only normal weight participants at the first visit of the study (RS-I-1). These analyses yielded similar results for the significant associations in the main analysis, although attenuated due to smaller sample size (Supplement 3.2.2).

DISCUSSION

Our findings underscore the importance of information regarding weight history in highlighting individuals at higher risk for metabolic syndrome and diabetes beyond current BMI status. In our population based study of middle-aged and elderly adults, we showed that the age when individuals become overweight (i.e. overweight timing) or the duration of overweight, can further explain the variation in their metabolic risk beyond the current BMI status. The onset of overweight during middle-age conferred a higher risk for metabolic syndrome than the onset of overweight later in life. Whereas, onset of overweight in middle-age or elderly had similar impact on the risk of diabetes. The duration of overweight, in particular being persistently overweight, increased the risk of metabolic syndrome and diabetes. Additionally, individuals who experienced fluctuating overweight during follow-up were at higher risk for diabetes.

Although current BMI levels are associated with increased risk of metabolic syndrome and diabetes,[1, 2] the age when individuals become overweight might provide additional information to identify individuals at risk of metabolic syndrome and diabetes. Notably, the adverse effect of overweight and obesity on cardio-metabolic risk factors during middle-age could be different than later in life (i.e. elderly). In our study, the onset of overweight in middle-age and elderly had similar effect on lipids metabolism (i.e. HDL cholesterol and triglycerides). However, the hazardous effect of overweight on metabolic syndrome was stronger among the individuals who became overweight before the age of 65 compared to those who became overweight after the age of 65. A potential explanation for this observation could be that individuals who are prone to deleterious effect of overweight might experience fatal disease earlier in life. Therefore, older overweight individuals may represent a subgroup of survivors who are resistant to the adverse effects of overweight.[23] Alternatively, this could be explained by the power of our study, the prevalence of metabolic syndrome in our study was slightly higher (53.4% versus 51.7%) among the individuals who became overweight before the age 65. The risk of diabetes mellitus did not differ by the timing in onset of overweight (i.e. middle-age onset versus elderly onset overweight). Our results indeed confirm previous findings that shifting from normal weight to overweight increases the risk for diabetes mellitus regardless of the age when this increase in weight happens.[24]

Duration of overweight may also provide further information regarding the metabolic risk of an individual beyond the current BMI status. Prolonged duration of overweight may result in additional metabolic changes, leading to the development of hypertension, dyslipidemia and diabetes.[8] The association between duration of overweight with metabolic syndrome among men and women younger than 65 years old has been previously reported.[8,10] In line with previous findings, our study of middle-aged and elderly population shows that individuals with persistent overweight had the greatest risk for metabolic syndrome and diabetes, even after controlling for current BMI levels. Moreover, the association between duration of overweight and metabolic syndrome in our study indicates that development of metabolic syndrome among overweight individuals needs time. This provides further evidence that being overweight without metabolic syndrome might not be a permanent state of the healthy metabolic profile, but rather a transient phase, moving towards glucose-metabolic abnormalities.[25] The results of our study, therefore, suggest to re-evaluate the metabolic status of overweight individuals without metabolic syndrome on a regular basis.

Our study further showed that individuals who experienced fluctuating overweight over time had a greater risk for diabetes mellitus. The increased risk for diabetes among individuals in the fluctuating overweight could be attributable to the risk of developing insulin resistance or hyperinsulinemia.[26,27] The increased insulin concentration might reflect a change in adiposity.[27] Although in our study we did not find an association between fluctuating overweight and abdominal obesity, other studies have found a positive association of weight fluctuation with waist–hip ratio or truncal adiposity.[28,29] Additionally, experimental studies in rats have shown an increase in visceral fat mass as a long-term consequence of weight cycling.[30]

The additional value of information on weight history and duration, beyond the current BMI status, in our study was particularly relevant when assessing the risk for diabetes. After taking into account the current BMI status, attenuation in the risk estimates was greater in association with metabolic syndrome and was less evident with diabetes. While information regarding the overweight history and duration can, in part, explain why some overweight individuals do not develop metabolic syndrome, our findings still support the value of current BMI status in assessing the risk of an individual for metabolic syndrome.

The past two decades have witnessed a massive shift towards the global epidemic of obesity and a striking increase in the number of individuals with metabolic syndrome worldwide.[1,2] With the presence of metabolic syndrome, the risk of cardiovascular disease increases by two to three folds.[31] These figures point towards an urgent need for implementation of preventive strategies among overweight individuals.[3] Our results that duration and onset of overweight impact the metabolic syndrome independent of current BMI status are important findings with direct clinical implications. Of note, the deleterious impact of persistent overweight or becoming overweight at middle-age on metabolic risk is an alarming signal that calls for renewed sustainable efforts for weight management approaches, particularly among this group of individuals.

Our study has several strengths. Taking advantage of the detailed longitudinal data, we had the opportunity to examine the transition between different weight categories from the middle-age to older ages within a period of 10 years. Furthermore, compared to previous studies [8,10] which were based on self-reported and recall weight history, we measured BMI and other cardio-metabolic risk factors at each visit by trained staff at our research center. However, the limitations of our study should be acknowledged. First, we were unable to determine the exact age at the onset of overweight or the exact duration of overweight, since we only had information on the BMI and age at each visit. However, limiting our analysis to those who were normal weight at the first visit and became overweight in the course of the study (thus their duration of overweight was known) yielded similar associations. Second, our population comprised white participants aged 55 years or older and the generalizability of our findings to younger and nonwhite populations remains uncertain.

In summary, our findings underscore the importance of information regarding weight history in highlighting individuals at higher risk for metabolic syndrome and diabetes beyond the current BMI status. Our study further suggests to re-evaluate the metabolic status of overweight individuals without metabolic syndrome on a regular basis.

Table 3.2.1 Characteristics of study population (N=3408)

Age (years)		72.1 ± 6.8
BMI (kg/m^2)		26.9 ± 3.9
Waist circumference (cm)		93.5 ± 11.3
Systolic BP (mmHg)		143.2 ± 21.1
Diastolic BP (mmHg)		75.3 ± 11.3
Medication for BP hypertension (N, %)		892 (26)
Glucose (mmol/l)		5.88 ± 1.33
Triglycerides (mmol/l)		1.51 ± 0.73
HDL cholesterol (mmol/l)		1.39 ± 0.40
Medication for hyperlipidemia (N, %)		456 (13)
Physical activity, Vigorous (%)		372 (11)
Education (N, %)	Primary	1595 (47)
	Secondary	1461 (43)
	Academic	352 (10)
Alcohol use (N, %)	< 1 glass/day	2056 (60)
	1-4 glasses/day (men); 1-2 glasses/day (women)	939 (28)
	> 4 glasses/day (men); > 2 glasses/day (women)	413 (12)
Smoking status (N, %)	Never	1102 (32)
	Former	1702 (50)
	Current	604 (18)
Comorbidities		764 (22)

Abbreviations: BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein. The table details characteristics of the study population at the third visit.
Values are mean ± standard deviation or numbers (percentages). Comorbidities include cardiovascular disease and cancer

Table 3.2.2 Illustration of the method used to identify the duration of overweight and the consequent categories of participants in our study

	Duration of overweight			
	Visit 1	**Visit 2**	**Visit 3**	**Categories**
Participant A	1	1	1	Normal weight
Participant B	1	2	2	Incident overweight
Participant C	1	1	2	Incident overweight
Participant D	1	2	1	Fluctuating overweight
Participant E	2	1	1	Fluctuating overweight
Participant F	2	2	1	Fluctuating overweight
Participant G	2	1	2	Fluctuating overweight
Participant H	2	2	2	Persistent overweight

The numerical 1 indicates the participant was normal weight and 2 overweight

Overweight duration was based on BMI status at visits 1, 2, and 3 and categorized as follows: 1) never overweight (n=931, 37.3%) 2) fluctuating overweight (n=329, 9.6%) (any shift in classification from overweight to non-overweight and vice versa) 3) incident overweight (n=315, 9.2%) (from non-overweight at one visit to overweight at the following visit) 4) persistent overweight (n=1833, 53.8%) (overweight at all 3 visits).

Further, the individual was categorized as 1) middle-age onset overweight (n=1176, 34.5%) if the first time classification of overweight happened before 65 years of age and 2) elderly onset overweight (n=1301, 38.2%) if the first time classification of overweight happened after 65 years of age.

Table 3.2.3 Odds ratios (95%CI) for metabolic syndrome and diabetes according to timing and duration of overweight

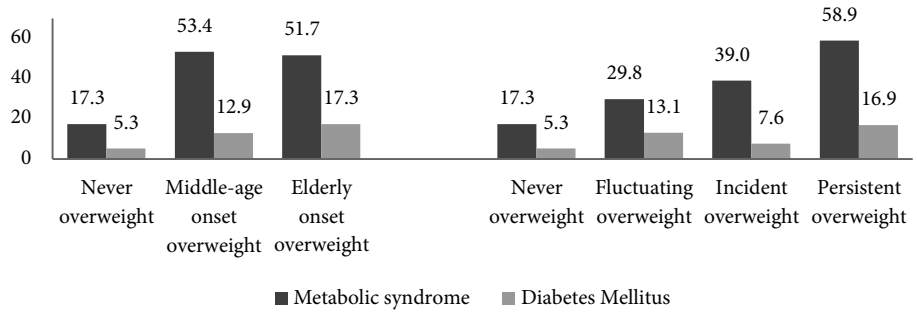
	Metabolic syndrome (n=1463/3408)		**Diabetes mellitus (n=426/3408)**	
	Model 1	**Model 2**	**Model 1**	**Model 2**
Overweight timing *				
Never overweight	Referent	Referent	Referent	Referent
Middle-age onset	6.27 (5.02-7.86)	1.50 (1.14-1.98)	3.30 (2.31-4.79)	1.77 (1.17-2.71)
Elderly onset	4.64 (3.75-5.78)	1.31 (1.00-1.70)	3.10 (2.23-4.39)	1.81 (1.24-2.67)
Overweight duration				
Never overweight	Referent	Referent	Referent	Referent
Fluctuating	2.04 (1.52-2.73)	1.25 (0.92-1.70)	2.52 (1.63-3.90)	2.09 (1.34-3.26)
Incident	3.12 (2.35-4.15)	1.40 (1.03-1.91)	1.53 (0.91-2.52)	1.13 (0.66-1.88)
Persistent	7.02 (5.78-8.57)	1.53 (1.15-2.04)	3.66 (2.69-5.07)	1.97 (1.33-2.96)

* Overweight timing was based on the age when the participant was categorized as being overweight for the first time. The individual was categorized as middle-age onset overweight if the first time classification of overweight happened before the age of 65 years and as elderly onset overweight if the first time classification of overweight happened after 65 years of age.

Model 1 adjusted for: age, gender, smoking, physical activity, education, alcohol use, diet and comorbidities.

Model 2 is additionally adjusted for current BMI levels.

Figure 3.2.1 Prevalence of metabolic syndrome and diabetes by overweight timing (A) and duration of overweight (B).



Overweight timing was determined using the individual's age at the visit at which the individual was for the first time classified as being overweight or obese (BMI≥25.0 kg/m^2).The individual was categorized as middle-age onset overweight if the first time classification of overweight happened before 65 years of age and elderly onset overweight if the first time classification of overweight happened after 65 years of age.
Overweight duration from middle-age to elderly was based on BMI status at visits 1, 2, and 3 and categorized as follows: 1) never overweight 2) fluctuating overweight (any shift in classification from overweight to non-overweight and vice versa) 3) incident overweight (from non-overweight at one visit to overweight at the following visit) 4) persistent overweight (overweight at all 3 visits).

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Supplement 3.2.1 Odds ratios (95%CI) for components of metabolic syndrome according to timing and duration of overweight

	Hypertension		Abdominal obesity		Low HDL cholesterol		Hypertriglyceridemia	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Overweight timing*								
Never overweight	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Middle-age onset	2.02 (1.64-2.50)	1.07 (0.81-1.41)	13.64 (10.58-17.71)	0.80 (0.57-1.13)	2.22 (1.78-2.78)	1.44 (1.10-1.89)	2.35 (1.89-2.92)	1.33 (1.02-1.74)
Elderly onset	1.79 (1.43-2.25)	1.04 (0.79-1.36)	9.42 (7.39-12.09)	0.78 (0.57-1.07)	2.35 (1.88-2.94)	1.62 (1.25-2.10)	2.15 (1.73-2.68)	1.31 (1.01-1.69)
Overweight duration								
Never overweight	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Fluctuating overweight	1.17 (0.88-1.56)	0.93 (0.69-1.25)	2.77 (1.99-3.83)	0.93 (0.65-1.32)	1.46 (1.08-1.98)	1.29 (0.94-1.76)	1.32 (0.97-1.78)	1.10 (0.80-1.49)
Incident overweight	1.96 (1.44-2.70)	1.33 (0.95-1.89)	4.04 (2.94-5.56)	0.65 (0.45-0.94)	2.08 (1.55-2.80)	1.70 (1.24-2.31)	2.08 (1.56-2.77)	1.54 (1.14-2.09)
Persistent overweight	2.12 (1.76-2.56)	1.02 (0.76-1.38)	18.65 (14.81-23.68)	0.77 (0.53-1.10)	2.49 (2.05-3.04)	1.66 (1.26-2.19)	2.48 (2.06-3.02)	1.37 (1.04-1.80)

* Overweight timing was based on the age when the participant was categorized as being overweight for the first time. The individual was categorized as middle-age onset overweight if the first time classification of overweight happened before the age of 65 years and as elderly onset overweight if the first time classification of overweight happened after 65 years of age.

Overweight duration from middle-age to elderly was based on BMI status at visits 1, 2, and 3 and categorized as follows: 1) never overweight 2) fluctuating overweight (any shift in classification from overweight to non-overweight and vice versa) 3) incident overweight (from non-overweight at one visit to overweight at the following visit) 4) persistent overweight (overweight at all 3 visits).

Model 1 adjusted for: age, smoking, physical activity, education, alcohol use, diet and comorbidities. In women, we additionally adjusted for years since menopause and hormone replacement therapy. Model 2 is additionally adjusted for current BMI levels.

Supplement 3.2.2 Odds ratios (95%CI) for metabolic syndrome and diabetes according to timing of overweight for individuals who were normal weight at the entry (first study visit) (n=1302)

	Metabolic syndrome (n= 295)		**Diabetes (n=78)**	
	Model 1	**Model 2**	**Model 1**	**Model 2**
Overweight timing*				
Never overweight	Referent	Referent	Referent	Referent
Middle-age onset	3.73 (2.40-5.79)	1.38 (0.81-2.34)	1.08 (0.35-2.70)	0.87 (0.26-2.42)
Elderly onset	2.37 (1.72-3.26)	0.89 (0.58-1.37)	1.69 (0.99-2.81)	1.35 (0.67-2.68)

This sensitivity analysis included only normal weight participants at the first visit of the study (RS-I-1).

* Overweight timing was based on the age when the participant was categorized as being overweight for the first time. The individual was categorized as middle-age onset overweight if the first time classification of overweight happened before 65 years of age and as elderly onset overweight if the first time classification of overweight happened after 65 years of age.

Model 1 adjusted for: age, smoking, physical activity, education, alcohol use, diet and comorbidities.

Model 2 is additionally adjusted for current BMI levels.

Chapter 4

Obesity, cardiovascular disease and mortality

4.1 Obesity in older adults and life expectancy with and without cardiovascular disease

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Abstract

Background: The prevalence of overweight and obesity is increasing globally and is an established risk factor for cardiovascular disease (CVD). Our objective was to evaluate the impact of overweight and obesity on life expectancy and years lived with and without CVD in older adults.

Methods: The study included 6636 individuals (3750 women) aged 55 years and older from the population-based Rotterdam Study. We developed multistate life tables by using prevalence, incidence rate and hazard ratios (HR) for 3 transitions (free-of-CVD-to-CVD, free-of-CVD-to-death, and CVD-to-death), stratifying by the categories of body mass index (BMI) at baseline and adjusting for confounders.

Results: During 12 years of follow-up, we observed 1035 incident CVD events and 1902 overall deaths. Obesity was associated with an increased risk of CVD among men (HR 1.57 (95% confidence interval (CI) 1.17, 2.11)) and women (HR 1.49 (95%CI 1.19, 1.86)), compared with normal weight individuals. Overweight and obesity were not associated with mortality in men and women without CVD. Among men with CVD, obesity compared to normal weight, was associated with a lower risk of mortality (HR 0.67 (95%CI 0.49, 0.90)). Overweight and obesity did not influence total life expectancy. However, obesity was associated with 2.6 fewer years (95%CI -4.8, -0.4) lived free from CVD in men and 1.9 (95%CI -3.3, -0.9) in women. Moreover, men and women with obesity lived 2.9 (95%CI 1.1, 4.8) and 1.7 (95%CI 0.6, 2.8) more years suffering from CVD compared to normal weight counterparts.

Conclusions: Obesity had no effect on total life expectancy in older individuals, but increased the risk of having CVD earlier in life and consequently extended the number of years lived with CVD. Due to increasing prevalence of obesity and improved treatment of CVD, we might expect more individuals living with CVD and for a longer period of time.

INTRODUCTION

Obesity is increasing globally and the association between body weight, morbidity and mortality has received widespread attention.[1] There is consensus on the association of overweight and obesity with mortality in young adults and middle-aged,[2] but there is no clear consensus for the elderly.[3-5] Several studies have reported that among older individuals the longest survival is observed in the overweight and obese range.[5-7] However, older individuals with obesity are still at higher risk to develop cardiovascular disease (CVD) in their remaining lifespan.[8] Therefore, the contribution of obesity to life expectancy and in particular life expectancy with and without CVD among older individuals is still of relevance.

Previous studies investigating the impact of overweight and obesity with total life expectancy have reported that obesity in adulthood is associated with a decrease in total life expectancy of 6-7 years, and severe obesity in men aged 20 to 30 will shorten life expectancy by 13 years, compared with normal weight individuals.[9,10] Another study evaluating the association of obesity at the age of 45 years with total life expectancy and life expectancy with and without CVD has shown that obesity not only reduces total life expectancy, but also reduces the number of years lived free of CVD by 6.0 years in men and 8.4 in women.[11] However, most of studies described have evaluated the effect among young adults, while the effect of obesity on survival in the elderly remains controversial.[3,5] Furthermore, these studies have used data from the Framingham Heart Study using information collected during the second half of the 20th century. In recent decades, an increase of obesity prevalence[12] has been observed along with improvements in prevention and treatment of CVD.[13]

Therefore, in a population-based study of subjects 55 years and older, we aimed to evaluate the impact of overweight and obesity in the average years lived with and without CVD. We constructed multistate life tables using data collected from 1997 and with over 12 years of follow up from the Rotterdam Study.

METHODS

Study population

This study was embedded within the Rotterdam Study, a prospective population-based cohort study among adults and elderly living in the Ommoord district of Rotterdam, The Netherlands. The baseline examination was completed between 1990 and 1993 by trained research assistants for 7983 participants (RS-I). In 2000–2001, the Rotterdam Study was extended with 3011 participants who had become ≥55 years of age or had moved into the study district (RS-II). The objectives and design of the Rotterdam Study have been described in detail elsewhere.[14]

For the current study, we used data from the participants attending the third examination of the original cohort (RS-I-visit 3, 1997–1999; n=4797) and the participants attending the first examination of the extended cohort (RS-II-visit 1, 2000–2001; n=3011).

We excluded participants who did not visit the research center, did not have information on body mass index (BMI) (n=1051, the baseline characteristics of this subgroup are presented in Supplement 4.1.1 in the supplementary material), or no information on smoking behavior

(n=40). Additionally, we excluded participants who had BMI ≤ 18.5 (n=51) to account for disease-related weight loss. Finally, we excluded participants without written informed consent (n=30). After exclusion, 6636 participants (3750 women) were available for the current analysis. All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Assessment of anthropometric measurements, health behaviors and laboratory measurements

Anthropometrics were measured in the research center by trained staff. Height and weight were measured with the participants standing without shoes and heavy outer garments. We calculated BMI by dividing weight with height squared (kg/m^2).[15] According to the WHO cut-off criteria, we composed BMI as a categorical variable with three categories: normal weight (18.5≤ BMI<25), overweight (25≤BMI<30) and obese (30≤BMI).[15] Smoking status was categorized as current smoker, former smoker and never smoker, and additionally we accounted for cigarettes smoked per day. Information on education was assessed according to the standard international classification of education and was composed into four categories: elementary education, lower secondary education, higher secondary education, and tertiary education.[16] Marital status was divided in single, married, widowed or divorced/separated. Physical activity was measured by questionnaire and expressed in METhours/week. For analysis, we divided the population in 3 equal groups (tertile).[17] Alcohol consumption was categorized as less than 1 glass/day, 1-4 glasses/day for men and 1-2 glasses/day for women, and > 4 glasses/day for men and > 2 glasses/day for women. Comorbidity was considered present when "non-obesity related cancers other than skin cancer" or chronic obstructive pulmonary disease was prevalent at baseline. We excluded from baseline comorbidities cancers which are associated with obesity,[18] or cancers that are curable and not likely to be related to weight loss or mortality, such as skin cancer.[19] Chronic obstructive pulmonary disease was defined as a type of obstructive lung disease characterized by airflow limitation not fully reversible.[20] Chronic obstructive pulmonary disease has been shown to be accompanied with weight loss.[21]

Hypertension, dyslipidemia and diabetes mellitus were considered as intermediates and not confounding variables in the association of obesity with CVD and mortality, therefore, in a sensitivity analysis, we repeated our analyses by excluding individuals with hypertension, dyslipidemia or diabetes. The presence of hypertension and dyslipidemia was based on medication information, whereas diabetes mellitus was defined as the documented use of medication or fasting plasma glucose level ≥ 110 mg/dL.

Assessment of outcome

The main outcome measures under study was incident non-fatal or fatal CVD and overall mortality. In the Rotterdam Study, 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. Definite and possible fatal coronary heart disease events are coded by using the definitions applied within the Cardiovascular Health Study and Atherosclerosis Risk in the Communities Study.[22] Stroke is defined as a syndrome of rapidly developing clinical signs of focal (or global) disturbance of

cerebral function, with symptoms lasting 24 h or longer or leading to death, with no apparent origin other than vascular.[23] Heart failure was defined using the criteria of the European Society of Cardiology as a combination of heart failure diagnosed by a medical specialist and the presence of typical symptoms of heart failure, such as breathlessness at rest or during exertion, ankle edema, and pulmonary crepitation, confirmed by objective evidence of cardiac dysfunction (chest X-ray, echocardiography).[24] Data on incident CVD is collected using an automated follow-up system, through gathering information from general practitioners working in the study area. Information about cause and circumstances of death was obtained from general practitioner medical records and from municipal records. Research physicians reviewed all available information and coded the events according to the International Classification of Diseases, 10th edition (ICD-10). A consensus panel, led by a physician with expertise in field, adjudicated the final cause of death according to ICD-10 codes using standardized definitions. The follow-up was complete until January 1, 2010.

Statistical analysis

We created population-based multistate life tables to calculate the differences in life expectancy and years lived with and without CVD in normal weight, overweight and obese groups.[25] We constructed three different health states: free of CVD, CVD and death. The possible transition directions were from free of CVD to CVD, free of CVD to death and from CVD to death. No backflows were allowed (e.g. from CVD to not having CVD), and only first event into state was considered.

First, we calculated the overall age- and sex-specific rates for each transition with Poisson regression using the Gompertz distribution to obtain smoothed age- and sex-specific rates. Second, we calculated the prevalence of normal weight, overweight and obesity by sex, 10-year age groups, and separately for subjects with and without CVD. Third, we computed gender specific hazard ratios comparing overweight and obese to normal weight individuals by using Poisson regression with "Gompertz" distribution in 2 models. Model 1 was adjusted for age; and Model 2 was adjusted for age, smoking status, cigarettes smoked per day (for current smokers), alcohol consumption, education, marital status, physical activity and comorbidities ("non-obesity related cancers other than skin cancer" or chronic obstructive pulmonary disease).

Finally, the three sets of transitions rates were calculated for each category of BMI separately using the (a) overall transition rates, the (b) adjusted hazard ratios (model 2) for CVD and mortality, and the (c) prevalence. Similar calculations have been described previously.[26, 27] The multistate life table started at age 55 years and closed at age 100 years.

Confidence intervals for all life expectancies and their differences were calculated using @RISK software (Anonymous 2000; MathSoft Inc, Cambridge, Mass), by Monte Carlo simulation (parametric bootstrapping) 10 000 runs.[28]

Although we adjusted for smoking and comorbidities, to exclude any potential bias caused by smoking or comorbidities we repeated the analysis among nonsmokers and individuals without comorbidities ("non-obesity related cancers other than skin cancer" or chronic obstructive pulmonary disease) at baseline (n=5117). Additionally, we estimated the life expectancy among participants without hypertension, hyperlipidemia and diabetes mellitus at baseline (n=3750).

Also we computed lifetables for individuals who were older than 65 years at baseline (n=4245). Moreover, we estimated the hazard ratios after excluding cardiovascular events (n=127) or deaths (n=145) during the first two years of follow-up to take in account the reverse causation.

To deal with missing values (less than 5%) for covariates including education, marital status, physical activity, and alcohol we used 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 version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria) for our analysis.

RESULTS

In total we observed 1035 (18.6%) incident CVD events and 1902 (28.7%) overall deaths over 12 years of follow-up. Thirty five percent of overall death were from CVD, and 28.5% were from malignant cancers. Compared to women, men at baseline were younger and smoked more, showed lower levels of BMI and physical activity, but higher education levels (Table 4.1.1).

Cardiovascular events and death

Table 4.1.2 shows the hazard ratios (HR) of the association between categories of BMI with risk of incident CVD and mortality among men and women. In multivariable adjusted model, obesity (as classified by BMI higher than 30) was associated with an increased risk of incident CVD among men (HR 1.57 (95% confidence interval (CI) 1.17, 2.11)) and women (HR 1.49 (95%CI 1.19, 1.86)) compared with normal weight individuals (Table 4.1.2).

Among men and women without CVD, overweight and obesity, compared to normal weight individuals, were not associated with mortality (Table 4.1.2, Model 2).

Among men with CVD, overweight and obesity, compared to normal weight, showed a decreased risk of mortality (HR (95%CI) 0.81 (0.66, 0.98) and 0.67 (0.49, 0.90), respectively). The association between overweight and obesity with mortality among women with CVD did not reach a statistical significance.

Total life expectancy and life expectancy with and without CVD

The association between normal weight, overweight and obesity with the risk of each transition (no CVD, CVD and death) was translated into number of years lived with and without CVD (Figure 4.1.1 and Table 4.1.3). Total life expectancy for men and women with overweight and obesity were not significantly different than normal weight counterparts. Compared to normal weight men, life expectancy of 55-year-old men in the overweight group was 0.1 (95%CI -0.8, 1.0) years longer, and in the obese group 0.3 years (95%CI -1.1, 1.6). For women, these differences were: 0.6 (95%CI -0.2, 1.3) and -0.2 (-1.2, 0.7) years respectively (Table 4.1.3). For both men and women, obesity was associated with fewer years lived without CVD and more years lived with CVD than their normal weight counterparts. Men and women with obesity lived 2.6 (95%CI -4.8, -0.4) and 1.9 (95%CI -3.3, -0.9) fewer years without CVD, respectively, than those in normal weight group. Additionally, obese men and women lived more years with CVD than their normal

weight counterparts; 2.9 (95%CI 1.1, 4.8) years for men and 1.7 (95%CI 0.6, 2.8) years for women (Figure 4.1.1 and Table 4.1.3).

Total life expectancy, number of years lived with and without CVD for normal weight, overweight and obese for non-smokers and individuals without prevalent comorbidities ("non-obesity related cancers other than skin cancer" and chronic obstructive pulmonary disease) are presented in Supplement 4.1.1, and for individuals without hypertension, dyslipidemia and diabetes are presented in Supplement 4.1.2, and for individuals older than 65 at baseline are presented in Supplement 4.1.3. As expected, total life expectancy increased for individuals who were nonsmokers and without comorbidities at baseline, or for individuals without diabetes, hypertension and dyslipidemia, but all differences among normal weight, overweight and obese individuals were similar to those found in the total population. However, differences of the BMI categories in total life expectancy and life expectancy with and without CVD became smaller for individuals older than 65 at baseline. Supplement 4.1.4 shows the baseline characteristics of individuals who did not visited the research center or without information of BMI. This subgroup of individuals were older than individuals included in study, and therefore, were less physically active. Additionally, when we repeated the main analysis after excluding deaths during first 2 years of follow-up, we found generally similar results (Supplement 4.1.5).

DISCUSSION

Overall we found that compared to normal weight, overweight and obesity in middle age and elderly have a considerable effect on years lived with and without CVD, although they had no effect on total life expectancy. Total life expectancy for obese men and women at age 55 years was not significantly different from the normal weight individuals. However, obesity was associated with 2.6 fewer years lived without CVD for men and 1.9 years for women. Moreover, men and women with obesity spent an extra of 2.9 and 1.7 years living with CVD, respectively.

The shorter life expectancy without CVD among men and women with obesity was due to increased CVD and mortality risk. Higher risk for CVD is reflected by an earlier occurrence of CVD over the lifespan and therefore, a shorter life expectancy without CVD. Furthermore, higher risk of mortality among individuals without history of CVD follows a decrease in the total life expectancy and consequently, a shorter life expectancy without CVD could be expected. We also found that compared to normal weight, individuals with obesity spent more years living with CVD. Years spent with CVD is a consequence of CVD risk in those without history of CVD, and mortality risk in those with history of CVD. In our study, obese individuals without history of CVD had an increased risk for CVD, while obese individuals with history of CVD had lower risk of mortality. Taken together, this indicate that individuals with obesity will spend more years living with CVD.

Our analysis indicated that obesity increased the risk of CVD in men and women, and the hazard ratios were comparable with other studies.[29, 30] The relation between obesity and mortality is well documented among younger and middle aged populations.[31] However, among the late middle aged as well as elderly, higher BMI has not been consistently associated with higher mortality risk.[3, 5] Additionally, a previous meta-analysis by Flegal et al., reported that overweight individuals are at lower risk of mortality, compared with normal weight individuals.[4] Our study do not report

a protective associations of an increased BMI in individuals without CVD. However, among overweight and obese men with CVD at baseline, after adjusting for possible confounders, we found that the risk of mortality decreased by 33% in obese individuals, compared with normal weight individuals. Although, the role of obesity among the older adults is still a topic of debate, some studies have suggested that being overweight and obese could serve as a nutritional deposit in hardship conditions such as inflammation and disease.[32, 33] In contrast, some studies have rejected this paradigm, attributing the lower risk of mortality to the fact that BMI becomes less sensitive to fat mass and body fat distribution in older individuals.[34] To reduce the potential effect of underlying disease, we performed a series of sensitivity analysis in individuals without hypertension, dyslipidemia and diabetes; in nonsmokers and without comorbidities at baseline. Restricting the analyses to these subgroups did not generally modify the life expectancies associated with obesity.

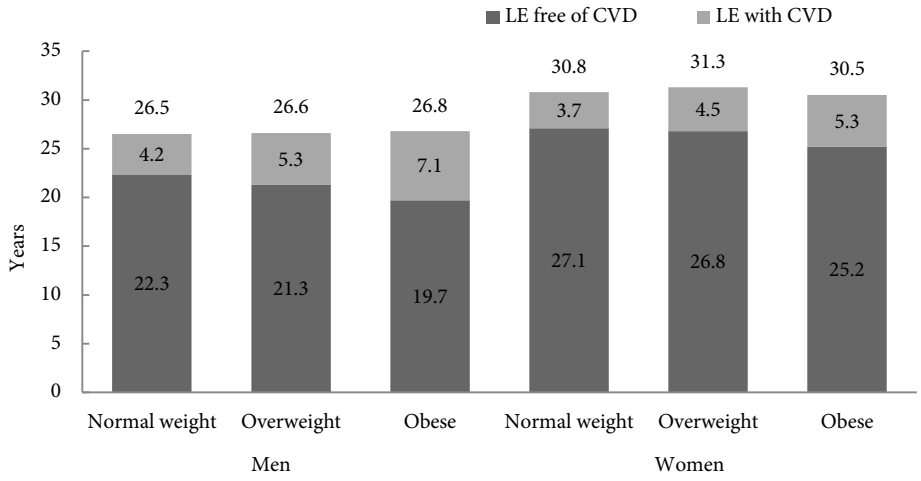
In our study, we found that the effect of overweight and obesity in total life expectancy is minimal. Earlier studies comprising the participants from the Framingham Heart Study showed larger differences in life expectancy between obese and normal weight.[9,11] Peeters et al., showed that at age of 40 years life expectancy differences for obese and normal weight men is 5.8 years in nonsmoker and 6.7 in smokers.[9] Another study by Pardo Silva et al., noted that men with obesity lived 3.3 years and women 6.9 years shorter from age 45 than those who were normal weight.[11] Additionally, this study showed that obese men and women aged 45 years live 6.0 and 8.4 years fewer free of CVD, whereas in our study the difference was smaller; 2.6 and 1.9 years for men and women, respectively.[11] The differences between our findings and those of previous studies from Framingham Heart Study could be explained by two factors. First, our participants were 10 to 15 years older at baseline, and the association of obesity on mortality might change with increasing age.[5] Secondly, the calendar time when the studies were conducted is different. While the Framingham Heart Study included participants from 1948-1950 and followed them up during the second half of the 20th century, our study included participants from 1997-2001 with follow up until 2010. There have been reports of progressive improvements in the treatment for cardiovascular risk factors after 1990, which resulted in the reduction of cardiovascular incidence and mortality rates.[13] Our analysis is comparable to the Health and Retirement Survey, a US prospective longitudinal study.[35] Similar to ours findings they reported that total life expectancy at age 55 in men and women was not affected by overweight and obesity. Nevertheless, they did not evaluate the impact of obesity on life expectancy with and without CVD.[35] Additionally, our findings on the influence of obesity on total life expectancy are consistent with earlier analyses within Rotterdam Study by Walter et al., in 2009 (conduced in RS-I, with baseline measures from 1990-1993).[36] Walter et al., evaluated the impact of overweight and obesity on disability and mortality by using a different approach from ours to calculate the total life expectancy, which took into account the recovery from disability.[36] However, in line with our findings Walter et al., concluded that obesity was not associated with a reduction in total life expectancy, but was associated with a higher risk of becoming and remaining disabled.[36] In the current analyses we found that obese individuals tend to have CVD earlier in life and will spend more time living with CVD.

The strengths of our study include availability of a long follow-up time with detailed and validated information on anthropometrics, CVD and mortality. Anthropometrics such as height and weight were measured in the research center by trained staff and do not depend on self-

reported information. Nevertheless, the studies which evaluate the association of obesity with mortality could be prone to incorrect adjustment for confounders such as smoking or weight loss related to diseases and comorbidities. In our study, we adjusted for smoking status and the cigarettes smoked per day. Also, we adjusted and additionally excluded participants that had "non-obesity related cancers other than skin cancer" or chronic obstructive pulmonary disease. Sensitivity analysis was also performed in individuals who did not died during the first 2 years of follow-up. We did not adjust for hypertension, dyslipidemia or diabetes since those factors could be considered intermediates and not confounders. However, we repeated the analysis among participants without hypertension and diabetes at the baseline.

Our study showed that among late middle age and elderly individuals overweight and obesity do not seem to have an impact on total life expectancy, but are associated with earlier and extended periods lived with CVD. The impact of obesity on life expectancy with and without CVD was larger in men than in women. Due to the increasing prevalence of obesity and the improved treatment of CVD, we might expect more individuals living with CVD and for a longer period of time. This will result in increasing costs of healthcare and poorer levels of quality of life.

Figure 4.1.1 Effect of obesity on life expectancy with and without cardiovascular disease (CVD) at age 55 years.



Body mass index (BMI) categories: Normal weight BMI is <25kg/m^2; Overweight BMI is 25-30kg/m^2 and Obese the BMI is ≥30kg/m^2. LE, life expectancy; CVD, cardiovascular disease.

Table 4.1.1 Baseline characteristics of study population (n=6636)

Characteristics	Men	Women
n	2886 (42%)	3750 (58%)
Age at interview (years)	68.7±7.9	69.7±8.4
Anthropometry		
BMI (kg m^{-2})	26.6±3.2	27.5±4.4
Normal (BMI 18.5-25)	944 (32.7)	1201 (32.0)
Overweight (BMI 25-30)	1545 (53.5)	1613 (43.0)
Obese (BMI 30+)	397 (13.8)	936 (25.0)
Social economic status		
Marital status		
Single	84 (3.0)	261 (7.0)
Married	2284 (79.1)	2008 (53.5)
Widowed	310 (10.7)	1099 (29.3)
Divorced/separated	208 (7.2)	382 (10.2)
Education		
Elementary	274 (9.5)	632 (16.6)
Lower secondary	870 (30.1)	2003 (53.4)
Higher secondary	1122 (38.9)	879 (23.4)
Tertiary	620 (21.5)	245 (6.6)
Lifestyle variables		
Smoking		
Never smoking	913 (31.6)	2310 (61.6)
Former smoker	1448 (50.7)	812 (21.7)
Current smoker	525 (18.2)	648 (16.7)
Daily cigarettes smoked	2.8±7.0	2.3±6.1
Alcohol (drinks/day)		
< 1 glass/day	1289 (44.7)	2674 (71.3)
1-4 glasses/day (men); 1-2 glasses/day (women)	1363 (47.2)	669 (17.8)
> 4 glasses/day (men); > 2 glasses/day (women)	234 (8.1)	407 (10.9)
Physical activity (METh)	73.8±43.9	92.1±43.3
Treatment for hypertension	641 (22.2)	997 (26.2)
Treatment for dyslipidemia	415 (14.4)	473 (12.6)
Diabetes mellitus	338 (15.1)	438 (11.7)
Comorbidities (cancer and chronic obstructive pulmonary disease)*	274 (9.5)	216 (5.8)

Values are means (SDs) or numbers (percentages) or median (IQR). BMI, body mass index.
*Cancer includes "non-obesity related cancers other than skin cancer"

Table 4.1.2 Hazard ratios for Cardiovascular disease (CVD) and Death for overweight and obese men and women.

		Men		Women	
Transition	**Categories**	**Model 1 HR (95% CI)†**	**Model 2 HR (95% CI) ‡**	**Model 1 HR (95% CI)†**	**Model 2 HR (95% CI) ‡**
Incident CVD	Normal weight	1.0	1.0	1.0	1.0
	Overweight	1.17 (0.95, 1.44)	1.19 (0.96, 1.47)	1.17 (0.95, 1.43)	1.20 (0.98, 1.47)
	Obese	1.56 (1.17, 2.09)	1.57 (1.17, 2.11)	1.47 (1.18, 1.83)	1.49 (1.19, 1.86)
Mortality among those without CVD	Normal weight	1.0	1.0	1.0	1.0
	Overweight	1.02 (0.85, 1.20)	1.06 (0.89, 1.27)	0.83 (0.70, 0.99)	0.86 (0.72, 1.03)
	Obese	1.03 (0.78, 1.36)	1.08 (0.81, 1.43)	1.01 (0.83, 1.22)	1.02 (0.83, 1.24)
Mortality among those with CVD	Normal weight	1.0	1.0	1.0	1.0
	Overweight	0.78 (0.65, 0.94)	0.81 (0.66, 0.98)	0.84 (0.66, 1.05)	0.92 (0.72, 1.16)
	Obese	0.64 (0.47, 0.86)	0.67 (0.49, 0.90)	0.76 (0.59, 0.98)	0.84 (0.64, 1.09)

*Adjusted for age.

†Adjusted for age, smoking, cigarettes smoked per day, education level, marital status, physical activity, alcohol use and comorbidities ("non-obesity related cancers other than skin cancer" or chronic obstructive pulmonary disease).

Table 4.1.3 Differences in life expectancy, in years, at age 55 for normal weight, overweight and obesity in men and women. (n=6636)

	Total LE	**Differences in total LE**	**LE free of CVD**	**Differences in number of years lived free of CVD**	**LE with CVD**	**Differences in number of years lived with CVD**
Men						
Normal weight	26.5 (26.0, 27.1)	Ref	22.3 (21.6, 23.0)	Ref	4.2 (3.8, 4.7)	Ref
Overweight	26.6 (26.1, 27.2)	0.1 (-0.8, 1.0)	21.3 (20.7, 22.0)	-1.0 (-2.1, 0.2)	5.3 (4.8, 5.8)	1.1 (0.3, 1.9)
Obese	26.8 (25.5, 28.1)	0.3 (-1.1, 1.6)	19.7 (17.7, 21.7)	-2.6 (-4.8, -0.4)	7.1 (5.4, 8.9)	2.9 (1.1, 4.8)
Women						
Normal weight	30.8 (30.3, 31.3)	Ref	27.1 (26.5, 27.7)	Ref	3.7 (3.2, 4.1)	Ref
Overweight	31.3 (30.7, 32.0)	0.6 (-0.2, 1.3)	26.8 (26.0, 27.6)	-0.3 (-1.3, 0.7)	4.5 (3.9, 5.2)	0.9 (0.1, 1.6)
Obese	30.7 (30.0, 31.5)	-0.2 (-1.2, 0.7)	25.2 (24.1, 26.1)	-1.9 (-3.3, -0.9)	5.3 (4.4, 6.3)	1.7 (0.6, 2.8)

LE, life expectancy; CVD, cardiovascular disease

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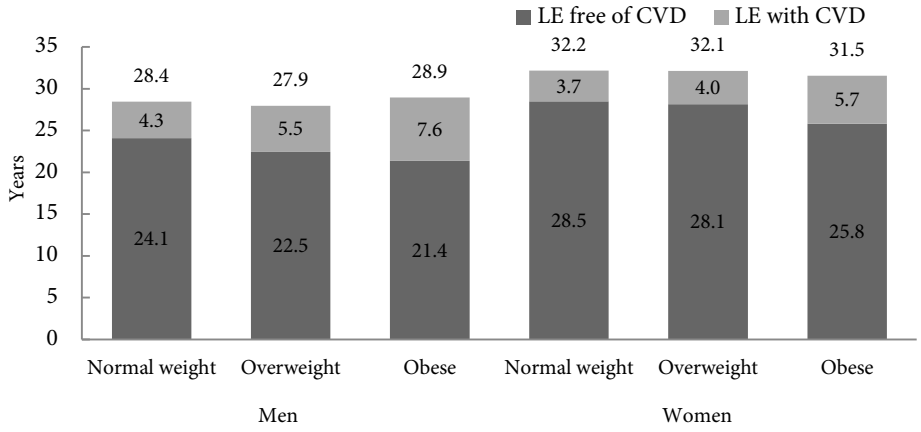
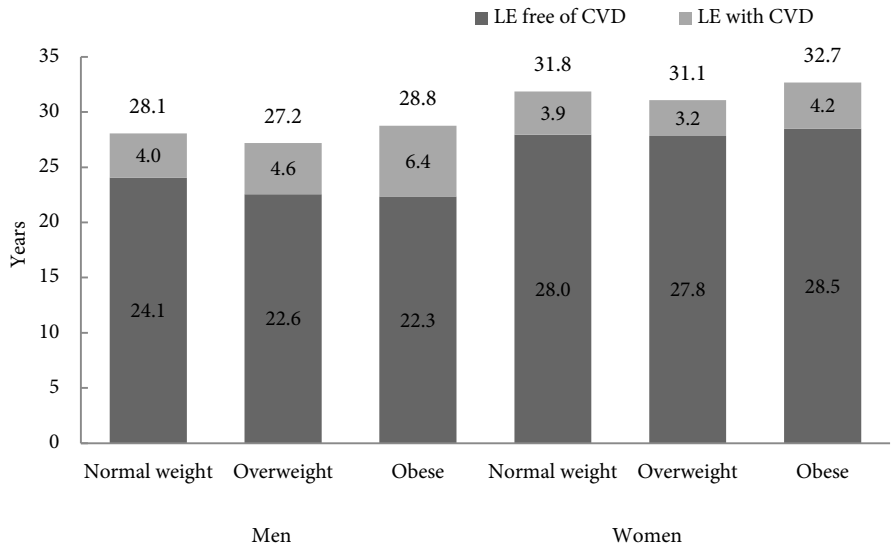
SUPPLEMENT FOR CHAPTER 4.1

Supplement 4.1.1 Effect of obesity on life expectancy with and without cardiovascular disease (CVD) at age 55 years among non-smokers individuals and without comorbidities† (n=5117).



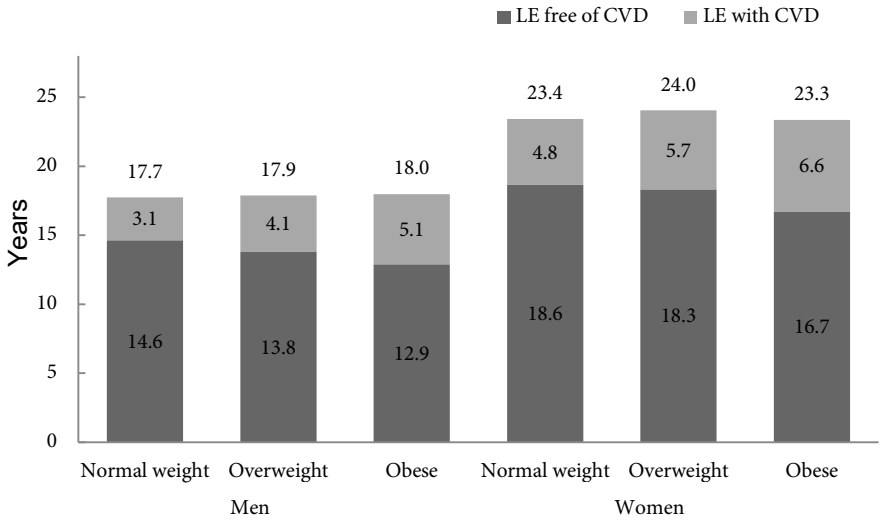
Body mass index (BMI) categories: Normal weight BMI is <25kg/m^2; Overweight BMI is 25-30kg/m^2 and Obese the BMI is ≥30kg/m^2. LE, life expectancy; CVD, cardiovascular disease.
†Comorbidities includes "non-obesity related cancers other than skin cancer" or chronic obstructive pulmonary disease

Supplement 4.1.2 Effect of obesity on life expectancy with and without cardiovascular disease (CVD) at age 55 years among individuals without hypertension, dyslipidemia and diabetes at baseline (n=3750).



Body mass index (BMI) categories: Normal weight BMI is <25kg/m^2; Overweight BMI is 25-30kg/m^2 and Obese the BMI is ≥30kg/m^2. LE, life expectancy; CVD, cardiovascular disease.

Supplement 4.1.3 Effect of obesity on life expectancy with and without cardiovascular disease (CVD) at age 65 years (n=4245).



Body mass index (BMI) categories: Normal weight BMI is <25kg/m^2; Overweight BMI is 25-30kg/m^2 and Obese the BMI is ≥30kg/m^2. LE, life expectancy; CVD, cardiovascular disease.

Supplement 4.1.4 Baseline characteristics† of individuals who did not visit the research center or did not have information on BMI (n=1051).

Characteristics	Men	Women
n	312 (42%)	739 (58%)
Age at interview (years)	73.6±9.7	77.1±10.8
Social economic status		
Marital status		
Single	11 (3.0)	55 (7.4)
Married	218 (79.1)	248 (33.6)
Widowed	61 (10.7)	372 (50.3)
Divorced/separated	22 (7.2)	64 (8.7)
Education		
Elementary	47 (15.1)	236 (31.9)
Lower secondary	99 (31.7)	346 (46.8)
Higher secondary	117 (37.5)	115 (15.6)
Tertiary	49 (15.7)	42 (5.7)
Lifestyle variables		
Smoking		
Never smoking	61 (21.0)	405 (62.8)
Former smoker	158 (54.3)	122 (18.9)
Current smoker	72 (24.7)	118 (18.3)
Daily cigarettes smoked	3.8±8.4	2.3±5.8
Alcohol (drinks/day)		
< 1 glass/day	146 (46.8)	533 (72.1)
1-4 glasses/day (men); 1-2 glasses/day (women)	141 (45.2)	131 (17.7)
> 4 glasses/day (men); > 2 glasses/day (women)	25 (8.0)	75 (10.1)
Physical activity (METh)	56.4±40.2	68.5±43.3
Treatment for hypertension	75 (25.3)	195 (28.1)
Treatment for dyslipidemia	36 (11.5)	55 (7.4)
Comorbidities (cancer† and chronic obstructive pulmonary disease)	48 (15.4)	51 (6.9)

*Baseline characteristics are based in home interview

†Cancer includes "non-obesity related cancers other than skin cancer"

Values are means (SDs) or numbers (percentages). BMI, body mass index

Supplement 4.1.5 Hazard ratios for Cardiovascular disease (CVD) and Death for overweight and obese men and women after excluding cardiovascular events (transition 1) or deaths (transition 2 and 3) during first 2 years of follow up.

		Men		**Women**	
Transition	**Categories**	**Model 1 HR (95% CI)†**	**Model 2 HR (95% CI) ‡**	**Model 1 HR (95% CI)†**	**Model 2 HR (95% CI) ‡**
Incident CVD	Normal weight	1.0	1.0	1.0	1.0
	Overweight	1.15 (0.92, 1.44)	1.18 (0.94, 1.48)	1.18 (0.96, 1.47)	1.22 (0.98, 1.51)
	Obese	1.52 (1.11, 2.08)	1.55 (1.13, 2.13)	1.49 (1.18, 1.87)	1.53 (1.21, 1.93)
Mortality among those without CVD	Normal weight	1.0	1.0	1.0	1.0
	Overweight	1.03 (0.86, 1.24)	1.08 (0.90, 1.30)	0.82 (0.68, 0.98)	0.84 (0.71, 1.01)
	Obese	1.13 (0.85, 1.50)	1.18 (0.88, 1.57)	0.99 (0.81, 1.20)	1.01 (0.83, 1.23)
Mortality among those with CVD	Normal weight	1.0	1.0	1.0	1.0
	Overweight	0.78 (0.64, 0.96)	0.82 (0.67, 1.01)	0.83 (0.66, 1.06)	0.91 (0.71, 1.16)
	Obese	0.67 (0.49, 0.91)	0.69 (0.50, 0.95)	0.75 (0.58, 0.97)	0.83 (0.63, 1.09)

†Adjusted for age.

‡Adjusted for age, smoking, cigarettes smoked per day, education level, marital status, physical activity, alcohol use and comorbidities ("non-obesity related cancers other than skin cancer" or chronic obstructive pulmonary disease).

4.2 Trajectories of body mass index before the diagnosis of cardiovascular disease: a latent class trajectory analysis

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ABSTRACT

Background: Patients with cardiovascular disease (CVD) are a heterogeneous group regarding their body mass index (BMI) levels at the time of diagnosis. To address the heterogeneity of CVD, we examined the trajectories of change in body mass index (BMI) and in other cardio-metabolic risk factors before CVD diagnosis.

Methods: The study included 6126 participants from the prospective population-based Rotterdam Study, followed over 22 years with clinical examinations every 4 years. Latent class trajectory analysis and mixed-effect models were used to develop trajectories of BMI and other cardio-metabolic risk factors respectively.

Results: During follow-up, 1748 participants developed CVD, among whom we identified 3 distinct BMI trajectories. Most of these participants (n=1534, 87.8%) had steady BMI levels during follow-up, comprising the "stable weight" group. This group showed decrease in mean high-density lipoprotein (HDL) cholesterol over time. The second group, the "progressive weight gain" group (n=112, 6.4%), showed a progressive increase in BMI levels. In this group, mean waist circumference increased, mean HDL cholesterol decreased and mean fasting glucose levels were fluctuating over follow-up. In the third group, the "progressive weight loss" group (n=102, 5.8%), BMI levels decreased during follow-up. This group showed a decrease in mean waist circumference and fasting glucose.

Conclusion: In conclusion, the majority of individuals who developed CVD had a stable weight during follow-up, suggesting that BMI alone is not a good indicator for identifying middle-aged and elderly individuals at high risk of CVD. Waist circumference, HDL cholesterol, and glucose trajectories differed between the identified BMI subgroups, further highlighting that CVD is a heterogeneous disease with different pathophysiological pathways.

INTRODUCTION

The association between obesity and cardiovascular disease (CVD) has been well established in observational studies.[1, 2] The causality of this relationship has also been recently reported using a Mendelian randomization approach.[3] Additionally, duration of obesity has been shown to be a risk factor for CVD,[4,5] diabetes,[6] and mortality,[7] independent of the baseline levels of body mass index (BMI). However, CVD is not only limited to obese individuals, and normal weight or overweight individuals may also experience a cardiovascular event.[8,9] Consequently, patients with CVD are a heterogeneous group with regard to their BMI levels at the time of diagnosis of CVD. Understanding the heterogeneity of CVD by exploring the distinct patterns of change in BMI levels prior to the diagnosis of CVD might carry important implications for improving disease prevention or treatment. For instance, each trajectory of BMI change prior to CVD could be accompanied by different trajectories of change in other cardio-metabolic risk factors. As such, identification of different population subgroups with similar risk factor patterns might serve to facilitate targeted cardiovascular prevention programs.

One way of exploring this heterogeneity is to group individuals with similar patterns of change in BMI over time through data-driven statistical methods such as latent class trajectory analysis.[10] Latent class trajectory analysis is an innovative statistical method used to identify subgroups (classes) of participants who are homogeneous with respect to the trajectory of one specific risk factor but heterogeneous as compared with other subgroups. Latent class trajectory analysis has recently been applied to study BMI development prior to diagnosis of diabetes.[11]

In the current study among a middle-aged and elderly population, we aimed to identify different trajectories of BMI development prior to a cardiovascular event. We also sought to explore the trajectories of concurrent cardio-metabolic risk factors, including blood pressure, lipids and glucose, within each identified BMI subgroup.

METHODS

Study population

The Rotterdam Study (RS) is a prospective population-based cohort study. In 1989-1993, the original cohort (RS-I) recruited 7983 (78% response rate) men and women aged 55 years and over from a well-defined suburb in the city of Rotterdam, the Netherlands. The participants of the Rotterdam Study have been followed-up for more than 22 years and the clinical data have been collected across five subsequent phases approximately 4 years apart. Each phase of the study included a home interview followed by two visits at the research center for clinical examinations. Details regarding the objectives and design of the Rotterdam Study have been reported previously.[12]

The present analysis was based on the original cohort (RS-I). From 7983 subjects participating at baseline, we excluded 225 participants without informed consent, 963 individuals with prevalent CVD (including: myocardial infraction (MI), coronary heart disease (CHD), heart failure, and stroke), 646 individuals without BMI measurements throughout phases 1-5, and 23 participants without information regarding CVD follow-up. Thus, the final sample included 6126 participants (77% of original sample) (Figure 4.2.1).

Assessment of Cardio-metabolic Risk Factors

Information on cardio-metabolic risk factors was collected through home interviews or measured at the study center visit as described previously.[13,14] Height and weight were measured in all five phases, whereas systolic blood pressure and waist circumference were measured in phases 1, 3, 4 and 5, and fasting total cholesterol, high-density lipoprotein (HDL) cholesterol and fasting plasma glucose were measured in phases 3, 4 and 5 (Figure 4.2.1). Height and weight were measured with the participants standing without shoes and heavy outer garments. BMI was calculated as weight divided by height squared (kg/m^2). Waist circumference was measured at the level midway between the lower rib margin and the iliac crest with participants in standing position without heavy outer garments and with emptied pockets, breathing out gently. Serum total cholesterol, HDL cholesterol, and glucose were measured using standard laboratory techniques. Blood pressure was measured at the right brachial artery with a random-zero sphygmomanometer with the participant in sitting position, and the mean of two consecutive measurements was used. Smoking status was classified as current smoking or others (former and never) in all phases. We assessed medication use for hypertension, hyperlipidemia and diabetes mellitus through interview.

Clinical outcome

The main outcome measure was incident CVD,[15] composed of coronary heart disease (CHD),[13] and stroke.[16] CHD was composed of fatal and non-fatal myocardial infarction and other CHD mortality. Stroke was composed of fatal and non-fatal stroke. Data on incident CVD were collected through an automated follow-up system, through gathering information from general practitioners working in the study area until January 1, 2012.

Statistical analysis

Our statistical analysis included two consequent steps. Initially, we used latent class trajectory analysis to identify groups of participants with distinct trajectories of BMI change during follow-up, until the occurrence of the first cardiovascular event.[10] Subsequently, within each identified BMI group, we developed the trajectories of change in other cardio-metabolic risk factors during the follow-up.[11]

The latent class trajectory analysis automatically divides the study population into classes, in such a way that participants in the same class tend to have similar trajectories of BMI change. By design of study we performed this analysis only in the population diagnosed with CVD during follow-up. Therefore, the observation period for the development of trajectories started retrospectively at the date of diagnosis with CVD. For the subjects within each group, the latent class trajectory model assumes that the BMI measurements follow a linear mixed-effects model with BMI as the dependent variable and time before CVD diagnosis (time 0), age, sex and phase of study as independent variables. The independent variable "time before CVD diagnosis" was used to describe the shape of the longitudinal trajectory of BMI, using a cubic specification (i.e., linear, quadratic, and cubic terms for the time before CVD diagnosis were entered as covariates into the model). The Bayesian information criterion (BIC) was used to choose the number of classes in the latent class trajectory model. The latent class trajectory model calculates a posterior

probability of membership in each latent class for each participant. Each participant is assigned to the class for which his/her posterior probability is the highest. To ensure that all obtained classes were of clinically meaningful size, we imposed the condition that each class should include at least 5% of participants and the mean of posterior probability of each class should be higher than 75%. Since the trajectories of change in BMI could differ between individuals who die during follow-up and among individuals who do not die or develop CVD during follow-up[17] we divided the rest of the population into two subgroups: 1) CVD-free and alive until end of follow-up and 2) non-CVD mortality.

For each identified BMI group (among individuals diagnosed with CVD) and the two other groups (CVD-free, and non-CVD mortality), we examined the trajectories in other cardio-metabolic risk factors including waist circumference; systolic and diastolic blood pressure; fasting total and HDL cholesterol; and fasting plasma glucose. Since the aggregated effect of combined risk factors on CVD might differ from each risk factor alone or from merely sum of risk factors, guidelines recommend to evaluate the 10-year CVD risk of an individual in clinical practice.[18] Therefore, we examined the trajectories of 10-year CVD risk in each group of BMI. The predicted 10-year CVD risk was calculated using the American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equation coefficients, which includes age, sex, total cholesterol, HDL cholesterol, systolic blood pressure, blood pressure lowering medication use, diabetes status, and smoking status in the prediction model.[15] These trajectories of cardio-metabolic risk factors were estimated using linear mixed-effects models. The independent variables in these linear mixed-effects models were follow-up time, age, sex, and study phase. Analyses of lipids were further adjusted for lipid-lowering treatment, analyses of blood pressure were further adjusted for anti-hypertensive treatment, and analyses of glucose were additionally adjusted for diabetes treatment. Quadratic and cubic terms for follow-up time were included in the BMI groups (latent classes) when significant ($p<0.05$). For individuals not developing CVD during follow-up (CVD-free and non-CVD mortality groups), year 0 is merely a time point in a normal life course, and we therefore fitted the trajectories by using linear models. Pair-wise differences in growth curves between BMI groups were tested using F-tests for each cardio-metabolic risk factor. Paired Chi-square test (for categorical variables) was used to compare participant characteristics between the groups.

Analyses were conducted using R statistical software, version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria), with the package "lcmm"(10). All tests were two-sided and we used a significance level of 5%.

RESULTS

Baseline characteristics of the study population are presented in Table 4.2.1. Overall, 6126 participants with a mean age of 69 years, mostly women (n= 3787, 61.8%), and overweight (mean BMI=26.3) were included in the study (Table 4.2.1). The median (interquartile range - IQR) of total follow-up was 14.7 (7.6; 18.3) years during which 28.5% of participants (n=1748) developed CVD. Among 4378 individuals who did not develop CVD, 2184 subjects (35.7%) remained alive until the end of follow-up and 2194 (35.8%) died from non-CVD causes. The baseline characteristics of these subgroups are presented in Supplement 4.2.1.

Patterns of BMI change over time

Among 1748 participants who developed CVD, we identified three groups with distinct trajectories of change in BMI levels. The largest group of individuals (n=1534, 87.8%) was classified in the first group and showed stable BMI levels over time. This group entered the study with an average BMI of 25.6 kg/m^2 and maintained this average BMI level during follow-up. Therefore, we named this group "stable weight". The second group comprised 112 (6.4%) individuals who entered the study with a mean BMI of 26.1 kg/m^2. This group experienced an increase in BMI during follow-up and the mean BMI reached the obesity range (e.g. BMI > 30). We named this group the "progressive weight gain" group. The third group included 102 individuals (5.8%) who initially started with an average BMI in the obese range (mean BMI=30.2 kg/m^2). In this group, the average BMI decreased to the overweight range and continued to decrease for the next 10 years. The mean BMI eventually reached the normal-weight range. We named this group the "progressive weight loss" group. (Figure 4.2.2 A).

Among 2184 subjects who did not develop CVD event and were alive until the end of follow-up, the "CVD-free" group, the average BMI remained stable. In this group the BMI ranged from 25.0 to 25.9 kg/m^2 during the follow-up. Among 2194 subjects who died of other causes during follow-up, the "non-CVD mortality" group, the average BMI at the start of the follow-up (average BMI=25.8 kg/m^2) was in the overweight range. This group slightly lost weight during follow-up and just before death their mean BMI was in the normal range (Figure 4.2.2 A).

While the analyses were performed in the total population, to plot the trajectories of change in BMI and in other cardio-metabolic risk factors, it was necessary to assume a hypothetical individual with a predefined sex and age. Therefore, the presented figures are sex specific. Figures 2 and 3 represent the trajectories for a hypothetical man of 65 years old. Similar trajectories for a hypothetical woman of 65 years of age are shown in Supplement 4.2.2 and 4.2.3.

Trajectories of waist circumference

Trajectories of waist circumferences differed significantly between the three groups ($p<0.001$ for all pairwise comparisons) (Figure 4.2.2 B). The trajectories for the "progressive weight loss" and "progressive weight gain" groups broadly resembled the trajectories of BMI in these groups. However, among individuals in the "stable weight" group, we observed a slight increase in the mean waist circumference during follow-up. The mean waist circumference in the "CVD-free" and "non-CVD mortality" groups decreased during follow-up (Figure 4.2.2 B).

Trajectories of blood pressure

Trajectories of systolic blood pressure among "stable weight", "progressive weight loss", and "progressive weight gain" groups were not significantly different ($p\geq0.208$ for all pairwise comparisons). The "stable weight" and "progressive weight loss" groups had a mean systolic blood pressure between 130-142 mmHg during follow-up. In the "progressive weight gain" group average systolic blood pressure levels increased during the follow-up from 120 mmHg to 138 mmHg before the cardiovascular event (Figure 4.2.2 C).

Trajectories of diastolic blood pressure for all groups of BMI were in the normal range during follow-up (< 80mmHg). The average diastolic blood pressure trajectory of the "progressive weight gain" group was significantly higher (p=0.012) than the "progressive weight loss" group. Similarly to the "progressive weight gain" group, the "stable weight" and the "CVD-free" groups experienced a modest increase in mean diastolic blood pressure during follow-up. Compared to the "stable weight" and "progressive weight gain" groups, the "progressive weight loss" group had the lowest mean diastolic blood pressure during follow-up. Among the "non-CVD mortality" group, the mean diastolic blood pressure decreased during follow-up and before death (Figure 4.2.2 D).

Trajectories of Lipids and Glucose

We found no differences in fasting total cholesterol levels between the three groups of individuals who developed CVD during follow-up ($p \geq 0.059$ for all pairwise comparisons). Overall, the trajectories of fasting total cholesterol followed those of BMI for the "stable weight" and "progressive weight loss" groups. However, the "progressive weight gain" group showed a decrease in average levels of total cholesterol. In this group, the mean total cholesterol levels decreased from 218 mg/dl to 190 mg/dl during follow-up. The average levels of total cholesterol (mean: 200 mg/dl) were stable for the "CVD-free" group (Figure 4.2.3 A). Average levels of HDL cholesterol for the three groups of "stable weight", "progressive weight loss" and "progressive weight gain" were lower compared to the "CVD-free" group. The mean levels of HDL cholesterol decreased significantly in the "progressive weight gain" and the "stable weight" groups during follow-up. The decrease in mean HDL levels was more pronounced in the "progressive weight gain" group compared to the "stable weight" group ($p<0.001$) (Figure 4.2.3 B).

Trajectories of fasting glucose differed between the three groups of "stable weight", "progressive weight loss" and "progressive weight gain" ($p<0.001$ for all pairwise comparisons). The "stable weight" group had an average fasting glucose level of 140 mg/dl, which remained stable during follow-up. Among the "progressive weight gain" group, the mean fasting glucose levels were fluctuating (increasing and decreasing) over the entire follow-up. For the "progressive weight loss" group we observed a decline in mean levels of fasting glucose from 200 mg/dl to 120 mg/dl during follow-up (Figure 4.2.3 C).

Trajectories of estimated 10-year CVD risk

Figure 4.2.3 D shows the 10-year predicted risk of CVD estimated by the ACC/AHA Pooled Cohort Equations algorithm.[15] Despite the differences in BMI trajectories, the 10-year predicted risk of CVD increased similarly during follow-up for all 3 groups of CVD patients. However, the "progressive weight gain" group had significantly higher mean 10-year predicted risk of CVD than the "stable weight" group ($p<0.001$). In the "progressive weight loss" group, the mean predicted CVD risk increased rapidly 10 years before the CVD diagnosis. The 10-year predicted risk of CVD for the "CVD-free" group was lower than 10-year predicted risk in all other groups.

Other characteristics

Table 4.2.2 shows characteristics of the participants at the time of CVD diagnosis for the "stable weight", "progressive weight gain" and "progressive weight loss" groups; or at the last examination for the "CVD-free" and "non-CVD mortality" groups. Compared to the "CVD-free" group, other groups were older and included more men. Individuals in the "stable weight" group were less likely to receive treatment for hypertension and lipids but more likely to smoke compared to the other two groups of "progressive weight loss" and "progressive weight gain". Interestingly, the proportion of participants with a family history of MI or stroke was significantly lower in the "stable weight" group compared to the "progressive weight gain" group.

DISCUSSION

In our prospective population-based cohort study of middle-aged and older adults followed every 4 years for over 22 years, we examined the development of different BMI trajectories prior to the diagnosis of CVD. By using latent class trajectory analysis, we found three distinct groups of BMI change among individuals who were diagnosed with CVD during follow-up. The majority of individuals (87.8%) who developed CVD had a stable BMI levels over time. These individuals were classified into the "stable weight" group. A small group of individuals who experienced CVD during follow-up (6.4%), which we refer to as the "progressive weight gain" group showed a progressive increase in their mean BMI level. The third group of individuals with a CVD event (5.8%), named the "progressive weight loss" group, experienced a decrease in their mean BMI level during follow-up. Our analysis revealed different patterns of change in other cardio-metabolic risk factors including waist circumference, HDL cholesterol, and glucose between the identified BMI trajectories. This finding further highlights that CVD is a heterogeneous disease with different pathophysiological pathways.

In general, the use of BMI as an accurate anthropometric measure in association with CVD and mortality among the elderly population has been challenged.[19-21] Recent data among middle-aged and elderly populations has demonstrated that the magnitude of relationship between elevated BMI levels and CVD weakens with age.[22] However, most of studies classified BMI into pre-defined categories which are currently debatable in relation to mortality.[23] Such an approach may also cause misclassification of individuals, especially those close to the cut-points for classification.[24] Instead of studying changes in pre-defined BMI categories, we chose to define subgroups of BMI change over time using latent class trajectory analysis. This type of statistical method is useful to explore heterogeneous growth patterns that would not be identified using conventional methods. Indeed, latent class trajectory analysis is more flexible, because it models group-specific average patterns of change in BMI during follow-up. Our latent class trajectory analysis indicated that among the majority of individuals who developed CVD during the follow-up, the mean BMI levels remained fairly stable (the "stable weight" group). Overall, within the "stable weight" group, the mean values for other cardio-metabolic risk factors also remained fairly stable overtime and their levels were relatively within normal clinical range. In this group, we only observed a slight increase in the mean waist circumference and a decrease in mean HDL cholesterol levels before the CVD diagnosis. However, the predicted 10-year CVD risk, which combines several cardio-metabolic risk factors into a single risk score, as recommended by the guidelines,[15] showed an increase among the "stable weight" group, indicating that this subgroup was at high risk for developing CVD. This finding highlights that among middle-aged and elderly

individuals BMI is not a good predictor of CVD risk [19,22] and further advocates consideration of a combination of multiple cardio-metabolic risk factors.[15,18]

The second group of individuals who developed CVD during follow-up, the "progressive weight gain" group, had a mean BMI level in the range of class II obesity (35-40 kg/m^2) at the time of CVD diagnosis. During follow-up, this group showed an increase in mean waist circumference, a decrease in mean HDL cholesterol levels, and a fluctuating pattern in fasting glucose levels. Previous studies, based on a single-time measurement, have highlighted that waist circumference could play a specific role in insulin resistance and dyslipidemia.[25] The findings of our study, using multiple measurements over time, give further support to this premise by showing that the increase in waist circumference was accompanied by decrease in HDL cholesterol levels during follow-up. Furthermore, we also observed a fluctuating pattern in fasting glucose levels among the "progressive weight gain" group in our study. Whether this variability in glucose levels can be attributed to an increase in BMI levels or waist circumference needs further investigation. However, recent evidence points towards the involvement of blood glucose fluctuation in the development of vascular injury in diabetes.[26] It has been demonstrated that fluctuations in blood glucose levels can increase oxidative stress in type 2 diabetes mellitus patients,[27] which results in cell dysfunction and tissue injury. The "progressive weight gain" group may therefore carry a large cardio-metabolic burden.

In young adults, weight loss is beneficial and is viewed as a positive response to lifestyle modification or medical treatment. However, among the elderly, weight loss has been associated with a high risk of mortality.[17,21,28] Our study comprised middle-aged and elderly individuals. Among the 3 identified BMI trajectories in our study, one distinct group showed a decline in mean BMI during follow-up (the "progressive weight loss" group). In this group, we observed a decrease in mean waist circumference as well as decreases in mean fasting glucose levels during follow-up. Despite the decreases in the mean levels of some cardio-metabolic risk factors, the predicted 10-year CVD risk showed an increase among the "progressive weight loss" group, demonstrating that this subgroup was at high risk for developing CVD. Similarly, among the group that did not develop CVD event but died of other causes (the "non-CVD mortality" group), the average BMI levels declined before death.

A unique advantage of this study was that we were able to assess the medication data for all BMI subgroups. Interestingly, we found that the "progressive weight gain" group had the highest proportion of treatment for hypertension and hyperlipidemia. Remarkably, the trajectories of systolic blood pressure and total cholesterol in the "progressive weight gain" group were not significantly different from the "stable weight" group. Moreover, although a bit more pronounced in the "progressive weight gain" group, the predicted 10-year CVD risk increased in all 3 groups of "stable weight", "progressive weight gain" and "progressive weight loss" during follow-up, exceeding the clinical threshold for treatment. This may suggest that the overweight and obese individuals gaining weight over time are more likely to be screened for CVD and subsequently receive medication. Notably, the "progressive weight gain" group only constituted a small proportion (around 6%) of participants developing CVD events in our study. Therefore, treating this group has a small impact on decreasing the overall burden of CVD in total population.

Strengths of the current study include the prospective study design, large sample size, very long follow-up time, and availability of repeated measurements for BMI together with detailed data on

cardio-metabolic risk factors and medication use over time. These all facilitated the analysis to create the latent classes and to estimate the trajectories of traditional cardio-metabolic risk factors. Our study overcomes the limitation of previous studies classifying BMI into pre-defined categories which is debatable among the elderly population in association with mortality.[23] Our statistical approach allows for exploring heterogeneous growth patterns that would not be identified using conventional methods. However, one disadvantage of latent class analysis is that it creates subgroups with very different sizes.[29] Therefore, comparison of subgroups, in terms of statistical power, can be difficult.

In conclusion, latent class trajectory analysis identified three distinct patterns of BMI development prior to a CVD event. The majority of individuals who developed CVD had a stable weight during follow-up, suggesting that BMI alone is not a good indicator for identifying middle-aged and elderly individuals at high risk of CVD. Moreover, the accompanying trajectories of waist circumference, HDL cholesterol, and glucose differed between the identified BMI subgroups, further highlighting that CVD is a heterogeneous disease with different pathophysiological pathways.

Table 4.2.1 Characteristics of study participants at their first clinical examination

Characteristics	**Total population (N=6126)**
Time before diagnosis/last visit, years	14.7 (7.6, 18.3)
Women (%)	3787 (61.8)
Current smoker (%)	1439 (23.5)
Antihypertensive treatment (%)	1035 (16.9)
Anti-diabetic treatment† (%)	240 (6.8)
Statins treatment† (%)	575 (16.3)
Age, years	68.8 ± 8.9
Glucose†, mg/dl	105.7 ± 24.2
Cholesterol†, mg/dl	226.6 ± 37.2
HDL cholesterol†, mg/dl	54.9 ± 15.6
Systolic blood pressure, mmHg	139.3 ± 22.1
Diastolic blood pressure, mmHg	73.9 ± 11.4
Body mass index, kg/m^2	26.3 ± 3.7
Waist circumference, cm	90.0 ± 11.1

*Values are mean ± SD, numbers (percentages), or median (IQR) .

Abbreviations: HDL, high density lipoprotein; CVD, cardiovascular disease; n, number.

†Fasting measurements of Lipids and glucose and treatment were available in the third and following rounds of the original Rotterdam Study cohort (N=3529).

Table 4.2.2 Characteristics of study participants at the time of the diagnosis for the three groups with cardiovascular disease or at last visit for the groups without cardiovascular disease (N=6126).

Characteristics*	**Individuals developing cardiovascular disease during follow-up (n=1748)**			**Individuals free of CVD during follow-up (n=4378)**	
	Stable weight (n=1534)	**Progressive weight gain (n=112)**	**Progressive weight loss (n=102)**	**CVD-free (n=2184)**	**Non-CVD mortality (n=2194)**
Age at diagnosis/last contact, years	75.7 ± 8.1	75.6 ± 7.3	79.4 ± 8.3	75.1 ± 7.1	77.2 ± 8.0
Women (%)	868 (56.6)	75 (67.0)†	66 (64.7)	1496 (68.5)†	1283 (58.5)
Ever smoker (%)	925 (60.3)	59 (52.7)	49 (48.0)†	885 (40.5)†§	1202 (54.8)†
Ever on antihypertensive treatment (%)	391 (25.5)	58 (51.8)†‡	47 (46.1)†	662 (30.3)‡§	570 (26.0)§
Ever on anti-diabetic treatment (%)	141 (9.2)	18 (16.1)	15 (14.7)	170 (7.8)‡§	143 (6.5)†‡§
Ever on statins treatment (%)	133 (8.7)	26 (23.2)†	14 (13.7)	460 (21.1)†	145 (6.6)‡§
Family history for myocardial infarction or stroke (%)	845 (55.1)	76 (67.9)†	62 (60.7)	1232 (56.4)§	1143 (52.1)§

*Values are mean ± SD or numbers (percentages).

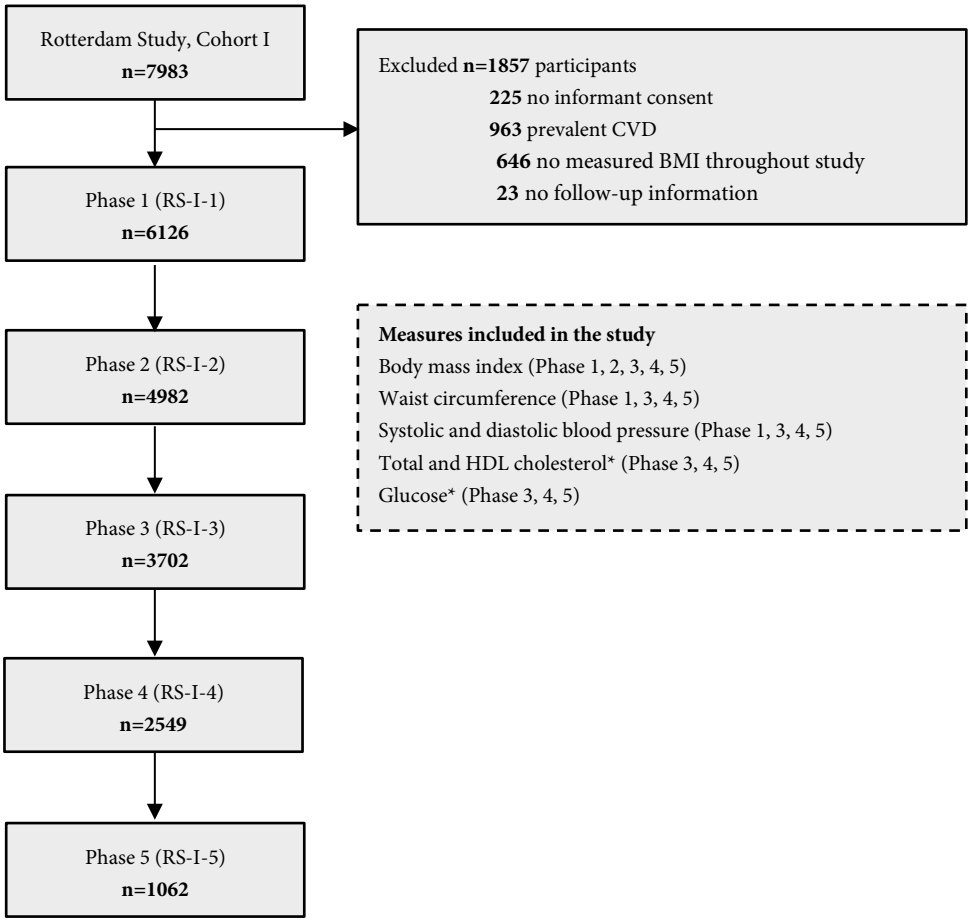
Abbreviations: CVD, cardiovascular disease; n, number.

† Significantly different from stable weight group (P for the difference <0.05).

‡ Significantly different from progressive weight loss group (P for the difference <0.05).

§ Significantly different from progressive weight gain group (P for the difference <0.05).

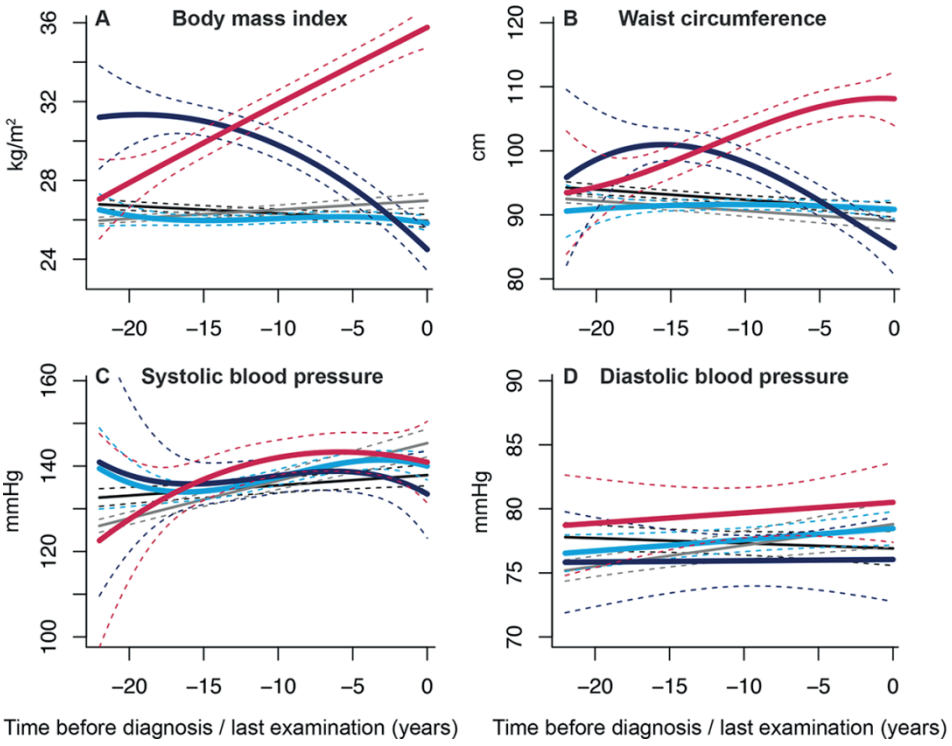
Figure 4.2.1 Flow diagram of the participants included at each phase.



Abbreviations: HDL, high density lipoprotein; CVD, cardiovascular disease; n, number.

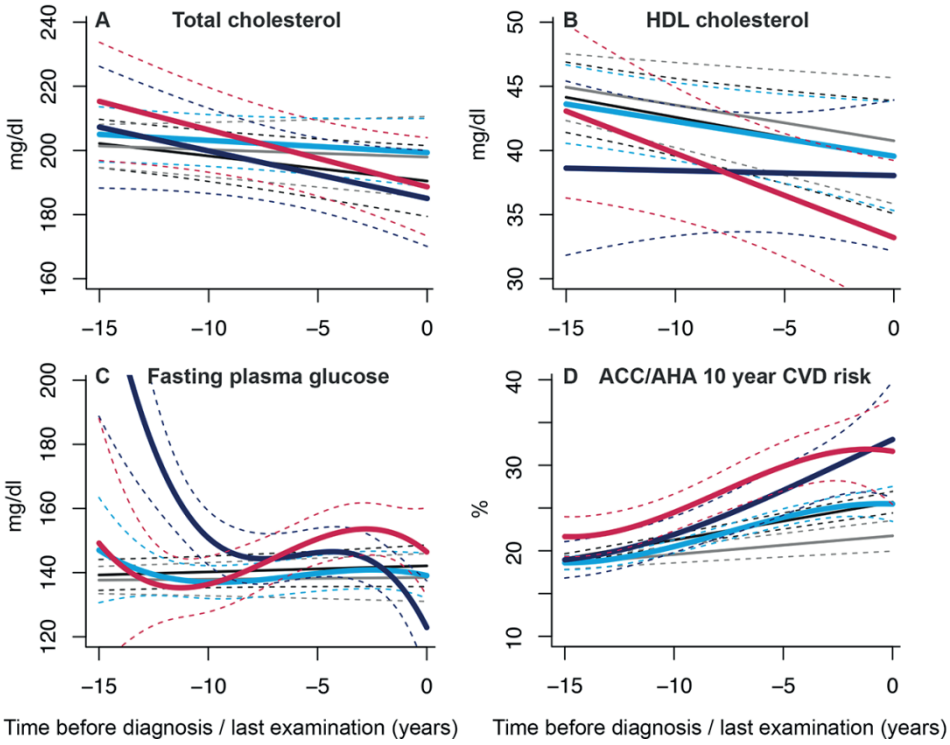
* Total cholesterol, HDL cholesterol and glucose are measured as fasting in phases 3, 4 and 5.

Figure 4.2.2 Trajectories of body mass index, waist circumference, systolic and diastolic blood pressure.



Trajectories for risk factors during 22 years of follow-up until diagnosis of CVD, death or censoring from the study. The figures represent a hypothetical men of 65 years old. Trajectories for blood pressure represent a person on anti-hypertensive treatment.
Light blue: "stable weight" (including 87.8% of CVD patients); dark blue: "progressive weight loss" (including 5.8% of CVD patients); red: "progressive weight gain" (including 6.4% of CVD patients); gray: "CVD-free"; black line: "non-CVD mortality" groups.
Similar trajectories for a hypothetical woman of 65 years of age are shown in Supplement 4.2.1.

Figure 4.2.3 Trajectories of fasting plasma glucose, total cholesterol, HDL cholesterol and predicted 10-year CVD risk.



Abbreviation: HDL cholesterol, high-density lipoprotein cholesterol; ACC/AHA, American College of Cardiology/American Heart Association

Trajectories for risk factors during 15 years of follow-up until diagnosis of CVD, death or censoring from the study. The figures represent a hypothetical man of 65 years, on lipid- or glucose-lowering treatment.

Light blue: "stable weight" (including 87.8% of CVD patients); dark blue: "progressive weight loss" (including 5.8% of CVD patients); red: "progressive weight gain" (including 6.4% of CVD patients); gray: "CVD-free"; black line: "non-CVD mortality" groups.

Similar trajectories for a hypothetical woman of 65 years of age are shown in Supplement 4.2.2.

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SUPPLEMENT FOR CHAPTER 4.2

Supplement 4.2.1 Characteristics of study participants at their first clinical examination.

Characteristics*	**Individuals developing CVD during follow-up (n=1748)**			**Individuals without CVD during follow-up (n=4378)**	
	Stable weight (n=1534)	Progressive weight gain (n=112)	Progressive weight loss (n=102)	CVD-free (n=2184)	Non-CVD mortality (n=2194)
Time before diagnosis/last visit, years	8.1 (4.04, 13.1)	11.2 (6.9, 14.6)	11.9 (9.2, 15.0)	18.7 (17.4, 19.6)	10.6 (5.7, 22.2)
Women (%)	868 (56.6)	75 (67.0)	66 (64.7)	1496 (68.5)	1282 (58.5)
Current smoker (%)	400 (26.1)	20 (18.9)	25 (25.0)	420 (19.4)	574 (26.2)
Antihypertensive treatment (%)	278 (18.1)	43 (38.1)	31 (30.8)	286 (13.1)	397 (18.1)
Anti-diabetic treatment† (%)	47 (8.0)	9 (14.1)	9 (12.2)	121 (6.5)	54 (6.0)
Statins treatment† (%)	79 (13.4)	16 (23.4)	8 (10.8)	379 (20.1)	93 (10.1)
Age, years	71.6 ± 8.8	69.4 ± 8.6	71.9 ± 7.7	62.9 ± 5.4	72.6 ± 8.7
Glucose†, mg/dl	106.2 ± 22.7	114.6 ± 27.5	115.1 ± 30.7	104.0 ± 22.5	107.4 ± 27.2
Cholesterol†, mg/dl	225.6 ± 36.3	225.9 ± 35.2	220.3 ± 35.7	229.6 ± 36.9	221.9 ± 38.2
HDL cholesterol†, mg/dl	52.7 ± 14.4	50.2 ± 14.8	50.9 ± 16.8	56.3 ± 15.0	53.9 ± 17.1
Systolic blood pressure, mmHg	144.7 ± 22.3	146.5 ± 20.6	144.9 ± 21.9	132.6 ± 20.2	141.7 ± 22.3
Diastolic blood pressure, mmHg	74.6 ± 12.0	77.5 ± 11.0	73.1 ± 11.2	73.8 ± 10.6	73.7 ± 12.0
Body mass index, kg/m^2	25.9 ± 3.2	31.7 ± 4.8	30.1 ± 4.2	26.2 ± 3.6	26.2 ± 3.9
Waist circumference, cm	90.1 ± 10.4	99.9 ± 13.2	97.2 ± 10.3	88.1 ± 10.9	91.1 ± 11.2

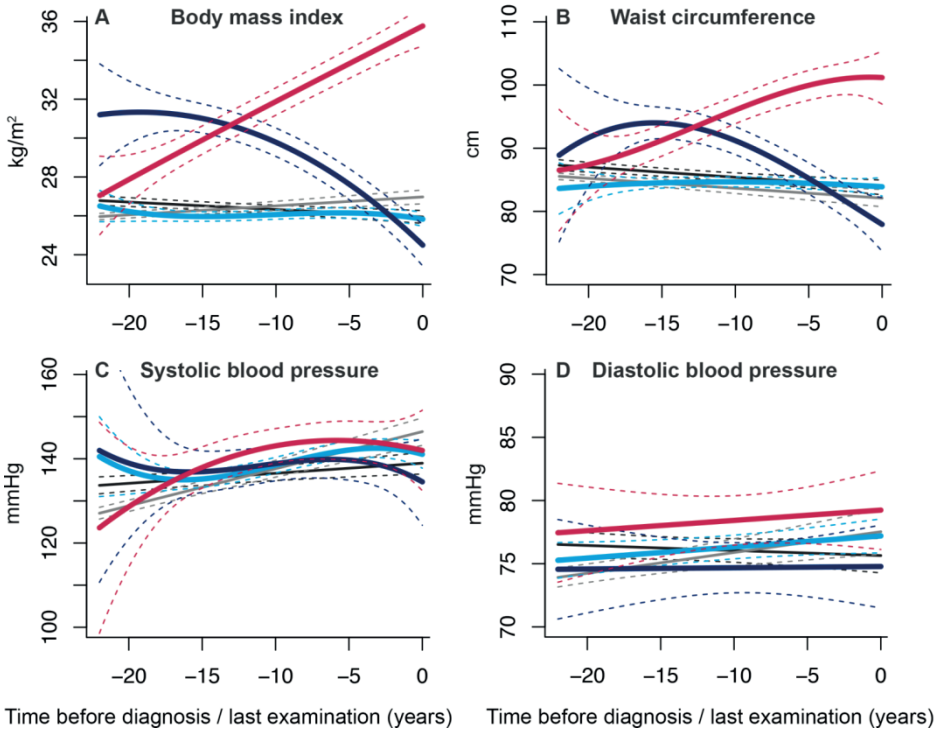
*Values are mean ± SD, numbers (percentages), or median (IQR) .

Abbreviations: HDL, high density lipoprotein; CVD, cardiovascular disease; n, number.

† Fasting measurements of Lipids and glucose and treatment were available in the third and following rounds of the original Rotterdam Study cohort (N=3529).

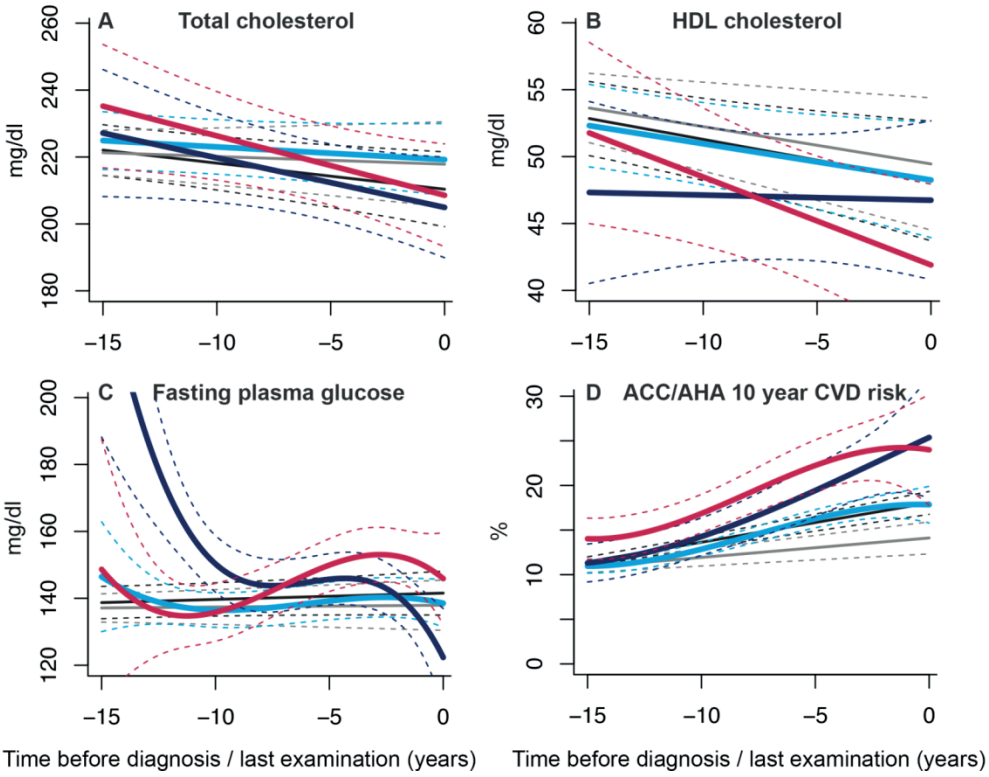
The mean values of the characteristics of study participants in Table 1S are based on single measures at the baseline/first visit in the Rotterdam Study. Therefore, a slightly difference from the predicted mean values presented in the Figures 4.2.2 and 4.2.3 might be observed.

Supplement 4.2.2 Trajectories of body mass index, waist circumference, systolic and diastolic blood pressure



Trajectories for risk factors during 22 years of follow-up until diagnosis of CVD, death or censoring from the study. The figures represent a hypothetical women of 65 years old. Trajectories for blood pressure represent a person on anti-hypertensive treatment.
Light blue: "stable weight" (including 87.8% of CVD patients); dark blue: "progressive weight loss" (including 5.8% of CVD patients); red: "progressive weight gain" (including 6.4% of CVD patients); gray: "CVD-free"; black line: "non-CVD mortality" groups.

Supplement 4.2.3 Trajectories of fasting plasma glucose, total and HDL cholesterol and ACC/AHA 10 year CVD risk



Abbreviation: HDL cholesterol, high-density lipoprotein cholesterol; ACC/AHA, American College of Cardiology/American Heart Association

Trajectories for risk factors during 15 years of follow-up until diagnosis of CVD, death or censoring from the study. The figures represent a hypothetical women of 65 years old, on lipid- or glucose-lowering treatment during 15 years of follow-up until diagnosis of CVD, death or censoring from the study.

Light blue: "stable weight" (including 87.8% of CVD patients); dark blue: "progressive weight loss" (including 5.8% of CVD patients); red: "progressive weight gain" (including 6.4% of CVD patients); gray: "CVD-free"; black line: "non-CVD mortality" groups.

Chapter 5

Obesity, physical activity and cardiovascular disease

5.1 The impact of physical activity on the association between overweight, obesity and cardiovascular disease risk

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Submitted for publication

ABSTRACT

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

Methods: This study included 5,344 participants aged 55 years or older from the prospective population-based Rotterdam Study. Participants were classified as having high or low level of physical activity using the median value. Following, 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 physical activity, thus forming 6 categories. We assessed the association of the combined categories with CVD risk by using Cox proportional hazard. High physical activity and normal weight was set as the reference group. In the multivariable model we adjusted for possible confounders including age, gender, smoking, alcohol consumption, education and diet.

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. In the multivariable model, overweight and obese participants with low physical activity were at increased risk of CVD, compared to normal weight individuals with high physical activity. 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 were not at increased risk of CVD. These associated HRs (95%CIs) were 1.02 (0.81-1.28) and 1.10 (0.81-1.49), respectively. When we stratified based on BMI, the risk for CVD in association with low physical activity increased in each strata of BMI. However, the associations reached statistical significance only in the overweight category (HR 1.27, 95%CI 1.04-1.55).

Conclusions: Our findings suggest that the impact of physical activity on CVD might outweigh that of BMI among the elderly. This emphasizes the importance of physical activity for all individuals and across all BMI strata, further highlighting the risk associated with inactivity even among the lean subjects.

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 decrease risk of CVD.[4,5] Therefore, physical activity might reduce the risks associated with overweight and obesity. These findings have led to the identification of the "fat but fit" phenomenon and raised the question to what extent physical activity can counterbalance the risk associated with overweight and obesity.

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.[6-10] A review combining these studies reported that only four out of eight studies favored the hypothesis that the risk for cardiovascular mortality was lower in individuals with high BMI and high physical activity levels compared to normal weight individuals with low levels of physical activity.[11] A study by Weinstein et al. which 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 increased levels of physical activity.[7] 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, whereas information among the elderly is scarce. Due to body composition changes with aging (i.e. increase of body fat and decrease of muscle mass), BMI becomes a less accurate reflection of fat mass among the elderly.[12] Moreover, the physical activity levels tend to decrease.[13] Therefore, the impact 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 association between BMI and CVD in middle-aged and elderly individuals. We also sought to examine the association of physical activity with CVD risk among different BMI categories.

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=3011). Of this combined total, 6,510 participants completed data collection for both physical activity and BMI. Following, 1,122 subjects 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 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.[14]

Assessment of anthropometrics and physical activity, and other covariates

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.[15] This questionnaire has been validated in which the test-retest reliability was 0.93 and the correlation with doubly labelled water was 0.61.[16] The adapted version of the Zutphen questionnaire includes questions regarding walking, cycling, sports, gardening and housekeeping activities. To quantify activity intensity, we used metabolic equivalent of task (MET). All activities mentioned in the questionnaire were assigned MET-scores, according to the 2011 updated version of the Compendium of Physical Activities.[17] 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. Alcohol use was defined as the amount of glasses per week. 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".[18] 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 visit (1989–1993) of the original cohort (RS-I) and in the third visit (2011–2012) of the extended cohort (RS-II). Information on diet were obtained through a 170-item validated semiquantitative food frequency questionnaire.[19] From the questionnaire, an overall healthy diet score representing 160 adherence to the Dutch dietary guidelines was calculated, as described previously.[20]

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.[21] 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 PA by using the median value. 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, thus forming 6 categories. Baseline characteristics of the study population are presented as mean ± SD (or frequency and percentage when appropriate) for the 6 subgroups formed by the physical activity levels (lower and higher) across different BMI categories. 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 subgroups described above in association with CVD, using normal weight with high levels of physical activity as the reference category. As secondary analysis, we separately estimated the HR and 95%CI for the associations of the BMI categories and physical activity levels with CVD risk. Additionally, we stratified the analysis by BMI categories to allow comparisons of CVD risk as function of physical activity. The high level of physical activity within each BMI category was the reference in the respective analyses. 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 and diet. 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 association between BMI and CVD. We did not observe a significant association of gender with either BMI, physical activity or the joint BMI and physical activity phenotypes.

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.[22] 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.

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).

RESULTS

Table 5.1.1 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 men, older and current smokers compared with participants with high level of physical activity. The overall and mean age of the population was 68.5 years (standard deviation: 7.9) and 60.1% was female. During a median follow-up of 10.3 years, there were 866 (16.2%) incident CVD events.

Table 5.1.2 presents the association of BMI categories and level of physical activity with incident CVD separately. Compared with normal weight individuals, being overweight (HR 1.13, 95%CI 0.97-1.57) or obese (HR 1.20, 95%CI 0.99-1.46) increased the risk for CVD, albeit not significantly. Compared with higher level of physical activities (irrespective of obesity),

individuals with low level of physical activity were at higher risk of CVD (HR 1.22, 95%CI 1.06-1.40).

Table 5.1.3 shows the association between joint physical activity and BMI subgroups 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: 1.82-1.30) and obese (HR: 1.12, 95%CI: 0.82-1.52) 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.

In Table 5.1.4, we present the association between level of physical activity and incident CVD in the analyses stratified by BMI. The group with high physical activity was the reference for each BMI category. The risk for CVD in association with low physical activity increased for each strata of BMI. The corresponding HRs (95%CIs) were 1.16 (0.90-1.49), 1.27 (1.06-1.57) and 1.17 (0.84-1.62), respectively. However, only the association in the overweight category reached statistical significance.

Sensitivity analyses

Supplement 5.1.1 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 5.1.2 and 5.1.3) as in the total population.

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 normal weight counterparts. In contrast, among individuals with lower level of physical activity, being overweight and obese was associated with increased risk of CVD. When the association of physical activity with CVD was evaluated on each strata of BMI, lower physical activity increased the risk for CVD across all BMI strata, particularly in overweight individuals. Moreover, reduced physical activity 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 the elderly

Similar studies of the joint association of BMI and physical activity with CVD are consistent with our findings.[6-10] A study comprised of 18,892 Finish men and women aged 25-74 years concluded that physical inactivity have an independent association with CVD risk, whereas obesity increases the risk through modification of other risk factors.[10] The Women Health Study found that the risk of coronary heart disease associated with elevated BMI is considerable reduced by increased physical activity levels.[7] However, the risk was not completely eliminated, which reinforce the importance of being lean and physically active.[7] Similarly, an analysis from Nurse's Health Study among 88,393 women aged 34 to 59 older revealed that being moderately physically active attenuated but did not eliminate the adverse effect of obesity on coronary heart disease risk.[6] Furthermore, they also showed that being lean did not counteract the increase risk associated with

physical inactivity.[6] In our population-based study, 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 increased risk of CVD while 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 the elderly.

Regarding physical activity, most of previous studies have included leisure time physical activity, whereas in our study we also included transportation and housework in the assessment of total physical activity. Therefore, our results extend previous findings and indicate that not only leisure time physical activity but also other domains of physical activity can be beneficial to reduce CVD risk. Moreover, our study has been conducted in an elderly population. Elderly individuals might have more difficulties in engaging in sports or exercise (leisure physical activity) and spend a relatively large proportion of their time on housework, compared to younger individuals.[24] Our study highlights the importance of the beneficial effects of moderate to vigorous-intensity physical activity as part of the daily life as supported in the recent recommendations.[25]

The mechanism underlying the harmful effect of overweight and obesity on CVD risk has been well reported. Adipose tissue releases free fatty acids, interleukins, and cytokines that influence cardiac function by acceleration of atherosclerosis processes, inflammation, endothelial and coagulation dysfunction.[23,24] 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.[24] This indicates that physical activity directly reduces and combats the harmful effect of the prothrombotic factors released by adipose tissue.[7,25]

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 with 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 increase risk associated with physical inactivity. Moreover, being physically active does not completely refute the increased risk of being obese. Therefore, our study confirms previous findings that physically active and lean individuals are at low risk of CVD [6,10] and extend these findings in the elderly. When we evaluated the risk of physical inactivity with CVD on each strata of BMI, we found that individuals with lower physical activity in the overweight group had significantly higher risk of CVD compared with high physical activity counterparts. However, normal weight and obese individuals with low physical activity were not significantly at increased risk of CVD compared to their counterpart with high physical activity. While physical activity is beneficial in each BMI category,[10] our findings indicate that the most beneficial effect of physical activity could be seen among overweight individuals. Overweight individuals are at intermediate risk of CVD, if compared to normal weight or obese individuals. This could be explained by the lower release of the adipose tissue products including free fatty acids, interleukins, cytokines and reduced acceleration process of atherosclerosis in overweight versus obese individuals. Therefore physical activity could completely eliminate the

adverse effect of these risk factors on CVD among overweight individuals. However, this statement needs further investigation.

Major strengths of the current study are its prospective population-based design, large sample size of adults aged over 55 years 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.[7] Additionally, our results are based on self-reported physical activity. Although our questionnaire has shown to be valid and reliable,[18] potential recall bias and social desirability cannot be excluded. 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 sensitivity analyses exclusion events that occurred within the first two years of follow up revealed comparable results.

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 PA levels. This suggests that regular PA reduces the CVD risk in older adults and that further benefits can be gained from maintaining a healthy weight.

Table 5.1.1 Characteristics at baseline as a function of metabolic health status and body mass index

	Low levels of physical activity			**High levels of physical activity**		
	Normal weight	**Overweight**	**Obese**	**Normal weight**	**Overweight**	**Obese**
n	841	1256	576	924	1279	468
Age, years	70.0 (8.8)	69.4 (8.6)	69.4 (8.5)	67.3 (6.9)	67.6 (7.0)	66.9 (7.0)
Women (%)	49.5	43.6	69.3	69.8	65.2	79.3
Body mass index	23.1 (1.41)	27.25 (1.38)	33.22 (3.19)	23.08 (1.49)	27.24 (1.39)	32.95 (2.74)
Physical activity	52.2 (18.4)	52.0 (18.6)	51.7 (18.9)	121.2 (34.2)	119.7 (33.6)	120.3 (35.1)
Current smoking (%)	23.2	16.6	15.1	21.4	15.8	12.0
Dutch health diet index	47.75 (11.25)	48.35 (11.27)	50.15 (10.34)	49.14 (10.93)	50.31 (10.99)	50.21 (11.02)
Alcohol use	0.50 (0.00, 3.65)	0.73 (0.00, 3.42)	0.90 (0.00, 3.72)	0.50 (0.00, 3.39)	0.59 (0.00, 3.62)	0.77 (0.00, 3.70)
Education (%)						
Elementary	11.2	11.9	16.8	11.8	12.6	16.5
Lower secondary	35.7	40.2	47.2	47.0	48.3	48.9
Higher secondary	35.6	31.3	24.8	27.4	29.0	27.8
Tertiary	17.6	16.6	11.1	13.9	10.1	6.8

Values are mean (SD) unless otherwise is indicated

Table 5.1.2 The association of body mass index, and physical activity levels with cardiovascular disease

		Events/n	**HR (95%CI)**
Body mass index	Normal weight	270/1765	1 (reference)
	Overweight	428/2535	1.13 (0.97-1.32)
	Obese	168/1044	1.20 (0.99-1.46)
Physical activity	High physical activity	367/2671	1 (reference)
	Low physical activity	499/2673	1.22 (1.06-1.40)

Analyses adjusted for age, gender, education, diet, alcohol and smoking. HR, hazard ratio; CI, confidence interval.

Table 5.1.3 The association between joint physical activity and body mass index subgroups with cardiovascular disease

		Events/n	HR (95%CI)
High physical activity	Normal weight	125/924	1 (reference)
	Overweight	179/1279	1.03 (0.82-1.30)
	Obese	63/468	1.12 (0.82-1.52)
Low physical activity	Normal weight	145/841	1.10 (0.86-1.40)
	Overweight	249/1256	1.33 (1.07-1.66)
	Obese	105/576	1.35 (1.04-1.75)

Analyses adjusted for age, gender, education, diet, alcohol and smoking. HR, hazard ratio; CI, confidence interval.

Table 5.1.4 The association of physical activity status with cardiovascular disease stratified by body mass index categories

		Events/n	HR (95%CI)
Normal weight	High physical activity	125/924	1 (reference)
	Low physical activity	145/841	1.17 (0.91-1.51)
Overweight	High physical activity	179/1279	1 (reference)
	Low physical activity	249/1256	1.27 (1.04-1.55)
Obese	High physical activity	63/468	1 (reference)
	Low physical activity	105/576	1.15 (0.83-1.60)

Analyses adjusted for age, gender, education, diet, alcohol and smoking. HR, hazard ratio; CI, confidence

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SUPPLMENT FOR CHAPTER 5.1

Supplement 5.1.1 The association between joint physical activity and body mass index subgroups with cardiovascular disease after taking in account competing risk

		Events/n	HR (95%CI)
High physical activity	Normal weight	125/924	1 (reference)
	Overweight	179/1279	1.06 (0.84-1.33)
	Obese	63/468	1.12 (0.83-1.51)
Low physical activity	Normal weight	145/841	1.02 (0.79-1.30)
	Overweight	249/1256	1.27 (1.02-1.57)
	Obese	105/576	1.30 (1.01-1.69)

Supplement 5.1.2 The association between joint physical activity and body mass index subgroups with cardiovascular disease in elderly (n=3238)

		Events/n	HR (95%CI)
High physical activity	Normal weight	96/524	1 (reference)
	Overweight	142/737	1.05 (0.81-1.36)
	Obese	54/259	1.24 (0.89-1.73)
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 (1.02-1.82)

Supplement 5.1.3 The association between joint physical activity and body mass index subgroups with cardiovascular disease after excluding first 2 years of follow-up

		Events/n	HR (95%CI)
High physical activity	Normal weight	101/924	1 (reference)
	Overweight	136/1279	0.97 (0.75-1.25)
	Obese	52/468	1.12 (0.80-1.56)
Low physical activity	Normal weight	114/841	1.13 (0.86-1.48)
	Overweight	187/1256	1.30 (1.02-1.66)
	Obese	82/576	1.33 (0.99-1.78)

5.2 Physical activity types and coronary heart disease risk in middle-aged and elderly persons

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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 5901 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 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=3011).[16] Of this combined total, 7,310 participants completed PA collection (see Figure 5.2.1). 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]

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 5.2.1 and the proportion of participants who reported engaging in the considered PA types is shown in Figure 5.2.2. The five most mentioned sports per gender are displayed in Supplement 5.2.1. 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.

Table 5.2.2 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 5.2.3). 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 5.2.2). Analyses split by gender revealed slightly stronger associations for women than for men, for total PA, cycling and domestic work (Supplement 5.2.3). 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 5.2.4-7). Stratifying our analyses by fatal and non-fatal CHD events indicated that the associations were stronger for fatal events (Supplement 5.2.8).

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] 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.

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.

Figure 5.2.1 Flow chart of participant inclusion for the Rotterdam Study, 1997-2012.

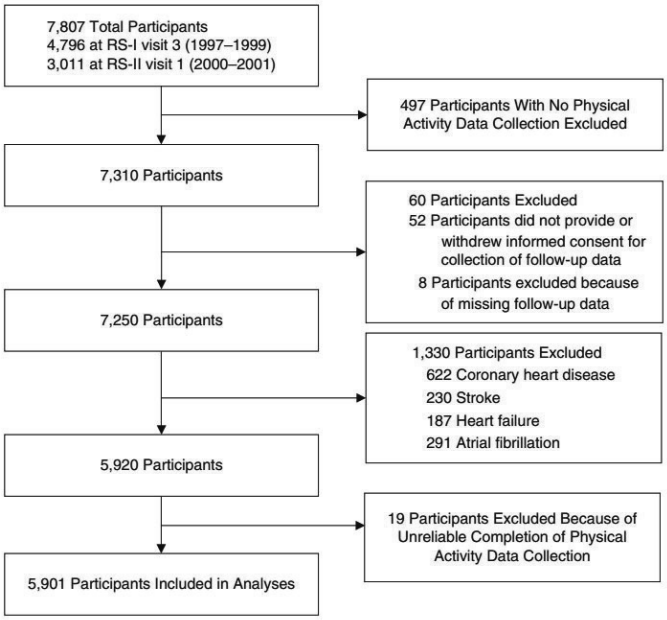


Figure 5.2.2 Proportion of participants by physical activity type for the Rotterdam Study, 1997-2012.

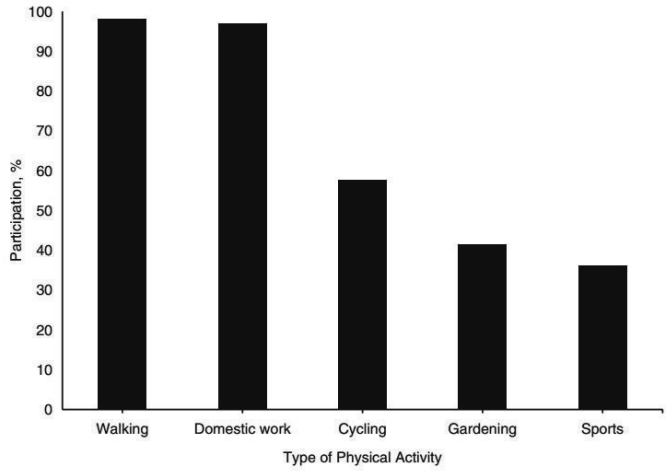
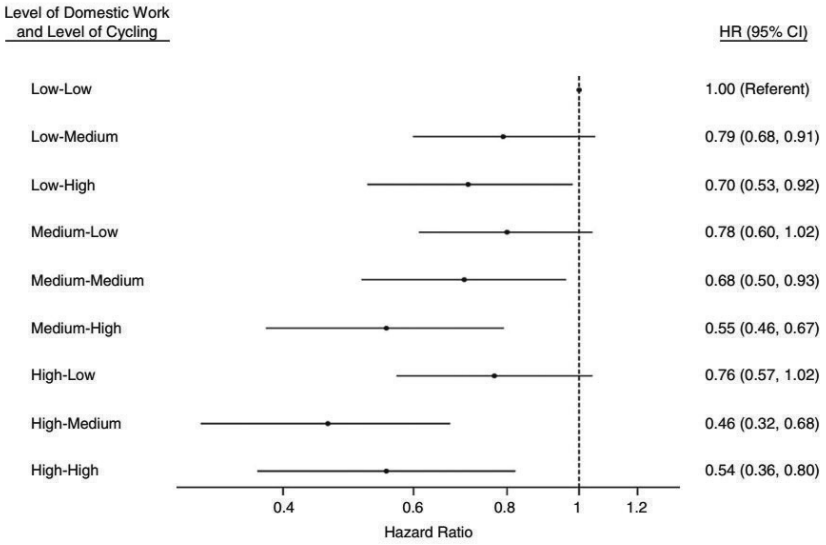


Figure 5.2.3 Hazard ratios and 95% confidence intervals of coronary heart disease for the combined domestic work and cycling variable in multivariable model 2, Rotterdam Study, 1997-2012.



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 5.2.1 Baseline Participant Characteristics by Tertile of Total PA, Rotterdam Study, 1997-2012

	Tertiles of total PA, MET·hours·week^{-1}		
Median (range)	**42.0 (<61.4)**	**77.5 (61.5-96.9)**	**126.7 (≥97.0)**
	Mean (SD)or %	**Mean (SD)or %**	**Mean (SD)or %**
Participants	1,967	1,968	1,966
Demographic factors			
Age, years	70.7 (9.7)	68.0 (7.7)	66.9 (7.0)
Female	46.6	66.0	71.9
Primary education	38.3	43.3	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	24.0	19.4	19.0
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	17.9	12.6	10.2
Using serum lipid reducing agents	7.8	10.9	9.2
Using anti-hypertensive medication with the indication of hypertension	24.3	25.0	20.5
Cardiovascular cases			
CHD event	13.8	9.9	8.9
Fatal CHD event, no.	7.1	3.7	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; SD, standard deviation.
a Weight (kg)/height (m)^2

Table 5.2.2 Association Between Total PA and Different Types of PA and CHD, Rotterdam Study, 1997-2012

Activity Type and Tertile of Physical Activity	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	1,967	272	1.00	1.00	1.00
2	1,968	195	0.76 (0.63, 0.92)	0.79 0.66, 0.96)	0.81 0.67, 0.99)
3	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	2,102	223	1.00	1.00	1.00
2	2,009	235	1.10 (0.92, 1.32	1.17 0.97, 1.41	1.16 0.96, 1.40)
3	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	1,967	280	1.00	1.00	1.00
2	1,970	203	0.78 (0.63, 0.95)	0.81 (0.66, 0.98)	0.81 0.66, 0.99)
3	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	2,488	324	1.00	1.00	1.00
2	1,871	182	0.73 (0.60, 0.88	0.76 (0.63, 0.92)	0.80 (0.65, 0.97)
3	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
Gardening[f]					
1	3,448	401	1.00	1.00	1.00
2	1,514	138	0.86 (0.70, 1.05	0.88 (0.71, 1.07)	0.90 (0.74, 1.10)
3	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	3,768	439	1.00	1.00	1.00
2	1,073	96	0.80 (0.64, 1.00	0.82 (0.66, 1.03)	0.84 (0.67, 1.05)

3	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.

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SUPPLEMENTAL FOR CHAPTER 5.2

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5.3 Physical activity types and life expectancy with and without cardiovascular disease

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ABSTRACT

Background: Higher levels of physical activity (PA) are associated with higher levels of total life expectancy (LE). Whether this effect differs by specific PA types remains unknown. We aimed to determine the contribution of specific PA types (i.e. walking, cycling, domestic work, sports and gardening) on total LE and LE with and without cardiovascular disease (CVD).

Methods: We constructed multistate life tables using data from the Rotterdam Study to calculate the effects of 3 levels of total PA (low, medium, and high) and PA types among populations older than 55 years. For the life table calculations, we used sex-specific prevalence, incident rates and hazard ratios for 3 transitions (healthy to death, healthy to disease, and disease to death) by levels of PA and adjusted for age, smoking, alcohol consumption, cancer and other PA types.

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 types of activity, 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 to also provide measures of the lifetime consequences of PA. Additionally, since individuals with prevalent CVD have 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 with 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 collecting information in the second half 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, in a population-based study of subjects 55 years and older, we aimed to evaluate the impact of total PA and PA types in the average years lived with and without CVD. We constructed multistate life tables using data collected from the year 1997 and with over 12 years of follow-up from the Rotterdam Study.

METHODS

Study population

This study was embedded within the Rotterdam Study, 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. The objectives and design of the Rotterdam Study have been described in detail elsewhere.[12]

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). Of this combined total, 7,310 participants completed PA collection. Subsequently, we excluded participants without informed consent (n=52) or without information regarding CVD follow-up (n=8). After exclusion, 7,254 participants (4,027 women) were available for the current analysis. Baseline information was collected through home interviews or was measured at the study centre visit as

described previously.[13,14] Information regarding the measurement of risk factors is provided as online supplementary material.

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. Questions on housekeeping activities were added in the current study.

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). If this was the case, we divided the time by two and computed a weighed estimate. Furthermore, the questionnaire contained one question in which participants could mention all the sports they practiced that were not captured by previous questions. If multiple sports were mentioned, we assumed that time spent in these sports was distributed equally.

To quantify the intensity of activity, we used metabolic equivalent of task (MET). We assigned MET-values to every activity provided 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 we could not assign a MET-value (e.g. under water hockey, "revalidation sports") were not used in the analyses (n=33; 2.8%).

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

Cardiovascular risk factors (covariates)

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". 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.

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.[15-17] 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.

Data analysis

We created multistate life tables to calculate the differences in LE and years lived with and without CVD in participants with low, medium and high levels of total PA and every type of PA. We constructed three different health states: free of CVD, CVD and death. The possible transition directions were from free of CVD to CVD, free of CVD to death and from CVD to death. No backflows were allowed, and only first entry into state was considered.[9,18]

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, for each tertile of every PA variable. Gender specific hazard ratios comparing high and medium PA categories to low PA for each PA variable were calculated using Poisson regression ("Gompertz" distribution) in 3 models.[9,15] 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.

Finally, the three sets of transitions rates were calculated for each tertile of total PA and every type of PA separately using the (a) overall sex-specific transition rates, the (b) adjusted hazard ratios (model 2) for CVD and mortality, and the (c) prevalence of PA by gender and absence or presence of CVD. Similar calculations have been described previously.[9,15] The multistate life table started at age 55 years and closed at age 100 years.

Confidence intervals for all life expectancies and their differences were calculated using @RISK software (Anonymous 2000; MathSoft Inc, Cambridge, Mass), by Monte Carlo simulation (parametric bootstrapping) 10 000 runs.[18,19]

To deal with missing values (less than 15%) for covariates we used 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 2,705 (33.0%) overall deaths over 10 years of follow-up. Compared to women, men at baseline were slightly younger and smoked more and showed lower levels of BMI and total PA levels (Table 5.3.1).

Hazard ratios (HRs) of men and women were very similar. Therefore, Table 5.3.2 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 5.3.1. Sex-specific HRs used for the analyses are presented in Supplement 5.3.2 and 5.3.3. 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 5.3.2). Compared to the low categories, the largest risk reductions were observed for the high categories of cycling, domestic work and gardening (Table 5.3.2).

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 5.3.3). 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 5.3.3). 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 physical activity, 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 5.3.3).

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.

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.

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 increased LE without CVD among men and women with higher PA levels was due to decreased risk of CVD and mortality. The lower risk for CVD is reflected by a delayed occurrence of CVD over the lifespan and therefore, an increased LE without CVD. Furthermore, the lower mortality risk in those without history of CVD resulted in an increase in the total number of years lived and consequently in 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, and mortality risk in those with CVD. 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.[3,20] Moreover the reduction in mortality risk among persons without history of CVD associated with total PA, is in line with previous studies.[21,22] Our results also confirm that total PA reduces mortality in persons with a history of CVD.[21,23,24] 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.[25] Additionally, a study within the Whitehall population reported similar HRs for all-cause mortality for cycling, sports and gardening.[26] In this study, domestic work did not reduce mortality risk, which might be related to the slightly younger participants (mean age 56 years). 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 patients 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.[25,27-31] Moreover, whereas the World Health Organization recommends to engage in 30 minutes of PA, 5 days a week, to gain health benefits,[32] 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,[33] 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.[34]

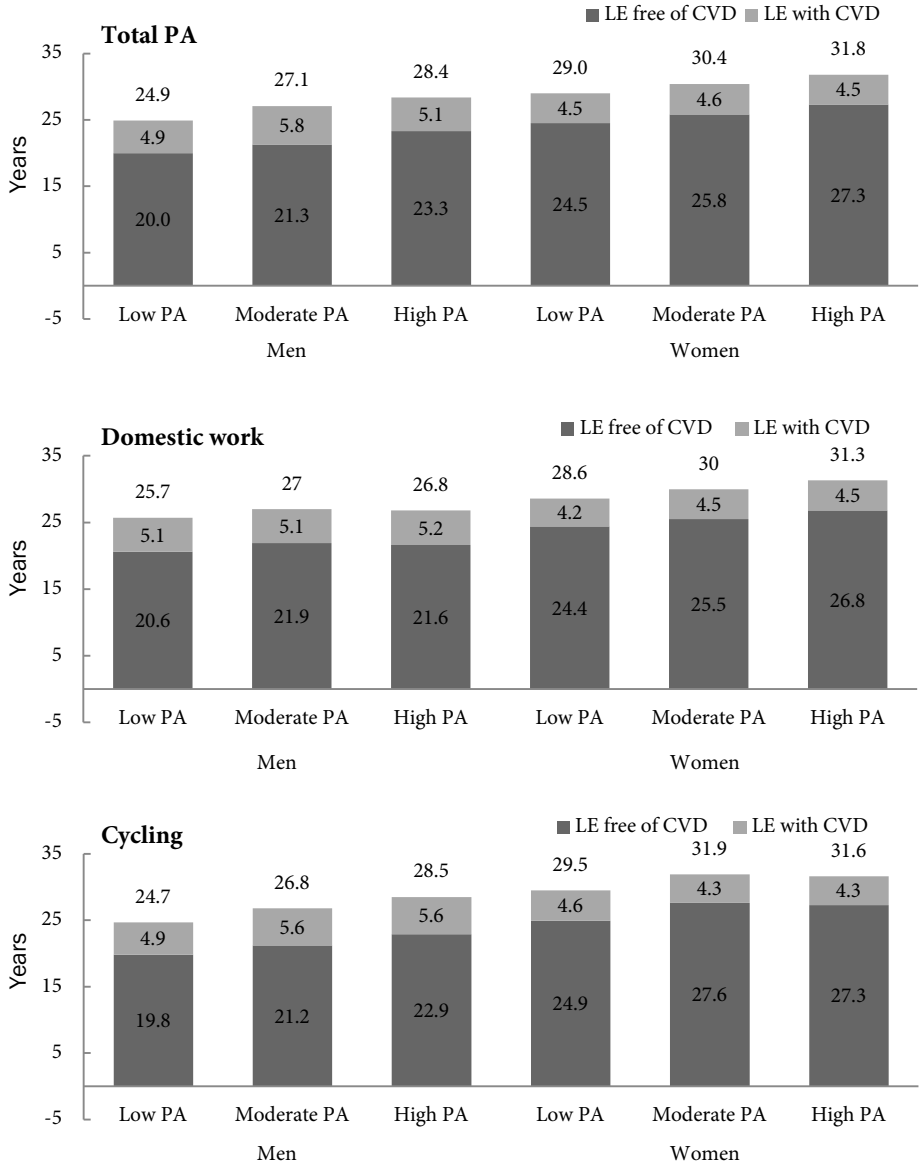
This study has some limitations. First, we collected no information about occupational PA, so we could not adjust for this in our main analyses. However, since only 11.5% was employed at baseline, we do not believe this would have significantly influenced our results. Second, we only measured PA at baseline, which can cause misclassification of PA over time. Moreover, our results are based on self-reported PA. Although our questionnaire has shown to be valid and reliable[35] potential recall bias and social desirability cannot be excluded. These last two limitations could have resulted in bias towards the null hypothesis. Finally, it may be hypothesized that people in poor health participate in PA less than others, creating the opportunity for reverse causation. However, we adjusted diabetes and hypertension in our third model and observed no major changes in the HRs.

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

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.

Figure 5.3.1 Effect of physical activity on life expectancy with and without cardiovascular disease (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 physical activity types were additionally adjusted for the other physical activity types. CVD indicates cardiovascular disease.

Table 5.3.1 Baseline characteristics of study population (n=7254)

	Men	**Women**
Participants	3,047 (42.0%)	4,207 (58.0%)
Demographic factors		
Age	69.3 ±8.1	70.7 ±8.9
Educational level		
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		
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		
Never	743 (24.4%)	2,551 (60.6%)
Former	1,779 (58.4%)	1,231 (29.3%)
Current	525 (17.2%)	425 (10.1%)
BMI, kg/m^2	26.5 ±3.2	27.4 ±4.2
Alcohol		
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	707 (23.2%)	1,143 (27.2%)
Using lipid reducing agents	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)
Family history of diabetes	234 (7.7%)	319 (7.6%)
Prevalent CVD	726 (23.8%)	536 (12.7%)

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

Table 5.3.2 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**
Number of events		1156	1569	1136
Total population		5982	5982	2220
	Median (Range) (MET-hours per week)	Model 2[a]	Model 2[a]	Model 2[a]
		HR (95% CI)	HR (95% CI)	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. 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.

Table 5.3.3 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 and 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)†
Men						
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)

Women						
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 hazard ratios adjusted for age, sex 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

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SUPLEMENT FOR CHAPTER 5.3

Supplement 5.3.1 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	**1156**		**1569**		**1136**	
Total population	**5982**		**5982**		**2220**	
	Model 1[a]	**Model 3[b]**	**Model 1[a]**	**Model 3[b]**	**Model 1[a]**	**Model 3[b]**
Total PA[c]						
Low	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	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	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	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	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	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	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	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	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	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	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	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	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	0.80 (0.67,0.94)	0.86 (0.72, 1.02)	0.77 (0.67,0.90)	0.83 (0.71,	0.80 (0.67,0.96)	0.81 (0.67, 0.98)

	No CVD to CVD		No CVD to death		CVD to death	
Number of events	**1156**		**1569**		**1136**	
Total population	**5982**		**5982**		**2220**	
	Model 1[a]	**Model 3[b]**	**Model 1[a]**	**Model 3[b]**	**Model 1[a]**	**Model 3[b]**
				0.97)		
High	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)
Gardening[h]						
Low	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	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	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. 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 5.3.2 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**		
Total population	**2319**			**2319**			**1118**		
	Model 1[a]	**Model 2[b]**	**Model 3[c]**	**Model 1[a]**	**Model 2[b]**	**Model 3[c]**	**Model 1[a]**	**Model 2[b]**	**Model 3[c]**
Total PA[d]									
Low	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	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	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	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	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	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	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	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	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	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderat	0.92 (0.74,1.	0.88 (0.71,1.	0.88 (0.71	0.89 (0.75,1.	0.83 (0.70,0.	0.82 (0.68	0.92 (0.76,1.	0.92 (0.76,1.	0.95 (0.78, 1.15)

	No CVD to CVD			No CVD to death			CVD to death		
Number of events	**487**			**678**			**574**		
Total population	**2319**			**2319**			**1118**		
	Model 1[a]	**Model 2[b]**	**Model 3[c]**	**Model 1[a]**	**Model 2[b]**	**Model 3[c]**	**Model 1[a]**	**Model 2[b]**	**Model 3[c]**
e	13)	08)	, 1.09)	06)	99)	, 0.99)	11)	11)	
High	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	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	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	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	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	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	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. 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 5.3.3 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**		
Total population	**3663**			**3663**			**1102**		
	Model 1[a]	**Model 2[b]**	**Model 3[c]**	**Model 1[a]**	**Model 2[b]**	**Model 3[c]**	**Model 1[a]**	**Model 2[b]**	**Model 3[c]**
Total PA[d]									
Low	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	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	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	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	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	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	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	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	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	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderat	0.97 (0.76,1.	0.99 (0.77,1.	0.98 (0.76	0.79 (0.65,0.	0.77 (0.63,0.	0.74 (0.60	1.03 (0.83,1.	0.98 (0.79,1.	0.96 (0.76, 1.21)

	No CVD to CVD			No CVD to death			CVD to death		
Number of events Total population	**669 3663**			**891 3663**			**562 1102**		
	Model 1[a]	**Model 2[b]**	**Model 3[c]**	**Model 1[a]**	**Model 2[b]**	**Model 3[c]**	**Model 1[a]**	**Model 2[b]**	**Model 3[c]**
e	24)	26)	, 1.27)	96)	93)	, 0.90)	28)	23)	
High	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	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	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	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	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Moderate	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	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. 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.

Chapter 6

General Discussion

The main aim of this thesis was to extend the existing knowledge on the relation between obesity and physical activity with cardiovascular disease (CVD) in the elderly. The first objective was to evaluate the role of traditional and novel anthropometric measures in prediction of CVD and mortality and to examine their correlation with fat and fat-free mass. The second objective was to assess the role of obesity, independently of metabolic syndrome, in association with CVD. Also, we evaluated the association of timing and duration of overweight with the risk of metabolic syndrome and with diabetes. The third objective was to calculate the contribution of obesity on total life expectancy and life expectancy with and without CVD, and additionally to identify the trajectories of body mass index (BMI) change prior to a CVD event. The final objective was to evaluate the joint effects of physical activity and BMI in association with CVD. Moreover, we aimed to address which type of physical activity contributes the most to decrease the risk of CVD and improve survival in the elderly population. All the studies in this thesis were conducted within the framework of the Rotterdam Study, a population-based cohort study among subjects aged 55 years and older.

In this chapter the main findings of this thesis are summarized. Furthermore, methodological considerations of these studies are addressed. Finally, potential clinical implications of the findings together with directions for future research are discussed.

MAIN FINDINGS

Anthropometric measures of general and central obesity in the elderly population

Among different anthropometric measures, most of the previous studies have focused on BMI in association with morbidity and mortality. While BMI is a widely accepted and an easily applicable measure of obesity, its use has limitations.[1] BMI only depends on height and weight and does not distinguish between the distribution of adipose tissue and muscle mass.[2,3] Furthermore, the relation between BMI and mortality has shown to be contradictory.[4] Therefore, to overcome these limitations, international guidelines advocate for the routine measurement of waist circumference (WC) and waist-to-hip ratio (WHR) in the assessment of adiposity to predict the mortality risk.[5] Additionally, recently new anthropometric measures, such as a body shape index (ABSI=WC/(BMI2/3×height1/2)) and waist-to-height ratio (WHtR) have been developed.[6] In chapter 2.1, I studied the association of BMI, WC, WHtR, WHR and ABSI with total, cardiovascular and cancer mortality in the elderly. Among the presented anthropometric measures, ABSI showed to have the strongest association with death from any cause in men and women, death from CVD in men, and death from cancer in women. However, the addition of ABSI to the model with traditional risk factors did not improve the c-statistic and provided only a modest improvement in model fit and risk stratification. These findings suggest that among the elderly ABSI, as a measure of body shape, could provide a better assessment of mortality risk than other traditional anthropometric measures.

We then explored the association of anthropometric measures with risk of CVD in chapter 2.2. BMI has been used to simplify cardiovascular risk prediction models by substituting total cholesterol and high-density lipoprotein cholesterol.[7] Recognizing the limitations of BMI to assess the risk of CVD in the elderly,[3] we aimed to find the anthropometric measure that could be most predictive for CVD risk. The most predictive anthropometric measure was the selected and used

to construct a non-laboratory-based model. We then compared this model with the model including laboratory measurements. In this chapter, we showed that among different anthropometric measures ABSI was the most informative anthropometric measure in prediction of CVD. In men, we demonstrated that a non-laboratory-based model including ABSI could predict CVD as accurately as the laboratory-based model including the lipid profile. In clinical settings where blood testing is inconvenient or unavailable, use of the non-laboratory-based model, which requires measurement of ABSI instead of lipids, could predict CVD risk as accurately as the laboratory-based model among middle-aged and elderly men.

In chapter 2.3 we addressed the association of BMI, WC and ABSI with fat and fat-free mass. In the elderly, the decrease in fat-free mass is usually associated with an increase in fat mass, a state referred to as sarcopenic obesity.[8,9] We aimed to evaluate which anthropometric measures are differentially associated with fat mass and fat-free mass and could therefore be used to identify individuals at risk of sarcopenic obesity. Our study demonstrated that while BMI and WC were both positively associated with fat mass and fat-free mass, ABSI provided a differential association with fat mass and fat-free mass in males. We showed that in men, ABSI was positively associated with fat mass, and negatively associated with fat-free mass. Since sarcopenic obesity is associated with increased fat mass and decreased fat-free mass, ABSI could be considered as a useful tool for identifying males at higher risk for sarcopenic obesity.

Overweight, obesity and metabolic health risk

One reason for the major impact of obesity on the development of CVD is that it often is accompanied by the metabolic syndrome; a cluster of dyslipidemia, hyperglycemia, and hypertension.[10] However, not all obese individuals display the presence of metabolic syndrome, which indicates that the risk of CVD could be different among obese subjects without metabolic syndrome. In this context, recent interest has focused on this subgroup of obese individuals, named metabolically healthy obese (MHO).[11,12] Whether being MHO is associated with CVD remains unclear and may depend on the age of the participants. Therefore in chapter 3.1 we examined the association of MHO with CVD among the elderly. We found that MHO individuals do not have a higher CVD risk, compared to normal weight individuals without metabolic syndrome. Presence of metabolic syndrome was strongly associated with the risk of CVD, and explained the increased CVD risk in all BMI categories. Therefore, this study suggests that preventive interventions targeting cardio-metabolic risk factors should be considered for the elderly, regardless of their weight status.

It is currently unclear why some overweight individuals appear to be resistant to the development of metabolic syndrome regardless any excess of body fat. One possibility is that history and duration of overweight could impact the development of metabolic syndrome.[13,14] Additionally, the age at which individuals start to gain weight (i.e. timing of weight gain) might play a role in increasing the metabolic risk. Therefore, in chapter 3.2 we evaluated the association of timing and duration of overweight with metabolic syndrome and with diabetes. This study revealed that the onset of overweight during middle-age conferred a higher risk for metabolic syndrome than the onset of overweight later in life. Furthermore, the duration of overweight, in particular being persistently overweight, increased the risk of metabolic syndrome and diabetes. Additionally, individuals who experienced fluctuating overweight during follow-up were at higher risk for

diabetes. This study demonstrated the importance of timing and duration of overweight as a determinant of metabolic risk in the elderly.

Obesity, cardiovascular disease and mortality

More than 100 epidemiologic studies have already examined the association between obesity, cardiovascular disease and mortality.[3,4] However, very few have quantified the life years lost due to obesity.[15,16] From a public health prospective, it is important to provide information beyond measures of relative risk, and to focus on the lifetime consequences of excess weight, such as years lived with and without CVD. In chapter 4.1, we evaluated the impact of overweight and obesity (as a function of BMI) on total life expectancy and the number of years lived with and without CVD. We showed that total life expectancy for obese men and women at age 55 years was not significantly different from normal weight individuals. However, obesity was associated with fewer number of years lived free of CVD and extended the number of years lived with CVD. Our study suggests that owing to the increasing prevalence of obesity, as well as improved treatment of CVD, we could expect more individuals living with CVD in future and for a longer period of time. From a public health prospective, this will have a profound impact on increasing costs of healthcare.

Although we showed in chapter 4.1 that obese individuals are at higher risk for developing CVD during the lifespan, CVD is not limited to obese individuals.[17] Indeed, patients with CVD comprise a heterogeneous group with regard to their BMI levels at the time of diagnosis. Exploring the patterns of change in BMI before the diagnosis of CVD, could have important implications for improving disease prevention and treatment. Therefore, in chapter 4.2, using latent class trajectory analysis, we explored the heterogeneity of change in BMI before the diagnosis of CVD. Latent class trajectory analysis is an innovative statistical method used to identify subgroups (classes) of individuals who are homogeneous with respect to the trajectory of one specific risk factor but heterogeneous as compared with other subgroups.[18] By using this method, in our study we identified three distinct trajectories of change in BMI before the diagnosis of CVD. Moreover, the identified BMI patterns were accompanied by different trajectories of other cardio-metabolic risk factors, which highlight the heterogeneity in development of CVD. Notably, the majority of individuals who developed CVD had a stable weight during follow-up, suggesting that BMI alone is not a good indicator for identifying middle-aged and elderly individuals at high risk of CVD. Waist circumference, HDL cholesterol, and glucose trajectories differed between the identified BMI subgroups, further highlighting that CVD is a heterogeneous disease with different pathophysiological pathways.

Obesity, physical activity and cardiovascular disease

Although overweight and obese individuals have a greater risk for CVD compared to normal weight individuals, this could partly be explained by their reduced physical activity levels.[19,20] Higher levels of physical activity are associated with lower risk of CVD. Hence, physical activity might reduce the burden of CVD risk associated with overweight and obesity. These findings have led to the identification of the "fat but fit" phenomenon and raised the question to what extent physical activity can counterbalance the risk associated with overweight and obesity. In chapter 5.1 we evaluated the joint effects of physical activity and BMI with the risk of CVD. We

showed that individuals who engage in higher levels of total physical activity are not at increased risk of CVD, regardless of being in overweight or obese. In contrast, overweight and obese individuals with lower total physical activity levels were at significantly increased risk of CVD. Additionally, the CVD risk was comparable between inactive normal weight participants and active obese participants. These findings on the one hand explain why some overweight and obese individuals are not at high risk of CVD, and on the other hand highlight the importance of promoting physical activity levels among overweight and obese individuals.

Most of the studies on the association of physical activity with CVD and with mortality are primarily focused on the effect of overall leisure time physical activity.[21] Therefore, it remains unclear what specific physical activity types contribute most to the beneficial effects of physical activity. Moreover, studies on this subject have generally assessed the associations only in terms of hazard ratios of the event.[22] These measures of association do not allow for the translation of results for public and individual health care planning. Complementing current knowledge with absolute measures such as life expectancy has been extensively recommended. Therefore, in chapter 5.2 we examined the association between physical activity types (i.e. walking, cycling, sports, domestic work and gardening) with coronary heart disease (CHD). Subsequently and in chapter 5.3, we assessed the impact of total physical activity on the average years lived with and without CVD. We showed that domestic work and cycling were the specific physical activity types strongly associated with decreased CHD risk (chapter 5.2) and were independently associated with large increases in total LE, and extending LE without CVD (chapter 5.3). Engaging in both cycling and domestic work resulted in a greater risk reduction than performing either activity alone. Our results therefore suggest focusing public health efforts on promoting physical activity -in particular cycling and domestic work- among the elderly with the aim to prevent future CVD events and improve survival.

METHODOLOGICAL CONSIDERATIONS

Assessment of obesity

The most common method of measuring overweight and obesity is the body mass index (BMI). The concept of BMI - a simple ratio of weight in relation to height - was developed by a Belgian statistician, Adolphe Quetelet, who published his "Quetelet Index" in 1832. In 1995, the World Health Organization (WHO) adopted it as a tool to determine the level of obesity. According to the WHO, an individual with a BMI of 30 or more is considered obese, and having a BMI equal to or more than 25 is considered overweight.[23] BMI has proven to be an invaluable tool for identifying individuals at increased risk of type 2 diabetes, cardiovascular disease, some types of cancer and mortality.[24] Although BMI is an easy measure of obesity, it is apparent that BMI does not take into account the distribution of body fat.[25] Body fat and fat distribution vary according to age, gender, ethnicity and level of physical activity.[26] Therefore, two individuals with exactly the same BMI can have very different patterns of body fat distribution and consequently a different risk of developing type 2 diabetes and cardiovascular disease. Another drawback of using BMI is that it doesn't always change even in situations in which the individuals are getting healthier. This is particularly for individuals who adopt a physically active lifestyle, along with a balanced diet, but are not necessarily cutting their total calorie intake. This lack of change in BMI or body

weight is too often interpreted as a failure, resulting in disappointed individuals resuming their inactive lifestyle and unhealthy eating patterns.[27]

The WHO recommends to use waist circumference (WC) and waist-to-hip ratio (WHR) as alternatives to BMI to assess the risk of cardio-metabolic disorders, since they are better correlated with abdominal fat distribution.[28] However, a key limitation of using WC is that it is sensitive to body size (height and weight) as well as to fat percentage and distribution. In the measurement of WHR, a disproportionately large hip circumference can hide the status of abdominal obesity.[29] While WC is a single measure and relatively easy to interpret, the clinical interpretation of WHR is quite complicated, because it is the ratio of two variables. A higher WHR could be the result of an increased WC or a reduced hip circumference.[29] Hip circumference is a reflection of pelvic width and is related to subcutaneous fat, greater gluteal muscle mass, or larger bone structure. Research has shown that in the elderly, a higher WHR may be an indicator of visceral obesity combined with muscle loss. Moreover, compared to BMI, WC and WHR are prone to errors during measurements, because of the high variability between the technicians. Therefore it is recommended that the measurement of WC and WHR should be performed by the same person.

Recently, a new anthropometric measure, a body shape index (ABSI), has been introduced. ABSI has been derived from WC and is independent of weight and height.[6] A high ABSI is an indication of a higher WC than expected for a given height and weight. Therefore, being correlated with WC but independent of weight and height, ABSI could have a differential association with morbidity and mortality that cannot be distinguished by BMI and WC alone. However we should acknowledge that ABSI is a relatively new measure, not validated widely across different populations, ethnicities, and age groups in relation to different outcomes. There is also no valid cut-offs for ABSI to label individuals as high risk for CVD or mortality.

Assessment of physical activity

Questionnaires are the most commonly used method to measure physical activity in large epidemiologic studies because they are practical, inexpensive, and put a low burden on participants. Questionnaires measure duration, frequency, and intensity of physical activity, and this information is obtained through interview (or computerized questionnaires) and is reported as activity scores or calories.[30] The advantages of questionnaires include cost effectiveness and ease of administration.[31] However, they also have well-recognized limitations. Self-reporting physical activity through questionnaires might be a cognitive challenge for many people, especially in the elderly.[32] Therefore, data obtained from questionnaires are prone to both random and systematic errors.[33] In general, subjects tend to over report physical activity and underreport sedentary behaviors that are influenced by cultural and social desirability factors. Although, most physical activity questionnaires have been developed and tested for their reproducibility and validity, the major drawback in physical activity questionnaire validation is lack of a true gold standard.[34]

In the Rotterdam Study physical activity was assessed with an adapted version of the Zutphen Physical Activity Questionnaire.[35] This questionnaire has been validated in which the test-retest reliability was 0.93 and the correlation with doubly labelled water was 0.61. The original Zutphen questionnaire contains questions regarding walking, cycling, sports, gardening and hobbies.[36] In

the Rotterdam Study questions on housekeeping activities were added to attain a more complete assessment of physical activity levels. 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. sports, gardening). Then we calculated a weighted estimate by dividing the reported time by two. 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.[36]

Reverse causality

Observational studies, which comprise the majority of epidemiologic studies, might be prone to bias when it comes to reverse causality. Reverse causation is a process in which the disease occurs before the occurrence of the risk factor and the risk factor is present as a result of the disease.[37] This is particularly important when interpreting results from the cross-sectional studies, in which the direction of the association cannot be established. It is well-known that obese individuals tend to reduce physical activity and increase sedentary behaviors.[38] Therefore, a cross-sectional relationship between physical activity and obesity could be biased due to reverse causation. As such, it is difficult to disentangle the true relation between obesity and physical activity in a cross-sectional study. Prospective studies of physical activity and obesity can diminish the issue of reverse causation by measuring baseline physical activity before assessment of outcome.[32] Nonetheless, reverse causation cannot be totally eliminated.[32] Therefore, our concurrent analyses of changes in physical activity and body weight might also be prone to reverse causation, since people who are gaining weight may subsequently reduce physical activity during follow-up.

Reverse causality could also be present when we study the association of obesity with mortality among the elderly, even in longitudinal studies such as the Rotterdam Study. Due to the relatively high prevalence of comorbidities among the elderly, there is a high chance for reverse causation. In this regard, older adults could have a different level of BMI because of their comorbidities, and this latter could also increase their mortality risk. Among the elderly, the artificial elevation of mortality in the lean group, as the result of reverse causation, could lead to an underestimation of the impact of overweight and obesity on CVD and mortality. To minimize the effect of reverse causality, it is warranted to examine the association between obesity and mortality with longer follow-up and to evaluate the associations after excluding the first 5 years of follow-up. In chapter 2.1 of this thesis when we studied the association of anthropometric measures with mortality we excluded deaths during the first 5 years of follow up to account for reverse causality. Another strategy that has been shown helpful to control for and to correct for the possible reverse causation is to stratify the analyses by physical activity level. Since prevalence of clinical and subclinical co-morbidities among physically active people is lower, analyses limited to individuals who are (adequately) physically active might be less prone to reverse causation.

Survival bias

Prospective cohort studies with multiple follow-up visits could be prone to survival bias. Survival bias is present in the studies that assess the effect of an "exposure" on survival or any other failure time, when the classification of "exposed" subjects requires that a person survives until the date

he/she is included in the study.[39] Evaluating an association at specific visit at follow-up, in fact includes only individuals who survived up to that visit. Survival bias of this nature impacts the relative risk estimates and generalizability of the study.[40] In this regard, the population studied will consist of individuals who are generally at lower risk than the general population. Consequently, the prognosis of this group will be better and not representative of the general population.[40] However, survival bias could be a problem when conducting a cross-sectional study and may not be an important issue in longitudinal studies.[41] In cross-sectional studies, healthy individuals are compared with individuals with prevalent diseases who survived this disease. In contrast, individuals who die soon after the onset of disease are never included in cross-sectional studies. In particular, if the exposure of interest is related to the prognostic factors, or if the exposure of interest itself is a prognostic determinant, the sample of cases contains a distorted frequency of the exposure. In longitudinal studies, participants with prevalent diseases are excluded at baseline, where after we use statistical methods (such as Cox proportional hazard models), to estimate the risk of developing a disease over time.[42] In this thesis, our data allowed us to conduct longitudinal studies and to use Cox Proportional Hazards analysis. However, in one study (Chapter 3.2) that we conducted the cross-sectional analysis we mention the limitation of survival bias.

Loss to follow-up due to refusal to participate in subsequent visits or withdrawals may also be a source of bias in cohort studies. This might introduce a significant bias if the loss to follow-up or withdrawals are different for different exposure categories (e.g. different categories based on obesity). For example, subjects may be more inclined to return for a follow-up examination if they have developed symptoms of the disease. This tendency may be different in the exposed and unexposed, resulting in an over- or under-estimation of the true effect.

Residual confounding

In observation studies, association between exposure and outcome could be biased because of confounding. Confounding can be caused by variables that are associated with both outcome and exposure and are not on the pathway between exposure and outcome.[43] When the confounder is not considered in analysis or cannot directly and accurately observed in study will lead to residual confounding.[43] Since out work presented in this thesis uses observational design could be prone of residual confounding. Anthropometric measures were measured by trained staff indicating that are less chances of residual confounding. However, the association between anthropometric measures and outcomes studied in this thesis are influenced by a number of lifestyle factors. For example, physical activity and diet will influence the weight status (i.e. obesity) and the body composition as described previously[44,45] and shown in Chapter 5.1. In the Rotterdam Study, physical activity and diet are measured through questionnaires. Questionnaires are prone to measurements error, and the measurements error in part could lead to residual confounding.[46] However, the measurement error per se is not a major issue for residual confounding, but the unmeasured confounders would play a significant role in residual confounding.[46] Although in the Rotterdam Study we have collected most of factors which might contribute as confounders in association between a exposure and outcome, residual still can be pressed in observed associations in this thesis.

Risk prediction

Risk prediction models have been used in clinical practice to identify individuals at high risk for developing CVD and to select those individuals for more intensive preventive interventions.[47] Traditional risk prediction models calculate a score for each individual based on the levels of risk factors (i.e. age, sex, total cholesterol, high-density-lipoprotein cholesterol, systolic blood pressure, smoking status).[48] The computed risk score is then converted into an absolute probability of developing CVD within a certain time frame. Researchers have conducted different studies to improve the performance of traditional risk prediction models by adding other novel risk factors to the model.[49,50] Other researchers aimed to simplify the traditional risk prediction models without sacrificing the performance of the model by substituting total cholesterol and high-density-lipoprotein cholesterol with BMI.[7] In their efforts to improve upon the existing models, some researchers fit the exact intercept and coefficients from the existing risk prediction models into their population. Since the models are fit for purpose in their development set, they might consequently not perform well in the new study. Therefore, if the new (updated) model is built using the new study data, including its own intercept and coefficients, it will outperform the old model. As such, the direct comparison between the two models is also not possible. As part of this thesis (Chapter 2.2) we compared the predictive performance of the traditional risk prediction model (laboratory based) in comparison with a simplified model (non-laboratory). We used data from the Rotterdam Study to develop both models (laboratory and non-laboratory based). Therefore, the intercept and coefficients required for model fit were both based on our population. This method allowed us to make an unbiased head to head comparison of the two models. However, the results might be specific for the current population study, limiting the generalizability of our findings. When interpreting the results regarding model improvement, one should also note the differences in gender and age ranges as well as other characteristics of various studies.

In this thesis, we evaluated the performance of non-laboratory based model in comparison with laboratory based model in middle-aged and elderly population. The predictive performance of the two models was assessed by studying discrimination and calibration.[51] Discrimination is the ability of a prediction model to assign a higher risk to individuals who will develop an event compared with those who will not develop an event. To quantify the discrimination the c-statistic test is used. A value of the c-statistic equal to 0.5 refers to no discriminative ability; a value of 1 means that the model is able to perfectly separate events from nonevents. The c-statistic equals the area under the receiver operating characteristic (ROC) curve for dichotomous outcomes. The ROC curve is a plot of sensitivity versus 1-specificity (often called the false-positive rate) that offers a summary of sensitivity and specificity across a range of cut points for a continuous predictor. Sensitivity in this context refers to the probability of being correctly classified at high risk given that an event occurred during the follow-up.[52] Similarly, specificity refers to the probability of being classified as not at high risk (i.e. as low risk) given that a person did not experience an event during follow-up. Calibration is the agreement between the predicted probabilities of the disease, based on the risk prediction models, and the actual incidence of events in the population.

Multistate life tables

In cohort studies, participants switch between different health statuses through follow-up time, sometimes leaving and then returning to the same health status. Such changes in health status

includes switching to smoking for nonsmokers; hypertension for normotensives; and change between healthy and disease states ending in death by different causes. Multistate life table is an appropriate and useful method to properly describe the complex transitions back and forth among multiple states measured in cohort studies.[53] These movements or transitions from one state to another form the fundamental concept underlying the multistate life table models.[53] However, for some states the transition is irreversible. In this thesis, our analysis on evaluating the effect of obesity on life expectancy with and without CVD can serve as an example: for this analysis we included 3 different states: "free of CVD", "history of CVD," and "death". The possible transitions were (I) from free of CVD to history of CVD, (II) from free of CVD to death, and (III) from history of CVD to death. No backflows were allowed and only the first entry into a state was considered.[54]

The construction of multistate life table consist of 3 steps. First, we needed to assess the risk associated with the exposure, such as overweight and obesity in our study, for each of the three transitions. Hazard ratios for overweight and obese individuals, compared with normal weight subjects, were calculated for death without prior cardiovascular disease, for CVD incidence, and for death among individuals with a history of cardiovascular disease. In our study, we calculated hazard ratios by performing Poisson regression (Gompertz distribution) and adjusting for potential confounders. Second, we calculated age- and sex-specific transition rates for each of the transitions involved. Third, we calculated the prevalence of normal weight, overweight and obese for different categories of gender and presence of cardiovascular disease. In this thesis (chapter 4.1 and chapter 5.3) we conducted a multistate lifetable analysis to evaluate the impact of overweight and obesity on the average years lived with and without CVD.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Practical implications

The ultimate goal of obesity and physical activity research is to improve the current guidelines, diagnostic models and therapeutic practices for cardio-metabolic disorders. In this thesis, we provided evidence that compared to traditional anthropometric measures (i.e. BMI, WC and WHR), ABSI showed the strongest association with cardiovascular disease, cardiovascular mortality, cancer mortality and all-cause mortality.[55,56] Additionally, we reported that ABSI could identify individuals at higher risk for sarcopenic obesity. Since ABSI is a measure of body shape, these findings indicate the importance of body composition and fat distribution among elderly individuals. Accurate measurement of the amount and distribution of body fat requires advanced imaging methods, including dual X-ray absorptiometry (DXA), which in most of cases is not available in clinical practice.[57] Therefore, ABSI could be a useful tool for measuring the adiposity in epidemiological studies and in clinical practice. Individuals with higher ABSI typically have apple-shaped bodies, meaning they have a larger waist circumference for a given weight and height.[6]

We provided new insights for a unique subgroup of obese individuals, who are metabolically healthy despite their increased adiposity.[12] While showing that metabolically healthy obese individuals are not at increased risk of CVD, we provided evidence that this observation could be explained by the poor predictive ability of BMI. Indeed, our study showed that among the elderly,

71.3% of the association between BMI and CVD was explained by the presence of other metabolic factors. Moreover, we showed that metabolically healthy obese is not a permanent state but rather a transient phase, moving towards metabolic abnormalities.[58] Therefore, in clinical setting, we suggest to evaluate metabolic factors regardless of the weight status of the individuals. Moreover, clinicians should not promote the metabolically healthy obese phenotype as a safe state; instead they are encouraged to re-evaluate the metabolic status on a regular basis.

Moreover, when we assessed the impact of obesity on CVD, we translated our results into more relevant and intuitive clinical measures such as the difference in survival time.[54] This facilitates conveying our findings to the general public and further simplify the public health implications of obesity on a population level. Our study indicated that while obesity did not impact total life expectancy, it was associated with fewer number of years lived free of CVD and extended the number of years lived with CVD. Therefore, from a public health prospective, we could expect more individuals living with CVD in future and for a longer period of time, which will have a profound impact on increasing costs of healthcare.

Finally, this thesis provided evidence that physical activity, in particular combination of different types of activity, may help to reduce CVD risk associated with being overweight and obese. We showed that besides the beneficial effect of total physical activity, in particular, engaging in cycling (leisure physical activity) and domestic work (non-leisure physical activity) will result in reduction of CVD risk.[59] Therefore, public health efforts on CVD prevention should target promoting a combination of different types of physical activity.

Future research directions

The findings of our study on the association between ABSI and CVD and mortality in middle-aged and elderly provide implications for further research. Our results call for further studies investigating the association of ABSI with CVD and mortality across different age groups. Further efforts should also aim to provide cutoffs to identify individuals at high risk of morbidity and mortality based on ABSI values.

In this thesis, we also provided evidence that MHO phenotype is not a permanent state but rather a transient phase, moving towards metabolic abnormalities. Therefore, we suggest to re-evaluate the metabolic status on a regular basis. Future research should aim to address the question of how frequently (i.e. every 2 years, 4 years, etc.) reassessment of the metabolic status should be occurring in order to efficiently prevent future risk associated with metabolic abnormalities.

We translated the relative risk of associations between obesity and CVD into more relevant and clinical intuitive measures such as the difference in survival time. We computed multistate lifetables to calculate the years lived with and without CVD in normal weight, overweight and obese individuals. Our results promote the use of this approach(e.g., multistate lifetables) in young adulthood and in different populations and in relation to different common disorders to facilitate positioning the findings into a more relevant framework for public health policy and programs.

Finally, physical activity showed to counterbalance CVD risk associated with overweight and obesity. Our study indicated that individuals who are engaged in higher levels of total physical activity are not at increased risk of CVD, regardless of being in the overweight or obese category.

Future studies should focus on examining the effects of overweight and obesity duration on health, while accounting for the impact of physical activity. As assessment of physical activity is moving from questionnaire-based techniques towards more objective tools such as Wrist-Worn Accelerometer (GENEActiv), further research is needed to elucidate how accelerometer-assessed physical activity can be used in epidemiological studies.

The progress of obesity and physical activity research has accelerated over past years. The complexity of the association between obesity and cardiometabolic disorders in older adults is increasingly being recognized. New frontiers are being set to unravel the paths from obesity and physical activity to metabolic disorders and cardiovascular diseases. Capitalizing the new tools and advances in assessing adiposity (e.g., ABSI, DXA) and physical activity (e.g., tri-axial accelerometers) will assure further development and progress in the field.

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Appendices

SUMMARY

The aim of this thesis was to extend the existing knowledge on the relationship between obesity and physical activity with cardiovascular disease (CVD) in the elderly. It has been estimated that by 2050 about 1.5 billion (16%) people will be aged 65 or older, doubling the current rates (8%) of the elderly worldwide. This global phenomenon arises the question to what extension obesity and physical activity will impact the health in the aging population.

In the second chapter we focused on traditional and novel anthropometric measures. In chapter 2.1 we showed that among different anthropometric measures including body mass index (BMI), waist circumference (WC) and waist to hip ratio (WHR), a body shape index (ABSI) had the strongest association with all-cause mortality in men and women, cardiovascular mortality in men, and cancer mortality in women. However, the addition of ABSI to the model with traditional risk factors did not improve the c-statistic and provided only a modest improvement in model fit and risk stratification.

The role of anthropometric measures to simplify the cardiovascular risk prediction models is evaluated in chapter 2.2. In this chapter, we showed that compared to traditional anthropometric measures (e.g., BMI, WC and WHR), ABSI was the most informative anthropometric measure in prediction of CVD. In men, we demonstrated that a non-laboratory-based model including ABSI could predict CVD as accurately as the laboratory-based model including the lipid profile. Therefore, in clinical settings where blood testing is inconvenient or unavailable, the use of non-laboratory-based model, which requires measurement of ABSI instead of lipids, could predict CVD risk as accurately as the laboratory-based model among middle-aged and elderly men.

In chapter 2.3 we addressed the association of BMI, WC and ABSI with fat and fat-free mass. We aimed to evaluate which anthropometric measures are differentially associated with fat mass and fat-free mass and could therefore be used to identify individuals at risk of sarcopenic obesity. Our study demonstrated that while BMI and WC were both positively associated with fat mass and fat-free mass, ABSI provided a differential association with fat mass and fat-free mass in males. We showed that in men, ABSI was positively associated with fat mass, and negatively associated with fat-free mass indicating that ABSI could be considered as a useful tool for identifying males at higher risk for sarcopenic obesity.

In third chapter we focused in association between overweight, obesity and metabolic health risk in the elderly. As outlined in chapter 3.1 we examined the association of metabolically healthy obese with risk of CVD. We found that metabolically healthy obese individuals do not have a higher CVD risk, whereas, the presence of metabolic syndrome increased the risk of CVD in all BMI categories. To explore why some overweight individuals are resistant to the development of metabolic syndrome regardless the excess of body fat in chapter 3.2 we evaluated the association of timing and duration of overweight with metabolic syndrome and with diabetes. Our study revealed that the onset of overweight during middle-age conferred a higher risk for metabolic syndrome. Furthermore, the duration of overweight, in particular being persistently overweight, increased the risk of metabolic syndrome and diabetes. This study demonstrated the importance of timing and duration of overweight as a determinant of metabolic risk from middle-aged to elderly.

In fourth chapter we focused in the association between obesity, cardiovascular disease and mortality by using a different approach to analyze the data, such as a multistate lifetable and latent class trajectory analysis. In chapter 4.1 we showed that total life expectancy for obese men and women at age 55 years was not significantly different from normal weight individuals. However, obesity was associated with fewer number of years lived free of CVD and extended the number of years lived with CVD. Recognizing that patients with CVD comprise a heterogeneous group with regard to their BMI levels at the time of diagnosis, in Chapter 4.2 we explored the patterns of change in BMI before the diagnosis of CVD. We identified three distinct trajectories of change in BMI before the diagnosis of CVD which were accompanied by different trajectories of other cardio-metabolic risk factors. Waist circumference, HDL cholesterol, and glucose trajectories differed between the identified BMI subgroups, further highlighting that CVD is a heterogeneous disease with different pathophysiological pathways.

In fifth chapter we focused in association between physical activity and obesity with CVD. In Chapter 5.1 we evaluated the joint effects of physical activity and BMI with the risk of CVD. This study indicated that older adults who are engaged in higher levels of total physical activity are not at increased risk of CVD, regardless of being in the overweight or obese category. In chapter 5.2 we evaluated specific types of physical activity (i.e. walking, cycling, sports, domestic work and gardening) in association with coronary heart disease. Subsequently and in Chapter 5.3, we assessed the impact of physical activity types on the average years lived with and without CVD. We showed that domestic work and cycling were strongly associated with decreases of coronary heart disease risk and extending life expectancy without CVD.

In sixth chapter we discussed the results of the studies mentioned in this thesis in a broader perspective, and also the relevant methodological considerations, clinical implications and future research directions.

SAMENVATTING

Het doel van deze scriptie was om de bestaande kennis over de relatie tussen obesiteit en lichamelijke beweging met hart-en vaatziekten (HVZ) bij ouderen te vergroten. Er wordt berekend dat in 2050 ongeveer 1.5 miljard (16%) van mensen 65 of ouder zullen zijn, een verdubbeling van de huidige (8%) aantal ouderen wereldwijd. Dit fenomeen leidt tot de vraag in hoeverre obesiteit en lichamelijke beweging van belang zullen zijn op de gezondheid van de verouderende bevolking.

In het tweede hoofdstuk hebben we ons gericht op traditionele en nieuwe antropometrische maten. In hoofdstuk 2.1 laten we zien dat tussen verschillende antropometrische maten, onder andere body mass index (BMI), waist circumference (WC) en waist to hip ratio (WHR), a body shape index (ABSI) was het meest sterk geassocieerd met alle oorzaken van mortaliteit in mannen en vrouwen, hart- en vaatziekten mortaliteit in mannen, en kanker mortaliteit in vrouwen. Desondanks heeft de toevoeging van ABSI aan modellen met traditionele risico factoren niet geleid tot een verbetering van de c-statistic en liet alleen een bescheiden verbetering in model fit en risico stratificatie zien.

In hoofstuk 2.2 wordt de rol van antropometrische maten in het vereenvoudigen van HVZ risico predictie modellen beoordeeld. In dit hoofdstuk laten we zien dat in vergelijking tot traditionele anthropometrische maten (o.a. BMI, WC en WHR), ABSI de meest informatieve anthropometrische maat was in het voorspellen van HVZ. Wij laten zien dat bij mannen een model zonder laboratoria metingen maar met ABSI net zo nauwkeurig HVZ kan voorspellen als een model inclusief laboratoria metingen zoals het lipide profiel. In klinische situaties waarbij bloedonderzoek onmogelijk is, kan het gebruik van het niet-laboratoria gebaseerde model, inclusief ABSI in plaats van het lipideprofiel, het risico op HVZ net zo nauwkeurig meten als het laboratoria-gebaseerde model bij mannen van middelbaar en oudere leeftijd.

In hoofdstuk 2.3 bespreken wij het verband tussen BMI, WC, en ABSI met vet en vetvrije massa. Wij onderzochten welke anthropometrische maten differentieel geassocieerd zijn met vetmassa en vetvrij massa en vervolgens gebruikt kan worden om mensen met risico op sarcopene obesiteit te herkennen. Onze studie laat zien dat terwijl BMI en WC beide positief geassocieerd zijn met vetmassa en vetvrije massa, ABSI verschilde in de associatie met vetmassa en vetvrije massa bij mannen. Bij mannen was ABSI positief geassocieerd met vetmassa en negatief geassocieerd met vetvrije massa, suggererend dat ABSI een nuttige maat kan zijn om mannen met risico op sarcopene obesiteit te herkennen.

In het derde hoofdstuk hebben we ons gericht op de associatie tussen overgewicht, obesiteit en de risico's voor de metabolische gezondheid in ouderen. In hoofdstuk 3.1 hebben wij de associatie met metabolisch gezonde obesiteit met risico op HVZ onderzocht. Wij laten zien dat metabolisch gezonde obese mensen geen hogere risico hebben op HVZ, terwijl de aanwezigheid van metabool syndroom de risico op CVD verhoogde in alle BMI categorieen. Om uit te zoeken waarom sommige personen met overgewicht geen metabool syndroom ontwikkelen ondanks overmatige lichaamsvet, hebben wij in hoofdstuk 3.2 het verband tussen de tijdstip en duur van overgewicht met metabool syndroom en diabetes. Onze onderzoek laat zien dat het beginnen van overgewicht tijdens de middelbare leetijd resulteerde in hogere risico op metabool syndroom. Daarnaast speelt het duur van overgewicht, vooral het doorzetten van overgewicht hebben, een rol in het verhogen van het risico op metabool syndroom en diabetes. Dit onderzoek laat zien dat wanneer en hoe

lang overgewicht aanwezig is van belang is voor het metabole risico in middelbaar en oudere leeftijd.

In het vierde hoofdstuk hebben wij ons gericht op de associatie tussen obesiteit, HVZ en mortaliteit door een andere aanpak te gebruiken voor de data-analyse, zoals de multistate lifetable en latent class trajectory analysis. In hoofdstuk 4.1 laten we zien dat de levensverwachting voor obese mannen en vrouwen van 55 jaar niet significant verschilde van degenen met normale gewicht. Obesiteit was wel geassocieerd met minder jaren geleefd zonder HVZ en meer jaren geleefd met HVZ. Herkennend dat patiënten met HVZ een heterogene groep zijn met betrekking tot hun BMI ten tijde van diagnose, hebben wij in hoofdstuk 4.2 onderzocht hoe BMI veranderd voordat de diagnose van HVZ wordt gesteld. Wij hebben drie verschillende trajectories van BMI verandering voorafgaand aan de diagnose van HVZ gevonden. die vergezeld waren door verschillende trajectories van andere cardio-metabolische risicofactoren. WC (buikomtrek), HDL cholesterol en glucose trajectories verschilde tussen de BMI subgroupen. Dit benadrukt verder dat HVZ een heterogene ziekte is met verschillende pathofysiologische oorzaken.

In het vijfde hoofdstuk hebben wij de associatie tussen lichamelijke beweging en obesiteit met HVZ onderzocht. In hoofdstuk 5.1 hebben wij het effect van lichamelijke beweging en BMI samen op het risico van HVZ geevalueerd. Deze studie laat zien dat oudere volwassenen die grotere hoeveelheid lichamelijk beweging ondernemen geen verhoogd risico hebben op HVZ, ongeacht of ze overgewicht hadden of obese waren. In hoofdstuk 5.2 beoordelen we specifieke vormen van lichamelijke beweging (o.a. Wandelen, fietsen, sporten, huishoudelijke taken en tuinieren) en de associatie met coronaire hartziekten. Vervolgens in hoofstuk 5.3 onderzoeken wij de gevolgen van de specifieke vormen van lichamelijke beweging op de gemiddelde jaren geleefd met en zonder HVZ. Wij laten zien dat huishoudelijke werk en fietsen sterk geassocieerd zijn met minder risico op HVZ en onafhankelijk geassocieerd met grote verhoging van de totale levensverwachting en verhoogde levensverwachting zonder HVZ.

In het zesde hoofstuk bespreken we de resultaten van de studies uit deze scriptie in een bredere context, en ook de relevante methodologische overwegingen, klinische gevolgen en toekomstige onderzoeks richtingen.

ABOUT THE AUTHOR

Klodian Dhana was born on April 22nd, 1982 in Kucove, Albania. He obtained his medical doctor degree on 2006 at the University of Tirana in Albania. Between 2006 and 2011, he was working as medical doctor in Albania. From 2011 to 2012, he was trained as a specialist in public health at the National Institute of Public Health in Tirana, Albania.

In 2012, he received a grant from European Union to start his PhD studies at the Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands. In the same year, he started a master of science in Clinical Epidemiology at Netherland Institute for Health Sciences (NIHES), and graduated in 2013. In fall 2014, he was awarded for outstanding scientific work and the best moderated poster in the European Society of Cardiology Congress in Barcelona, Spain. Finding Clinical Epidemiology as an interesting field for population studies, during his PhD he participated in the Doctor of Science program in Clinical Epidemiology and received his degree in 2015. During his PhD, he worked under the supervision of Dr. Maryam Kavousi and Prof. Oscar H. Franco, on different topics as described in this thesis. He will continue working as postdoctoral research fellow in the Department of Nutrition at Harvard T.H Chan School of Public Health, Harvard University, Boston, MA, USA.

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LIST OF PUBLICATIONS AND MANUSCRIPTS

Published papers

Dhana K, Berghout MA, Peeters A, Ikram MA, Tiemeier H, Hofman A, Nusselder W, Kavousi M, Franco OH. Obesity in older adults and life expectancy with and without cardiovascular disease. International Journal of Obesity 2016

Jaspers L, **Dhana K**, Muka T, Meun C, Kiefte-de Jong JC, Hofman A et al. Sex steroids, sex hormone-binding globulin and cardiovascular health in men and postmenopausal women: the Rotterdam Study. J Clin Endocrinol Metab 2016: jc20161435.

Dhana K, Koolhaas C, van Rossum E.F.C, Ikram MA, Hofman A, Kavousi M, Franco OH. Metabolically healthy obesity and the risk of cardiovascular disease in the elderly population. PLOS One 2016

Dhana K, Koolhass C, Schoufour J, Rivadeneira F, Hofman A, Kavousi M, Franco OH. Association of anthropometric measures with fat and fat-free mass in the elderly: the Rotterdam Study. Maturitas. 2016

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. American Journal of Epidemiology 2016

Collaboration NCDRF. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4· 4 million participants. The Lancet 2016

Dhana K, van Rosmalen J, Vistisen D, Ikram MA, Hofman A, Franco OH, Kavousi M: Trajectories of body mass index before the diagnosis of cardiovascular disease: a latent class trajectory analysis. European Journal of Epidemiology 2016

Muka T, Vargas KG, Jaspers L, Wen KX, **Dhana K**, Vitezova A, Nano J, Brahimaj A, Colpani V, Bano A, Kraja B, Zaciragic A, Bramer WM, Dijk GM, Kavousi M, Franco OH: Estrogen receptor beta actions in the female cardiovascular system: A systematic review of animal and human studies. Maturitas 2016

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van Dijk GM, Maneva M, Colpani V, **Dhana K**, Muka T, Jaspers L, Kavousi M, Franco OH: The association between vasomotor symptoms and metabolic health in peri- and postmenopausal women: a systematic review. Maturitas 2015

Dhana K, Ikram MA, Hofman A, Franco OH, Kavousi M: Anthropometric measures in cardiovascular disease prediction: comparison of laboratory-based versus non-laboratory-based model. Heart 2015

NCD Risk Factor Collaboration (NCD-RisC). Effects of diabetes definition on global surveillance of diabetes prevalence and diagnosis: a pooled analysis of 96 population-based studies with 331,288 participants. Lancet Diabetes Endocrinology 2015

Submitted Papers

Dhana K, Ligthart S, Hofman A, Dehghan A, Franco OH, Kavousi M. Timing and duration of overweight in association with metabolic syndrome and diabetes among middle-aged and elderly.

Dhana K, Koolhaas C, Ikram MA, Hofman A, Kavousi M, Franco OH. The impact of physical activity on the association between overweight, obesity and cardiovascular disease.

Dhana K*, Koolhaas C*, 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

Dhana K*, Nano J*, Ligthart S, Peeters A, Hofman A, Nusselder W, Dehghan A, Franco OH. Obesity in older adults and life expectancy with and without diabetes

Berghout MA, **Dhana K**, Ligthart S, Peeters A, Hofman A, Nusselder W, Dehghan A, Franco OH. Diabetes and life expectancy with and without cardiovascular disease

Koolhaas C, **Dhana K**, Schoufour JD, Hofman A, van Rooij FJ, Franco OH. Physical activity types and health-related quality of life among middle-aged and elderly adults.

Koolhaas C, **Dhana K**, van Rooij FJ, Kocevska D, Hofman A, Franco OH, Tiemeier H. Objectively measured sedentary time and mortality: The Rotterdam Study

Muka T.*,Ke-xin W.*, El-Khodor B, **Dhana K**, Nano J, Pulido T, Kraja B, Zaciragic A, Bramer WM, Troup J, Chowdhury R, Dehghan A, Franco OH. The role of DNA Methylation and Histone Modifications on Neurodegenerative Diseases: A Systematic Review.

Braun KVE.*, Voortman T.*, **Dhana K**, Troup J, Bramer WM, Troup J, Chowdhury R, Dehghan A, Muka T, Franco OH. DNA methylation and dyslipidemia: a Systematic Review.

Colpani V, Baena CP, Jaspers L, van Dijk GM, Farajzadegan Z, **Dhana K**, Tielemans M, Voortman T, Freak-Poli R, Veloso GGV, Chowdhury R, Kavousi M, Muka T, Franco OH. The association between lifestyle factors with cardiovascular disease and mortality in middle-aged and elderly women: systematic review and meta-analysis.

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Nano J, Muka T, Cepeda M, Voortman T, **Dhana K**, Brahimaj A, Dehghan A, Franco OH. Association of Circulating Total Bilirubin with Metabolic Syndrome and Type 2 Diabetes risk: Systematic Review and Meta-Analysis.

**denotes equal contribution*

PHD PORTFOLIO SUMMARY

Name of PhD Student	Klodian Dhana
Erasmus MC Department	Epidemiology
PhD Period	August 2012-July 2016
Promotor	Prof. dr. Oscar H. Franco
Co-promotor	Dr. Maryam Kavousi

Training	Year	ECTS
Courses and workshops		
Master of Science, Clinical Epidemiology, NIHES	2013	70
Doctor of Science, Clinical Epidemiology, NIHES	2015	70
Biomedical English Writing	2014	1.4
Integrity in Scientific Research, Erasmus MC	2014	2.0
Systematic Literature Retrieval	2015	0.4
Advanced Medical Writing and Editing	2015	0.4
Meeting and conferences		
Clinical Epigenetic Society 2016 in Dusseldorf, Germany	2016	0.5
European Congress of Epidemiology 2015 in Maastricht, the Netherlands	2015	1.5
Congress of the European Society of Cardiology 2014 in Barcelona, Spain	2014	1.5
Netherlands Association for the Study of Obesity 2013 in Oosterbeek, The Netherlands	2013	0.5
Teaching activities- Supervising master students		
Teaching assistant, Principles of Research in Medicine and Epidemiology, NIHES	2014	1
Teaching assistant, Markers and Prediction Research, NIHES	2015	1
Adela Brahimaj, Anthropometric measures in association with	2013	2

second events of cardiovascular disease		
Chantal Koolhaas, Physical activity types and coronary heart disease risk in the middle-aged and elderly	2014	2
Mathilde Berghout, Impact of diabetes mellitus on life expectancy and years lived with cardiovascular disease	2015	2
Other		
Per review of articles for scientific journals	2014-16	2