Epidemiology of Gait and Daily Functioning
The role of the nervous system

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Epidemiology of Gait and Daily Functioning
The role of the nervous system

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De rol van het zenuwstelsel

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*These authors contributed equally to the respective manuscript.

Part 1

General Introduction

Across the world, people continue to live longer, resulting in increasing numbers of older people.[1] Age-related functional deficiencies, such as problems in gait and daily functioning, will therefore become a major issue for society.[2, 3] People with problems in gait and daily functioning are at high risk to lose independence, which will eventually lead to institutionalization.[2, 4] Furthermore, poor gait and daily functioning are strong risk factors of various morbidities, such as falling, and even death.[5-7] However, little remains known on the underlying processes leading to problems in gait and daily functioning.

Both gait and daily functioning are complex processes, requiring integration of input from various systems, such as the proprioceptive, vestibular, and visual system.[3, 8-12] The nervous system has a central role in this integration, with the peripheral nervous system conducting the information, which is subsequently processed by the brain. Deficiencies of the nervous system, particularly the brain, may therefore have a large impact on gait and daily functioning.

With aging and various neurological diseases, such as dementia and Parkinson's disease, pathology accumulates in the brain.[13, 14] Brain pathology may be visualized as structural brain changes using magnetic resonance imaging (MRI) and as microstructural brain changes with diffusion tensor imaging (DTI).[13, 15-17] Both structural and microstructural brain changes are known to strongly affect brain functioning, as measured by cognition. However, much less is known on how this loss of brain functioning affects gait and daily functioning.

Gait assessment typically encompassed visual inspection or measurement of gait velocity by stopwatch. Recent developments have enabled more detailed gait assessment using electronic walkways.[18] These electronic walkways enable assessment of many gait parameters, such as stride length, stance time, and stride width, that are all correlated with each other.[18, 19] Various studies have demonstrated that these parameters can be comprehensively summarized into fewer independent gait domains by principal components analysis.[5, 11, 20] These gait domains may represent independent underlying substrates that together constitute the gait pattern. Different gait domains are likely to be influenced by different abilities, and as such may provide unique information on underlying (brain) pathology.[9-12]

Daily functioning is commonly assessed using questionnaires on activities of daily living (ADL). ADL consist of both simple and physical basic activities of daily living (BADL), such as eating, and cognitively more challenging instrumental activities of daily living (IADL), e.g. meal preparation.[21] Gait, or walking, is generally included as one of the basic activities of daily living. However, walking is required to perform many other basic and instrumental activities of daily living. Importantly, proper functioning in both BADL and IADL is essential to function independently in society.

Investigation of determinants of gait and daily functioning is crucial to identify intervention targets to prevent or reduce problems in gait and daily functioning, and thereby related morbidity and mortality. The overall aim of my thesis was to extend knowledge on these determinants, with a special focus on the nervous system. Additionally, I investigated other possible determinants of gait and daily functioning, such as genetics, lifestyle factors, and various diseases.

In part 2, I discuss articles reporting on neurological correlates of gait, first focussing on the effects of aging on gait (2.1) and the relations between cognitive domains and gait domains (2.2). Next, I describe the associations of cortical and subcortical grey matter with gait (2.3), followed by the associations of microstructural white matter changes with gait (2.4). In the last chapter of this part, I address the associations of pain in the lower body with gait (2.5).

In part 3 of this thesis, projects regarding the neurological correlates of daily functioning are discussed. In the first chapter, I discuss the relationship between gait and daily functioning (3.1). In the following chapter (3.2), I describe the trajectories of cognition and daily functioning before dementia diagnosis. Chapter 3.3 describes the relation of structural and microstructural brain changes to incident impairment in daily functioning. Subsequently, I integrated chapters 3.2 and 3.3, by studying relations of structural brain changes to change in cognition and daily functioning during long follow-up, focusing on the role of dementia (3.4). In the final chapter of this part (3.5), I discuss the associations of restless legs syndrome with physical functioning, including daily functioning and gait.

Part 4 addresses the relations of other factors to gait and daily functioning, initiating with the role of genetics in gait (4.1). Subsequently, I focuss on a specific Parkinson's risk gene profile and their relation with incident Parkinson's disease and daily functioning (4.2). Next, I discuss lifestyle factors, namely alcohol, coffee, and tobacco consumption, in relation to gait (4.3). In the last two chapters of this part, I describe relations of two non-neurological diseases to gait, namely Chronic Obstructive Pulmonary Disease (4.4) and osteoarthritis (4.5).

Finally, in the general discussion, I integrate findings across the previous parts, and discuss their clinical implications and directions for future studies.

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Part 2

Neurological correlates of gait

Chapter 2.1

Gait patterns in a community-dwelling population aged 50 years and older

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Abstract

Poor gait is an important risk factor for falls and associated with higher morbidity and mortality. It is well established that older age is associated with worse gait, but it remains unclear at what age this association is first seen. Moreover, previous studies focused mainly on normal walking, but gait also encompasses turning and tandem walking. In a large study of community-dwelling middle-aged and elderly persons we investigated the association of age with gait, focusing on normal walking, turning and tandem walking. In 1500 persons aged 50 years and over, we measured gait using an electronic walkway. Participants performed normal walks, turning and a tandem walk. With principal components analysis of 30 variables we summarized gait into five known gait factors: Rhythm, Variability, Phases, Pace and Base of Support; and uncovered two novel gait factors: Tandem and Turning. The strongest associations with age were found for Variability (difference in Z-score -0.29 per 10 years increase (95% confidence interval: -0.34; -0.24)), Phases (-0.31 per 10 years (-0.36; -0.27)) and Tandem (-0.25 per 10 years (-0.30; -0.20)). Additionally, these factors already showed association with the youngest age groups, from 55 to 60 years of age and older. Our study shows that Variability, Phases and Tandem have the strongest association with age and are the earliest to demonstrate a poorer gait pattern with higher age. Future research should further investigate how these gait factors relate with gait-related diseases in their earliest stages.

Introduction

Proper gait is very important to function independently in a community. Not only is gait an important indicator of general health, but poor gait is also a predictor of adverse events, such as falls and mortality.[1-6] Various studies have shown that higher age is associated with worse gait.[5, 7-12] With increasing life expectancy, gait disturbances are therefore expected to become even more frequent.[5]

Gait is a highly complex concept and can be studied using many different variables. These variables include simple measurements such as velocity, step length and step width, but also more complex measurements such as the variability within variables.[7, 8, 13] Consequently, the overlap across studies in variables used to study gait is limited. Ideally, gait is studied using as many variables as possible, but this would result in multiple testing as well as collinearity across variables. In recent years, various studies have sought to solve this issue by principal components analysis (PCA). Using PCA on seven and eight variables, two studies summarized gait into three independent factors, referred to as Pace, Rhythm and Variability.[4, 6] These factors were found to be associated with cognitive decline and risk of falls.[4, 6] Another study expanded on this finding by including 15 additional gait variables in the PCA and uncovered two additional gait factors, which were named Phases and Base of Support.[9] Consecutively, the factors were found to be associated with age and sex.[9] The five gait factors described so far are all based on normal walking.[4, 6, 9] However, gait is a broader concept encompassing not only normal walking, but also turning and tandem (heel-to-toe) walking among others. Little is known about the effect of age on these aspects of gait. Furthermore, it is unknown whether these other aspects constitute additional gait factors or whether these can be captured by the previously described gait factors of normal walking. Another consideration is that previous studies on aging and gait focused on elderly populations (60 years and over). The question remains whether the association between age and gait already starts at an earlier age. Investigating the earliest age-related changes in gait would provide novel insights into the normal aging progress and can serve as a basis to study pathologic gait disturbances. The aim of our study was to investigate the association between age and gait in a population-based cohort study of middle-aged and elderly persons. We not only investigated normal walking, but also focused on turning and tandem walking. Similar to previous studies, we used PCA to summarize gait into a few independent factors.

Methods

Setting

The study was embedded in the Rotterdam Study, a prospective, population-based cohort

study, originally started in 1990.[14] The initial cohort was expanded in 2000 and 2005 and currently totals 14,926 persons. At study entry and during follow-up every 3–4 years, each participant undergoes a home interview and extensive physical examination at the research center. At these assessments height and weight are measured, and self-reported chronic diseases are recorded. From March 2009 onwards, gait assessment has been implemented in the core protocol. The current study comprises all participants that completed gait assessment until March 2011. All participants gave written informed consent. The study has been approved by the institutional Medical Ethics Committee.

Gait assessment

Gait was assessed with a 5.79 m long walkway (GAITRite Platinum; CIR systems, USA: 4.88 m active area; 120 Hz sampling rate) with pressure sensors, activated by the pressure of footfalls. This device is an accurate system to determine gait parameters.[15-18]

Participants were asked to perform a standardized protocol consisting of three different types of walking: normal walk, turning and tandem walk. In the normal walk, participants walked over the walkway at their own pace. This walk was performed four times in both directions (eight recordings). In turning, participants walked over the walkway, turned halfway and returned to the starting position (one recording). In the tandem walk, participants walked tandem (heel-to-toe) over a line visible on the walkway (one recording). Examples of the three walks can be found in Supplement 1.

In recordings of the normal and tandem walks, footsteps that did not fall entirely on the walkway at the start and the end were deleted. The first recording of the normal walk was treated as a practice walk and not included in the analyses. Recordings of individual walks were removed if instructions were not followed correctly or when fewer than four footprints were available for analyses. Spatiotemporal variables were calculated by the walkway software.

Study population

Between March 2009 and March 2011, we invited 1905 participants for gait assessment. Of these, 405 were excluded for various reasons: 196 participants were removed for technical reasons; 21 participants were excluded for use of walking aids, self-reported prosthesis or Parkinson's disease; 113 participants were excluded because of a too poor physical ability to walk; 41 participants were removed because they had fewer than 16 steps available for analyses, which lowers the validity of their gait parameters[19]; 14 participants refused to participate; nine participants refused to perform all walks; nine participants were removed because they did not follow instructions; and two participants did not perform the walks for other reasons.

After exclusion, 1500 participants were included in the analyses.

Statistical analysis

PCA with varimax rotation was performed on 30 variables to derive independent summarizing factors. A description of these 30 gait variables can be found in Supplement 2. These were all variables that could be reliably measured using the GAITRite. Preliminary analysis did not suggest differences between legs; hence the mean of both legs was taken.

Factors were selected from the PCA if their eigenvalue was one or higher, signifying that each factor explains at least as much variance as a single variable. Communalities were calculated, reflecting the amount of variance in the variable explained by all factors. Variables were appointed to a certain factor if their correlation with the factor was -0.5. If necessary, factors were inverted so that lower values represent "worse" gait. The PCA yielded standardized factors (Z-scores) that were uncorrelated to each other.

Multiple linear regression analyses were used to determine the independent associations between demographics (age, sex, height and weight) and gait factors. Analyses involving tandem walk related variables were adjusted for the step length and step count in the tandem walk. We applied Bonferroni correction for 28 tests to correct for multiple testing. Additional adjustments were made for self-reported osteoarthritis and rheumatoid arthritis. We also calculated mean Z-scores of gait factors per 5-year age strata and per sex using ANOVA, adjusted for height and weight. Differences between sexes in the effects of age were tested using interaction terms (age*sex).

All statistical analyses were performed using SPSS PASW version 17.0.2 for Windows.

Results

Characteristics of the study population are summarized in Table 1. Mean age was 68.8 years, and 817 (54.5%) were women. After summing all normal walks, an average of 41.75 (standard

Table 1. Population characteristics

Characteristic	Total (n = 1500)	Men (n = 683)	Women (n = 817)
Age, years	68.8 (10.1)	69.2 (10.3)	68.4 (9.9)
Height, cm	168.5 (9.4)	175.7 (7.1)	162.6 (6.6)
Weight, kg	78.0 (14.7)	85.1 (13.7)	72.1 (12.7)
Self-reported locomotor disorders			
Osteoarthritis, n	343 (22.9 %)	118 (17.3 %)	225 (27.5 %)
Rheumatoid Arthritis, n	46 (3.1 %)	14 (2.0 %)	32 (3.9 %)

Values are means (standard deviations) or numbers of participants (percentages).
Abbreviations: cm, centimeters; kg, kilograms; n, number

deviation (SD) 8.92) steps was available per participant. For turning an average of 4.88 (SD 0.87) steps was available, and for the tandem walk an average of 12.99 (SD 2.76) steps was available.

The mean and SD of the variables used in the PCA are shown in Table 2. The PCA summarized these 30 variables into seven independent factors, explaining 87.3% of the total variance in gait (Table 2). In line with previous studies and based on the variables constituting these factors, we labelled these: Rhythm, Variability, Phases, Pace, Tandem, Turning and Base of Support.[4, 6, 9] High communalities (≥0.60) were found for all original gait variables, except double step. All variables contributed to a factor with a correlation higher than 0.5 (Table 2). The correlations between each gait variable and each gait factor can be found in Supplement 3.

Table 2. Summarization of gait variables within independent gait factors

Variable/Factor	Percentage explained [a]	Mean (SD)	Communality [b]	Correlation with factor [c]
Rhythm	21.5 %			
Single Support Time, s		0.42 (0.03)	0.99	-0.96
Swing Time, s		0.42 (0.03)	0.99	-0.96
Step Time, s		0.55 (0.05)	0.99	-0.94
Stride Time, s		1.11 (0.10)	0.99	-0.94
Cadence, steps/min		109.0 (9.3)	0.98	0.94
Stance Time, s		0.68 (0.07)	0.99	-0.84
Variability	20.0 %			
Stride Length SD, cm		4.71 (1.68)	0.83	-0.89
Step Length SD, cm		2.92 (0.96)	0.82	-0.87
Stride Velocity SD, cm/s		6.04 (1.92)	0.78	-0.86
Stride Time SD, s		0.03 (0.02)	0.86	-0.80
Step Time SD, s		0.02 (0.01)	0.88	-0.79
Stance Time SD, s		0.03 (0.01)	0.88	-0.79
Swing Time SD, s		0.02 (0.01)	0.82	-0.71
Single Support Time SD, s		0.02 (0.01)	0.82	-0.71
Double Support Time SD, s		0.02 (0.01)	0.60	-0.57
Phases	19.0 %			
Single Support, %GC		38.3 (1.6)	0.99	0.97
Swing, %GC		38.3 (1.6)	0.99	0.97
Stance, %GC		61.7 (1.6)	0.99	-0.97
Double Support, %GC		23.5 (3.2)	0.99	-0.96
Double Support Time, s		0.26 (0.05)	0.99	-0.83

Table 2. Summarization of gait variables within independent gait factors (continued)

Variable/Factor	Percentage explained [a]	Mean (SD)	Communality [b]	Correlation with factor [c]
Pace	9.8 %			
Stride Length, cm		129.8 (17.0)	0.92	0.82
Step Length, cm		64.7 (8.5)	0.92	0.82
Velocity, cm/s		118.0 (18.5)	0.92	0.69
Tandem	7.2 %			
Sum of Feet Surface, fraction		0.34 (0.71)	0.87	-0.92
Sum of Step Distance, cm		9.1 (17.0)	0.84	-0.90
Double Step, n		0.08 (0.32)	0.41	-0.63
Turning	6.1 %			
Turning Step Count, n		4.88 (0.87)	0.87	-0.91
Turning Time, s		2.81 (0.62)	0.85	-0.85
Base of Support	3.7 %			
Stride Width SD, cm		2.34 (0.76)	0.73	-0.79
Stride Width, cm		10.1 (4.0)	0.69	0.63
Total	87.3 %			

[a] The percentage explained is the amount of total variance in all gait variables explained by this factor.
[b] The communality is the amount of variance of the variable explained by all gait factors.
[c] Factors were inverted so that lower values represent "worse" gait. The numbers shown represent correlations after the inversion.
Abbreviations: SD, standard deviation; s, seconds; min, minutes; cm, centimeters; %GC, percent of the gait cycle time; n, number

Table 3 shows the multivariable adjusted associations of age, sex, height and weight with the gait factors. Higher age was significantly associated with a lower Z-score on all factors but Rhythm, which showed a higher Z-score with age. Strongest associations with age were found for Phases: difference in Z-score per 10 years increase in age -0.31 (95% confidence interval: -0.36; -0.27), Variability: -0.29 per 10 years (-0.34; -0.24) and Tandem: -0.25 per 10 years (-0.30; -0.20).

Figure 1 shows the mean Z-scores across factors in 5-year age strata per sex. For both men and women, the earliest decrease in Z-score was seen for Variability, followed by Tandem and Phases: these three factors already showed a decrease in the earliest age-categories (55-60 years and older).

Women had a significantly lower Z-score on Phases, Pace and Base of Support, while men had a significantly lower Z-score on Rhythm. No significant interaction between age and sex was found for any of the gait factors ($p > 0.05$).

Larger height was associated with lower Rhythm, Variability and Base of Support and

Table 3. Independent associations between the demographics and the gait factors

	Rhythm	Variability	Phases	Pace	Tandem [a]	Turning	Base of Support
Age, per 10 years increase	**0.06 (0.01; 0.10)**	**-0.29 (-0.34; -0.24)**	**-0.31 (-0.36; -0.27)**	**-0.14 (-0.18; -0.10)**	**-0.25 (-0.30; -0.20)**	**-0.08 (-0.13; -0.03)**	**-0.14 (-0.19; -0.08)**
Female vs. Male	**0.52 (0.39; 0.65)**	-0.08 (-0.22; 0.06)	**-0.15 (-0.28; -0.03)**	**-0.42 (-0.54; -0.30)**	-0.12 (-0.26; 0.03)	-0.10 (-0.25; 0.04)	**-0.43 (-0.57; -0.28)**
Height, per 10 cm increase	**-0.27 (-0.35; -0.20)**	**-0.14 (-0.23; -0.06)**	**0.19 (0.12; 0.26)**	**0.42 (0.35; 0.49)**	-0.03 (-0.12; 0.05)	0.01 (-0.08; 0.10)	**-0.17 (-0.26; -0.09)**
Weight, per 10 kg increase	**0.05 (0.01; 0.08)**	**0.04 (0.00; 0.09)**	**-0.42 (-0.45; -0.38)**	0.01 (-0.02; 0.05)	0.00 (-0.04; 0.04)	**-0.08 (-0.12; -0.03)**	**0.09 (0.05; 0.13)**

Numbers represent changes in Z-score of the gait factors with their 95% confidence interval. A lower Z-score represents "worse" gait. Results in bold represent significant findings ($p<0.05$)

[a] Additionally adjusted for step length and step count of the tandem walk

Abbreviations: cm, centimeter; kg, kilogram

higher Phases and Pace. Higher weight was associated with lower Phases and Turning, and higher Rhythm, Variability and Base of Support.

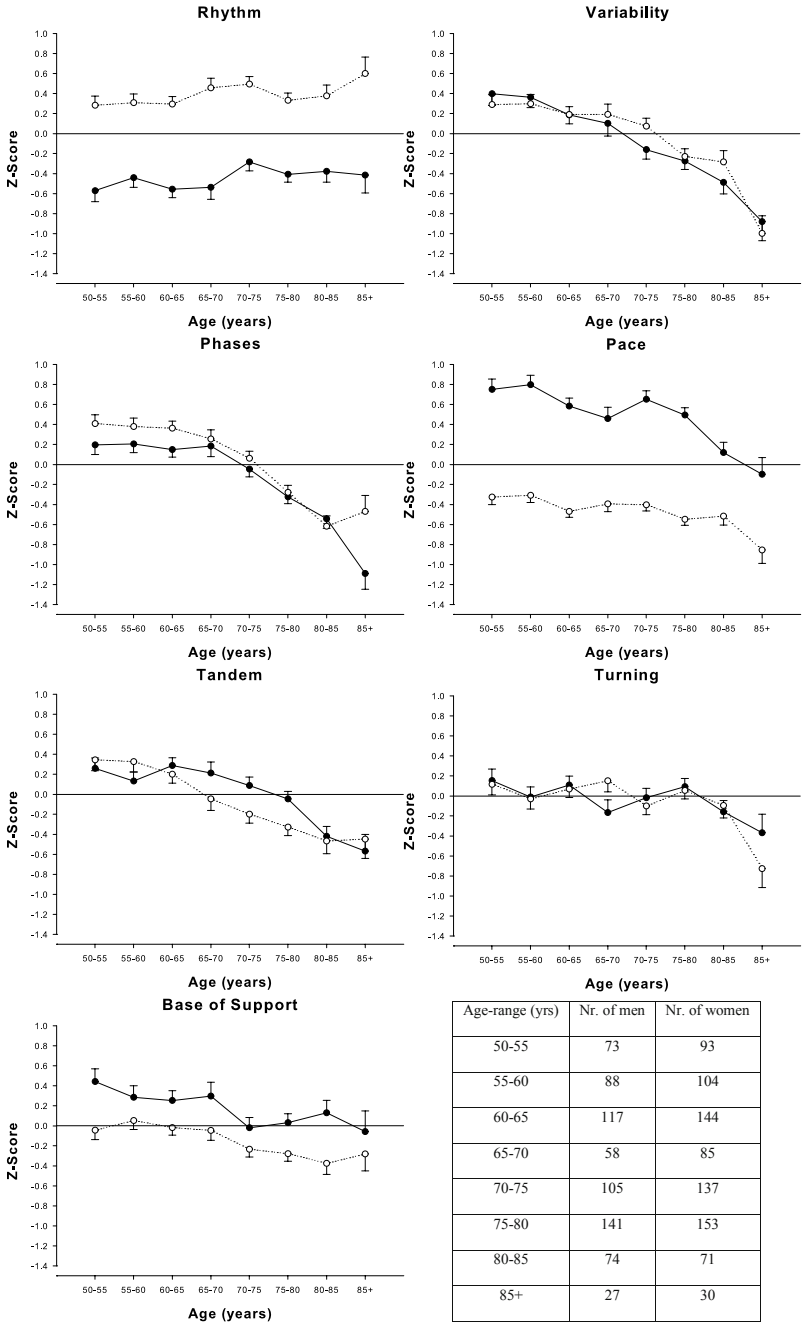
After Bonferroni correction the associations of age with Rhythm and Turning were no longer significant. The associations of sex with Phases and weight with Rhythm and Variability did not survive Bonferroni correction either.

After adjustment for self-reported osteoarthritis and rheumatoid arthritis the associations remained similar: for example the association between age and Variability became -0.30 per 10 years (-0.35; -0.25), between sex and Phases became -0.14 (-0.27; -0.02) and between weight and Turning became -0.07 (-0.12; -0.03). For the other factors, too, the associations remained unchanged.

Discussion

Our study showed that gait assessed by normal walking, turning and tandem walking can be summarized in 7 independent factors, which are Rhythm, Variability, Phases, Pace, Tandem, Turning, and Base of Support. We found that higher age was associated with worse gait as reflected in Variability, Phases, Pace, Tandem and Base of Support. The factor to show an association with the youngest age group was Variability, followed by Tandem and Phases. Between the sexes, women had poorer Pace and Base of Support, but better Rhythm than men.

The strengths of our study include the popu-



Age-range (yrs)	Nr. of men	Nr. of women
50-55	73	93
55-60	88	104
60-65	117	144
65-70	58	85
70-75	105	137
75-80	141	153
80-85	74	71
85+	27	30

Figure 1. The association between age and gait factors, in 5-year strata and by sex. A lower Z-score on a gait factor corresponds with worse gait. Black dots represent men and white dots represent women. Dots are height and weight adjusted means. Error bars represent the standard errors of the mean.

lation-based design, the large sample size, the relatively wide age-range, the many variables included and the different types of walk investigated. Our study also has some limitations. First, the cross-sectional design precludes the repeated assessment of age- related changes within participants. Second, participants only walked at their normal pace. Future studies should investigate whether results differ when walking at higher or lower velocity. Third, apart from normal walking, turning, and tandem walking, gait comprises other aspects which were not investigated, such as running, backward walking, and backward tandem walking. Inclusion of other walking conditions may reveal additional gait factors. Finally, our study sample was drawn from the general population and thus relatively healthy compared to clinic-based samples, both in terms of cognitive and physical health. This precluded the investigation of the effect of clinical disease on gait.

We found that gait can be summarized in seven independent factors. Of these, four factors were constituted by exactly the same variables as in another study summarizing gait: Rhythm, representing most temporal variables of the normal walk; Phases, representing support time variables as percentages of the gait cycle and double support time; Pace, representing stride- and step length and velocity; and Base of Support, representing stride width and its variability.[9] For Variability, which represents all variability variables excluding stride width variability, the same constituting variables were found as well, but we expanded this finding by showing that single support- and double support variability represent the same underlying factor. This supports the suggestion that all variability variables, except for stride width variability, represent the same underlying process.[9] The high correspondence of the gait factors we found for normal walking with those found in other studies demonstrates their robustness, and suggests that adding more gait variables to the factor analysis would not substantially change the composure of the already identified gait factors for normal walking.[4, 6, 9] Extending these findings, we identified two new factors representing additional walking conditions: Tandem, representing errors in the tandem walk and Turning, representing the number of turning steps and turning time. This result shows that investigating turning and tandem walking besides normal walking indeed yields additional information. Given that other studies have shown variables constituting Turning and Tandem to be associated with falls, this suggests that measuring Turning and Tandem may provide incremental value in assessing fall risk.[20, 21]

We found that higher age was associated with worse values on Variability, Phases, Pace, Tandem and Base of Support. This is in line with previous studies that found similar associations with individual variables constituting these factors.[7, 8, 10, 11] A previous study using summarizing factors only found an association with age for Phases and Pace, but not for Rhythm, Variability and Base of Support.[9] This discrepancy could be due to less power, or the narrower age-range in that study. While other studies have found gait velocity to influence associa-

tions between age and gait, in our study gait velocity is part of a separate factor, Pace.[8, 22] This ensures that associations found for all other factors are largely independent from gait velocity.

We found Variability, Phases and Tandem to associate strongest with age and to be associated already with the youngest age groups. Interestingly, variables that constitute these factors have also been associated with falls.[1, 2, 4, 20] This insinuates that assessing gait may aid in identifying those at the highest risk of falls. Furthermore, the association of these factors with age and falls suggests that interventions of gait that are aimed at reducing the risk of falls should focus on improving Variability, Phases and Tandem. Furthermore, the difficulty in the visual assessment of especially Variability and Phases, suggests that electronic walkways for measuring gait may have a role in clinical practice to assess gait disturbances in their earliest stages.

Although higher age was also associated with worse Pace and Base of Support, these associations demonstrated smaller effect sizes and only showed differences at a higher age. The associations with age for Rhythm and Turning did not survive Bonferroni correction and should therefore be confirmed by future studies.

In our study, women had better Rhythm, but worse Pace and Base of Support compared to men. This suggests that women walk with quicker, but smaller steps, and have a narrower but more variable stride width. These findings are in line with other studies, which found similar associations for these factors or constituting variables.[7, 9, 10] We did not find differences between men and women in the association between age and gait.

The various factors together explain a high proportion of the total variance in gait. Each gait factor represents a different group of highly correlated variables. The factors are also independent from each other; ensuring that any association found for one factor has additional value over the associations found with other factors. Therefore, the use of gait factors has several advantages over the use of conventional gait variables. Previous studies have already demonstrated the use of gait factors in the assessment of various clinical outcomes, such as risk of falls and cognitive impairment.[4, 6] One study found that worse Phases and, independently, Variability are associated with a higher risk of falls.[4] However, they did not recommend specific cut-off values to be used clinically. Furthermore, another study demonstrated that worse Rhythm and Pace may indicate a decline in global cognition, memory or executive functioning. Furthermore, they found that worse Rhythm and Variability are associated with an increased risk of dementia.[6] Additionally, many other morbidities appear to be associated with gait, such as sensory impairment, mobility disability and arterial stiffness.[13, 23, 24] Unravelling the associations between gait and these morbidities will aid in further understanding the aging process. Furthermore, assessment of gait may aid in the early detection or prediction of these morbidities. However, more research is needed before this can be materialized.

Conclusions

In conclusion, our study shows that gait can be summarized in seven independent factors: Rhythm, Variability, Phases, Pace and Base of Support representing normal walking, and Turning and Tandem originating from turning and tandem walking. This suggests that turning and tandem walking provide additional information on gait beyond normal walking. We found that higher age is associated with worse gait, with the strongest associations for Variability, Phases and Tandem. These were also the gait factors to show an association with the youngest age groups. Future studies should investigate the processes under- lying this association between age and gait and investigate its association with the development of gait disorders and other morbidities.

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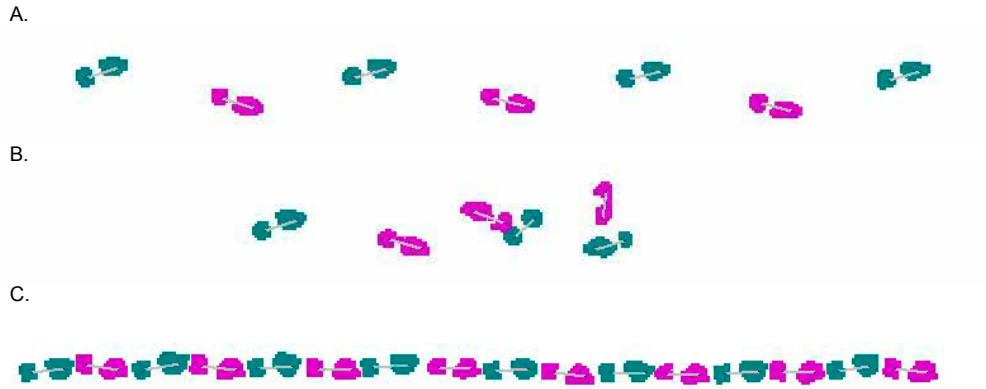
Supplement 1. **Examples of the three walks performed.** A. The normal walk; B. Turning; C. The tandem walk. For turning only the part of the walk used in the analyses is shown.



Supplement 2. Variable definitions

Variable/Factor	Definition	Indication of worse gait[a]
Rhythm		**lower**
Single Support Time	The time elapsed between the last contact of the opposite foot and the first contact of the next footfall of the opposite foot when a foot touches the ground	higher
Swing Time	The time elapsed between the last contact of the current footfall to the first contact of the next footfall on the same foot in seconds	higher
Step Time	The time elapsed between the first contact of one foot and the first contact of the opposite foot	higher
Stride Time	The elapsed time between the first contacts of two consecutive footfalls of the same foot in seconds	higher
Cadence	The number of steps/minute	lower
Stance Time	The time elapsed between the first contact and the last contact of two consecutive footfalls on the same foot in seconds. It is initiated by heel contact and ends with the toe off of the same foot	higher
Variability		**lower**
Stride Length SD	The standard deviation in the Stride Length in centimeters	higher
Step Length SD	The standard deviation in the Step Length in centimeters	higher
Stride Velocity SD	The standard deviation in the Stride Velocity (Stride Length/Stride Time) in centimeters/second	higher
Stride Time SD	The standard deviation in the Stride Time in seconds	higher
Step Time SD	The standard deviation in the Step Time in seconds	higher

Variable/Factor	Definition	Indication of worse gait[a]
Stance Time SD	The standard deviation in the Stance Time in seconds	higher
Swing Time SD	The standard deviation in the Swing Time in seconds	higher
Single Support Time SD	The standard deviation in the Single Support Time in seconds	higher
Double Support Time SD	The standard deviation in the Double Support Time in seconds	higher
Phases		**lower**
Single Support (%GC)	The Single Support Time as a percentage of the Stride Time	lower
Swing (%GC)	The Swing Time as a percentage of the Stride Time	lower
Stance (%GC)	The Stance Time as a percentage of the Stride Time	higher
Double Support (%GC)	The Double Support Time as a percentage of the Stride Time	higher
Double Support Time	The amount of time that two feet are on the ground at the same time within one footfall in seconds	higher
Pace		**lower**
Stride Length	The distance between the heel points of two consecutive footprints of the same foot on the line of progression in centimeters	lower
Step Length	The distance between the heel points of two consecutive opposite footprints on the line of progression in centimeters	lower
Velocity	The velocity in centimeters/second	lower
Tandem		**lower**
Sum of Feet Surface	The sum of the surfaces of the side steps[b] as a percentage of the surface of a normal step	higher
Sum of Step Distance	The sum of the distances of the side steps[b] from the line on the walkway in centimeters	higher
Double Step	A double-step was a step with one foot, followed by a step with the same foot, where both feet were on the line of the walkway	higher
Turning		**lower**
Turning Step Count	The number of steps used within the Turning Time	higher
Turning Time	The turning time was defined as the time between the last contact of the second foot before the first turn foot and the first contact of the second foot with a normal angle coming out of the turn. In which the first turn foot is defined as the first foot deviating from the normal angle of the feet (subject dependent)	higher

Variable/Factor	Definition	Indication of worse gait[a]
Base of Support		**lower**
Stride Width SD	The standard deviation in the Stride Width in centimeters	higher
Stride Width	The distance from heel center of one footprint to the line of progression formed by two footprints of the opposite foot in centimeters	lower

[a] "lower" indicates that lower values are considered worse gait, "higher" indicates that higher values are considered worse gait.
[b] A sidestep was defined as a step next to the line on the walkway, which was followed by a step with the same foot or a step with the other foot.
Abbreviations: SD, standard deviation; %GC, as a percentage of the gait cycle time, the cycle time equals the stride time.

Supplement 3. Correlations between the gait variables and the factors.

Gait variable	Rhythm	Variability	Phases	Pace	Tandem	Turning	Base of Support
Single Support Time	-0.96	-0.09	0.22	0.04	0.06	-0.03	0.00
Swing Time	-0.96	-0.09	0.22	0.04	0.06	-0.03	0.00
Step Time	-0.94	-0.16	-0.27	-0.04	0.02	-0.05	0.01
Stride Time	-0.94	-0.16	-0.27	-0.04	0.02	-0.05	0.01
Cadence	0.94	0.14	0.27	0.02	-0.03	0.04	-0.01
Stance Time	-0.84	-0.18	-0.49	-0.08	0.00	-0.05	0.02
Stride Length SD	0.01	-0.89	-0.12	0.13	-0.07	-0.08	-0.03
Step Length SD	-0.00	-0.87	-0.15	0.11	-0.09	-0.11	-0.01
Stride Velocity SD	0.18	-0.86	0.05	0.07	0.01	0.06	-0.07
Stride Time SD	-0.29	-0.80	-0.14	-0.34	-0.01	-0.00	-0.00
Step Time SD	-0.32	-0.79	-0.15	-0.35	-0.04	-0.05	0.04
Stance Time SD	-0.32	-0.79	-0.19	-0.33	-0.02	-0.05	0.03
Swing Time SD	-0.37	-0.71	-0.11	-0.37	-0.05	-0.12	0.10
Single Support Time SD	-0.37	-0.71	-0.11	-0.37	-0.05	-0.12	0.10
Double Support Time SD	-0.32	-0.57	-0.22	-0.33	-0.01	-0.07	-0.08
Single Support (%GC)	0.07	0.13	0.97	0.16	0.06	0.05	-0.02
Swing (%GC)	0.07	0.13	0.97	0.16	0.06	0.05	-0.02
Stance (%GC)	-0.07	-0.13	-0.97	-0.16	-0.06	-0.05	0.02
Double Support (%GC)	-0.07	-0.13	-0.96	-0.18	-0.07	-0.04	0.01
Double Support Time	-0.49	-0.17	-0.83	-0.16	-0.04	-0.05	0.01
Stride Length	-0.13	0.22	0.35	0.82	0.15	0.19	-0.05
Step Length	-0.13	0.22	0.35	0.82	0.15	0.19	-0.05
Velocity	0.39	0.25	0.43	0.69	0.11	0.18	-0.05

Gait variable	Rhythm	Variability	Phases	Pace	Tandem	Turning	Base of Support
Sum of Feet Surface	0.05	-0.09	-0.08	-0.10	-0.92	-0.01	-0.09
Sum of Step Distance	0.04	-0.06	-0.06	-0.05	-0.90	-0.03	-0.10
Double Step	0.02	-0.01	-0.05	-0.06	-0.63	0.03	0.11
Turning Step Count	0.07	-0.09	-0.07	-0.13	-0.03	-0.91	0.01
Turning Time	-0.25	-0.10	-0.07	-0.20	0.05	-0.85	0.04
Stride Width SD	-0.04	-0.17	-0.08	0.23	-0.09	-0.09	-0.79
Stride Width	-0.11	-0.27	-0.24	0.26	-0.08	-0.27	0.63

Factors were inverted so that lower values represent "worse" gait. The numbers shown represent correlations after the inversion.
Abbreviations: SD, standard deviation; %GC, as a percentage of the gait cycle time, the cycle time equals the stride time.

Chapter 2.2

Cognition and gait show a distinct pattern of association

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Abstract

Background: With brain aging, cognition and gait deteriorate in several domains. However, the interrelationship between cognitive and gait domains remains unclear. We investigated the independent associations between cognitive and gait domains in a community-dwelling population.
Methods: In the Rotterdam Study, 1232 participants underwent cognitive and gait assessment. Cognitive assessment included memory, information processing speed, fine motor speed, and executive function. Gait was summarized into seven independent domains: Rhythm, Variability, Phases, Pace, Tandem, Turning, and Base of Support. With multivariate linear regression, independent associations between cognitive and gait domains were investigated.
Results: Information processing speed associated with Rhythm, fine motor speed with Tandem, and executive function with Pace. The effect sizes corresponded to a 5- to 10-year deterioration in gait.
Conclusions: Cognition and gait show a distinct pattern of association. These data accentuate the close, but complicated, relation between cognition and gait, and they may aid in unravelling the broader spectrum of the effects of brain aging.

Introduction

Age-related pathology of the brain may cause a decline in various cognitive domains, such as memory, executive function, and information processing speed.[1, 2] Cognitive decline may ultimately lead to mild cognitive impairment and dementia.[2]

Gait is a complex motor function that is also heavily affected by age-related brain pathology.[3, 4] Gait is a strong indicator of health, and poor gait is associated with higher mortality, morbidity, and risk of falls.[5-7] Gait can be measured in several conditions, such as normal walking, turning, and tandem walking, and gait yields many parameters. These parameters in turn constitute fewer independent gait domains, such as Rhythm, Variability, Pace, Turning, and Base of Support, which together provide a comprehensive description of gait.[8-10] A few recent studies have shown associations of certain gait domains with different brain areas; for example, step width (part of Base of Support) is associated with the pallidum whereas step length (part of Pace) is associated with the sensorimotor- and dorsolateral prefrontal cortex.[3, 4]

Given that cognition and gait closely reflect brain functioning, several studies have studied the link between the two.[9, 11-13] These studies did so by investigating global cognition or gait velocity, but they did not study separate domains.[11-13] It is conceivable that certain cognitive domains may associate with certain gait domains, both affected by a single corresponding brain area. The one study to investigate associations among specific cognitive and gait domains found Pace to be associated with attention and executive function.[9] Additionally, they found Rhythm, Variability, and Pace to associate with cognitive decline and incident dementia.[9]

Still, given that cognition and gait are broad concepts, it remains unknown how various other cognitive and gait domains are associated. Moreover, most previous studies did not consider correlations among cognitive and gait domains, making it difficult to discern their independent effects.

In a population-based study, we investigated the independent associations between cognitive domains and gait domains. To more comprehensively assess gait, we investigated normal walking, turning, and tandem walking.

Methods

Setting

This study was embedded in the Rotterdam Study, a prospective population-based cohort in the Netherlands aimed to investigate causes and determinants of chronic diseases in the middle-aged and elderly.[14] The cohort was initially defined in 1990 and expanded in 2000 and 2005. In 1990 and 2000, all inhabitants aged 55 years and older of Ommoord, a suburb of Rotterdam, were invited to participate in the study. In 2005, all inhabitants aged 45 years and

older were invited. A total of 14,926 persons agreed to participate (response rates of 78, 67, and 65%). At study entry and during follow-up every 3–4 years, each participant underwent a home interview and extensive physical examination at the research centre. At these assessments, height and weight were measured and self-reported chronic diseases were recorded. During the interview at study entry, the attained level of education was assessed according to the standard classification of education.[14] From March 2009 onward, gait assessment has been implemented in the core protocol of all subcohorts. The current study comprises all participants that completed gait assessment until March 2011. The study has been approved by the Medical Ethics Committee of the Erasmus Medical Centre. All participants gave written informed consent.

Assessment of cognitive function

Cognitive function was assessed with the following neuropsychological test battery: the Mini-Mental State Examination (MMSE)[15], the Stroop test[16], a 15-word verbal learning test (based on Rey's recall of words[17]), the Letter-Digit Substitution Task (LDST)[18], a word fluency test (animal categories)[19], and the Purdue Pegboard test.[20] To obtain more robust measures, z-scores were first calculated for all separate tests by subtracting the individual value by the population mean and dividing by the standard deviation (SD). Then, z-scores for different tests were combined into compound scores for memory, executive function, information processing speed, global cognition, and fine motor speed as reported previously.[21] The z-scores for the Stroop tasks were inverted for use in these compound scores because higher scores on the Stroop task reflect worse performance whereas higher scores on all other tests reflect a better cognitive performance. The compound score for memory was calculated as the average of the z-scores for the immediate and delayed recall of the 15-word verbal learning test. Executive function was constructed by averaging the z-scores for the Stroop interference subtask, the Word Fluency Test (number of animals in 1 minute), and the LDST (number of correct digits in 1 minute). Information processing speed was the average of the z-scores for the Stroop reading and Stroop color naming test and the LDST. Fine motor speed was defined by the z score for the Purdue Pegboard test (both hands). For global cognition, we used the average of the z-scores of the Stroop task (average of all three subtasks), the LDST, the Word Fluency Test, the immediate and delayed recall of the 15-word verbal learning test, and the Purdue Pegboard test (both hands). For each compound score, new z-scores were calculated.

Gait assessment

A description of the gait assessment has been published previously.[10] Gait was assessed with a 5.79-m long walkway (GAITRite Platinum; CIR systems, Sparta, NJ: 4.88-m active area;

120-Hz sampling rate) with pressure sensors. This device is considered an accurate system to determine gait parameters.[22-24]

Participants performed a standardized gait protocol consisting of three different walking conditions: normal walk, turning, and tandem walk. In the normal walk, participants walked over the walkway at their own pace. This walk was performed 4 times in both directions (eight recordings). In turning, participants walked over the walkway at their own pace, turned halfway, and returned to the starting position (one recording). In the tandem walk, participants walked tandem (heel-to-toe) over a line visible on the walkway (one recording).

In recordings of the normal and tandem walks, footsteps not falling entirely on the walkway at the start and at the end were removed before the analyses. The first recording of the normal walk was treated as a practice walk and was not included in the analyses. Recordings of individual walks were removed if instructions were not followed correctly or when fewer than four footprints were available for analyses. Spatiotemporal variables were calculated by the walkway software.

Consecutively, principal components analysis on 30 gait variables was used to derive summarizing factors, as previously reported.[10]Within the principal components analysis, varimax rotation was used to ensure that the factors were totally independent from each other. Factors were selected if their eigenvalue was 1 or higher, indicating that each factor explains at least as much variance as a single variable. We appointed variables to a certain factor if their correlation with the factor was 0.5 or higher. Although a gait variable could attribute to several factors, none of the gait variables had a correlation of 0.5 or higher with

Table 1. Description of the characteristics of the gait domains

Gait domain	Characteristic
Rhythm	A reflection of most temporal gait variables, such as cadence, stance time and swing time. A lower value indicates a lower cadence.
Variability	A reflection of most variability gait variables, such as stride length variability and stance time variability. A lower value indicates higher variability.
Phases	A reflection of gait variables on the ratio between stable and instable walking time, such as the double support percentage of the gait cycle and the swing percentage of the gait cycle. A lower value indicates a higher double support percentage.
Pace	A reflection of distance related gait variables, such as stride length and gait velocity. A lower value indicates a shorter stride length.
Tandem	A reflection of gait variables on the amount of errors in the tandem walk, such as the side steps and double steps. A lower value indicates more errors in the tandem walk.
Turning	A reflection of turn related gait variables, such as the number of turn steps and turning time. A lower value indicates a slower turn.
Base of Support	A reflection of width related gait variables, such as the stride width and the stride width variability. A lower value indicates a smaller stride width, but higher stride width variability.

more than one factor. If necessary, factors were inverted so that lower values always represent "worse" gait. This applied to all factors except for Pace. Seven factors were derived from this principal components analysis, in which each factor represents a different independent gait domain: Rhythm, Variability, Phases, Pace, Tandem, Turning, and Base of Support.[10] Rhythm, Variability, Phases, Pace, and Base of Support have also been found in other studies, whereas Tandem and Turning recently were additionally identified from our study (Table 1).[8-10] Similar to global cognition, we calculated a global gait score by summing all gait factors, dividing by the number of gait factors, and subsequently calculating a new z score.

Educational categorization

Education was divided into seven categories: 0 = primary education, 1 = lower vocational education, 2 = lower secondary education, 3 = intermediate vocational education, 4 = general secondary education, 5 = higher vocational education, and 6 = university.

Study population

Between March 2009 and March 2011, 1905 participants were invited for gait assessment. Of these, 405 were excluded for various reasons: 196 participants were removed for technical reasons; 21 participants were excluded for use of walking aids, self-reported prosthesis, or Parkinson's disease; 113 participants were excluded because of too poor physical ability to walk; 41 participants were removed because they had fewer than 16 steps available for analyses, which lowers the validity of their gait parameters[25]; 14 participants refused to participate; 9 participants refused to perform all walks; 9 participants were removed because they did not follow instructions; and 2 participants did not perform the walks for other reasons. Of the remaining 1500 persons, an additional 248 participants were excluded because of missing cognitive data and another 20 participants because their educational level was unknown. In total 1232 participants were included in the analyses.

Statistical analysis

Linear regression analyses were used to determine the associations of MMSE and global cognition with the separate gait domains. We also investigated the association of global cognition (in quintiles) with global gait using univariate analyses of variance (ANOVA) and analyzed the P trend for linearity.

We subsequently investigated the associations of individual cognitive domains with the gait domains. First, we used linear regression analyses to investigate the associations for the separate cognitive domains with the gait domains. Given weak to strong correlations across cognitive domains (see Supplement 1), we consecutively used multivariate linear regression

analyses including all cognitive domains. This way, we investigated the independent associations of the various cognitive domains with each independent gait domain.

All analyses were adjusted for the following potential confounders: age (at the time of the assessment of cognitive function), sex, height, weight, education, subcohort, and the interval between cognition and gait assessment in days. Analyses with Tandem were additionally adjusted for the step length and step count in the tandem walk. To address the robustness of our findings, Bonferroni correction was performed for all linear regression analyses involving cognitive domains (for 28 tests).

We note that all above-mentioned associations were tested against the null hypothesis of no association. For the multivariate analyses, we also directly compared effect sizes across associations with each other. We did this only for associations that were significantly different from the null after Bonferroni correction. The effect size of such association between cognitive domain and gait domain was compared to the effect sizes with other gait domains.

We also performed sensitivity analyses to investigate any effect of selective dropout of persons that were physically unable to walk. We did so by imputing global gait for these persons with the lowest global gait score among the available population. We subsequently compared results from linear regression before and after including these persons.

Alternatively, we divided global cognition and global gait into quintiles and placed the persons unable to walk in the worst quintile of global gait. Consecutively, we calculated Spearman's correlations before and after including these persons.

Finally, adjustment for self-reported osteoarthritis and rheumatoid arthritis was performed to determine their influence on the investigated associations.

All statistical analyses were performed using SPSS PASW version 17.0.2 for Windows.

Results

Population characteristics are presented in Table 2. The mean age was 66.3 years (SD 11.8), and 54.7% of the participants were women. The mean MMSE was 28.0 (SD 1.8) and the median educational level was intermediate vocational education. Excluded participants were more often female than the included participants and were significantly older ($p < 0.05$). After adjustment for age and sex, excluded participants also had shorter stature, a lower education, and a lower MMSE score compared with the included participants (all $p < 0.05$).

MMSE and global cognition were significantly associated with Variability and Pace (Table 3). In addition, global cognition was also significantly associated with Rhythm and Turning.

In Figure 1, a strong association between global cognition and global gait is seen (difference in z score of global gait per SD increase of global cognition: 0.26 [95% confidence interval: 0.19; 0.32]). When investigating cognition in quintiles, persons in the lower three quintiles

Table 2. Population characteristics

Characteristic	Total (n = 1232)	Men (n = 558)	Women (n = 674)	Excluded (n = 673, 398 women)
Age, years	66.3 (11.8)	67.0 (12.0)	65.7 (11.5)	72.9 (11.8)[b]
Height, cm	168.8 (9.4)	175.9 (7.0)	162.9 (6.6)	166.2 (9.6)[c]
Weight, kg	78.3 (14.7)	85.2 (13.9)	72.5 (12.7)	76.8 (14.5)
MMSE, points	28.0 (1.8)	27.9 (1.8)	28.1 (1.7)	27.3 (2.5)[c]
Education[a]	3 (1; 3)	3 (2; 5)	2 (1; 3)	2 (1; 3)[c]
Self-reported movement disorders				
Osteoarthritis, n	278 (22.6)	96 (17.2)	182 (27.0)	179 (26.6)
Rheumatoid Arthritis, n	34 (2.8)	10 (1.8)	24 (3.6)	34 (5.1)

Values are means (standard deviations) or numbers of participants (percentages).

[a] For education the median (inter quartile range) is shown.

[b] Excluded participants were significantly older than the included population ($p < 0.05$).

[c] Excluded participants differed significantly from the included population in these characteristics, after adjustment for age and sex.

Abbreviations: cm, centimeters; kg, kilograms; n, number

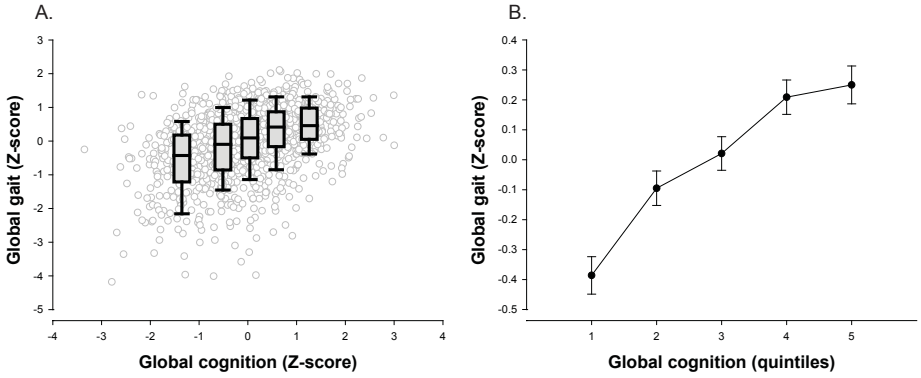

Figure 1: The association between global cognition and global gait. A: A scatterplot of global gait against global cognition including a boxplot presenting the 90th, 75th, median, 25th, and 10th percentile of global gait within quintiles of global cognition (unadjusted values). B: A plot of the adjusted means of global gait with their standard errors per quintile of global cognition. Each consecutive higher quintile of global cognition demonstrates higher global gait. A higher Z-score on global gait corresponds with better gait. Dots are means, adjusted for age, sex, height, weight, education, interval between gait and cognition measurements in days and the sub-cohort. Error bars represent the standard errors of the mean.

Table 3. Associations for the global cognition measures and the cognitive domains with the gait domains

Global cognition scores	Gait domains						
	Rhythm	Variability	Phases	Pace	Tandem[a]	Turning	Base of Support
MMSE	0.02 (-0.01; 0.05)	**0.06 (0.02; 0.09)**	0.00 (-0.03; 0.03)	**0.04 (0.01; 0.06)**	-0.03 (-0.06; 0.00)	0.02 (-0.01; 0.06)	-0.01 (-0.04; 0.02)
Global cognition	**0.19 (0.12; 0.25)**	**0.20 (0.13; 0.27)**	-0.01 (-0.07; 0.05)	**0.20 (0.14; 0.25)**	0.07 (0.00; 0.14)	**0.12 (0.05; 0.19)**	-0.07 (-0.14; 0.01)
Cognitive domains							
Memory	0.05 (-0.01; 0.11)	0.09 (0.03; 0.15)	-0.06 (-0.11; -0.01)	**0.10 (0.06; 0.15)**	0.00 (-0.06; 0.06)	0.08 (0.01; 0.14)	-0.06 (-0.13; 0.00)
Information processing speed	**0.19 (0.13; 0.24)**	**0.16 (0.10; 0.22)**	0.05 (0.00; 0.11)	**0.12 (0.07; 0.17)**	0.02 (-0.04; 0.08)	**0.11 (0.04; 0.17)**	-0.03 (-0.09; 0.04)
Fine motor speed	**0.10 (0.04; 0.16)**	**0.12 (0.05; 0.18)**	0.01 (-0.05; 0.07)	0.08 (0.02; 0.13)	**0.12 (0.06; 0.19)**	0.07 (0.00; 0.14)	0.00 (-0.06; 0.07)
Executive function	**0.16 (0.10; 0.22)**	**0.18 (0.11; 0.25)**	0.04 (-0.02; 0.10)	**0.18 (0.13; 0.23)**	0.05 (-0.01; 0.12)	0.08 (0.01; 0.15)	-0.03 (-0.10; 0.04)

Values represent the change in z-scores (with 95% confidence intervals) of gait per point increase for MMSE or per standard deviation increase for global cognition and the cognitive domains. For MMSE and Global cognition, results in bold represent significant findings against the null hypothesis of no association ($p<0.05$). For the cognitive domains, results in bold represent significant findings against the null hypothesis of no association after Bonferroni correction for 28 tests ($p<0.0018$). All analyses were adjusted for age, sex, height, weight, education, sub-cohort and the interval between cognition and gait assessment in days.

[a] Additionally adjusted for the step count and step size within the tandem walk.

Table 4. Independent associations between the cognitive domains and the gait domains

	Gait domains						
Cognitive domains	Rhythm	Variability	Phases	Pace	Tandem[a]	Turning	Base of Support
Memory	0.00 (-0.06; 0.06)	0.04 (-0.02; 0.11)	-0.08 (-0.14; -0.03)	0.06 (0.01; 0.11)	-0.01 (-0.07; 0.05)	0.06 (-0.01; 0.12)	-0.06 (-0.13; 0.00)
Information processing speed	**0.15 (0.07; 0.23)**	0.07 (-0.02; 0.16)	0.06 (-0.01; 0.14)	0.00 (-0.07; 0.07)	-0.04 (-0.13; 0.05)	0.10 (0.00; 0.19)	-0.01 (-0.10; 0.09)
Fine motor speed	0.06 (-0.01; 0.12)	0.07 (0.00; 0.14)	0.00 (-0.06; 0.06)	0.04 (-0.02; 0.09)	**0.12 (0.05; 0.19)**	0.05 (-0.03; 0.12)	0.01 (-0.06; 0.08)
Executive function	0.04 (-0.05; 0.13)	0.10 (0.01; 0.19)	0.02 (-0.06; 0.10)	**0.15 (0.08; 0.23)**	0.06 (-0.04; 0.15)	-0.02 (-0.12; 0.08)	-0.01 (-0.11; 0.09)

Values represent the change in z-scores (with 95% confidence intervals) of gait per standard deviation increase in the cognitive domain. Results in bold represent significant findings against the null hypothesis of no association after Bonferroni correction for 28 tests ($p<0.0018$). All analyses were adjusted for age, sex, height, weight, education, sub-cohort, the interval between cognition and gait assessment in days, and the other cognitive domains.

[a] Additionally adjusted for the step count and step size within the tandem walk.

had worse gait than persons in the highest quintile ($p < 0.05$). Moreover, this association demonstrated a significant P trend for linearity ($p < 0.001$).

Table 3 also shows that without adjustment for other cognitive domains, several cognitive domains were significantly associated with various gait domains.

In Table 4, the associations between cognitive domains and gait domains are shown after multivariable modelling, thereby exploring independent associations. Three associations were found to survive Bonferroni adjusted statistical thresholds: information processing speed was associated with Rhythm (difference in z score of Rhythm per SD increase of information processing speed: 0.15 [95% confidence interval: 0.07; 0.23]), fine motor speed was associated with Tandem (0.12 [0.05; 0.19]), and executive function was associated with Pace (0.15 [0.08; 0.23]). When using conventional limits of nominal significance ($p < 0.05$), five other suggestive associations emerged: memory became associated with Phases and Pace, information processing speed became associated with Turning, and fine motor speed and executive function became associated with Variability.

The effect size of the association between information processing speed and Rhythm was significantly larger than the effect size of information processing speed with Pace, but not that with Tandem (Supplement 2). The effect size of fine motor speed with Tandem did not differ significantly from the effect size of fine motor speed with Rhythm and Pace. Neither did the effect size of executive

function with Pace differ significantly from the effect size of executive function with Rhythm and Tandem.

In the sensitivity analyses, after imputing gait values for the persons that were missing in the original analyses, the Spearman's correlation and the linear regression showed a stronger association between global cognition and global gait than in the original analyses (Spearman's correlation of 0.38 as opposed to 0.36, linear regression 0.32 [0.24; 0.40] compared with 0.26 [0.19; 0.32]).

Adjustment for self-reported osteoarthritis and rheumatoid arthritis did not change the results.

Discussion

Our study shows that cognitive domains and gait domains are tightly associated, with a putative pattern of certain cognitive domains with gait domains: information processing speed was associated with Rhythm, fine motor speed was associated with Tandem, and executive function was associated with Pace. Suggestive associations were also found for memory with Phases and Pace, for information processing speed with Turning, and for fine motor speed and executive function with Variability.

The strengths of our study include the population-based design, the large sample size, the different walking conditions included, and the many independent gait domains investigated. Moreover, we also made our cognitive domains independent from each other by adjustment in a multivariable model.

However, our study also has some limitations. First, the cross-sectional design precluded the possibility to investigate the time-dependent relation between gait and cognition. Secondly, our population was selected to be relatively healthy, both cognitively and physically; hence, generalizability of our results may be restricted to a healthy population. However, our sensitivity analyses suggest that the exclusion of persons unable to walk has most likely led to an underestimation of the strength of association between cognition and gait. Thirdly, apart from normal walking, turning, and tandem walking, gait also comprises other walking conditions, such as running, backward walking, and backward tandem walking, which were not included in this study. Finally, several cognitive domains, such as attention, were also not tested in our study.

We demonstrated that better global cognition was associated with better global gait over the whole range of global cognition. This suggests that this association is not driven by persons at

the lower end of the spectrum of cognitive ability. Instead, even in persons with average and good cognitive ability, cognition associates with gait.

MMSE and global cognition were most strongly associated with Variability, followed by Pace. Global cognition was also significantly associated with Rhythm and Turning. These results correspond with previous studies that found similar associations for global cognition with these gait domains or constituting variables.[9, 12, 26]

Apart from their strong mutual association, gait variability and cognition are also associated with the risk of falls.[5, 27, 28] Thus, gait variability may be the most important gait-related intermediate in the association between cognition and risk of falls.

In a basic model with no adjustment for correlations among cognitive domains, we found that several cognitive domains associated with various gait domains. This demonstrates the close relationship between cognition and gait, but it also accentuates the correlation among the cognitive domains.

When investigating independent associations in multivariable models, a possible distinct pattern of associations emerged: information processing speed was significantly associated with Rhythm, fine motor speed was associated with Tandem, and executive function was associated with Pace. Suggestive associations were also found for memory with Phases and Pace, for information processing speed with Turning, and for fine motor speed and executive function with Variability. Because of the adjustment for other cognitive domains and the use of independent gait domains, these results suggest specific associations between cognitive domains and gait domains. However, direct comparison showed few significant differences in effect size among the associations. Only the effect size of the association between information processing speed and Rhythm differed significantly from that with Pace. Therefore, we cannot be certain that the associations found between cognition and gait are indeed domain specific.

The only other study investigating associations between cognitive domains and gait domains found a significant association between executive function and Pace, but it did not find the suggestive associations for memory with Pace and executive function with Variability.[9]

Most other studies on cognition and gait investigated gait with gait velocity, which was found to be associated with memory, information processing speed, and executive function.[11, 13] However, gait velocity (= step length/step time) is reflected by two gait domains: Rhythm (via step time) and Pace (via step length).[10] Our results suggest that the Rhythm part of gait velocity is associated with information processing speed whereas the Pace part may be mainly associated with memory and executive function.

The association found between fine motor speed and Tandem is new and suggests that brain areas important for fine motor speed may also be important to maintain balance in gait.

It was surprising to note that the strong association found between global cognition and Variability was not reflected by a specific cognitive domain. Previous studies suggested that gait variability is foremost associated with executive function.[29, 30] However, our results

suggest that the association between cognition and Variability is not domain specific, but a global association distributed about equally over the cognitive domains, with only a suggestive predilection toward fine motor speed and executive function. Future studies are needed to validate the suggestive associations found in our study.

The relevance of the effect of these associations may be better interpreted when compared with the effect of age on gait, which has recently been reported from our study: The effect of a 1 SD poorer performance in fine motor speed on Tandem corresponds to the effect of 5 years of aging whereas the effect of a 1 SD poorer performance in executive function on Pace corresponds to even 10 years of aging.[10]

The strong associations between specific cognitive and gait domains demonstrate the close and intricate relationship between cognition and gait. This close relationship is likely explained by the effect of common underlying brain pathology. Indeed, previous studies have already shown pathologies in certain areas of the brain to be associated with specific cognitive and specific gait domains.[2-4, 31] Nonetheless, an alternative explanation of poor cognitive functioning leading to gait disturbances because of impaired motor control should also be considered. However, although some studies did find that cognitive functioning was associated with a future decline in gait, other studies found poor gait to predict future cognitive decline whereas others found cognition and gait to deteriorate concurrently.[9, 11-13, 32] However, future studies are needed to further unravel the etiology of the associations between cognition and gait.

In conclusion, we found a distinct pattern in the associations between cognitive domains and gait domains: information processing speed was associated with Rhythm, fine motor speed was associated with Tandem, and executive function was associated with Pace. These results accentuate the close, but complicated, relationship between cognition and gait and may aid in unraveling the broader spectrum of the effects of brain aging. Future studies should also further explore the role of gait deterioration in incipient dementia and other neurodegenerative disease in old age.

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Supplement 1. Partial correlations among the cognitive domains.

	Memory	Information processing speed	Fine motor speed	Executive function
Memory	1	0.31 (0.00)	0.06 (0.02)	0.35 (0.00)
Information processing speed	0.31 (0.00)	1	0.23 (0.00)	0.73 (0.00)
Fine motor speed	0.06 (0.02)	0.23 (0.00)	1	0.24 (0.00)
Executive function	0.35 (0.00)	0.73 (0.00)	0.24 (0.00)	1

Numbers represent the partial correlations (p-values), adjusted for age and sex.

Supplement 2. Significance of the differences in effect size among the associations found for the cognitive domains and gait domains.

	Gait domains		
Associations	Rhythm	Pace	Tandem
Information processing speed – Rhythm	-	**0.006**	0.073
Fine motor speed – Tandem	0.194	0.070	-
Executive function – Pace	0.054	-	0.131

Values represent p-values for the difference in effect size between the association and the effect sizes found for associations with the respective cognitive domain and the other gait domains.

Chapter 2.3

The role of cortical and subcortical grey matter in cognition and gait

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Submitted.

Abstract

Background: Cognition and gait are shown to be closely related, but it remains unclear whether this relationship is also reflected by similar involvement of brain grey matter structures. In a non-demented community-dwelling population, we investigated the role of cortical and subcortical grey matter in with cognition and gait.
Methods: In the population-based Rotterdam Study, 2864 participants underwent magnetic resonance imaging (MRI), yielding volumes of 74 cortical and eight subcortical grey matter structures. Cognition was assessed using an extensive cognitive test battery and summarized into four independent cognitive domains. Similarly, gait was assessed by electronic walkway and summarized into seven independent gait domains. Subsequently, cognitive and gait domains were averaged into global cognition and gait scores.
Results: Larger volumes of cortical structures in predominantly frontal and temporal lobes and subcortical structures associated with both better cognition and gait. Larger cortical volumes only associated with better executive functioning, Variability (less step-to-step variability), and Pace (larger steps). In contrast, subcortical volumes associated with cognition across fine motor speed, executive functioning, and information processing speed as well as Phases (duration of double support), Pace, and Tandem (errors in tandem walking). Associations of cortical and subcortical brain structures with cognition and gait were largely independent from each other.
Conclusions: In a community-dwelling population, similar cortical and subcortical grey matter structures may independently associate with specific domains of both cognition and gait.

Introduction

Brain grey matter, comprising both cortical and subcortical structures, is essential for many functions, such as cognition and physical functioning.[1-4] With aging and various neurological diseases, pathology accumulates in these structures, leading to atrophy, which may severely impair these functions.[1, 5-8] Traditionally, cognition and physical functioning are considered as separate entities, with different grey matter structures being involved.[9, 10] However, recent studies have demonstrated a more complex pattern, suggesting many of these structures to be involved in both cognition and physical functioning.[2, 9, 11-13] For example, basal ganglia, traditionally thought to mainly influence physical functioning, have been found to also affect cognition, which may derive from their connections to the prefrontal and limbic cortex.[9] Similarly, the temporal lobe, traditionally related to cognition, has recently been found to also relate to physical functioning.[2, 10]

Cognition may be assessed with a wide range of cognitive tests, which are typically assigned to specific domains, such as memory, executive functioning, and fine motor speed.[14] Although designed to assess cognition, many cognitive tests and domains also require some degree of physical functioning to be performed. In turn, many physical functions, such as gait, have been found to rely on cognition.[15, 16] Similar to cognition, gait can be summarized

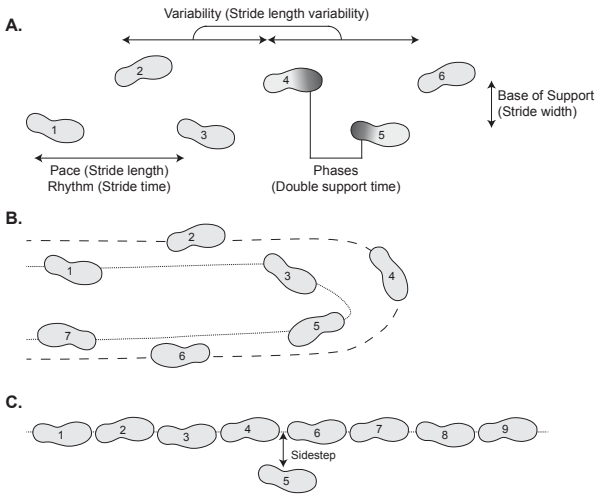

Figure 1. The three walking conditions with the gait domains of normal walking. A. Normal walk. The gait domains are presented through highly correlating gait parameters, which are described between parenthesis. B. Turn. Only the part of the turn used for the calculation of the parameters is presented. In this example, turning time was defined as the time between last contact of foot one until first contact of foot seven. Turning step count was calculated as the number of feet minus two (five in this example). C. Tandem walk. The depicted sidestep would be considered an error in tandem walking.

into seven independent gait domains (Figure 1), which relate in different degrees to cognitive functioning.[15-17] Hence, instead of separate entities, cognition and physical functioning may be considered two aspects of the same spectrum, with many abilities requiring a combination of both functions.

Against this background, it is surprising that very few studies investigated associations of grey matter volumes with both cognition and physical functioning, such as gait.[3, 18] Furthermore, studies rarely carried out a comprehensive study of grey matter volumes with cognition or gait, mainly focusing on specific regions of interest.[1-4, 6, 11-13, 18-24] Additionally, studies covered only small part of the cognitive and gait domains, without taking mutual correlations into account. A detailed investigation of grey matter volumes with a comprehensive cognitive and gait assessment may provide new insight into the distinct and overlapping functions of specific grey matter structures.

In non-demented community-dwelling individuals, we investigated associations of volumes in a wide range of cortical and subcortical grey matter structures with a comprehensive set of independent cognitive and gait domains.

Methods

Setting

The study was performed as part of the Rotterdam Study, a population-based cohort study in the Netherlands.[25] The Rotterdam Study was initiated in 1990, inviting all inhabitants aged 55 years and older of Ommoord, a suburb of Rotterdam, to participate. The study was extended in 2000 and 2006, this last time inviting all inhabitants aged 45 years and older. At baseline and each visit of follow-up, participants undergo a home interview and extensive medical examinations at the research center. At these visits, height and weight were assessed. At baseline, educational level was evaluated and categorized into: 0 = primary education, 1 = lower vocational education, 2 = lower secondary education, 3 = intermediate vocational education, 4 = general secondary education, 5 = higher vocational education, and 6 = university. Missing values on education (1.3%) were imputed by the mean of five imputations, based on age, sex, height, and weight. From March 2009 onwards, gait assessment has been included in the core study protocol. The current study includes all participants invited for gait assessment between March 2009 and March 2012. The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. A written informed consent was obtained from all participants.

MRI acquisition

Brain MRI was performed using a 1.5 tesla scanner with an eight-channel head-coil (GE Healthcare, Milwaukee, WI). MRI acquisition included proton-density weighted, fluid attenuated inversion recovery-weighted, and T1-weighted sequences.[26] Freesurfer 5.1 with the Destrieux atlas was used to automatically segment the brain, deriving intracranial volume, supratentorial brain volume, white matter hypointensity (lesion) volume, and volumes of 74 cortical and eight subcortical brain structures.[27, 28] Since preliminary analyses showed similar associations for structures of left and right hemispheres, volumes of cortical and subcortical structures of both hemispheres were combined. Abbreviations used for the cortical structures in the figures were based on a previous study, and are presented in Supplement 1.[29]

Lacunar infarcts were defined as focal parenchymal lesions ≥3mm without involvement of the cortex.[30]

Cognitive assessment

Cognition was assessed using an extensive neuropsychological test battery[31], including the following: time taken in the Stroop subtasks (three measures)[32]; number of animals named in the Word Fluency test[33]; number of pins with left, right, and both hands in the Purdue Pegboard test[34]; correct answers in the immediate, delayed, and recognition 15-Word Verbal Learning Test (15-WLT)[35]; correct answers in the Letter-Digit Substitution Task (LDST)[36], and correct answers in the Design Organization Test (DOT).[37]

Principal components analysis with varimax rotation was used to summarize these cognitive tests into four mutually independent cognitive domains (Supplement 2). Cognitive tests were attributed to a domain if they had a correlation ≥0.5 with that domain. We labelled the domains: fine motor speed, reflecting all Purdue Pegboard tests; executive functioning, reflecting the DOT, WFT, LDST, and Stroop colour-word interference subtask; memory, reflecting all 15-WLT tests; and information processing speed, reflecting the Stroop reading and colour naming subtasks. The four cognitive domains explained 72.5% of variance among the cognitive tests. If necessary, domains were inverted so that lower values represent "worse" cognition. The cognitive domains were averaged and z-standardized (subtracting the mean and dividing by the standard deviation [SD]) into Global Cognition.

Gait assessment

Gait assessment was performed on the same day as the MRI acquisition. Details on the gait assessment protocol have been published previously.[17] In short, gait was assessed using a 5.79m electronic walkway (4.88m active area, 120Hz sampling rate; GAITRite Platinum; CIR systems, Sparta, NJ), which is considered an accurate gait assessment tool.[38-40] Gait was

assessed in three walking conditions: normal walk, turn, and tandem walk. In normal walk, participants walked at their usual pace across the walkway. This walk was performed eight times, of which the first walk was considered a practice walk and excluded from analysis. In turn, participants walked at their usual pace, turned halfway, and returned to their starting position. In tandem walk, participants walked heel-to-toe on a line across the walkway.

Principal components analysis with varimax rotation was used to summarize 30 gait parameters into seven independent gait domains, as described previously: Rhythm, reflecting stride time and single support time, among others; Phases, reflecting double support time and single support as a percentage of the stride time; Variability, reflecting variability in time and length among strides; Pace, reflecting stride length and velocity; Tandem, reflecting errors in tandem walking; Turning, reflecting turning time and turning step count; and Base of Support, reflecting both stride width and stride width variability (Figure 1).[17] Similar to cognition, lower values on the gait domains may be considered "worse" gait. The gait domains were z-standardized for the current population. Additionally, they were averaged and z-standardized into Global Gait.

Study population

Between March 2009 and March 2012, 3651 participants were invited for gait assessment. 282 participants did not complete gait assessment for following reasons: physical problems (n=204), technical problems (n=57), refusal (n=19), and other reasons (n=2). Of 3369 participants that underwent complete gait assessment, 239 were excluded for technical reasons, 34 for performing less than 16 steps of normal walking, lowering validity of gait parameters[41], 27 for not following instructions, 27 for dementia or missing data on dementia, and 3 for use of walking aids.

Of 3039 participants with valid gait data, 5 refused MRI assessment and 32 did not complete MRI for claustrophobia, physical problems, or technical reasons. 105 participants were excluded for cortical infarcts or large incidental findings on MRI. Furthermore, we excluded 33 participants for segmentation problems, due to e.g. motion artefacts. Hence, 2864 participants were included in the analyses of brain volumes with gait.

Of 2864 participants with complete MRI and gait data, 2860 were invited for cognitive assessments. Of these, 138 participants refused to undergo cognitive testing, 5 did not respond, 3 were incapable for physical problems, 1 moved from the study area, and 1 had died before invitation. Of 2712 participant that underwent cognitive assessments, 2164 completed the entire neuropsychological test battery (non-completion was mostly due to time shortage). Hence, 2164 participants were included in the analysis of brain volumes with cognition.

Statistical analysis

All brain volumes were z-standardized for the total population.

We used linear regression analyses to investigate associations of cortical and subcortical brain volumes with global cognition, global gait, the cognitive domains, and the gait domains

All analyses were adjusted for age, sex, height, weight, education, and intracranial volume. Analyses on cognition were additionally adjusted for interval between MRI and cognitive assessment. Analyses on cognitive domains were adjusted for the other cognitive domains to ensure total independence of the associations. Similarly, analyses on gait domains were adjusted for the other gait domains. Analyses on Tandem were additionally adjusted for step length and step count in the tandem walk.

To adjust for multiple testing we used the eigenvalues of correlation matrices, which were calculated separately for the cortical volumes, subcortical volumes, Global Cognition and Global Gait, and all domains (both cognitive and gait).[42] This resulted in corrected significance thresholds of $p_{corrected}<5.6*10^{-4}$ for cortical and $p_{corrected}<5.1*10^{-3}$ for subcortical brain volumes with Global Cognition and Global Gait; and corrected significance thresholds of $p_{corrected}<10.1*10^{-5}$ for cortical and $p_{corrected}<9.3*10^{-4}$ for subcortical brain volumes with cognitive and gait domains.

To investigate whether associations of cortical and subcortical brain volumes with gait were driven by cognition, we repeated analyses for associations with gait that survived multiple testing, while adjusting for the cognitive domains nominally associated ($p<0.05$) with the respective brain structure. Similarly, we investigated whether associations with the cognitive scores remained while adjusting for the gait domains nominally associated with the respective brain structure.

As a sensitivity analysis, we investigated whether additional adjustment of the associations for white matter lesion volume and presence of lacunar infarcts changed results.

Results

Participants were on average 66.8 (SD 8.9) years old and 55.3% were women (Table 1). On average, cognitive assessment was performed 0.7 (SD 0.9) years after MRI and gait assessment. People without cognitive assessment were significantly less tall, less highly educated, and had smaller intracranial and total brain volume ($p<0.05$). No significant differences were found for the other population characteristics.

Associations of cortical grey matter volumes with cognition

Cortical volumes of the temporal lobe were found to associate strongest with Global Cogni-

Table 1. Population characteristics at MRI and gait assessment

	Total (n=2864)	With cognition (n=2164)
Age, years	66.8 (8.9)	66.8 (8.7)
Females, n	1583 (55.3%)	1190 (55.0%)
Education[a]	3 (3)	3 (2.25)
Height, cm	169.1 (9.3)	169.4 (9.3)
Weight, kg	78.5 (14.3)	78.6 (14.3)
Intracranial volume, ml	1473.5 (164.0)	1479.9 (164.0)
Supratentorial brain volume, ml	899.1 (99.2)	903.4 (99.1)
White matter lesion volume, ml	3.6 (3.8)	3.6 (3.8)
Presence of lacunar infarcts, n	147 (5.1%)	110 (5.1%)

Values are means (standard deviations) or numbers of participants (percentages).
Abbreviations: n, numbers of people; cm, centimeters; kg, kilograms; ml, milliliters.
[a] Median (IQR).

tion (Figure 2). Larger volume of the middle temporal gyrus (0.08 SD per SD larger volume [95% confidence interval: 0.04; 0.13]) and angular gyrus (0.07 SD [0.03; 0.11]) were associated with higher Global Cognition.

Cortical grey matter volumes only associated significantly with executive functioning and not with the other cognitive domains. A wide range of cortical structures across all lobes associated with executive functioning, with significant associations for the orbital gyri, precentral gyrus, subcentral gyrus and sulci, temporal plane of the superior temporal gyrus, postcentral gyrus, angular gyrus, and superior occipital gyrus.

After additional adjustment for the gait domains nominally associated with the respective cortical volumes, associations of cortical volumes with Global Cognition and the cognitive domains remained largely unchanged.

Associations of subcortical grey matter volumes with cognition

Larger volume of all subcortical structures except the caudate associated with higher Global Cognition (Figure 3).

In contrast to the cortical volumes, associations of subcortical grey matter volumes were spread across the cognitive domains. A larger amygdala and hippocampus associated significantly with higher executive functioning, while a larger pallidum and ventral diencephalon associated with better fine motor and information processing speed.

Similar to the cortical structures, additional adjustment for the associated gait domains hardly affected the associations of subcortical structures with Global Cognition and the cognitive domains.

	Global Cognition	Global Gait	Fine Motor Speed	Executive Functioning	Memory	Information Processing Speed	Rhythm	Phases	Variability	Pace	Tandem	Turning	Base of Support
Frontal													
TrFPoG/S	0.02	0.01	-0.02	**0.07**	-0.01	0.01	-0.01	0.02	0.00	0.01	0.02	0.00	-0.01
FMarG/S	0.03	-0.02	-0.02	0.06	0.00	0.04	-0.02	-0.01	0.01	0.00	0.01	-0.01	-0.03
MFS	0.02	0.01	0.01	0.04	0.00	0.02	-0.01	0.04	0.04	0.00	0.02	-0.05	0.01
LOrS	0.00	0.01	-0.01	0.06	-0.03	0.00	-0.03	0.02	0.02	0.02	0.00	0.02	0.00
SbOrS	0.01	0.00	-0.02	0.02	0.00	0.03	0.00	-0.01	0.01	0.00	0.02	-0.01	-0.02
OrS	0.06	0.07	0.06	0.09	-0.02	0.04	-0.02	0.05	**0.12**	0.04	0.06	0.01	-0.03
RG	0.04	0.02	0.00	0.06	0.02	0.02	-0.03	0.00	0.04	0.03	0.02	0.03	0.01
InfFGOrp	0.02	0.03	0.00	0.04	0.00	0.01	-0.02	0.03	0.03	0.03	0.02	0.02	0.01
MFG	0.02	0.04	0.05	0.07	-0.04	-0.02	0.01	0.03	0.04	0.01	0.02	-0.02	-0.01
OrG	0.07	0.02	0.00	**0.12**	0.01	0.04	-0.06	0.03	0.07	0.05	0.02	0.01	-0.01
InfFGTrip	0.01	0.06	0.01	0.07	-0.03	0.00	0.00	0.01	0.01	0.04	0.03	0.04	0.03
InfFS	-0.02	0.03	0.00	0.04	-0.04	-0.05	0.00	0.01	0.04	0.00	0.03	0.01	0.00
MedOrS	-0.02	0.00	-0.03	0.02	-0.02	-0.03	0.02	0.00	0.00	0.01	-0.01	-0.02	-0.02
SupFG	0.01	**0.09**	0.02	0.09	-0.06	0.00	0.02	0.03	0.05	0.04	0.04	0.04	0.01
SupFS	0.00	0.02	0.01	0.04	0.00	-0.05	-0.01	0.00	0.06	0.01	0.04	-0.01	-0.01
InfFGOpp	0.03	0.04	0.01	0.06	0.00	0.01	-0.03	0.00	0.03	0.04	0.04	0.03	0.00
InfPrCS	0.01	0.02	0.00	0.07	0.00	-0.02	-0.01	0.00	0.04	0.02	0.04	0.01	-0.02
SupPrCS	0.02	0.02	0.03	0.02	0.01	-0.01	-0.01	0.01	0.01	0.01	0.02	-0.01	0.04
PrCG	0.02	0.06	0.02	**0.09**	-0.03	-0.01	0.01	0.03	0.06	0.05	0.03	0.01	-0.03
SbCG/S	0.02	-0.01	-0.01	**0.10**	-0.03	-0.01	-0.05	0.01	0.01	0.04	0.03	0.00	-0.03
CS	0.03	**0.07**	0.02	0.07	-0.05	0.03	-0.01	0.04	0.07	0.06	0.04	0.02	0.00
Insula													
ALSHorp	0.02	0.03	-0.01	0.03	0.00	0.04	-0.03	0.02	0.03	0.03	0.02	0.01	0.02
ACirInS	0.00	-0.01	-0.02	0.04	-0.01	-0.01	-0.02	0.02	0.01	-0.01	-0.01	0.00	-0.01
ALSVerp	0.01	0.05	0.02	0.06	-0.04	0.00	-0.01	0.02	0.04	0.04	0.02	0.03	0.00
ShoInG	0.05	0.07	0.03	0.07	-0.01	0.06	-0.01	0.03	**0.09**	0.06	0.05	0.02	-0.03
SupCirInS	0.03	0.03	0.00	0.09	-0.02	0.01	-0.02	0.02	0.05	0.03	0.01	0.01	-0.02
LoInG/ClnS	0.04	0.06	0.01	0.06	0.03	0.02	0.00	0.03	0.04	0.05	0.01	0.03	0.00
InfCirInS	0.02	0.05	0.05	0.03	-0.06	0.04	-0.02	0.04	0.03	0.05	0.05	0.01	0.01
PosLS	0.02	0.02	0.02	0.08	-0.03	0.00	-0.01	0.01	0.02	0.03	-0.01	0.02	0.00
Limbic													
ACgG/S	0.02	-0.01	0.00	0.06	-0.01	0.00	-0.02	-0.05	0.01	0.01	0.04	0.02	-0.04
MACgG/S	0.07	-0.01	0.07	0.08	0.03	0.02	-0.04	-0.02	-0.01	0.06	0.05	0.02	-0.05
SbCaG	0.07	0.05	0.08	0.05	0.01	0.05	0.01	0.01	0.04	0.04	0.03	0.02	0.00
PerCaS	-0.01	-0.01	-0.02	0.02	0.03	-0.04	-0.01	-0.01	-0.01	0.02	0.02	-0.02	-0.03
MPosCgG/S	0.05	0.06	0.06	0.08	0.01	0.00	0.00	0.03	0.05	0.03	0.06	0.01	-0.01
CgSMarp	0.04	0.06	0.07	0.08	0.00	-0.02	0.02	0.04	0.05	0.01	0.04	0.01	-0.01
PosDCgG	0.04	-0.01	0.02	0.06	0.03	0.01	-0.02	-0.02	-0.01	0.03	-0.02	-0.01	0.01
PosVCgG	-0.02	-0.02	0.01	0.00	-0.02	-0.05	0.00	-0.02	0.00	-0.01	0.00	-0.02	0.01
Temporal													
TPo	0.06	0.03	0.02	0.07	0.03	0.03	0.00	-0.02	0.07	0.04	0.03	-0.02	-0.02
PoPl	0.04	0.04	0.02	0.07	-0.01	0.03	-0.01	0.02	0.05	0.04	0.02	0.00	-0.01
SupTGLp	0.05	**0.10**	0.07	0.06	-0.04	0.05	0.01	0.07	0.07	0.05	0.07	0.01	0.00
HG	0.01	0.03	0.02	0.07	-0.08	0.02	0.00	0.03	0.02	0.03	0.00	0.01	-0.02
ATrCoS	0.04	0.05	0.01	0.04	0.01	0.04	-0.02	0.03	0.05	0.02	0.05	0.04	0.01
TrTS	0.00	0.04	0.02	0.04	-0.05	0.00	-0.01	0.01	0.04	0.05	0.02	0.01	0.01
MTG	0.08	0.06	0.05	0.07	0.08	0.02	-0.03	0.02	0.08	0.07	0.05	0.03	-0.02
TPl	0.06	0.04	0.05	**0.11**	-0.01	0.02	-0.02	0.05	0.03	0.05	0.04	0.01	-0.01
InfTG	0.05	**0.09**	0.00	0.07	0.02	0.04	0.03	0.08	0.06	0.02	0.05	0.04	-0.03
InfTS	0.03	0.02	0.03	0.03	0.03	-0.01	-0.01	0.03	0.04	0.03	0.00	0.01	-0.01
SupTS	0.05	0.06	0.04	0.07	0.02	0.01	-0.04	0.03	0.08	**0.07**	0.06	0.01	-0.03
Parietal													
PosCG	0.04	0.04	0.03	**0.10**	-0.02	0.01	0.00	0.01	0.02	0.05	0.00	0.00	0.01
SuMarG	0.05	0.03	0.02	0.06	0.02	0.03	-0.03	0.01	0.03	0.04	0.02	0.03	0.02
PaCL/S	0.01	0.05	0.02	0.04	-0.03	0.00	0.00	0.02	0.03	0.01	0.02	0.01	0.04
PosCS	0.05	0.02	0.08	0.08	0.00	0.01	-0.04	0.00	0.06	0.04	0.03	0.00	0.01
JS	0.01	0.02	0.03	-0.01	0.00	0.01	0.00	0.00	0.01	0.01	0.04	-0.01	-0.01
SbPS	0.02	-0.01	0.02	0.03	0.00	0.00	0.00	0.00	-0.01	0.00	-0.03	0.03	-0.02
IntPS/TrPS	0.03	0.00	0.04	0.07	-0.03	0.02	-0.02	0.02	0.02	0.01	0.03	0.00	-0.03
SupPL	0.03	0.04	0.04	0.06	-0.01	0.01	0.00	-0.02	0.02	0.04	0.02	0.03	0.02
PrCun	0.03	0.03	0.03	0.04	-0.03	0.03	-0.03	-0.02	0.01	0.05	0.02	0.05	0.02
AngG	**0.07**	0.03	0.06	**0.09**	0.00	0.05	-0.02	0.00	0.02	0.06	0.03	0.01	-0.03
POcS	0.05	0.04	0.06	0.06	0.01	0.01	-0.01	0.01	0.05	0.03	0.04	-0.01	0.02
Occipital													
PaHipG	0.05	0.03	0.02	0.06	0.02	0.04	0.00	0.01	0.02	0.02	0.04	0.00	0.00
CoS/LinS	0.07	0.01	0.05	0.06	0.03	0.05	-0.04	0.01	0.06	0.05	0.03	0.00	-0.03
LOcTS	0.05	0.07	0.06	0.05	0.01	0.03	-0.02	0.03	0.05	**0.08**	0.07	0.02	-0.03
FuG	0.05	0.00	0.07	0.06	-0.02	0.03	-0.03	-0.02	0.03	0.05	0.03	-0.02	-0.04
CcS	0.02	0.00	0.02	0.06	-0.02	0.00	-0.01	0.01	0.00	0.00	0.04	-0.02	0.00
LinG	0.02	0.01	0.01	0.06	0.01	-0.02	-0.02	0.01	0.00	0.02	0.05	0.01	0.01
AOcS	0.03	0.05	0.00	0.05	0.01	0.02	0.02	0.02	0.03	0.04	0.04	0.01	-0.03
InfOcG/S	0.02	0.03	0.01	0.05	0.00	-0.01	-0.01	0.03	0.00	0.01	0.02	0.03	-0.01
SupOcS/TrOcS	0.04	0.01	0.03	0.06	0.01	0.00	0.00	0.04	0.00	0.01	0.00	-0.02	0.00
PosTrCoS	0.02	0.03	0.02	0.05	-0.02	0.01	0.00	0.02	-0.01	0.03	0.04	0.01	-0.02
Cun	0.04	0.03	0.07	0.06	0.00	-0.02	0.00	0.01	0.03	0.02	0.06	-0.03	0.00
MOcG	0.04	0.07	0.05	0.07	0.04	-0.04	0.01	0.05	0.02	0.03	0.01	0.05	0.02
MOcS/LuS	0.02	0.00	0.02	0.02	0.02	0.00	0.00	-0.03	0.01	0.01	0.02	-0.03	0.02
SupOcG	0.04	0.04	0.06	**0.09**	-0.01	-0.01	0.01	0.00	0.02	0.02	0.03	0.03	0.01
OcPo	0.02	0.02	0.03	0.04	0.00	-0.01	-0.03	0.01	0.02	0.03	0.02	0.01	0.01

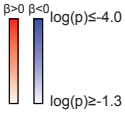

Figure 2. Associations of cortical grey matter volumes with cognition and gait. Values represent differences in standard deviations of cognition or gait per standard deviation larger cortical volume. The intensity in red and blue reflects significance of the associations, from $p<0.05$ to $p<10^{-4}$. Values in bold survived multiple testing for the respective associations, i.e. $p_{corrected}<5.6*10^{-4}$ for the global scores and $p_{corrected}<10.1*10^{-5}$ for cognitive and gait domains. All associations were adjusted for age, sex, height, weight, educational level, and intracranial volume. Associations for Tandem were additionally adjusted for step count and mean step size in the tandem walk. The abbreviations used for the cortical structures in Figure 2 are presented in Supplement Table 1.

	Global Cognition	Global Gait	Fine Motor Speed	Executive Functioning	Memory	Information Processing Speed	Rhythm	Phases	Variability	Pace	Tandem	Turning	Base of Support
Nucleus accumbens	**0.07**	0.02	0.02	0.03	0.04	**0.08**	-0.01	-0.02	-0.01	0.02	0.02	0.02	0.01
Amygdala	**0.07**	**0.06**	0.03	**0.08**	0.07	0.02	0.03	0.03	0.03	0.03	0.04	0.02	-0.02
Caudate	-0.02	-0.04	-0.01	0.00	-0.03	-0.01	-0.03	**-0.09**	0.00	-0.01	0.02	-0.03	0.02
Hippocampus	**0.08**	**0.07**	0.05	**0.11**	0.06	0.00	0.03	0.06	0.03	0.05	0.04	0.03	-0.06
Pallidum	**0.10**	0.05	**0.08**	0.04	0.02	**0.12**	0.01	0.02	0.03	0.05	0.04	0.03	-0.04
Putamen	**0.06**	0.00	0.03	0.04	0.01	0.08	-0.01	-0.05	0.04	0.03	0.02	0.00	-0.01
Thalamus	**0.12**	**0.09**	0.09	0.07	0.04	0.11	0.03	0.00	0.04	**0.07**	0.08	0.00	-0.01
Ventral diencephalon	**0.13**	**0.09**	**0.10**	0.04	0.06	**0.13**	0.03	0.01	0.03	0.06	**0.09**	0.03	0.00

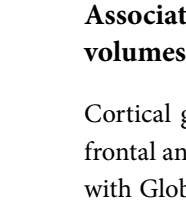

Figure 3. Associations of subcortical grey matter volumes with cognition and gait. Values represent differences in standard deviations of cognition or gait per standard deviation larger subcortical volume. The intensity in red and blue reflects significance of the associations, from $p<0.05$ to $p<10^{-4}$. Values in bold survived multiple testing for the respective associations, i.e. $p_{corrected}<5.1*10^{-3}$ for the global scores and $p_{corrected}<9.3*10^{-4}$ for cognitive and gait domains. All associations were adjusted for age, sex, height, weight, educational level, and intracranial volume. Associations for Tandem were additionally adjusted for step count and mean step size in the tandem walk. Abbreviations: CC, corpus callosum.

Associations of cortical grey matter volumes with gait

Cortical grey matter volumes in particularly the frontal and temporal lobe were found to associate with Global Gait. Larger volumes of the superior frontal gyrus (0.09 SD [0.04; 0.13]), central sulcus (0.07 SD [0.03; 0.11]), lateral aspect of the superior temporal gyrus (0.10 SD [0.06; 0.15]), and inferior temporal gyrus (0.09 SD [0.04; 0.13]) associated with higher Global Gait.

Similar to Global Gait, strongest associations were found for cortical structures of the frontal and temporal lobe with Variability and Pace. Significant associations were found of the orbital sulci and short insular gyri with Variability, and the superior temporal and lateral occipito-temporal sulcus with Pace.

After additional adjustment for nominally associated cognitive domains, associations of cortical structures with Global Gait and the gait domains remained largely unchanged. Only associations of the superior frontal gyrus and central sulcus with Global Gait clearly attenuated, but remained nominally significant ($p<0.05$).

Associations of subcortical grey matter volumes with gait

Larger amygdala, hippocampus, thalamus, and ventral diencephalon volumes associated with higher Global Gait.

We found an inverse association for the caudate, with a larger caudate associating with lower Phases (-0.09 SD [-0.12; -0.05]). In contrast, a larger thalamus associated with higher Pace and a larger ventral diencephalon with higher Tandem.

For subcortical structures, adjustment for cognitive domains resulted in the attenuation of

most associations with Global Gait, with only the association for the thalamus remaining nominally significant. In contrast, associations of subcortical structures with the specific gait domains remained largely unchanged after their respective adjustments.

Additional adjustment for white matter lesion volume and presence of lacunar infarcts only marginally attenuated the associations, with all associations remaining at least nominally significant.

Discussion

In a community-dwelling population, we found larger volumes of cortical and subcortical structures to associate with better cognition and gait. Cortical structures were mainly associated with executive functioning, Variability, and Pace. In contrast, associations for subcortical structures were spread across cognitive domains, Phases, Pace, and Tandem. The associations of cortical and subcortical grey matter structures with cognition and gait were found to be largely independent from each other.

Strengths of our study include the large community-dwelling population, automated quantification of many cortical and subcortical grey matter structures, extensive neuropsychological test battery to assess cognition, and objective gait assessment in three walking conditions. Additionally, we ensured associations found for a cognitive or gait domain to be independent from those of other cognitive or gait domains. However, since most previous studies used original correlated parameters, comparison of our findings with other studies is limited. Any previous findings with original parameters that we did not find with the corresponding domain may thus have derived from other correlated domains, for which we adjusted.

Limitations of the study include its cross-sectional design, precluding the investigation of temporal relationships of grey matter volumes with cognition and gait. Additionally, since assessments were performed at the research center, participants were likely to be relatively healthy, especially in analyses on cognition. Hence, generalization of our findings may be limited to a relatively healthy population.

To the best of our knowledge, we are the first study to describe associations of a wide range of cortical and subcortical brain volumes with a comprehensive cognitive and gait assessment. Although none of the associations for brain structures survived multiple testing for both cognitive and gait scores, practically all associations for cognition were accompanied by nominally significant associations in gait, and vice versa. Most associations of brain structures with both cognition and gait were found in the frontal lobe, temporal lobe, and subcortical

structures. This similar pattern of associations clearly supports the hypothesis that many brain structures contribute to both cognition and physical functioning. Yet, additional adjustments suggested that, although some overlap may be present, the contribution of specific brain structures to cognition and gait is largely independent from each other.

In contrast to previous studies, we found the role of cortical structures in cognition to be largely restricted to executive functioning.[1, 4, 5, 43, 44] Most associations were found for cortical structures in the frontal lobe, which supports the important role of the frontal lobe in these higher-order cognitive processes.[45] Yet, our study indicates that many other areas across the cortex are also involved in executive functioning.

Surprisingly, although strong associations were also found for the frontal cortex, cortical structures in the temporal lobe were most strongly associated with gait. The temporal lobe is traditionally considered to have a main role in cognitive functioning, but is now shown to also have an important role in gait, and thus physical functioning.[10] This notion is supported by a few recent studies that found similar associations of structures in the temporal lobe with gait.[2, 11, 12] Interestingly, we found cortical grey matter volumes to specifically associate with Pace and Variability, which have been found to relate most strongly to executive functioning.[16] The wide range of (nominally significant) associations of cortical volumes with Pace corresponds to similar findings with larger stride and step length in previous studies.[2, 3, 11] However, we are the first study to report larger cortical volumes, particularly in the frontal, insular, and temporal lobe, to associate with better Variability (less step-to-step variability). These associations are particularly important, because more step-to-step variability is a strong risk factor for future (injurious) falls.[46, 47]

Compared to cortical brain structures, even stronger associations were found for subcortical brain volumes, in particular with cognition. Also, a different pattern of associations was seen, with larger subcortical structures relating to better fine motor speed, information processing speed, Phases, and Tandem in addition to Pace and executive functioning. Strongest associations were found for the ventral diencephalon and thalamus with both cognition and gait. Furthermore, all other subcortical structures, except the caudate, associated with cognition. Hence, our study emphasizes the importance of subcortical structures in cognition, which may be even larger than for gait. Surprisingly, we found a much stronger association of the hippocampus with executive functioning than with memory. This contrasts with the main role in memory that has been attributed to the hippocampus in previous studies.[10, 48] Instead, our findings suggest the hippocampus to be more important in executive functioning, which in turn may facilitate memory. Interestingly, we found a strong inverse association of a larger caudate, and to a lesser extent putamen, associating with worse Phases (longer duration of double support). The caudate and putamen, together called the striatum, are thought to have both an excitatory and inhibitory effect on motor functions via different pathways.[9, 49] Our

findings suggest that, with atrophy of the striatum, the inhibitory pathway weakens, resulting in a disinhibited gait pattern with less double support.

Conclusions

In a community-dwelling population, cortical and subcortical grey matter volumes show similar patterns of associations with cognition as compared to gait. These associations of grey matter volumes with cognition and gait are largely independent from each other. Interestingly, patterns of associations across cognitive and gait domains clearly differ between cortical and subcortical grey matter volumes. Hence, our findings suggest that many cortical and subcortical grey matter structures may independently contribute to specific domains of both cognition and gait.

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Supplement 1. Abbreviations used for cortical structures.

Abbreviation	**Definition**
Frontal lobe	
TrFPoG/S	Transverse frontopolar gyri and sulci
FMarG/S	Fronto-marginal gyrus (of Wernicke) and sulcus
MFS	Middle frontal sulcus
LOrS	Lateral orbital sulcus
SbOrS	Suborbital sulcus (sulcus rostrales, supraorbital sulcus)
RG	Gyrus rectus
InfFGOrp	Orbital part of the inferior frontal gyrus
MFG	Middle frontal gyrus
OrG	Orbital gyri
InfFGTrip	Triangular part of the inferior frontal gyrus
InfFS	Inferior frontal sulcus
MedOrS	Medial orbital sulcus
SupFG	Superior frontal gyrus
SupFS	Superior frontal sulcus
InfFGOpp	Opercular part of the inferior frontal gyrus
InfPrCS	Inferior part of the precentral sulcus
SupPrCS	Superior part of the precentral sulcus
PrCG	Precentral gyrus
SbCG/S	Subcentral gyrus (central operculum) and sulci
CS	Central sulcus
Insula	
ALSHorp	Horizontal ramus of the anterior segment of the lateral sulcus
ACirInS	Anterior segment of the circular sulcus of the insula
ALSVerp	Vertical ramus of the anterior segment of the lateral sulcus
ShoInG	Short insular gyri
SupCirInS	Superior segment of the circular sulcus of the insula
LoInG/CInS	Long insular gyrus and central insular sulcus
InfCirInS	Inferior segment of the circular sulcus of the insula
PosLS	Posterior ramus of the lateral sulcus
Limbic lobe	
ACgG/S	Anterior part of the cingulate gyrus and sulcus
MACgG/S	Middle-anterior part of the cingulate gyrus and sulcus
SbCaG	Subcallosal area and gyrus
PerCaS	Pericallosal sulcus
MPosCgG/S	Middle-posterior part of the cingulate gyrus and sulcus

Supplement 1. Abbreviations used for cortical structures. (continued)

Abbreviation	**Definition**
CgSMarp	Margnial branch of the cingulate sulcus
PosDCgG	Posterior-dorsal part of the cingulate gyrus
PosVCgG	Posterior-ventral part (isthmus) of the cingulate gyrus
Temporal lobe	
Tpo	Temporal pole
PoPl	Polar plane of the superior temporal gyrus
SupTGLp	Lateral aspect of the superior temporal gyrus
HG	Heschl's gyrus (anterior transverse temporal gyrus)
ATrCoS	Anterior transverse collateral sulcus
TrTS	Transverse temporal sulcus
MTG	Middle temporal gyrus
TPl	Temporal plane of the superior temporal gyrus
InfTG	Inferior temporal gyrus
InfTS	Inferior temporal sulcus
SupTS	Superior temporal sulcus
Parietal lobe	
PosCG	Postcentral gyrus
SuMarG	Supramarginal gyrus
PaCL/S	Paracentral lobule and sulcus
PosCS	Postcentral sulcus
JS	Sulcus intermedius primus (of Jensen)
SbPS	Subparietal sulcus
IntPS/TrPS	Intraparietal sulcus and transverse parietal sulci
SupPL	Superior parietal lobule
PrCun	Precuneus
AngG	Angular gyrus
POcS	Parieto-occipital sulcus
Occipital lobe	
PaHipG	Parahippocampal gyrus, parahippocampal part of the medial occipito-temporal gyrus
CoS/LinS	Medial occipito-temporal sulcus (collateral sulcus) and lingual sulcus
LOcTS	Lateral occipito-temporal sulcus
FuG	Lateral occipito-temporal gyrus (fusiform gyrus)
CcS	Calcarine sulcus
LinG	Lingual gyrus, lingual part of the medial occipito-temporal gyrus
AOcS	Anterior occipital sulcus and preoccipital notch (temporo-occipital incisure)
InfOcG/S	Inferior occipital gyrus and sulcus

Supplement 1. Abbreviations used for cortical structures. (continued)

Abbreviation	**Definition**
SupOcS/TrOcS	Superior occipital sulcus and transverse occipital sulcus
PosTrCoS	Posterior transverse collateral sulcus
Cun	Cuneus
MOcG	Middle (or lateral) occipital gyrus
MOcS/LuS	Middle occipital sulcus and sulcus lunatus
SupOcG	Superior occipital gyrus
OcPo	Occipital pole

Supplement 2. Correlations of cognitive tests with the cognitive domains.

Domain	Fine motor speed	Executive functioning	Memory	Information processing speed
Amount of variance explained	20.2%	18.7%	18.4%	15.1%
Letter digit substitution task, nr of correct answers	0.33	**0.65**	0.18	0.30
Stroop reading task, time taken	-0.13	-0.19	-0.11	**-0.86**
Stroop colour naming task, time taken	-0.12	-0.26	-0.13	**-0.84**
Stroop interference task, time taken	-0.18	**-0.62**	-0.11	-0.43
Word Fluency test, nr of animals	0.05	**0.68**	0.18	0.16
Purdue Pegboard test: both hands, nr of pins	**0.87**	0.20	0.08	0.08
Purdue Pegboard test: right hand, nr of pins	**0.83**	0.13	0.14	0.12
Purdue Pegboard test: left hand, nr of pins	**0.86**	0.15	0.06	0.12
Word Verbal Learning test: immediate, nr of correct answers	0.14	0.27	**0.83**	0.12
Word Verbal Learning test: delayed, nr of correct answers	0.13	0.25	**0.86**	0.06
Word Verbal Learning test: recognition, nr of correct answers	0.03	0.01	**0.79**	0.11
Design Organization Test, nr of correct answers	0.18	**0.82**	0.13	0.06

Values in bold reflect correlations ≥0.5 of a cognitive test with the respective domain, which is the threshold to be attributed to a certain domain.
Abbreviations: nr, number.

Chapter 2.4

Associations of microstructural integrity in specific white matter tracts with human gait

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Abstract

Gait is a complex sequence of movements, requiring cooperation of many brain areas, such as the motor cortex, somatosensory cortex, and cerebellum. However, the connecting white matter tracts that form essential networks for communication across these brain areas to facilitate proper gait remains unclear. Using diffusion tensor imaging and an electronic walkway, we investigated associations of microstructural integrity in fourteen brain white matter tracts with gait, within 2330 community-dwelling individuals. Better microstructural white matter integrity associated with better gait, including larger steps, less double support, less step-to-step variability, and quicker turning. Strongest associations were found for thalamic radiations, emphasizing the importance of thalamocortical communication in gait. Additionally, strong associations were found for association tracts and forceps major, suggesting importance of intact cortex-to-cortex communication and interhemispheric visuospatial integration. These findings provide further insight into which networks of brain communication are important for human gait.

Introduction

The walking pattern, or gait, is a complex sequence of movements requiring integration of various inputs, including proprioceptive, vestibular, and visual information.[1-4] To properly integrate these inputs, many brain areas, such as the motor cortex, somatosensory cortex, and cerebellum, are involved, which are connected through a network of white matter tracts.[2, 5, 6] Damage to the white matter may therefore quickly lead to gait deficiencies.[7-9] Yet, it remains unclear which white matter tracts are essential for communication across brain areas during gait. Knowledge on involvement of specific tracts may aid in understanding how different brain areas form a network to facilitate a proper walking pattern. In turn, this may aid in better understanding the effects of localized brain lesions on gait.[6]

Gait deficiencies are common in the elderly and strongly associate with a higher fall risk and mortality.[10-14] Gait is assessable by electronic walkway through many correlated gait parameters, which may be summarized into seven independent gait domains (Figure 1).[15] Since

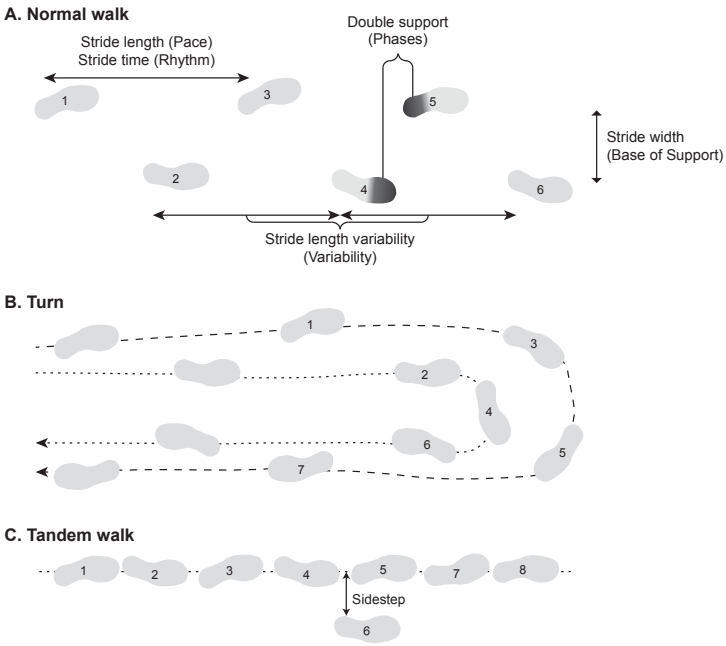

Figure 1. The three walking conditions. A. Normal walk, including constituting parameters of the five gait domains of normal walking: Rhythm, Phases, Variability, Pace, and Base of Support. B. Turn. The numbered feet are used for calculations on the parameters. Turning time is calculated from last contact of foot one until first contact of foot seven. Turning step count was the number of feet minus two (five). C. Tandem walk, including a side step which is considered an error in tandem walking.

different brain areas seem to influence different gait domains, specific white matter tracts may also be involved in specific gait domains.[16, 17]

Previous studies mainly used magnetic resonance imaging (MRI) to study macrostructural white matter pathology, i.e. white matter lesions, with human gait, suggesting involvement of thalamic radiations and corpus callosum.[7, 8] Recently, diffusion tensor imaging (DTI) has enabled visualization of microstructural white matter integrity in the brain, including normal-appearing white matter, which is invisible on conventional MRI.[18] Importantly, DTI enables assessment of microstructural integrity along entire white matter tracts, making it particularly suitable to investigate tract-specific associations.[19]

Previous studies mainly used DTI to assess global or voxel-specific microstructural white matter integrity, finding worse integrity, particularly in the corpus callosum, to associate with worse gait.[20-26] However, their global or voxel-based methods complicated investigation of tract-specific associations. Additionally, these studies investigated original parameters covering only part of the gait domains, without accounting for mutual correlations as reported previously.[15]

We investigated associations of microstructural integrity in normal-appearing white matter and specific white matter tracts with human gait, independent from macrostructural white matter pathology. Furthermore, we explored tract-specific associations with gait, independent from microstructural integrity in normal-appearing white matter.

Methods

Setting

The current study is embedded in the Rotterdam Study, a population-based cohort study in Ommoord, a suburb of Rotterdam, the Netherlands.[27] The Rotterdam Study was initiated in 1990 when all inhabitants of Ommoord aged 55 years or older were invited to participate. The Rotterdam Study was extended in 2000 and 2006, this last time inviting inhabitants aged 45 years and older. At baseline and each follow-up visit, participants undergo a home interview and extensive medical examinations at the research center. From 2005 onwards, all participants are invited for brain MRI. From March 2009 onwards, gait assessment was included in the study protocol. The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. A written informed consent was obtained from all participants.

MRI acquisition and processing

Brain MRI was performed using a 1.5-tesla scanner with an 8-channel head coil (GE Healthcare, Milwaukee, WI).[28] MRI included T1-weighted, proton-density weighted, and fluid-attenuated inversion recovery weighted (FLAIR) sequences. For diffusion weighted imaging (DWI), a single shot diffusion-weighted spin echo echo-planar imaging sequence was performed. The maximum b-value was 1000 s/mm^2 in 25 non-collinear directions. Additionally, three volumes were acquired without diffusion weighting (b-value = 0 s/mm^2). Phase and frequency encoding directions were swapped for part of the participants.[29] Therefore, we adjusted for phase encoding direction in the analyses.

Automated tissue segmentation was used to segment grey matter, white matter, white matter lesions, and cerebrospinal fluid.[30, 31] These segmentations were co-registered to the tract segmentation to obtain tract-specific white matter lesion volumes. Supratentorial intracranial volume was calculated as the sum of grey matter, normal-appearing white matter, white matter lesions, and cerebrospinal fluid.

Diffusion-weighted volumes were co-registered using affine registrations to adjust for subject motion and eddy currents.[32] The gradient vectors were realigned to their effective direction using the rotation component of the co-registration.[33] A Levenberg Marquardt estimator was used to fit the diffusion tensors. These tensor images were used to calculate fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity. Transformations were also used to resample DWI-data into a 2.5mm cubic resolution for the ball and stick diffusion model needed for probabilistic tractography.

Probabilistic tractography

Tractography was performed as described previously.[19, 29] We used PROBTRACKX, a probabilistic Bayesian framework for white matter tractography, available in FSL (version 4.1.4).[34] We identified 14 white matter tracts, of which 11 were identified for both left and right hemispheres.[19] Tracts were categorized into brainstem, projection, association, limbic, and callosal tracts. To account for partial coverage of the medial lemniscus on MRI, alternative seed masks were used (increasingly more cranial) until acceptable coverage was achieved (seed mask volume >0.7 ml). We adjusted for this difference in position of the seed mask in analyses pertaining the medial lemniscus.

We performed white matter tract segmentation by thresholding the normalized tract density images.[29] The tract volumes derived from this segmentation were used to adjust analyses for tract-specific atrophy and partial volume effects in segmentations. Standard quality checks were performed visually, and segmentations that did not cover the majority of the tract anatomy or veered off into neighboring tracts were not included in the analyses.[29]

Gait assessment

Details on our gait assessment protocol have been reported previously.[15] In short, gait was assessed using a 5.79 meter long electronic walkway (4.88 meter active area, GAITRite Platinum, CIR systems, Sparta, NJ, USA), in three different walking conditions: normal walk, turn, and tandem walk. In normal walk, participants were instructed to walk at their usual pace across the walkway. The normal walk was performed eight times, of which the first was considered a practice walk and excluded from analyses. In turn, participants were instructed to walk at their usual pace over the walkway, turn halfway, and return to the starting position. In tandem walk, participants were instructed to walk heel-to-toe over a line that was visible on the walkway.

Principal components analysis with varimax rotation was used to summarize 30 gait parameters into fewer independent gait domains, while capturing the maximum amount of variance. We derived seven gait domains, as previously described: Rhythm, reflecting cadence and stride time, among others; Phases, reflecting double support time and double support as a percentage of the gait cycle; Variability, reflecting the variability in length and time among strides; Pace, reflecting stride time and velocity; Tandem, reflecting errors in the tandem walk; Turning, reflecting turning time and turning step count; and Base of Support, reflecting stride width and its variability (Figure 1).[15] These gait domains were averaged and restandardized into the z-score Global Gait.

Covariates

At the home interview and during examinations at the research center, height, weight, educational level, and Mini-Mental State Examination (MMSE, global cognition) were assessed.[35] Educational level was categorized into seven categories: 0 = primary education, 1 = lower vocational education, 2 = lower secondary education, 3 = intermediate vocational education, 4 = general secondary education, 5 = higher vocational education and 6 = university. Missing values on MMSE and level of education were imputed by the average of five imputations, based on age, sex and the other covariates. 0.7% of variables were imputed in this way.

Study population

Between 2006 and 2011, 5989 people were invited for MRI assessment. Of the 5429 persons that were eligible, 4849 participated (89.3%). 63 participants did not complete the MRI protocol for physical problems (e.g. back pain) or technical problems. For 159 participants, DTI was not valid for technical reasons (e.g. artifacts or segmentation issues). Of the remaining participants, 154 were excluded for presence of cortical infarcts.

Of 4473 participants with usable DTI and MRI data, 2833 were invited for gait assessment

between March 2009 and March 2012. For 503 participants, gait data could not be obtained or used for the following reasons: 230 for technical reasons; 148 for physical inability; 52 for dementia; 30 for performing less than 16 steps in normal walk, lowering validity of gait parameters[36]; 24 for not following instructions; 15 for refusal; 3 for use of walking aids; and 1 for other reasons.

Finally, 2330 participants with both DTI and gait data were included in the analysis.

Statistical analysis

Global diffusion measures, including fractional anisotropy and mean, axial, and radial diffusivity, were calculated as mean values from the normal-appearing white matter.

Median diffusion measures of white matter tracts were calculated for voxels inside the tract segmentations. White matter tracts that had left/right homologues were (voxel wise) averaged if both segmentations were available. If not, the segmentation that was available, if any, was used instead. Subsequently, we calculated z-scores for all diffusion measurements, to facilitate comparison of associations across tracts.

Linear regression analyses were used to investigate associations of diffusion measures in the normal-appearing white matter with Global Gait and the gait domains, adjusted for age, sex, height, weight, education, interval between MRI and gait assessment, phase encoding direction of the diffusion scan, intra-cranial volume, normal-appearing white matter volume, white matter lesion volume, and MMSE.

Similarly, we used linear regression analyses to investigate associations of tract-specific diffusion measurements, fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity, with Global Gait. Additionally, we investigated associations of tract-specific mean diffusivity (the diffusion measurement least affected by crossing fibers) with the gait domains.

Analyses on specific tracts were adjusted for age, sex, height, weight, education, interval between MRI and gait assessment, phase encoding direction of the diffusion scan, intra-cranial volume, and tract-specific white matter and white matter lesion volumes. Furthermore, analyses on gait domains were adjusted for the other domains to ensure total independence of the associations found.

We corrected for multiple comparisons using the eigenvalues of the correlation matrix for the diffusion measurements, yielding 2 independent tests for global diffusion measurements, 24 independent tests for all tract-specific diffusivity measures, and 6 tests for mean diffusivity of all white matter tracts.[37] This resulted in a threshold of $p<0.25$ for associations of diffusion measurements in normal-appearing white matter with Global Gait (two independent tests); $p<0.0036$ for associations of diffusion measurements in normal-appearing white matter with the gait domains (2*7 tests); $p<0.0021$ for associations of tract-specific diffusion measure-

ments with Global Gait (24 tests); and p<0.0012 for associations of tract-specific mean diffusivity with the gait domains (6*7 tests).

In a sensitivity analysis, we explored whether tract-specific associations with Global Gait remained after adjusting for respective global diffusion measures in the normal-appearing white matter.

All analyses were performed using R version 3.1.0.

Results

Mean age of the population was 66.0 years (standard deviation [SD] 9.2) and 54.9% were women (Table 1). Mean interval between brain MRI and gait assessment was 2.8 years (SD 1.7).

Table 1. Population characteristics.

Characteristic	Total (n = 2330)
Age, years	65.9 (9.2)
Women, n	1283 (55.1%)
Height, cm	169.3 (9.2)
Weight, kg	78.5 (14.3)
Education[a]	3 (3)
Mini-Mental State Examination, points	28.2 (1.6)
Intra-cranial volume, ml	1340.6 (131.1)
Normal appearing white matter volume, ml	399.6 (60.8)
White matter lesion volume, ml	5.4 (8.4)
Presence of lacunar infarcts, n	153 (6.6%)
Fractional anisotropy	0.34 (0.02)
Mean diffusivity, 10^{-3} mm^2/s	0.74 (0.03)
Axial diffusivity, 10^{-3} mm^2/s	1.02 (0.03)
Radial diffusivity, 10^{-3} mm^2/s	0.60 (0.03)

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

[a] Education is presented as median (inter-quartile range).

Abbreviations: kg, kilograms; ml, milliliters; mm^2/s, squared millimeters per second.

Table 2. Associations of global diffusion measures of normal-appearing white matter with gait.

	Global Gait	Rhythm	Phases	Variability	Pace	Tandem[a]	Turning	Base of Support
Fractional anisotropy	**0.10 (0.06; 0.15)**	0.01 (-0.03; 0.05)	**0.07 (0.03; 0.10)**	0.05 (0.01; 0.09)	**0.07 (0.04; 0.11)**	0.01 (-0.03; 0.06)	0.05 (0.00; 0.09)	0.02 (-0.03; 0.06)
Mean diffusivity	**-0.16 (-0.22; -0.11)**	0.00 (-0.05; 0.05)	**-0.08 (-0.13; -0.04)**	**-0.11 (-0.17; -0.05)**	**-0.10 (-0.14; -0.05)**	-0.04 (-0.10; 0.02)	**-0.12 (-0.18; -0.06)**	-0.04 (-0.09; 0.02)
Axial diffusivity	**-0.15 (-0.21; -0.09)**	0.02 (-0.04; 0.07)	-0.06 (-0.12; -0.01)	**-0.13 (-0.19; -0.06)**	**-0.07 (-0.12; -0.03)**	-0.04 (-0.10; 0.02)	**-0.14 (-0.20; -0.07)**	-0.04 (-0.10; 0.03)
Radial diffusivity	**-0.15 (-0.20; -0.10)**	0.00 (-0.05; 0.04)	**-0.08 (-0.13; -0.04)**	**-0.10 (-0.15; -0.04)**	**-0.10 (-0.14; -0.06)**	-0.04 (-0.09; 0.02)	**-0.10 (-0.16; -0.05)**	-0.03 (-0.09; 0.02)

Values represent differences in standard deviations of gait (95% confidence intervals) per standard deviation higher value in the diffusion measure. Results in bold were significant with a $p_{corrected}<0.025$ for Global Gait and $p_{corrected}<0.0036$ for the gait domains. All analyses were adjusted for age, sex, height, weight, education, interval between MRI and gait assessment, phase encoding direction of the diffusion scan, intra-cranial volume, normal-appearing white matter volume, natural log-transformed white matter lesion volume, presence of lacunar infarcts, and Mini-Mental State Examination.

[a] Additionally adjusted for step count and mean step size in the tandem walk.

Associations of global diffusion measures in the normal-appearing white matter with gait

Higher fractional anisotropy (0.10 SD per SD higher fractional anisotropy [95% confidence interval: 0.06; 0.15]) and lower mean diffusivity (-0.16 SD [-0.22; -0.11]), driven by both axial and radial diffusivity, associated with higher Global Gait (Table 2). Higher fractional anisotropy also associated with higher Phases (0.07 SD [0.03; 0.10]) and Pace (0.07 SD [0.04; 0.11]), while higher mean diffusivity, driven by axial and radial diffusivity, associated with lower Phases (-0.08 SD [-0.13; -0.04]), Variability (-0.11 SD [-0.17; -0.05]), Pace (-0.10 SD [-0.14; -0.05]), and Turning (-0.12 SD [-0.18; -0.06]).

Associations of tract-specific diffusion measures with Global Gait

Associations of fractional anisotropy and mean diffusivity in specific white matter tracts with Global Gait are depicted in Figure 2. Strongest associations were found of fractional anisotropy in the callosal and association tracts with Global Gait (Table 3). Furthermore, mean diffusivity in nearly all tracts associated with Global Gait, with strongest associations for

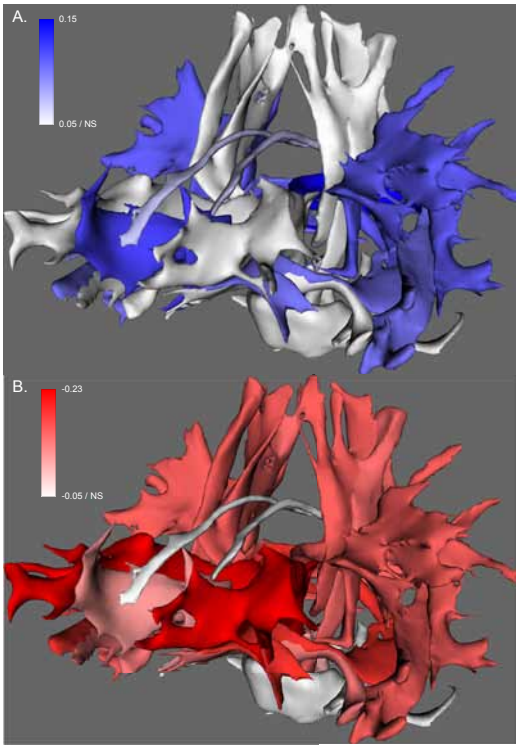

Figure 2. Associations of tract-specific fractional anisotropy and mean diffusivity with Global Gait. Intensities in blue and red indicate the strength (β) of the associations. Associations in white were non-significant. A. Associations of tract-specific fractional anisotropy. Strongest associations were found for the forceps major (medial posterior) and minor (medial anterior). B. Associations of tract-specific mean diffusivity. Strongest associations were found for the anterior thalamic radiation (lateral anterior), posterior thalamic radiation (posterior medial), and inferior fronto-occipital fasciculus (inferior anterior to posterior)

Table 3. Associations of tract-specific microstructural integrity with Global Gait

	Model I				Model II			
	FA	MD	AxD	RaD	FA	MD	AxD	RaD
Brainstem								
Middle cerebellar peduncle	-0.01	-0.05	-0.05	-0.03	-0.02	-0.01	-0.02	0.00
Medial lemniscus[a]	0.02	**-0.10**	-0.06	**-0.08**	-0.01	-0.04	-0.04	-0.01
Projection								
Corticospinal tract	0.04	**-0.15**	**-0.09**	**-0.09**	0.00	-0.05	-0.02	0.00
Anterior thalamic radiation	0.06	**-0.23**	**-0.23**	**-0.21**	-0.01	**-0.16**	**-0.20**	**-0.12**
Posterior thalamic radiation	**0.11**	**-0.19**	**-0.13**	**-0.19**	0.06[b]	**-0.12**	-0.09[b]	-0.10[b]
Superior thalamic radiation	0.04	**-0.16**	**-0.12**	**-0.11**	-0.01	-0.06	-0.05	-0.02
Association								
Inferior fronto-occipital fasciculus	**0.10**	**-0.19**	**-0.13**	**-0.18**	0.05	-0.10[b]	-0.07[b]	-0.09[b]
Inferior longitudinal fasciculus	**0.10**	**-0.16**	**-0.16**	**-0.16**	0.05	-0.07	**-0.12**	-0.06
Superior longitudinal fasciculus	**0.11**	**-0.16**	**-0.17**	**-0.15**	0.04	-0.06	-0.12[b]	-0.04
Uncinate fasciculus	0.07	**-0.14**	**-0.11**	**-0.12**	0.00	-0.01	-0.01	0.00
Limbic								
Cingulate gyrus part of the cingulum	**0.07**	-0.06	0.02	**-0.09**	0.03	0.08	0.06	0.02
Parahippocampal part of the cingulum	0.02	-0.05	-0.05	-0.05	0.00	0.01	-0.01	0.01
Callosal								
Forceps major	**0.14**	**-0.16**	-0.03	**-0.16**	**0.09**	-0.07[b]	0.00	-0.08[b]
Forceps minor	**0.12**	**-0.12**	-0.02	**-0.15**	0.06[b]	0.04	0.03	-0.03

Values represent differences in standard deviations of Global Gait per standard deviation higher value in the diffusion measure. Results in bold were significant with a $p_{corrected}<0.0021$. Model I: adjusted for age, sex, height, weight, education, interval between MRI and gait assessment, phase encoding direction of the diffusion scan, Mini-Mental State Examination, intra-cranial volume, presence of lacunar infarcts, and tract-specific white matter and natural log-transformed white matter lesion volume. Model II: Model I, adjusted for the respective diffusion measurement in normal-appearing white matter.

[a] Additionally adjusted for the variable position of the seed mask.[29]

[b] Remaining suggestive associations ($p<0.05$).

Abbreviations: FA, fractional anisotropy; MD, mean diffusivity; AxD, axial diffusivity; RaD, radial diffusivity.

Table 4. Associations of tract-specific mean diffusivity with the gait domains.

	Rhythm	Phases	Variability	Pace	Tandem[a]	Turning	Base of Support
Brainstem							
Middle cerebellar peduncle	0.00	-0.01	-0.07	-0.02	-0.02	-0.02	-0.01
Medial lemniscus	0.01	-0.03	-0.07	**-0.08**	-0.04	-0.03	-0.05
Projection							
Corticospinal tract	-0.01	**-0.08**	**-0.10**	**-0.07**	-0.03	**-0.10**	-0.04
Anterior thalamic radiation	-0.03	**-0.18**	**-0.13**	**-0.12**	-0.07	-0.09	-0.04
Posterior thalamic radiation	-0.03	**-0.11**	**-0.13**	**-0.11**	-0.08	-0.10	0.00
Superior thalamic radiation	0.00	**-0.10**	**-0.10**	-0.07	-0.07	**-0.11**	-0.02
Association							
Inferior fronto-occipital fasciculus	-0.01	**-0.12**	**-0.14**	**-0.10**	-0.05	**-0.11**	-0.03
Inferior longitudinal fasciculus	0.00	-0.07	**-0.12**	**-0.09**	-0.03	**-0.13**	-0.04
Superior longitudinal fasciculus	-0.03	**-0.10**	**-0.12**	-0.06	-0.01	**-0.10**	-0.05
Uncinate fasciculus	0.02	-0.07	-0.08	**-0.09**	-0.03	**-0.11**	-0.05
Limbic							
Cingulate gyrus part of the cingulum	0.00	-0.01	-0.07	-0.05	-0.02	-0.04	0.01
Parahippocampal part of the cingulum	-0.01	0.01	-0.03	-0.02	-0.04	-0.02	-0.04
Callosal							
Forceps major	-0.01	**-0.10**	**-0.10**	**-0.09**	-0.02	**-0.11**	-0.03
Forceps minor	0.03	**-0.08**	**-0.11**	**-0.09**	-0.06	-0.06	-0.02

Values represent differences in standard deviations of gait domains per standard deviation higher mean diffusivity. Results in bold were significant with a $p_{corrected}<0.0012$. All analyses were adjusted for age, sex, height, weight, education, interval between MRI and gait assessment, phase encoding direction of the diffusion scan, Mini-Mental State Examination, intra-cranial volume, presence of lacunar infarcts, and tract-specific white matter and natural log-transformed white matter lesion volume.

[a] Additionally adjusted for step count and mean step size in the tandem walk.

[b] Additionally adjusted for the variable position of the seed mask.[29]

thalamic radiations and association tracts. The tract-specific associations of axial and radial diffusivity with Global Gait were similar to each other, although stronger associations were found for radial diffusivity with callosal tracts and the cingulate gyrus part of the cingulum.

Associations of tract-specific mean diffusivity with separate gait domains

The strongest associations with Phases were found for higher mean diffusivity in the anterior thalamic radiation, followed by weaker associations for the other projection tracts, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, and callosal tracts (Figure 3A, Table 4). Higher mean diffusivity across many projection, callosal, and association tracts associated with both lower Variability and Pace (Figure 3B-C). In contrast to Phases, strongest associations of mean diffusivity with Turning were found for association tracts and the forceps major (Figure 3D). No significant associations were found for Rhythm, Tandem, and Base of Support.

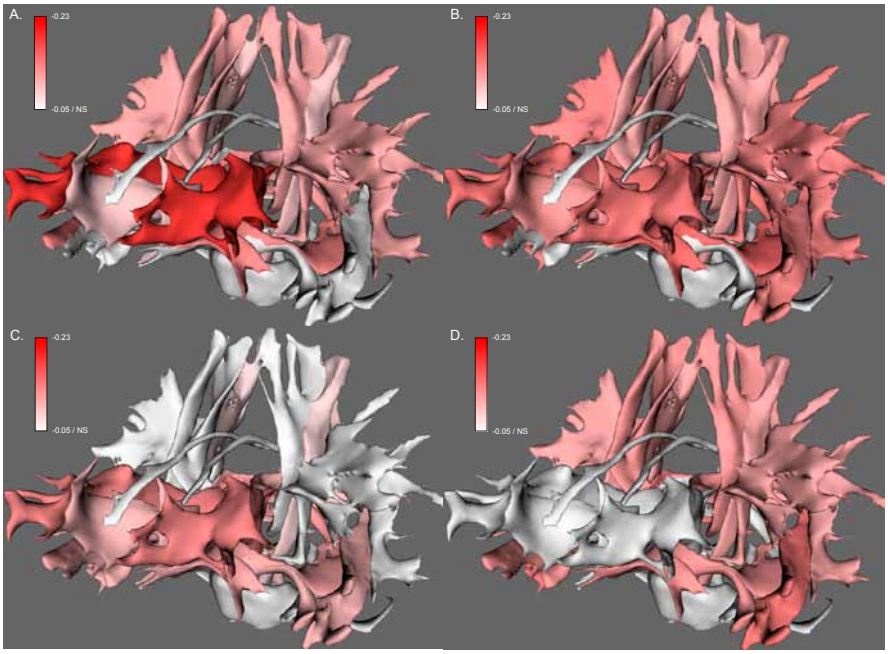

Figure 3. Associations of tract-specific mean diffusivity with Phases, Variability, Pace, and Turning. The intensity in red indicates the strength (β) of the associations. Associations in white were non-significant. Widespread associations of tract mean diffusivity with Phases (A), Variability (B), Pace (C), and Turning (D) can be appreciated. For Phases, most associations were found with projection tracts, in particular the anterior thalamic radiation (A, medial anterior). In contrast, most associations were found of association tracts with Turning, in particular the inferior longitudinal fasciculus (D, lateral inferior).

Sensitivity analysis

After additional adjustment of tract-specific analyses for global diffusion measures in normal-appearing white matter, we found that associations remained for diffusion measures in the anterior and posterior thalamic radiation, inferior longitudinal fasciculus, and forceps major with Global Gait. Additionally, suggestive associations ($p<0.05$) remained for diffusion measures in the inferior fronto-occipital fasciculus, superior longitudinal fasciculus, and forceps minor.

Discussion

In a community-dwelling population, we found better microstructural white matter integrity to relate to better gait, as reflected by Global Gait, Phases, Variability, Pace, and Turning. Strongest associations were found for microstructural integrity of thalamic radiations, association tracts, and forceps major. Even after adjustment for global white matter integrity, associations among these tracts with gait remained.

Study strengths include the objective assessment of gait in three walking conditions and assessment of microstructural integrity in fourteen white matter tracts. Additionally, our adjustment for macrostructural white matter changes (e.g. white matter atrophy and lesion volume) indicates our findings reflect associations of subtle white matter changes with gait. Moreover, explorative analyses enabled identification of tract-specific associations independent of global integrity in normal-appearing white matter. Finally, our study in relatively healthy community-dwelling individuals ensures that findings contribute to the general knowledge on which white matter tracts are involved in human gait.

Limitations include the (semi) cross-sectional design, precluding investigation of temporal relationships. Also, we investigated only fourteen of many tracts. Furthermore, although assessing complete white matter tracts has the advantage of taking into account damage along the entire tract, information about specific locations is lost. Yet, voxel-based methods have the disadvantage of uncertainty in allocation of voxels to tracts, due to closeness of the tracts and potential misregistration, which complicates investigation of tract-specific associations.

In community-dwelling individuals, we found better microstructural integrity in normal-appearing white matter and a wide range of white matter tracts to associate with better gait. We are the first study to investigate associations of tract-specific microstructural integrity with a comprehensive gait assessment, limiting comparison to other studies. Yet, previous studies, mainly using voxel-based methods, did find similar widespread associations, assessing either global gait scores or parameters constituting Rhythm, Pace, or Base of Support.[21, 25, 26] In our

study, better microstructural white matter integrity specifically associated with better Phases (less double support), Variability (less gait variability), Pace (larger steps), and Turning (less turning time). The associations for Pace correspond to the many voxels related to stride length in a previous study, but were now found to be independent from macrostructural white matter pathology.[21] We could not confirm previously found associations of microstructural white matter integrity with parameters constituting Rhythm and Base of Support.[20, 21, 25] However, our use of mutually independent domains may indicate that previously found associations with these correlated parameters have actually derived from other gait domains, e.g. Phases or Pace. Our findings may be particularly important, because Phases, Variability, Pace, and Turning relate to (injurious) fall risk and mortality.[10-12, 38] Since poor microstructural white matter integrity may predispose white matter lesions, which may be preventable by treating cardiovascular risk factors, similar treatment may reduce loss of microstructural integrity.[39, 40] In turn, our findings suggest that such treatment may aid to reduce gait deterioration, and thereby related health problems.

Of the various tracts, strongest associations were found of thalamic radiations with gait. Thalamic radiations are important for communication through the thalamus among cortices, cerebellum, and basal ganglia.[2,5,26,30,31] Previous studies have already suggested importance of such communication in gait.[2, 5, 6, 41, 42] Strongest associations of anterior and posterior thalamic radiations indicate largest importance of connections between thalamus and frontal, posterior parietal, and occipital cortex, in particular to control duration of double support (Phases) and step-to-step variability (Variability).[6] The many associations for association tracts suggest additional importance of direct cortex-to-cortex communication in gait.[6] These findings support involvement of higher-level neural functioning, which conforms to the close link between cognition and gait.[43, 44] Involvement of callosal tracts in gait is supported by previous studies, which found strongest associations for the forceps minor (genu).[21, 23, 26] Our study supports involvement of the forceps minor in gait, but, similar to a study on white matter lesions, suggests larger importance of the forceps major (splenium), particularly in turning.[8] The corpus callosum facilitates interhemispheric communication, with the forceps major being especially important for visuospatial integration.[6, 45, 46] As such, the forceps major may aid in inter-limb coordination, which may be essential in gait.

Importantly, various associations of tract-specific microstructural integrity with Global Gait, including those for anterior and posterior thalamic radiations, inferior longitudinal fasciculus, and forceps major, remained even after adjusting for microstructural integrity in normal-appearing white matter. Hence, these white matter tracts may be essential in gait control, independent from any involvement of global white matter.

Conclusions

In community-dwelling individuals, better microstructural white matter integrity associates with better gait, including less double support, less gait variability, larger steps, and quicker turning. Microstructural integrity in thalamic radiations, association tracts, and forceps major associates most strongly with gait. Hence, these tracts may be most essential for communication among brain areas to facilitate normal gait in humans.

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Chapter 2.5

Chronic joint pain in the lower body is associated with gait differences independent from radiographic osteoarthritis

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Abstract

Objective: Gait is an important indicator of health and gait deficiencies are strong risk factors of falls and death. Chronic pain in the lower body may impair gait and thus lead to gait-related morbidity and mortality. We investigated the associations between pain in the lower body and gait in a community dwelling population, and their dependence on osteoarthritis (OA).

Methods: The study included 2304 participants from the Rotterdam Study, a population-based cohort study in the Netherlands, that underwent gait assessment by electronic walkway. Gait was summarized into seven gait domains, i.e. Rhythm, Variability, Phases, Pace, Tandem, Turning, and Base of Support. Chronic pain in the lower body was assessed using pain homunculi. OA was defined as a Kellgren and Lawrence score of 2 or higher on radiographs of the hip and/or knee.

Results: Participants with chronic pain in the lower body, especially in the leg and hip, had slower Rhythm, longer Phases (longer double support), and less Pace (smaller steps). After excluding OA-cases these associations remained. Additionally, we found unilateral pain to associate with larger gait asymmetry and gait differences in both painful and unpainful leg.

Conclusion: Chronic pain in the lower body associates with gait differences in a community-dwelling population independent from OA. Participants with pain were found to walk with slower and smaller steps and longer double support. Additionally, we found unilateral pain to associate with larger gait asymmetry and gait differences in both painful and unpainful leg. Care and treatment for chronic pain might help to decrease gait problems and thereby fall risk and associated mortality.

Introduction

Chronic pain is very common in elderly people and results in impairment of daily functioning. Chronic pain in the lower body is often a cause of decreased mobility, which is related to lower quality of life. Especially in the older population, this decreased mobility not only relates to quality of life, but also to higher mortality.[1-4]

Gait assessment, by electronic walkway, may provide a very accurate measurement of this decreased mobility. Gait is an accurate indicator of health and poor gait is strongly associated with a higher risk of falls and mortality.[3, 5-9] Gait is a complex concept that can be assessed using many parameters. Previous studies have shown that these many parameters can be summarized into seven gait domains, comprehensively capturing the gait pattern.[10, 11]

Previous studies on the associations between pain and gait parameters mainly focused on osteoarthritis (OA), which is the most common cause of pain in the lower body of elderly people.[12-18] The clinical definition of osteoarthritis not only includes joint pain, but also joint damage on radiographs. Since joint damage does not necessarily mean joint pain and vice versa, studying associations independent of OA will inform about the true effect of lower body pain on gait. In addition, recognizing differences in gait between OA-related and unrelated pain might provide opportunities to distinguish people with true OA from those having musculoskeletal pain due to other factors.

Furthermore, better understanding of the relationship between lower body pain and gait may allow for new interventions to decrease pain and gait problems, and hence related morbidity and mortality. We investigated associations of pain in the lower body with gait in a community dwelling population of middle-aged and elderly individuals.

Methods

Setting

This study is part of the Rotterdam Study, a large prospective population-based cohort study of men and women aged 45 years and older in the Netherlands. The study design and rationale are described elsewhere in detail.[19] In summary, the Rotterdam Study aims to investigate determinants of chronic diseases in the elderly. The study was initiated in 1990 inviting all inhabitants aged 55 years and older from Ommoord, a suburb of Rotterdam, and was extended in 2000 again inviting all inhabitants aged 55 years and older. In 2006, the study was further extended inviting all inhabitants aged 45 years and older. At baseline and each follow-up visit, all participants undergo a home interview and extensive set of examinations at the research center.

The Rotterdam Study has been approved by the medical ethics committee according to

the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare, and Sports of the Netherlands. A written informed consent was obtained from all participants.

Assessment of chronic joint pain

A pain homunculus was presented to the participants in order to assess chronic joint pain. The pain homunculus showed a picture of the front and the back of the human body. Participants were asked the following question: "Did you have pain anywhere in your body, for at least half of the days, during the last six weeks?". Painful sites were marked with a circle by the participant. The homunculi were then scored using a template assigning the circles to 14 different joint pain regions, including neck, shoulders, elbows, hands, low back, hips, knees and feet. For the current study, we used pain scores of the hips, knees, feet, legs and low back. Additionally, we created a summary score for 'widespread pain in the lower body', in which we summed pain in the left leg, right leg and low back and divided this score by three.

Gait assessment

The full gait assessment protocol has been published previously.[11] In short, gait was assessed using a 5.79m long electronic walkway with pressure sensors. (GAITRite Platinum; CIR systems, Sparta, NJ: 4.88m active area; 120Hz sampling rate), which is considered to be an accurate system for gait assessment.[20-22]

Participants followed a standardized gait protocol consisting of three walking conditions: normal walk, turning and tandem walk. In normal walk, participants were asked to walk at their usual pace across the walkway. This walk was performed eight times, with the first walk being considered a practice walk and not used for gait parameter calculations. In turning, participants walked at their usual pace across the walkway, turned halfway, and returned to their starting position. In tandem walk, participants walked heel-to-toe over a line that was visible on the walkway.

Principal components analysis was used to summarize mean gait parameters of both legs into seven gait domains, as previously described: 1. Rhythm, reflecting cadence and single support time; 2.Variability, reflecting variability in step length and time; 3.Phases, reflecting double support time and single support time as a percentage of the total stride time; 4. Pace, reflecting step length and velocity; 5. Tandem, reflecting errors in tandem walking; 6. Turning, reflecting the number of steps and time needed to turn; and 7. Base of Support, reflecting stride width and stride width variability.[11]

To investigate walking behavior of a single leg, we used the highest correlating gait parameters from the gait domains, that could be computed for a single leg: single support time for Rhythm, step length variability for Variability, single support percentage for Phases, step length for Pace, and stride width variability for Base of Support. We did not derive single leg

gait parameters for Tandem and Turning. To study gait asymmetry, values on gait parameters of the right leg were subtracted from the values on gait parameters of the left leg.

Study population

Between March 2009 and March 2012, 3651 persons were invited for gait assessment. We excluded 163 individuals for perceived physical inability to perform gait assessment, 115 because of having a hip or knee prosthesis and 27 because of technical problems,. Thirty-four subjects were excluded because they completed less than 16 steps of normal walking on the walkway, reducing validity of the gait parameters.[23] Furthermore, 12 participants refused gait assessment, 3 participants were excluded for the use of walking aids on the walkway, one for not following instructions and 2 for other reasons.

Of the remaining 3294 participants, only 2304 had pain homunculi data available, because the pain homunculi had temporarily been removed from the study protocol. These 2304 participants were used in the analysis.

Statistical analysis

We investigated associations between pain in the lower body and gait in four different ways. First, we used the gait domains to study associations of pain in the lower body with gait in both legs.

Second, we investigated associations of unilateral pain with gait asymmetry. Here, individuals with bilateral pain in the studied body part were excluded. For these analysis, we recoded pain in the left leg as 1 and pain in the right leg as -1 and the absence of pain as 0. Hence, a positive association would imply that unilateral pain results in larger asymmetry with higher values of the gait parameters in the painful leg compared to the unpainful leg.

Third, to elucidate gait differences in the painful leg, we used the gait parameters of the painful leg in people having unilateral pain, and the mean gait parameters of both legs for individuals free of pain in the respective body part.

Fourth, to elucidate gait differences in the unpainful leg, we used gait parameters of the unpainful leg in people with unilateral pain in the lower body, and the mean of both legs for individuals free of pain.

We used linear regression analysis to investigate the associations of chronic pain in the lower body with the different gait domains, gait asymmetry, gait in the painful leg, and gait in the unpainful leg. All analysis were adjusted for age, sex, height, weight and time interval between pain and gait assessment. Analysis on Tandem were additionally adjusted for mean step length and step count in the tandem walk.

To investigate whether analysis were driven by OA, we repeated the analysis on associations between pain in the lower body and the gait domains, after excluding participants with

OA in the hip or knee. These analysis were performed in a sub-population, in which OA was rated on radiographs as a Kellgren and Lawrence score of 2 or higher.[24]

Subsequently, we investigated whether gait differs for presence of OA in individuals with pain in hip and/or knee, by associating hip and knee osteoarthritis with the seven gait domains.

SPSS version 21.0 (SPSS INC., Chicago, USA) was used for all analysis.

Results

Characteristics of the study population are described in Table 1. Mean age of the participants was 63.5 years and 54.8% were female. Pain in the lower body was present in 35.6% of the subjects, with pain in the lower back, hip, knee or foot being present in respectively 17.1%, 8.6%, 16.4% and 7.9% participants.

Table 1. Population characteristics

Characteristic	Total (n = 2304)
Age, years	63.5 (7.5)
Females, n	1262 (54.8%)
Height, cm	170.0 (9.2)
Weight, kg	79.5 (14.7)
Pain in the lower body, n	820 (35.6%)
Pain lower back, n	395 (17.1%)
Pain Hip, n	198 (8.6%)
Pain Knee, n	377 (16.4%)
Pain Foot, n	183 (7.9%)

Values are means (standard deviations) or numbers of participants (percentages).
Abbreviations: cm, centimeters; kg, kilograms; n, number.

Associations between pain in the lower body and gait domains

Widespread pain in the lower body was associated with lower Rhythm (-0.19 SD, p=0.005), Phases (-0.20 SD p= 0.002) and Pace (-0.19 SD, p=0.003), while Variability was higher in individuals with widespread lower body pain (0.16 SD, p=0.046)(Table 2). When we examined pain in the leg and low back separately, we observed that leg pain resulted in lower Rhythm, Phases and Pace, while low back pain was only associated with lower Pace. Further stratification into separate locations in the leg showed that the majority of the differences in

Table 2. Associations of pain in the lower body with the gait domains

Domain	Rhythm	Variability	Phases	Pace	Tandem[a]	Turning	Base of Support
Pain lower body[b]	**-0.19**** **(-0.33; -0.06)**	**0.16*** **(0.00; 0.31)**	**-0.20**** **(-0.34; -0.07)**	**-0.19**** **(-0.31; -0.07)**	0.02 (-0.13; 0.17)	0.01 (-0.14; 0.17)	0.03 (-0.12; 0.18)
Pain lower back	-0.06 (-0.16; 0.04)	0.05 (-0.06; 0.16)	-0.05 (-0.15; 0.05)	**-0.10*** **(-0.19; -0.01)**	-0.03 (-0.14; 0.08)	0.04 (-0.07; 0.16)	-0.05 (-0.16; 0.06)
Pain leg	**-0.11*** **(-0.20; -0.02)**	0.08 (-0.02; 0.18)	**-0.15**** **(-0.23; -0.06)**	**-0.10*** **(-0.18; -0.02)**	0.03 (-0.07; 0.12)	-0.01 (-0.11; 0.09)	0.04 (-0.06; 0.14)
Pain hip	-0.13 (-0.26; 0.01)	0.03 (-0.13; 0.18)	**-0.19**** **(-0.32; -0.06)**	**-0.16*** **(-0.28; -0.03)**	0.12 (-0.03; 0.27)	0.04 (-0.11; 0.19)	0.07 (-0.08; 0.22)
Pain knee	-0.09 (-0.19; 0.01)	0.01 (-0.10; 0.12)	-0.04 (-0.14; 0.06)	-0.07 (-0.16; 0.03)	0.04 (-0.07; 0.15)	-0.03 (-0.14; 0.08)	0.05 (-0.06; 0.17)
Pain foot	-0.06 (-0.20; 0.08)	0.08 (-0.08; 0.24)	**-0.14*** **(-0.28; 0.00)**	-0.08 (-0.21; 0.05)	-0.04 (-0.20; 0.12)	-0.02 (-0.17; 0.14)	0.06 (-0.10; 0.22)

Values represent differences in z-scores of gait (95% confidence interval) for pain in the respective body part. A lower value of gait represents worse gait. Pain was scored as 1 = yes and 0 = no. Results in bold survived thresholds of nominal significance ($^{*}p < 0.05$; $^{**}p < 0.005$). All analysis were adjusted for age, sex, height, weight, and time interval between pain and gait assessment. N = 2139.

[a] Additionally adjusted for the step count and step size within the tandem walk.

[b] Pain lower body = (pain in lower back + pain left leg + pain right leg) / 3.

gait were driven by hip pain. In addition, pain in the foot was associated with Phases (-0.14 SD, p=0.047), while knee pain was not significantly associated with gait differences, despite larger power compared to hip and foot pain.

Associations of unilateral pain with gait asymmetry, gait in painful and gait in unpainful leg

Unilateral pain in the leg associated with larger gait asymmetry in step length, with larger step length in the painful leg compared to the unpainful leg (0.42 cm, p=0.003) (Table 3). Additionally, unilateral pain in the leg associated with smaller step length and shorter single support percentage in both the painful and the unpainful leg compared to participants without leg pain. (Supplement 1)

Unilateral pain in the hip associated with more asymmetry in step length and single support percentage, with larger step length (0.50 cm, p=0.023) and shorter single support percentage (-0.24%, p=0.045) in the painful leg compared to the unpainful leg (Table 3). Similar

Table 3. Associations of unilateral pain in the leg, hip, knee and foot with gait asymmetry between both legs

Domain	*Rhythm*	*Variability*	*Phases*	*Pace*	*Base of Support*
Gait parameter	Single Support Time (0.1 s)	Step length SD (cm)	Single Support Phase (%)	Step length (cm)	Stride width SD (cm)
Unilateral pain leg					
Asymmetry	-0.01 (-0.03; 0.00)	0.01 (-0.08; 0.11)	-0.13 (-0.28; 0.02)	**0.42** (0.14; 0.70)**	0.01 (-0.05; 0.07)
Unilateral pain hip					
Asymmetry	-0.02 (-0.05; 0.00)	-0.13 (-0.27; 0.02)	**-0.24* (-0.47; -0.01)**	**0.50* (0.07; 0.94)**	-0.05 (-0.15; 0.04)
Unilateral pain knee					
Asymmetry	-0.01 (-0.03; 0.01)	0.07 (-0.06; 0.19)	-0.09 (-0.29; 0.10)	0.05 (-0.31; 0.41)	0.02 (-0.06; 0.10)
Unilateral pain foot					
Asymmetry	-0.01 (-0.04; 0.02)	**0.26** (0.09; 0.42)**	-0.11 (-0.38; 0.16)	**0.65* (0.15; 1.15)**	0.01 (-0.10; 0.12)

Values represent differences in gait parameters (95% confidence interval) for presence of pain in the respective body part. Results in bold survived thresholds of nominal significance ($^{*}p < 0.05$; $^{**}p < 0.005$). All analysis were adjusted for age, sex, height, weight, and time interval between pain and gait assessment. Leg: n = 2012; hip: n = 2231; knee: n=2103; foot: n = 2215.

Asymmetry: difference in gait asymmetry between painful and unpainful leg compared to asymmetry between both legs of people without pain.

Abbreviations: s, seconds; SD, standard deviation; cm, centimetres; n, number of participants.

to unilateral leg pain, we found unilateral hip pain to associate with shorter single support percentage in the painful leg and smaller steps and shorter single support percentage in the unpainful leg, compared to participants without hip pain. (Supplement 1)

Unilateral pain in the foot was also associated with larger asymmetry in step length, with larger steps in the painful leg compared to the unpainful leg (Table 3). Unilateral foot pain was also associated with smaller steps and shorter single support percentage in the painful leg and smaller steps in the unpainful leg. (Supplement 1) Furthermore, we found unilateral foot pain to associate with larger asymmetry in step length variability, with larger step length variability in the painful leg compared to the unpainful leg (0.26 cm, p=0.003). Additionally, we found unilateral foot pain to associate with larger step length variability in the painful leg compared to people without pain. (Table 3)

We found no significant associations between unilateral knee pain and gait. (Table 3 and Supplement 1)

Role of OA in associations between pain in the lower body and gait

After excluding 582 participants with radiographic hip and/or knee osteoarthritis, the associations remained largely unchanged (Supplement 2), suggesting that associations of lower body pain with gait were not driven by hip and/or knee OA.

When investigating OA-related gait differences in people with pain in the hip or knee, we found painful hip OA to associate with lower Variability compared to pain without hip OA (-0.45 SD, p=0.026). For painful knee OA, no significant associations with the gait domains were found. (Table 4)

Table 4. Relation between gait domains and OA in participants with pain in the hip or knee

Domain	Rhythm	Variability	Phases	Pace	Tandem[a]	Turning	Base of Support
OA hip	0.23	**-0.45***	0.03	-0.08	-0.08	-0.29	0.00
	(-0.15; 0.62)	**(-0.85; -0.05)**	(-0.34; 0.41)	(-0.41; 0.24)	(-0.48; 0.32)	(-0.68; 0.11)	(-0.41; 0.41)
OA knee	0.15	-0.01	0.16	0.12	-0.12	-0.06	-0.07
	(-0.07; 0.37)	(-0.24; 0.22)	(-0.05; 0.38)	(-0.07; 0.30)	(-0.35; 0.11)	(-0.28; 0.17)	(-0.30; 0.16)

Values represent differences in z-scores of gait (95% confidence interval) for presence of osteoarthritis in the respective body part. Osteoarthritis was scored as 1 = yes and 0 = no. Results in bold survived thresholds of nominal significance (*p < 0.05). All analysis were adjusted for age, sex, height, weight and the interval between OA and gait assessment and . (n= 419 of which 25 hip OA and 98 knee OA)

[a] Additionally adjusted for the step count and step size within the tandem walk

Discussion

In this study, we show that chronic pain in the lower body is associated with gait differences in community-dwelling individuals. Pain in the lower body is associated with Rhythm (taking slower steps), Pace (taking smaller steps), Variability (less variability among steps) and Phases (longer double support time). These associations are mainly driven by pain in the leg, especially the hip, and remained after exclusion of participants with OA. Furthermore, we found unilateral pain to associate with larger gait asymmetry and gait differences in both the painful and unpainful leg.

To the best of our knowledge, we are the first population-based study to investigate the relation of pain in the lower body with the gait pattern. Few studies have investigated the relation between pain and gait, which mainly focused on pain due to OA, one of the commonest causes of joint pain in the elderly. Hence, comparison of our findings with previous studies is limited. We found pain in the lower body to particularly associate with slower and smaller steps with longer double support. These associations correspond to findings of previous studies, which investigated pain with gait in knee OA patients.[16-18] In our study, these associations were especially driven by pain in the hips. Interestingly, the associations remained after excluding participants with OA, suggesting that they were independent. Hence, pain in the lower body may have clinical impact outside of OA, as longer double support is related to an increased risk of falling and gait speed (Rhythm, Phases, and Pace combined) is strongly related to mortality.[3,9] Treatment of pain in the lower body may thus aid in improving gait and thereby decrease gait-related morbidity and mortality.

Apart from general gait differences, we also found unilateral pain in the legs to associate with larger gait asymmetry and differences in gait of both painful and unpainful leg. Unilateral leg, hip and foot pain showed similar patterns of associations in larger step length asymmetry with larger step length in the painful compared to the unpainful leg. Interestingly, unilateral pain associated with smaller steps of both painful and unpainful leg, but, due to the larger effect in the unpainful leg, also presented this asymmetry. A similar but inverse pattern was appreciated for single support percentage, where both painful and unpainful leg showed less single support as a percentage of the stride time. In contrast to step length, the stronger association in the painful leg lead to larger asymmetry for unilateral hip pain, with less single support in the painful leg. In part, this difference in single support percentage may be explained by the relatively larger steps for the painful compared to unpainful leg, since during a step the leg is not in single support. This finding is in contrast with a previous study in OA where they found shorter step length and longer single support percentage in the osteoarthritic compared to the non-osteoarthritic leg, supporting independence of our findings from OA.[13] Our associations of less single support percentage in both painful and unpainful leg do correspond

to a recent review on effects of osteoarthritis on gait in osteoarthritic and non-osteoarthritic leg.[25] Most likely, these associations are the result of a compensatory mechanism to reduce load on the painful leg, by way of increasing its step length, reducing its single support, and increasing double support. Interestingly, we found unilateral foot pain to associate with larger asymmetry in step length variability, with larger step length variability in the painful leg. This association is especially important, because larger variability is considered a strong risk factor of falling, including particularly injurious falls.[7-9]

Similar to a previous study, we found no associations of knee pain with gait.[26] Since directionality of associations was similar to hip and foot with smaller effect sizes, knee pain most likely has a less pronounced effect on gait and may therefore require more power for the identification of associations.

Joint pain is one of the hallmarks of OA, a common joint disease in older people that may have devastating consequences.[27] In a clinical setting, it is often difficult to distinguish OA-related pain from pain caused by other pathologies without radiographic examinations. Both hip and knee OA strongly affect the gait pattern, suggesting a possible role for gait assessment in differentiating OA-related pain from pain due to other causes.[13, 25] Interestingly, we found people with pain and OA to have larger gait variability (lower Variability) compared to people with pain only. This finding may indicate that gait assessment can aid in identifying OA in people with pain. However, since the association was relatively weak, this finding requires replication in future studies.

Strengths of our study include the large community-dwelling population, enabling us to identify associations that may be generalizable to the general population. Additionally, the gait assessment in different walking conditions, including turning and tandem walking, gives a comprehensive description of the gait differences with chronic pain. Furthermore, because we did not focus on a single pathological origin of pain, we could provide information on the relations of general pain with the gait pattern.

Limitations of our study include that gait was assessed at the research center, which may have prevented participants with severe gait problems from participating. Our results may therefore only be generalizable to a relatively healthy elderly population. Additionally, due to the cross-sectional study design, we are not able to identify the temporal relationship between pain in the lower body and gait. Although it is most likely that pain leads to gait differences, it is also possible that a deviant gait pattern causes joint pain. Hence, associations may be bidirectional, implicating that both interventions targeting pain may improve the gait pattern and interventions targeting gait may decrease pain. Future studies should further investigate this possible bi-directionality in the associations between lower body pain and gait.

Conclusions

In a community-dwelling population, chronic lower body pain is associated with gait differences, independent of OA. Individuals with pain in the lower body take slower and shorter steps with longer double support. Additionally, unilateral pain associates with larger gait asymmetry, and gait differences in both painful and unpainful leg. Our results further suggest that gait patterns might aid in distinguishing between OA and other pathology in people with joint pain. Future studies should investigate whether treatment of lower body pain aids in improving gait, and thereby reduces gait-related morbidity and mortality.

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Supplement 1. Associations of unilateral pain in the leg, hip, knee and foot with gait in the painful and unpainful leg.

Domain	*Rhythm*	*Variability*	*Phases*	*Pace*	*Base of Support*
Gait parameter	Single Support Time (s)	Step length SD (cm)	Single Support Phase (%)	Step length (cm)	Stride width SD (cm)
Unilateral pain leg					
Painful leg	0.02 (-0.02; 0.05)	0.04 (-0.05; 0.14)	**-0.30** (-0.46; -0.13)**	**-0.84* (-1.58; -0.11)**	0.05 (-0.05; 0.16)
Unpainful leg	0.03 (-0.01; 0.06)	0.03 (-0.06; 0.13)	**-0.20* (-0.36; -0.03)**	**-1.28** (-2.02; -0.54)**	0.04 (-0.06; 0.15)
Unilateral pain hip					
Painful hip	0.01 (-0.05; 0.07)	-0.06 (-0.19; 0.08)	**-0.57** (-0.81; -0.32)**	-0.90 (-1.98; 0.17)	-0.08 (-0.23; 0.07)
Unpainful hip	0.03 (-0.02; 0.09)	0.07 (-0.07; 0.21)	**-0.35** (-0.60; -0.11)**	**-1.43* (-2.51; -0.35)**	-0.03 (-0.18; 0.12)
Unilateral pain knee					
Painful knee	0.02 (-0.03; 0.07)	0.10 (-0.02; 0.22)	-0.09 (-0.30; 0.12)	-0.31 (-1.23; 0.60)	0.05 (-0.08; 0.18)
Unpainful knee	0.03 (-0.02; 0.07)	0.04 (-0.07; 0.16)	-0.04 (-0.25; 0.16)	-0.38 (-1.30; 0.53)	0.03 (-0.10; 0.15)
Unilateral pain foot					
Painful foot	-0.01 (-0.08; 0.05)	**0.21* (0.05; 0.36)**	**-0.30* (-0.58; -0.02)**	**-1.32* (-2.56; -0.09)**	0.08 (-0.09; 0.25)
Unpainful foot	0.00 (-0.07; 0.06)	-0.05 (-0.20; 0.11)	-0.21 (-0.49; 0.07)	**-1.97** (-3.20; -0.74)**	0.07 (-0.10; 0.24)

Values represent differences in gait parameters (95% confidence interval) for presence of pain in the respective body part. Results in bold survived thresholds of nominal significance ($^{*}p < 0.05$; $^{**}p < 0.005$). All analysis were adjusted for age, sex, height, weight, and time interval between pain and gait assessment. Leg: n=2012; Hip: n = 2231; Knee: n = 2103; Foot: n = 2215.

Painful leg: Difference between gait parameters of painful leg for cases (subjects with unilateral pain) and mean gait parameters for controls (subjects without pain)

Unpainful leg: Difference between gait parameters of unpainful leg for cases (subjects with unilateral pain) and mean gait parameters for controls (subjects without pain)

Abbreviations: s, seconds; SD, standard deviation; cm, centimetres; n, number of participants.

Supplement 2. Associations of pain in the lower body with gait domains, without participants with osteoarthritis

Domain	Rhythm	Variability	Phases	Pace	Tandem[a]	Turning	Base of Support
Pain lower body[b]	**-0.20*** **(-0.36; -0.04)**	**0.21*** **(0.02; 0.39)**	**-0.24**** **(-0.40; -0.08)**	**-0.18*** **(-0.33; -0.03)**	0.00 (-0.16; 0.16)	0.02 (-0.16; 0.21)	0.08 (-0.10; 0.26)
Pain lower back	-0.06 (-0.17; 0.06)	0.08 (-0.05; 0.21)	-0.03 (-0.14; 0.08)	-0.10 (-0.20; 0.01)	-0.04 (-0.16; 0.07)	0.05 (-0.08; 0.18)	-0.04 (-0.17; 0.09)
Pain leg	**-0.11*** **(-0.22; 0.00)**	0.10 (-0.02; 0.22)	**-0.19**** **(-0.29; -0.09)**	-0.08 (-0.18; 0.02)	0.00 (-0.11; 0.11)	0.00 (-0.12; 0.12)	0.05 (-0.06; 0.17)
Pain hip	-0.15 (-0.32; 0.01)	0.03 (-0.16; 0.22)	**-0.26**** **(-0.42; -0.10)**	-0.14 (-0.29; 0.02)	0.06 (-0.10; 0.23)	0.09 (-0.10; 0.28)	0.14 (-0.05; 0.32)
Pain knee	-0.08 (-0.21; 0.05)	0.05 (-0.10; 0.19)	-0.08 (-0.20; 0.05)	-0.07 (-0.19; 0.04)	0.02 (-0.11; 0.15)	-0.03 (-0.17; 0.12)	0.07 (-0.07; 0.21)
Pain foot	-0.03 (-0.20; 0.14)	0.09 (-0.10; 0.28)	-0.13 (-0.29; 0.04)	-0.01 (-0.16; 0.15)	-0.12 (-0.29; 0.05)	-0.03 (-0.22; 0.16)	0.07 (-0.12; 0.26)

Values represent differences in z-scores of gait (95% confidence interval) for pain in the respective body part. A lower value of gait represents worse gait. Pain was scored as 1 = yes and 0 = no. Results in bold survived threshold of nominal significance (*$p < 0.05$; **$p < 0.005$). All analysis were adjusted for age, sex, height, weight, and time interval between pain and gait assessment. (n=1557)

[a] Additionally adjusted for the step count and step size within the tandem walk

[b] Pain lower body = (pain in lower back + pain left leg + pain right leg) / 3.

Part 3

Neurological correlates of daily functioning

Chapter 3.1

Gait shows a sex-specific pattern of associations with daily functioning

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Abstract

Background: Gait is increasingly considered an important indicator of health. Yet, little is known on the relation of gait with established health indicators, e.g. daily functioning. Although gait differs by sex, it is unknown whether different gait domains provide different health indicators in men or women. We investigated how gait associates with basic and instrumental activities of daily living (BADL and IADL) in community-dwelling persons.
Methods: In 2500 participants of the population-based Rotterdam Study (aged ≥50yrs), gait was assessed by electronic walkway and summarised into seven independent gait domains: Pace, Rhythm, Phases, Tandem, Turning, Variability, Base of Support, which were averaged into Global Gait. We assessed BADL with the disability index of the Stanford Health Assessment Questionnaire and IADL with the Instrumental Activities of Daily Living scale. BADL and IADL were analysed as continuous scores, and dichotomised: with impairment defined as moderate to very severe disability.
Results: In men, Global Gait, Pace, and Rhythm associated with BADL in linear analyses. In contrast, all domains except Base of Support associated with BADL or IADL in women. Associations of Global Gait and Phases with BADL were significantly stronger in women (p-interaction<0.05). Similarly, associations of Global Gait, Rhythm, and Phases with IADL were stronger in women (p-interaction<0.05). For dichotomised analyses, higher Global Gait, Pace, and Rhythm associated with less BADL-impairment in men, while Global Gait associated with less BADL and IADL-impairment in women.
Conclusions: In men, Pace and Rhythm may suffice as health indicators, while women may require comprehensive gait assessment to better estimate their health status.

Introduction

Daily functioning is an important indicator of health that requires integration of many abilities.[1, 2] With aging, people deteriorate in daily functioning, leading to loss of independence and institutionalization.[2, 3] Daily functioning is generally assessed using activities of daily living (ADL), including physical basic ADL (BADL), e.g. dressing, and cognitive instrumental ADL (IADL), e.g. finance management.[4] Proper functioning across this whole spectrum is an indicator of health and essential to function independently in society.

Similarly, the walking pattern, or gait, is increasingly considered an important indicator of health.[5, 6] Poor gait is a strong risk factor of both falls and death.[5, 7-10] Additionally, gait relates to many abilities, such as cognition, and may even be a risk factor of dementia.[11-15] Hence, studies have increasingly suggested that gait may be a valid outcome measure of health in both clinical and research settings.[5, 6] Little is known on the relation of gait with established health indicators, such as BADL and IADL that are commonly studied as outcome measures.

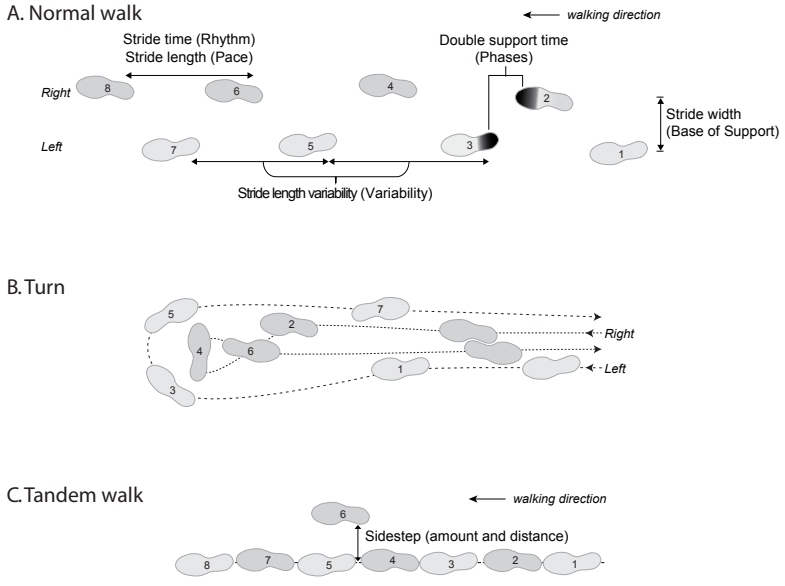

Figure 1. The three walking conditions. A: Normal walk, including five gait parameters that constitute different gait domains. B: Turn. Only feet that were taken into account for the turning time or turning step count calculation were numbered. In this case, turning step count was 5 (number of feet minus 2). Turning time was calculated from last contact of foot 1 until first contact of foot 7. C: Tandem walk. Sidesteps were quantified as the distance from the line on the walkway and the surface of the sidestep foot on the walkway, relative to the average normal foot. Additionally, double steps with the same foot on the line were considered errors.

More importantly, although gait differs strongly between the sexes, sex-differences in associations of gait with BADL and IADL have not been investigated.[16]

Gait is a complex concept, assessed using many different parameters. Recently, for ease of interpretation and use in research, studies have summarised these parameters into seven independent gait domains that together comprehensively describe gait (Figure 1).[16, 17] Pace, which captures gait velocity, has been investigated as a health indicator and associates with BADL and IADL, but sex-differences have not been investigated.[1, 18-20] Also, relations of other domains with BADL and IADL have not been studied intensively. Different gait domains reflect different abilities, such as physical strength, cognition, and balance, and each may provide unique information in relation to BADL and IADL.[11-13, 15]

In a population-based study of community-dwelling older people, we investigated sex-specific associations of various gait domains with BADL and IADL.

Methods

Setting

The study was embedded in the Rotterdam Study.[21] The current study includes participants aged 50 years and older. At baseline and every 3-4 years of follow-up, participants undergo home interviews, including questionnaires on BADL and IADL, and medical examinations at the research centre. During examinations, height, weight, Center for Epidemiologic Studies Depression Scale (CES-D)[22], and Mini-Mental State Examination score (MMSE, cognition)[23] are assessed. Gait assessment was implemented from March 2009 onwards, and until December 2011 3242 participants were invited for gait assessment. All participants gave written informed-consent. The study was approved by the medical ethics committee.

Gait assessment

Details on the gait assessment protocol are described elsewhere.[16] Gait was assessed with a 5.79 meter long electronic walkway (4.88 meter active area; GAITRite Platinum; CIR systems, Sparta, NJ, USA), in three conditions: normal walk, turn, and tandem walk (Figure 1). In normal walks, participants walked over the walkway at their usual pace. This was performed eight times. In turn, participants walked at their usual pace over the walkway, turned halfway, and returned to the starting position. In tandem walk, participants walked tandem (heel-to-toe) over a line visible on the walkway. The first normal walk was considered a practice walk and excluded from analyses. The other seven normal walks were combined for calculation of gait parameters in normal walking. Turning time and turning step count were calculated from the turning condition after removing feet that did not belong to the turn (see Figure 1).

Sidesteps in tandem walking were quantified by the distance from the line, and the surface of the sidestep on the walkway as a percentage of the average normal foot. Additionally, double steps on the line with the same foot were considered errors in tandem walking.

Principal components analysis (PCA) was used to reduce the number of gait parameters into fewer gait domains, while capturing the largest amount of variance. Gait domains should explain at least as much variance as a single parameter. The 30 gait parameters included in the PCA were summarised into seven independent gait z-scores, or domains, as described previously: Base of Support, reflecting stride width and stride width variability; Pace, reflecting stride length and velocity; Phases, reflecting percentage of time supporting on two feet compared to one; Rhythm, reflecting stride time and cadence; Tandem, reflecting errors in tandem walking; Turning, reflecting turning time and amount of turning steps; and Variability, reflecting variability in length and time among strides (Figure 1, Supplement 1).[16] The gait domains explain 86.3% of total variance among gait parameters. If necessary, gait domains were inverted so that lower values reflect "worse" gait. Global Gait was calculated as the average of the gait domains.

Assessment of basic activities of daily living

BADL was assessed using the disability index from the Stanford Health Assessment Questionnaire.[24] The disability index consists of 20 items constituting eight components: dressing and grooming, arising, eating, walking, hygiene, grip, reach, and activities. In our study, two of three items belonging to the eating component (ability to cut meat and ability to lift a glass of milk) were combined into one. Items were scored from 0-3, with higher scores indicating worse ability: 0=without any difficulty, 1=with some difficulty, 2=with much difficulty, 3=unable to. Component scores were calculated as the highest scored item available, belonging to that component. We calculated two BADL-scores. Overall BADL-scores were calculated by summing all component scores, obtaining scores between 0-24. Similarly, we calculated BADL-scores without the walking component, obtaining scores between 0-21. In line with previous studies, overall BADL-scores from 0-8 were considered no to mild disability and above 8 moderate to very severe disability.[25] For BADL without walking, we considered scores from 0-7 no to mild disability, and above 7 moderate to very severe disability.

Assessment of instrumental activities of daily living

IADL was assessed based on the IADL-scale by Lawton and Brody.[26] The IADL-scale consists of eight items: telephone use, medication maintenance, shopping, travelling on your own, finance management, laundry, housekeeping, and meal preparation. Consistent with BADL, we scored items from the IADL-scale from 0-3. For telephone use, participants using an adapted phone were categorised as 2 (with much difficulty).

Activities that were not performed were scored as non-applicable. For men, 12.7% of variables were scored as non-applicable, while 1.0% of variables were scored as non-applicable for women. To prevent loss of data, imputation of non-applicable values has been suggested and adopted by previous studies.[4, 27] To estimate ability in items that were scored as non-applicable for a person, we imputed these variables using the mean of five imputations, based on age, sex, scores on all items of BADL, and scores on the other IADL items. IADL-scores were calculated by summing all item scores, obtaining scores between 0-24. Similar to BADL, scores from 0-8 were considered no to mild disability and above 8 moderate to very severe disability.

Study population

Of 3242 invited participants, 245 participants did not perform all walking conditions for various reasons: 172 for perceived physical inability; 53 for technical reasons; 18 for refusal; and two for language problems.

Of 2997 remaining participants, 497 were excluded from analyses for the following reasons: 222 random persons for technical reasons; 104 for medical history of stroke; 78 for missing BADL and IADL-data; 33 for having fewer than 16 steps of normal walking available for analyses, lowering validity of gait parameters[28]; 26 for not following instructions; 20 for dementia or Parkinson's disease; 11 for missing MMSE or CES-D data; and three for use of walking aids. Finally, 2500 participants were included in analyses.

Statistical analysis

All analyses were performed sex-stratified or with sex*gait interaction terms included. Furthermore, all gait domains were included in the same model to ensure independence of their associations with BADL and IADL.

Associations of gait with BADL and IADL were investigated in two ways.

First, BADL and IADL were investigated as continuous scores. Linear regression analyses were used to investigate associations of Global Gait and gait domains with BADL-score, BADL-score without walking, and IADL-score. To easily appreciate the pattern of associations of gait domains with BADL and IADL, we visualised these associations in a figure.

Second, BADL and IADL-scores were dichotomised, with scores above 8 (moderate to very severe disability) considered impaired and scores between 0-8 considered unimpaired. Similarly, BADL without walking was dichotomised, with scores above 7 considered impaired and between 0-7 unimpaired. Binary logistic regression analyses were used to investigate associations of Global Gait and separate gait domains with impairment in BADL, BADL without walking, and IADL.

Analyses were adjusted for age, height, weight, MMSE, CES-D, time interval between home interview and gait assessment, and mean step length and step count in the tandem walk.

Analyses including sex*gait interaction terms were adjusted for sex. To adjust for multiple testing, we used Bonferroni corrections for 14 tests ($p<0.0036$).

To investigate whether gait domains aid in distinguishing sex-specific associations with BADL and IADL above gait velocity alone, we repeated the linear analyses with additional adjustment for gait velocity. Gait domains were considered to provide additional information when associations remained nominally significant ($p<0.05$).

We checked the residuals in the linear regression analyses for normality. In men, associations with IADL showed non-normal residuals. Therefore, we repeated these using negative binomial regression analysis as a sensitivity analysis.

All statistical analyses were performed using IBM SPSS version 20.0.0.1 for Windows.

Results

In our sample, 1371 (54.8%) participants were women. Men were on average 67.9 years old and women 67.0 years (Table 1). On average, gait and ADL assessments were taken 15 months

Table 1. Population characteristics

Characteristic	Men (n = 1129)	Women (n = 1371)	$p_{differences}$ [a]
Age, years	67.9 (9.4)	67.0 (8.9)	0.017
Height, cm	176.2 (6.8)	163.2 (6.4)	<0.001
Weight, kg	85.3 (12.6)	72.4 (12.6)	<0.001
MMSE score, points	28.0 (1.7)	28.2 (1.6)	0.18
CES-D, points	3.7 (5.3)	6.2 (7.5)	<0.001
BADL, points	1.6 (2.1)	2.8 (3.0)	<0.001
IADL, points	1.7 (2.3)	1.0 (1.7)	<0.001
Velocity, cm/s	123.7 (17.8)	119.3 (17.6)	0.005
Global Gait, SD	0.0 (1.0)	0.0 (1.0)	<0.001
Pace, SD	0.5 (0.9)	-0.4 (0.8)	<0.001
Rhythm, SD	-0.5 (1.0)	0.4 (0.9)	<0.001
Phases, SD	-0.1 (0.9)	0.1 (1.1)	0.03
Tandem, SD	0.0 (0.9)	0.0 (1.1)	0.008
Turning, SD	0.0 (1.0)	0.0 (1.0)	0.15
Variability, SD	-0.1 (1.0)	0.1 (1.0)	0.35
Base of Support, SD	0.2 (1.1)	-0.1 (0.9)	<0.001

Values are means (standard deviations).

[a] P-values for differences in the population characteristics between the sexes, adjusted for age. For gait parameters, these were additionally adjusted for height and weight.

(SD 24.2) apart. Men were older, taller, heavier, and had higher CES-D than women (all p<0.05). Men had lower BADL-scores than women (1.6 versus 2.8 points, p<0.05), but higher IADL-scores (1.7 versus 1.0 points, p<0.05). Men were less often impaired in BADL than women (1.8% versus 5.8%, p<0.05), while being more often impaired in IADL (2.1% versus 0.7%, p<0.05). Gait velocity, Global Gait, and all gait domains except Turning and Variability differed significantly between the sexes (p<0.05).

Linear associations of gait with BADL and IADL.

In women, higher values on all gait domains except Variability and Base of Support associated with lower BADL-score, with strongest associations for Global Gait, Pace, Rhythm, and Phases (Figure 2). For men, a similar but weaker pattern of associations was seen. Only higher Global Gait, Pace, and Rhythm associated with lower BADL-score in men. Significant

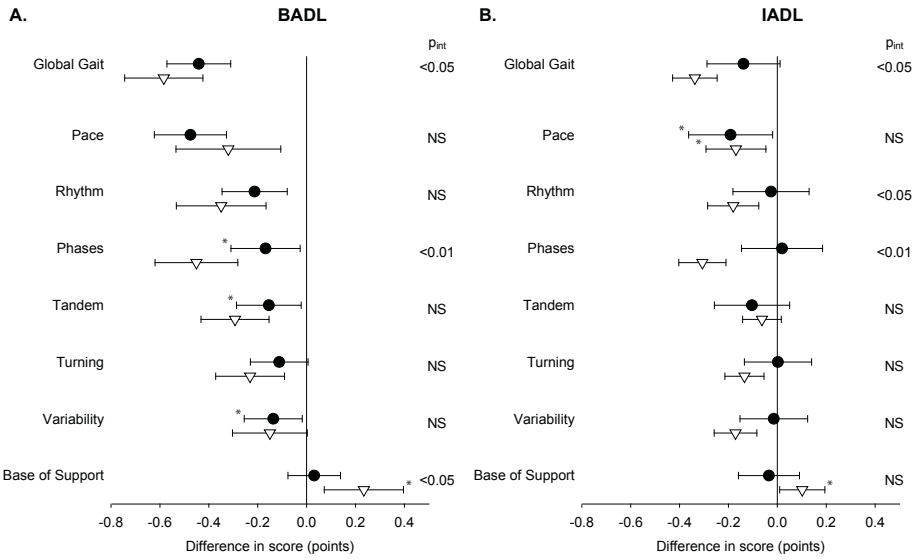

Figure 2. Linear associations of gait with BADL and IADL, stratified for sex. Dots represent the effect sizes from the linear analyses on the associations of Global Gait and the gait domains with BADL and IADL for men (black dots) and women (white triangles). Error bars represent the 95% confidence intervals. Asterisks mark the associations that did not survive Bonferroni correction for 14 tests (p<0.0036). The p_{int} represent the p-values for the sex*gait interaction terms. All analyses were adjusted for age, height, weight, time interval between assessments, Mini-Mental State Examination, Center for Epidemiologic Studies Depression Scale, and for mean step length and step count in the tandem walk. All gait domains were included in the same models for the analyses. A: Associations of gait with BADL, stratified for sex. B: Associations of gait with IADL, stratified for sex.

sex-interactions were found, with stronger associations of Global Gait, Phases, and Base of Support with BADL-score in women (p<0.05).

For IADL-score, women showed a similar pattern of associations as for BADL-score, but with smaller effect sizes (Figure 2). Higher values on all gait domains except Pace, Tandem and Base of Support associated with a lower IADL-score in women, with strongest associations for Global Gait and Phases. In men, the pattern of associations for IADL-score was even weaker, resulting in no significant associations. Significant sex-interactions were found, with stronger associations of Global Gait, Rhythm, and Phases with IADL-score in women (p<0.05).

Dichotomous associations of gait with impairment in BADL and IADL.

In women, only higher Global Gait associated with a lower probability of BADL and IADL-impairment (Table 2). In men, higher Global Gait, Pace, and Rhythm associated with lower probability of BADL-impairment. Significant sex-interactions were found, with stronger associations of Global Gait and Pace with BADL-impairment in men than women (p<0.05).

Table 2. Associations of gait with dichotomised impairment in daily functioning, sex stratified

	BADL			IADL		
	Men n/N 20/1129 OR (95% CI)	Women n/N 80/1371 OR (95% CI)	p_{int}	Men n/N 24/1121 OR (95% CI)	Women n/N 9/1363 OR (95% CI)	p_{int}
Global Gait	**0.36 (0.22; 0.58)**	**0.70 (0.56; 0.87)**	<0.01	0.84 (0.55; 1.29)	**0.48 (0.28; 0.82)**	<0.05
Pace	**0.33 (0.17; 0.66)**	0.80 (0.56; 1.13)	<0.01	0.75 (0.44; 1.30)	0.92 (0.32; 2.68)	NS
Rhythm	**0.50 (0.32; 0.78)**	0.75 (0.56; 1.00)	NS	0.91 (0.56; 1.47)	0.47 (0.19; 1.17)	NS
Phases	0.85 (0.51; 1.40)	0.77 (0.59; 1.01)	NS	0.86 (0.53; 1.40)	0.62 (0.28; 1.36)	NS
Tandem	0.72 (0.47; 1.10)	0.85 (0.69; 1.04)	NS	1.15 (0.68; 1.96)	0.70 (0.40; 1.22)	NS
Turning	0.76 (0.47; 1.21)	0.91 (0.73; 1.14)	NS	1.09 (0.71; 1.69)	0.53 (0.31; 0.90)	<0.05
Variability	0.92 (0.58; 1.47)	0.92 (0.74; 1.14)	NS	1.22 (0.80; 1.86)	1.29 (0.60; 2.80)	NS
Base of Support	1.00 (0.63; 1.59)	1.21 (0.93; 1.58)	NS	0.81 (0.55; 1.20)	1.27 (0.61; 2.66)	NS

Values represent odds ratios of impairment (95% confidence interval) per standard deviation higher gait. Results in bold represent significance findings after Bonferroni correction for 14 tests ($p < 0.0036$). The p_{int} represent the p-values of the sex*gait interaction terms. All analyses were adjusted for age, height, weight, time interval between assessments, MMSE, CES-D, and analyses on gait domains for mean step length and step count in the tandem walk. All gait domains were included in the same models for the analyses. Abbreviations: BADL, basic activities of daily living; IADL, instrumental activities of daily living.

In contrast, Global Gait and Turning associated more strongly with IADL-impairment in women ($p<0.05$).

Sensitivity analyses

Associations of gait with BADL without walking followed a similar pattern as associations with BADL including walking, but were slightly attenuated (Supplement 2).

After additional adjustment for gait velocity, all associations remained significant, except for associations of Pace and Rhythm with BADL and IADL in women (Supplement 3).

Similar to our linear regression analysis, we found no associations of Global Gait or the gait domains with IADL using negative binomial regression analysis (Supplement 4).

Discussion

In a community-dwelling population, we found a sex-specific relation between gait and daily functioning. In men, only Pace and Rhythm associated with BADL, while all gait domains except Base of Support associated with either BADL or IADL in women. Additionally, associations of gait with BADL and IADL were generally stronger in women than men. All associations remained after additional adjustment for gait velocity, except for associations of Pace and Rhythm with BADL and IADL in women.

Strengths of our study include the large population-based sample, objective assessment of various gait domains, investigation of both BADL and IADL, and investigation of sex-differences in analyses.

A limitation is that, due to its cross-sectional design, we could not establish whether gait differences predict incident impairment or decline in daily functioning. Additionally, participants visiting the research center were likely to be relatively healthy, as reflected by the little impairment in our population. Hence, generalization of our findings may be restricted. Furthermore, we were not able to investigate abilities underlying the associations between gait and daily functioning. Another issue is the difference in amount of non-applicable values between men and women. However, because we used data from participants of the study to impute non-applicable values and did not use gait in the imputation, we most likely did not introduce spurious associations. If anything, wrong imputations may have led to noise and thus fewer significant associations. We also note that there are differences in the prevalence of BADL and IADL problems between men and women. Hence, the sex-differences may in part be explained by this difference. Finally, we only used BADL and IADL to indicate health status. Gait may show different patterns of associations with aspects of health not captured by BADL or IADL.

In our study, we found nearly all gait domains to associate with BADL and IADL in women or men. The associations of Pace and Rhythm with BADL in men and women are supported by previous associations of gait velocity and stride length with BADL.[1, 19, 20] A possible explanation for the relation between gait and ADL is that poor gait in itself hinders people in their daily functioning, because many daily activities require the ability to walk. The removal of walking from BADL only slightly attenuated the associations of gait with BADL. This slight attenuation may partly be explained by the fact that walking is also needed to perform various other activities. Another explanation of the associations between gait and daily functioning is that both require proper functioning of various organ systems, such as musculoskeletal, cardiovascular, and central nervous system.[1, 2, 11-15] Therefore, findings may reflect deficiencies in organ systems affecting both gait and daily functioning. Yet, an important advantage of using gait domains over ADL questionnaires to assess health may be their larger detail on abilities that may actually be affected.

Our main findings are the strong sex-differences in the relation between gait and daily functioning. Generally, gait was more strongly associated with BADL and IADL in women compared to men. Only Pace and Rhythm associated with BADL in men, while all gait domains except Base of Support associated with either BADL or IADL in women. Moreover, significant sex-interactions were found, with stronger associations of Phases and Base of Support with BADL and Rhythm, and Phases with IADL in women. In contrast, Pace associated more strongly with BADL-impairment in men. These sex-interactions suggest that various gait domains associate differently with BADL and IADL in women compared to men.

The sex-differences in our analyses may derive from sex-specific abilities relied upon when performing daily activities. Men may rely more on physical strength to perform daily activities, because physical strength is strongly associated with Pace and Rhythm.[13] The strong associations of Pace and Rhythm with BADL-impairment suggest that men use physical strength to compensate for decline in other abilities, such as balance and cognition, resulting in a large decline of daily functioning once strength fails. Although women may also partly rely on physical strength to perform daily activities, as reflected by Pace and Rhythm, they may additionally depend on other abilities, such as cognition, to perform daily activities. Gait domains such as Phases, Tandem, and Turning are less dependent on physical strength, but rely more on other abilities such as cognition, vision, and balance.[7, 12, 13, 15] Together, this may have resulted in stronger associations of these domains with BADL in women. The stronger associations of gait with IADL in women compared to men also support the notion that women rely more on other abilities than physical strength to perform daily activities. IADL depend more on cognitive functioning than BADL, and these associations suggest a more important role of cognition in the relation between gait and daily functioning in women.

Regardless of the mechanism behind the sex-differences, our findings suggest differences between the sexes in the strength of gait domains as indicators of daily functioning, and thus health. In men, only Pace and Rhythm, constituting gait velocity, associated with BADL or IADL. Interestingly, adjustment for gait velocity did not change these associations. This indicates that separate assessment of Pace and Rhythm may provide more information on daily functioning in men than gait velocity alone. Although Pace and Rhythm were among the strongest domains to associate with BADL and IADL in women, other gait domains, such as Phases, Tandem, and Variability, also associated strongly with BADL or IADL. Importantly, while associations of Pace and Rhythm with BADL and IADL became non-significant in women after adjustment for gait velocity, associations of these other gait domains remained. Hence, in women, a more comprehensive gait assessment may be required to better capture health.

Taken together, comprehensive gait assessment, compared to gait velocity alone, may provide more information on the abilities involved in daily functioning, and thus on health.

Conclusions

In a community-dwelling population, associations of gait with BADL and IADL are strongly sex-specific. In men, only Pace and Rhythm, constituting gait velocity, and Global Gait associate with BADL in linear associations, while all gait domains except Base of Support associate with either BADL or IADL in women. In men, Global Gait, Pace, and Rhythm also associate with impairment in BADL, while Global Gait associates with BADL and IADL in women. A comprehensive gait assessment may provide a better estimate of daily functioning than gait velocity alone, and thus be a better indicator of health.

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Supplement 1. Correlations between gait parameters and gait domains.

	Gait domains						
Gait variables	Pace	Rhythm	Phases	Tandem	Turning	Variability	Base of Support
Stride Length	0.86	-0.13	0.31	0.13	0.16	0.15	-0.04
Step Length	0.86	-0.13	0.31	0.13	0.17	0.15	-0.04
Velocity	0.72	0.41	0.40	0.09	0.17	0.19	-0.04
Single Support Time	-0.04	-0.96	0.23	0.05	-0.03	-0.09	0.01
Swing Time	0.04	-0.96	0.23	0.05	-0.03	-0.09	0.01
Step Time	-0.05	-0.94	-0.27	0.02	-0.05	-0.15	0.02
Stride Time	-0.05	-0.95	-0.27	0.02	-0.05	-0.15	0.02
Cadence	0.03	0.94	0.27	-0.02	0.05	0.13	-0.02
Stance Time	-0.09	-0.84	-0.50	0.00	-0.06	-0.16	0.02
Single Support (%ST)	0.16	0.06	0.97	0.06	0.04	0.10	-0.02
Swing (%ST)	0.16	0.06	0.97	0.06	0.04	0.10	-0.02
Stance (%ST)	-0.16	-0.06	-0.97	-0.06	-0.04	-0.10	0.02
Double Support (%ST)	-0.17	-0.05	-0.97	-0.07	-0.04	0.10	0.01
Double Support Time	-0.16	-0.47	-0.85	-0.04	-0.05	-0.14	0.02
Sum of Feet Surface[a]	-0.11	0.05	-0.08	-0.91	-0.03	-0.06	-0.09
Sum of Step Distance[a]	-0.07	0.04	-0.04	-0.90	-0.06	-0.04	-0.10
Double Step[b]	-0.03	0.01	-0.06	-0.57	0.03	-0.03	0.09
Turning Step Count	-0.13	0.06	-0.06	-0.05	-0.92	-0.09	0.03
Turning Time	-0.20	-0.28	-0.07	0.02	-0.85	-0.08	0.03
Stride Length SD	0.13	0.01	-0.13	-0.07	-0.09	-0.88	-0.01
Step Length SD	0.10	-0.01	-0.14	-0.09	-0.11	-0.87	0.01
Stride Velocity SD	0.08	0.18	0.03	0.00	0.04	-0.86	-0.07
Stride Time SD	-0.36	-0.30	-0.13	0.00	0.00	-0.78	0.00
Step Time SD	-0.37	-0.33	-0.13	-0.02	-0.03	-0.76	0.05
Stance Time SD	-0.37	-0.33	-0.14	-0.01	-0.02	-0.77	0.02
Swing Time SD	-0.42	-0.41	-0.05	-0.05	-0.09	-0.66	0.09
Single Support Time SD	-0.42	-0.41	-0.05	-0.05	-0.09	-0.66	0.09
Double Support Time SD	-0.40	-0.35	-0.09	-0.01	-0.05	-0.53	-0.10
Stride Width SD	0.23	-0.02	-0.07	-0.09	-0.07	-0.19	-0.76
Stride Width	0.22	-0.10	-0.22	-0.05	-0.22	-0.27	0.65

Values represent the correlations of the gait parameters with the respective gait domains created with the principal components analysis.

[a] Of sidesteps in the tandem walk.

[b] In the tandem walk.

Abbreviations: SD, standard deviation; %ST, as a percentage of the stride time, the time between two footfalls of the same foot.

Supplement 2. Associations of gait with BADL without walking, sex stratified

	BADL score without walking		BADL-impairment without walking	
	Men β (95% CI)	Women β (95% CI)	Men OR (95% CI)	Women OR (95% CI)
Global Gait	**-0.33 (-0.44; -0.21)**	**-0.43 (-0.57; -0.29)**	**0.41 (0.25; 0.69)**	**0.70 (0.56; 0.89)**[a]
Pace	**-0.37 (-0.50; -0.24)**	-0.24 (-0.43; -0.05)	0.40 (0.19; 0.82)	0.77 (0.54; 1.11)[a]
Rhythm	**-0.15 (-0.26; -0.03)**	**-0.28 (-0.44; -0.12)**	0.50 (0.31; 0.82)	0.73 (0.54; 0.98)
Phases	-0.10 (-0.22; 0.03)	**-0.35 (-0.49; -0.20)**[a]	0.77 (0.44; 1.34)	0.78 (0.59; 1.03)
Tandem	-0.11 (-0.23; 0.00)	**-0.23 (-0.35; -0.11)**	0.78 (0.48; 1.27)	0.83 (0.67; 1.03)
Turning	-0.08 (-0.18; 0.02)	-0.15 (-0.27; -0.03)	0.71 (0.43; 1.16)	1.03 (0.82; 1.30)
Variability	-0.10 (-0.20; 0.01)	-0.11 (-0.25; 0.02)	1.02 (0.60; 1.71)	0.88 (0.70; 1.11)
Base of Support	0.00 (-0.09; 0.10)	**0.22 (0.07; 0.36)**[a]	1.35 (0.79; 2.30)	1.25 (0.95; 1.66)

Values represent differences in score or odds ratios of impairment (95% confidence interval) per standard deviation higher gait. All analyses were adjusted for age, height, weight, time interval between assessments, MMSE, CES-D, and analyses on gait domains for mean step length and step count in the tandem walk. All gait domains were included in the same models for the analyses. Results in bold represent significance findings after Bonferroni correction for 14 tests ($p < 0.0036$).

Abbreviations: BADL, basic activities of daily living; OR, odds ratio.

[a] Significant sex-interaction ($p < 0.05$).

Supplement 3. Sex-specific linear associations of gait domains with BADL and IADL, adjusted for gait velocity.

	BADL		IADL	
	Men β (95% CI)	Women β (95% CI)	Men β (95% CI)	Women β (95% CI)
Pace	**-0.50 (-0.81; -0.18)**	-0.07 (-0.47; 0.33)	0.11 (-0.26; 0.47)	0.00 (-0.23; 0.23)
Rhythm	**-0.23 (-0.44; -0.01)**	-0.19 (-0.47; 0.10)	0.16 (-0.09; 0.41)	-0.07 (-0.23; 0.09)
Phases	-0.18 (-0.40; 0.03)	**-0.30 (-0.57; -0.04)**	0.19 (-0.06; 0.44)	**-0.21 (-0.35; -0.06)**
Tandem	**-0.16 (-0.29; -0.02)**	**-0.27 (-0.41; -0.12)**	-0.07 (-0.22; 0.09)	-0.04 (-0.13; 0.04)
Turning	-0.12 (-0.25; 0.02)	**-0.17 (-0.33; -0.01)**	0.07 (-0.08; 0.23)	**-0.09 (-0.19; 0.00)**
Variability	**-0.14 (-0.28; 0.00)**	-0.08 (-0.26; 0.09)	0.07 (-0.10; 0.23)	**-0.13 (-0.23; -0.02)**
Base of Support	0.03 (-0.08; 0.14)	**0.21 (0.05; 0.38)**	-0.05 (-0.18; 0.07)	0.09 (0.00; 0.18)

Values represent difference in score (95% confidence interval) per standard deviation higher gait. Results in bold survived thresholds of nominal significance ($p < 0.05$). All analyses were adjusted for age, height, weight, time interval between assessments, MMSE, CES-D, gait velocity, and analyses on gait domains for mean step length and step count in the tandem walk. All gait domains were included in the same models for the analyses. Abbreviations: BADL, basic activities of daily living; IADL, instrumental activities of daily living.

Supplement 4. Sex-specific negative binomial associations of gait with BADL and IADL.

	BADL			IADL		
	Men β (95% CI)	Women β (95% CI)	p_{int}	Men β (95% CI)	Women β (95% CI)	p_{int}
Global Gait	**-0.21 (-0.29; -0.14)**	**-0.18 (-0.23; -0.13)**	NS	-0.07 (-0.16; 0.02)	**-0.26 (-0.34; -0.18)**	<0.01
Pace	**-0.24 (-0.32; -0.16)**	-0.10 (-0.18; -0.02)	<0.01	-0.08 (-0.19; 0.03)	-0.12 (-0.24; 0.01)	NS
Rhythm	-0.10 (-0.18; -0.02)	**-0.12 (-0.19; -0.05)**	NS	-0.02 (-0.11; 0.06)	**-0.15 (-0.26; -0.05)**	NS
Phases	-0.06 (-0.14; 0.02)	**-0.13 (-0.19; -0.07)**	NS	0.04 (-0.06; 0.13)	**-0.24 (-0.32; -0.15)**	<0.01
Tandem	-0.07 (-0.14; 0.01)	**-0.08 (-0.13; -0.04)**	NS	-0.05 (-0.13; 0.03)	-0.05 (-0.12; 0.01)	NS
Turning	-0.05 (-0.12; 0.02)	**-0.08 (-0.13; -0.03)**	NS	-0.01 (-0.09; 0.08)	-0.09 (-0.17; -0.01)	NS
Variability	-0.05 (-0.12; 0.01)	-0.01 (-0.07; 0.04)	NS	-0.02 (-0.11; 0.07)	-0.11 (-0.19; -0.02)	NS
Base of Support	0.00 (-0.07; 0.06)	0.07 (0.01; 0.13)	NS	-0.03 (-0.1; 0.04)	0.08 (-0.01; 0.16)	NS

Values represent difference in score (95% confidence interval) per standard deviation higher gait. Results in bold represent significance findings after Bonferroni correction for 14 tests ($p < 0.0036$). The p_{int} represent the p-values of the sex*gait interaction terms. All analyses were adjusted for age, height, weight, time interval between assessments, MMSE, CES-D, and analyses on gait domains for mean step length and step count in the tandem walk. All gait domains were included in the same models for the analyses. Abbreviations: BADL, basic activities of daily living; IADL, instrumental activities of daily living.

Chapter 3.2

Trajectories of cognition and daily functioning in the preclinical phase of dementia

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Submitted.

Abstract

Background: Although the pre-clinical phase of dementia is known to be characterized by decline in cognition and daily functioning, little is known on the temporal sequence of these deficits. We investigated differences in trajectories of decline in cognition and daily functioning between people with pre-clinical dementia and controls, during 18 years of follow-up.
Methods: The study is a nested case-control sample from the population-based Rotterdam Study. 778 incident demented participants were matched to 1556 controls, based on age, sex, and education. Dementia was subtyped into Alzheimer's disease and vascular dementia. Cognition and daily functioning were repeatedly assessed with subjective memory complaints, Mini-Mental State Examination (MMSE), cognitive instrumental activities of daily living (IADL), and physical basic activities of daily living (BADL).
Results: In pre-clinical dementia, participants first showed memory complaints already 16 years before diagnosis, followed by gradual decline in MMSE from 12 years before diagnosis onwards. This decline accelerated around 7 years before diagnosis, which was closely followed by IADL decline. Lastly, BADL decline started 4-5 years before diagnosis. Pre-clinical Alzheimer's disease showed earlier decline in cognition but later in daily functioning compared to vascular dementia. Higher education related to better baseline MMSE, but an earlier decline before dementia. *APOE*-ε4 carriers with pre-clinical dementia declined less in daily functioning compared to non-carriers.
Interpretation: During the preclinical phase of incipient dementia, people first report memory complaints, followed by decline in global cognition, cognitive daily functioning, and finally physical daily functioning. These trajectories differ by dementia subtype, educational level, and *APOE*-ε4 carrier status.

Introduction

Dementia is a common disease in the elderly, characterized by both cognitive impairment and impairment in daily functioning.[1, 2] Typically, persons with dementia have a long pre-clinical phase, during which impairment in these functions gradually develops and ultimately leads to clinical symptoms. However, the temporal pattern of deterioration during this pre-clinical phase is largely unknown. Insight in the long-term trajectories of cognition and daily functioning before dementia is important, because it may aid physicians in early identification of people likely to become demented. Furthermore, it may aid clinical studies in identifying which people may benefit most from interventions, and are thus suitable for trials on prevention or intervention for dementia.

Only one study investigated the pattern of deterioration in preclinical dementia, focusing on Alzheimer's disease (AD).[3, 4] Two reports from this study suggested cognition to decline as early as 15 years before AD diagnosis.[3, 4] Additionally, they found functioning on instrumental activities of daily living (IADL), which are cognitively more challenging activities of daily living, to start declining around seven years before AD. Interestingly, one of these reports also suggested differences in trajectories of cognition for level of education, which indicates a role for cognitive reserve.[3]

However, much remains unknown on the patterns of deterioration in pre-clinical dementia. For example, surprisingly little is known on pre-clinical trajectories of more physical basic activities of daily living (BADL), even though these are part of the diagnostic criteria for dementia.[5] Similarly, although *APOE*-ε4 carrier status is considered one of the most important risk factors of dementia, it is unknown whether pre-clinical trajectories in cognition and daily functioning differ for *APOE*-ε4 status.[6] Finally, little is known on trajectories of decline for dementias other than AD, such as vascular dementia.

We aimed to investigate trajectories of decline in cognition and daily functioning before dementia diagnosis. Importantly, we also investigated differences in these trajectories for *APOE*-ε4 carrier status, education, and dementia subtypes.

Methods

Setting

The study is embedded in the Rotterdam Study, a population-based cohort study based in Ommoord, a suburb of Rotterdam, in the Netherlands.[7] The study was initiated in 1990, inviting all inhabitants of Ommoord aged 55 years and older. 7983 participants (78%) agreed to participate. Until 2011, the study has had a total of five visits, including four follow-up visits: between 1993-1995, 1997-1999, 2002-2004, and 2009-2011. At baseline and each follow-up

visit, participants undergo a home interview and medical examinations at the research centre. Educational level was determined at baseline and categorised into primary education or less versus higher education. *APOE*-genotyping was performed as previously described.[8] The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. A written informed consent was obtained from all participants.

Assessment of memory complaints and cognition

Memory complaints were assessed using three questions, which could be answered by yes or no. These questions were: "Do you have more trouble remembering things than before?"; "Does it happen more often that you are on your way to do something and forget what you wanted to do?"; and "Do you more often have trouble finding words during a conversation?"

Cognition was objectively assessed using the Mini-Mental State Examination (MMSE).[9]

Assessment of basic activities of daily living

BADL was assessed using the disability index of the Stanford Health Assessment Questionnaire.[10] The questionnaire consists of 20 items constituting 8 components: activities, arising, dressing and grooming, eating, hygiene, grip, reach, and walking. In our study, two of three items of eating (ability to cut meat and drink a glass of milk) were combined into one. All items could be scored from 0 to 3, with higher scores reflecting worse ability: 0 = no difficulty, 1 = some difficulty, 2 = much difficulty, and 3 = unable to. Component scores were calculated as the highest scored item belonging to the respective component. Subsequently, BADL was calculated as the sum of the eight components.

Assessment of instrumental activities of daily living

IADL was assessed using the Instrumental Activities of Daily Living scale.[11] The IADL-scale consists of eight items: shopping, washing, travelling on your own, finance management, phoning, medication use, housekeeping, and meal preparation. Similar to BADL, items were coded from 0 to 3, with higher scores reflecting worse ability. For IADL, items scored as non-applicable were imputed using the mean of five imputations, based on age, sex, scores on BADL items, and scores on other IADL items. Imputation of non-applicable values has been suggested and implemented by previous studies to prevent loss of data.[12, 13] Imputations were performed separately for each study visit, with 5.3% or less of variables imputed per visit. Subsequently, IADL was calculated by summing the eight items.

Dementia diagnosis

Participants were followed-up for incident dementia using a three step protocol.[14] First, participants were screened for dementia at baseline and follow-up visits using the MMSE and Geriatric Mental State schedule (GMS).[9, 15] Second, participants with a score ≤25 on the MMSE or >0 on the GMS underwent further assessment using the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) diagnostic interview.[16]Third, participants suspected of having dementia based on this assessment were examined by a neurologist, and underwent extensive neuropsychological testing. In addition to the screening, participants were continuously monitored for diagnosis of dementia through medical records of the general practitioner's office and the Regional Institute for Outpatient Mental Health Care (RIAGG). Diagnoses of dementia were made according to the accepted DSM-III-R criteria for all-cause dementia, NINCDS-ADRDA criteria for Alzheimer's disease, and NINDS-AIREN criteria for vascular dementia.[5, 17, 18] Dementia follow-up was complete until January 1st of 2011.

Study population

The study consists of a matched nested case-control sample from the Rotterdam Study. All participants diagnosed with dementia during follow-up were included as cases, if met the following criteria: they were non-demented and had been assessed for MMSE, IADL, and BADL at the baseline visit; and they participated at the visit before dementia diagnosis, to ensure they were dementia-free at that visit. Participants used as controls had to have the following characteristics: they had been assessed for MMSE, IADL, and BADL at the baseline visit; they participated at the visit before diagnosis of the matched dementia case, to ensure they were dementia-free until that visit; they were determined to be dementia-free until the visit following the diagnosis of the matched dementia case; and they were matched to a dementia case by age (± 3 years), sex, and education. We matched two controls for every dementia case at follow-up, resulting in inclusion of 778 dementia cases and 1556 controls. Due to missing data on some measures, numbers of participants may slightly vary across analyses.

Statistical analysis

We used the "lcmm" function from the "lcmm" package in R to investigate differences in trajectories of decline in memory complaints, MMSE, IADL, and BADL with incident dementia. A link function with quadratic splines was used to account for the ceiling effects of memory complaints, MMSE, IADL, and BADL. The number and position of splines were defined based on the lowest Bayesian information criterion (BIC) in a basic model including age, sex, education, their interactions with time, age*time^2, time itself, time^2, and time^3. We included both random intercepts and random slopes over time. Time was calculated from diagnosis of

dementia for people with incident dementia. For matched controls, the follow-up to dementia from the matched case was subtracted from the follow-up of the control.

We investigated up to cubic associations of incident dementia with memory complaints, MMSE, IADL, and BADL over time (i.e. interactions with time, time^2, and time^3), adjusting for any non-time dependent effect of incident dementia. These analyses were repeated for incident AD and vascular dementia, in which participants with other or undefined dementia subtypes were excluded. For visualization of the trajectories in memory complaints, MMSE, IADL, and BADL, the models including all interactions of dementia with time, time^2, and time^3 were used.

To investigate interactions of education with incident dementia, we included interaction-terms of education with dementia and up to time^2 in the models.

To investigate interactions with *APOE*-ε4, we included *APOE*-ε4 carrier status, its interaction with up to time^2 and their interactions with incident dementia in the analyses.

All analyses were adjusted for the basic model of age, sex, education, their interactions with time, age*time^2, time itself, time^2, and time^3.

To investigate differences in memory complaints, MMSE, IADL, and BADL at each visit separately, the same "lcmm" method was used adjusted for age at visit, time, sex, and education.

Since the splines link function estimates can vary across analyses, effect sizes cannot be readily interpreted and compared across analyses. Hence, we only report the significance of differences in the analyses. Effect sizes may be compared using the figures.

We used nominal thresholds of statistical significance ($p<0.05$). All analyses were performed using R version 3.1.0.

Results

The average age at (matched) dementia diagnosis was 82.1 years (standard deviation [SD] 6.7) and 67.2% were women. 1056 participants (45.2%) had attained only a primary education or less. Of 778 dementia cases, 624 (80.2%) were identified as AD and 76 (9.8%) as vascular dementia. *APOE* genotyped data was available in 2217 participants, of which 655 (29.5%) were *APOE*-ε4 carriers. Furthermore, 42.3% of dementia cases were *APOE*-ε4 carriers and 23.2% of controls. The number of participants included per visit prior to dementia diagnosis are presented in Table 1.

Trajectories before all-cause dementia

Incident demented participants already had more memory complaints at 16 years before diagnosis, and this difference gradually increased over time (Figure 1). We found this difference

Table 1. Number of incident dementia cases and controls across visits.

Visit[a]	Time to dementia, years (SD)	Cases, n	Controls, n
-4	-15.5 (2.2)	257	514
-3	-11.5 (2.7)	494	997
-2	-7.3 (2.7)	643	1262
-1	-3.1 (2.0)	778	1556
1	1.5 (1.8)	370	936

[a] Negative visits represent visits before dementia diagnosis, while positive visits represent visits after diagnosis.

to reflect a significant quadratic larger increase in memory complaints in incident demented participants. The amount of memory complaints was significantly different at all visits, from the fourth visit before dementia (~15.5 years before diagnosis) onwards (all $p<0.02$).

We found a significant cubic larger decline in MMSE in incident demented compared to non-demented participants, reflected by a slow decline in MMSE from 14 years before dementia diagnosis, which accelerated around seven years before diagnosis (Figure 1). Furthermore, MMSE differed significantly at each visit from the third visit before dementia (~11.5 years before diagnosis) onwards (all $p<0.02$).

Similar to MMSE, we found a significant cubic larger decline in IADL for incident demented participants, reflected by an increased decline from around six years before diagnosis (Figure 1). A trend of difference in IADL was already present at the second visit before dementia diagnosis (~7.3 years before, $p=0.09$), which became significant from the first visit before diagnosis (~3.1 years before) onwards ($p<0.004$).

We found a significant linear larger decline in BADL for incident demented participants compared to dementia-free participants, reflected by a differentiation in BADL at around five years before dementia diagnosis (Figure 1). A trend of difference in BADL was present at the first visit before dementia ($p=0.07$), but only became significant at the first visit after diagnosis (~1.5 years after, $p=0.005$).

Trajectories before dementia subtypes

Similar to all-cause dementia, participants with incident AD already had more memory complaints at ~16 years before dementia, while those with vascular dementia only started to accumulate memory complaints at ~12 years before diagnosis. Additionally, participants with incident AD started to deteriorate earlier in MMSE compared to those with incident vascular dementia (~11 years before diagnosis compared to ~4 years, Figure 2). Although participants with incident AD and vascular dementia started declining in IADL at the same time (~5-6 years before diagnosis), those with vascular dementia declined more strongly. Participants with incident AD declined much later in BADL compared to incident vascular dementia (~1

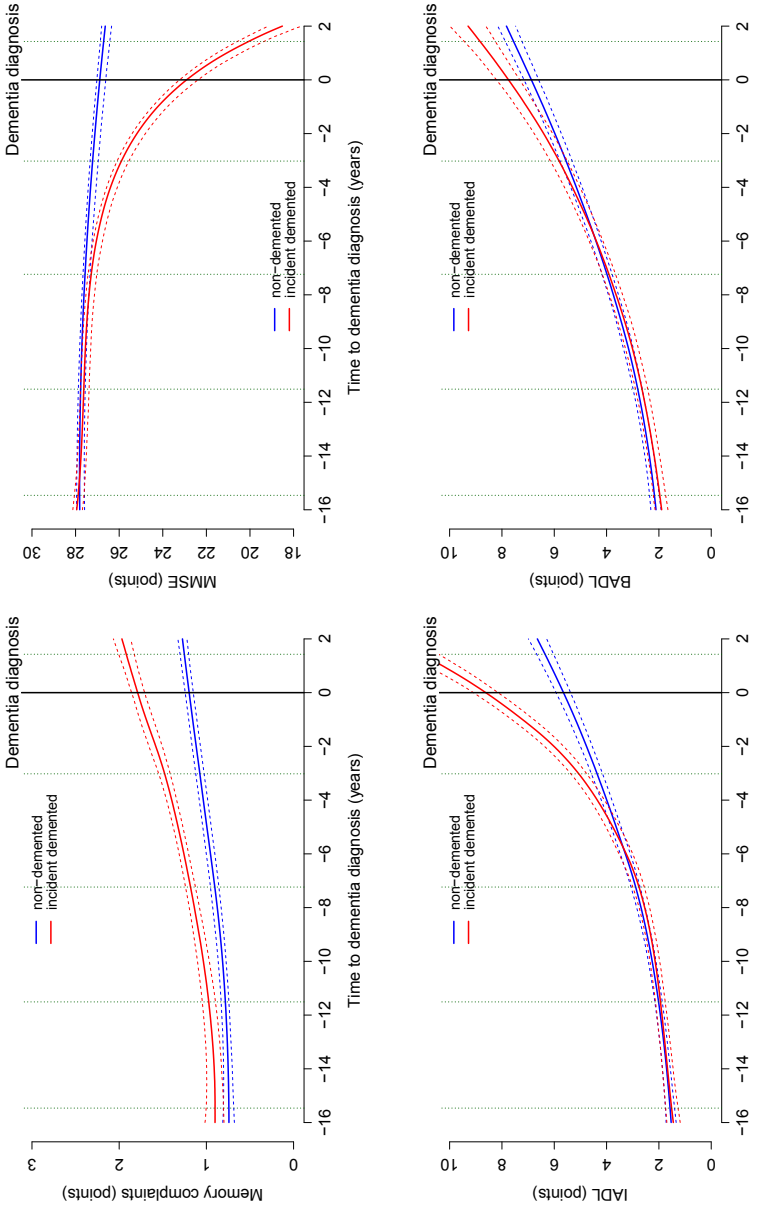

Figure 1. Trajectories of decline in cognition and daily functioning before dementia diagnosis. The trajectories are derived from the lcmm analyses and plotted for the mean age, sex, and education. The vertical dark green dotted lines are the mean visit dates. The red lines represent the incident dementia cases and the blue lines the controls. The dotted lines around the red and blue lines reflect the 95% confidence intervals.

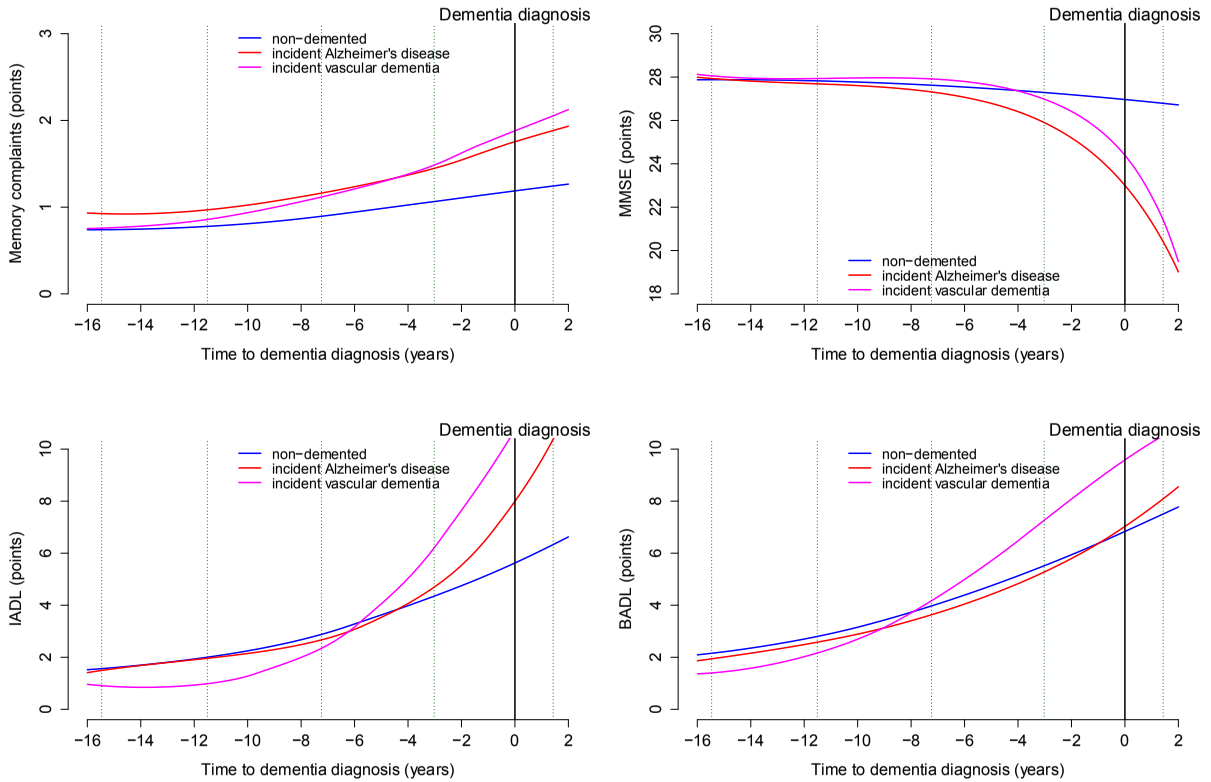

Figure 2. Trajectories of decline in cognition and daily functioning before Alzheimer's disease and vascular dementia. The trajectories are derived from the lcmm analyses and plotted for the mean age, sex, and education. The vertical dark green dotted lines are the mean visit dates. The red lines represent the incident Alzheimer cases, the pink lines the incident vascular dementia cases, and the blue lines the controls.

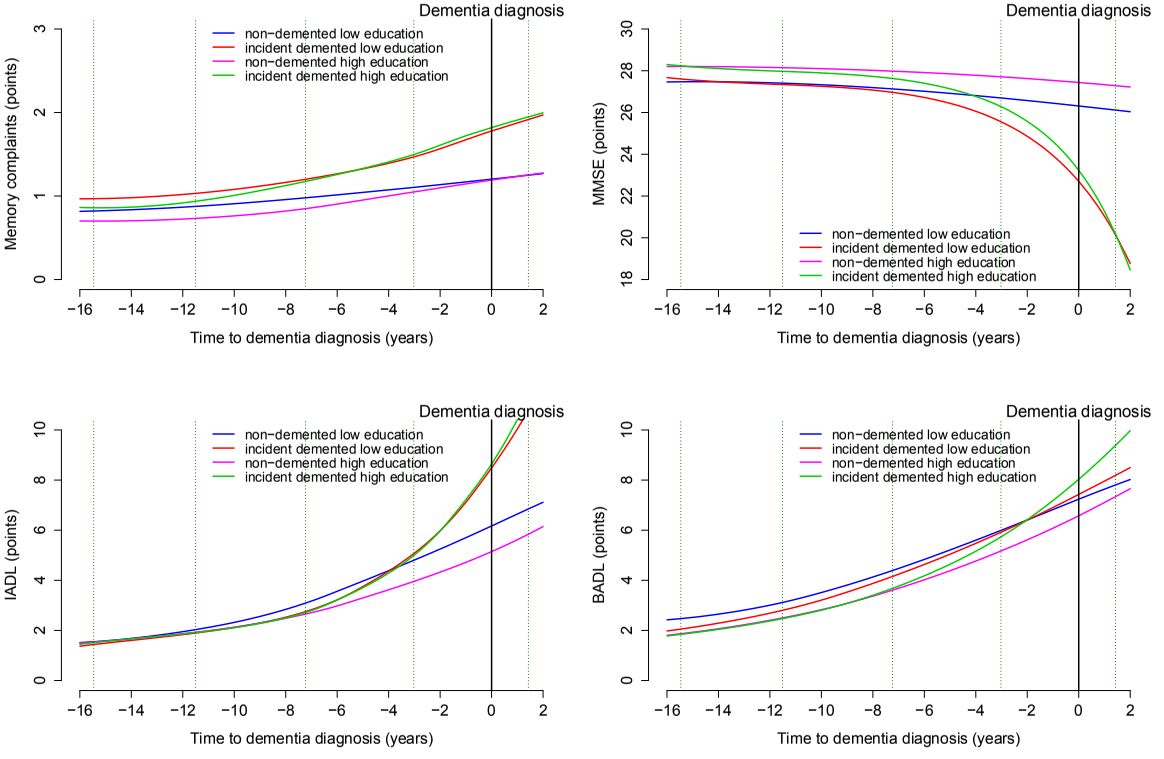

Figure 3. Trajectories of decline in cognition and daily functioning before dementia diagnosis, stratified by education. The trajectories are derived from the lcmm analyses and plotted for the mean age and sex. The vertical dark green dotted lines are the mean visit dates. The light green lines represent the incident demented cases with high education, the red lines the incident dementia cases with low education, the pink lines the controls with high education, and the blue lines the controls with low education.

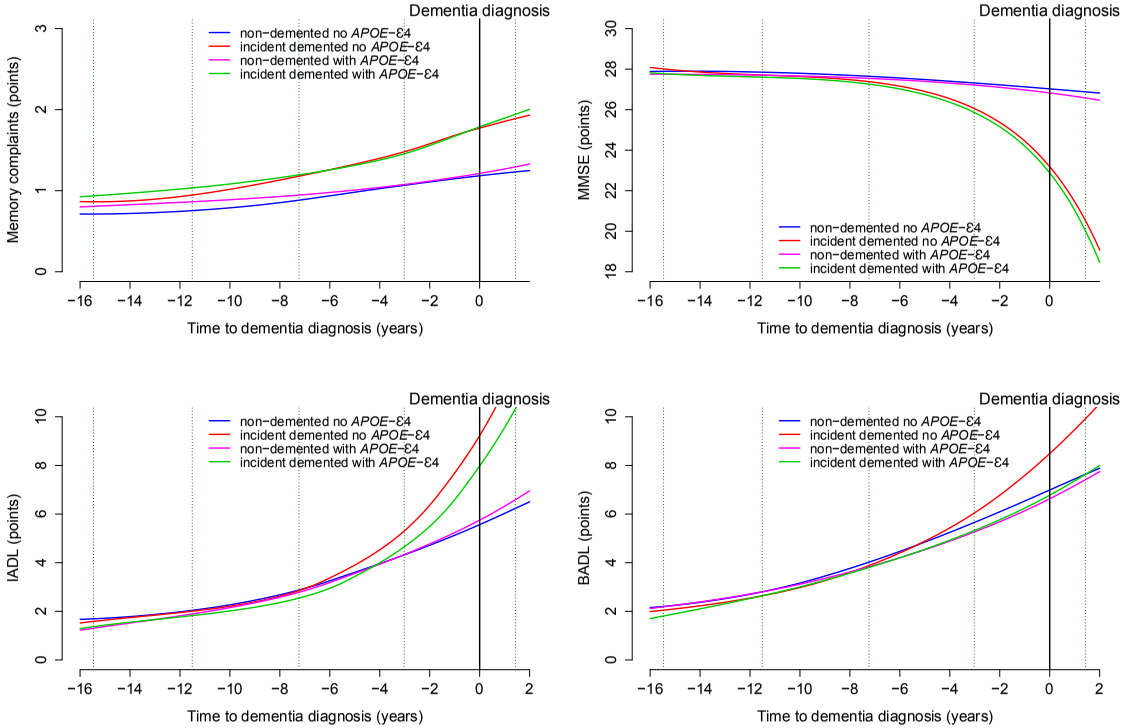

Figure 4. Trajectories of decline in cognition and daily functioning before dementia diagnosis, stratified by *APOE*-ε4 carrier status. The trajectories are derived from the lcmm analyses and plotted for the mean age, sex, and education. The vertical dark green dotted lines are the mean visit dates. The light green lines represent the *APOE*-ε4 carriers with incident dementia, the red lines the non *APOE*-ε4 carriers with incident dementia, the pink lines the *APOE*-ε4 carriers without incident dementia, and the blue lines the non *APOE*-ε4 carriers without dementia.

years before diagnosis compared to ~7 years). We found significant cubic increased decline in MMSE and IADL, quadratic in memory complaints, and linear in BADL for incident AD. For vascular dementia, we found a significant cubic increased decline for MMSE, quadratic for IADL, and linear for memory complaints and BADL.

Interactions with education

We found a significant linear interaction for education on the trajectory of MMSE before dementia ($p_{interaction}$=0.02). Incident demented participants with a higher education started with a higher MMSE, but towards dementia diagnosis declined faster compared to lower educated participants, resulting in similar MMSE two years after diagnosis (Figure 3). Although similar patterns were seen for memory complaints and BADL, no significant interactions were found. The interaction with education for MMSE was found for incident AD, but not for vascular dementia.

Interactions with *APOE*-ε4 carrier status

We found no differences for *APOE*-ε4 carrier status in trajectories of memory complaints and MMSE before incident dementia (Figure 4). Decline in IADL before dementia started later for *APOE*-ε4 carriers, which was supported by a significant linear interaction term ($p_{interaction}$=0.02). For BADL, we found increased decline in non *APOE*-ε4 carriers with incident dementia, while *APOE*-ε4 carriers with incident dementia showed no increased decline at all. This difference was supported by an interaction with quadratic less decline in BADL before dementia for *APOE*-ε4 carriers ($p_{interaction}$=0.003).

Similar interactions of *APOE*-ε4 in IADL and BADL were found for incident AD. For vascular dementia, only a linear interaction was found of *APOE*-ε4 carrier status with BADL.

Discussion

During the pre-clinical phase, persons who went on to develop dementia declined more quickly in memory complaints, MMSE, IADL, and BADL compared to non-demented participants. Earliest decline was found for memory complaints at 16 years before diagnosis. Next, MMSE declined, followed by IADL, and finally BADL. These trajectories were similar for AD, while participants with vascular dementia declined later in cognition but earlier in BADL. Higher educated persons started with better MMSE, but declined faster before dementia diagnosis. *APOE*-ε4 carriers had similar trajectories in MMSE and memory complaints before dementia compared to non-carriers, but declined less quickly in IADL and BADL.

Strengths of our study are the large number of demented participants included, investigation of trajectories in all of memory complaints, MMSE, IADL, and BADL, separate investigation of all-cause dementia, AD, and vascular dementia, and investigation of interactions with education and *APOE*-ε4 carrier status.

Limitations of our study include the ceiling effects in our measures of cognition and daily functioning. Possibly, earlier decline would have been found with continuous measures. Similarly, MMSE may not be the best measure of objective cognitive dysfunction. E.g. objective memory assessment may be more sensitive, as suggested by a previous study.[3] Furthermore, we used questionnaires to assess daily functioning and memory complaints, which are reliant on self-report. People that become demented may not report problems in daily functioning and memory accurately. However, this issue is most pronounced in the last years before dementia, suggesting reliable findings in earlier years.

Our study demonstrates the long trajectories of decline in cognition and daily functioning in the preclinical phase of dementia. We found a clear hierarchical decline with first memory complaints, then decline in global cognition (MMSE), followed by decline in more cognitive daily functioning (IADL), and finally simpler basic daily functioning (BADL). Comparison of our results for all-cause dementia with previous studies are limited, because those only investigated incident AD.[3, 4] Nonetheless, results were similar, with earliest deterioration in cognition from 16 years before dementia diagnosis, which increased dramatically from 7 years before dementia, closely followed by decline in IADL.[3, 4] Interestingly, we found the earliest symptoms of incident dementia for memory complaints, at 16 years before diagnosis. Importantly, as our follow-up started at 16 years before diagnosis, memory complaints may already have been present even earlier in the disease process. This finding is in line with studies which have suggested that people may notice memory deterioration before cognitive tests are able to detect it.[19, 20] Yet, since we did not have objective measurements of memory available, we cannot ascertain whether these tests would have been able to detect similar differences, as have previously been identified for higher educated people.[3] Participants with incident dementia deteriorated last in BADL, from around 5 years before diagnosis onwards.

Since most dementia cases in our sample had AD, trajectories of cognition and daily functioning before AD closely resembled those for all-cause dementia. Yet, clear differences were appreciated compared to vascular dementia. Participants with incident AD were earlier to deteriorate in cognition, as reflected by memory complaints and MMSE. In contrast, participants with incident vascular dementia deteriorated earlier and faster in daily functioning, especially the more physical BADL. These differences between AD and vascular dementia may be driven by differences in (localisation of) pathology. AD pathology is thought to first affect the hippocampus and temporal lobe, which are most involved in cognition and memory.[21-23]

In contrast, people with vascular dementia may accumulate more global structural brain changes, which are known to also affect daily functioning.[13, 21, 23]

We found higher educated people to start with better cognition compared to lower educated people, but to decline earlier before incident dementia. Although a previous study could not statistically verify this difference, we found a significant interaction with higher educated people declining more quickly in cognition, as reflected by MMSE.[3] We found this same interaction for AD, but not for vascular dementia, most likely due to less power. Nonetheless, the interaction supports the cognitive reserve hypothesis, suggesting that higher educated people can withstand more brain pathology before deteriorating in cognition.[3, 24] Yet, further research is required to investigate whether similar amounts of brain pathology indeed have different effects on cognition in higher compared to lower educated people.

To the best of our knowledge, we are the first study to investigate influence of *APOE*-ε4 carrier status on trajectories of cognition and daily functioning before dementia. Although *APOE*-ε4 is the strongest genetic risk factor for late-onset AD, its relationship with cognition and daily functioning is less clear.[6, 25-28] In our study, we found no differences for *APOE*-ε4 carriers in trajectories of cognition before dementia. However, we did find *APOE*-ε4 carriers with incident dementia to decline less in daily functioning compared to non-carriers. Similar associations were found for both AD and vascular dementia. Hence, *APOE*-ε4 may prevent deterioration in daily functioning due to brain pathology. A previous study found similar protective effects of *APOE*-ε4 on decline in daily functioning of AD patients.[26] Possibly, this effect is due to difference in brain morphology or the pattern of brain aging.[29] Future studies should further investigate the interrelationship of *APOE*-ε4, the brain, and incident dementia.

Conclusions

Incident dementia has a long pre-clinical trajectory of decline in cognition and daily functioning which may already start at 16 years before clinical diagnosis. People first report memory complaints, followed by decline in global cognition, cognitive IADL, and finally physical BADL. These trajectories of decline differ by dementia subtype, education, and *APOE*-ε4 carrier status.

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Chapter 3.3

Structural and microstructural brain changes predict impairment in daily functioning

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Abstract

Background: Brain changes on magnetic resonance imaging (MRI) reflect accumulating pathology and have clinically disabling consequences, such as dementia. However, little is known on the relation of these MRI-markers with daily functioning in non-demented individuals. We investigated whether structural and microstructural brain changes associate with impairment in activities of daily living in a community-dwelling population.
Methods: Between 2005-2009, 2025 stroke-free non-demented participants (aged 59.9 years) from the population-based Rotterdam Study underwent brain-MRI, yielding global MRI-markers, focal MRI-markers, and microstructural MRI-markers. We used the Stanford Health Assessment Questionnaire to assess basic and the Instrumental Activities of Daily Living Scale to assess instrumental activities of daily living. Follow-up on activities of daily living was obtained between 2008-2013 (mean follow-up 5.7 years). We used linear regression to analyze continuous scores of daily living and logistic regression for incident impairment.
Results: 82 participants became impaired in basic and 33 in instrumental activities of daily living. Smaller brain and hippocampal volume and higher diffusivity associated with larger change in activities of daily living. Smaller brain volume (odds ratio 4.05 per standard deviation (/SD) (95% confidence interval: 1.81-9.02)), larger white matter lesion volume (1.33 /SD (1.02-1.72)) and higher mean (1.55 /SD (1.11-2.15)), axial (1.49 /SD (1.08-2.07)), and radial diffusivity (1.51 /SD (1.09-2.10)) associated with higher risk of impairment in basic activities of daily living.
Conclusions: In community-dwelling individuals, brain changes associate with deterioration and incident impairment in daily functioning.

Introduction

Normal aging and neurological diseases, such as dementia, are often accompanied by impairment in cognitive and daily functioning.[1] Previous studies have shown strong associations of poor cognition with worse daily functioning.[2-4] Moreover, cognitive decline is often accompanied by concurrent decline in daily functioning.[5] Despite this co-occurrence, it is primarily deterioration in daily functioning, rather than cognition that leads to loss of independence and institutionalization. Therefore, unravelling determinants of daily functioning is important to understand processes leading towards loss of independence.

Structural brain changes, as visualized on magnetic resonance imaging (MRI), are strong determinants of cognitive impairment, even in non-demented persons.[6, 7] Recently, microstructural integrity of white matter, which is invisible on conventional MRI but can be quantified on diffusion tensor imaging (DTI), has also been shown to associate with cognition.[8, 9] Although the role of structural and microstructural brain changes in cognitive impairment is clear, little is known on their relation with daily functioning.

Daily functioning is generally assessed by activities of daily living , including physical basic activities, e.g. eating, and more cognitive instrumental activities, e.g. meal preparation.[10]

Previous studies investigating brain changes in relation to activities of daily living were mainly clinic-based.[2, 11-13] Yet, public health impact is best evaluated in a community-dwelling population. Additionally, these studies rated structural brain changes visually, while automated quantification may disentangle more subtle associations.[2, 11-13] Furthermore, study of microstructure may show whether brain pathology invisible on conventional MRI leads to deterioration in daily functioning.

We investigated whether structural and microstructural brain changes associate with deterioration in basic and instrumental activities of daily living in non-demented community-dwelling individuals.

Methods

Setting

The study was embedded in the Rotterdam Study, a population-based cohort study.[14] In 1990 and 2000 all inhabitants of Ommoord, a suburb of Rotterdam, aged 55 years and older were invited to participate. In 2006, the cohort was extended, inviting all inhabitants aged 45 years and older. Every three to four years, participants are re-invited for follow-up examinations. At baseline and follow-up visits, participants undergo an interview, including activities of daily living questionnaires, and medical examinations. In August 2005, MRI-scanning was

included in the study protocol. The study has been approved by the Medical Ethics Committee of the Erasmus MC. All participants gave written informed consent.

The current study is based on participants from the second and third subcohort of the Rotterdam Study, who underwent MRI-scanning until September 2009. We invited 4595 participants for MRI-scanning. We excluded individuals for dementia (n=14), history of clinical stroke (n=103), or MRI contraindications (e.g. pacemaker or claustrophobia, n=340). Of 4138 eligible persons, 3794 agreed to participate. For 45 persons, MRI-scanning was not completed due to physical or technical problems and 96 were excluded for artefacts, cortical infarcts, or large meningiomas.

Due to lack of personnel, the questionnaires were removed from the interview between February and August 2006, leading to 669 random persons being excluded. In total, 2984 participants had complete and valid baseline data.

Follow-up assessment of daily functioning was performed between December 2008 and August 2013. Eighty-eight participants died before follow-up. Of remaining participants, 2229 were re-invited, of whom 160 refused to participate, 21 did not respond, 11 were unable to participate, 9 had missing follow-up data, and 3 had moved out of the study area. Finally, we included 2025 participants in the analyses.

Our DTI-protocol was implemented only in MRI-scans of participants from the third subcohort (n=1283).

MRI acquisition and processing

Brain MRI-scanning was performed using a 1.5-tesla scanner with an 8-channel head coil (GE Healthcare, Milwaukee, WI), and included T1-weighted, proton-density weighted, fluid-attenuated inversion recovery-weighted, T2*-weighted sequences and DTI.[15]

Automated tissue classification based on a k-nearest neighbor classifier algorithm extended with white matter lesion segmentation was used to quantify supratentorial brain, grey matter, white matter, white matter lesion, and intracranial volume.[16, 17] Total white matter volume was the sum of normal appearing white matter and white matter lesion volume.

Hippocampus was segmented automatically based on an intensity model and a spatial probability map.[18]

Lacunar infarcts were rated as focal parenchymal lesions (3-15 mm in size) without involvement of cortical grey matter.[19] Microbleeds were rated as focal hypointensities on T2*-weighted sequences.[20]

After affine registrations to T1-images to adjust for subject motion and eddy currents, DTI-images were resampled at an isotropic resolution of $1mm^3$, and a Levenberg-Marquard non-linear least-squares estimator was used to fit diffusion tensors.[21, 22] These were then used to derive fractional anisotropy and mean, axial, and radial diffusivity images.[23, 24] The diffu-

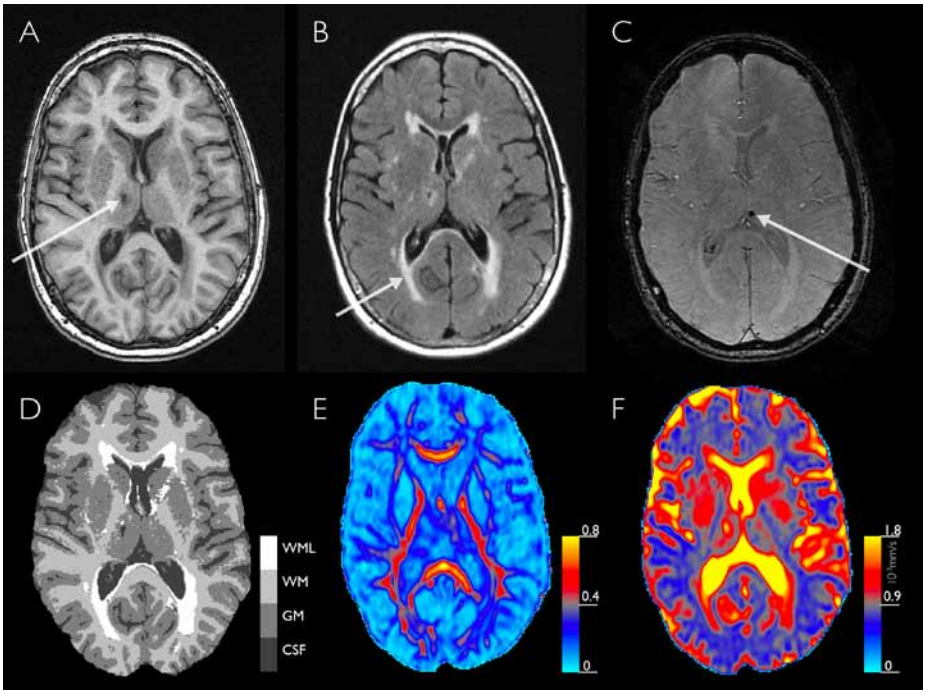

Figure 1. Structural and microstructural brain changes on MRI. Left on the image corresponds to right in the brain. A: Lacunar infarct (arrow) on T1-weighted image. B: White matter lesions (arrow) on FLAIR image. C: Cerebral microbleed (arrow) on T2*-weighted image. D: Tissue segmentation with each tissue type represented in a different grey value (darkest grey = cerebrospinal fluid, grey = grey matter, light grey = normal appearing white matter, white = white matter lesion). E: DTI-map of fractional anisotropy with larger values indicating larger anisotropy. F: DTI-map of mean diffusivity with larger values indicating larger diffusivity.

sion images were combined with tissue segmentations to obtain measurements in the normal appearing white matter. Lower fractional anisotropy and higher mean diffusivity indicate poorer white matter integrity.

Global MRI-markers of atrophy comprise brain, grey matter, total white matter, and hippocampal volume. Focal MRI-markers comprise white matter lesion volume, lacunar infarcts, and microbleeds. Microstructural MRI-markers comprise fractional anisotropy and mean, axial, and radial diffusivity. Figure 1 shows an overview.

Basic activities of daily living

Basic activities of daily living was assessed with the disability index from the Stanford Health Assessment Questionnaire, consisting of 20 items constituting eight components: dressing

and grooming, arising, eating, walking, hygiene, grip, reach, and activities.[25] We combined two out of three items of eating (ability to lift a glass of milk and ability to cut meat) into one. Items were scored from 0 to 3, as follows: 0 = without difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to. Component scores were calculated as the highest scored item per component.[25] Hence, items scored as non-applicable or missing were accounted for by properly scored items in their respective components. The basic activities of daily living score was then calculated by summing all components, obtaining a score between 0 and 24. We considered scores from 0 to 8 as no to mild disability and from 8 to 24 as moderate to very severe disability.[26]

Instrumental activities of daily living

Instrumental activities of daily living was assessed based on the Lawton and Brody Instrumental Activities of Daily Living scale.[27] The instrumental activities of daily living scale consists of eight items: telephone use, shopping, travelling on your own, management of finances, laundry, medication maintenance, meal preparation, and housekeeping. We scored items of the instrumental activities of daily living scale from 0 to 3. For telephone use, participants using an adapted telephone were scored as 2 (with much difficulty).

Items scored as non-applicable were imputed by the mean of five imputations, based on age, sex, and scores on all basic and other instrumental activities of daily living. Imputation was performed separately for baseline and follow-up, with 5.3% of the variables being imputed. Imputation of non-applicable values has been suggested and adopted to prevent loss of data.[10, 28] Instrumental activities of daily living score was calculated by summing all items, obtaining a score between 0 and 24. We considered scores from 0 to 8 as no to mild disability and from 8 to 24 as moderate to very severe disability.

Covariates

During home interview and examinations at the research center, height, weight, blood pressure, glucose level, total cholesterol level, high-density lipoprotein (HDL) level, smoking, Mini-Mental State Examination (MMSE)[29], and Center for Epidemiologic Studies Depression Scale (CES-D)[30] were assessed. Additionally, use of anti-diabetic and blood pressure lowering medication was evaluated. Body mass index (BMI) was calculated as weight divided by the squared height. Diabetes mellitus was defined as fasting blood glucose level >= 7.0 mmol/L, non-fasting blood glucose level >= 11.1 mmol/L, or use of anti-diabetic medication. Missing values (0.5%) were imputed using means of five imputations, based on age, sex, and the other covariates. Imputed values for use of anti-diabetic and blood pressure lowering medication were rounded to either zero or one.

Statistical analysis

White matter lesion volumes were natural log transformed to obtain a normal distribution. Continuous MRI-markers were Z-standardized (subtracting the mean and dividing by the standard deviation).

Associations of MRI-markers with cross-sectional functioning and change in BADL and IADL were investigated in two ways.

First, we used basic and instrumental activities of daily living as continuous outcomes, with change analyzed as the score at follow-up, adjusted for baseline score.[31] Linear regression analyses were used to investigate associations of MRI-markers with basic and instrumental activities, both cross-sectionally and longitudinally.

Second, basic and instrumental activities of daily living scores were dichotomized at a score of 8. Persons with scores between 0 and 8 were considered unimpaired, and persons with scores from 8 to 24 impaired. Incident impairment in activities of daily living was defined as the transition from being unimpaired at baseline to impaired at follow-up. Binary logistic regression analyses were used to model associations of global, focal, and microstructural MRI-markers with prevalent and incident impairment in basic and instrumental activities. Participants who were already impaired at baseline were not included in analyses of incident impairment.

Analyses were adjusted for age, sex, MMSE, CES-D, BMI, systolic blood pressure, diastolic blood pressure, blood pressure lowering medication use, current or past smoking, diabetes mellitus, total cholesterol, and HDL. Global MRI-markers (except brain volume) were included in one model to investigate independent associations. Similarly, focal MRI-markers were included in one model. Analyses of global and focal MRI-markers were adjusted for intracranial volume and subcohort. Analyses of microstructural MRI-markers were adjusted for total white matter volume and white matter lesion volume. Longitudinal analyses were adjusted for time between visits.

To adjust for multiple testing, we used separate Bonferroni-thresholds for global, focal, and microstructural MRI-markers, to take into account correlations among these markers: 6 tests ($p_{corrected}<0.008$) for global MRI-markers (3 "independent" determinants: grey matter, white matter, and hippocampus and 2 outcomes: basic and instrumental activities of daily living), 6 tests ($p_{corrected}<0.008$) for focal MRI-markers (3 determinants and 2 outcomes), and 4 tests ($p_{corrected}<0.012$) for microstructural MRI-markers (2 determinants: fractional anisotropy and mean diffusivity (consisting of axial and radial diffusivity) and 2 outcomes).

In sensitivity analyses, we repeated analyses for incident impairment with additional adjustment for baseline scores.

Analyses were performed using IBM SPSS version 21.0.0.1 for Windows.

Results

Mean age at baseline was 59.9 years (standard deviation (SD) 7.0) and 54.7% of participants were women (Table 1). Mean basic activities of daily living score at baseline was 1.8 (SD 2.5) and mean instrumental activities of daily living score 1.3 (SD 1.9). Average follow-up time was 5.7 (SD 0.6) years and average change was 0.88 points (SD 2.47) in basic and 0.24 (SD 2.25) in instrumental activities of daily living. Of 1967 participants without baseline basic activities of daily living impairment, 82 (4.2%) became impaired during follow-up. Of 1982

Table 1. Baseline population characteristics

	Total (n = 2025)
Age, years	59.9 (7.0)
Females	1107 (54.7%)
MMSE, points	28.2 (1.6)
CES-D, points	4.8 (6.7)
Body mass index, kg/m^2	27.5 (4.1)
Systolic blood pressure, mmHg	135.7 (19.0)
Diastolic blood pressure, mmHg	82.1 (10.4)
Use of blood pressure lowering medication	457 (22.6%)
Total cholesterol, mmol/L	5.7 (1.0)
High-density lipoprotein, mmol/L	1.5 (0.4)
Current or past smoking	1397 (69.0%)
Diabetes mellitus	126 (6.2%)
Brain volume, ml	948.8 (98.8)
Grey matter volume, ml	532.1 (53.4)
Total white matter volume, ml	416.8 (56.5)
Hippocampal volume, ml	6.0 (0.6)
White matter lesion volume, ml	3.7 (4.6)
Lacunar infarcts	77 (3.8%)
Microbleeds	306 (15.1%)
Fractional anisotropy[a]	0.33 (0.01)
Mean diffusivity[a], 10^{-3} mm^2/s	0.73 (0.02)
Axial diffusivity[a], 10^{-3} mm^2/s	1.01 (0.02)
Radial diffusivity[a], 10^{-3} mm^2/s	0.60 (0.02)

Values are means (standard deviations) or numbers of participants (percentages).

[a] Only in 1283 participants.

Abbreviations: MMSE, Mini-Mental State Examination; CES-D, Center for Epidemiologic Studies Depression Scale; kg, kilograms; m, meters; mmHg, millimeter mercury; mmol/L, millimol per liter; ml, milliliters; mm^2/s, squared millimeters per second.

Table 2. Longitudinal associations of global MRI-markers with change and incident impairment in activities of daily living

	BADL		IADL	
	Change in score β (95% CI)	Incident impairment OR (95% CI)	Change in score β (95% CI)	Incident impairment OR (95% CI)
Brain volume	**0.65 (0.30; 0.99)**	**4.05 (1.81; 9.02)**	**0.51 (0.20; 0.82)**	3.25 (0.94; 11.25)
Grey matter volume	**0.38 (0.14; 0.62)**	**2.29 (1.30; 4.04)**	**0.31 (0.10; 0.53)**	1.94 (0.82; 4.60)
Total white matter volume	**0.32 (0.10; 0.53)**	**2.03 (1.22; 3.39)**	0.22 (0.03; 0.41)	1.83 (0.84; 3.99)
Hippocampus volume	0.11 (-0.01; 0.22)	1.16 (0.89; 1.52)	**0.16 (0.05; 0.26)**	1.23 (0.83; 1.83)

Values represent differences in change or odds ratios of incident impairment in BADL or IADL (95% confidence interval) per standard deviation smaller volume. An increase in the BADL or IADL score represents deterioration in activities of daily living. Results in bold survived Bonferroni correction ($p_{corrected}$<0.008).

All analyses are adjusted for age, sex, Mini-Mental State Examination, Center for Epidemiologic Studies Depression Scale, subcohort, time between visits, intracranial volume, body mass index, systolic blood pressure, diastolic blood pressure, use of blood pressure lowering medication, current or past smoking, diabetes mellitus, total cholesterol level, high-density lipoprotein level, and, if applicable, other global MRI-markers.

Abbreviations: BADL, Basic Activities of Daily Living; IADL, Instrumental Activities of Daily Living; CI, confidence interval; OR, odds ratio.

Table 3. Longitudinal associations of focal MRI-markers with change and incident impairment in activities of daily living

	BADL		IADL	
	Change in score β (95% CI)	Incident impairment OR (95% CI)	Change in score β (95% CI)	Incident impairment OR (95% CI)
White matter lesions[a], per SD larger volume	0.11 (-0.01; 0.23)	1.33 (1.02; 1.72)	0.07 (-0.04; 0.18)	1.08 (0.72; 1.62)
Lacunar infarcts, yes versus no	0.08 (-0.46; 0.61)	0.61 (0.17; 2.17)	0.00 (-0.47; 0.48)	1.04 (0.27; 3.99)
Microbleeds, yes versus no	0.06 (-0.22; 0.35)	0.90 (0.47; 1.71)	0.09 (-0.16; 0.34)	1.62 (0.69; 3.80)

Values represent differences in change or odds ratios of incident impairment in BADL or IADL (95% confidence interval). An increase in the BADL or IADL score represents deterioration in activities of daily living.

All analyses are adjusted for age, sex, Mini-Mental State Examination, Center for Epidemiologic Studies Depression Scale, subcohort, time between visits, intracranial volume, body mass index, systolic blood pressure, diastolic blood pressure, use of blood pressure lowering medication, current or past smoking, diabetes mellitus, total cholesterol level, high-density lipoprotein level, and the other focal MRI-markers. No associations survived Bonferroni correction ($p_{corrected}$<0.008).

[a] Natural log transformed.

Abbreviations: BADL, Basic Activities of Daily Living; IADL, Instrumental Activities of Daily Living; CI, confidence interval; OR, odds ratio; SD, standard deviation.

Table 4. Longitudinal associations of microstructural MRI-markers with change and incident impairment in activities of daily living

	BADL		IADL	
	Change in score β (95% CI)	Incident impairment OR (95% CI)	Change in score β (95% CI)	Incident impairment OR (95% CI)
Fractional anisotropy	-0.12 (-0.25; 0.02)	0.78 (0.56; 1.08)	-0.01 (-0.12; 0.10)	1.07 (0.56; 2.04)
Mean diffusivity	**0.19 (0.05; 0.33)**	**1.55 (1.11; 2.15)**	0.10 (-0.01; 0.21)	1.03 (0.55; 1.92)
Axial diffusivity	0.16 (0.01; 0.30)	1.49 (1.08; 2.07)	0.13 (0.02; 0.24)	1.12 (0.60; 2.09)
Radial diffusivity	**0.18 (0.04; 0.32)**	1.51 (1.09; 2.10)	0.08 (-0.03; 0.19)	0.98 (0.52; 1.85)

Values represent differences in change or odds ratios of incident impairment in BADL or IADL (95% confidence interval) per standard deviation larger value of the microstructural MRI-marker. An increase in the BADL or IADL score represents deterioration in activities of daily living. Results in bold survived Bonferroni corrections ($p_{corrected}<0.012$).

All analyses are adjusted for age, sex, Mini-Mental State Examination, Center for Epidemiologic Studies Depression Scale, time between visits, body mass index, systolic blood pressure, diastolic blood pressure, use of blood pressure lowering medication, current or past smoking, diabetes mellitus, total cholesterol level, high-density lipoprotein level, total white matter volume, and log transformed white matter lesion volume.

Abbreviations: BADL, Basic Activities of Daily Living; IADL, Instrumental Activities of Daily Living; CI, confidence interval; OR, odds ratio.

participants without baseline instrumental activities of daily living impairment, 33 (1.7%) became impaired.

Cross-sectional associations are presented in Supplements 1-3.

In longitudinal analyses, smaller brain volume associated with larger change in both basic and instrumental activities of daily living, driven by grey and white matter volume (Table 2). Smaller brain volume (odds ratio 4.05 per SD smaller volume (95% confidence interval: 1.81-9.02)), grey matter volume (2.29 (1.30-4.04)), and total white matter volume (2.03 (1.22-3.39)) also associated with higher risk of incident impairment in basic activities. Smaller hippocampal volume associated with larger change in instrumental activities.

We found no associations of focal MRI-markers with change or impairment in either basic or instrumental activities, after Bonferroni correction (Table 3).

Higher mean and radial diffusivity in brain white matter associated with larger change in basic activities (Table 4). Higher mean diffusivity also associated with higher risk of impairment in basic activities of daily living (1.55 (1.11-2.15)).

In sensitivity analyses, additional adjustment for baseline scores yielded similar results.

Discussion

In non-demented community-dwelling individuals, we found structural and microstructural brain changes to associate with deterioration and incident impairment in activities of daily living. Smaller brain volume associated with larger deterioration in basic and instrumental activities, and higher risk of impairment in basic activities of daily living. Smaller hippocampal volume associated with larger deterioration in instrumental activities. Worse white matter microstructural integrity associated with larger deterioration and incident impairment in basic activities of daily living.

The main novelty of our study is that we found structural and microstructural brain changes to associate with deterioration and incident impairment in activities of daily living in community-dwelling, stroke-free, and non-demented individuals. Previous studies were mainly clinic-based, thereby including selected participants with possibly incipient dementia.[2, 11, 12, 32] Our study now indicates that, even in relatively young and healthy non-demented individuals, brain pathology may lead to impairment in daily functioning. Interestingly, we found only weak cross-sectional associations, suggesting little impairment in daily functioning at baseline. In contrast, strong longitudinal associations emphasize the large impact brain pathology may have on public health, extending further than only persons who seek medical help and have a high risk of incident dementia. Additionally, we found that brain pathology may affect both physical basic and cognitively more demanding instrumental activities. Together, our findings suggest that interventions aimed at preventing or reducing progression of brain pathology may prevent impairment in a wide range of daily activities. Since vascular risk factors and vascular pathology have an important role in accumulating brain pathology, these may be important targets for preventive interventions. Clinicians should be aware that treatment of vascular pathology should not only aim to prevent cardiovascular disease, but also brain pathology. Indeed, various studies have already indicated that treatment of hypertension may reduce progression of brain pathology.[33, 34] Still, future studies should first investigate the feasibility of treatment of vascular risk factors to slow progression of brain pathology and subsequent impairment in daily functioning.

Direct comparison of our findings with previous studies is limited. We used quantitative measurements to rate brain atrophy and white matter lesions, while previous studies graded these visually. Additionally, previous studies often used different questionnaires and rarely investigated activities of daily living continuously. Still, some remarks can be made.

We found smaller brain volume, driven by both grey and white matter, to associate with larger deterioration in basic and instrumental activities. Additionally, we found smaller brain volume to associate with higher risk of incident impairment in basic activities. These associations are supported by two studies showing ventricular enlargement to associate with incident

activities of daily living disability.[2, 13] Importantly, we now find that one standard deviation smaller brain volume associates with a fourfold higher risk of incident basic activities of daily living impairment. In our dataset, this corresponds to the effect on basic activities of being 25 years older in age. This demonstrates the huge clinical impact brain pathology may have on daily functioning. Although we found similar associations of brain volume with deterioration in instrumental activities continuously, none were found with incident impairment in instrumental activities. This may be explained by smaller numbers leading to lower power.

In line with another study, we found smaller hippocampus volume to associate with deterioration in instrumental activities.[32] Hippocampus volume did not associate with change in basic activities, which underscores the main role of the hippocampus in cognition and less so in physical ability.

We did not find convincing associations of focal MRI-markers with basic or instrumental activities. This may be explained by the focal nature of such pathology. In contrast, atrophy is diffuse and often affects large areas of the brain and is therefore more likely to affect brain regions important for activities of daily living. Also, diffuse continuous MRI-markers have more statistical power than focal dichotomous MRI-markers.

We are the first study to demonstrate that microstructural white matter changes, i.e. mean, axial, and radial diffusivity, associate with deterioration and incident impairment in basic activities of daily living. Importantly, these associations were independent from total white matter and white matter lesion volume. These findings suggest that brain pathology invisible on conventional MRI provides additional information above volumetric measures in predicting who will deteriorate in daily functioning.

Strengths of our study include the population-based design, investigation of various structural and microstructural brain changes, quantitative measurement of brain atrophy and white matter lesions, and longitudinal assessment of both basic and instrumental activities of daily living.

A limitation is that follow-up MRI was unavailable. Therefore, we could not establish whether change in brain pathology coincided with change in activities of daily living. Another limitation is that participants may be relatively healthy, because they were required to participate in two interviews and an MRI-examination. Therefore, generalization of our findings may be limited to a relatively healthy population.

Conclusions

In a community-dwelling population of non-demented individuals, structural and micro-structural MRI-markers of brain pathology are associated with deterioration and incident impairment in daily functioning.

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Supplement 1. Cross-sectional associations of global MRI-markers with activities of daily living

	BADL		IADL	
	Score β (95% CI)	Prevalent impairment OR (95% CI)	Score β (95% CI)	Prevalent impairment OR (95% CI)
Brain volume	0.27 (-0.09; 0.62)	1.12 (0.41; 3.04)	0.19 (-0.09; 0.46)	2.78 (0.67; 11.54)
Grey matter volume	0.18 (-0.07; 0.43)	0.84 (0.42; 1.66)	0.13 (-0.06; 0.32)	1.13 (0.42; 3.03)
Total white matter volume	0.13 (-0.09; 0.35)	1.38 (0.73; 2.59)	0.11 (-0.07; 0.28)	2.22 (0.90; 5.45)
Hippocampus volume	0.00 (-0.12; 0.12)	0.76 (0.54; 1.06)	-0.04 (-0.14; 0.05)	1.13 (0.71; 1.82)

Values represent differences in score or odds ratios of prevalent impairment in BADL or IADL (95% confidence interval) per standard deviation smaller volume. A higher BADL or IADL score represents worse functioning in activities of daily living. All analyses are adjusted for age, sex, Mini-Mental State Examination, Center for Epidemiologic Studies Depression Scale, subcohort, intracranial volume, body mass index, systolic blood pressure, diastolic blood pressure, use of blood pressure lowering medication, current or past smoking, diabetes mellitus, total cholesterol level, high-density lipoprotein level, and, if applicable, other global MRI-markers.

Abbreviations: BADL, Basic Activities of Daily Living; IADL, Instrumental Activities of Daily Living; CI, confidence interval; OR, odds ratio.

Supplement 2. Cross-sectional associations of focal MRI-markers with activities of daily living

	BADL		IADL	
	Score β (95% CI)	Prevalent impairment OR (95% CI)	Score β (95% CI)	Prevalent impairment OR (95% CI)
White matter lesions[a], per SD larger volume	0.08 (-0.04; 0.21)	1.22 (0.90; 1.64)	0.16 (0.07; 0.26)	1.54 (1.00; 2.38)
Lacunar infarcts, yes versus no	-0.28 (-0.83; 0.27)	0.99 (0.25; 3.87)	-0.08 (-0.50; 0.34)	0.36 (0.06; 2.09)
Microbleeds, yes versus no	-0.09 (-0.38; 0.20)	0.66 (0.29; 1.51)	-0.08 (-0.30; 0.14)	0.62 (0.19; 2.06)

Values represent differences in score or odds ratios of prevalent impairment in BADL or IADL (95% confidence interval). A higher BADL or IADL score represents worse functioning in activities of daily living. All analyses are adjusted for age, sex, Mini-Mental State Examination, Center for Epidemiologic Studies Depression Scale, subcohort, intracranial volume, body mass index, systolic blood pressure, diastolic blood pressure, use of blood pressure lowering medication, current or past smoking, diabetes mellitus, total cholesterol level, high-density lipoprotein level, and the other focal MRI-markers.

[a] Natural log transformed.

Abbreviations: BADL, Basic Activities of Daily Living; IADL, Instrumental Activities of Daily Living; CI, confidence interval; OR, odds ratio; SD, standard deviation.

Supplement 3. Cross-sectional associations of microstructural MRI-markers with activities of daily living

	BADL		IADL	
	Score β (95% CI)	Prevalent impairment OR (95% CI)	Score β (95% CI)	Prevalent impairment OR (95% CI)
Fractional anisotropy	-0.11 (-0.24; 0.03)	0.94 (0.61; 1.46)	-0.02 (-0.12; 0.08)	0.63 (0.30; 1.32)
Mean diffusivity	0.12 (-0.03; 0.26)	1.01 (0.65; 1.58)	0.00 (-0.10; 0.11)	1.57 (0.74; 3.31)
Axial diffusivity	0.07 (-0.07; 0.22)	0.95 (0.59; 1.52)	-0.01 (-0.12; 0.09)	1.36 (0.60; 3.11)
Radial diffusivity	0.12 (-0.02; 0.26)	1.04 (0.67; 1.61)	0.01 (-0.09; 0.12)	1.61 (0.78; 3.31)

Values represent differences in score or odds ratios of prevalent impairment in BADL or IADL (95% confidence interval) per standard deviation larger value of the microstructural MRI-marker. A higher BADL or IADL score represents worse functioning in activities of daily living. All analyses are adjusted for age, sex, Mini-Mental State Examination, Center for Epidemiologic Studies Depression Scale, body mass index, systolic blood pressure, diastolic blood pressure, use of blood pressure lowering medication, current or past smoking, diabetes mellitus, total cholesterol level, high-density lipoprotein level, total white matter volume, and log transformed white matter lesion volume. Abbreviations: BADL, Basic Activities of Daily Living; IADL, Instrumental Activities of Daily Living; CI, confidence interval; OR, odds ratio.

Chapter 3.4

The role of dementia in the associations of structural brain changes with decline in cognition and daily functioning

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Submitted.

Abstract

Structural brain changes are markers of dementia and decline in cognition and daily functioning. It is unknown whether incipient dementia drives the associations with cognition and daily functioning. We investigated associations of brain changes with change in cognition and daily functioning over 15 years of follow-up, and assessed the role of dementia. Between 1995-1996, 463 persons underwent brain-MRI, yielding brain volumetrics. We assessed cognition using Mini-Mental State Examination (MMSE) and daily functioning using instrumental and basic activities of daily living (IADL and BADL) up to seven times between 1990-2011. Analyses were performed both including and excluding incident demented participants. Smaller brain volume associated with larger decline in MMSE, IADL, and BADL. Frontal lobe volume associated strongest with decline in IADL and BADL, and temporal lobe volume with decline in MMSE. After excluding incident demented participants (n=63), associations with IADL and BADL remained, while associations with MMSE disappeared. Hence, the relation of structural brain changes with cognition is largely driven by incipient dementia, while the relation with daily functioning is not.

Introduction

With aging, pathology accumulates in the brain, leading to deterioration in cognition and daily functioning.[1] Impairment in cognition and daily functioning can be very debilitating and results in loss of independence, which may ultimately lead to institutionalization.[1] Hence, impairment in cognition and daily functioning may severely reduce a person's quality of life.

Cognition is commonly assessed using the Mini-Mental State Examination (MMSE), which is a reflection of global cognitive functioning.[2] In general, daily functioning is assessed by activities of daily living (ADL), including physical basic ADL (BADL), e.g. dressing and eating, and cognitively more challenging instrumental ADL (IADL), e.g. meal preparation and finance management.[3] Together, MMSE, IADL, and BADL capture the whole spectrum from cognition to daily functioning. Studying determinants of decline across this spectrum may provide novel insights into differences and overlap in underlying pathology.

In its extreme form, impairment in cognition and daily functioning may lead to dementia.[1] Structural brain changes are strong markers of dementia, which can be visualized using magnetic resonance imaging (MRI) and include atrophy of the brain, hippocampus, and lobes, as well as white matter lesions and lacunar infarcts.[4, 5] Of these, especially hippocampal and temporal lobe atrophy are strongly associated with an increased risk of dementia.[4] However, even in non-demented persons, various structural brain changes have been found to associate with decline in cognition and daily functioning.[5-9]

Previous studies relating brain changes to decline in cognition and daily functioning were often clinical and had relatively short follow-up.[5-17] Hence, participants in these studies may have already been subject to undetected incipient dementia, which may have driven the associations reported.

We aimed to investigate associations of structural brain changes with change in cognition and daily functioning in a community-dwelling population, during up to 15 years of follow-up. Importantly, we investigated dependence of these associations on incident dementia.

Methods

Setting

The study was embedded in the Rotterdam Study, a population-based cohort study in the Netherlands.[18] The study initiated in 1990 when all inhabitants of Ommoord, a suburb of Rotterdam, aged 55 years and older were invited to participate. At baseline and every follow-up visit, all participants undergo a home interview and medical examinations at the research center. At all visits, global cognition was assessed with the Mini-Mental State Examination (MMSE).[2] The Rotterdam Study has been approved by the medical ethics committee accord-

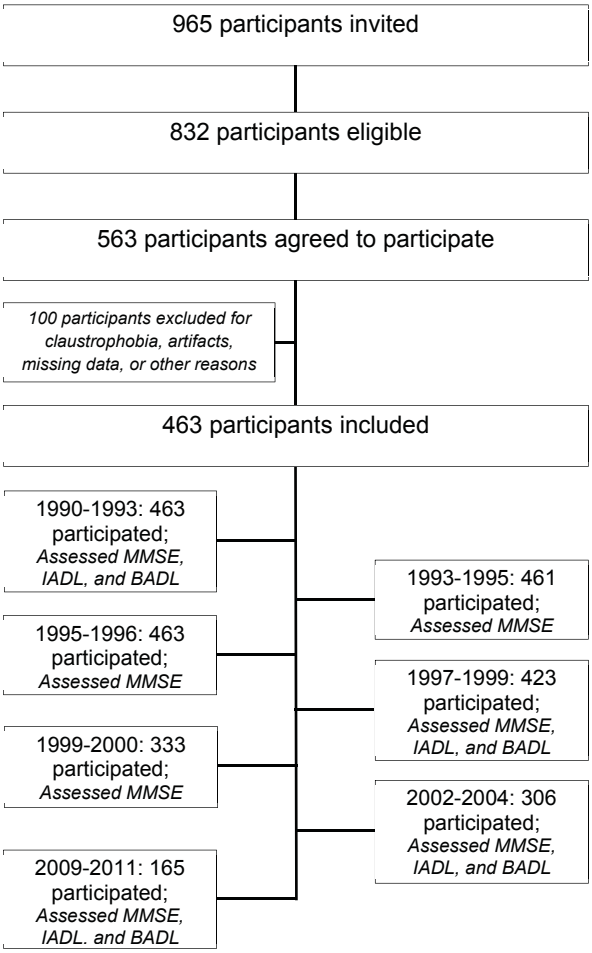

Figure 1. Flowchart of the study population.

ing to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. A written informed consent was obtained from all participants.

Between 1995 and 1996, 965 participants of the Rotterdam Study were invited to participate in the Rotterdam Scan Study, to undergo additional more extensive medical examinations, including MRI.[6, 19] The participants were randomly invited, based on strata of age (five years) and by sex.[6] After excluding people with contraindications for participation (contraindications for MRI, blindness, or dementia), 832 were eligible to participate. 563 persons agreed to undergo MRI (68%). 52 participants did not complete the MRI protocol due to claustrophobia. Additionally, we excluded 21 participants for artifacts on MRI or other technical reasons.

Another 24 participants were excluded for presence of cortical infarcts on MRI, and two for missing dementia data. Furthermore, one participant was excluded for missing data on level of education.

Finally, 463 participants were included in the study. For technical reasons, mostly motion artifacts, hippocampus volumes could only be estimated in a subset of 420 participants.

In total, MMSE, IADL, and BADL were assessed at up to seven visits. A population flow chart including the number of participants per visit is provided in Figure 1. The main reason for drop-out during follow-up was death.

MRI acquisition and processing

Brain MRI-imaging was performed using a 1.5-tesla MRI system (VISION MR, Siemens AG, Erlangen, Germany). The MRI acquisition included a T1-weighted, proton-density weighted, T2-weighted, and a high-resolution inversion-recovery double contrast 3D HASTE sequence.[20]

Automated brain tissue classification based on a k-nearest neighbor classifier algorithm was used to quantify supratentorial brain, grey matter, white matter, and white matter lesion volume.[20, 21] Total white matter volume was the sum of normal appearing white matter and white matter lesion volume. Automated lobar segmentation was used to determine volumes of the frontal, temporal, parietal, and occipital lobes.[4]

Hippocampal volumes were manually outlined on coronal HASTE-slices reconstructed perpendicular to the long axis of the hippocampus.[22]

Lacunar brain infarcts were rated visually as focal parenchymal hyperintensities on T2-weighted images with corresponding hypointensity on T1-weighted images (3 mm in size or larger) without involvement of the cortical grey matter.[5]

Assessment of basic activities of daily living

BADL was assessed with the Dutch version of the disability index from the Stanford Health Assessment Questionnaire.[23] The disability index consists of 20 items constituting eight different components: activities, arising, dressing and grooming, eating, grip, hygiene, reaching, and walking. In our study, two out of the three items for eating (ability to lift a glass of milk and ability to cut meat) were combined into one. Each item could be scored from 0 to 3, with higher scores indicating worse ability: 0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to perform. Component scores were calculated as the highest scored item belonging to that component. Hence, items scored as non-applicable or missing were accounted for by the properly scored items in the respective component. Subsequently, the BADL disability index was calculated by summing the component scores,

obtaining a score between 0 and 24. For ease of interpretation, we did not divide the score by eight as is commonly done.[23]

Assessment of instrumental activities of daily living

IADL was assessed using the Dutch version of the Instrumental Activities of Daily Living scale by Lawton and Brody.[24] The IADL scale consists of eight items: finance management, housekeeping, laundry, meal preparation, medication maintenance, phoning, shopping, and travelling on your own. Similar to the disability index, we scored each item from 0 to 3. For telephone use, participants that used an adapted telephone were scored as 2 (with much difficulty).

For IADL, items that were scored as non-applicable were imputed by the mean of five imputations, based on age, sex, scores on all items of BADL, and scores on the other IADL items. Imputation was performed separately for each visit. Overall, 5.3% or less of variables were imputed for each study round. Imputation of non-applicable values has been suggested and adopted to prevent loss of data.[3, 9] The IADL-score was subsequently calculated by summing all items, also obtaining a score between 0 and 24, with higher scores indicating worse ability.

Diagnosis of dementia

Participants were evaluated for incident dementia using a 3-step protocol.[25] Participants were screened for dementia at baseline and follow-up visits using the MMSE and the Geriatric Mental State schedule (GMS).[26] Participants scoring ≤25 on the MMSE or >0 on the GMS underwent the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) diagnostic interview.[27] Participants that were suspected of having dementia based on this interview were further examined by a neurologist, and underwent extensive neuropsychological testing. In addition to the screening, the cohort was continuously monitored for diagnoses of dementia through medical records of the general practitioner's office and the Regional Institute for Outpatient Mental Health Care (RIAGG). Diagnoses of dementia were made based on the internationally accepted DSM-III-R criteria. Follow-up on dementia was complete until January 1st of 2011.

Covariates

During the interview and examinations at date of MRI, level of education, height (meters), weight (kilograms), systolic and diastolic blood pressure (mmHg), smoking status, glucose level (mmol/L), total cholesterol level (mmol/L), high-density lipoprotein (HDL) level (mmol/L), use of blood pressure lowering medication, and use of anti-diabetic medication were evaluated. Level of education was divided into seven categories: 0 = primary education

or less, 1 = intermediate vocational education, 2 = intermediate general education, 3 = higher vocational education, 4 = higher general education, 5 = college, 6 = university. Body mass index (BMI) was calculated as weight divided by the squared height. Diabetes mellitus was defined as a non-fasting glucose level >=11.1 mmol/L, or use of anti-diabetic medication or insulin.

Statistical analysis

White matter lesion volumes were natural log transformed to obtain a normal distribution. Subsequently, all volumetric MRI-markers were Z-standardized (subtracting the mean and dividing by the standard deviation).

We used linear mixed models to investigate associations of MRI-markers with annual change in MMSE, IADL, and BADL. Random effects for slope and intercept were included to account for between-person differences and within-person correlations across time. In all analyses, MRI-markers and their interaction with time were included in the same models. Grey matter volume and total white matter volume were included in one model to investigate their independent effects. All analyses were adjusted for age, sex, education, their interactions with time, age*time^2, time, and time^2. All analyses on volumetric MRI-markers were additionally adjusted for intracranial volume and intracranial volume*time. The age used in the analyses was calculated at the date of MRI. Similarly, the time used in the analyses was calculated from date of MRI.

To investigate dependence of associations on incipient dementia, analyses were repeated after excluding participants that were diagnosed with dementia during follow-up. Furthermore, we tested whether effect sizes of associations before and after excluding participants with incident dementia differed significantly.

To visualize effects of brain volume on MMSE, IADL, and BADL over time, we created quartiles of brain volume adjusted for intracranial volume. Subsequently, linear mixed models were used to determine the trajectories of decline in MMSE, IADL, and BADL per quartile of total brain volume across visits, adjusted for the same covariates as specified above. These analyses were again repeated after excluding participants that were diagnosed with dementia during follow-up.

To investigate influence of cardiovascular risk factors on the associations, we repeated analyses adjusting for cardiovascular risk factors (BMI, systolic blood pressure, diastolic blood pressure, blood pressure lowering medication, current or past smoking, diabetes mellitus, total cholesterol level, and HDL level) and their interactions with time.

All analyses were performed using IBM SPSS version 21.0.0.1 for Windows.

Results

Mean age of the study population was 68.4 years (standard deviation (SD) 7.9) at initial visit (1990-1993) and 73.1 (SD 7.8) at date of MRI (1995-1996). 51.8% of participants were women. Mean MMSE-score at initial visit was 28.2 (SD 1.5) points, mean IADL-score 2.0 (SD 3.0) points, and mean BADL-score 2.4 (SD 3.4) points. Mean follow-up from date of MRI was 7.4 years (SD 4.7, max 14.9 years). Mean total follow-up from the initial visit was 12.1 years (SD 4.8, max 20.0 years). 63 (13.6%) of participants were diagnosed with dementia over follow-

Table 1. Population characteristics at date of MRI.

	Non-demented (n=400)	Incident demented (n=63)
Age, years	72.7 (7.7)	76.0 (7.7)[a]
Females, n	200 (50.0%)	40 (63.5%)[a]
Education[b]	2 (3)	1 (3)
Brain volume, ml	876.8 (97.6)	853.1 (103.9)
Grey matter volume, ml	525.1 (55.2)	518.4 (54.6)
Total white matter volume, ml	351.7 (83.1)	334.7 (78.0)
Hippocampus volume[c], ml	6.5 (0.8)	6.4 (0.8)
Frontal lobe volume, ml	310.8 (38.0)	303.0 (38.7)
Temporal lobe volume, ml	176.1 (20.4)	169.8 (22.3)
Parietal lobe volume, ml	179.1 (21.7)	174.2 (22.9)
Occipital lobe volume, ml	101.7 (13.0)	97.9 (13.7)
White matter lesion volume, ml	13.4 (15.2)	17.8 (17.7)
Lacunar infarcts, n	95 (23.8%)	16 (25.4%)
Body mass index, kg/m^2	26.3 (3.5)	25.7 (3.4)
Systolic blood pressure, mmHg	145.6 (20.8)	145.6 (20.5)
Diastolic blood pressure, mmHg	76.5 (11.3)	77.8 (13.0)
Blood pressure lowering medication, n	152 (38.0%)	21 (33.3%)
Ever smoker, n	289 (72.3%)	36 (57.1%)
Diabetes, n	21 (5.3%)	4 (6.3%)
Total cholesterol level, mmol/L	5.9 (1.0)	6.0 (1.2)
High-density lipoprotein level, mmol/L	1.3 (0.4)	1.3 (0.4)

Values are means (standard deviations) or numbers of participants (percentages).

[a] Age and sex were significantly different between incident demented and dementia-free remaining participants ($p<0.05$), none of the other differences were significant after adjusting for age and sex.

[b] Median (interquartile range).

[c] Non-demented: n=362; Incident demented: n=58.

Abbreviations: n, number of participants; ml, milliliters; kg, kilograms; m, meters; mmHg, millimeter mercury; mmol/L, millimol per liter.

Table 2. Associations of MRI-markers with change in cognition and daily functioning in the overall population.

	Annual change in		
	MMSE	**IADL**	**BADL**
Brain volume, per SD smaller	**-0.12 (-0.18; -0.06)**	**0.26 (0.15; 0.37)**	**0.19 (0.09; 0.29)**
Grey matter volume[a], per SD smaller	**-0.08 (-0.12; -0.04)**	**0.16 (0.08; 0.24)**	**0.09 (0.02; 0.17)**
Total WM volume[a], per SD smaller	**-0.10 (-0.15; -0.05)**	**0.22 (0.13; 0.31)**	**0.15 (0.07; 0.24)**
Hippocampus volume, per SD smaller	-0.01 (-0.03; 0.01)	0.04 (0.00; 0.08)	0.01 (-0.03; 0.05)
Frontal lobe volume, per SD smaller	**-0.04 (-0.09; 0.00)**	**0.18 (0.10; 0.25)**	**0.14 (0.07; 0.21)**
Temporal lobe volume, per SD smaller	**-0.09 (-0.13; -0.05)**	**0.12 (0.04; 0.20)**	0.06 (-0.01; 0.13)
Parietal lobe volume, per SD smaller	**-0.07 (-0.11; -0.03)**	**0.09 (0.02; 0.16)**	**0.08 (0.02; 0.14)**
Occipital lobe volume, per SD smaller	-0.02 (-0.05; 0.01)	0.02 (-0.04; 0.07)	0.00 (-0.05; 0.05)
WML volume[b], per SD larger	**-0.03 (-0.05; -0.01)**	0.00 (-0.04; 0.03)	0.03 (0.00; 0.07)
Lacunes, yes versus no	-0.02 (-0.06; 0.03)	0.07 (-0.01; 0.16)	0.06 (-0.02; 0.14)

Values represent annual changes in MMSE, IADL, or BADL-score (with 95% confidence intervals). All analyses were adjusted for age, sex, education, intracranial volume (if applicable), their interactions with time, time, time^2, age*time^2, and the respective MRI-marker.

[a] Grey matter volume and total white matter volume were included in the same model.

[b] White matter lesion volumes were natural log transformed.

Abbreviations: MMSE, Mini-Mental State Examination; IADL, instrumental activities of daily living; BADL, basic activities of daily living; SD, standard deviation; WM, white matter; WML, white matter lesion.

up. Population characteristics of participants remaining dementia-free and participants with incident dementia are shown in Table 1. We found no significant differences in MMSE, IADL, and BADL between participants with and without incident dementia at the initial visit.

Smaller brain volume, driven by both grey and white matter, associated with larger decrease in MMSE-score (-0.12 points per SD per year (-0.18; -0.06)), while associating with larger increase in IADL (0.26 points per SD per year (0.15; 0.37)) and BADL-score (0.19 points per SD per year (95% confidence interval: 0.09; 0.29)) (Table 2). Smaller hippocampus volume only showed a trend of an association with larger increase in IADL-score ($p<0.10$).

Smaller frontal, temporal, and parietal lobe volume associated with larger decrease in MMSE-score and with larger increase in IADL-score (Table 2). Furthermore, smaller frontal and parietal lobe volume associated with larger increase in BADL-score.

Larger white matter lesion volume associated with larger decrease in MMSE-score, while lacunar infarcts did not associate with change in either MMSE, IADL, or BADL-score (Table 2).

When excluding participants that became incident demented, all associations of MRI-markers with change in MMSE-score became non-significant, except for the associations of

Table 3. Associations of MRI-markers with change in cognition and daily functioning, excluding incident demented participants.

	Annual change in		
	MMSE	**IADL**	**BADL**
Brain volume, per SD smaller	-0.03 (-0.08; 0.02)	**0.17 (0.07; 0.28)**	**0.17 (0.06; 0.27)**
Grey matter volume[a], per SD smaller	-0.01 (-0.05; 0.03)	**0.11 (0.03; 0.19)**	**0.09 (0.01; 0.17)**
Total WM volume[a], per SD smaller	-0.02 (-0.07; 0.02)	**0.15 (0.06; 0.24)**	**0.14 (0.05; 0.23)**
Hippocampus volume, per SD smaller	0.01 (-0.01; 0.03)	0.03 (-0.01; 0.07)	0.02 (-0.02; 0.06)
Frontal lobe volume, per SD smaller	0.00 (-0.04; 0.04)	**0.14 (0.07; 0.22)**	**0.13 (0.06; 0.21)**
Temporal lobe volume, per SD smaller	**-0.04 (-0.08; 0.00)**	**0.08 (0.00; 0.15)**	0.06 (-0.02; 0.14)
Parietal lobe volume, per SD smaller	-0.03 (-0.06; 0.01)	0.03 (-0.03; 0.10)	0.06 (-0.01; 0.12)
Occipital lobe volume, per SD smaller	-0.01 (-0.03; 0.02)	-0.02 (-0.07; 0.03)	-0.02 (-0.07; 0.04)
WML volume[b], per SD larger	**-0.02 (-0.04; 0.00)**	-0.02 (-0.05; 0.02)	0.03 (0.00; 0.07)
Lacunes, yes versus no	-0.02 (-0.06; 0.02)	0.04 (-0.05; 0.12)	0.07 (-0.01; 0.15)

Values represent annual changes in MMSE, IADL, or BADL-score (with 95% confidence intervals). All analyses were adjusted for age, sex, education, intracranial volume (if applicable), their interactions with time, time, time^2, age*time^2, and the respective MRI-marker.

[a] Grey matter volume and total white matter volume were included in the same model.

[b] White matter lesion volumes were natural log transformed.

Abbreviations: MMSE, Mini-Mental State Examination; IADL, instrumental activities of daily living; BADL, basic activities of daily living; SD, standard deviation; WM, white matter; WML, white matter lesion.

temporal lobe and white matter lesion volume (Table 3). The associations of MRI-markers with IADL-score slightly attenuated, with only associations of temporal and parietal lobe volume becoming non-significant. Associations of MRI-markers with BADL-score remained similar, with only the association of parietal lobe volume becoming non-significant.

When testing significance of the change in effect size of associations after excluding incident demented participants, the association of brain volume with change in MMSE-score was found to become significantly weaker ($p<0.05$). However, effect sizes for associations of brain volume with IADL and BADL-score did not differ significantly.

Participants in the lowest quartile with smallest brain volumes showed larger change in MMSE, IADL, and BADL compared to participants in the highest quartile (all p-trends<0.05, Figure 2). After excluding participants who became incident demented, p-trends remained significant for IADL and BADL, but became non-significant for MMSE.

After additional adjustment for cardiovascular risk factors, longitudinal associations of MRI-markers with MMSE, IADL, and BADL slightly attenuated. Only the association of grey matter volume with change in BADL-score for participants without incident dementia became non-significant.

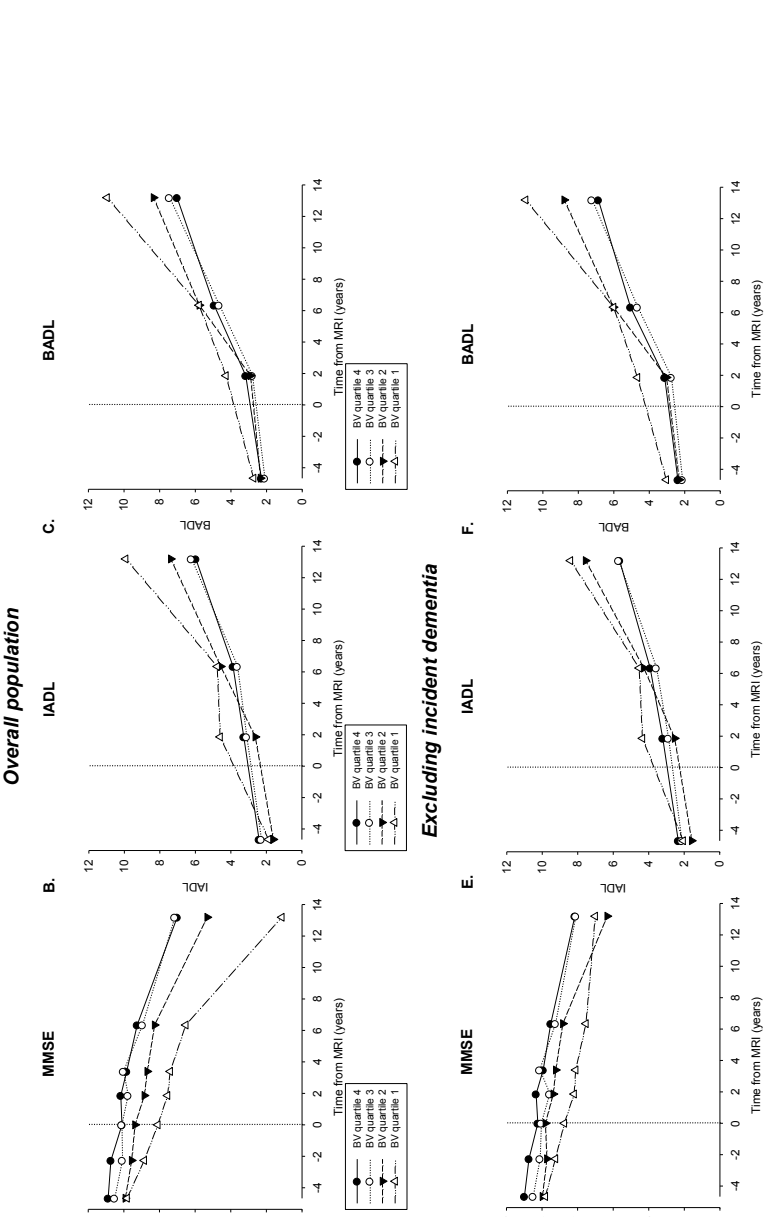

Figure 2. Trajectories of change in cognition and daily functioning across quartiles of brain volume. Symbols are estimates of cognition and daily functioning at the various visits for each quartile of brain volumes (BV), calculated from linear mixed models. Lower scores on MMSE reflect worse cognition, while higher scores on IADL and BADL reflect worse daily functioning. Higher quartiles of brain volume represent participants with larger brain volumes adjusted for intracranial volume. The vertical dotted lines at 0 years indicate the date of MRI.

Discussion

In a community-dwelling population, we found structural brain changes to associate with larger decline in MMSE, IADL, and BADL during up to 15 years of follow-up. Smaller brain volume, driven by grey and white matter, associated with larger decline in MMSE, IADL, and BADL, while white matter lesions only associated with MMSE. Smaller frontal lobe volume especially associated with IADL and BADL, while temporal lobe volume associated with MMSE and IADL. When excluding participants with incident dementia, associations with IADL and BADL only slightly attenuated, while associations of MRI-markers with MMSE disappeared.

Strengths of our study include the population-based setting, long follow-up, assessment of MMSE, IADL, and BADL at various visits, quantitative measurement of brain, grey matter, white matter, and lobar volumes and white matter lesions, and repeating analyses while excluding participants with incident dementia.

A limitation of our study was that we used only one time-point of MRI. Therefore, we could not investigate whether decline in cognition or daily functioning coincided with progression of structural brain changes. Another limitation was the sole use of MMSE to assess cognition. Other cognitive tests may better assess cognitive domains that are less related to dementia. However, in our study, only MMSE was consistently assessed in all visits from the initial visit onwards, hence we only included MMSE as cognitive measurement. Furthermore, participants may have been relatively healthy, because they were required to come to the research center for multiple examinations. Hence, we may have underestimated the true rates of decline in cognition and daily functioning in the population from which this sample was derived. Generalizability of our study may thus be restricted to a relatively healthy population.

One of our key findings is that we found associations of structural brain changes, especially brain atrophy, with cognitive decline to be in large part explained by incident dementia. When excluding participants with incident dementia, nearly all associations between structural brain changes and MMSE disappeared. Previous studies found similar associations between brain changes and cognitive decline, but, due to short follow-up, were unable to disentangle the influence of incident dementia on this relationship.[5, 7, 12, 15-17] Our study now suggests that brain changes relating to cognitive decline nearly always lead to dementia. Importantly, this may indicate that structural brain changes related to cognitive decline are as good as always early signs of incipient dementia advancing to clinical dementia. Hence, this finding emphasizes the usefulness of structural brain changes as a preclinical marker of dementia.

In contrast to cognitive decline, the relation between structural brain changes and decline in daily functioning was largely independent from incident dementia. This suggests that

structural brain changes may directly impact daily functioning, or that the relation between brain changes and decline in daily functioning is driven by a different disease process. Interestingly, we did find a more pronounced attenuation of associations after excluding participants with incident dementia for the cognitively challenging IADL compared to the more physical BADL. This attenuation in IADL may directly reflect the disappearing relation between structural brain changes and cognitive decline, as shown by MMSE, and emphasizes the cognitive nature of IADL.

Although these findings suggest differences in underlying (brain) pathology causing decline in cognition and daily functioning, we cannot ascertain what these pathologies are. The fact that incident dementia explains the relation between structural brain changes and cognitive decline is suggestive of an important role for dementia-related pathology, such as amyloid deposition.[28] In contrast, the relation between structural brain changes and decline in daily functioning seems to have a different, unknown, origin. Adjustment for cardiovascular risk factors only slightly attenuated associations, suggesting that cardiovascular disease did not play a major role in this relationship. Nonetheless, as of yet, treatment of cardiovascular risk factors has been the only successful intervention to reduce progression of structural brain changes.[29, 30] Interestingly, differences in underlying pathology may now imply that different interventions are needed to prevent progression of structural brain changes related to cognitive decline opposed to those related to decline in daily functioning. Further research is needed to determine these underlying (brain) pathologies, to aid the development of new interventions to prevent progression of structural brain changes and consequent impairment.

Similar to previous studies, we found smaller brain volume, driven by both grey and white matter, to associate with decline in both cognition and daily functioning.[7-11, 15-17] In line with a previous study, we found temporal lobe volume to be strongest related with cognitive decline, as reflected by MMSE.[16] To the best of our knowledge, we are first to report that especially frontal lobe volume is strongly related to change in daily functioning, as reflected by both IADL and BADL. Interestingly, temporal lobe volume was also important in relation to the more cognitive IADL. Hence, an intact frontal lobe seems to be most important for retaining proper (physical) daily functioning, while the temporal lobe is especially important for cognition. The parietal lobe associates less strongly with change in both cognition and daily functioning. Although distinct associations were found among brain lobes with cognition and daily functioning, we found little difference in attenuation of associations after excluding participants with incident dementia. Hence, we cannot ascertain whether the difference in the role of dementia on associations with cognition and daily functioning is reflected by difference in location of pathology.

Similar to previous studies, we found larger white matter lesion volume to associate with larger cognitive decline.[7, 11, 12, 15, 17] However, in contrast to other studies, we did not find an association between white matter lesion volume and decline in daily functioning.[8, 13, 14] Pos-

sibly, this may imply that a one-time measurement of white matter lesions does not properly represent change in white matter lesions during a long follow-up period. Alternatively, white matter lesions may not be sufficiently accurate as a measurement of underlying white matter pathology.

Conclusions

In a community-dwelling population, structural brain changes are related to decline in both cognition and daily functioning. Most importantly, the relationship of structural brain changes with cognitive decline is largely driven by dementia, while their relation with decline in daily functioning seems to be due to an independent process.

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Chapter 3.5

The impact of restless legs syndrome on physical functioning

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Sleep Medicine, in press.

Abstract

Objectives: To investigate whether restless legs syndrome (RLS) is associated with impaired physical functioning using subjective and objective assessments.
Methods: Between 2006 and 2013, 6,240 participants (mean age 67.2; 57.7% females) of the prospective population-based Rotterdam Study were cross-sectionally investigated for presence of restless legs syndrome using a questionnaire. Physical functioning was assessed subjectively with the Stanford Health Assessment Questionnaire (basic activities of daily living) and the Instrumental Activities of Daily living scale (instrumental activities of daily living). Additionally, physical functioning was assessed objectively by quantifying fine motor performance with the Purdue Pegboard Test and by quantifying gait with an electronic walkway.
Results: Restless legs syndrome was present in 13.5% of the participants. Persons with restless legs had more impairment in basic (difference in score 0.74, 95% CI 0.45;1.04) and instrumental activities of daily living (difference in score 0.32, 95% CI 0.06;0.57) than persons without restless legs. This association was strongest when symptoms were present two or more times a week (basic activities of daily living score difference 1.67, 95% CI 1.19;2.15). The association between restless legs syndrome and activities of daily living attenuated strongly after adjusting for sleep quality, using the Pittsburgh Sleep Quality Index. There was no association with the Purdue Pegboard Test score nor with gait.
Conclusions: Although individuals with restless legs syndrome experience more impairment in subjectively assessed activities of daily function than persons without restless legs, this seemed to be mediated by poor sleep quality. Moreover, no association was found with objectively assessed physical functioning.

Introduction

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by uncomfortable leg sensations and an urge to move the legs, which may also affect arms and other body parts. RLS patients often experience motor symptoms such as rhythmic movements of the legs, called periodic limb movements.[1] Prevalence of RLS varies from 1% to 15% among different ethnic populations.[2] The pathophysiology of RLS is not completely understood. Changes in iron metabolism and subsequent dopaminergic dysfunction probably play an important role in the pathophysiology of the disease, but the exact mechanisms remain unclear.[3-5] Other factors that have been associated with RLS include gender, pregnancy, body mass index (BMI), diabetes mellitus, renal failure, and socio-economic status.[2, 3, 6-12]

Although most RLS symptoms occur at night, several studies have revealed the impact of RLS on daily functioning. Problems not only include daytime sleepiness and concentration difficulties, which can be attributed to sleep disruption, but also physical dysfunction, which involves both arms and legs.[2, 6, 9, 13-21] Whereas previously assessed physical functioning was mainly self-reported and thus subjective, more objective measures can be obtained by quantifying motor performance. Functioning of the legs can be assessed using electronic walkways that quantify gait, while functioning of the arms can be assessed with tests for manual dexterity, such as the Purdue Pegboard Test.[22-24] These tests are able to capture subtle changes in motor performance and deterioration in such functions may impair persons in daily living and is related to future morbidity.[25-28]

We investigated the associations of RLS with physical functioning, assessed both subjectively using activities of daily living (ADL) questionnaires and objectively using these test for gait and manual dexterity.

Methods

Setting

This study was embedded in the Rotterdam Study, a prospective population-based cohort study in the Netherlands. The main aim of this study is to investigate causes of chronic diseases in the elderly.[29] The study started in 1990 and was expanded in 2000 and 2006. Over the years, 14,926 participants aged 45 years and older, living in the Ommoord district of Rotterdam, have been enrolled in the Rotterdam Study. At baseline and every three to four years of follow-up, participants undergo a home interview and a comprehensive set of examinations at the research center. From 2006 onwards the home interview was extended with a RLS questionnaire.

The Rotterdam Study has been approved by the medical ethics committee according to

the Wet Bevolkingsonderzoek ERGO (Population Study Act Rotterdam Study), executed by the ministry of Health, Welfare and Sports of the Netherlands. Written informed consent was obtained from all participants.

Study population

Between August 2006 and May 2013 6438 participants were interviewed. We excluded participants who had missing data concerning either the RLS (131 participants) or the ADL questionnaires (67 participants). This resulted in a total of 6240 participants with available RLS and ADL data. Gait was only assessed between March 2009 and December 2011, after implementation of an electronic walkway. Of the 6240 participants with RLS and ADL data, 2211 had complete gait data available. Data on the Purdue Pegboard Test was available in 5213 participants. The majority of missing data for the Purdue Pegboard Test was a result of physical limitations of the participants, or due to violation of the test protocol and was not related to RLS status.

Assessment of restless legs syndrome

RLS was assessed with a questionnaire, based on the international restless legs syndrome study group (IRLSSG) 2003 criteria, which are commonly used in epidemiological studies.[1, 11, 30] Three questions were asked: 1) "When sitting or lying still, do you sometimes have unpleasant – crawling, itchy or burning – sensations in your calves or legs?" Answers included: "not during the last month", "less than once a week", "once or twice a week" and "more than twice a week". 2) "Can these sensations only be relieved by movement?" Answers included: "yes", "no" and "not applicable". 3) "Are these unpleasant sensations worse in the evening or at night compared with during the day?" Answers included: "yes", "no" and "not applicable". In order to meet the IRLSSG criteria for RLS, the last two questions had to be answered positively. Participants who answered "not during the last month" on the first question or "no" to the second or third question were considered as having no RLS. The frequency of RLS symptoms was extracted from the answer to the first question.

Subjective assessment of physical functioning

Two standardized questionnaires were used to evaluate functioning in activities of daily living: a Dutch version of the Stanford Health Assessment Questionnaire was used to assess basic activities of daily living (BADL) and a Dutch version of the Instrumental Activities of Daily Living scale was used to evaluate instrumental activities of daily living (IADL).[31, 32]

The BADL disability score includes questions of locomotor activities, fine movements and other activities, involving both upper and lower extremities. The score consists of 20 items

within eight components: dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities.[31, 33] Each item could be rated from 0 to 3, with higher scores indicating worse ability (0 = no difficulty, 1 = some difficulty, 2 = much difficulty, 3 = unable to). Component scores were calculated as the item with the highest score (most severe disability) belonging to that component. The total disability score was calculated as the sum of the eight components (range 0-24). A score of 0 to 8 reflects mild to moderate disability, 8 to 16 moderate to severe disability and higher than 16 severe to very severe disability.[33]

The IADL scale, contains a more complex set of activities: using a telephone, shopping, food preparation, housekeeping, laundering, transportation, medication maintenance, and management of finances.[32] Consistent with BADL, these eight components were scored from 0 to 3, with higher scores indicating worse ability. For the IADL scale, 5.3% of the variables were scored as not applicable. These values were imputed by multiple imputation using five iterations based on age, sex, the scores on all items of the BADL, and the scores on the other available IADL items. The overall IADL score was then calculated by summing the scores of the eight components.

Objective assessment of physical functioning

Physical functioning of arms and legs was assessed objectively by quantifying gait with an electronic walkway and by quantifying fine motor performance with the Purdue Pegboard Test.

Gait was assessed with a 5.79 meter long walkway with pressure sensors (4.88 meter active area, GAITRite Platinum; CIR systems, USA). Participants who visited the research center between March 2009 and December 2011 were asked to perform a standardized walking protocol. Details about the gait assessment have been described elsewhere.[24] In brief, the protocol consisted of normal walk, turning and tandem walk. In normal walk, participants walked over the walkway at their own pace. This walk was recorded eight times. To examine turning, the participants walked over the walkway at their own pace, turned halfway, and returned to their starting position (one recording). For tandem walk, participants walked heel-to-toe over a straight line visible on the walkway (one recording). The first recording of the normal walk was treated as practice walk and was not included in the analyses. The walkway software was used to calculate 30 different spatiotemporal gait variables. Principle component analysis was used to summarize these variables into seven independent gait factors (explaining 87.3% of the total variance in gait), each representing a different gait domain: Rhythm (stride time and cadence), Pace (stride length and velocity), Phases (percentage of time supporting on both feet compared to one), Variability (variability in length and time among strides), Base of Support (stride width and stride width variability), Tandem (errors in tandem walking) and Turning (time and amount of turning steps). When necessary, factors were inverted so that

lower values indicate "poorer" gait. Details about the principle component analysis and the different domains have been described elsewhere.[24, 28]

The Purdue Pegboard Test was used to assess fine motor skills of the upper extremities, also called manual dexterity.[22] The pegboard has been widely used and proved to be a useful tool to detect subtle motor dysfunction, especially in patients with early Parkinson's disease.[25, 34, 35] The pegboard contains two parallel rows with 25 holes. Participants were asked to place as many pins as possible into the holes within 30 seconds starting at the top row. This test was repeated three times: first with the preferred hand, next with the other hand and finally with two hands simultaneously. The number of correctly placed pins (in the first two tests) or pairs of pins (in the third test) is summed to calculate the final score of the test.

Additional measurements

The home interview comprised information about alcohol consumption, smoking status, level of education, medication use and sleep quality (assessed with the Pittsburgh Sleep Quality Index, PSQI).[36] The examinations at the research center included blood sampling and measurement of height and weight. Alcohol use was assessed based on self-reported consumption per month and converted into grams of ethanol per day. Smoking was analyzed as current cigarette smoking versus non-smoking (never and past smoking). Education was dichotomized in primary education only or higher education (vocational and higher). Diabetes mellitus was defined as a fasting glucose level >7.0 mmol/L, or use of anti-diabetic therapy. Body mass index (BMI) was calculated by dividing a person's weight by the square of their height. Medication that is frequently prescribed in RLS syndrome was documented. This includes antiparkinson medication, such as dopamine agonist, and anti-epileptics, such as pregabalin and gabapentin.

Statistical analysis

We investigated the association between the presence of RLS and subjective ADL functioning (BADL and IADL) with two different analyses. First, we used multiple linear regression analysis to investigate the association of RLS with the continuous BADL and IADL scores and scores on their separate components. Second, we dichotomized BADL and IADL with a score between 0 and 8 (no to moderate impairment) considered not impaired, and a score over 8 (moderate to very severe impairment) considered impaired. Binary logistic regression analyses were then used to investigate the association between RLS and impairment in BADL and IADL. Additionally, we investigated the associations between frequency of RLS symptoms and the BADL and IADL scores using univariate analysis of variance. Last, we performed sensitivity analysis, investigating the association of RLS with ADL restricting to participants

with gait data. The associations of RLS (presence and frequency) with objective gait domains and the Purdue Pegboard Test were investigated with multiple linear regression analysis.

All analyses were adjusted for age, sex, body mass index, alcohol use, smoking, diabetes mellitus, education and medication use. Additionally, we adjusted the ADL analyses separately for sleep quality because of the reported strong effect of RLS on sleep. Gait analyses were adjusted for height and weight instead of BMI to emphasize the effect of height. Analyses involving tandem walking were additionally adjusted for step length and step count in tandem walking. Differences between males and females were tested by adding interaction terms to the models. All statistical analyses were performed using the SPSS statistical package, version 20.0 for Windows (IBM Corp., Armonk, NY).

Results

In total 6240 participants (57.7% females) were included in the analyses (Table 1). RLS was present in 840 participants (13.5%). Prevalence of RLS was higher in females than in males (18.0% compared to 7.2%). Participants with RLS consumed less alcohol and had worse scores on the PSQI than those without RLS. Age specific prevalence showed a peak at age 55-60 of 16.4%. The mean BADL score in the entire population was 3.12 (95% confidence interval (CI) 3.03; 3.22, range 0-24) and the mean IADL score was 2.00 (95% CI 1.92; 2.07, range 0-24).

Table 1. Characteristics of the study population

	Without restless legs syndrome n=5400	**With restless legs syndrome** n=840
Age, years	67.3 (11.2)	66.6 (11.2)
Females, %	54.7	77.3
Body mass index, kg/m^2	27.5 (4.4)	27.8 (4.4)
Alcohol use, grams/day	6.8 (7.8)	5.8 (7.1)
Current smoking, %	16.0	16.5
Diabetes mellitus, %	12.4	11.1
Primary education only, %	8.8	10.6
PSQI score	4.2 (3.6)	5.9 (4.0)
Medication use[a], %	2.3	3.1

Values represent percentages for categorical variables and means (standard deviations) for continuous variables. Percentages are calculated without missing values.

[a] Medication use includes use of antiparkinson medication and/or anti-epileptics.

Abbreviations: PSQI, Pittsburgh Sleep Quality Index, higher score indicates poorer sleep quality.

Restless legs syndrome and subjectively assessed physical functioning

RLS was associated with higher BADL scores (0.74 points higher, 95% CI 0.45; 1.04) and a higher probability of having impairment in BADL (odds ratio 1.54, 95% CI 1.15; 2.07), while RLS related to only small differences in IADL score (0.32 points higher, 95% CI 0.06; 0.57). No association was found between RLS and having IADL impairment (odds ratio 0.96, 95% CI 0.60; 1.53). After adjusting for sleep quality the associations between RLS and ADL attenuated strongly, both in BADL and IADL score and in BADL impairment (Table 2).

Table 2. Association between the presence of restless legs syndrome and subjective physical functioning

	Basic activities of daily living		**Instrumental activities of daily living**	
	Difference in score (95% CI)	Odds ratio (95% CI)	Difference in score (95% CI)	Odds ratio (95% CI)
Model 1	0.74 (0.45;1.04)	1.54 (1.15;2.07)	0.32 (0.06;0.57)	0.96 (0.60;1.53)
Model 2	0.38 (0.05;0.71)	1.20 (0.84;1.70)	0.25 (-0.03;0.53)	0.93 (0.53;1.61)

Values represent the difference in ADL (activities of daily living) score and odds ratios for impairment in ADL (95% confidence intervals), between restless legs syndrome (RLS) and no restless legs syndrome. Higher ADL scores reflect poorer ADL.

Model 1: adjusted for age, sex, body mass index, alcohol use, smoking, diabetes mellitus, education, and medication use

Model 2: Model 1, additionally adjusted for PSQI score

Individuals with RLS were more severely disabled in all components of BADL and in the following three IADL components: shopping, housekeeping and transportation (Supplement 1). However, after adjusting for sleep quality, these associations attenuated strongly.

The associations were stronger for persons who experienced RLS symptoms two or more times a week (Figure 1). Individuals with RLS symptoms more than two days a week scored 1.67 points higher on BADL score (95% CI 1.19; 2.15) than participants without RLS and 0.86 points higher on IADL score (95% CI 0.45; 1.28). Adjustment for sleep quality slightly attenuated these associations too (Figure 1).

When restricting these analyses to the 2211 participants with gait data similar associations were found (Supplement 2).

No significant sex-interaction terms were found in any of the analyses.

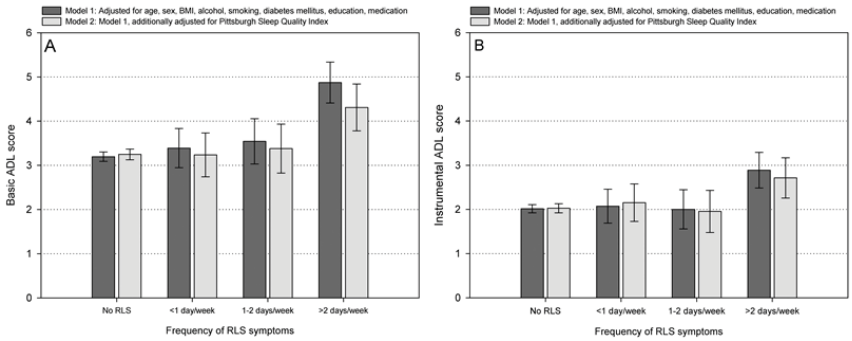

Figure 1. Frequency of RLS symptoms and activities of daily living scores. Mean adjusted ADL scored per frequency of RLS symptoms. Error bars represent the 95% confidence interval around the mean. A: Basic activities of daily living. B: Instrumental activities of daily living

Restless legs syndrome and objectively assessed physical functioning

The prevalence of RLS in the subsample of participants with gait assessment was 13.1%. RLS did not associate with any of the gait domains (Table 3). Higher frequency of RLS symptoms was also not associated with gait. Similarly, no associations were found between RLS and Purdue Pegboard Test scores.

Discussion

In this population-based cohort study we found that RLS was associated with more severe self-reported impairment in ADL, especially BADL. The effect of RLS on disability scores was most pronounced in participants with RLS symptoms occurring more than two days a week. These associations attenuated strongly after adjusting for sleep quality. RLS was not associated with either gait or scores on the Purdue Pegboard Test.

We found associations between RLS and subjective impairment in physical functioning. This is also reported in previous studies, mainly concerning more vigorous activities, such as running and climbing a set of stairs, and some components of ADL.[2, 6, 9, 13-20] In our study, RLS was associated with all BADL components, and with three out of eight IADL components: shopping, housekeeping and transportation, which are more physical items in this scale. The reason for this consistently found impairment in physical functioning in persons with RLS is unclear. It can be a result of sleep disturbance and daytime sleepiness, but other mechanisms have also been proposed. These include the associated dopaminergic dysfunction, and more recently, autonomic dysfunction or abnormal activation of the central pattern generator, which is a network of spinal neurons involved in the control of rhythmic locomotor pattern

Table 3. Association between the presence of restless legs syndrome and objective physical functioning

	Gait domains							Manual dexterity
	Rhythm	Variability	Phases	Pace	Base of Support	Turning	Tandem[a]	Purdue Pegboard
Model 1	-0.06 (-0.18;0.05)	0.01 (-0.11;0.13)	0.04 (-0.08;0.16)	-0.03 (-0.14;0.07)	0.06 (-0.06;0.19)	0.04 (-0.08;0.16)	0.05 (-0.07;0.18)	0.23 (-0.11;0.57)
Model 2	-0.10 (-0.24;0.03)	0.01 (-0.13;0.15)	0.02 (-0.10;0.14)	-0.08 (-0.20;0.04)	0.01 (-0.13;0.16)	0.05 (-0.10;0.20)	0.08 (-0.07;0.24)	0.19 (-0.21;0.59)

Values for gait domains represent differences in Z-scores (with 95% confidence interval) between restless legs syndrome (RLS) compared to no RLS. Values for the Purdue Pegboard Test represent difference in correctly placed pins between RLS compared to no RLS. Higher values represent better performance.

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, height, weight, alcohol use, smoking, diabetes mellitus, education, and medication use.

[a] Additionally adjusted for step length and step count in tandem walk.

generation and modulation.[21, 37, 38] In contrast to previous studies that investigated the association between RLS and daily functioning, an innovative element of our study is that we also assessed physical functioning with more objective measures. If impaired physical functioning is caused by an underlying pathophysiological mechanism, changes in these measurements of physical functioning would also be expected. However, we did not find an association of RLS with manual dexterity or gait, which is in accordance with the limited existing literature.[39] This suggests that motor performance between individuals with and without RLS does not differ and that self-reported disability in activities of daily living has no apparent pathophysiological explanation.

Another reason for the discrepancy in our results between subjective and objective assessment of physical functioning could be due to methodological issues. We assessed RLS with a questionnaire that included a frequency measure, but no severity measure. Severely affected participants may have more impairment in their physical functioning that we were not able to assess. This might have led to an underestimation of the true impact of RLS on physical functioning. It is also possible that the measurements we used to assess objective physical functioning were not the most suitable tests to detect potential changes in motor function in RLS patients. Alternatively, the discrepancy could be because both RLS and ADL are assessed by means of a questionnaire

examined by the same interviewer. Therefore, it is possible that part of the associations we found between RLS and ADL are the result of common method bias.[40] The associations of RLS with gait and manual dexterity may thus be more reliable as they are measured independently.

We suggest that the associations we found for RLS with self-reported disability are more a reflection of a person's general well-being or quality of life. Indeed, adjusting for sleep quality in the ADL analyses, as an intermediate, supports this hypothesis. RLS does not cause diminished physical functioning, but the lack of sleep accompanying RLS does influence an individual's perception of his physical functioning. This highlights the importance of recognition of RLS and the accompanied sleep disturbances. Improving sleep quality in patients with RLS will have a large beneficial effect on an individual's quality of life.

The strengths of our study include the population-based design, large number of participants, inclusion of symptom frequency into our analyses and, unlike other studies, use of both subjective and objective measurements of physical functioning. There are also limitations to our work. We only investigated the associations between RLS and physical functioning cross-sectionally. Our diagnosis of RLS is based on self-reported symptoms without a neurological examination and although the IRLSSG criteria were used, secondary RLS or RLS mimics, such as peripheral neuropathy, could not be excluded. This may have led to an overestimation of the prevalence. However, the prevalence of RLS in our study corresponds to prevalence reported in literature.[2] Another limitation of our study is that we did not incorporate severity of RLS symptoms into our assessment. Although we used information about the frequency of symptoms, which might not totally reflect clinically relevant RLS, this could have influenced our findings leading to an underestimation of the effect of RLS on physical functioning. We used gait and manual dexterity as tests to quantify motor performance, but this probably covers only a part of motor performance. A last limitation is that data about gait and manual dexterity was not available for the entire study sample, but we did not have any indication for selection biases.

To conclude, in our community-dwelling population, we found RLS to associate with self-reported impairment in daily functioning. However, this association seemed to be predominantly mediated by poor sleep quality. Additionally, RLS did not associate with the objective measurement of physical functioning, namely gait and manual dexterity. Therefore, we conclude that physical functioning is not affected in patients with RLS.

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Part 4

Genetic, lifestyle, and disease correlates of gait and daily functioning

Chapter 4.1

Heritability and genome-wide association analyses of human gait

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Submitted.

Abstract

Human gait is a complex neurological and musculoskeletal function, of which the genetic basis remains largely unknown. To determine the influence of common genetic variants on gait parameters, we studied 2946 participants of the Rotterdam Study, a population-based cohort of unrelated elderly individuals. We assessed 30 gait parameters using an electronic walkway, which yielded 7 independent gait domains after principal component analysis. Genotypes of participants were imputed to the 1000 Genomes reference panel for generating genetic relationship matrices to estimate heritability of gait parameters, and for subsequent genome-wide association scans to identify specific variants. Gait domains with the highest age- and sex-adjusted heritability were Variability (h^2 = 61%), Rhythm (37%), and Tandem (32%). For other gait domains, heritability estimates attenuated after adjustment for height and weight. Genome-wide association scans identified a variant on 1p22.3 that was significantly associated with single support time, a variable from the Rhythm domain (rs72953990; N=2946; p = $2.30x10^{-8}$). In conclusion, human gait has highly heritable components that are explained by common genetic variation, which are partly attributed to height and weight. Collaborative efforts are needed to identify robust single variant associations for the heritable parameters.

Introduction

The planning and execution of human gait requires a delicate integration of sensory information and motor commands.[1] Consequently, gait is affected by a wide range of diseases, including disorders of the brain, muscles, and joints.[1-5] Problems in gait strongly increase the risk of adverse health outcomes, including morbidities (e.g. falls) and death.[3] Although it is known that various environmental factors contribute to inter-individual variation in gait, it remains unclear to what extent genetics plays a role.

Variation in gait is associated with age and sex, but also with several complex traits such as height, weight and cognitive function, which are all highly polygenic and heritable.[6-8] Walking speed was found to be heritable in two twin studies, suggesting that gait follows a similar genetic pattern.[9-11] However, walking speed alone does not capture the complexity of human gait, which consist of many more measurable components.[12] Additionally, to our knowledge, no genome-wide association scan (GWAS) has been performed to identify genetic variants that are associated with gait.

Here, we comprehensively assessed gait using an electronic walkway and determined the heritable component of the various parameters comprising gait, followed by genome-wide association scans for the heritable parameters.

Methods

Setting

The Rotterdam Study is a prospective, population-based study that investigates 14926 inhabitants of Rotterdam aged 45 years or over.[13] Subjects were enrolled during three recruitment phases (1990, 2000, and 2006) and visit the research center every 3-4 years for various medical examinations. Genotyping was successfully performed on 11496 subjects. In March 2009, gait assessment was introduced in the study protocol. The Medical Ethics Committee of the Erasmus Medical Center and the review board of The Netherlands Ministry of Health, Welfare and Sports both approved the study. Written informed consent was obtained from all subjects.

Gait assessment

A 5.79-m long pressure-activated walkway (GAITRite Platinum; CIR systems, Sparta, NJ: 4.88-m active area; 120-Hz sampling rate) was used to accurately measure gait parameters, as described previously.[14, 15] Participants performed standardized walking protocols over the walkway. First, participants walked eight times across the walkway at their own pace (normal walk). Second, participants walked at their usual pace, turned halfway, and returned to the starting position (turning). Third, participants walked tandem (i.e. heel-to-toe) over a line on

the walkway (tandem walk). The first normal walk was considered a practice walk and not included in the analysis. All other recordings were visually inspected and individual footsteps were identified and marked for further processing by the walkway software, from which 30 spatiotemporal (gait) parameters were derived. Principal component analysis with varimax rotation identified 7 independent components with eigenvalues of 1 or higher, representing the following gait domains: Rhythm, Phases, Variability, Pace, Tandem, Turning and Base of Support.

Study population

Between March 2009 and March 2012, 3651 people were invited for gait assessment. Of these, 129 did not complete gait assessment for the following reasons: 69 for physical problems, 45 for technical reasons, 13 for refusal, and 2 for other reasons. Additionally, we excluded 34 participants for performing less than 16 steps in normal walking, lowering validity of the gait parameters; 3 for using walking aids on the walkway; and 1 for not following instructions. Of 3484 remaining participants, 2946 were genotyped. Since not all participants completed all walking conditions, the numbers of participants included across analyses vary.

Genotyping

The three subcohorts of the Rotterdam Study were genotyped with the 550K (cohort 1), 550K duo (cohort 2) and 610K (cohort 3) Illumina arrays. We removed samples with a call rate below 97.5%, gender mismatch, excess autosomal heterozygosity, duplicates or family relations and ethnic outliers, and variants with call rates below 95.0%, failing missingness tests, Hardy–Weinberg equilibrium p-values$<10^{-6}$, and minor allele frequencies<1%. Genotypes were imputed using MACH/minimac software to the 1000 Genomes phase I version 3 reference panel (entire population).

Heritability analysis

To estimate heritability in our sample of unrelated individuals, we used Genome-wide Complex Trait Analysis (GCTA).[16] This method compares genotypic similarity between individuals to their phenotypic similarity. The 1000 Genomes imputed genotypes were filtered on imputation quality ($R^2 < 0.5$) and allele frequency (MAF < 0.01). Pairwise genetic relatedness between all individuals was calculated, and for pairs with more than 0.02 genotype similarity one person was removed.

Heritability analyses were performed for the 7 gait domains and (secondarily) for all 30 variables separately. Adjustments were made for age, sex, and the first 10 principal components of population stratification (model 1), and additionally for height (model 2) and weight

(model 3). For the Tandem domain, step count and step length during the tandem walk were also included as covariates.

Polygenic scores

Polygenic scores were created from variants associated with height (N=180) and BMI (N=32) at genome-wide significance in the largest available sample.[6, 17] Variants were weighted by multiplying the beta coefficient for the corresponding trait with the number of alleles. For each individual, the weighted allele scores were added together to generate the polygenic score.

Genome-wide association scan

Genome-wide association analyses were conducted in the three subcohorts using the R package ProbABEL (version 0.42). Gait parameters were analyzed under an additive model with linear regression, covarying for age and sex, height, weight, and first two principal components. The results were adjusted for genomic control and meta-analyzed using the METAL software.[18] Variants with an $R^2 < 0.5$ and a minor allele frequency < 0.05 were removed. Genome-wide significance was established at $p < 5x10^{-8}$. Manhattan and quantile-quantile plots were generated in R (version 3.1.0), and regional association plots using LocusZoom.[19]

Functional annotation of genetic variants

Genetic variants showing evidence of association with gait parameters were further examined for potential biological function using publicly available databases: Regulomedb, GWASdb, rSNPBase, HaploReg, and SNVrap.

Statistical analysis

Cohort-specific results were meta-analyzed using inverse variance meta-analysis. Polygenic scores were transformed into z-scores so that effects are expressed per standard deviation increase for each score. A Bonferroni correction for 14 tests (2 polygenic scores and 7 gait domains) was applied, resulting in a significance threshold of $p < 0.0036$. Association analyses of the polygenic scores with gait domains were performed in SPSS version 22, IBM.

Results

Mean (SD) age was 68.2 (9.5) years, 1604 (54.4%) were women. Table 1 shows basic demographic and anthropometric characteristics of the total study population as well as the population with all gait measurements available, which were similar.

Table 1. Study population characteristics

Characteristic	Total population (N=2946)	Sub-population (N=2588)
Age, years	68.2 (9.5)	67.3 (9.1)
Women, n	1604 (54.4%)	1396 (53.9%)
Height, cm	169.2 (9.3)	169.5 (9.2)
Weight, kg	78.6 (14.3)	78.8 (14.2)
MMSE score, points	28.0 (2.0)	28.1 (1.8)

Values are means (standard deviations) or numbers of participants (percentages).
Abbreviations: n, numbers of people; cm, centimeters; kg, kilograms; MMSE, Mini-Mental State Examination; SD, standard deviation.

Heritability of gait parameters

The Variability, Rhythm and Tandem domains showed the highest age- and sex-adjusted heritability, which remained after correction for height and weight, but decreased slightly for Rhythm after including height. The Variability domain was more heritable than any of its constituting parameters. For Rhythm, most variables had higher estimates than the domain score, which was most pronounced for single support time and swing time (ρ = .99). The other gait domains had a smaller heritable component (<.25) and were strongly attenuated after adjustment for height (Pace) and weight (Base of Support, Phases).

To explore whether these decreases in heritability after adjustment for height and weight were due to specific genetic variants related to these traits, polygenic scores of height and body mass index (BMI) were studied in relation to gait (Table 3). Indeed, the polygenic height score was associated with Rhythm and Pace, but not after adjustment for height itself. The BMI score did not associate with any gait domain after multiple testing correction, but showed a nominally significant effect on Turning that became stronger after adjustment for weight.

Table 2. Heritability estimates of gait domains and parameters, adjusted for age, sex, height and weight

Gait domain (PVE) / parameter	Mean (SD)	Correlation with factor	Heritability estimate (SE)		
			Model 1	Model 2	Model 3
Variability (18.2%)			.61 (.23)	.63 (.23)	.58 (.23)
Stride length SD, cm	4.58 (1.67)	-0.88	.42 (.21)	.43 (.21)	.42 (.21)
Step length SD, cm	2.86 (0.94)	-0.86	.39 (.21)	.38 (.21)	.37 (.21)
Stride velocity SD, cm/s	5.91 (1.97)	-0.87	.33 (.21)	.34 (.21)	.28 (.21)
Stride time SD, s	0.03 (0.02)	-0.77	.22 (.21)	.24 (.21)	.26 (.21)
Step time SD, s	0.02 (0.01)	-0.75	.24 (.21)	.24 (.21)	.28 (.21)
Stance time SD, s	0.03 (0.01)	-0.76	.32 (.21)	.34 (.21)	.37 (.21)
Swing time SD, s	0.02 (0.01)	-0.65	.01 (.21)	.01 (.21)	.01 (.21)
Single support time SD, s	0.02 (0.01)	-0.65	.01 (.21)	.01 (.21)	.01 (.21)
Double support time SD, s	0.02 (0.01)	-0.52	.35 (.22)	.36 (.22)	.36 (.22)
Rhythm (21.7%)			.37 (.24)	.28 (.24)	.27 (.24)
Single support time, s	0.42 (0.04)	-0.96	.56 (.21)	.45 (.21)	.44 (.22)
Swing time, s	0.42 (0.04)	-0.96	.56 (.21)	.45 (.21)	.44 (.22)
Step time, s	0.55 (0.05)	-0.94	.38 (.21)	.30 (.21)	.34 (.21)
Stride time, s	1.10 (0.10)	-0.94	.41 (.21)	.33 (.21)	.37 (.21)
Cadence, steps/min	109.8 (9.5)	0.94	.42 (.21)	.32 (.21)	.35 (.21)
Stance time, s	0.67 (0.07)	-0.83	.20 (.21)	.15 (.21)	.23 (.21)
Tandem (6.9%)			.32 (.23)	.32 (.23)	.34 (.23)
Sum of sidestep distance, cm	9.56 (17.0)	-0.90	.35 (.22)	.35 (.22)	.36 (.22)
Sum of sidestep surface, fraction	0.32 (0.64)	-0.91	.28 (.22)	.28 (.22)	.32 (.23)
Double step, n	0.07 (0.28)	-0.54	.07 (.23)	.07 (.23)	.06 (.23)
Pace (11.0%)			.22 (.23)	.02 (.23)	.03 (.23)
Stride length, cm	130.9 (18.2)	0.85	.26 (.21)	.15 (.21)	.18 (.21)
Step length, cm	65.2 (9.13)	0.85	.26 (.21)	.15 (.21)	.18 (.21)
Velocity, cm/s	119.5 (20.1)	0.72	.26 (.21)	.27 (.21)	.31 (.21)
Base of Support (3.5%)			.20 (.23)	.21 (.23)	.11 (.23)
Stride width SD, cm	2.40 (0.84)	-0.73	.15 (.21)	.16 (.21)	.15 (.21)
Stride width, cm	10.3 (4.02)	0.67	.24 (.20)	.23 (.20)	.21 (.20)
Phases, (18.8%)			.13 (.23)	.13 (.23)	.01 (.23)
Single support, %GC	38.6 (1.87)	0.97	.18 (.21)	.21 (.21)	.06 (.21)
Swing, %GC	38.6 (1.87)	0.97	.18 (.21)	.21 (.21)	.07 (.21)
Stance, %GC	61.4 (1.87)	-0.97	.18 (.21)	.22 (.21)	.07 (.21)
Double support, %GC	23.0 (3.75)	-0.97	.19 (.21)	.23 (.21)	.07 (.21)
Double support time, s	0.25 (0.06)	-0.85	.14 (.21)	.18 (.21)	.05 (.21)
Turning (5.9%)			.10 (.24)	.10 (.24)	.07 (.24)
Turning step count, n	4.94 (0.91)	-0.92	.03 (.23)	.03 (.23)	.03 (.23)
Turning time, s	2.83 (0.63)	-0.85	.25 (.22)	.27 (.23)	.26 (.23)

Abbreviations: GC, gait cycle time; PVE, percentage of variance explained; SD, standard deviation; SE, standard error.

Table 3. Associations of polygenic scores of height and weight with gait domains, before and after adjusting for height and weight

	Variability		Rhythm		Tandem		Pace		Base of Support		Phases		Turning	
Polygenic score	**β (SE)**	**P**	**β (SE)**	**P**	**β (SE)**	**P**	**β (SE)**	**P**	**β (SE)**	**P**	**β (SE)**	**P**	**β (SE)**	**P**
Height score, unadjusted for height	-.024 (.019)	.212	*-.057 (.018)*	*.002*	.002 (.019)	.922	*.049 (.016)*	*.003*	-.015 (.019)	.450	.021 (.017)	.208	.008 (.020)	.688
Height score, adjusted for height	.002 (.019)	.915	-.013 (.018)	.465	.003 (.020)	.872	-.003 (.016)	.857	.012 (.020)	.542	-.006 (.017)	.726	.001 (.020)	.942
BMI score, unadjusted for weight	.023 (.019)	.224	.016 (.017)	.350	-.005 (.019)	.775	-.003 (.016)	.832	.003 (.019)	.864	-.032 (.019)	.089	.049 (.020)	.013
BMI score, adjusted for weight	.021 (.019)	.260	.015 (.017)	.401	-.004 (.019)	.822	-.003 (.016)	.862	.000 (.019)	.985	-.016 (.017)	.332	.052 (.020)	.008

All analyses were adjusted for age, sex, height, and weight, unless otherwise stated. For Tandem, additional adjustments were made for the step count and step length during the tandem walk. Betas are expressed per standard deviation of the polygenic score. Associations surviving multiple testing ($p<0.0036$) are indicated in italic. Abbreviations: BMI, body mass index; SE, standard error.

Table 4. Genetic variants at 12 loci associated with heritable gait domains Variability, Rhythm, Tandem, or their highest heritable parameters ($p<1x10^{-6}$)

Gait parameter	Genetic variant	Locus	Position	Closest gene(s)	Variant type	A1	A2	Freq	Discovery sample			Heterogeneity	
									β (SE)	P	N	I^2	P
Variability	rs11914070	22q11.21	18965628	*DGCR5*	Intronic	T	C	0.39	-.136 (.026)	$1.64x10^{-7}$	2588	0.0	.85
Stride length SD	rs6560039	9q22.1	90474946	*XXyac-YM21GA2.4*	Upstream	T	C	0.22	-.230 (.044)	$2.22x10^{-7}$	2946	0.0	.97
Stride length SD	rs7932614	11p14.3	26045601	*ANO3*	Intergenic	A	G	0.57	-.246 (.049)	$4.19x10^{-7}$	2946	70.6	.03
Rhythm	rs72953990	1p22.3	88064857	*LMO4*	Intergenic	A	G	0.14	-.192 (.037)	$2.43x10^{-7}$	2588	48.0	.15
Rhythm	rs71321217	9p23	10036568	*PTPRD*	Intronic	I	R	0.27	.144 (.029)	$7.65x10^{-7}$	2588	45.8	.16
Rhythm	rs10823991	10q21.1	53794532	*PRKG1*	Intronic	A	T	0.27	.138 (.028)	$9.72x10^{-7}$	2588	0.0	.85
Single support time	rs72953990	1p22.3	88064857	*LMO4*	Intergenic	A	G	0.14	.0069 (.0012)	$2.30x10^{-8}$	2946	0.0	.71
Single support time	rs80092143	13q31.3	91057759	*MIR622*	Intergenic	C	G	0.89	-.0065 (.0013)	$6.88x10^{-7}$	2946	17.4	.30
Tandem	rs11054786	12p13.2	12458665	*MANSC1, LRP6*	Intergenic	T	C	0.90	.590 (.121)	$9.89x10^{-7}$	736[a]	-	-
Tandem	rs77292326	18p11.21	11737231	*GNAL*	Intronic	A	T	0.06	-.294 (.058)	$4.10x10^{-7}$	2588	70.8	.03
Sum sidestep distance	rs10800713	1q32.1	200548745	*KIF14*	Intronic	A	T	0.73	-2.431 (.472)	$2.62x10^{-7}$	2736	0	.71
Sum sidestep distance	rs146647518	14q23.3	67529620	*GPHN*	Intronic	A	G	0.06	8.183 (1.561)	$1.58x10^{-7}$	1346[a]	-	-
Sum sidestep distance	rs80050017	19q13.33	51383200	*KLK2*	3prime UTR	T	G	0.06	5.213 (1.031)	$4.24x10^{-7}$	2736	82.7	0.003

[a] Variant missing in some cohorts due to insufficient imputation quality.

Abbreviations: A1, effect allele; A2, reference allele; Freq, frequency of the effect allele; SD, standard deviation; SE, standard error; N, sample size.

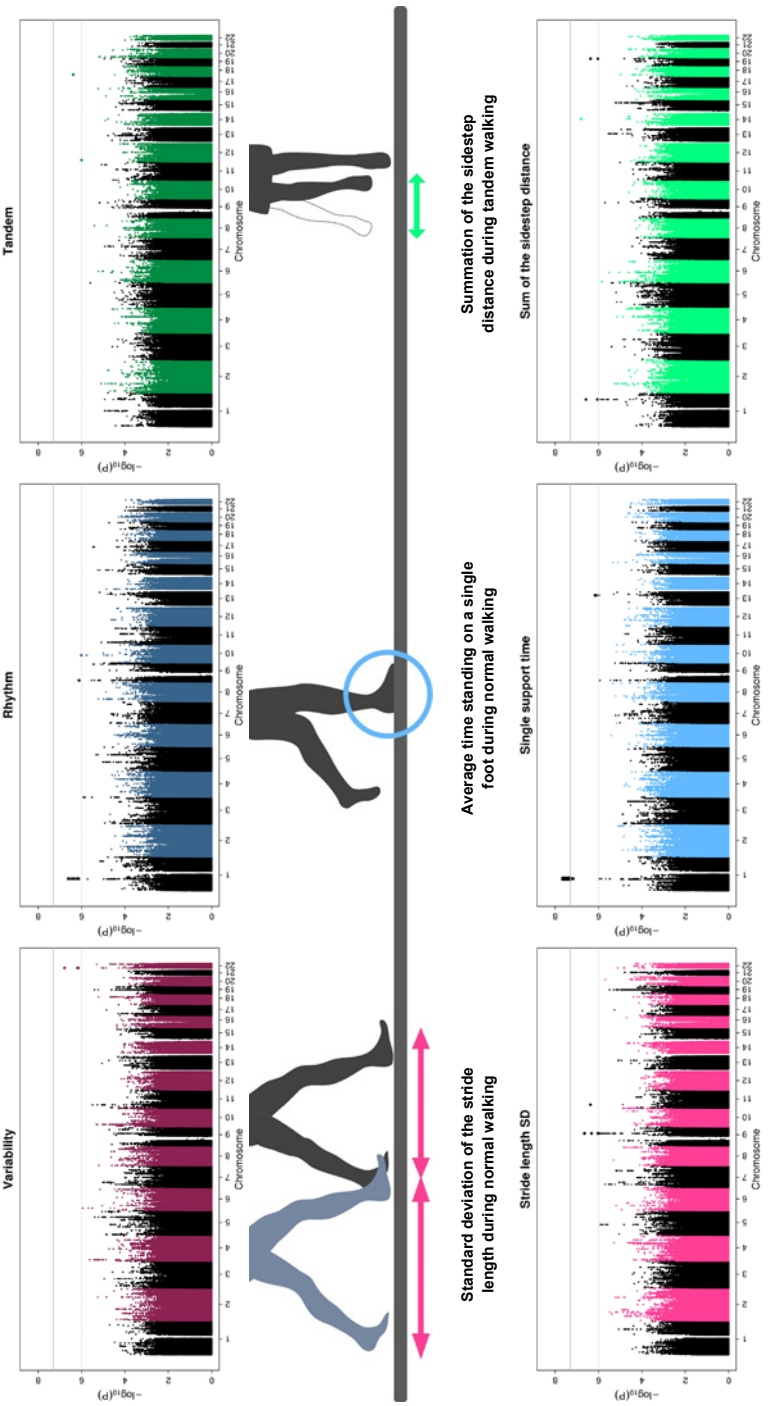

Figure 1. Common genetic variants associated with the three most heritable gait domains and their highest heritable parameters.

GWAS of gait parameters

GWASs were performed for the three gait domains showing moderate to high heritability (Variability, Rhythm, and Tandem) and their highest heritable parameter (stride length SD, single support time, and sum of the sidestep distance, respectively). Figure 1 shows the Manhattan plots for these traits, with all loci having variants with a p-value < $1x10^{-6}$ summarized in Table 4. Eight variants at 1p22.3 near *LMO4* reached genome-wide significance for single support time (top variant rs72953990; minor allele frequency (MAF) = 0.14; p = $2.30x10^{-8}$), and were also associated with the Rhythm domain (p = $2.43x10^{-7}$). No variants reached genome-wide significance for the other gait traits.

Intronic variants in *PTPRD* (rs71321217; 9p23; p = $7.65x10^{-7}$) and *PRKG1* (rs10823991; 10q21; p = $9.72x10^{-7}$) showed suggestive association with Rhythm. For Variability a variant in *DGCR5* (rs11914070; 22q11.21; p = $1.64x10^{-7}$), and for stride length SD two variants at 9q22.1 and 11p14.3 were found, of which 11p14.3 showed significant heterogeneity across the three cohorts. The most reliable signal for Tandem and sum of the sidestep distance was located on 1p32.1 in *KIF14*, with top variant rs10800713 showing evidence of transcription factor binding affinity.

Discussion

Here we determined the contribution of common genetic variants to an extensive range of gait parameters, for which the genetic basis is largely unknown. Subsequently, we performed a genome-wide association scan to identify specific loci influencing gait. We found that the heritability of gait varies across domains and we identified a variant influencing single support time.

Gait is an important indicator of health.[3] Identifying factors that contribute to variation in gait could aid our understanding of gait dysfunction and its associated diseases. Given the highly complex cooperation of multiple organ systems that is required for gait, it is not surprising that we found a genetic architecture that is similar to other complex traits (i.e., height, cognition), which are partly determined by multiple common genetic variants, each with a small effect. Others have studied the heritability of walking speed, which mainly forms the Pace domain, and found estimates between 16% and 60%.[9-11] Similar to Pajala *et al.*, we found walking speed to be only moderately heritable (17%). However, the comprehensive and quantitative gait assessment in our study enabled us to investigate the genetic influence on the gait pattern in more detail than walking speed alone. Interestingly, we found the genetic influence to be much larger on several other gait domains, particularly Variability, Rhythm and Tandem.

Variability was found to be the most heritable (58%). It captures the irregularity in walking

and is believed to be particularly related to cognitive functioning.[15] Interestingly, none of the variables comprising Variability had a heritability >42%, suggesting that the principal component analysis extracted a true genetic (and biological) construct. Although Variability had the highest heritability, no genome-wide significant variants were identified. Importantly, we did not have enough power to detect small effects. However, this does not preclude the possibility of a different genetic architecture. For example, Variability could be influenced by numerous variants with only a small effect that jointly have a large influence but make identification of specific variants difficult. Furthermore, it is possible that the gait variables comprising this domain each have distinct genetic determinants with larger effects, but that these signals become diluted when analyzing the domain as a whole. However, no genome-wide significant variants were detected for the highest heritable variable, stride length variability.

We did identify a variant that reached significance in the GWAS of single support time, the highest heritable gait parameter of Rhythm. This variant lies close to the *LMO4* gene, which encodes the transcriptional regulator Lim-only 4. Interestingly, recent work has identified murine *Lmo4* as a central developmental regulator of the diversity of motor cortex projection neuron subpopulations.[20] Cederquist *et al.* report that loss of *Lmo4* function disrupted the molecular identity of neurons in rostral motor cortex and caused aberrant projections to the spinal cord.[20] Rhythmical activities are thought to be generated by a neural network (the central pattern generator) that resides in the spinal cord, and could potentially link *LMO4* to Rhythm.[21]

Furthermore, a larger sample size seems particularly promising for detecting genetic variants that associate with Variability, Rhythm, or Tandem. Other gait domains initially showed small to moderate heritability, but the estimates strongly attenuated after adjusting for height and weight. To investigate whether the reduction in heritability was due to genetic variants that primarily associate with these traits, but not with gait, we explored the effect of established variants for height and BMI in relation to gait. Indeed, the polygenic score of height was associated with the same gait variables that showed attenuation after adjustment for height. The BMI score did not show significant associations with the gait domains. Given the lower number of variants for BMI (32) compared to height (180), it is likely that the polygenic score of BMI is less powerful to detect effects. This is underlined by the fact that the BMI score was not convincingly associated with BMI in our sample ($p = 0.056$), contrary to the height score with height ($p = 6.5 \times 10^{-47}$). As a whole, our analyses thus seem to suggest that Pace, Base of Support, and Phases are potentially not very heritable beyond their correlation with height and weight, and the polygenic score of height adds an additional line of evidence to this finding.

Important to note is that the heritability estimates calculated using GCTA represent narrow-sense heritability, and thus only take into account the additive genetic portion of the phenotypic variance while leaving out non-additive effects. Furthermore, GCTA only uses

the variants provided as input for determining the genetic similarity. However, causal variants that are not in included (e.g., rare variants) but are in linkage disequilibrium with those that are in the analysis will also be indirectly used. Another limitation that is inherent to GCTA analyses is the dependence on unrelated individuals, which produces relatively large standard errors for the heritability estimates in our sample of less than 3000 persons. This emphasizes the main limitation of our study, namely its low power. Although it is well known that the largest effect sizes typically explain less than 1% of the phenotypic variance of similar quantitative traits [22], we performed this study for several reasons: First, we provide estimates of genetic influence on a comprehensive set of gait parameters, which could serve to direct future genetic studies of gait and as an incentive for larger initiatives. Second, we excluded to a reasonable degree the possibility of genetic variants having large effects on gait. Third, we are not aware of additional studies that have both quantitatively assessed gait and genome-wide genotyping, making this in fact the largest available sample for genetic studies on gait.

In conclusion, we found that human gait is comprised of various heritable domains. A large number of variants remain to be identified for gait, but this will require large-scale collaborative efforts.

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Chapter 4.2

Genetic risk of Parkinson's Disease: association, prediction, and subclinical effects

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Submitted.

Abstract

Objective: Recent genome-wide association studies have identified 26 independent risk variants for Parkinson's Disease (PD), but their clinical relevance remains unknown. We investigated whether a genetic risk score based on these variants is associated with the risk of incident PD, and whether the risk score improves prediction of PD. We also studied whether the risk score is associated with basic daily activities in healthy individuals.

Methods: Within the population-based Rotterdam Study, we genotyped 26 independent genetic risk variants for PD and constructed a genetic risk score in 7170 participants who were free of parkinsonism and dementia at baseline (1990 or 2000). Participants were followed-up for the onset of parkinsonism, dementia or death until January 1, 2011 (mean follow-up 12.7 years). We used cox proportional hazard models and C-statistics to study the relationship between the genetic risk score and incident PD, adding the risk score to age, sex, smoking and parental PD. In an independent sample of 2997 persons free of parkinsonism and dementia, we studied whether the PD risk genes were associated with impaired basic daily activities (BADL).

Results: The genetic risk score was associated with a higher risk of incident PD (hazard ratio 1.63 [95% confidence interval=1.02;2.59]), but did not result in a substantially better prediction (change in C=0.011 [-0.010;0.031]). The genetic risk score was associated with a higher probability of any impairment in BADL (odds ratio=1.32 [1.03;1.69]).

Conclusions: Genetic variants of PD are associated with the risk of incident PD in the general population and with impairment in BADL in individuals without PD, but do not meaningfully improve the clinical prediction of PD beyond age, sex and smoking.

Introduction

Parkinson's Disease (PD) is the second most common neurodegenerative disorder among the elderly.[1] Clinically, the disease is characterized by parkinsonism, an absence of markers suggestive of other causes, and supportive prospective criteria.[2] Clinical PD is preceded by a prodromal phase during which neurodegeneration has already started, but the signs defining parkinsonism are not present.[3] During this period, individuals often experience a combination of early motor and non-motor signs and symptoms that could affect their daily activities, ranging from subtle movement deficits under challenging conditions to autonomic dysfunction, rapid eye movement sleep behavior disorder, and depression.[4]

Although several factors are associated with an increased risk of incident PD, none of these factors alone enables the identification of persons at high risk for the disease.[1, 5] During the last decade, several studies have suggested a substantial genetic contribution to PD, with a large proportion of these contributing genes still to be identified.[6] With the recent identification of six additional risk loci for PD, genome-wide association studies have yielded a total of 26 independent risk variants.[7] However, the ability of these risk loci to predict PD in community-dwelling persons remains unknown. Also, it is unclear whether these risk variants evoke symptoms related to PD in individuals without clinical parkinsonism, that lead to subtle problems in daily functioning. Investigating their predictive accuracy and their subclinical effect on daily activities may aid in elucidating the role of these genes in prodromal PD.

We hypothesized that a genetic risk score based on currently identified risk loci would be a risk factor for incident PD, and that the genetic risk score would improve prediction of PD. Furthermore, we hypothesized that PD genes may also affect daily activities in individuals without parkinsonism. We studied these hypotheses within a large, prospective, population-based study.

Methods

Setting

The study was embedded in the Rotterdam Study, a population-based cohort study in the Netherlands.[8, 9] The original study cohort (RS-I) started in 1990 and consisted of 7983 community-dwelling people aged 55 years and older, residing in the suburb Ommoord, Rotterdam. They were re-examined every 3 to 4 years, with the last re-examination between 2009 and 2011. In 2000, the cohort was expanded with 3011 people aged 55 years and older (RS-II). The last follow-up examination for this subcohort took place between 2011 and 2012. In 2006, the cohort was further extended with 3932 inhabitants aged 45 years and older (RS-III).

For this report, all participants in RS-I and RS-II free of parkinsonism and dementia at baseline with available genotype information on all 26 risk loci for PD were eligible (n=7705). Participants in the third sub-cohort of the Rotterdam Study were not included because baseline information on their dementia status had not been processed completely at the time of this study. Of the remaining persons, 7224 were interviewed at baseline on their smoking habits (never, past, current) and parental history of PD. Finally, 54 persons refused to provide informed consent, leaving 7170 participants (93.1%) for PD prediction analyses. We followed participants for the development of PD from baseline until the first of: onset of parkinsonism, onset of dementia, death or 1 January 2011.

We assessed basic activities of daily living (BADL) during the last center visit round of both cohorts (RS-I in 2009-2011 and RS-II in 2011-2012) in participants free of incident parkinsonism or dementia. We invited 3855 individuals, of whom (79.0%) agreed to participate and were able to participate. Twenty-five persons were excluded because of unknown smoking status at time of the BADL assessment and another twenty-four persons did not complete their BADL assessment, leaving 2997 persons for BADL analyses.

Genotyping

The Illumina 550K (RSI), 550K duo, and 610 quad (RSII) arrays were used for genotyping. We removed samples with call rate below 97.5%, gender mismatch, excess autosomal heterozygosity, duplicates or family relations and ethnic outliers, and variants with call rate below 95.0%, failing missingness test, Hardy–Weinberg equilibrium p-value<10^{-6}, and minor allele frequency<1%. Genotypes were imputed using MACH/minimac software to the 1000 Genomes phase I version 3 reference panel (all population).

Ascertainment of parkinsonism and Parkinson's Disease

At baseline, all participants were screened at the research center for signs of parkinsonism.[10] Individuals who screened positive received a structured clinical workup by a research physician specialized in neurologic disorders to establish parkinsonism. Persons who were suspected of having PD were further evaluated by an experienced neurologist.

During follow-up, we used four overlapping modalities to screen for potential parkinsonism: in-person screening, in-person interviews, use of antiparkinson medication, and clinical monitoring alerts.[11] Of all persons who screened positive in any of these methods, complete medical records were studied and case reports were drawn up covering all potentially relevant information to establish presence and subtype of parkinsonism. These case reports were evaluated by a panel led by an experienced neurologist. PD was only diagnosed after exclusion of parkinsonism associated with preexistent dementia, use of anti-dopaminergic drugs, cerebrovascular disease, multiple system atrophy, or progressive supranuclear palsy.[10]

Ascertainment of dementia

Participants were screened for dementia at baseline and follow-up examinations using a three-step protocol, comprising two brief tests of cognition to screen all subjects and the Cambridge Examination for Mental Disorders of the Elderly in individuals with positive screen results.[12, 13] Additional information was obtained from in-person examination by a neuropsychologist, clinical monitoring and neuro-imaging . A consensus panel, led by a neurologist, decided on the final diagnosis in accordance with standard criteria using the DSM-III-R criteria for dementia.

Basic activities of daily living

Basic activities of daily living (BADL) was assessed based on the disability index from the Stanford Health Assessment Questionnaire, which consisted of 20 items constituting eight components: dressing and grooming, arising, eating, walking, hygiene, grip, reach, and activities.[14] In our study, two out of three items of eating (ability to lift a glass of milk and ability to cut meat) were combined into one. Items were scored from 0 to 3, as follows: 0 = without difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to. Component scores were calculated as the highest scored item per component.[14] The BADL score was calculated by summing all components, obtaining a score between 0 and 24. We considered scores from 0 to 8 as no to mild disability and from 8 to 24 as moderate to severe disability.[15]

Statistical analysis

We constructed a genetic risk score for each individual, by adding up their number of risk alleles weighted by the log-transformed, reported risk-increasing or risk-decreasing effect size for the association with PD.[7] A higher genetic risk score corresponds to a larger weighted number of risk alleles and thus a higher risk of PD. We used Cox proportional hazard models to study whether the genetic risk score was associated with incident PD independent from age, sex and smoking (never, past, current). We also investigated whether the risk score improved prediction of PD by comparing the C-statistic of three models: model I included age and sex, model II additionally comprised smoking and parental PD, and model III also included the genetic risk score. In addition, we used logistic regression models to calculate the area under the receiver operator characteristic curve at 10 years of follow-up for the three prediction models. In separate subanalyses, we added interaction terms between the genetic risk score and age, sex, smoking and parental PD to the second model.

To study the association between the genetic risk score and activities of daily living, we dichotomized BADL scores for having any difficulty in daily functioning or none. We used a binary logistic regression model to analyze the association of the genetic risk score with any

difficulty in BADL, adjusting for age, sex and smoking. In separate subanalyses, we added interaction terms between the genetic risk score and age, sex and smoking to the model. Furthermore, we used multinomial logistic regression models to examine the association of the genetic score with mild and moderate to severe BADL impairment separately. Also, we examined associations between the genetic risk score and impairment on each BADL domain separately using logistic regression models. Finally, we used a logistic regression model to examine the association between each of the 26 single risk variants with any impairment in BADL, adjusting for age, sex and the other risk variants and Bonferroni correction for 28 comparisons (p=0.05/28).

Results

Characteristics of the study population at risk for PD and the persons examined for daily activities are presented in Table 1. During follow-up (mean 12.7 years, standard deviation 5.5 years), 106 (1.5%) individuals suffered from incident PD and 973 (13.6%) from incident dementia, while a total of 3,443 (48.0%) persons died. Of all incident PD cases, 75 were diagnosed during the first ten years of follow-up.

Table 1. Population characteristics

Characteristic	At risk for PD (n=7170)	ADL examination (n=2997)
Women, n	4135 (57.7%)	1756 (58.6%)
Age at baseline, years	67.3 (8.4)	76.8 (6.6)
Smoking		
Never, n	2353 (32.8%)	1036 (34.6%)
Past	3237 (45.1%)	1672 (55.8%)
Current	1580 (22.0%)	289 (9.6%)
Parental PD		
No, n	6962 (97.1%)	-
1 parent with PD, n	205 (2.9%)	-
2 parents with PD, n	3 (<0.1%)	-
BADL		
no impairment, n	-	461 (15.7%)
mild impairment, n	-	2017 (67.3%)
moderate to severe impairment, n	-	519 (17.3%)

Values are means (standard deviations) or numbers of participants (percentages). Smoking status was assessed at baseline for PD risk prediction analyses and during the last center visit for BADL analyses.
Abbreviations: PD, Parkinson's Disease; BADL, basic activities of daily living.

Table 2. Prediction of Parkinson's Disease

	HR (95% CI)	C-statistic (95% CI)
Model I		0.659 (0.601; 0.718)
Age, years	1.07 (1.05; 1.10)	
Female vs. male	0.59 (0.40; 0.88)	
Model II		0.687 (0.630; 0.743)
Age, years	1.07 (1.05; 1.10)	
Female vs. male	0.44 (0.27; 0.70)	
Smoking (never)	1.00 (Reference)	
Smoking (past)	0.59 (0.36; 0.97)	
Smoking (current)	0.40 (0.20; 0.81)	
≥1 vs. 0 parents with PD	1.30 (0.41; 4.11)	
Model III		0.697 (0.635; 0.760)
Age, years	1.07 (1.05; 1.10)	
Female vs. male	0.44 (0.27; 0.70)	
Smoking (never)	1.00 (Reference)	
Smoking (past)	0.59 (0.36; 0.97)	
Smoking (current)	0.41 (0.21; 0.81)	
≥1 vs. 0 parents with PD	1.25 (0.39; 3.97)	
Genetic risk score, SD	1.63 (1.02; 2.59)	

Abbreviations: HR, hazard ratio for Parkinson's Disease; CI, confidence interval; PD, Parkinson's Disease; SD, standard deviations.

In Table 2, we show that the genetic risk score was independently associated with the onset of PD. The hazard ratio (HR) per standard deviation increase in risk score was 1.63 [95% confidence interval=1.02;2.59; two-tailed p value=0.038]. Adding smoking and parental PD to age and sex yielded a borderline significant improvement in prediction of incident PD (change in C=0.027 [-0.003;0.057]), while addition of the genetic risk score did not further improve the predictive ability of the model (change in C=0.011 [-0.010;0.031]). There was no significant interaction between the genetic risk score and any of the covariates in the model (p>0.10 for all interaction terms). At ten years of follow-up, differences in discrimination between the three models were very small, as shown in figure 1.

The genetic risk score was associated with any impairment in BADL (odds ratio, OR=1.31 [1.03;1.69]; p=0.03). There was no significant interaction of the genetic risk score with age, sex, or smoking (p>0.10 for all interaction terms). As shown in table 3, the genetic risk score was significantly associated with mild impairment (OR=1.36 [1.06;1.74]; p=0.02), but not with moderate to severe impairment (OR=1.08 [0.77;1.49]; p=0.66) in separate analyses.

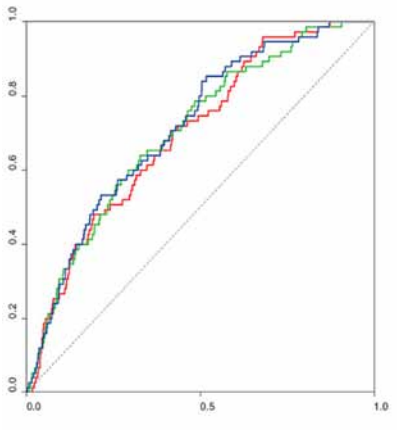

Figure 1. 10-year follow-up for incident Parkinson's Disease: three prediction models. Area under the receiver-operating-characteristic curves at ten years of follow-up: Model I (age + sex): 0.698. Model II (model I + smoking + parental Parkinson's Disease): 0.705. Model III (model II + genetic risk score): 0.716.

In contrast to the overall BADL-score, the genetic risk score was not associated with any of the eight BADL domains separately (p>0.20 for each domain).

None of the 26 single risk variants was associated with impairment in BADL after Bonferroni correction. Interestingly, the PD risk alleles in the *STK39* (rs1474055; OR=1.20[1.03;1.41]; p=0.022) and *GCH1* (rs11158026; OR=1.18[1.00;1.384]; p=0.046) loci were nominally associated with any impairment in BADL, while associations with the risk allele in *CCDC62* (rs11060180; OR=1.15[0.99;1.33]; p=0.067) and in *GBA-SYT11* (rs35749011; OR=1.70[0.95;3.04]; p=0.076) loci were borderline nominally significant. None of the remaining 22 variants was nominally associated with any impairment in BADL (p>0.10 for each variant).

Table 3. Associations of the genetic risk score with basic activities of daily living

Basic activities of daily living	Odds ratio (95%CI)
No impairment	1.00 (reference)
Any impairment	1.32 (1.03; 1.69)
Mild impairment	1.36 (1.06; 1.74)
Moderate to severe impairment	1.08 (0.77; 1.49)

Values represent odds ratios per standard deviation higher genetic risk score. Reference category for both mild and moderate to severe impairment is no impairment. All analyses were adjusted for age, sex and smoking.
Abbreviations: 95%CI, 95% confidence interval.

Discussion

In this large population-based sample with over ten years of follow-up, we found that a genetic risk score for PD based on the most recent set of genome-wide significant variants was associated with a modest but significant increase in the risk of PD. However, in addition to age, sex, smoking status at baseline and parental PD, the genetic risk score hardly improved the prediction of incident PD. In cross-sectional analyses, we further found that the genetic risk score was associated with any impairment in BADL.

One of the strengths of this study is its prospective, population-based nature. As far as we know, only case–control studies have previously been employed to examine the use of a genetic risk score for PD to discriminate between PD cases and healthy controls.[16, 17] These studies excluded a large number of patient groups with clinical and possibly genetic overlap with PD, such as essential tremor and Alzheimer dementia. While this approach ensures maximum distinction between cases and controls, it also limits the predictive value for incident PD of those studies. Prospective studies such as the Rotterdam Study have the advantage that all participants were included and followed up using the same methodology, and following up persons in the general population presumably ensured a realistic estimate of the risk of incident PD. Several limitations of our study should be noted, however. We were probably underpowered to detect interaction of the genetic risk score with traditional risk factors and parental PD. Also, we note that part of the RS-I cohort used for prediction of PD was also among the discovery cohorts of the PD genes. However, its proportion was very small and therefore unlikely to have influenced our current findings.[7]

Although neuroprotective agents with sustainable effects on PD progression remain elusive, the main motivation for learning how to predict PD is to identify PD patients as early as possible.[18] At this stage, PD manifestations can often be treated or delayed effectively, and surveillance could allow early symptomatic treatments, perhaps with long-term benefits on quality of life.[19, 20] Over the past few years, genetic risk scores have been shown to be of marginal value in prediction of diseases with strong preexistent demographic and clinical factor-based predictive models.[21, 22] However, they have enabled improvement in prediction of diseases without such models.[23, 24] In this study of more than 7000 individuals, we showed that addition of a genetic risk score for PD did not improve prediction beyond age, sex, smoking and parental PD. Thus, our findings do not support a role for routine PD risk allele genotyping in a clinical setting at this time. As more PD risk variants become known, however, their incorporation into the risk score may explain more of the genetic risk that has been implied by familial aggregation of PD.[25] It is possible that the addition of rare risk alleles with

large effects, or a larger number of common risk alleles with small individual effects, further improves discrimination between PD cases and controls.[26]

To our knowledge, this is the first study to investigate the relationship of a genetic risk score for PD with daily activities in the general population. We found that the genetic risk score was associated with any impairment in BADL, suggesting that the PD risk alleles may relate to prodromal symptoms of PD in the general population. Our findings expand on a recent study that demonstrated that PD risk alleles in the *MAPT* and *CCDC62* loci were associated with the development of parkinsonian motor signs after exclusion of patients with a PD diagnosis.[27] Interestingly, there was a borderline significant nominal association between the risk variant in the *CCDC62* locus and any impairment in BADL in this study. In addition, two risk variants that were not examined in aforementioned study (the recently identified risk allele on the *GCH1* locus, and the risk allele on the *STK39* locus) were nominally associated with any impairment in BADL in our population.[7] These findings support the hypothesis that alleles with an established association with PD may also affect prodromal phenotypes linked with PD in the general PD-free population.

In summary, in this study in the general population, a genetic risk score based on 26 independent risk variants was associated with a higher risk of incident PD and a larger probability of impairment in BADL, but did not result in a substantially better prediction of PD beyond age, sex, smoking and parental PD. Our results suggest that the use of this weighted combination of known risk loci is not yet as useful for the prediction of the risk of PD as it is for further elucidating the etiology of the disease.

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Chapter 4.3

Consumption of alcohol, coffee, and tobacco is associated with gait

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Submitted.

Abstract

Objectives: Gait is an important health indicator, relating strongly to the risk of falling, morbidity, and mortality. In a community-dwelling population, we investigated associations of alcohol, coffee, and tobacco consumption with gait.

Methods: 2546 non-demented participants from the Rotterdam Study underwent gait assessment by electronic walkway. We measured gait velocity and Global Gait, which is the average of seven gait domains: Rhythm, Phases, Variability, Pace, Tandem, Turning, and Base of Support. Alcohol drinking, coffee drinking, and current or past smoking were assessed by questionnaires. With ANCOVA we investigated associations of alcohol drinking, coffee drinking, and smoking with Global Gait, gait velocity, and the seven individual gait domains.

Results: 81.9% of participants drank alcohol, 92.4% drank coffee, 17.3% were current smokers, and 50.9% were past smokers. Moderate alcohol intake (1-3 glasses/day) associated with better gait, as measured by Global Gait (0.20 standard deviations [SD, 95% confidence interval: 0.10; 0.31]), gait velocity (2.65 cm/s [0.80; 4.50]), Rhythm, and Variability. Drinking high amounts of coffee (>3 cups/day) associated with better Global Gait (0.18 SD [0.08; 0.28]), gait velocity (2.63 cm/s [0.80; 4.45]), Pace, Turning, and Variability. Current smoking associated with worse Global Gait (-0.11 SD [-0.21; 0.00]), gait velocity (-3.47 cm/s [-5.33; -1.60]), Rhythm, and Pace, compared to non-smokers.

Conclusions: In a community-dwelling population, drinking coffee and moderate amounts of alcohol relate to better gait, while smoking is related to worse gait. Further studies are required to evaluate whether interventions targeting substance consumption may aid to prevent or reduce gait deterioration and thereby related health problems.

Introduction

Alcohol, coffee, and tobacco are widely consumed substances in the general population and have addictive properties.[1-6] Alcoholic beverages, coffee, and tobacco contain many different components, which have various effects on health with chronic use.[1-5, 7-9] Whilst excessive consumption of these substances is usually considered detrimental, beneficial effects of coffee and moderate alcohol intake have also been described.[1, 3, 5, 6, 9, 10] However, consumption of these substances also reflects lifestyle and socioeconomic status, which may obscure direct biological effects.[2, 11-13] For instance, moderate alcohol drinking is most prevalent in persons with higher education who may have a healthier lifestyle.[2, 13]

Gait is considered an accurate reflection of general health.[14, 15] Gait is influenced by many organ systems, including the central and peripheral nervous system, cardiovascular system, and musculoskeletal system.[16-20] Damage to any of these systems may impair gait, which in turn can severely impair daily functioning and increase the risk of falling, morbidity, and mortality.[14, 21-24] Conventionally, gait velocity is used as an overall marker to assess gait. However, gait is a complex concept consisting of many domains, e.g. Base of Support (stride width), Rhythm (cadence), and Variability (gait variability among steps).[25] These gait domains reflect different abilities, such as physical strength and cognition, and hence may relate distinctively to various aspects of health.[16, 19, 20] Investigating alcohol, coffee, and tobacco consumption in relation to composite gait domains and gait velocity may provide additional insight into the overall beneficial or detrimental effect of these substances on general health, delineating possible interventions to improve gait and thereby health.

Previous studies of gait were restricted to substance abuse and therefore did not inform on the associations of overall intake of alcohol, coffee, and tobacco with gait in the general population.[26]

We aimed to investigate associations of alcohol drinking, coffee drinking, and smoking with gait in a community-dwelling population.

Methods

Setting

The study was embedded in the Rotterdam Study, a population-based cohort study in the Netherlands.[27] In 1990 and 2000, all inhabitants of Ommoord, a suburb of Rotterdam, aged 55 years and older were invited to participate. In 2006 the cohort was further extended, inviting all inhabitants aged 45 years and older. All participants undergo regular home interviews and extensive medical examinations at the research centre. From March 2009 onwards, gait assessment was included in the core study protocol. The current study includes all participants

that underwent gait assessment between March 2009 and March 2012. The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare, and Sports of the Netherlands. A written informed consent was obtained from all participants.

Assessment of alcohol drinking, coffee drinking, and smoking

The intake of alcohol and coffee was assessed as part of a 389-item semi-quantitative food frequency questionnaire (FFQ), based on an existing validated FFQ developed for Dutch adults.[28, 29] Included questions in the FFQ were the frequency of consumption of food items over the last month, the amount and type of the food item, and preparation methods. Portion sizes were estimated using standardised household measures for glasses and cups per day.[30] The dietary data were converted into nutrient intakes (i.e. total energy) per day using the Dutch Food Composition Table of 2011.[31] At each visit, the home interview included questions on whether participants smoked cigarettes, cigars, or pipe, or whether they have smoked any in the past. Additionally, participants were asked how many cigarettes they smoked in their period of smoking. Cigarette pack-years were calculated as the duration of self-reported smoking (years) multiplied by the number of daily smoked cigarettes, divided by twenty. Missing data on smoking were imputed using a last observation carried forward method.

Gait Assessment

Details about our gait assessment protocol have been published previously.[25] In short, gait was assessed using an 5.79 meter long electronic walkway (4.88 meter active area; GAITRite Platinum; CIR systems, Sparta, NJ, USA). Participants performed three walking conditions: normal walk, turn, and tandem walk. In normal walk, participants were asked to walk at regular pace across the walkway. The normal walk was performed eight times, of which the first walk was considered a practice walk and excluded from analyses. In turn, people walked across the walkway, turned halfway, and returned to their starting position. In tandem walk, participants walked heel-to-toe over a line visible on the walkway, until they were off the walkway.

A principal components analysis was used to summarise the gait data into seven independent gait domains, as previously described: Rhythm, reflecting cadence and single support time, among others; Phases, reflecting double support time and double support as a percentage of the gait cycle; Variability, reflecting stride length variability and stride time variability; Pace, reflecting stride length and velocity; Tandem, reflecting errors in the tandem walk; Turning, reflecting turning step count and time; and Base of Support, reflecting stride width and stride width variability.[25] Subsequently, a Global Gait score was calculated by averaging the seven gait domains.[16] In addition to Global Gait, we investigated gait velocity as a general

gait measure, which is the most commonly used gait parameter and strongly associates with mortality.[24]

Covariates

At the home interview and examinations at the research centre, height, weight, education, working status, marital status, Mini-Mental State Examination (MMSE), blood pressure, total cholesterol level, high-density lipoprotein (HDL) level, glucose level, use of blood pressure lowering medication for indication hypertension, use of anti-diabetic medication, and functioning on activities of daily living (ADL) were assessed. Education was divided into seven categories: 0, primary education; 1, lower vocational education; 2, lower secondary education; 3, intermediate vocational education; 4, general secondary education; 5, higher vocational education; 6, university. Working status was dichotomised as currently being paid for work, or not. Marital status was categorised into five categories: never married, married, widowed, divorced, or having a Living Apart Together (LAT) relationship, which were recoded as dummy variables. Diabetes mellitus was defined as a fasting blood glucose level >= 7.0 mmol/L, non-fasting glucose level >= 11.1 mmol/L, or use of anti-diabetic medication. ADL were assessed using the disability index from the Stanford Health Assessment Questionnaire.[32] Missing values on these covariates were imputed by the mean of five imputations, based on age, sex, and other covariates. 0.8% of variables were imputed in this way. Imputed values for use of anti-diabetic and blood pressure lowering medication were rounded to either zero or one. Imputed values on education were rounded to integers.

Study population

Between March 2009 and March 2012, 3651 participants were invited for gait assessment.

Of these, 282 did not perform all walking conditions for the following reasons: 204 for perceived physical inability, 57 for technical reasons, 19 for refusal, and 2 for other reasons.

Of remaining 3369 participants, 239 had to be excluded for technical reasons (e.g. errors impeding parameter calculation), 45 because of dementia or missing data on dementia, 34 for performing less than 16 steps in the normal walk, lowering the validity of measurements[33], 27 for not following the instructions correctly, and 3 for using walking aids. Of 3021 remaining participants, 475 missed FFQ data. Finally, 2546 participants were included in the analyses.

Statistical analysis

Associations of alcohol and coffee drinking with gait were investigated in two ways. First, both alcohol drinking and coffee drinking were dichotomised into drinking or non-drinking.

Second, alcohol drinking was categorised into drinking no, drinking 0-1, drinking 1-3, or

drinking >3 glasses of alcohol per day.[9] Coffee drinking was similarly categorised, but due to the low number of people drinking no coffee, we decided to combine the first two categories into one. Hence, coffee drinking was categorised into three categories: drinking ≤1, drinking 1-3, or drinking >3 cups of coffee per day.

Smoking was categorised into never smokers, past smokers, and current smokers. Additionally, we investigated the associations for smoking using the number of pack-years smoked.

ANCOVAs were used to investigate associations of alcohol drinking, coffee drinking, and smoking with Global Gait, gait velocity, and the gait domains.

Since quadratic relationships have been reported for alcohol drinking with cardiovascular disease and mortality, we also investigated quadratic relationships of alcohol drinking with gait.[5] This was done by including both the number of glasses of alcohol consumed daily and its quadratic term in linear analyses.

All analyses were adjusted for age, sex, subcohort, interval between assessments, height, weight, education, working status, marital status, and energy intake. Analyses including Tandem were additionally adjusted for the mean step size and step count in the tandem walk. The analyses on pack-years of smoking were additionally adjusted for ever smoking cigars or pipe.

To investigate influence of cardiovascular risk factors and cognition on associations, all analyses were repeated while additionally adjusting for consumption of the other substances, cardiovascular risk factors (systolic blood pressure, diastolic blood pressure, use of blood pressure lowering medication, total cholesterol, high-density lipoprotein, and diabetes mellitus), and MMSE.

To investigate whether the relation was driven by general well-being, we performed sensitivity analyses for the fully adjusted associations of substance consumption with Global Gait and gait velocity, by additionally adjusting for ADL.

Furthermore, we explored possible interactions by sex in the associations of substance consumption with Global Gait and gait velocity, by adding sex*substance consumption interaction terms in the analyses.

All analyses were performed using IBM SPSS version 21.0.0.1 for Windows.

Results

Mean age of participants was 68.0 years (standard deviation [SD] 8.8) and 55.7% were women (Table 1). A total of 92.4% drank coffee, 81.9% drank alcohol, 17.3% were current smokers, and 50.9% were past smokers. On average, participants drank 3.0 cups (SD 2.0) of coffee and 1.2 glasses (SD 1.5) of alcohol per day. Mean gait velocity was 121.8 cm/s (SD 17.8).

Table 1. Population characteristics

Characteristic	Total (n = 2546)
Age, yrs	68.0 (8.8)
Women, n	1418 (55.7%)
Height, cm	169.0 (9.2)
Weight, kg	77.9 (13.7)
Education[a]	3 (3)
Current paid work, n	786 (30.9%)
Energy intake (1000 kcal/day)	2.2 (0.8)
Total cholesterol, mmol/L	5.5 (1.1)
High-density lipoprotein, mmol/L	1.5 (0.4)
Systolic blood pressure, mmHg	142.4 (22.1)
Diastolic blood pressure, mmHg	84.1 (11.0)
Blood pressure lowering drug use, n	848 (33.3%)
Diabetes mellitus, n	264 (10.4%)
MMSE, points	28.1 (1.7)
Coffee drinkers, n	2353 (92.4%)
Coffee intake, cups/day	3.0 (2.0)
Alcohol drinkers, n	2085 (81.9%)
Alcohol intake, glasses/day	1.2 (1.5)
Past smokers, n	1296 (50.9%)
Current smokers, n	441 (17.3%)

Values are means (standard deviations) or numbers of participants (percentages).
[a] Median (interquartile range).

Associations of alcohol, coffee, and tobacco consumption with Global Gait and gait velocity

Drinking any alcohol was associated with higher Global Gait (0.13 SD [95% confidence interval: 0.04; 0.22]) and gait velocity (2.04 cm/s [0.41; 3.66]), after adjustment for age, sex, subcohort, interval between assessments, height, weight, education, working status, marital status, and energy intake (Table 2). Drinking 1-3 glasses of alcohol per day was associated with higher Global Gait (0.20 SD [0.10; 0.31]) and gait velocity (2.65 cm/s [0.80; 4.50]) compared to drinking no alcohol. Additionally, drinking >3 glasses of alcohol per day associated with higher Global Gait (0.15 SD [0.00; 0.29]). However, we found no associations of drinking 0-1 glasses of alcohol per day compared to not drinking any alcohol. We found a significant quadratic association between daily alcohol drinking and Global Gait, with the highest Global Gait for drinking moderate amounts of alcohol.

Table 2. Associations of drinking alcohol, drinking coffee, and smoking with Global Gait and gait velocity

	Global Gait, SD	Gait Velocity, cm/s
Alcohol		
0 glasses/day (n=461)	0	0
0-1 glasses/day (n=1025)	0.08 (-0.02; 0.18)	1.62 (-0.12; 3.35)
1-3 glasses/day (n=808)	**0.20 (0.10; 0.31)**	**2.65 (0.80; 4.50)**
>3 glasses/day (n=252)	**0.15 (0.00; 0.29)**	2.15 (-0.37; 4.66)
Coffee		
≤1 cups/day (n=363)	0	0
1-3 cups/day (n=584)	**0.13 (0.01; 0.25)**	**2.74 (0.67; 4.80)**
>3 cups/day (n=1599)	**0.18 (0.08; 0.28)**	**2.63 (0.80; 4.45)**
Smoking		
Pack-years, /10	-0.01 (-0.03; 0.01)	**-0.60 (-0.94; -0.27)**

Values are differences in gait (95% confidence interval). Results in bold survived thresholds of nominal significance ($p<0.05$). Analyses are adjusted for age, sex, subcohort, interval between assessments, height, weight, education, working status, marital status, and energy intake.
Abbreviations: SD, standard deviations.

We found no significant associations of drinking coffee versus not drinking coffee with Global Gait and gait velocity. However, we did find that drinking 1-3 and >3 cups of coffee per day was associated with higher Global Gait (1-3 cups: 0.13 SD [0.01; 0.25], >3 cups: 0.18 SD [0.08; 0.28]) and gait velocity (1-3 cups: 2.74 cm/s [0.67; 4.80], >3 cups: 2.63 cm/s [0.80; 4.45]), compared to drinking 0-1 cups of coffee per day.

Current smoking was associated with lower Global Gait (-0.11 SD [-0.21; 0.00]) and gait velocity (-3.47 cm/s [-5.33; -1.60]), compared to never smoking. We found no associations of past smoking with Global Gait or gait velocity. A higher number of pack-years of smoking only associated with lower gait velocity (-0.60 cm/s per 10 pack-years [-0.94; -0.27]).

Additional adjustment for consumption of other substances, cardiovascular risk factors, and MMSE attenuated the results. However, the associations of drinking any alcohol and 1-3 glasses of alcohol with Global Gait and gait velocity remained; the associations of drinking >3 cups of coffee per day with Global Gait and gait velocity remained; and the association of current smoking and pack-years of smoking with gait velocity remained.

After further adjustment for ADL, associations hardly changed. Only the association between drinking any alcohol versus none and gait velocity became borderline non-significant ($p=0.06$).

We found no significant sex interactions for the associations.

Associations of alcohol, coffee, and tobacco consumption with gait domains

Drinking any alcohol only associated with higher Phases (0.09 SD [0.00; 0.17], Table 3). Additionally, drinking 0-1 glasses of alcohol per day was associated with higher Phases but lower Base of Support compared to drinking no alcohol. Drinking 1-3 glasses of alcohol per day was associated with higher Rhythm.

Table 3. Associations of drinking alcohol with individual gait domains

	Rhythm	Phases	Variability	Pace	Tandem[a]	Turning	Base of Support
Yes versus no	0.07 (-0.03; 0.16)	**0.09 (0.00; 0.17)**	0.08 (-0.02; 0.18)	0.06 (-0.02; 0.14)	0.07 (-0.02; 0.17)	0.04 (-0.06; 0.14)	-0.09 (-0.19; 0.01)
0 glasses/ day	0	0	0	0	0	0	0
0-1 glasses/ day	0.02 (-0.08; 0.12)	**0.10 (0.01; 0.19)**	0.05 (-0.06; 0.16)	0.05 (-0.04; 0.14)	0.07 (-0.03; 0.18)	0.03 (-0.08; 0.14)	**-0.13 (-0.24; -0.02)**
1-3 glasses/ day	**0.11 (0.01; 0.22)**	0.08 (-0.01; 0.18)	0.11 (0.00; 0.22)	0.08 (-0.02; 0.17)	0.07 (-0.04; 0.19)	0.08 (-0.04; 0.20)	-0.03 (-0.14; 0.09)
>3 glasses/ day	0.14 (0.00; 0.28)	0.04 (-0.09; 0.17)	0.05 (-0.06; 0.16)	0.05 (-0.04; 0.14)	0.08 (-0.08; 0.23)	-0.04 (-0.20; 0.11)	-0.04 (-0.20; 0.11)

Values are differences in standard deviations of gait (95% confidence interval) compared to not drinking any alcohol. Results in bold survived thresholds of nominal significance ($p<0.05$). Analyses are adjusted for age, sex, subcohort, interval between assessments, height, weight, education, working status, marital status, and energy intake.
[a] Additionally adjusted for mean step length and step count in the tandem walk.

Table 4. Associations of drinking coffee with individual gait domains

	Rhythm	Phases	Variability	Pace	Tandem[a]	Turning	Base of Support
Yes versus no	-0.02 (-0.15; 0.11)	0.09 (-0.04; 0.21)	0.13 (-0.01; 0.28)	0.06 (-0.06; 0.18)	-0.06 (-0.20; 0.09)	0.08 (-0.07; 0.22)	-0.05 (-0.20; 0.09)
≤1 cups/ day	0	0	0	0	0	0	0
1-3 cups/ day	0.06 (-0.06; 0.17)	0.05 (-0.05; 0.16)	0.10 (-0.03; 0.23)	**0.13 (0.02; 0.23)**	0.00 (-0.13; 0.12)	0.12 (-0.01; 0.25)	-0.10 (-0.23; 0.03)
>3 cups/ day	0.04 (-0.07; 0.14)	0.08 (-0.02; 0.17)	**0.15 (0.04; 0.26)**	**0.11 (0.02; 0.20)**	0.01 (-0.10; 0.12)	**0.14 (0.02; 0.25)**	-0.03 (-0.14; 0.09)

Values are differences in standard deviations of gait (95% confidence interval) compared to not drinking any coffee. Results in bold survived thresholds of nominal significance ($p<0.05$). Analyses are adjusted for age, sex, subcohort, interval between assessments, height, weight, education, working status, marital status, and energy intake.
[a] Additionally adjusted for mean step length and step count in the tandem walk.

Table 5. Associations of smoking with individual gait domains

	Rhythm	Phases	Variability	Pace	Tandem[a]	Turning	Base of Support
Never	0	0	0	0	0	0	0
Past	-0.05 (-0.13; 0.03)	-0.03 (-0.10; 0.04)	0.03 (-0.05; 0.12)	-0.01 (-0.08; 0.06)	0.03 (-0.06; 0.11)	0.06 (-0.03; 0.15)	-0.04 (-0.13; 0.05)
Current	**-0.11 (-0.22; -0.01)**	-0.04 (-0.14; 0.05)	0.07 (-0.05; 0.18)	**-0.11 (-0.21; -0.02)**	-0.04 (-0.15; 0.07)	0.01 (-0.10; 0.13)	-0.03 (-0.15; 0.09)
Packyrs, /10	-0.01 (-0.03; 0.01)	**-0.02 (-0.04; 0.00)**	0.01 (-0.01; 0.03)	**-0.03 (-0.05; -0.01)**	0.01 (-0.01; 0.03)	0.00 (-0.02; 0.03)	0.00 (-0.02; 0.02)

Values are differences in standard deviations of gait (95% confidence interval). Results in bold survived thresholds of nominal significance (p<0.05). Analyses are adjusted for age, sex, subcohort, interval between assessments, height, weight, education, working status, marital status, and energy intake.

[a] Additionally adjusted for mean step length and step count in the tandem walk.

Abbreviations: Packyrs, pack-years.

We found no associations of drinking coffee compared to not drinking coffee with any gait domain (Table 4). However, drinking 1-3 cups of coffee per day associated with higher Pace and drinking >3 cups of coffee per day with higher Variability, Pace, and Turning compared to drinking ≤1 cup of coffee.

Current smoking associated with lower Rhythm (-0.11 SD [-0.22; -0.01]) and Pace (-0.11 SD [-0.21; -0.02], Table 5). We found no associations of past smoking with any gait domain. A higher number of pack-years of smoking was associated with lower Phases and Pace.

After additional adjustment for consumption of other substances, cardiovascular risk factors, and MMSE, results attenuated. Yet, all associations of drinking alcohol with Rhythm, Phases, and Base of Support; drinking >3 cups of coffee daily with Turning; current smoking with Pace; and pack-years of smoking with Phases and Pace remained significant.

Discussion

In this community-dwelling population, drinking coffee and moderate amounts of alcohol were associated with better gait, while smoking associated with worse gait. These findings remained after adjustment for use of other substances, cardiovascular risk factors, MMSE, and ADL. Drinking alcohol was also associated with better Rhythm and Phases; drinking coffee with better Variability, Pace, and Turning; and smoking with worse Rhythm, Phases, and Pace.

Strengths of our study include the large population-based sample, assessing the consumption of alcohol, coffee, and tobacco, and objective assessment of gait in three walking conditions.

Our study also has limitations. The cross-sectional design of this study precluded investigation of causality. Since it is unlikely for gait to cause differences in alcohol, coffee, or tobacco consumption, our findings suggest that substance consumption affects gait. However, these associations may also result from reverse causality, i.e. people may change their substance consumption due to health problems that also affect their gait. Nonetheless, that the associations hardly changed after adjustment for the general health indicator ADL indicates that the impact of reverse causality may not be large, and is suggestive of a true relation. Conceptually, ADL adjustment may even be over adjusting, since gait, or walking, is included as part of ADL and many activities require walking to be executed. Another issue is confounding by socio-behavioural factors, i.e. a healthier lifestyle may relate to a different substance consumption and gait pattern.[2, 11-13] In order to account for these factors, we adjusted analyses for working status, marital status, education, and energy intake. The remaining associations suggest that our findings are not entirely explained by socio-behavioural factors, but residual effects may still exist which may explain the associations found. Another problem is that consumption of alcohol, coffee, and tobacco was assessed by questionnaires. Questionnaires are subject to reporting bias, with people often underreporting their daily use.[34] Yet, most likely, this will have led to an underestimation of the true effects of substance consumption on gait. Furthermore, our participants were required to undergo gait assessment at the research centre. Hence, generalizability of our study may be restricted to a relatively healthy population.

To the best of our knowledge, this is the first study to investigate associations of alcohol, coffee, and tobacco consumption with the gait pattern in the general population. Previous studies have investigated the relation of substance abuse and used different gait measures, complicating comparison of our findings to theirs.[26] We found that drinking one to three glasses of alcohol daily was associated with better Global Gait and gait velocity. Additionally, we found a quadratic relationship of alcohol drinking with Global Gait, corresponding to the relationship of alcohol drinking with cardiovascular disease, disability, and mortality.[3, 5] This relationship supports a possible positive effect of drinking alcohol in moderate amounts on health.[5] Drinking more than one cup of coffee per day associated with better Global Gait and gait velocity. In contrast to alcohol, this relationship did not seem to be quadratic, suggesting a general beneficial effect of coffee consumption on gait and health. However, the weak associations of drinking any amount of coffee versus none indicate a possible threshold effect, with only drinking over one cup of coffee per day relating to better health. Current smoking related to worse Global Gait and gait velocity. In contrast to current smoking, no associations were found for past smoking. This lack of associations may be due to less exposure or recovery from part of the alleged damage done by smoking. In support of this suggestion, we found a higher amount of pack-years of smoking to associate with worse gait velocity.

The clinical importance of our findings is emphasised by our results for gait velocity, which

is a strong predictor of survival.[24] All of alcohol, coffee, and tobacco consumption associated with gait velocity, even after mutual adjustment.

The possible effect of alcohol, coffee, and tobacco consumption on gait may be explained by several pathways and mechanisms. Various components of alcoholic beverages, coffee, and smoking, e.g. alcohol, polyphenols, caffeine, nicotine, and others, have been found to affect many organ systems, including the cardiovascular, central nervous, and musculoskeletal system.[1-8, 10] Better cognition, e.g. executive functioning or attention, less cardiovascular disease, or greater muscle strength may provide the pathways through which substance consumption affects gait.[16-20] To investigate involvement of the cardiovascular and central nervous system, we adjusted for cardiovascular risk factors and MMSE in additional models. The attenuation of associations after adjustment indeed suggests some involvement of these organ systems. However, remaining associations may suggest that other organ systems are also involved. Future research should investigate the possible pathways for effects of substance consumption on gait in more detail, including mediation by other organ systems.

When investigating associations of gait domains, alcohol drinking weakly associated with better Rhythm (quicker steps) and Phases (less double support) at light to moderate amounts. These associations indicate that alcohol drinking increases gait velocity due to taking quicker steps and spending less time in double support. However, because all domain-specific associations were relatively weak, moderate alcohol drinking most likely has a general beneficial effect on gait, which is spread across all gait domains.

We found that drinking especially large amounts of coffee (>3 cups) associated with better Variability (less gait variability), Pace (larger steps), and Turning (less turning time). The association with Pace suggests that coffee drinking mainly increases gait velocity through larger step size. Yet, associations of coffee drinking with Variability and Turning are especially important, because both are strongly related to the risk of falling.[23, 35] Therefore, the observed associations suggest that drinking coffee may reduce the risk of falls and thereby fall-related morbidity and mortality.

Current smoking associated with worse Rhythm and Pace. Additionally, more pack-years of smoking associated with worse Phases and Pace. These associations show that smoking mainly relates to gait velocity, constituted by slower and smaller steps with longer double support.

Conclusions

In a community-dwelling population, drinking coffee and moderate amounts of alcohol associates with better gait, while current smoking is related to worse gait. Future studies should

investigate whether interventions targeting substance consumption may aid in reducing or preventing gait deterioration, and thereby prevent related health problems.

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Chapter 4.4

Gait patterns in Chronic Obstructive Pulmonary Disease

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Abstract

Background: Gait disturbances are a potential systemic manifestation of chronic obstructive pulmonary disease (COPD), which may lead to disability and falls in patients with COPD. Although walking endurance tests are extensively performed in patients with COPD, studies assessing the gait pattern including gait kinematics, are sparse.
Objectives: To investigate associations of COPD and lung function parameters with various gait domains and to explore a potential link with falling.
Methods: Cross-sectional analysis within the Rotterdam Study, a prospective population-based cohort study in persons aged ≥ 55 years. Spirometry was used to assess lung function and confirm the diagnosis of COPD. Gait was measured using an electronic walkway and summarized into seven gait domains: Rhythm, Phases, Pace, Base of Support, Tandem, Turning, and Variability.
Results: Persons with COPD (n = 196) exhibited worse Rhythm (z-score -0.21, 95%CI: -0.36; -0.06) compared to persons with normal lung function (n = 898) independent of age, sex, height, primary education, smoking and use of analgesics. This effect was most pronounced in COPD persons with dyspnea and severe airflow limitation or frequent exacerbations (GOLD D, -0.83 SD, 95%CI: -1.25; -0.41). Similarly, all lung function measurements except FVC associated with Rhythm. Additionally, FEV1 associated with Pace, FVC with Pace and Phases, FEV1/FVC with Phases, and DLCOc with Pace and Turning. Fallers with COPD had significantly worse Rhythm compared to non-fallers with COPD, fallers without COPD, and non-fallers without COPD.
Conclusions: This study demonstrates that people with COPD have worse Rhythm, especially fallers with COPD. Additionally, impaired lung function parameters and frequent exacerbations associated with worse gait. These results suggest that COPD may affect gait quality in addition to walking endurance.

Introduction

Worldwide, COPD is a leading cause of morbidity and mortality.[1] COPD is primarily characterized by persistent airflow limitation that is associated with an abnormal inflammatory response of the lungs to noxious particles or gases.[2] However, its systemic effects also have an important impact on symptoms and prognosis.[1] Even in COPD patients with mild disease severity, cardiovascular comorbidities and muscle weakness precede the development of functional limitations.[3] Since COPD also affects function and mobility, persons with COPD have an increased risk of falling.[3-8] Falling is a major health concern, representing one of the main causes of pain, disability and death in the elderly.[7, 9] Even without injuries, a fall can negatively impact the quality of life of an individual through fear of falling, which often inhibits performing activities.[10]

Poor gait is one of the main risk factors of falls and an important indicator of general health.[11-13] Gait is affected by various organ systems, such as the central nervous system, cardiovascular system, and musculoskeletal system, and poor gait is a strong risk factor of death.[14-18] COPD may affect gait through any of these systems by inducing hypoxia or systemic inflammation.

Gait is a complex concept that can be assessed using many parameters, which can be summarized into seven gait domains.[17] As of yet, COPD has mostly been associated with a shorter walking distance. Associations of COPD and lung function parameters with specific gait domains may give an indication of the pathways underlying their associations with gait. In turn, this knowledge may aid in identifying better intervention strategies to prevent future falling in patients with COPD.

The aim of this study was to investigate the associations of COPD and lung function parameters with various gait domains, in a community-dwelling population. Moreover, we evaluated the influence of COPD severity by airflow limitation, symptoms and/or frequent exacerbations. Additionally, we explored a potential link between gait differences in COPD and falling.

Methods

Setting

The present study is embedded within the Rotterdam Study (RS), a population based cohort study aimed at assessing the occurrence and risk factors of chronic diseases in the elderly.[19] The study was initiated in 1990 (RS-I), when all inhabitants aged ≥55 of the suburb Ommoord, in Rotterdam, were invited to participate. This study was extended in 2000 (RS-II) and another time in 2006 (RS-III), this last time inviting all inhabitants aged ≥45. At baseline and

every 3 to 4 years of follow-up participants undergo a home interview and medical examinations at the research centre, including spirometry. From March 2009 onwards, gait assessment has been implemented in the core protocol.[19] The home interview included standardized questionnaires on smoking including cumulative smoking history and history of falls in the past 12 months. The present study comprises all participants from the first two cohorts (RS-I and RS-II) who completed gait assessment and spirometry successfully until December 2011. The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. A written informed consent was obtained from all participants.

Assessment of lung function parameters and COPD

Spirometry and diffusing capacity were performed using a Master Screen® PFT Pro (CareFusion, San Diego, CA) by trained paramedical personnel according to the ATS/ERS guidelines.[20, 21] The diagnosis of COPD was based on an obstructive spirometry examination according to the modified Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [proportion of the forced vital capacity exhaled in the first second (FEV1/FVC) < 70%] and classified into mild and moderate/severe airflow limitation by forced expiratory volume in one second (FEV1)% predicted of ≥ 80%, <80% respectively.[22, 23] Furthermore, participants with COPD were also classified according to the updated GOLD group categorization into group A (low risk, less symptoms), B (low risk, more symptoms), C (high risk, less symptoms) and D (high risk, more symptoms).[1] Exacerbations were counted as the total number of moderate and severe exacerbations in the year 2010. Frequent exacerbators were defined as COPD persons having at least two moderate or severe exacerbations.

Gait assessment

Gait was assessed with a 5.79 m long electronic walkway with 1.27 cm wide pressure sensors (4.88 m active area; GAITRite Platinum; CIR systems Inc., Sparta, New Jersey USA).[17] The walkway checked for activation of the pressure sensors at 120Hz. The standardized gait protocol includes three different walking conditions (Figure 1): normal walk, turn and tandem walk. In normal walk, participants were asked to walk at their usual pace across the walkway, until they were of the walkway. The normal walk was performed four times in both directions (eight recordings). In turn, participants were asked to walk at their usual pace across the walkway, turn halfway and return to their starting position (one recording). In tandem walk, participants were asked to walk tandem (heel-to-toe) over a line visible on the walkway until they were off the walkway (one recording). The first recording of the normal walks was considered a practice walk and not included in the analyses.

All gait parameters from the normal walk were automatically quantified by the walkway

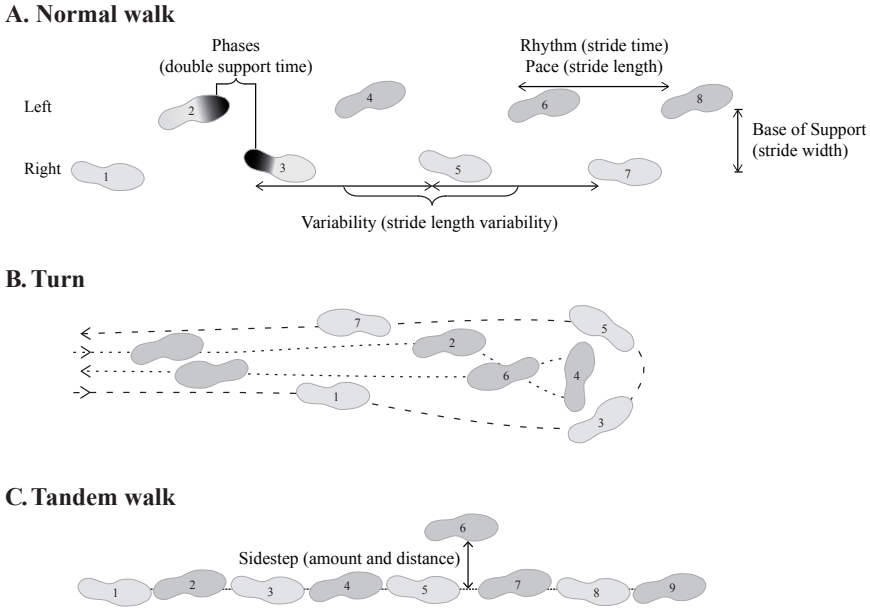

Figure 1: The three walking conditions, including the five gait domains of normal walking. The gait domains of normal walking are visualized using constituting gait parameters, which are mentioned in parenthesis. For turn, only the feet used in the calculation of turning time and turning step count are numbered. Turning time was calculated as the time between foot off of foot 1 until first contact of foot 7. Turning step count was calculated as the number of steps in the turn minus one. In this figure, turning step count would be five.

software. Parameters were quantified for both steps and strides, e.g. step length is the distance between two opposite feet on the line of progression, while stride length is the distance between two feet of the same side on the line of progression. Variability measures were quantified as standard deviations of the gait parameters among steps or strides. Turning time was calculated from the walkway generated data as the time between foot off of the first foot and first contact of the last foot (Figure 1). Turning step count was calculated as the automatically quantified number of steps in the turn minus one. Errors in tandem walking were calculated as the distance of sidesteps from the line and the surface of these sidesteps, with aid of the automatically generated surface and distance parameters from the walkway software. Additionally, we scored the number of double steps, i.e. two consecutive steps with the same foot on the line, as errors in tandem walking.

As previously described, principal components analysis was used to summarize 30 gait parameters, including 25 from normal walking, 2 from turn and 3 from tandem walking,

into fewer independent gait domains, while capturing the largest amount of variance. Each gait domain had to explain at least as much variance as a single gait parameter. Varimax rotation was used to ensure that the gait domains were mutually independent. We found seven independent gait domain: Rhythm, Variability, Phases, Pace, Tandem, Turning and Base of Support.[17] Among others, Rhythm reflects cadence and stride time; Variability reflects stride length and time variability; Phases reflects double support time and double support as a percentage of the gait cycle; Pace reflects stride length and velocity; Tandem reflects errors in tandem walking; Turning reflects the number of turning steps and turning time; and Base of Support reflects stride width and its variability. Finally, Global Gait was calculated by summing all gait domains, dividing by the number of gait domains, and subsequently calculating a new z score.[15] To facilitate interpretation of our findings, we additionally included the two most commonly assessed gait parameters, velocity and cadence, and the highest constituting gait parameters of the three domains strongest associated with COPD and lung function: single support time for Rhythm, stride length for Pace, and single support percentage for Phases. Single support time reflects the absolute time (in seconds) that a person supports on one leg during one stride, while single support percentage reflects the relative time (in %) that a person supports on one leg during one stride. For interpretation, lower velocity, cadence, stride length and single support percentage is considered worse gait, while lower single support time is considered better.

Statistical analyses

Differences between persons with and without COPD were studied using Mann-Whitney U test for continuous variables and Chi-Square test for categorical variables. Univariate ANCOVAs and linear regression analyses were used to investigate associations of COPD and lung function respectively, with the gait domains. Age, sex, height, weight, primary education, MMSE, pack years and use of analgesics (N02) within 90 days preceding gait assessment were considered as potential confounders and models were adjusted for those showing trends of an association with both COPD and gait ($p<0.10$). Models including tandem walk were additionally adjusted for step count and mean step length. We repeated these analyses to investigate associations of lung function and COPD with velocity, cadence, stride length, single support time and single support percentage. For gait domains that associated with COPD, we further investigated an association with falls by univariate ANCOVAs. Since cognition has been shown to be very strongly associated with gait, we performed a sensitivity analysis repeating all analyses additionally adjusted for MMSE. In this way we could whether any of our associations were the result of residual confounding by cognition. Statistical analyses were performed using SPSS, version 20.0 for Windows (IBM, North Castle, NY).

Results

Between March 2009 and December 2011, 1791 participants were invited for gait assessment. Of these, 199 participants did not perform all walking conditions for the following reasons: 152 for physical inability, 36 for technical reasons, and 11 for refusal. Of remaining 1592 participants, 182 had to be excluded for technical reasons, 26 for completing less than 16 steps in the normal walks, lowering validity of the measurements[24], 7 for not following instructions, and 2 for using walking aids. Of the 1375 participants with complete and valid gait data, 1247 had interpretable spirometry data available. Of these, participants with a restrictive spirometry (n=46) or asthma (n=107) were excluded. Baseline characteristics of the study population (n=1094) are presented in Table 1. Among participants, 196 (17.9%) persons had COPD (96 mild COPD and 100 moderate to severe COPD). COPD persons were slightly

Table 1. Baseline characteristics of the study population.

Characteristic	No COPD (n = 898)	COPD (n = 196)	p-value[a]
Age [years]	74.2 (5.2)	75.5 (5.5)	0.003
Sex [females]	483 (53.8)	76 (38.8)	<0.001
Height [cm]	167.3 (8.9)	170.5 (8.9)	<0.001
Weight [kg]	76.2 (12.7)	80.8 (18.7)	0.877
Body Mass Index [kg/m^2]	27.2 (3.7)	26.6 (3.7)	0.049
Primary education [n]	89 (10.1%)	33 (17.1%)	0.013
MMSE-score [points]	27.9 (1.8)	27.8 (1.9)	0.957
Past smoker [n]	508 (56.6%)	125 (63.8%)	<0.001
Current smoker [n]	67 (7.5%)	35 (17.9%)	<0.001
Pack-years [pack-years]	12.6 (18.3)	25.2 (25.9)	<0.001
Analgesics [n]	37 (4.1%)	14 (7.1%)	0.051
Velocity [cm/s]	118.2 (18.3)	115.1 (19.1)	0.122
FEV1 [%]	110.9 (16.3)	80.8 (18.7)	<0.001
FVC [%]	111.9 (16.7)	99.2 (20.9)	<0.001
FEV_1/FVC [%]	78.6 (4.7)	63.4 (6.0)	<0.001
$DL_{CO,c}$ [%][b]	97.5 (15.3)	89.1 (18.5)	<0.001
$DL_{CO,c}$/Va [%][b]	111.6 (17.2)	105.3 (21.1)	<0.001

Categorical variables are expressed as numbers of participants (percentages). Values of continuous variables are expressed as means (standard deviations).

[a] p-values for differences between participants with COPD and without COPD, adjusted for age and sex (if applicable).

[b] Total n = 942.

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; $DL_{CO,c}$, diffusing capacity of the lungs measured using carbon monoxide and corrected for the hemoglobin concentration; FEV_1, forced expiratory volume in one second; FEV_1/FVC, proportion of the forced vital capacity exhaled in the first second; MMSE, mini–mental state examination; Va, alveolar volume.

Table 2. Associations between COPD, lung function and the gait domains, adjusted for potential confounders.

	COPD	FEV1 (/10%)	FEV1/FVC (/10%)
Global Gait	0.02 (-0.14; 0.17)	**0.05 (0.03; 0.08)**	-0.01 (-0.09; 0.07)
Rhythm	**-0.21 (-0.36; -0.06)**	**0.04 (0.01; 0.07)**	**0.11 (0.04; 0.19)**
Variability	0.11 (-0.05; 0.27)	0.00 (-0.03; 0.03)	-0.04 (-0.13; 0.04)
Phases	0.12 (-0.03; 0.28)	0.01 (-0.02; 0.04)	**-0.10 (-0.18; -0.02)**
Pace	-0.05 (-0.19; 0.08)	**0.06 (0.04; 0.09)**	0.02 (-0.04; 0.09)
Tandem[a]	0.00 (-0.16; 0.15)	0.03 (0.00; 0.06)	0.05 (-0.03; 0.13)
Turning	0.03 (-0.13; 0.20)	0.00 (-0.03; 0.03)	-0.01 (-0.10; 0.07)
Base of Support	0.04 (-0.12; 0.20)	-0.01 (-0.04; 0.03)	-0.05 (-0.13; 0.04)
	FVC (/10%)	$DL_{CO,c}$ (/10%)	$DL_{CO,c}$/Va (/10%)
Global Gait	**0.08 (0.04; 0.11)**	**0.05 (0.01; 0.08)**	0.02 (-0.02; 0.05)
Rhythm	0.03 (-0.01; 0.06)	**0.06 (0.03; 0.10)**	**0.06 (0.03; 0.10)**
Variability	0.01 (-0.02; 0.05)	0.01 (-0.03; 0.05)	0.02 (-0.02; 0.05)
Phases	**0.04 (0.00; 0.07)**	0.00 (-0.04; 0.04)	-0.03 (-0.07; 0.00)
Pace	**0.08 (0.05; 0.11)**	**0.07 (0.03; 0.10)**	0.03 (0.00; 0.06)
Tandem[a]	0.03 (-0.01; 0.06)	0.00 (-0.04; 0.04)	-0.01 (-0.04; 0.03)
Turning	0.01 (-0.03; 0.05)	**-0.05 (-0.09; -0.01)**	-0.03 (-0.07; 0.00)
Base of Support	0.00 (-0.03; 0.04)	0.02 (-0.02; 0.06)	0.01 (-0.03; 0.05)

Values represent differences in standard deviations of gait (95% Confidence Interval). Values in bold survived thresholds of nominal significance ($p < 0.05$). A lower value of gait represents worse gait. All analyses were adjusted for age, sex, height, primary education, pack-years and use of analgesics.

[a] Additionally adjusted for the step count and step size within the tandem walk.

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; FEV_1, forced expiratory volume in one second; FEV_1/FVC, proportion of the forced vital capacity (FVC) exhaled in the first second; $DL_{CO,c}$, diffusing capacity of the lungs measured using carbon monoxide and corrected for the hemoglobin concentration; Va, alveolar volume.

older, less often female, smoke(d) more frequently and presented with worse lung function parameters.

We found COPD to associate with lower Rhythm (-0.21 SD [95%CI: -0.36; -0.06], Table 2) independent of age, sex, height, primary education, pack-years of cigarette smoking and use of analgesics. Regarding the lung function parameters, higher FEV_1 associated significantly with higher Global Gait, Rhythm and Pace; higher FEV_1/FVC with higher Rhythm but lower Phases.(Table 2) Additionally, higher FVC associated significantly with higher Global Gait, Phases and Pace; higher diffusing capacity $DL_{CO,c}$ with higher Global Gait, Rhythm and Pace but lower Turning; and higher $DL_{CO,c}$/Va with higher Rhythm.(Table 2)

Regarding the influence of disease severity, COPD persons with moderate/severe airflow

limitation significantly related to lower Rhythm compared to persons without COPD.(Table 3) Both COPD with and without frequent exacerbations associated with lower Rhythm, with the effect size for COPD with frequent exacerbations being four times larger than for COPD without frequent exacerbations (-0.65 SD [95%CI: -1.04; -0.27] compared to -0.16 SD [95%CI: -0.31; 0.00] respectively, Table 3).

Figure 2 represents the gradual decrease of the age and sex-adjusted Z-scores of walking Rhythm over the GOLD 2011 categories. GOLD group C and D were significantly related

Table 3. Stratified analyses of the associations between COPD and the gait domains, adjusted for potential confounders.

	Mild COPD	Moderate/severe COPD	Infrequent exacerbator	Frequent exacerbator
Global Gait	0.14 (-0.06; 0.34)	-0.11 (-0.32; 0.09)	0.05 (-0.11; 0.21)	-0.23 (-0.63; 0.17)
Rhythm	-0.16 (-0.35; 0.04)	**-0.27 (-0.46; -0.07)**	**-0.16 (-0.31; 0.00)**	**-0.65 (-1.04; -0.27)**
Variability	0.06 (-0.15; 0.27)	0.17 (-0.04; 0.39)	0.09 (-0.07; 0.26)	0.26 (-0.16; 0.68)
Phases	0.06 (-0.14; 0.27)	0.18 (-0.03; 0.39)	0.12 (-0.04; 0.28)	0.13 (-0.28; 0.54)
Pace	0.06 (-0.11; 0.23)	-0.17 (-0.35; 0.00)	-0.03 (-0.16; 0.11)	-0.30 (-0.65; 0.05)
Tandem[a]	0.16 (-0.04; 0.37)	-0.18 (-0.39; 0.03)	-0.02 (-0.18; 0.15)	0.10 (-0.32; 0.51)
Turning	0.20 (-0.01; 0.42)	-0.14 (-0.36; 0.07)	0.04 (-0.13; 0.21)	-0.04 (-0.47; 0.39)
Base of Support	-0.04 (-0.25; 0.17)	0.12 (-0.09; 0.34)	0.05 (-0.11; 0.22)	-0.07 (-0.49; 0.36)
	COPD A	COPD B	COPD C	COPD D
Global Gait	**0.26 (0.05; 0.46)**	-0.19 (-0.42; 0.04)	0.02 (-0.56; 0.61)	**-0.48 (-0.92; -0.05)**
Rhythm	-0.06 (-0.26; 0.13)	-0.21 (-0.43; 0.01)	**-0.73 (-1.29; -0.17)**	**-0.83 (-1.25; -0.41)**
Variability	0.11 (-0.11; 0.32)	0.08 (-0.17; 0.32)	0.32 (-0.30; 0.93)	0.15 (-0.31; 0.61)
Phases	**0.30 (0.09; 0.51)**	-0.10 (-0.33; 0.14)	0.33 (-0.26; 0.93)	-0.08 (-0.53; 0.37)
Pace	0.12 (-0.06; 0.29)	-0.18 (-0.38; 0.02)	-0.24 (-0.75; 0.27)	**-0.40 (-0.78; -0.02)**
Tandem[a]	0.02 (-0.19; 0.24)	-0.07 (-0.31; 0.17)	0.17 (-0.44; 0.78)	0.04 (-0.41; 0.50)
Turning	0.08 (-0.14; 0.30)	-0.01 (-0.26; 0.24)	-0.01 (-0.64; 0.62)	-0.01 (-0.48; 0.47)
Base of Support	0.11 (-0.11; 0.32)	-0.04 (-0.28; 0.20)	0.26 (-0.36; 0.88)	-0.13 (-0.59; 0.34)

Values represent differences in z-scores of gait (95% Confidence Interval). A lower value of gait represents worse gait. Values in bold survived thresholds of nominal significance ($p < 0.05$). All analyses were adjusted for age, sex, height, primary education, pack-years, and use of analgesics. COPD was defined as $FEV_1/FVC < 70\%$ and categorized according to the modified Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of airflow limitation 2007 into mild COPD (GOLD1; $FEV_1 \geq 80\%$pred) or moderate/severe COPD (GOLD2&3; $FEV_1 < 80\%$pred) and according to the updated GOLD group categorization 2013. A (low risk, less symptoms), B (low risk, more symptoms), C (high risk, less symptoms) and D (high risk, more symptoms). Exacerbations were counted as the total number of moderate and severe exacerbations in the year 2010. Frequent exacerbators were defined as COPD persons having at least two moderate or severe exacerbations.

[a] Additionally adjusted for the step count and step size within the tandem walk.

Abbreviation: COPD, Chronic Obstructive Pulmonary Disease.

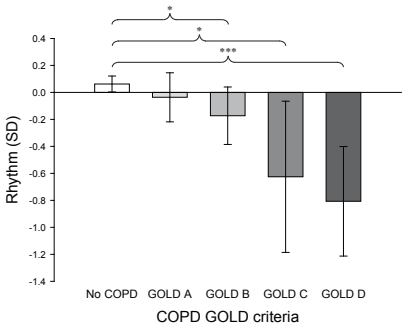

Figure 2: Means of walking Rhythm across the COPD GOLD 2011 categories, adjusted for age and sex. Error bars represent the 95% confidence interval. * p < 0.05 ; ** p < 0.005; ***p < 0.001 by ANCOVA.

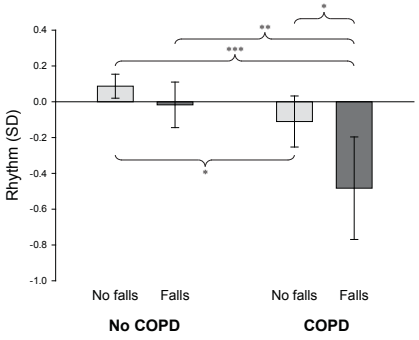

Figure 3: Means of walking Rhythm stratified for COPD and a history of falls, adjusted for age and sex. Error bars represent the 95% confidence interval. * p < 0.05 ; ** p < 0.005; ***p < 0.001 by ANCOVA.

to lower Rhythm and GOLD group D related moreover to lower Global Gait score and Pace compared to persons without COPD.(Table 3) In contrast, GOLD group A associated with higher Global Gait and Pace.

234 (21.4%) participants reported that they had fallen in the past 12 months, including 195 (21.7%) subjects without COPD versus 39 (19.9%) subjects with COPD ($p_{difference}$=0.564). Figure 3 shows Rhythm to be lowest in COPD persons who fell in the previous year. Fallers with COPD had significantly lower Rhythm than fallers without COPD (p=0.004), non-fallers with COPD (p=0.022), and non-fallers without COPD (p<0.001), after adjustment for age and sex. These differences remained significant after additional adjustment for height, primary education, pack-years of cigarette smoking and use of analgesics.

We found a very similar pattern of associations for the original gait parameters as for the gait domains. COPD was associated with a lower cadence and longer single support time. GOLD group A associated with higher velocity, stride length and single support percentage. GOLD groups C and D associated with lower cadence and longer single support time and group D additionally with lower velocity. With regard to lung functions, we found higher FEV_1 to associate with higher velocity and cadence, shorter single support time and larger stride length; higher FEV_1/FVC to associate with shorter single support time but also shorter single support percentage; higher $DL_{CO,c}$ with higher velocity and cadence, shorter single support time and larger stride length; and higher $DL_{CO,c}$/Va to associate with higher cadence and shorter single support time. When additionally adjusting for MMSE, our associations hardly

changed. Only the association of COPD without frequent exacerbations became borderline non-significant (p=0.055).

Discussion

In this large population based cohort study, we demonstrated that COPD and continuous lung function parameters associated with gait. We found COPD to be specifically associated with taking slower steps (lower Rhythm). Moreover, a clinical association between Rhythm and falls according to the COPD status, was observed. Additionally, we found better lung function in all parameters to associate with better gait, especially in Rhythm and Pace.

We are the first study to comprehensively investigate the associations of COPD and lung function parameters with the gait pattern. A lower walking distance during a six-minute walk or shuttle walk test, has been extensively reported in people with COPD; however, literature on gait velocity and other gait deficits is scarce.[8] Our results show that COPD is especially related with taking slower steps (lower Rhythm). This indicates that any slowing in gait velocity is mainly driven by a lower cadence instead of taking smaller steps. This notion was supported by the associations found with the original gait parameters. A possible explanation for this decrease in cadence may be an adaption mechanism to cope with impaired walking endurance due to lack of oxygen supply. Taking slower steps may decrease oxygen need of the leg muscles and thus allow for long distance walking in people with impaired lung function. The lower Rhythm might further result from systemic effects of COPD on the brain, cardiovascular system, muscle strength or bone mineralization.[8, 23, 25-28] Beauchamp *et al.* found that gait deficits in patients with COPD were similar to patients with an elevated fall risk or neuromuscular disease.[5] The increased risk of falling in patients with COPD is thought to be caused by an inability to respond quickly in circumstances of instability.[5] Our finding of an especially low Rhythm in fallers with COPD may reflect this inability, because people who take steps slowly may also be slower at reacting to imbalances. However, further research is needed to determine whether this association of low Rhythm with a history of falling in people with COPD is also reflected in future falling.

The effect of COPD on Rhythm was especially strong in more severe COPD, which is in line with a recent study by Yentes *et al.*[29] Similarly, we found the severest COPD GOLD category to associate with worse Global Gait and Pace. In contrast, GOLD A was related to better Global Gait and Phases. These positive associations may be the result of a healthy selection effect, i.e. GOLD A represents the most healthy people with COPD who may have better gait than the general population.

Our study also demonstrates that continuous lung function parameters associate with gait.

Less airflow limitation (i.e. higher FEV_1) was associated with better Global Gait, Rhythm, and Pace (larger steps). Less airflow obstruction (FEV_1/FVC) associated with better Rhythm, but worse Phases (more double support). The associations of higher FVC and lower FEV_1/FVC with better Phases may indicate that Phases is more related to restrictive lung disorders. A preserved diffusing capacity $_{DLCO,c}$ associated with better Global Gait, Rhythm and Pace, but worse Turning (longer turning time). The latter result suggests that when the lungs transfer less oxygen to the blood and carbon dioxide from the blood, persons have a lower cadence, take smaller steps and more turning steps and time. When dividing the $DL_{CO,c}$ by the alveolar volume, it only remained significantly associated with Rhythm. We found very similar associations of lung function with the original gait parameters, supporting our suggestions.

The main strength of our study is that we for the first time investigated associations of different gait domains, including different walking conditions, with COPD and lung function in a community-dwelling population. Furthermore, we investigated the influence of disease severity – taking into account exacerbations and the updated GOLD categories besides the severity of airflow limitation- on the association of COPD with the gait domains and explored associations of the related gait domain with falling. To cope with confounding, all analyses in our observational study were adjusted for potential confounders that showed a trend of an association with both COPD and gait.[6, 17, 30]

A first potential limitation of this study is that persons with severe COPD and very poor lung function might be less likely to come to the research centre for gait assessment. However, if anything, this selective refusal of participation would have underestimated the strength of association of COPD and worse lung function with gait disturbances. Second, given the cross-sectional analysis and the retrospective interrogation of falls, we cannot infer causality. Consequently, the worse Rhythm in COPD patients may lead to more falls, or, falls in COPD patients may aggravate anxiety and unsecured gait leading to worse Rhythm.[6]

In conclusion, COPD associates with worse gait, especially with taking slower steps, in a community-dwelling population. Additionally, less airflow limitation, more forced vital capacity, and better oxygen diffusion capacity associate with better gait, as especially reflected by quicker and larger steps. Further research should investigate the underlying mechanisms of these associations, to enable development of proper intervention strategies to prevent falling in patients with COPD.

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Chapter 4.5

Asymptomatic radiographic hip osteoarthritis is associated with gait differences, especially in women

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Submitted.

Abstract

Objectives: Hip and knee osteoarthritis (OA) are debilitating diseases that impair gait at severe stages. Although associations between OA and gait are established for normal walking, little is known on its relation with turning and tandem (heel-to-toe) walking. Additionally, it is unknown how asymptomatic OA associates with gait, and whether associations differ by sex. We investigated how symptomatic and asymptomatic hip and knee OA associate with gait in community-dwelling individuals.

Methods: In 2385 participants of the population-based Rotterdam Study, gait was assessed by electronic walkway and summarised into seven gait domains. Hip and knee radiographs were graded for radiographic OA (ROA) using the Kellgren and Lawrence (K&L) score. Linear regressions were used to investigate associations between ROA and gait. Analyses were repeated including only participants with asymptomatic ROA, defined as a K&L-score of 2 without pain.

Results: In total, 154 participants (6.5%) had hip ROA and 493 (16.8%) knee ROA. We found no associations of knee ROA with gait. Hip ROA associated with Rhythm (0.27 SD [95%CI: 0.11; 0.43], p<0.001), Tandem (-0.25 SD [-0.42; -0.07], p=0.005), and Turning (-0.28 SD [-0.46; -0.10], p=0.003). Associations between hip ROA and gait differed significantly between men and women. Hip ROA associated with Tandem and Turning in men, while associating with Rhythm and Base of Support in women. Asymptomatic hip ROA associated with Rhythm and Tandem.

Conclusions: Hip ROA, but not knee ROA, associates with gait differences in normal walking, turning, and tandem walking in community-dwelling individuals. These associations differ between the sexes, and are even present for asymptomatic ROA.

Introduction

Osteoarthritis (OA) is a debilitating disease that limits people in daily functioning, eventually leading to loss of independence.[1, 2] Prevalence of hip and knee OA is high in the elderly (7-30% in people aged ≥65 years) and expected to increase even more due to the aging population and increasing prevalence of obesity.[2-4] Both hip and knee OA are characterised by joint pain and stiffness, which may severely impair locomotion and gait.[5-9]

Gait is an important indicator of health and poor gait associates with higher fall risk and mortality.[10-14] Gait is a complex concept that can be assessed using many parameters. These parameters, as assessed by electronic walkways, can be summarised into seven independent gait domains that comprehensively describe gait.[15, 16]

Of these gait domains, previous studies found hip and knee OA to associate with Base of Support (larger step width), Pace (slower gait velocity), Phases (shorter support on both legs), Rhythm (higher cadence), and Variability (larger gait variability among steps).[5-9] Additionally, OA in only one leg (one-sided OA) was found to associate with larger gait asymmetry.[6-8]

Yet, previous studies included participants with mainly severe and symptomatic OA.[5-9] Little is known on associations of subclinical and asymptomatic OA with gait, which requires investigating a community-dwelling population. Early identification of people with OA may allow for early, and hence expectedly more effective, intervention.[17] Another consideration is that previous studies only focused on associations of OA with gait in normal walking.[5-9] However, the ability to turn and walk tandem may deteriorate earlier with developing OA because of the complex nature of these walking conditions. Additionally, although sex-differences in associations of knee OA with gait have been reported, it is unknown whether sex influences associations of hip OA with gait.[9]

We aimed to investigate associations of radiographic hip and knee OA with gait in normal walking, turning, and tandem walking, in a community-dwelling population. Additionally, we investigated sex-differences in associations of OA with gait.

Methods

Setting

This study was embedded in the Rotterdam Study, a population-based cohort study from the Netherlands.[18] In 1990 and 2000, all inhabitants of Ommoord, a suburb of Rotterdam, aged 55 years and older were invited to participate. In 2006, the cohort was extended by inviting all inhabitants of Ommoord aged 45 years and older. At baseline and every 3-4 years of follow-up, participants undergo a home interview and extensive medical examination at the research centre. From March 2009 onwards, gait assessment was included in the study

protocol. The current study includes all participants that completed gait assessment between March 2009 and December 2011. This study was approved by the medical ethical committee of the Erasmus MC. All participants gave written informed consent.

Assessment of hip and knee OA

Weight-bearing anteroposterior radiographs of knee and hip were obtained as previously described.[19] Hip and knee OA were scored using the Kellgren and Lawrence (K&L) grading system. Radiographic OA (ROA) was defined as a K&L-score of two or higher.[20]

In a sub-population, joint pain was identified with pain homunculi, showing a picture of the front and back of the human body. Participants were asked: "Did you have pain anywhere in your body, for at least half of the days, during the last six weeks?" If answered positively, participants had to mark painful areas with circles. Subsequently, a template was used to assign these areas to 14 different joint pain regions. For the current study, only pain in hip or knee was considered.

We considered a joint to have asymptomatic ROA when having a K&L-score of 2 without pain.

Gait assessment

Details on our gait assessment protocol have been described elsewhere.[16] In short, gait was assessed using a 5.79 meter long electronic walkway (4.88 meter active area; GAITRite Platinum; CIR systems, Sparta, NJ, USA). Participants walked in three walking conditions: normal walk, turn, and tandem walk. In normal walk, participants walked at their usual pace over the walkway. This process was performed eight times, of which the first recording was regarded as a practice walk and excluded from analyses. In turn, participants walked at their usual pace over the walkway, turned halfway, and returned. In tandem walk, participants walked heel-to-toe over a straight line present on the walkway.

Principal components analysis was used to summarise gait (means of both legs) into seven independent domains, as described previously: Base of Support, reflecting stride width and stride width variability; Pace, reflecting step length and velocity; Phases, reflecting double support time and single support phase (single support as a percentage of the gait cycle); Rhythm, reflecting cadence and single support time; Tandem, reflecting errors in tandem walking; Turning, reflecting turning time and turning step count; and Variability, reflecting step length variability and step time variability.[16] To evaluate walking behaviour of a single leg, we used the highest correlating gait parameter from those domains that could be calculated for a single leg: step width variability for Base of Support, step length for Pace, single support phase for Phases, single support time for Rhythm, and step length variability for Variability.[16] We did not assess walking behaviour of a single leg for Tandem and Turning. Gait asymmetry

was calculated as the value on gait parameters of the left leg minus the value on parameters of the right leg.

Study population

Between March 2009 and December 2011, 3242 persons were invited for gait assessment.

Of these, 108 persons did not undergo gait assessment for the following reasons: perceived physical inability (n=52), technical reasons (n=43), refusal (n=11), and other reasons (n=2).

Of the remaining participants, we excluded 34 participants for performing less than 16 steps in normal walks[21], 13 participants for use of walking aids, and one person for not following instructions.

Of 3086 participants with valid gait assessments, 2512 had radiographs available of both hips and/or both knees. Of these, 127 participants were excluded for having a total hip or knee replacement. Of 2385 included participants, 2292 had gradable radiographs available of both hips and 2361 of both knees.

Participants were used in four distinct analyses (see next section). In the first analysis on gait domains, 212 participants were excluded for missing the turn or tandem walk, resulting in 2087 participants included in analyses on hip ROA and 2154 on knee ROA.

In analyses of one-sided hip ROA with gait asymmetry, gait of the osteoarthritic leg, and gait of the non-osteoarthritic leg, 49 participants were excluded for having hip ROA in both legs. Similarly, 182 participants were excluded in analyses of one-sided knee ROA for having knee ROA in both legs. Hence, 2243 participants were included in analyses on one-sided hip ROA and 2179 in analyses on one-sided knee ROA.

Statistical analysis

We performed four distinct analyses to investigate associations of hip and knee ROA with gait.

First, we used gait domains to investigate associations between hip and knee ROA with gait in both legs.

Second, to analyse gait asymmetry, we recoded ROA of hip and knee as 1 if present in the left leg and -1 if present in the right leg. Participants without hip or knee ROA were coded as 0. Hence, positive associations between ROA and gait asymmetry imply that one-sided ROA relates to larger gait asymmetry with higher values of gait parameters in the osteoarthritic leg. In contrast, negative associations imply larger gait asymmetry with higher values in gait parameters of the non-osteoarthritic leg.

Third, to analyse gait in the osteoarthritic leg of participants with one-sided hip or knee ROA, we used gait parameters of the ROA leg for participants with one-sided ROA, and means of both legs for participants free of the respective ROA.

Fourth, in analyses of the non-osteoarthritic leg, we used gait parameters of the leg without ROA for participants with one-sided ROA, and means of both legs for participants without ROA.

Linear regression analyses were used to investigate associations of hip or knee ROA with gait domains, gait asymmetry, gait in the osteoarthritic leg, and gait in the non-osteoarthritic leg. Univariate ANOVAs were used to calculate mean z-scores of gait domains per K&L-score. All analyses were adjusted for age, sex, height, weight, and time interval between radiographic and gait assessment. Analyses on Tandem were additionally adjusted for mean step length and step count in the tandem walk.

Analyses were repeated after sex-stratification and with sex*ROA interaction terms included. To investigate whether associations were driven by gait velocity, all analyses were repeated while adjusting for gait velocity.[6, 7]

To investigate whether associations remained for asymptomatic ROA, analyses were repeated in the sub-population with pain data available, including only participants without ROA or with asymptomatic ROA.

All statistical analyses were performed using IBM SPSS version 21.0.0.1 for Windows.

Results

Participants had a mean age of 65.9 years (Standard deviation [SD] 8.9) and 53.6% were women (Table 1). Of 2385 participants, 512 (21.5%) had ROA. Of these, 112 (4.7%) had ROA in hip only, 358 (15.0%) in knee only, and 42 (1.8%) in both hip and knee. Differences in prevalence of hip and knee ROA between men and women were non-significant.

Table 1. Population characteristics.

	Total (n = 2385)	Men (n = 1106)	Women (n = 1279)
Age, years	65.9 (8.9)	66.6 (9.2)	65.4 (8.6)
Height, cm	169.6 (9.2)	176.5 (6.6)	163.5 (6.4)
Weight, kg	78.7 (14.3)	85.7 (12.6)	72.6 (12.9)
ROA[a] , n	512 (21.5%)	227 (20.5%)	266 (20.8%)
Hip ROA, n	154 (6.5%)	74 (6.7%)	80 (6.3%)
One-sided hip ROA, n	105 (4.4%)	44 (4.0%)	61 (4.8%)
Knee ROA, n	400 (16.8%)	176 (15.9%)	224 (17.5%)
One-sided knee ROA, n	218 (9.1%)	102 (9.2%)	116 (9.1%)

Values are means (standard deviations) or numbers of participants (percentages).

[a] Radiographic hip or knee osteoarthritis.

Abbreviations: n, number of participants; cm, centimetres; kg, kilograms; ROA, radiographic osteoarthritis.

Of 154 participants with hip ROA, 105 (68.2%) had one-sided hip ROA. Of 400 participants with knee ROA, 218 (54.5%) had one-sided knee ROA.

Associations of ROA with gait domains

Hip ROA associated with higher Rhythm (0.27 SD [95% confidence interval: 0.11; 0.43], p<0.001), lower Tandem (-0.25 SD [-0.42; -0.07], p=0.005), and lower Turning (-0.28 SD [-0.46; -0.10], p=0.003) (Table 2).

Table 2. Associations of radiographic hip and knee osteoarthritis with gait.

	Base of Support	Pace	Phases	Rhythm	Tandem[a]	Turning	Variability
Hip ROA	0.13 (-0.05; 0.31)	-0.10 (-0.24; 0.04)	0.04 (-0.12; 0.19)	**0.27 (0.11; 0.43)**	**-0.25 (-0.42; -0.07)**	**-0.28 (-0.46; -0.10)**	-0.09 (-0.27; 0.09)
Knee ROA	0.03 (-0.09; 0.14)	0.04 (-0.06; 0.13)	-0.02 (-0.12; 0.08)	-0.03 (-0.13; 0.08)	-0.11 (-0.23; 0.01)	-0.11 (-0.23; 0.01)	0.06 (-0.06; 0.17)

Values represent differences in z-scores of gait (95% confidence interval) for presence of osteoarthritis in one or two legs. All analyses were adjusted for age, sex, height, weight, and the time interval between radiographic and gait assessment. Results in bold represent nominally significant associations (p<0.05).

[a] Additionally adjusted for the step count and step size within the tandem walk.

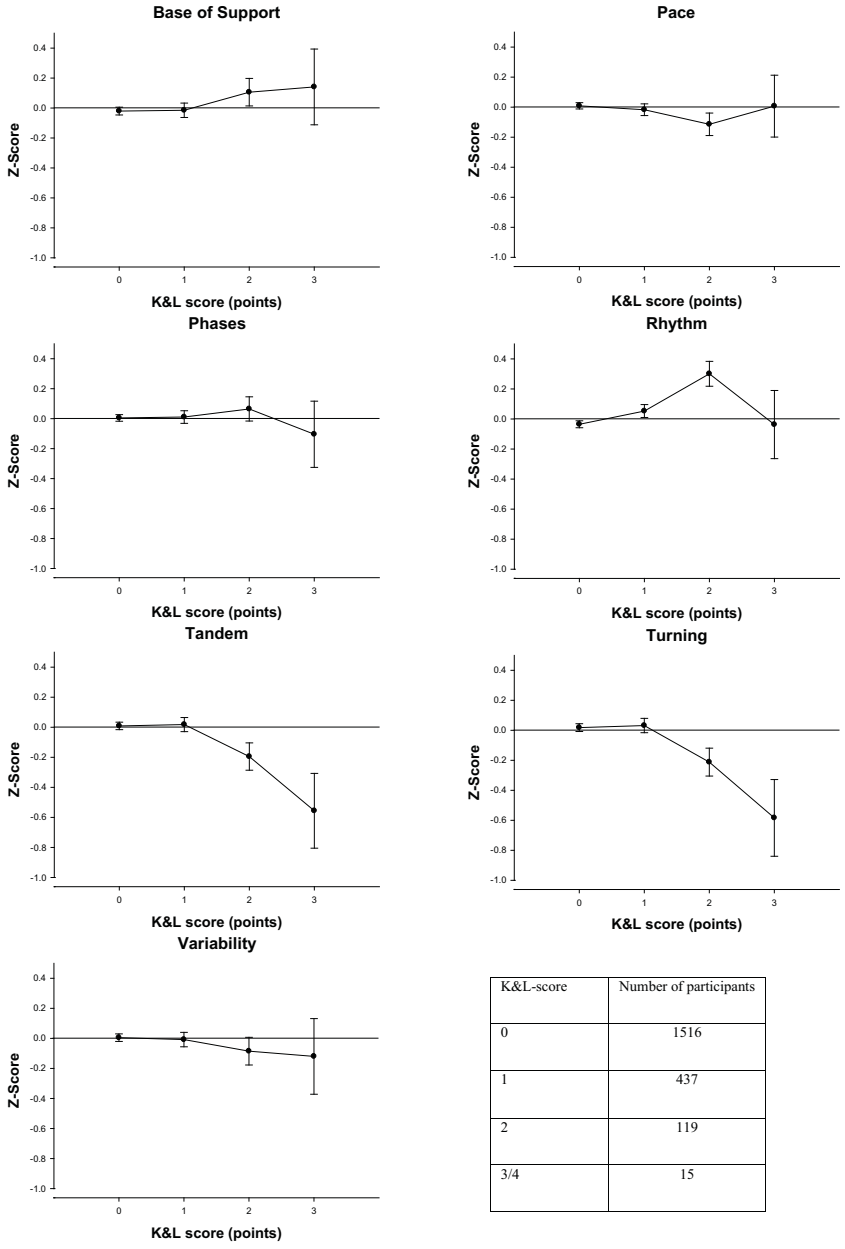
Abbreviations: ROA, radiographic osteoarthritis.

Table 3. Associations of radiographic hip osteoarthritis with gait, stratified for sex.

	Base of Support	Pace	Phases	Rhythm	Tandem[a]	Turning	Variability
Men	-0.01 (-0.29; 0.26)	-0.12 (-0.34; 0.10)	0.11 (-0.11; 0.33)	0.23 (-0.01; 0.47)	**-0.32 (-0.55; -0.09)**	**-0.33 (-0.58; -0.09)**	0.03 (-0.23; 0.28)
Women	**0.27 (0.04; 0.50)**	-0.09 (-0.28; 0.10)	-0.02 (-0.24; 0.19)	**0.30 (0.09; 0.52)**	-0.17 (-0.43; 0.09)	-0.23 (-0.49; 0.03)	-0.21 (-0.45; 0.03)

Values represent differences in z-scores of gait (95% confidence interval) for presence of radiographic hip osteoarthritis in one or two legs. All analyses were adjusted for age, sex, height, weight, and the time interval between radiographic and gait assessment. Results in bold represent nominally significant associations (p<0.05).

[a] Additionally adjusted for the step count and step size within the tandem walk.



K&L-score	Number of participants
0	1516
1	437
2	119
3/4	15

Figure 1. Z-scores of gait domains across Kellgren and Lawrence scores. Dots are means adjusted for age, sex, height, weight, and time interval between radiographic and gait assessment. Error bars represent standard errors of the means.

In Figure 1, higher K&L-scores of the hip are shown to associate with lower Tandem (p-trend=0.03) and Turning (p-trend=0.03), but higher Rhythm (p-trend<0.001). No significant p-trends were found across K&L scores for the other gait domains.

In sex-stratified analyses, hip ROA associated with lower Tandem (-0.32 SD [-0.55; -0.09], p=0.006) and Turning (-0.33 SD [-0.58; -0.09], p=0.008) in men, while associating with higher Base of Support (0.27 SD [0.04; 0.50], p=0.02) and Rhythm (0.30 SD [0.09; 0.52], p=0.005) in women (Table 3).

Knee ROA did not associate with any gait domain, but did demonstrate trends of an association with Tandem (-0.11 SD [-0.23; 0.01], p=0.08) and Turning (-0.11 SD [-0.23; 0.01], p=0.06) (Table 2).

In sex-stratified analyses, we found an association of knee ROA with Tandem (-0.23 SD [-0.40; -0.07], p=0.006) in women (Supplement 1). Additionally, we found this association to be significantly stronger (p=0.005) for women than men.

Adjustment for gait velocity did not change associations for hip or knee ROA.

Associations of one-sided ROA with gait

One-sided hip ROA associated with larger gait asymmetry, with shorter single support time and phase but larger step length in the osteoarthritic compared to the non-osteoarthritic leg (Table 4).

Additionally, one-sided hip ROA associated with shorter single support time and phase of the osteoarthritic leg and larger step length and step length variability of the non-osteoarthritic leg.

When stratifying for sex, all associations described above were present in women (Table 5).

Additionally, one-sided hip ROA associated with larger step length variability of the osteoarthritic leg in women. In men, no associations were found for one-sided hip ROA.

We found significant sex-interactions, with associations of one-sided hip ROA with shorter single support phase of the osteoarthritic (p=0.004) and non-osteoarthritic leg (p=0.03) being stronger in women than men.

One-sided knee ROA did not associate with gait differences (Table 4). Similarly, we found no associations in sex-stratified analyses of one-sided knee ROA (Supplement 2).

Adjustment for gait velocity did not change associations for one-sided hip or knee ROA.

Table 4. Associations of one-sided radiographic hip and knee osteoarthritis with gait.

	SW Variability (cm)	SL (cm)	SS Phase (%)	SS Time (0.1s)	SL Variability (cm)
Asymmetry					
Hip ROA	-0.02 (-0.12; 0.07)	**0.68 (0.21; 1.16)**	**-0.36 (-0.62; -0.11)**	**-0.04 (-0.07; -0.02)**	-0.12 (-0.27; 0.03)
Knee ROA	-0.05 (-0.12; 0.02)	0.24 (-0.09; 0.58)	-0.12 (-0.29; 0.06)	-0.01 (-0.03; 0.01)	0.04 (-0.07; 0.14)
Osteoarthritic leg					
Hip ROA	-0.07 (-0.24; 0.10)	-0.71 (-1.98; 0.55)	**-0.36 (-0.65; -0.08)**	**-0.09 (-0.16; -0.03)**	0.12 (-0.03; 0.28)
Knee ROA	-0.03 (-0.14; 0.09)	0.52 (-0.37; 1.42)	-0.09 (-0.29; 0.11)	0.00 (-0.04; 0.04)	0.01 (-0.10; 0.13)
Non-osteoarthritic leg					
Hip ROA	-0.05 (-0.21; 0.12)	**-1.40 (-2.67; -0.13)**	0.02 (-0.27; 0.30)	-0.05 (-0.11; 0.01)	**0.24 (0.08; 0.40)**
Knee ROA	0.02 (-0.09; 0.14)	0.26 (-0.64; 1.16)	0.03 (-0.17; 0.23)	0.01 (-0.03; 0.06)	-0.02 (-0.14; 0.09)

Values represent differences in gait parameters of asymmetry, osteoarthritic leg, or non-osteoarthritic leg (95% confidence interval) for presence of one-sided ROA versus no ROA of the respective body part. Analyses were adjusted for age, sex, height, weight, and time interval between radiographic and gait assessment. Results in bold represent nominally significant associations ($p<0.05$).

Abbreviations: ROA, radiographic osteoarthritis; SW, stride width; cm, centimetres; SL, step length; SS, single support; s, seconds.

Table 5. Sex-stratified associations of one-sided radiographic hip osteoarthritis with gait.

	SW Variability (cm)	SL (cm)	SS Phase (%)	SS Time (0.1s)	SL Variability (cm)
Asymmetry					
Men	-0.04 (-0.20; 0.11)	0.18 (-0.64; 0.99)	-0.19 (-0.59; 0.21)	-0.03 (-0.07; 0.02)	-0.11 (-0.35; 0.13)
Women	-0.01 (-0.14; 0.12)	**1.03 (0.46; 1.59)**	**-0.49 (-0.82; -0.16)**	**-0.06 (-0.09; -0.02)**	-0.13 (-0.33; 0.07)
Osteoarthritic leg					
Men	-0.03 (-0.30; 0.25)	-0.43 (-2.44; 1.57)	0.09 (-0.32; 0.49)	-0.04 (-0.14; 0.06)	-0.01 (-0.26; 0.24)
Women	-0.10 (-0.31; 0.10)	-1.00 (-2.63; 0.63)	**-0.66 (-1.05; -0.27)**	**-0.13 (-0.21; -0.05)**	**0.24 (0.04; 0.44)**
Non-osteoarthritic leg					
Men	0.02 (-0.26; 0.29)	-0.62 (-2.63; 1.38)	0.34 (-0.07; 0.74)	-0.01 (-0.11; 0.09)	0.10 (-0.14; 0.35)
Women	-0.10 (-0.30; 0.11)	**-2.05 (-3.68; -0.41)**	-0.19 (-0.58; 0.20)	-0.08 (-0.16; 0.01)	**0.36 (0.15; 0.56)**

Values represent differences in gait parameters of asymmetry, osteoarthritic leg, or non-osteoarthritic leg (95% confidence interval) for presence of one-sided radiographic hip osteoarthritis versus no radiographic hip osteoarthritis. All analyses were adjusted for age, sex, height, weight, and the time interval between radiographic and gait assessment. Results in bold represent nominally significant associations ($p<0.05$).

Abbreviations: SW, stride width; cm, centimetres; SL, step length; SS, single support; s, seconds.

Associations of asymptomatic ROA with gait

Of 2385 participants, 1909 (80.0%) had pain data available, including 80 participants with hip ROA and 288 with knee ROA. Of these, 60 (75.0%) participants had asymptomatic hip ROA and 177 (61.5%) asymptomatic knee ROA.

After restriction to asymptomatic ROA, hip ROA remained significantly associated with Rhythm, Tandem, and single support time of the osteoarthritic leg in the overall population. In women, hip ROA remained significantly associated with Rhythm, larger gait asymmetry in single support time and phase, and single support time in both the osteoarthritic and non-osteoarthritic leg.

No associations remained for asymptomatic knee ROA.

Discussion

Our study shows that hip ROA associates with gait in a community-dwelling population. We found this relation to remain when restricting to asymptomatic hip ROA. Hip ROA associated with gait differences in Rhythm, Tandem, and Turning. One-sided hip ROA was associated with larger gait asymmetry, and differences in gait parameters of both the osteoarthritic and non–osteoarthritic leg. Associations between hip ROA and gait were mainly driven by women. Knee ROA only associated with Tandem in women.

Strengths of our study include the population-based setting, assessment of gait in three walking conditions, radiographic classification of OA, investigation of sex-differences, and restriction to participants with asymptomatic OA.

Limitations of our study include the inability to assess gait mechanics, e.g. flexion angles and rotation moments. Additionally, the cross-sectional design precluded investigation of whether gait differences are a consequence of OA, or whether a deviant gait pattern increases the probability of developing (more severe) OA. Finally, gait was assessed at the research centre. Therefore, we may have missed people with severe OA that inhibited them to come to the research centre. Additionally, people with OA that did visit the research centre may have refused gait assessment more often. Hence, our findings may only be generalizable to a relatively healthy population with less severe OA cases.

We found hip ROA to associate with gait differences in a community-dwelling population, even when restricting our osteoarthritic participants to those with asymptomatic hip ROA. Previous studies used clinic-based samples of patients with more advanced and severe hip OA.[6, 7] Our findings imply that hip OA may already impact gait at an early stage, in absence of pain symptoms. Interestingly, not only did hip ROA associate with gait differences in normal

walking, but also in turning and tandem walking. This suggests that assessment of turning and tandem walking may provide additional information to identify people with early-stage hip OA. Previous research has already highlighted the importance of identifying OA at an early stage, to increase effectiveness of interventions to prevent or reduce its progress.[17] Our results suggest that gait assessment may aid in such an early identification of hip OA.

Similar to a previous study, we found hip ROA to associate with taking quicker steps (higher Rhythm).[6] In contrast to that study, we found no association of hip ROA with larger stride width (higher Base of Support) in the overall population, but only in women. Both taking quicker steps and larger stride width have been suggested to be compensatory mechanisms to reduce pain.[6] However, our findings suggest that the quicker steps may instead result from a reduced motion range of the OA hip, because associations remained after restriction to participants with asymptomatic ROA.[6, 22] To the best of our knowledge, we are the first study to report that persons with hip ROA, especially men, have more difficulty in turning and tandem walking. These associations may be especially important, because problems in turning and tandem walking may reflect balance deficits that increase fall risk.[11, 23] Hence, decreased range of hip motion in participants with hip OA may increase fall risk and thus risk of fractures and other related morbidities.

Consistent with previous research, we found one-sided hip ROA to associate with larger gait asymmetry, with shorter single support time and phase but larger step length in the osteoarthritic compared to the non-osteoarthritic leg.[6] The asymmetry in single support time and phase came from shorter single support on the osteoarthritic leg compared to normal, while asymmetry in step length came from shorter step length of the non-osteoarthritic leg. These associations are presumably compensatory mechanisms to avoid load on the osteoarthritic leg, which is supported by their attenuation after restriction to asymptomatic ROA. We found one-sided hip ROA to additionally associate with larger step length variability in the non-osteoarthritic leg. Larger step length variability of the non-osteoarthritic leg may reflect adaptations to unexpected limitation of movement or sudden onset of pain in the osteoarthritic leg. A previous study only found an association with step length variability in the osteoarthritic leg.[7] We found a similar association, but only in women. In general, larger gait variability suggests loss of gait control, and is clinically important through its strong association with the risk of falling.[12, 13]

We found associations of hip ROA with gait to be generally stronger in women than men. Only associations of hip ROA with Tandem and Turning were stronger in men. We found significant sex-interactions, with one-sided hip ROA associating stronger with single support phase of osteoarthritic and the non-osteoarthritic leg in women compared to men. These sex-differences suggest that women may either alter their gait pattern at an earlier stage of hip OA or change their gait pattern to a greater extent as an adaptive mechanism to reduce pain. Alternatively, a certain gait pattern, with higher prevalence in women (e.g. due to different

anatomy of the pelvis), may lead to larger wear and tear of the hip joint, and thus to OA. Notwithstanding the mechanism, these findings suggest that, when using gait to identify hip OA, sex should be taken into account.

In contrast to most previous studies, we only found trends of associations for knee ROA with gait.[5, 6, 8, 9] This discrepancy may be explained by the relatively few participants with severe knee OA in our study. Possibly, knee OA only affects gait at more severe stages, or more power is needed to identify the subtle associations of subclinical knee OA with gait. Otherwise, restricted movement of the knee may be compensated by movement of the hip, while restricted movement of the hip may be harder to compensate, resulting in gait differences at an earlier stage.

Conclusions

In a community-dwelling population, hip OA associates with gait differences in normal walking, turning, and tandem walking. These associations were also found for asymptomatic hip OA, suggesting that gait patterns already change in absence of pain symptoms. One-sided hip OA associates with larger gait asymmetry and gait differences in both osteoarthritic and non-osteoarthritic leg. Associations of hip OA with gait are generally stronger in women than men. These findings suggest that, especially in women, gait assessment could aid in early identification of persons with hip OA.

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Supplement 1. Associations of radiographic knee osteoarthritis with gait, stratified for sex.

	Base of Support	Pace	Phases	Rhythm	Tandem[a]	Turning	Variability
Men	0.04 (-0.15; 0.22)	-0.05 (-0.20; 0.10)	-0.10 (-0.24; 0.05)	-0.14 (-0.29; 0.02)	0.05 (-0.10; 0.20)	-0.11 (-0.28; 0.05)	0.09 (-0.08; 0.26)
Women	0.03 (-0.11; 0.18)	0.12 (0.00; 0.24)	0.06 (-0.08; 0.20)	0.08 (-0.06; 0.21)	**-0.23 (-0.40; -0.07)**	-0.11 (-0.28; 0.06)	0.00 (-0.15; 0.16)

Values represent differences in z-scores of gait (95% confidence interval) for presence of radiographic knee osteoarthritis in one or two legs. All analyses were adjusted for age, sex, height, weight, and the time interval between radiographic and gait assessment. Values in bold represent nominally significant associations (p<0.05).
[a] Additionally adjusted for the step count and step size within the tandem walk.

Supplement 2. Sex-stratified associations of one-sided radiographic knee osteoarthritis with gait.

	SW Variability (cm)	SL (cm)	SS Phase (%)	SS Time (0.1s)	SL Variability (cm)
Asymmetry					
Men	0.00 (-0.10; 0.10)	0.31 (-0.23; 0.84)	-0.06 (-0.33; 0.21)	-0.01 (-0.04; 0.02)	0.00 (-0.17; 0.16)
Women	-0.09 (-0.18; 0.01)	0.17 (-0.25; 0.59)	-0.16 (-0.40; 0.08)	-0.01 (-0.04; 0.01)	0.07 (-0.07; 0.22)
Osteoarthritic leg					
Men	-0.01 (-0.20; 0.17)	0.26 (-1.10; 1.62)	-0.10 (-0.37; 0.18)	0.04 (-0.02; 0.11)	0.02 (-0.15; 0.19)
Women	-0.04 (-0.19; 0.11)	0.77 (-0.43; 1.96)	-0.04 (-0.32; 0.24)	-0.04 (-0.10; 0.02)	0.03 (-0.12; 0.18)
Non-osteoarthritic leg					
Men	-0.01 (-0.19; 0.18)	-0.05 (-1.42; 1.31)	0.02 (-0.25; 0.30)	0.06 (-0.01; 0.13)	0.02 (-0.15; 0.19)
Women	0.06 (-0.09; 0.21)	0.54 (-0.66; 1.74)	0.08 (-0.21; 0.36)	-0.03 (-0.09; 0.03)	-0.04 (-0.19; 0.10)

Values represent differences in gait parameters of asymmetry, osteoarthritic leg, or non-osteoarthritic leg (95% confidence interval) for presence of one-sided radiographic knee osteoarthritis versus no knee osteoarthritis. All analyses were adjusted for age, sex, height, weight, and the time interval between radiographic and gait assessment. Results in bold represent nominally significant associations (p<0.05).
Abbreviations: SW, stride width; cm, centimetres; SL, step length; SS, single support; s, seconds.

Part 5

General Discussion

In this thesis I extended the knowledge on determinants of gait and daily functioning, with a main focus on the role of the nervous system. Gait and daily functioning are important indicators of health, which strongly relate to the risk of future morbidity and mortality.[1-7] Investigation of determinants of gait and daily functioning may enable identification of new intervention targets to prevent deterioration in gait and daily functioning, and thereby related health problems. In this chapter, I describe some methodological considerations of my studies, discuss the main findings, expand on clinical implications, and provide directions for future studies.

Methodological considerations

Study design

All studies reported in this thesis are performed as part of the Rotterdam Study, a population-based cohort study in the Netherlands.[8] Population-based studies are generally less affected by selection bias as compared to clinical-based studies. Hence, findings from this study may be easily generalized to the underlying population. However, since the Rotterdam Study took place in Ommoord, a suburb of Rotterdam that is mainly inhabited by middle-class white individuals, our findings may only be generalizable to similar populations. Furthermore, since the Rotterdam Study is dependent on voluntary participation of individuals, a different selection bias may also exist. People who do not participate in (part of) the Rotterdam Study may be less healthy compared to those who do participate. Therefore, generalization of the findings in this thesis may be limited to relatively healthy individuals.

Another important issue in research is confounding. To tackle this issue in our studies, we assessed an extensive set of covariates at each visit. Subsequently, analyses were adjusted for covariates that were considered to be potential confounders. Yet, residual confounding may still be present, due to unknown confounders or covariates that were not assessed. However, adjustment for potential confounders may also lead to over-adjustment. Potential confounders may also be intermediates or common outcomes in the relationship under investigation. In such circumstances, adjustment for these potential confounders will generally lead to an underestimate of any true underlying associations.

Although fully automated assessments should be free of information bias, information bias may play a role in other types of assessments. In particular, interviews may be influenced by information bias, including both participant-related and researcher-related biases. Participants may answer questions differently due to recall bias, which may result from e.g. diseases experienced by themselves or by family members, or response bias, e.g providing a socially desirable answer. Alternatively, the interviewer's interpretation of the answers provided by the participant may be influenced by e.g. the visual health aspect of the participant. However,

since these biases are not directly related to a specific research question, they may often be non-differential (i.e. not affecting the associations of interest). Furthermore, data processing and analyses were performed blinded for other covariates, reducing the probability of differential information bias. Yet, although we try to restrict the amount of information bias to the lowest possible level, residual differential biases may still exist.

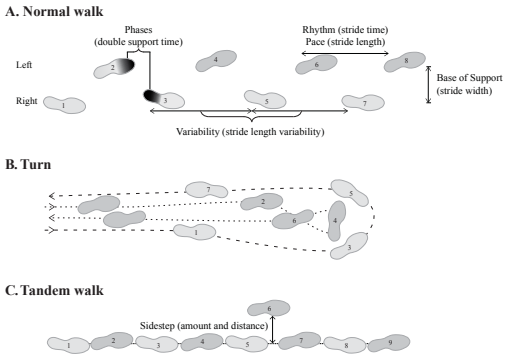
Gait assessment

We used an extensive gait protocol to comprehensively assess the gait pattern, including three walking conditions: normal walking, turning, and tandem (heel-to-toe) walking. This protocol was designed to capture deviating gait patterns related to neurological diseases and adverse health outcomes. Although turning and tandem walking indeed have been specifically linked with neurological disease, e.g. Parkinson's disease, new insights have presented other walking conditions, such as initiation and dual-task walking, which may provide even further information.[9-12] These walking conditions will be introduced in a future gait protocol, not included in this thesis.

Main advantages of our extensive gait assessment protocol include the objective assessment using an electronic walkway with pressure sensors. The walkway detected footfalls using pressure sensors sized 1.27 *1.27 cm, which were checked for activation at 120Hz. Gait assessment by electronic walkway is considered very accurate, and can be used to derive many gait parameters.[13-16]

Unfortunately, different gait parameters have been used interchangeably across studies. This severely complicates direct comparison of findings. Yet, investigation of all parameters would lead to problems with multiple testing. Additionally, many of these gait parameters are mutually correlated, obscuring which gait parameter truly drives an association. These mutual correlations are rarely taken into account, but may complicate understanding of underlying processes. To account for these issues with original gait parameters, we followed the example of several previous studies by summarizing gait parameters (means of both legs) into fewer gait domains, using principal components analysis (PCA).[1, 5, 17]

This PCA resulted in seven independent gait domains that comprehensively capture the gait pattern, explaining 87.3% of the variance among gait parameters (chapter 2.1). We found five gait domains of normal walking: Base of Support, reflecting stride width and stride width variability; Pace, reflecting stride length and velocity; Phases, reflecting the absolute double support time and relative support variables, e.g. double support as a percentage of the stride time; Rhythm, reflecting most temporal variables such as stride time and swing time; and Variability, reflecting variability in both length and time among steps (see Figure). Furthermore, the PCA revealed two separate gait domains for the other walking conditions: Turning, reflecting turning time and turning step count; and Tandem, reflecting errors (sidesteps or



double steps) in tandem walking. The gait domains from normal walking corresponded very well to those found in previous studies, demonstrating their robustness and reproducibility.[1, 5, 17] The separate gait domains for turning and tandem walking suggest that these walking conditions may provide additional information on the gait pattern that is not captured by parameters of normal walking. Importantly, previous studies have shown that worse performance on any of these gait domains, or constituting parameters, associates with a higher risk of falling.[5, 18-22] Furthermore, gait velocity (mainly constituting Pace) is considered a very strong risk factor of death.[6] Worse Rhythm and Variability, and to a lesser extent Pace, have even been associated with an increased risk of dementia.[1] Hence, investigation of all gait domains is important, since deficiencies in any domain may have independent clinical consequences.

Assessment of daily functioning

We assessed daily functioning using two questionnaires: the disability index of the Stanford Health Assessment Questionnaire and the Instrumental Activities of Daily Living scale of Lawton and Brody.[23, 24] The disability index is a very extensive questionnaire including 20 items, e.g. eating and walking, which assesses the more physical and simple basic activities of daily living (BADL). The Instrumental Activities of Daily Living scale is a commonly used questionnaire to assess cognitively more challenging instrumental activities of daily living (IADL), e.g. meal preparation and finance management. Assessment of both BADL and IADL provides a comprehensive picture of how people function in daily living across activities.

However, although the disability index and IADL-scale are extensive and commonly used questionnaires to assess BADL and IADL, they are subject to general questionnaire issues such as reporting bias. People often under- or over-report problems in daily living, leading to inaccurate estimates of true daily functioning. These inaccuracies have most likely led to larger standard errors in our analyses and thus an underestimation of any true underlying associations.

Main findings

Neurological correlates of gait

Both the nervous system and gait are known to deteriorate with age.[17, 25-27] To investigate whether deterioration in the nervous system may also lead to gait differences, it is first important to understand the general aging effects on gait. Research on this subject has mainly been limited to normal walking, while little is known on deterioration in other walking conditions. Furthermore, previous research has solely focused on elderly populations (i.e. 60 years and older) and little is known on when gait truly starts to deteriorate. In chapter 2.1, we show that differences in the gait pattern may already be present at 55-60 years of age. Earliest and strongest deterioration with age were found for Variability, Phases, and Tandem, followed by Pace and Base of Support. Turning was only found to deteriorate at old age (≥80 years), while Rhythm did not deteriorate with age at all. Yet, although these findings clearly demonstrate the deterioration in gait with age, they do not reveal which underlying processes drive these associations.

The concurrent decline in brain functioning, generally measured by cognition, may be an important pathway through which aging leads to gait deterioration.[28, 29] Cognition may be assessed using various cognitive tests, which reflect different cognitive domains, such as memory, executive functioning, fine motor speed, and information processing speed.[30] Various studies have investigated the link between cognition and gait using global cognition scores or gait velocity, but little is known on relations between cognitive and gait domains.[31-33] In chapter 2.2, we investigated associations of global cognition and cognitive domains with the gait domains. To investigate independent associations, we included all cognitive domains in the same models. This resulted in a specific pattern of associations with only executive functioning associating with Pace, fine motor speed with Tandem, and information processing speed with Rhythm. Hence, the speed of thinking relates to how quickly a person steps, the ability to perform fine motor tasks to the ability to walk heel-to-toe, and the ability to complete more advanced cognitive tasks to step size. In contrast, only global cognition associated with Variability, suggesting a general relation with cognition across domains.

The close relationship found between cognition and gait is suggestive of involvement of similar brain regions. Various studies have indeed suggested that some brain structures may influence both cognition and gait.[34-38] However, no study has comprehensively investigated associations of brain structures with both cognition and gait. In chapter 2.3, we used magnetic resonance imaging (MRI) to determine volumes in a wide range of cortical and subcortical grey matter structures. Subsequently, we investigated whether these cortical and subcortical volumes associated with cognition and gait. We found similar patterns of associations for cognition and gait, with particularly subcortical volumes and cortical volumes in the frontal and temporal lobe relating to both cognition and gait. Interestingly, we found cortical volumes to

be specifically associated with executive functioning, Pace, and Variability. In contrast, subcortical volumes showed associations across cognitive domains, Phases, Pace, and Tandem. These findings indicate that cortical and subcortical brain structures may be important for different aspects of cognition and gait. Surprisingly, associations of grey matter structures with cognition and gait were found to be largely independent from each other. Therefore, the close relationship between cognition and gait reported in chapter 2.2 may not be entirely explained by similar involvement of grey matter structures.

The brain, however, also contains white matter. White matter is composed of many different tracts that enable communication among different grey matter structures.[39] Since many grey matter structures are involved in the gait pattern, such communication may be essential for gait. Previous studies have indeed found that damage to the white matter, globally assessed as white matter lesions, may severely impair the gait pattern.[40-42] However, it remains unclear which specific white matter tracts are most essential for proper gait. In chapter 2.4, we used diffusion tensor imaging (DTI) to assess microstructural white matter integrity in specific white matter tracts.[43, 44] We found better microstructural integrity of many white matter tracts to associate with better gait, particularly Phases, Variability, Pace, and Turning. Strongest associations were found of thalamic radiations, followed by association and callosal tracts. Thalamic radiations are involved in the communication among cortices, basal ganglia, and the cerebellum, which has been suggested to be important in motor functioning.[39, 45-48] Associations for association tracts indicate additional importance of direct cortex-to-cortex communication in gait, while associations for callosal tracts indicate importance of interhemispheric communication. Importantly, various associations of these tracts remained, even while adjusting for global microstructural white matter integrity. Hence, these tracts may be essential in gait control, apart from any involvement of global white matter.

Apart from transporting signals within the brain, white matter also transports signals from and to peripheral areas. Pain is such a signal, which may disrupt gait especially when located in the lower body.[49-51] So far, relations of pain in the lower body with gait have only been investigated as part of osteoarthritis, one of the commonest diseases to cause pain in the lower body.[49-51] However, other diseases, such as polyneuropathy, spinal disc herniation, and myopathies, may cause lower body pain with gait deficiencies as a consequence.[52] In chapter 2.5, we showed that pain in the lower body associates with worse Rhythm, Phases, and Pace, independent from osteoarthritis. Furthermore, we found unilateral pain in leg, hip, or foot to associate with larger gait asymmetry. These findings clearly show that lower body pain may have an impact on the gait pattern. However, more research is needed to investigate whether different causes of low body pain have different effects on gait.

Neurological correlates of daily functioning

Similar to gait, daily functioning is affected by dysfunction of the nervous system.[53, 54] Gait and daily functioning are closely related, as many daily activities require walking.[55] However, it is unknown which gait domains are most important to properly function in daily activities. Additionally, although both gait and daily functioning differ by sex, sex-differences in their relationship have not been investigated.[56] We investigated sex-specific associations between gait and daily functioning, using both physical BADL and more cognitive IADL (chapter 3.1). We found a sex-specific pattern of associations with only Pace and Rhythm associating with BADL in men, while all gait domains except Base of Support associated with BADL or IADL in women. These sex-differences may reflect differences in abilities relied upon when performing daily activities. Men may be more dependent on physical strength, which strongest relates to Pace and Rhythm, while women may rely more on other abilities such as cognition, balance, and vision.[1, 57, 58] Indeed, when investigating associations of the Mini-Mental State Examination (MMSE, global cognition) with BADL in the same dataset, we find a significant sex-interaction with a stronger association in women ($p<0.05$). This supports a larger impact of cognition on daily functioning in women than in men.

Dementia is an extreme form of impairment in cognition and daily functioning.[4] Dementia is a devastating disease with a long preclinical phase, in which impairment in cognition and daily functioning gradually develops, eventually leading to clinical symptoms. However, little is known on the temporal sequence of decline in these functions. In chapter 3.2, we investigated trajectories of decline in cognition, assessed by subjective memory complaints and MMSE, and daily functioning, in preclinical dementia. We found that, in preclinical dementia and Alzheimer's disease, people first have memory complaints, already at 16 years before diagnosis, followed by deterioration in global cognition (MMSE), then decline in IADL, and finally decline in BADL. Interestingly, these trajectories strongly differed for vascular dementia. Compared to Alzheimer's disease and all-cause dementia, incident vascular dementia related to earlier deterioration in BADL, but later in cognition. This difference may reflect a difference in (location of) pathology. In Alzheimer's disease this pathology may be more restricted to the hippocampus and temporal lobe, while more global brain pathology may be present for vascular dementia.[30, 59, 60]

We investigated the effects of brain pathology on daily functioning in chapter 3.3, using MRI and DTI to assess structural, e.g. brain volume, and microstructural brain changes, i.e. microstructural white matter integrity. We found smaller brain volume, driven by both grey and white matter, to associate with larger decline in both IADL and BADL, during 6 years of follow-up. Importantly, one standard deviation smaller brain volume yielded a fourfold risk of incident impairment in BADL, corresponding to the effect of 25 years of age. This demonstrates the huge clinical impact brain pathology may have on daily functioning. Additionally,

microstructural brain changes associated with decline in daily functioning above effects of structural brain changes. Hence, brain pathology invisible on conventional MRI may have additional impact on daily functioning, above the effect of brain volume.

In chapter 3.4, we combined findings from chapters 3.2 and 3.3, by investigating the involvement of incipient dementia in the effects of brain pathology on cognition and daily functioning. We found the associations of structural brain changes with decline in MMSE to largely depend on dementia, while those with IADL and BADL did not. These stark differences may indicate differences in underlying brain pathology. The strong link with dementia suggests dementia-related pathology, e.g. amyloid deposition, to be involved in associations of brain changes with MMSE.[61] In contrast, associations of brain changes with daily functioning may derive from different, so far unknown, pathology.

Restless legs syndrome (RLS) may reflect such pathology, although its relation to structural brain changes has been up for debate.[62, 63] RLS is a neurological disorder thought to derive from iron insufficiency in the brain resulting in decreased dopaminergic function, which may lead to impairment in daily functioning.[64, 65] Yet, most symptoms of RLS, i.e. uncomfortable leg sensations and an urge to move the legs, occur at night, and it is unclear whether impairment in daily functioning is due to the syndrome or lack of sleep. Moreover, it is unclear whether RLS also affects objective measures of physical functioning, such as gait and manual dexterity. Indeed, we found no associations of RLS with either gait or manual dexterity. Furthermore, although initially RLS did associate with worse daily functioning, this association disappeared when adjusting for sleep quality. Hence, any possible effect of RLS on daily functioning seems to be mediated by sleep quality.

Genetic, lifestyle, and disease correlates of gait and daily functioning

Since aspects of the nervous system, e.g. cognition, and other determinants of gait are highly heritable, genetics may also have a role in gait.[66-68] In chapter 4.1, we indeed found that various gait domains, particularly Variability, Rhythm, and Tandem, are highly heritable (>30%). Yet, most likely due to low power, we only identified one significant hit in the genome wide association scans (GWAS), namely for single support time (Rhythm). Interestingly, this hit was close to the *LMO4* gene, which encodes the transcriptional regulator Lim-only 4.[69] Loss of *Lmo4* is thought to cause aberrant projections to the spinal cord, in which central pattern generators are located, and may hence affect gait rhythm.[69, 70] However, larger studies are needed to further disentangle the role of genetics in the gait pattern.

In the next chapter (4.2), we focused on a specific set of genetic loci that were previously found to associate with Parkinson's disease (PD).[71] PD is a neurological disease primarily characterized by physical symptoms, which may lead to problems in daily functioning.[72, 73] We investigated whether these risk loci predicted incident PD and whether they associated

with problems in BADL in people without PD, by creating a genetic risk score. Although the genetic risk score associated with the risk of incident PD, it did not substantially improve prediction. Importantly, a higher genetic risk score also associated with a higher probability of problems in BADL for people without PD. This suggests that impact of these risk loci may not be limited to people developing PD, but may also affect people who remain PD-free.

Apart from genetic predisposition, lifestyle may also impact gait and daily functioning. Lifestyle may be divided into many components, including substance consumption. Alcohol, coffee, and tobacco consumption have been found to affect various organ systems, e.g. cardiovascular, nervous, and musculoskeletal system.[74-79] Through any of these organ systems, substance consumption may also influence gait. Indeed, in chapter 4.3, we found that drinking coffee and moderate amounts of alcohol are good for the gait pattern, while smoking is bad. Importantly, since associations remained after adjustment for BADL, these associations do not seem to be driven by reverse causality. Hence, substance consumption may provide a valid intervention target to prevent gait deficiencies, and thereby related health problems.

The respiratory system may be one of the organs through which smoking affects the gait pattern.[80] In chapter 4.4, we investigated whether the respiratory system indeed influences the gait pattern, by assessing Chronic Obstructive Pulmonary Disease (COPD) and lung function. We found COPD to especially associate with worse Rhythm (slower steps), independent from the effects of smoking. Furthermore, we found worse lung function to associate with worse Rhythm and Pace. These associations may reflect an adapted gait pattern to the reduced walking endurance due to less supply of oxygen to leg muscles. A gait pattern with smaller and slower steps may require less oxygen to be performed.

Like the respiratory system, gait also depends on the musculoskeletal system. Osteoarthritis is a musculoskeletal disease of the joints with a pronounced effect on gait.[81-85] Previous studies on associations of osteoarthritis with gait were performed in clinical settings, and therefore the effects of subclinical osteoarthritis on gait remain unknown. In chapter 4.5, we studied associations of radiographic osteoarthritis with gait in a community-dwelling population. Radiographic hip osteoarthritis was found to associate with a worse gait pattern, even in participants without pain (asymptomatic osteoarthritis), suggesting that hip osteoarthritis may already impact gait at a subclinical stage. In contrast, we barely found associations of knee osteoarthritis with gait, suggesting little effect of subclinical knee osteoarthritis on gait.

Clinical Implications

Clinical implications of this thesis may be divided into three parts: the use of assessment of gait and daily functioning to identify underlying pathology, clinical outcomes of poor gait and daily functioning, and possible interventions and treatments to prevent these outcomes.

The role of gait and daily functioning in identification of underlying pathology

In this thesis, I demonstrated that many pathologies and factors influence gait and daily functioning. Gait and daily functioning may therefore be accurate health indicators that can be used to assess health status.[7, 86] Various studies have already suggested the use gait assessment as a marker of health, to determine whether a person should undergo surgery.[87, 88] Furthermore, slow gait speed is already incorporated as a criterion in the definition of frailty, a clinical syndrome that indicates people to be at high risk of adverse events.[89, 90]

Especially gait may also be used to differentiate between different pathologies underlying poor health status. We found large differences among pathologies in their relation to the gait pattern. A clear example is the possible use of the gait pattern to identify hip osteoarthritis. We found subclinical hip osteoarthritis to already demonstrate a different gait pattern compared to persons without osteoarthritis. Moreover, among people with pain in hip or knee, we found hip osteoarthritis to associate with worse Variability (larger gait variability). Together, these findings indicate that the gait pattern may be useful in the identification of early hip osteoarthritis, both in people with symptoms and those without.

The specific associations we found of grey and white matter structures and cognition with the gait pattern suggest that gait may also be used to identify people at higher risk for neurological disease. Furthermore, specific gait patterns may even indicate increased risk of specific neurological diseases, as has been suggested by a previous study.[1] This study found associations of worse Rhythm and Variability with increased risk of all-cause dementia, while Pace specifically related to the risk of vascular dementia.[1] However, more studies are needed to investigate the use of the gait pattern to estimate risk of neurological diseases. In particular large population-based studies with long follow-up and a comprehensive gait assessment may have an important role in unravelling the use of gait as a predictor of neurological disease.

Clinical outcomes of gait and daily functioning

As mentioned previously, deterioration in gait and daily functioning may have devastating consequences. Problems in gait and daily functioning strongly increase the risk of death.[6, 91] Furthermore, a poor gait pattern is strongly related to the risk of falls, which in itself is a major cause of morbidity and death.[5, 21, 92] Gait and daily functioning are closely related, as problems in gait will eventually lead to problems in daily functioning.[55] Problems in daily functioning precipitate loss of independence, which will ultimately lead to institutionalization.[4] Therefore, it is important to prevent or reduce problems in gait and daily functioning, to prevent related health problems.

Interventions and treatments to prevent or reduce decline in gait and daily functioning

Preventing or reducing problems in gait and daily functioning may be achieved in several ways. Adjustment of lifestyle provides a first opportunity to prevent problems in gait and daily functioning. In chapter 4.3 we showed that drinking moderate amounts of alcohol, drinking coffee, and non-smoking relate to better gait. Hence, interventions targeting substance consumption may aid in the prevention of gait problems and subsequent problems in daily functioning. Additionally, previous studies have shown that a larger amount of physical activity may aid in preventing and reducing problems in gait and daily functioning.[93]

Apart from any direct effect on gait or daily functioning, aforementioned prevention methods may also work via prevention of structural and microstructural brain changes or other related pathology. Treatments or interventions targeting pathologies that affect gait or daily functioning, are another way to prevent deterioration in gait and daily functioning. Treatment of cardiovascular risk factors, i.e. hypertension, has been shown to reduce progression of brain changes, and may thereby reduce deterioration in gait and daily functioning.[94, 95] Additionally, this thesis shows that interventions aimed at preventing progression of osteoarthritis, lower body pain, or COPD may aid to prevent gait problems.

A last option for intervention is physical therapy, directly targeting problems in gait and daily functioning. Certain exercise programs have already shown such potential by improving gait or daily functioning.[96, 97]

However, still too little is known on the effects of these interventions on gait and daily functioning. Therefore, more research is needed to identify which methods are most suitable for prevention or reduction of problems in gait and daily functioning.

Directions for future research

Although this thesis provides a broad overview of diseases and organ systems related to gait and daily functioning, much remains unknown. Particularly for gait, most research so far has been performed in smaller clinic-based studies on specific diseases, such as osteoarthritis, Parkinson's disease, or stroke.[81, 98, 99] Also in population-based settings, gait research has mainly focused on neurological disease, brain, and cognition, while other organ systems have rarely been investigated. However, insight into the influence of these organ systems, such as the cardiovascular, musculoskeletal, and vestibular system, on gait, may aid in further understanding why people deteriorate in gait and provide targets for intervention.

The role of the nervous system in gait also requires further investigation. Most research on gait and daily functioning has focused on the central nervous system, and very little remains known on the influence of the peripheral nervous system. Additionally, use of new MRI

technologies, such as functional MRI (fMRI), may aid in further disentangling how the brain controls the gait pattern and daily functioning. Furthermore, more longitudinal studies are needed to determine the temporal relationship of brain pathology with the gait pattern.

Another important topic for future research is the previously mentioned use of the gait pattern to identify people at higher risk for disease, such as dementia, osteoarthritis, and Parkinson's disease. Early identification of people at risk of disease allows for earlier intervention, which may result in better effects. Additionally, more research is needed to investigate the use of gait as a health indicator and predictor of adverse events in general. Although gait speed, mainly constituting Pace, is already included in the definition of frailty and has been found to strongly relate to mortality, much less is known on other gait domains.[6, 89] However, since various other domains have shown specific associations with falls, disability, and disease in our and other studies, they may also aid in better identification of persons at increased risk of adverse events.[5, 21] A previous study also indicated the need for more research investigating the addition of other gait domains to define frailty, to further enhance frailty risk prediction and classification.[100] Yet, as we showed in chapter 3.1, researchers should be aware of potential sex-differences in such use of gait assessment.

Another interesting topic for future research is the identification of measures for "physical or gait reserve". Cognitive reserve is a widely used term for the finding that some people have a lower risk of dementia, either through better pre-morbid levels of cognition or better compensatory capacity of the brain.[101] Conventionally, education is used as such a measure of built up cognitive reserve. Potentially, a similar reserve trait may be present for physical functioning and gait. However, due to the many organ systems involved, the concept may be even more difficult to study for gait than for cognition. Similar to cognition, education may have a reserve role in gait through better pre-morbid gait or better compensatory capacity of the brain. Yet, since gait is a physical function, other factors, such as physical fitness (through exercise or sports) and cartilage thickness in early life, may also provide "gait reserve". Importantly, identification of measures for "gait reserve" may provide intervention targets for early prevention of gait deterioration. However, such measures for "gait reserve" are still undiscovered.

In conclusion, gait and daily functioning are important health indicators that reflect underlying pathology from many organ systems. Brain pathology not only affects cognition but also has large impact on gait and daily functioning. Hence, assessment of gait and daily functioning may have an important role in both neurological and general practice.

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Part 6

Summary / Samenvatting

Summary

The nervous system has a central role in gait and daily functioning, since it integrates signals from many organ systems to facilitate both functions. Damage to particularly the nervous system may therefore have large impact on gait and daily functioning. In turn, deterioration in gait and daily function may have severe consequences, such as loss of independence, institutionalization, morbidities, and even death. Investigation of determinants of both gait and daily functioning may aid in identifying intervention targets to prevent decline in gait and daily functioning, and thereby related health problems.

The aim of the studies in this thesis was to investigate determinants of gait and daily functioning, with a main focus on the nervous system. All studies in this thesis were embedded in the Rotterdam Study, a large prospective population-based cohort study among inhabitants of Ommoord, a suburb of Rotterdam, the Netherlands, aged 45 years and older.

In part 2, neurological correlates of gait are described. We used an electronic walkway to assess gait in three walking conditions, normal walk, turn, and tandem (heel-to-toe) walk, using 30 gait parameters. In chapter 2.1 we investigated whether these many parameters could be summarized into less gait domains and how these gait domains relate to age and sex. Using principal components analysis, we found that the 30 gait parameters could be summarized into seven gait domains. These gait domains included five for the normal walk: Base of Support, Pace, Phases, Rhythm, and Variability, which closely correspond to the domains found in previous studies. Additionally, we identified one domain for turn, Turning, and one for tandem walk, Tandem. With age, earliest and strongest deterioration was found for Variability, Phases, and Tandem, followed by Pace and Base of Support. Additionally, we found Base of Support, Pace, and Rhythm to differ between men and women.

Chapter 2.2 describes associations of cognitive domains with gait domains. In first analyses, we found many cognitive domains to associate with Pace, Rhythm, Tandem, Turning, and Variability. However, when adjusting cognitive domains for each other, we found specific associations with executive functioning relating to Pace, information processing speed to Rhythm, and fine motor speed to Tandem. In contrast, no specific domain associated with Variability and Turning, suggesting a more general relation to cognition.

In chapter 2.3, we studied associations of cortical and subcortical grey matter volumes with cognition and gait. We found similar patterns of associations with particularly subcortical volumes and cortical volumes in the frontal and temporal lobe associating with both cognition and gait. Larger cortical volumes were specifically associated with better executive functioning, Pace, and Variability. In contrast, associations of subcortical volumes were found across most cognitive domains, Pace, Phases, and Tandem. Hence, although similar

grey matter structures may influence both cognition and gait, this influence may be restricted to specific cognitive or gait domains. Chapter 2.4 describes associations of microstructural integrity in specific white matter tracts with gait. We found worse microstructural integrity in nearly all white matter tracts to associate with worse gait, specifically in Pace, Phases, Turning, and Variability. Strongest associations with gait were found for thalamic radiations, association tracts, and callosal tracts. Hence, these tracts may be most important for communication in gait. In chapter 2.5, we showed that lower body pain associates with worse Pace, Phases, and Rhythm, independent from osteoarthritis. Furthermore, we found unilateral leg pain to associate with gait differences in symmetry, painful leg, and unpainful leg.

Part 3 of this thesis describes neurologic determinants of daily functioning. Daily functioning was assessed through both physical basic activities of daily living (BADL) and cognitively more challenging instrumental activities of daily living (IADL). In the first chapter (3.1), we investigated the link between gait and daily functioning. We found a sex-specific pattern of associations with only Pace and Rhythm associating with BADL in men, while all gait domains except Base of Support associated with BADL or IADL in women.

In chapter 3.2 we used a nested case-control sample of over 2300 people to investigate the trajectories in cognition and daily functioning in preclinical dementia. We found people that become demented to first present with memory complaints at 16 years before diagnosis, followed by deterioration in global cognition (Mini-Mental State Examination [MMSE]), IADL, and finally BADL. These trajectories were found to vary for educational level, *APOE*-ε4 carrier status, and dementia subtype. Chapter 3.3 describes associations of structural and microstructural brain changes with decline and incident impairment in daily functioning. We found structural brain changes, in particular smaller brain volume, to associate with larger decline in daily functioning and a higher chance of incident impairment. Additionally, we found microstructural brain changes to associate with larger decline in daily functioning, above any effects of structural brain changes. In chapter 3.4 we combined chapters 3.2 and 3.3 by investigating the role of incipient dementia in associations of structural brain changes with decline in cognition and daily functioning. We found associations of structural brain changes with cognition (MMSE) to be largely driven by incipient dementia, while associations with daily functioning were not.

In chapter 3.5, we investigate associations of restless legs syndrome (RLS) with daily functioning, gait, and manual dexterity. We found no associations of RLS with gait and manual dexterity. Additionally, we found associations of RLS with daily functioning to disappear after adjustment for sleep quality, suggesting any effect of RLS on daily functioning to be largely driven by lack of sleep.

In part 4, we describe associations of genetics, lifestyle factors, and non-neurological diseases

with gait and daily functioning. In chapter 4.1, we showed specific gait domains, namely Variability, Rhythm, and Tandem, to be highly heritable (>30%). In genome-wide association scans, we additionally identified a significant hit, near *LMO4*, that was associated with single support time, the highest correlating gait parameter of Rhythm. In chapter 4.2, we focused on a specific genetic risk score for Parkinson disease (PD), and found this risk score to associate with incident PD. However, the risk score did not improve prediction of PD above traditional risk factors. Importantly, we also found a higher genetic risk score to associate with a higher probability of impairment in BADL in people free of PD. Hence, the genetic risk score may have impact even in a general PD-free population.

In chapter 4.3, we investigated associations of lifestyle factors, namely substance consumption, with gait. We found drinking coffee and moderate amounts of alcohol to associate with better gait, while smoking associated with worse gait. Additionally, we found these associations to be independent from BADL, suggesting that the associations were not driven by reverse causality. In the next two chapters, we investigated associations of two non-neurological diseases with gait. In chapter 4.4, we showed that Chronic Obstructive Pulmonary Disorder associates with worse Rhythm. Additionally, we found worse lung function to associate with worse Rhythm and Pace. Chapter 4.5 describes the associations of hip and knee osteoarthritis with gait. We found hip osteoarthritis to associate with gait differences, especially in women. These associations were even found in people without pain (asymptomatic), suggesting that hip osteoarthritis may already affect the gait pattern at a subclinical stage. In contrast, very few associations were found for knee osteoarthritis, suggesting little effect of subclinical knee osteoarthritis on gait.

Part 5 provides a general discussion of main findings, methodological considerations, clinical implications, and directions for future studies.

Samenvatting

Het zenuwstelsel heeft een centrale rol in het looppatroon en dagelijks functioneren, aangezien het signalen vanuit vele orgaansystemen integreert om zodoende deze functies mogelijk te maken. Schade aan met name het zenuwstelsel kan daarom grote invloed hebben op het looppatroon en dagelijks functioneren. Achteruitgang in zowel het looppatroon als het dagelijks functioneren kan ernstige gevolgen hebben, zoals opname in een verzorgingstehuis, morbiditeit (zoals vallen) en zelfs de dood. Onderzoek naar determinanten van het looppatroon en dagelijks functioneren kan helpen bij het ontdekken van interventie- en behandelingsopties om zodoende achteruitgang in het looppatroon en dagelijks functioneren, en gerelateerde gezondheidsproblematiek, te voorkomen.

Het doel van de studies in dit proefschrift was het onderzoeken van determinanten van het looppatroon en dagelijks functioneren, met name in het zenuwstelsel. Alle studies in dit proefschrift waren onderdeel van de Rotterdam Studie, een grote bevolkingsstudie onder inwoners uit de wijk Ommoord, in Rotterdam, van 45 jaar of ouder.

In deel 2 van dit proefschrift worden neurologische determinanten van het looppatroon beschreven. We hebben gebruik gemaakt van een elektronische loopmat om het looppatroon te onderzoeken in drie loopcondities, de normale loop, omkeerloop, en koorddansersgang (voetje-voor-voetje), door middel van 30 loopparameters. In hoofdstuk 2.1 onderzochten we of deze vele loopparameters konden worden samengevat in minder loopdomeinen en of deze loopdomeinen relateerden aan leeftijd en geslacht. Door middel van een principiële component analyse vonden wij dat de 30 loopparameters konden worden samengevat in zeven loopdomeinen. Van deze loopdomeinen kwamen er vijf uit de normale loop: Fase, Ritme, Stapbreedte, Tempo en Variabiliteit, welke sterk overeenkwamen met loopdomeinen die gevonden waren door voorgaande studies. Buiten domeinen voor de normale loop, vonden we één domein voor de omkeerloop, Omkeren, en één voor de koorddansersgang, Koorddansersgang. De eerste en sterkste achteruitgang met de leeftijd werd gevonden voor de Variabiliteit, Fase en Koorddansersgang, gevolgd door Tempo en Stapbreedte. Verder vonden we dat Ritme, Stapbreedte en Tempo verschillen tussen mannen en vrouwen.

In hoofdstuk 2.2 beschrijven we associaties tussen cognitieve domeinen en loopdomeinen. Eerst vonden we dat veel verschillende cognitieve domeinen associëren met Koorddansersgang, Omkeren, Ritme, Tempo en Variabiliteit. Echter, nadat we de cognitieve domeinen voor elkaar corrigeerden, vonden we zeer specifieke associaties, waarbij executief functioneren relateerde aan Tempo, informatieverwerkingssnelheid aan Ritme en fijne motorsnelheid aan Koorddansersgang. We vonden echter geen specifieke domeinen geassocieerd met Variabiliteit en Omkeren, wat suggereert dat deze sterker relateren aan globale cognitie.

Hoofdstuk 2.3 beschrijft de associaties tussen corticale en subcorticale grijze stof volumina met cognitie en het looppatroon. We vonden sterke associaties van met name subcorticale volumina en corticale volumina in de frontaal- en temporaalkwab met zowel cognitie als het looppatroon. Grotere corticale volumina associeerden specifiek met beter executief functioneren, Tempo en Variabiliteit. Associaties voor subcorticale volumina, daarentegen, werden gevonden voor vrijwel alle cognitieve domeinen, Fase, Koorddansersgang en Tempo. Hoewel dezelfde grijze stof structuren dus zowel cognitie als het looppatroon zouden kunnen beïnvloeden, lijkt deze invloed gelimiteerd tot specifieke cognitieve en loopdomeinen. In hoofdstuk 2.4 onderzochten wij associaties van microstructurele integriteit in specifieke witte stof banen met het looppatroon. Wij vonden dat slechtere microstructurele integriteit in bijna alle witte stof banen gerelateerd was aan een slechter looppatroon, in met name Fase, Omkeren, Tempo en Variabiliteit. De sterkste associaties werden gevonden voor thalamus radiaties, associatie banen en callosale banen. Communicatie door deze witte stof banen lijkt dus belangrijk te zijn voor een goed looppatroon. Hoofdstuk 2.5 beschrijft de associaties van pijn in het onderlichaam met het looppatroon. Wij toonden aan dat onderlichaampijn associeert met een slechter looppatroon in Fase, Ritme en Tempo, onafhankelijk van artrose. Verder vonden we dat pijn in een enkel been associeert met verschillen in het looppatroon wat betreft symmetrie, het pijnlijke been en het niet pijnlijke been.

Deel 3 van dit proefschrift beschrijft de neurologische determinanten van het dagelijks functioneren. Het dagelijkse functioneren werd onderzocht met behulp van fysieke basis activiteiten van het dagelijks leven (BADL) en cognitief meer uitdagende instrumentele activiteiten van het dagelijks leven (IADL). In het eerste hoofdstuk (3.1) onderzochten wij de relatie tussen het looppatroon en het dagelijks functioneren. We vonden een geslachts-specifiek patroon van associaties, met alleen Ritme en Tempo relaterend aan BADL in mannen, terwijl vrijwel alle loopdomeinen associeerden met BADL of IADL in vrouwen.

In hoofdstuk 3.2 maakten wij gebruik van een nested case-control populatie van meer dan 2300 mensen om het traject van achteruitgang in cognitief en dagelijks functioneren in preklinische dementie te onderzoeken. We vonden dat mensen met preklinische dementie als eerste geheugenproblemen ondervonden, al zo'n 16 jaar voor de diagnose, gevolgd door achteruitgang in globale cognitie (gemeten door de Mini-Mental State Examination [MMSE]), in IADL en uiteindelijk in BADL. Verder vonden wij dat deze trajecten van achteruitgang verschillen voor het behaalde onderwijsniveau, *APOE*-ε4 dragerschap en het subtype van dementie. Hoofdstuk 3.3 beschrijft de associaties van structurele en microstructurele breinveranderingen met achteruitgang en incidente beperking in het dagelijks functioneren. We vonden dat structurele breinveranderingen, met name kleinere brein volumina, associëren met een grotere achteruitgang en grotere kans op incidente beperking in het dagelijks functioneren. Daarnaast vonden we dat microstructurele breinveranderingen associëren met

grotere achteruitgang in het dagelijks functioneren, onafhankelijk van structurele breinveranderingen. In hoofdstuk 3.4 combineerden we de hoofdstukken 3.2 en 3.3 door de rol van dementie in de associaties tussen structurele breinveranderingen en achteruitgang in cognitie en het dagelijks functioneren te onderzoeken. We vonden dat associaties van structurele breinveranderingen met achteruitgang in cognitie (MMSE) voor een groot gedeelte verklaard werden door incidente dementie, terwijl dit niet zo was voor associaties met het dagelijks functioneren.

In hoofdstuk 3.5 onderzochten wij de associaties van het restless legs-syndroom (RLS) met het dagelijks functioneren, het looppatroon, en manuele behendigheid. We vonden geen associaties van RLS met het looppatroon en manuele behendigheid. Verder verdwenen de associaties van RLS met het dagelijks functioneren na het corrigeren voor de kwaliteit van het slapen. Daarom zal enig effect van RLS op het dagelijks functioneren met name gedreven worden door een gebrek aan slaap.

In deel 4 bestudeerden wij de associaties van genetica, levensstijl factoren en niet-neurologische ziekten met het looppatroon en het dagelijks functioneren. In hoofdstuk 4.1 vonden wij dat met name bepaalde loopdomeinen, namelijk Variabiliteit, Ritme en Koorddansersgang voor een groot deel erfelijk zijn (>30%). In genome-wide associatie scans vonden wij tevens een significante hit, nabij *LMO4*, welke geassocieerd was met de tijd van het steunen op één been per stapcyclus, de hoogst gecorreleerde loopparameter van Ritme. In hoofdstuk 4.2 concentreerden wij ons op een specifieke genetische risico score voor de ziekte van Parkinson, en vonden dat deze geassocieerd was met incidente Parkinson. Echter, de risico score verbeterde de predictie van Parkinson niet. Het hebben van een hogere genetische risico score associeerde wel met een hogere kans op het hebben van problemen in BADL in mensen zonder Parkinson. Daarom zou de genetische risico score dus ook invloed kunnen hebben in mensen zonder Parkinson.

In hoofdstuk 4.3 onderzochten wij de associaties van levensstijl factoren, namelijk de consumptie van alcohol, koffie en tabak, met het looppatroon. We vonden dat het drinken van koffie en middelmatige hoeveelheden alcohol relateert met een beter looppatroon, terwijl roken slecht is voor het looppatroon. Bovendien vonden wij dat deze relaties onafhankelijk zijn van BADL, wat suggereert dat de relaties niet gedreven werden door omgekeerde causaliteit. In de volgende twee hoofdstukken onderzochten wij associaties van twee niet-neurologische ziekten met het looppatroon. In hoofdstuk 4.4 lieten wij zien dat Chronische Obstructieve Longziekte (COPD) associeert met een slechter Ritme. Daarnaast vonden wij dat een slechtere longfunctie associeerde met een slechter Ritme en Tempo. In hoofdstuk 4.5 toonden wij aan dat heup artrose associeert met verschillen in het looppatroon, met name in vrouwen. Deze associaties werden zelfs gevonden in mensen zonder pijn (asymptomatisch), wat suggereert dat heup artrose het looppatroon al zou kunnen beïnvloeden in een subklinische fase.

Daarentegen werden er vrijwel geen associaties gevonden voor knie artrose, wat suggereert dat subklinische knie artrose weinig invloed heeft op het looppatroon.

Deel 5 betreft een algemene discussie van de belangrijkste bevindingen, methodologische overwegingen, klinische implicaties en onderwerpen voor toekomstige studies.

Part 7

Dankwoord

PhD Portfolio

List of Publications

About the Author

Dankwoord

Het is alweer lang geleden dat ik hier, bij de epidemiologie, als jonge student aan het onderzoek ben begonnen. Op dat moment wist eigenlijk niet eens of ik daadwerkelijk wel onderzoek wou doen, alleen dat ik iets miste binnen de studie geneeskunde. Bij binnenkomst werd mij vrijwel onmiddellijk het "gait" project in de schoot geworpen, een nieuw onderzoeksproject waar eigenlijk niemand iets van wist. Als nieuwsgierige student stortte ik me al snel in de "gait" scene, en hoe langer ik ermee werkte, hoe meer ik aan het project was verknocht. Voordat ik het wist werd ik gevraagd om dit onderzoek te continueren als promotie-traject, een voorstel wat ik natuurlijk niet kon weigeren. Ik heb een fantastische tijd gehad op zowel de 21e als de 28e verdieping en vind het jammer dat deze nu ten einde is. Graag wil ik bij deze iedereen bedanken die een bijdrage heeft geleverd aan de mooie jaren die ik hier heb gehad.

Allereerst wil ik graag mijn promotor prof.dr. Albert Hofman bedanken, zonder wie het onderzoek wat ik heb gedaan nooit mogelijk was geweest. Beste Bert, jouw enthousiasme voor het onderzoek heeft mij erg geïnspireerd en mij laten zien hoe leuk onderzoek kan zijn. Daarbuiten zal ik onze vele goede en vooral ook gezellige gesprekken bij de koffiemachine nooit vergeten.

Eveneens wil ik graag mijn copromotoren dr. Arfan Ikram en dr. Jos van der Geest hartelijk bedanken. Arfan, allereerst natuurlijk bedankt dat je me hebt uitgenodigd om bij de neuro-epidemiologie promotieonderzoek te gaan doen. Onze tweewekelijkse onderzoeksmeetings heb ik altijd als erg leuk ervaren, mede omdat wij daarin onze hoofden over veel methodologische onderwerpen hebben kunnen breken. Van je goede schrijftips en sterke commentaar heb ik erg veel geleerd. Jos, dank voor alle hulp die je mij hebt gegeven bij het analyseren van de eerste stapjes van de loopmat. Ook wil ik je graag bedanken voor alle bemoedigende woorden en de gezellige koffie-gesprekken waarin we over onderzoek, maar ook over vele andere onderwerpen konden praten.

Tevens wil ik prof.dr. Kleinrensink, prof.dr. de Deyn en prof.dr. Bonifati hartelijk danken voor het plaatsnemen in de leescommissie en de bereidwilligheid om tijdens de verdediging te opponeren. Ook de overige leden, prof.dr. Jaddoe en dr. Smits, wil ik ten zeerste bedanken voor het zitting nemen in mijn promotiecommissie.

Daarnaast wil ik graag dr. Vernooij en prof.dr. Breteler bedanken. Meike, ook al was je niet mijn directe begeleider, toch was je altijd erg betrokken bij onze projecten en vaak de eerste om commentaar te geven, dank daarvoor. Ook wil ik je graag bedanken voor het mij leren om hersen MRI's te beoordelen, wat mijn interesse in de radiologie zeker heeft gewekt. Beste

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De Rotterdam Studie was nooit zo'n groot succes geweest zonder de vele deelnemers en gemotiveerde medewerkers, mijn dank voor jullie bereidwilligheid en motivatie. In het speciaal wil ik graag Lydia, Pauli, Charlotte, Marja, Dilan en Hanan bedanken voor hun grote inzet voor het loopmatonderzoek. Na wat opstart problemen in de eerste jaren is het onderzoek door jullie inzet toch een groot succes geworden! Tevens wil ik alle collega's van het datamanagement team bedanken. Beste Jolande, Frank, Nano, Eric en beide René's hartelijk dank voor alle hulp en ondersteuning bij data- en computerproblemen en voor jullie harde werk bij het managen van de enorme hoeveelheid data die de Rotterdam Studie rijk is. Hiernaast wil ik de vrouwen van het secretariaat, m.n. Gabriëlle, Hetty, Erica en Jacqueline, bedankt voor alle hulp in de afgelopen jaren.

Alle co-auteurs wil ik bedanken voor hun commentaar en suggesties, welke mijn artikelen altijd sterker hebben gemaakt. Lies, Marjolein, Hieab en Sirwan, het was erg plezierig om met jullie samen artikelen te schrijven en de resultaten mogen er, mijns inziens, zijn! Jory, naast je uitstekende commentaar op mijn artikelen wil ik je natuurlijk ook danken voor alle tijd en moeite die jij in het introduceren van de loopmat in de Rotterdam Studie hebt gestopt. Marius, dank voor alle uitleg en hulp bij de vele technische beeldverwerkingsaspecten die ik in mijn artikelen gebruikt heb. Prof.dr. Niessen, prof.dr. van der Lugt, dr. van Meurs, prof. dr. Bierma-Zeinstra, prof.dr. Brusselle, prof.dr. Stricker en prof.dr. Tiemeier bedankt voor al jullie opbouwende commentaar en de goede inhoudelijke discussies die we gevoerd hebben.

Natuurlijk wil ik ook al mijn collega-onderzoekers van de epidemiologie bedanken voor de leuke tijden die we samen gehad hebben. Allereerst wil ik graag al mijn huidige en oud kamergenoten, Anke, Ben, Eline, Hieab, Jorge, Lies, Liz, Renée, Renske, Ryan, Saira en Vincent, bedanken voor de altijd even uitstekende kamersferen. Ben, Eline, Hieab, Jorge, Lies, Liz, Renée, and Saira thank you all for all the fun we had at the 21st floor with the facts of the week, Spanish and Dutch lessons, and other brilliant topics. Jorgito, gracias por invitarme a Colombia para visitar, he tenido un tiempo maravilloso y espero de volver a verte otra vez. Hieab and Ryan, thank you both for the great discussions on highly complex methodological topics as well as some of the weirdest topics I've ever encountered. Additionally, I'd like to thank you both for your willingness to help me with any problems I encountered during my research. Daarnaast wil ik ook graag alle andere collega's van de neuro-epidemiologie, Abbas, Ana, Daniel, Elisabeth, Frank, Hazel, Hoyan, Jasper, Jory, Lotte, Mariëlle, Marileen, Michiel, Rens, Saloua, Sirwan, Tavia en Unal, bedanken voor onze vele gezellige meetings, gesprekken en uitjes.

Graag wil ik ook mijn vrienden bedanken voor de steun en de vele leuke uitstapjes die we gemaakt hebben. Met name wil ik de mannen van BMR, de Medics, de Rotterdamsche Stapmaten en Westersingel 8b bedanken. Bedankt voor de leuke vakanties, (zeil)weekendjes en stapavonden, zonder de nodige ontspanning had ik het werk niet kunnen volbrengen. Ook wil ik graag Jacqueline bedanken voor haar vrolijkheid en steun, en haar begrip voor de laatste drukke maanden van mijn promotietijd.

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PhD Portfolio

Name PhD student:	Vincentius Jacobus Alphonsus Verlinden
Erasmus MC Department:	Epidemiology
Research School:	NIHES
PhD period:	2011-2014
Supervisors:	Dr. M.A. Ikram, Dr. J.N. van der Geest, and Prof.dr. A. Hofman

1. PhD training	**Year**	**ECTS**
Research skills		
- Master of Science in Clinical Epidemiology, Netherlands Institute of Health Sciences, Rotterdam, The Netherlands	2008-2011	
International conferences		
- AAICAD, Paris, France – Oral presentation	2011	2
- VasCog, Lille, France – Poster presentation	2011	1.3
- AD/PD, Florence, Italy – Poster presentation	2013	1.3
- AAIC, Copenhagen, Denmark – Oral & poster presentation, session chair	2014	3
Invited lectures		
- Research seminar at the DZNE, Bonn, Germany	2013	2
- Research seminar at the Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands.	2014	1
Seminars and workshops		
- Weekly research seminars, Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands	2008-2014	6

2. Teaching activities		
Teaching assistant		
- "Study design", NIHES, Rotterdam	2012	1
- "The practice of Epidemiologic Analysis", NIHES, Rotterdam	2012, 2013	2
- "Biostatistical Methods I: basic principles." NIHES, Rotterdam	2013, 2014	2
Supervisor		
- Master thesis of Ana Maksimovic: Depression and gait	2012-2013	4
- Master thesis Sebastián Valk Bonilla: Bone density, body composition, and gait	2012-2013	4
- Medical student Jasper Verbruggen: Prevalence and growth of meningiomas	2013	1.5

3. Other		
Reviewer		
- Reviewing activities for various journals (e.g. Journal of Neurology, Neurosurgery, and Psychiatry; Lancet Neurology; Plos One; Neurobiology of Aging)	2011-2014	4

Complete List of Publications and Manuscripts

1. **Verlinden VJ**, Ikram MA. Looppatronen binnen de Rotterdam Study. Neuropraxis 2012;1:9-13.
2. **Verlinden VJ***, van der Geest JN*, Hoogendam YY, Hofman A, Breteler MM, Ikram MA. Gait patterns in a community-dwelling population aged 50 years and older. Gait Posture 2013;37:500-5.
3. **Verlinden VJ**, van der Geest JN, Hofman A, Ikram MA. Cognition and gait show a distinct pattern of association in the general population. Alzheimers Dement 2014;10:328-35.
4. **Verlinden VJ**, van der Geest JN, Hoogendam YY, Hofman A, Niessen WJ, van der Lugt A, Vernooij MW, Ikram MA. The role of cortical and subcortical grey matter in cognition and gait. Submitted.
5. **Verlinden VJ**, de Groot M, Cremers LG, van der Geest JN, Hofman A, Niessen WJ, van der Lugt A, Vernooij MW, Ikram MA. Associations of microstructural integrity in specific white matter tracts with human gait. Submitted.
6. De Kruijf M*, **Verlinden VJ***, Huygen FJ, Hofman A, van der Geest JN, Uitterlinden AG, Bierma-Zeinstra SM, Ikram MA, van Meurs JB. Chronic joint pain in the lower body is associated with gait differences independent from radiographic osteoarthritis. Submitted.
7. **Verlinden VJ**, van der Geest JN, Heeringa J, Hofman A, Ikram MA. Gait shows a sex-specific pattern of associations with daily functioning in a community-dwelling population of older people. Gait Posture 2014; 41:119-24.
8. **Verlinden VJ**, van der Geest JN, de Bruijn RF, Hofman A, Koudstaal PJ, Ikram MA. Trajectories of cognition and daily functioning in the preclinical phase of dementia, during 18 years of follow-up. Submitted.
9. **Verlinden VJ**, van der Geest JN, de Groot M, Hofman A, Niessen WJ, van der Lugt A, Vernooij MW, Ikram MA. Structural and microstructural brain changes predict impairment in daily functioning. Am J Med 2014; 127:1089-96.
10. **Verlinden VJ**, van der Geest JN, Hofman A, Niessen WJ, van der Lugt A, Vernooij MW, Ikram MA. The role of dementia in the associations of structural brain changes with decline in cognition and daily functioning. Submitted.
11. Hanewinckel R*, Maksimovic A*, **Verlinden VJ**, van der Geest JN, Hofman A, van Doorn PA, Boon AJ, Tiemeier HW, Ikram MA. The impact of restless legs syndrome on physical functioning. Sleep Med; in press.
12. Adams HH*, **Verlinden VJ***, Callisaya M, van Duijn CM, Hofman A, Thomson R, Uitterlinden AG, Vernooij MW, van der Geest JN, Srikanth V, Ikram MA. Heritability and Genome-Wide Association Analyses of Human Gait. Submitted.
13. Nalls MA, Pankratz N, Lill CM, Do CB, Hernandez DG, Saad M, DeStefano AL, Kara E, Bras J, Sharma M, Schulte C, Keller MF, Arepalli S, Letson C, Edsall C, Stefansson H, Liu

X, Pliner H, Lee JH, Cheng R; International Parkinson's Disease Genomics Consortium (IPDGC); Parkinson's Study Group (PSG) Parkinson's Research: The Organized GENetics Initiative (PROGENI); 23andMe; GenePD; NeuroGenetics Research Consortium (NGRC); Hussman Institute of Human Genomics (HIHG); Ashkenazi Jewish Dataset Investigator; Cohorts for Health and Aging Research in Genetic Epidemiology (CHARGE): DeStefano A, Seshadri S, Choi SH, Frank S, Bis JC, Psaty BM, Rice K, Longstreth Jr WT, Ton TGN, Jain S, van Duijn CM, Hofman A; Uitterlinden AG, **Verlinden VJ**, Koudstaal PJ; North American Brain Expression Consortium (NABEC); United Kingdom Brain Expression Consortium (UKBEC); Greek Parkinson's Disease Consortium; Alzheimer Genetic Analysis Group, Ikram MA, Ioannidis JP, Hadjigeorgiou GM, Bis JC, Martinez M, Perlmutter JS, Goate A, Marder K, Fiske B, Sutherland M, Xiromerisiou G, Myers RH, Clark LN, Stefansson K, Hardy JA, Heutink P, Chen H, Wood NW, Houlden H, Payami H, Brice A, Scott WK, Gasser T, Bertram L, Eriksson N, Foroud T, Singleton AB. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat Genet 2014; 46: 989-93.

14. Darweesh SK*, **Verlinden VJ***, Adams HH*, Uitterlinden AG, Hofman A, Stricker BH, van Duijn CM, Koudstaal PJ, Ikram MA. Genetic risk of Parkinson's Disease in the general population: association, prediction, and subclinical effects. Submitted.
15. **Verlinden VJ**, Maksimovic A, Mirza SS, Ikram MA, Kiefte-de Jong JC, Hofman A, Franco OH, Tiemeier H, van der Geest JN. Consumption of alcohol, coffee, and tobacco is associated with gait in a community-dwelling population. Submitted.
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17. Lahousse L*, **Verlinden VJ***, van der Geest JN, Joos GF, Hofman A, Stricker BH, Brusselle GG, Ikram MA. Gait patterns in Chronic Obstructive Pulmonary Disease: the Rotterdam Study. Eur Respir J; in press.
18. Lahousse L, Maes B, **Verlinden VJ**, Ziere G, Zillikens MC, Uitterlinden AG, Rivadeneira F, Tiemeier H, Joos GF, Hofman A, Ikram MA, Franco OH, Brusselle GG, Stricker BH. Chronic Obstructive Pulmonary Disease, comorbidities and frailty: the Rotterdam Study. Submitted.
19. **Verlinden VJ***, de Kruijf M*, Bierma-Zeinstra SM, Hofman A, Uitterlinden AG, Ikram MA, van Meurs JB, van der Geest JN. Asymptomatic radiographic hip osteoarthritis is associated with gait differences, especially in women. Submitted.

*These authors contributed equally to the respective manuscript.

About the Author

Vincentius J.A. Verlinden was born on August 24th 1986 in Odijk, the Netherlands. After graduating from the "Montessori Lyceum Herman Jordan" in Zeist (2004) he started to study Computer Science at Utrecht University, Utrecht. After completing two years of Computer Science, he started medical school at the Erasmus University Rotterdam. During the second year in medical school he was invited to participate in the Master of Science programme in Clinical Epidemiology by the Netherlands Institute of Health Sciences. As a part of this programme he attended the Harvard University Summer School in 2010 and worked at the Department of Epidemiology at the Erasmus MC under supervision of prof.dr. M.M.B. Breteler, prof.dr. A. Hofman, dr. M.A. Ikram, and dr. J.N. van der Geest. In 2011 he obtained his Master of Science degree in both Medicine and Health Sciences (specialisation: Clinical Epidemiology). In 2011 he started his PhD research at the Department of Epidemiology under supervision of prof.dr. A. Hofman, dr. M.A. Ikram, and dr. J.N. van der Geest, as described in this thesis. As of October 2014, Vincentius has started his internships as part of his medical studies.