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Psychiatric and lifestyle determinants of gait in a community-dwelling population

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Psychiatric and lifestyle determinants of gait in a community-dwelling population

Introduction

In most countries worldwide, the percentage of people aged over 60 years is growing faster than that of any other age group. Population ageing can be considered as success of the progress of public health policies and socioeconomic development, but it also challenges society to maximize the health and functional capacity of older people as well as their social participation and security.

Aging itself leads to physiological impairment of nearly every organ system, and to progressive problems with heart, lungs, chronic diseases, diabetes mellitus, central and peripheral nervous system, kidneys, locomotor system, circulation and mental health. Genetic, environmental, and psychosocial factors may increase a general susceptibility to diseases, resulting in the co-occurrence of disorders in late life.

Proper gait is an important factor of person's independent function and quality of life. Gait is not only an important indicator of general health, but impaired gait is also a predictor of adverse events, such as falls and mortality. Multiple studies have shown that higher age is associated with worse gait.

With increasing life expectancy, gait disturbances are therefore expected to become even more prevalent.

In order to improve cardiorespiratory and muscular fitness, bone and functional health, reduce the risk of chronic disease, sleep disorders, depression and cognitive decline, older adults should perform physical activity to enhance balance and prevent falls, while older adults who cannot do the recommended amounts of physical activity due to health conditions should be as physically active as their abilities and conditions allow.

Investigation of determinants of gait may help in better understanding of risk factors and mechanisms included in gait deterioration which could lead to early detection of health problems linked with worse gait and possible prevention of gait-related conditions and disorders.

Methodological considerations

All studies have been performed using data from 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. The study started in 1990 and was expanded in 2000 and 2006. Over the years, 14,926 participants have been enrolled in the Rotterdam Study. All inhabitants of the Ommoord district of Rotterdam who were 55 years or older were selected from the municipal population register and invited to participate in the study.
In 2006, people above the age of 45 years were invited. There were no other selection criteria. At baseline and every three to four years of follow-up, all participants undergo a home interview and a comprehensive set of examinations at the research center. Participants are invited for these follow-up assessments in a random order. From 2009 onwards the gait assessments have been implemented in the study.
The Rotterdam Study has been approved by the Medical Ethics Committee of Erasmus University Medical Center (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. The Rotterdam Study has been entered into the Netherlands National Trial Register and into the WHO International Clinical Trials Registry Platform under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

All the studies in this thesis had cross-sectional design, which precludes hard conclusions on the causal direction.
Since population based studies are less likely to be affected by selection bias compared to clinical studies and reports, the findings from Rotterdam Study can be generalized to underlying population. However, the Rotterdam Study took place in the district inhabited mostly by middle-

class white individuals; therefore, the results obtained can be more applicable to similar populations rather than general. Another issue that can lead to possible selection bias is that the participation in the Rotterdam Study is voluntary and the people accepting to participate might be different from the ones who do not participate.

In population based epidemiological research, it is also essential to take confounding into account. In order to minimize confounding in our study, we were extensively investigating the covariates at each visit. Additionally, all analyses were adjusted for covariates that were considered as potential confounders. However, the issue of residual confounding remains.

This might be a consequence of covariates that were not assessed in our study.

Since the potential confounders may simultaneously be the intermediates in investigated associations, adjustment for these could lead to possible over adjustment that could lead to underestimation of results.

Another possible bias in our study may be common method bias. If both determinant and outcome assessed by a questionnaire are examined by the same interviewer, it is possible that part of that kind of associations we found are the result of common method bias.

Another type of bias that we should consider is information bias. Participants might give the incorrect answers due to recall bias. Concerns to give the most commonly socially acceptable answer may lead to response bias. Even though the information bias is not likely to occur in automated assessments, it is not possible to completely exclude the possibility of information bias especially in interview-based data collection.

Gait assessment

In Rotterdam Study, we used the gait protocol to extensively assess three different walking conditions: normal walking, turning and tandem (heel to toe) walk. The purpose of this protocol was to detect worsening of gait patterns related to neurological, psychiatric, cardiovascular, locomotor and other general health impairment.

The main strength of our extensive gait assessment protocol is the objectivity due to use of a 5.79 m long walkway (GAITRite Platinum; CIR systems, USA: 4.88 m active area; 120 Hz sampling

rate) with pressure sensors, that are activated by the pressure of footfalls. This device is an accurate system to determine different gait parameters.

Gait is a highly complex concept and can be studied using many different variables. Consequently, the overlap across studies in variables used to study gait is limited. Even though in an ideal setting, gait is studied using as many variables as possible, this would result in multiple testing as well as collinearity across variables. Different studies have sought to tackle this issue by principal components analysis (PCA). PCA with varimax rotation was performed on 30 variables to derive independent summarizing factors.

The PCA summarized these 30 variables into seven independent domains, explaining 87.3% of the total variance in gait. These domains were: 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). Previous studies have shown that worse performance gait domains are associated with higher risk of falling, death, cognitive impairment and dementia. This implies that investigation of gait domains may contribute to early detection and prevention of severe health impairment consequences.

Determinants assessment

Diabetes and impaired fasting glucose assessment

Presence of diabetes mellitus and impaired fasting glucose was evaluated using laboratory data derived from blood sampling performed at the research center and with data on medication use.

Medication use was assessed by self-report and by going through the medication cabinets in the home of the participants during the home interview. Diabetes was defined as a fasting glucose level ≥7.0 mmol/L, a non-fasting glucose level ≥11.1 mmol/L (if fasting samples were not available) or use of anti-diabetic therapy. Impaired fasting glucose was defined according to the American Diabetes Association (ADA) 2010 diagnostic criteria as a fasting glucose level between 5.6 mmol/L and 6.9 mmol/L in the absence of diabetes. However, the duration of diabetes, impaired fasting glucose and history of anti-diabetic medication use were not available, which could contribute to better understanding and interpretation of our results. Additionally, we

were not able to distinguish the participants with type 1 diabetes from the ones with type 2 diabetes that is more common to occur later in life.

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.

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 and 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. The urge to move the legs was not assessed with the questionnaire. More extensive questionnaire and physical examination of the patient would be beneficial for a better understanding of RLS symptomatology, underlying pathology and clinical presentation of this disorder.

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).

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. 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. 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. Consistent with BADL, these eight components were cored from 0 to 3, with higher scores indicating worse ability. The overall IADL score was calculated by summing the scores of the eight components.

Although disability index is validated and commonly used questionnaire to assess BADL and IADL, are subject to reporting bias. Participants are likely to over or under report their difficulties in daily living, leading to inadequate estimation of true daily functioning.

Coffee, alcohol and tobacco consumption assessment

Alcohol and coffee consumption were assessed as part of a 389-item semi quantitative food frequency questionnaire (FFQ), based on a validated FFQ for Dutch adults. Questions included consumption frequency of food items over the past month, their amount, type and preparation. Portion sizes were estimated using standardized household measures for glasses and cups. Initially, grams of alcohol or coffee consumed were calculated, from which number of glasses (10 g per glass) or cups (125 g per cup) were estimated. Dietary data were converted into daily nutrient intake (total energy) using the Dutch Food Composition Table of 2011. Every visit, home interviews included questions on whether participants smoked cigarettes, cigars or pipe, or whether they had smoked previously. Additionally, participants were asked how many cigarettes they smoked in their period of smoking. We did not ask participants who did not consume alcohol or coffee in the past month whether they consumed alcohol or coffee earlier and for how long they have quit. Hence, associations may have suffered from reverse causality, that is, people changing substance consumption because of health problems that also affect gait. Another problem is that substance consumption was assessed by questionnaires, which are subject to reporting bias, especially underreporting.

Main findings

Effects of diabetes and impaired fasting glucose on gait

Worse gait, more depressive symptoms, impaired physical functioning and diabetes are all related with aging, due to deterioration of all organ systems and slowness of physiological mechanisms and processes that occur in older age.

Gait is influenced by different organ systems, including the central and peripheral nervous system, central and peripheral circulation and the musculoskeletal system.

All of these systems can be affected by diabetes mellitus and impaired fasting glucose. Since microvascular pathology can be present in early phases of disease development already, it implies that subtle changes in specific gait domains can not only be found in participants with diabetes, but also in persons having only impaired fasting glucose.

Previous, smaller studies that investigated the association of diabetes with spatiotemporal variables of gait found an association with a decrease in cadence (constituting the domain Rhythm) and with lower gait velocity and shorter stride length (both constituting the domain Pace), but the large, population based approach in this field is missing. Additionally, the previous studies mostly investigated the separated gait variables, while the study with specific gait domains has not been reported yet. In our study, we found an association with Pace, which might result from damage to the vasculature of the legs or feet or be due to damage of the proprioceptive system in case of neuropathy. We found a strong independent association of diabetes with errors in tandem walking. Even subtle changes in the feet and lower limbs, as well as ocular pathology that can occur due to diabetes mellitus may affect proper performance in tandem walk. In our study gait was not significantly different in participants with impaired fasting glucose than in participants with normoglycemia. Early decline in gait when moving away from the normal glucose range was especially noticeable in the domains Pace and Tandem.

Lifestyle effects on gait

Additionally, I investigated the associations of lifestyle factors, including coffee, alcohol and tobacco consumption with gait domains.

Coffee, alcohol and tobacco have shown significant effects on the cardiovascular, cerebrovascular, respiratory, locomotor and musculoskeletal system. The effect of substance consumption on gait can be seen through the effects on any of these systems. As expected, I have found that coffee consumption and moderate alcohol drinking are beneficial for gait, while tobacco smoking was worsening the gait.

Proper control of substance use and interventions in over-consumption can lead to prevention of gait deterioration and the improvement of condition in all the systems suffering from substance abuse as well as improvement of general health overall.

The impact of sleep disorders and depressive symptoms on gait and physical functioning

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.

Most RLS symptoms occur at night, but some studies have revealed an impact of RLS on daily functioning. Problems not only include daytime sleepiness and concentration difficulties, which can be attributed to nighttime sleep disruption, but also physical dysfunction, which involves both arms and legs.

In this population-based cohort study I 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 after adjusting for sleep quality or depressive symptoms. RLS was not associated with either gait or scores on the Purdue Pegboard Test.

It is possible that sleep disturbance and depressive symptoms, which are often seen in RLS patients and are associated with impairment in physical functioning, are acting as intermediates.

Indeed, when adjusting for these variables, the associations between RLS and ADL weakened, indicating that at least part of the association can be explained by a person's general well-being or quality of life.

Study 1

Publication:

Gait characteristics in older adults with diabetes and impaired fasting glucose: The Rotterdam Study.

Maksimovic A, Hanewinckel R, Verlinden VJ, Ligthart S, Hofman A, Franco OH, van Doorn PA, Tiemeier H, Dehghan A, Ikram MA.

J Diabetes Complications. 2016 Jan-Feb;30(1):61-6. doi: 10.1016/j.jdiacomp.2015.10.006. Epub 2015 Oct 20.

Methods

The study was embedded in the Rotterdam Study, a population based cohort in the Netherlands that started in 1990. At the start of the study in 1990 and again in 2000, all people living in the Ommoord district of Rotterdam, aged 55 years and older were selected from the municipal population records and invited to participate in the study.

In total, 14,926 out of 20,744 invited persons agreed to participate in the study (overall response rate 72%).

From March 2009 onwards, gait assessment was implemented in the core protocol of the study. The current study includes all participants that underwent gait assessment between March 2009 and March 2012. During this period 3666 persons were invited for gait measurements; after exclusion of 600 persons (due to physical health reasons, technical problems, not following or completing the entire protocol, having fewer than 16 steps available for analyses, repeated assessment and other reasons), 3066 participants were eligible for the study; 3019 of them had information about diabetes mellitus available. These 3019 participants were included in the analyses.

Diabetes mellitus and impaired fasting glucose assessment

Presence of diabetes mellitus and impaired fasting glucose was evaluated using laboratory data derived from blood sampling performed at the research center and with data on medication use.

Gait assessment

Gait was assessed using a 5.79 meter long electronic walkway (4.88 meter of active area; GAITRite Platinum; CIR systems, Sparta, NJ, USA), that has been validated before. Three walking conditions were recorded: normal walk, turning and tandem walk. In normal walk, participants were asked to walk across the electronic walkway at their own pace. In the 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. The walkway software was used to generate 30 different spatiotemporal gait variables. Principal components analysis (PCA) was used to summarize these 30 gait variables into independent gait domains, while capturing the largest amount of variance. Varimax rotation was used to make sure that the gait domains were mutually independent. The PCA resulted in seven independent domains: Rhythm, Variability,Phases, Pace, Base of Support, Tandem and Turning. Among others, Rhythm represents cadence and stride time; Phases represent double support time and double support as a percentage of the gait cycle; Variability represents variability in stride length and stride time; Pace represents velocity and stride length; Base of Support represents stride width and stride width variability; Tandem represents errors in tandem walking; and Turning represents the number of turning steps and turning time. These domains were standardized and, when necessary, inverted so that lower values indicate “worse” gait. Additionally, Global Gait was calculated by averaging the seven independent gait domains into one standardized Z-score.

Assessment of covariates

The home interview comprised questionnaires about smoking (current cigarette smoking versus non-smoking) and alcohol consumption (converted to grams per day). Examinations at the research center included measurement of height (in cm), weight (in kg) and mean systolic and diastolic blood pressure from two consecutive measurements (in mmHg). Total cholesterol and HDL-cholesterol were measured in serum (mmol/L). Use of lipid lowering medication (statins,

ezetimibe, or fibrates) and antihypertensive medication (diuretics, calcium-channel blockers, ACE-inhibitors or beta-blockers) was also documented during the home interview.

Results

In our sample of 3019 participants, 1782 participants (59.0%) had a plasma glucose within the normal range, 921 participants (30.5%) had impaired fasting glucose and 316 participants (10.5%) had diabetes. Participants with normoglycemia were on average younger than participants with impaired fasting glucose or diabetes. In the normoglycemia group 60.9% of participants were female, while this proportion was 45.2% and 43.4% in the impaired fasting glucose and diabetes group respectively. Normoglycemic participants had lower weight and systolic blood pressure and fewer people used lipid- lowering or antihypertensive medication compared to participants with impaired fasting glucose and diabetes. Diabetes mellitus was associated with worse Global Gait (difference in Z-score −0.19, 95% confidence interval (CI) −0.30; −0.07) compared to normoglycemic persons after adjustment for age, sex, height and weight. Specifically, participants with diabetes had worse Pace (difference in Z-score−0.20, 95% CI−0.30;−0.10) and Tandem (difference in Z-score−0.21, 95% CI−0.33;−0.09) than participants with normoglycemia. After additional adjustment for cardiovascular risk factors and medications, only Tandem remained worse (difference in Z-score −0.20, 95% CI −0.33; −0.07) in participants with diabetes compared to participants with normoglycemia. The attenuation of the association with Pace and Global Gait was mainly driven by the inclusion of antihypertensive medication and total cholesterol into the analyses. Impaired fasting glucose was not associated with Global Gait, nor with any of the specific gait domains. However, for several domains the effect estimates for impaired fasting glucose were between those of diabetes and normoglycemia. This was especially noticeable for the domains Pace and Tandem.

Higher glucose levels were not associated with gait within participants with normoglycemia nor within individuals with normoglycemia or impaired fasting glucose combined. There were some indications for a non-linear relation of glucose with Rhythm, Turning and Global Gait, but these associations did not survive correction for multiple testing. We did not observe a consistent pattern of effect modification by sex in any of the analyses.

Conclusion

In our community-dwelling population, the presence of diabetes mellitus was associated with worse Global Gait, Pace and Tandem. This relationship is mainly mediated by cardiovascular risk factors. Impairment in gait seems to occur early in the process of developing diabetes mellitus. It may be beneficial to detect and treat abnormal fasting glucose levels and diabetes in early stages in order to prevent future gait impairment in middle-aged and elderly people. Furthermore, within diabetes care, tight regulation of blood pressure and cholesterol levels might be important to prevent or reduce the development of gait problems.

Study 2

Publication

The associations of alcohol, coffee and tobacco consumption with gait in a community-dwelling population.

Verlinden VJ, Maksimovic A, Mirza SS, Ikram MA, Kiefte-de Jong JC, Hofman A, Franco OH, Tiemeier H, van der Geest JN. Eur J Clin Nutr. 2016 Jan;70(1):116-22. doi: 10.1038/ejcn.2015.120. Epub 2015 Jul 29.

Methods

Setting

The study was embedded in the Rotterdam Study, a population-based cohort study in Ommoord, a suburb of Rotterdam, the Netherlands. Participants undergo home interviews and extensive medical examinations at the research center. From March 2009 onwards, gait assessment was included in the study protocol. The current study includes all participants who underwent gait assessment between March 2009 and March 2012.

Assessment of alcohol, coffee and tobacco consumption

Alcohol and coffee consumption were assessed as part of a 389-item semiquantitative food frequency questionnaire (FFQ), based on a validated FFQ for Dutch adults. Questions included consumption frequency of food items over the past month, their amount, type and preparation.

Gait assessment

Gait was assessed using a 5.79-m-long electronic walkway (4.88m active area; GAITRite Platinum; CIR systems, Sparta, NJ, USA).Participants performed three walking conditions: normal walk, in which participants walked at regular pace; turn, in which people turned 180°; and tandem walk, in which people walked heel-to-toe over a line. Principal component analysis was used to summarize gait into seven independent gait domains: Rhythm, reflecting stride time; Phases, reflecting double support as a percentage of the stride time; Variability, reflecting variability in stride length; Pace, reflecting stride length; Tandem, reflecting errors in tandem walking; Turning, reflecting turning time; and Base of Support, reflecting stride width. As gait domains are z-scores (scores with mean 0 and standard deviation (SD) 1), the unit of the gait domains is SD. For interpretation of effect sizes, SD of gait domains can be compared with SD of correlated parameters. Global Gait was calculated by summing the gait domains and dividing by seven and subsequently restandardized into a z-score. Additionally, we investigated gait velocity as a general gait measure, which is the most commonly used gait parameter and strongly associates with mortality. Gait assessment was blinded to FFQ assessment and vice versa.

Covariates

At home interviews and examinations at the research center, height, weight, education, working status, marital status, Mini-Mental State Examination (MMSE), blood pressure, total cholesterol, high-density lipoprotein and glucose level, use of blood pressure lowering medication for indication hypertension, use of antidiabetic medication and functioning on activities of daily living (ADL) were assessed. Education was assessed as the highest attained degree of participants. Diabetes mellitus was defined as a fasting blood glucose level $\geqslant$ 7.0 mmol/l, non-fasting glucose level $\geqslant$11.1 mmol/l or use of antidiabetic medication. ADLs were assessed using the disability index from the Stanford Health Assessment Questionnaire.

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 (computer problems or water leakage), 19 for refusal and 2 for other reasons. Out of the remaining 3369 participants, 239 were excluded for technical reasons (e.g. feet falling outside the walkway, poor electronic registration, computer crashes, errors during parameter calculation or other reasons), 34 for performing fewer than 16 steps in normal walk, 27 for not following instructions and 3 for using walking aids. Dementia was assessed as described previously (MMSE). As demented participants are more likely to erroneously answer the FFQ because of memory problems, we excluded 45 people for having dementia or missing dementia data. Of 3021 remaining participants, 475 missed FFQ data. Finally, 2546 participants were included in the analyses.

Results

Median age of participants was 68.1 years (interquartile range 13.1, minimum 50.0, maximum 93.9) and 55.7% were women. In all, 92.4% consumed coffee, 81.9% consumed alcoholic beverages, 17.3% were current smokers and 50.9% were past smokers. All population characteristics (except diastolic blood pressure) differed significantly by sex. On average, gait was assessed 1.8 years (Standard deviation (SD) 2.0) after the FFQ. Mean gait velocity was 121.8 cm/s (Standard deviation (SD) 17.8).

Variance in gait was similar across categories of substance consumption.

Associations with Global Gait and gait velocity

Consuming alcoholic beverages was associated with a higher Global Gait score (0.13 Standard deviation. (95% confidence interval: 0.04; 0.22)) and gait velocity (2.04 cm/s (0.41; 3.66)). Consuming 1–3 glasses of alcohol daily was associated with higher Global Gait and gait velocity compared with consuming no alcohol. Additionally, consuming >3 glasses of alcohol daily was associated with a higher Global Gait score.

We found no significant associations of consuming coffee versus not consuming coffee. However, when collapsing the groups consuming 1–3 and >3 cups of coffee daily we noticed higher Global Gait and gait velocity compared to the group consuming $\leqslant$ 1 cups of coffee.

Current smoking was associated with lower Global Gait (−0.11 S.D. (−0.21; 0.00)) and gait velocity (−3.47 cm/s (−5.33; − 1.60)), compared with never smoking. We found no associations for past smoking. More pack-years of smoking were associated with lower gait velocity. Additional adjustment for consumption of other substances, cardiovascular risk factors and MMSE attenuated the results. However, the associations of consuming any alcohol and 1–3 glasses of alcohol daily with Global Gait and gait velocity; of consuming >3 cups of coffee daily with Global Gait and gait velocity; and of current smoking and pack-years of smoking with gait velocity remained.

After further adjustment for ADL, only the association of consuming any alcohol versus none with gait velocity became nonsignificant (P = 0.06). We found no significant interactions with sex.

Associations with gait domains

Consuming any alcohol associated with higher Phases. Additionally, consuming 0–1 glasses of alcohol daily associated with higher Phases but lower Base of Support compared with consuming no alcohol. Consuming 1–3 glasses of alcohol daily associated with higher Rhythm. We found no associations of consuming coffee compared with not consuming coffee with any gait domain. However, consuming 1–3 cups of coffee daily associated with higher Pace and consuming >3 cups with higher Variability, Pace and Turning, compared with consuming ⩽ 1 cups of coffee.

Current smoking was associated with lower Rhythm and Pace (Table 5). We found no associations for past smoking. More packyears of smoking were associated with lower Phases and Pace.

Additional adjustment for consumption of other substances, cardiovascular risk factors and MMSE attenuated the results. Yet, associations of consumption of alcoholic beverages with Rhythm,

Phases and Base of Support; consuming >3 cups of coffee daily with Turning; current smoking with Pace; and pack-years of smoking with Phases and Pace remained significant.

Conclusion

Consuming coffee and moderate amounts of alcoholic beverages associates with better gait, whereas smoking relates to worse gait.

Study 3.

Publication

The impact of restless legs syndrome on physical functioning in a community-dwelling population of middle-aged and elderly people.

Hanewinckel R, Maksimovic A*, Verlinden VJ, van der Geest JN, Hofman A, van Doorn PA, Boon AJ, Tiemeier H, Ikram MA.*

Sleep Med. 2015 Mar;16(3):399-405. doi: 10.1016/j.sleep.2014.11.013. Epub 2015 Jan 14.

**authors contributed equally*

Methods

This study was embedded in the Rotterdam Study, a prospective population-based cohort study in the Netherlands.

The study started in 1990 and was expanded in 2000 and 2006. Over the years, 14,926 participants have been enrolled in the Rotterdam Study. All inhabitants of the Ommoord district of Rotterdam who were 55 years or older were selected from the municipal population register and invited to participate in the study. In 2006, people above the age of 45 years were invited.

Population for analysis

Between August 2006 and May 2013 6,431 participants were interviewed.

We excluded participants who had missing data concerning either the RLS or the ADL questionnaires, who were demented or not screened for dementia.

The final study population consisted of 5,960 participants. Gait was only assessed between March 2009 and December 2011, after implementation of an electronic walkway. Of the 5,960 participants with RLS and ADL data, 2,548 had complete gait data available. Data on the Purdue Pegboard Test was available in 5,125 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.

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).

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. 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.

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. 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

The Purdue Pegboard Test was used to assess fine motor skills of the upper extremities, also called manual dexterity. 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. 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 included obtaining information about alcohol and coffee consumption, smoking status, level of education, self reported osteoarthritis, depressive symptoms (assessed with the Center for Epidemiologic Studies Depression scale, CES-D and sleep quality (assessed with the Pittsburgh Sleep Quality Index, PSQI). 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 nonsmoking (never and past smoking). Education was dichotomized in primary education only or higher education (vocational and higher).

Medication use was assessed by self-report and by going through the medication cabinets in the house. The examinations at the research center included blood sampling (glucose and creatinine) and measurement of height, weight and blood pressure. Body mass index was calculated by dividing a person's weight by the square of their height. Cardiovascular diseases (coronary heart disease and stroke) were assessed through active follow-up and adjudicated using standardized Definitions. Diabetes mellitus was defined as a fasting glucose level >7.0 mmol/L, or use of anti-diabetic therapy.

Hypertension was defined as a mean systolic blood pressure (average from two readings) above 140 mmHg, diastolic blood pressure above 90 mmHg, or use of antihypertensive medication. Use of lipid lowering medication was documented and medication that is frequently prescribed in RLS syndrome was also documented and combined into one variable. This includes anti-

Parkinson medication, such as dopamine agonist or levodopa but also anti-epileptics, such as pregabalin and gabapentin.

Results

In total 5,960 participants (57.5% females) were included in the analyses. Age ranged from 46 to 98 years (46–55 years: 1048 subjects, 18%; 56–65 years: 1445 subjects, 24%; 66–75 years: 1840 subjects, 31%; >75 years: 1627 subjects, 27%). RLS was present in 816 participants (13.7%). Prevalence of RLS was higher in females than in males (18.3% compared to 7.5%). Age specific prevalence showed a peak at age 55–60 of 17.0%. Participants with RLS were younger and had worse scores on the PSQI and the CES-D than those without RLS. The mean BADL score in the entire population was 3.06 (95% confidence interval (CI) 2.97;3.16, range 0–24) and the mean IADL score was 1.91 (95% CI 1.83;1.99, range 0–24).

Restless legs syndrome and subjectively assessed physical functioning

When adjusting for multiple potential confounders, RLS was associated with higher BADL scores (0.65 points higher, 95% CI 0.41;0.90) and a higher probability of having impairment in the BADL (odds ratio 1.85, 95% CI 1.35;2.53), while RLS related to only small differences in the IADL score (0.28 points higher, 95% CI 0.09;0.48). No association was found between RLS and having IADL impairment (odds ratio 0.97, 95% CI 0.55;1.72). After adjusting for sleep quality or depressive symptoms the associations between RLS and ADL attenuated, both in BADL and IADL score and in BADL impairment. The effect of sleep quality was stronger for BADL, while adjusting for depressive symptoms had a larger effect on IADL. Individuals with RLS were more severely disabled in all components of the BADL and in the following three IADL components: shopping, housekeeping, and transportation. However, after adjusting for sleep quality, most of these associations attenuated strongly. The associations were stronger for persons who experienced RLS symptoms two or more times a week. Individuals with RLS symptoms more than two days a week scored 1.69 points higher on BADL score (95% CI 1.28;2.09) than participants without RLS and 0.77 points higher on IADL score (95% CI 0.44;1.09). Adjustment for sleep quality and depressive symptoms slightly attenuated these associations too, but the results remained significant. When restricting these analyses to the

2,341 participants with all data available (RLS, ADL, gait and manual dexterity) similar associations were found. No significant sex-interaction terms were found in any of the analyses.

Restless legs syndrome and objectively assessed physical functioning

The prevalence of RLS in the subsample of participants with gait assessment was 13.4%. RLS did not associate with any of the gait domains, nor with the strongest correlated gait variable within each gait domain. Higher frequency of RLS symptoms was also not associated with gait. Similarly, no associations were found between RLS and Purdue Pegboard Test scores.

Conclusion

In our community-dwelling population of middle aged and older people, we found RLS to associate with self reported impairment in daily functioning. We did not find an association between RLS and gait or manual dexterity. This indicates that impairment in basic ADL does not originate from a pathophysiological mechanism that affects motor performance.
However, there may be processes involved that are not covered by our measurements of gait and manual dexterity. Moreover, we found that the association between RLS and subjective measurements of daily functioning attenuated after adjusting for sleep or mood disturbance, indicating that at least part of the association can be explained by a person's general well-being or quality of life.

Deutschsprachige Zusammenfassung

In den meisten Ländern der Welt wächst der Prozentsatz der Menschen über 60 Jahre schneller als der jeder anderen Altersgruppe. Die Alterung der Bevölkerung kann als Erfolg des Fortschritts der öffentlichen Gesundheitspolitik und der sozioökonomischen Entwicklung angesehen werden, aber sie fordert die Gesellschaft auch heraus, die Gesundheit und die Funktionsfähigkeit älterer Menschen sowie ihre soziale Teilhabe und Sicherheit zu maximieren.

Das Altern selbst führt zu physiologischen Beeinträchtigungen fast aller Organsysteme und zu fortschreitenden Problemen mit Herz, Lunge, chronischen Krankheiten, Diabetes mellitus, zentralem und peripherem Nervensystem, Nieren, Bewegungsapparat, Kreislauf und psychischer Gesundheit. Genetische, ökologische und psychosoziale Faktoren können die allgemeine Anfälligkeit für Krankheiten erhöhen, was zum Auftreten von Störungen im Alter führt.

Das sichere Gehen ist ein wichtiger Faktor für die eigenständige Funktion und Lebensqualität des Menschen. Der Gang ist nicht nur ein wichtiger Indikator für den allgemeinen Gesundheitszustand, sondern auch ein Indikator für unerwünschte Ereignisse wie Stürze und Mortalität. Mehrere Studien haben gezeigt, dass ein höheres Alter mit einem schlechteren Gang verbunden ist.

Mit zunehmender Lebenserwartung werden daher immer häufiger Gangstörungen erwartet.

Um die kardiorespiratorische und muskuläre Fitness, die Knochen- und Funktionsgesundheit zu verbessern, das Risiko von chronischen Krankheiten, Schlafstörungen, Depressionen und kognitivem Rückgang zu verringern, sollten ältere Erwachsene körperliche Aktivität ausüben, um das Gleichgewicht zu verbessern und Stürze zu verhindern, während ältere Erwachsene, die aufgrund gesundheitlicher Bedingungen die empfohlenen Mengen an körperlicher Aktivität nicht leisten können, so körperlich aktiv sein sollten, wie es ihre Fähigkeiten und Bedingungen zulassen.

Die Untersuchung der Determinanten des Gehens kann zum besseren Verständnis der Risikofaktoren und Mechanismen beitragen, die in der Verschlechterung des Gehens enthalten sind, was zu einer frühzeitigen Erkennung von Gesundheitsproblemen im Zusammenhang mit dem schlechteren Gehverhalten und einer möglichen Vorbeugung von gangbezogenen Erkrankungen und Störungen führen könnte.

In der Rotterdam-Studie haben wir drei verschiedene Gehzustände umfassend bewertet: normales Gehen, Drehen und Tandemgehen (von Ferse zu Zehe). Der Zweck dieses Protokolls war es, eine Verschlechterung der Gangmuster in Zusammenhang mit neurologischen, psychiatrischen, kardiovaskulären, motorischen und anderen allgemeinen Gesundheitsschäden festzustellen.

Auswirkungen von Diabetes und beeinträchtigtem Nüchternglukosewert auf den Gang

In unserer Studie fanden wir einen Zusammenhang mit dem Schritttempo, der sich aus einer Schädigung der Gefäße der Beine oder Füße oder einer Schädigung des propriozeptiven Systems im Falle einer Neuropathie ergeben kann. Wir fanden einen starken unabhängigen Zusammenhang von Diabetes mit Fehlern beim Tandemgehen. Selbst subtile Veränderungen an den Füßen und unteren Gliedmaßen sowie Augenpathologien, die aufgrund von Diabetes mellitus auftreten können, können die korrekte Leistung beim Tandemgehen beeinträchtigen. In unserer Studie war der Gang bei Teilnehmern mit beeinträchtigtem Nüchternglukosespiegel nicht signifikant anders als bei Teilnehmern mit Normoglykämie. Ein frühzeitiger Rückgang des Gehens, wenn man sich vom normalen Glukosebereich abwendet, war insbesondere in den Bereichen Schritttempo und Tandem zu beobachten.

Lifestyle-Effekte auf das Gangbild

Kaffee, Alkohol und Tabak haben signifikante Auswirkungen auf das kardiovaskuläre, zerebrovaskuläre, respiratorische, motorische und muskuloskelettale System. Die Auswirkungen des Substanzkonsums auf den Gang lassen sich an den Auswirkungen auf eines dieser Systeme ablesen. Wie erwartet, habe ich festgestellt, dass Kaffeekonsum und mäßiger Alkoholkonsum für das Gehen von Vorteil sind, während das Tabakrauchen das Gehen verschlechterte.

Eine angemessene Kontrolle des Drogenkonsums und Interventionen bei übermäßigem Konsum können dazu führen, dass eine Verschlechterung des Gehens und eine Verbesserung des Zustands in allen Systemen, die unter Drogenmissbrauch leiden, verhindert wird, sowie die allgemeine Gesundheit insgesamt verbessert wird.

Die Auswirkungen von Schlafstörungen und depressiven Symptomen auf den Gang und die körperliche Leistungsfähigkeit

In dieser populationsbasierten Kohortenstudie fand ich heraus, dass RLS (Restless-Legs-Syndrom) mit schwereren selbstberichteten Beeinträchtigungen bei ADL (Aktivitäten des täglichen Lebens) verbunden war, insbesondere BADL (Basisaktivitäten des täglichen Lebens). Die Wirkung von RLS auf die Invaliditätswerte war am stärksten bei Teilnehmern mit RLS-Symptomen, die mehr als zwei Tage pro Woche auftraten. Diese Assoziationen schwächten sich nach Korrektur für die Schlafqualität oder depressive Symptome ab. RLS war weder mit dem Gang noch mit den Ergebnissen des Purdue Pegboard Test verbunden.

Es ist möglich, dass Schlafstörungen und depressive Symptome, die bei RLS-Patienten häufig auftreten und mit einer Beeinträchtigung der körperlichen Funktion verbunden sind, als konfundierende Faktoren wirken. In der Tat, wenn man diese Variablen berücksichtigt, schwächten sich die Assoziationen zwischen RLS und ADL ab, was darauf hindeutet, dass zumindest ein Teil der Assoziation durch das allgemeine Wohlbefinden oder die Lebensqualität einer Person erklärt werden kann.

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Gait characteristics in older adults with diabetes and impaired fasting glucose: The Rotterdam Study

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ABSTRACT

Aims: To investigate the association of diabetes mellitus and impaired fasting glucose with gait in the general middle-aged and elderly population.
Methods: We performed a cross-sectional study on 3019 participants from the population-based Rotterdam Study (aged >45 years, 54% women). The presence of diabetes mellitus and impaired fasting glucose was evaluated by measuring serum glucose levels and by documenting anti-diabetic treatment. Participants underwent gait analysis using an electronic walkway. Thirty gait variables were summarized into five independent gait domains for normal walking (*Rhythm*, *Variability*, *Phases*, *Pace* and *Base of Support*), one for turning (*Turning*) and one for walking heel to toe (*Tandem*), which were averaged into *Global Gait*. Linear regression analyses were performed to determine the association of diabetes, impaired fasting glucose and continuous glucose levels within the normal range with gait.
Results: Diabetes mellitus was associated with worse *Global Gait* (Z-score difference −0.19, 95% confidence interval (CI) −0.30; −0.07), worse *Pace* (−0.20, 95% CI −0.30; −0.10) and worse *Tandem* (−0.21, 95% CI −0.33; −0.09), after adjusting for age, sex, height and weight. The association with *Tandem* remained significant after additional adjustment for cardiovascular risk factors. Impaired fasting glucose and continuous glucose levels within the normal range were not associated with any of the gait domains.
Conclusion: In our population-based study diabetes mellitus was associated with worse *Global Gait*, which was mostly reflected in *Pace* and *Tandem*. These associations were partly driven by other cardiovascular risk factors, emphasizing the importance of optimal control of cardiovascular risk factor profiles in patients with diabetes.

1. Introduction

Diabetes mellitus is common in the elderly population and is as a serious threat to an older person's quality of life. Complications such as polyneuropathy, retinopathy and peripheral artery disease can already be present at the moment of diagnosis of the disease (Raman, Gupta, Krishna, Kulothungan, & Sharma, 2012). This suggests that microvascular as well as macrovascular changes already occur in early stages of diabetes and perhaps even in a state before overt diabetes develops, which is often referred to as prediabetes (Tabak, Herder, Rathmann, Brunner, & Kivimaki, 2012). These complications directly (neuropathy, peripheral artery disease) or indirectly (muscle weakness, ulcerations, cerebrovascular disease) lead to walking instability, falls, and fall-related injuries (Allet et al., 2008; Andersen, 2012; England et al., 2014; Lalli et al., 2013; Raspovic, 2013; Roman de Mettelinge, Cambier, Calders, Van Den Noortgate, & Delbaere, 2013; Volpato & Maraldi, 2011; Volpato et al., 2012). To detect the impact of diabetes on walking and lower limb performance in an early stage, extensive assessment of gait in different walking conditions may be useful (Allet et al., 2008).

Gait is a complex concept that is increasingly recognized as a marker of general health (Studenski et al., 2011; Verlinden, van der Geest, Hofman, & Ikram, 2014). Gait is influenced by different organ systems, including the central and peripheral nervous system, central and peripheral circulation and the musculoskeletal system, all of which can be affected by diabetes mellitus. Dysfunction in any of these

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systems may lead to gait impairment, which in turn is associated with an increased risk of falling and higher mortality (Verlinden et al., 2013; Verghese, Holtzer, Lipton, & Wang, 2009). Gait can be measured using many different spatiotemporal variables, which can be summarized into seven independent gait domains (Fig. 1): *Rhythm* (cadence, stride time), *Variability* (variability in stride length and stride time), *Phases* (double support percentage of gait cycle), *Pace* (stride length, velocity), *Base of Support* (stride width and stride width variability) *Tandem* (number of side steps in walking heel to toe) and *Turning* (number of steps and turning time) (Verlinden et al., 2014, 2013).

Previous case–control studies reported lower walking speed and cadence in individuals with diabetes (Allet et al., 2009, 2008), but population-based data about the relation between diabetes and the gait pattern are lacking. In addition, since microvascular pathology can be present already early in the course of the disease (Raman et al., 2012), we hypothesized that subtle changes in specific gait domains can not only be found in participants with diabetes, but also in persons having only impaired fasting glucose or even a glucose level in the high range of normal.

Therefore, we aimed to investigate the association of diabetes mellitus and prediabetes (impaired fasting glucose) with gait and its separate domains in a community-dwelling population.

2. Methods

2.1. Study setting, study design and study population

The study was embedded in the Rotterdam Study, a population-based cohort in the Netherlands that started in 1990. At the start of the study in 1990 and again in 2000, all people living in the Ommoord district of Rotterdam, aged 55 years and older were selected from the municipal population records and invited to participate in the study. In 2006 the cohort was extended with individuals that moved into the study area, aged 45 years and older. Residential area (zip code) and age were the only eligibility criteria used for inclusion of participants. In total, 14,926 out of 20,744 invited persons agreed to participate in the study (overall response rate 72%). At baseline and every 3–4 years of follow-up, all participants undergo a home interview and extensive medical examinations at the research center.

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare, and Sports of the Netherlands, implementing the "Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study)". A written informed consent to participate in the study and to obtain information from their treating physicians was obtained from all participants (Hofman et al., 2015).

From March 2009 onwards, gait assessment was implemented in the core protocol of the study. The current study includes all participants that underwent gait assessment between March 2009 and March 2012. During this period 3666 persons were invited for gait measurements; after exclusion of 600 persons (207 persons were excluded due to physical health reasons, 296 because of technical problems, 46 participants did not follow or complete the entire protocol, 34 persons had fewer than 16 steps available for analyses, 15 had a repeated assessment and 2 persons were excluded for other reasons), 3066 participants were eligible for the study; 3019 of them had information about diabetes mellitus available. These 3019 participants were included in the analyses.

2.2. Diabetes mellitus and impaired fasting glucose assessment

Presence of diabetes mellitus and impaired fasting glucose was evaluated using laboratory data derived from blood sampling

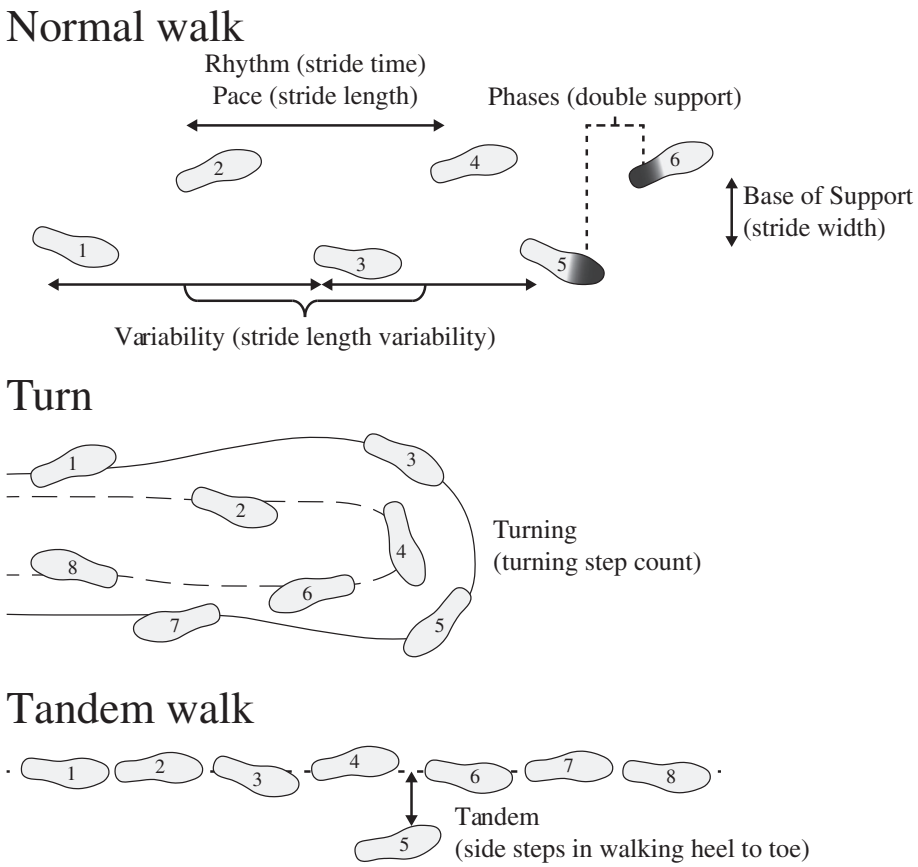

Fig. 1. The three recorded walking conditions, including five domains for normal walk (*Rhythm*, *Variability*, *Phases*, *Pace*, and *Base of Support*), one for the turn (*Turning*), and one for tandem walk (*Tandem*).

performed at the research center and with data on medication use. Medication use was assessed by self-report and by going through the medication cabinets in the home of the participants during the home interview. Diabetes was defined as a fasting glucose level ≥7.0 mmol/L, a non-fasting glucose level ≥11.1 mmol/L (if fasting samples were not available) or use of anti-diabetic therapy (Nolan, Damm, & Prentki, 2011). Impaired fasting glucose was defined according to the ADA 2010 diagnostic criteria as a fasting glucose level between 5.6 mmol/L and 6.9 mmol/L in the absence of diabetes (Tabak et al., 2012).

2.3. Gait assessment

Gait was assessed using a 5.79 meter long electronic walkway (4.88 meter of active area; GAITRite Platinum; CIR systems, Sparta, NJ, USA), that has been validated before (Bilney, Morris, & Webster, 2003; McDonough, Batavia, Chen, Kwon, & Ziai, 2001; Menz, Latt, Tiedemann, Mun San Kwan, & Lord, 2004). Three walking conditions were recorded: normal walk, turning and tandem walk. In normal walk, participants were asked to walk across the electronic walkway at their own pace. In the 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.

The walkway software was used to generate 30 different spatiotemporal gait variables; 25 for normal walk, 2 for turning and 3 for tandem walk. Principal components analysis (PCA) was used to summarize these 30 gait variables into independent gait domains, while capturing the largest amount of variance. Varimax rotation was used to make sure that the gait domains were mutually independent. The PCA resulted in seven independent domains: *Rhythm*, *Variability*, *Phases*, *Pace*, *Base of Support*, *Tandem* and *Turning*. Among others, *Rhythm* represents cadence and stride time; *Phases* represent double support time and double support as a percentage of the gait cycle; *Variability* represents variability in stride length and stride time; *Pace* represents velocity and stride length; *Base of Support* represents stride width and stride width variability; *Tandem* represents errors in tandem walking; and *Turning* represents the number of turning steps and turning time (see Supplementary Table 1 and Fig. 1). More details about the principal component analyses can be found elsewhere (Verlinden et al., 2014; Verlinden et al., 2013). These domains were standardized and, when necessary, inverted so that lower values indicate "worse" gait. Additionally, *Global Gait* was calculated by averaging the seven independent gait domains into one standardized Z-score.

2.4. Assessment of covariates

The home interview comprised questionnaires about smoking (current cigarette smoking versus non-smoking) and alcohol consumption (converted to grams per day). Examinations at the research center included measurement of height (in cm), weight (in kg) and mean systolic and diastolic blood pressure from two consecutive measurements (in mmHg). Total cholesterol and HDL-cholesterol were measured in serum (mmol/L). Use of lipid lowering medication (statins, ezetimibe, or fibrates) and antihypertensive medication (diuretics, calcium-channel blockers, ACE-inhibitors or beta-blockers) was also documented during the home interview.

2.5. Statistical analysis

We used multivariable linear regression analyses to investigate the association of diabetes with *Global Gait* and specific gait domains. Next, we performed analyses of impaired fasting glucose. Additionally, we investigated the association of continuous glucose levels on gait in individuals with a glucose level within the normal range and in individuals with a normal or an impaired fasting glucose combined. All analyses were performed using two models. The first model was adjusted for age, sex, height and weight; the second model was additionally adjusted for cardiovascular risk factors and medication use (mean systolic and mean diastolic blood pressures, smoking, alcohol use, total cholesterol, HDL-cholesterol, antihypertensive medication and lipid lowering medication). Analyses involving *Tandem* were additionally adjusted for step length and step count in the tandem walk (Verlinden et al., 2013). Effect modification by sex was tested by adding an interaction term into the models. We applied Bonferroni correction for seven tests (reflecting the seven independent gait domains) to correct for multiple testing (p-value < 0.007). We assessed potential non-linear associations for the continuous glucose levels with gait using spline regression in R version 3.2.0. All other reported statistical analyses were performed using the SPSS statistical package, version 21 for Windows (IBM Corp., Armonk, NY).

3. Results

We compared population characteristics between participants and non-participants. Results of this analyses can be found in Supplementary Table 2. There were more females and more people being treated for hypertension in the non-participants, and non-participants were on average older.

In our sample of 3019 participants, 1782 participants (59.0%) had a plasma glucose within the normal range, 921 participants (30.5%) had impaired fasting glucose and 316 participants (10.5%) had diabetes. Participants with normoglycemia were on average younger than participants with impaired fasting glucose or diabetes. In the normoglycemia group 60.9% was female, while this was 45.2% and 43.4% in the impaired fasting glucose and diabetes group respectively. Normoglycemic participants had a lower weight and systolic blood pressure and fewer people used lipid-lowering or antihypertensive medication compared to participants with impaired fasting glucose and diabetes (Table 1).

Diabetes mellitus was associated with worse *Global Gait* (difference in Z-score −0.19, 95% confidence interval (CI) −0.30; −0.07) compared to normoglycemic persons after adjustment for age, sex, height and weight. Specifically, participants with diabetes had worse *Pace* (difference in Z-score −0.20, 95% CI −0.30; −0.10) and *Tandem* (difference in Z-score −0.21, 95% CI −0.33; −0.09) than participants with normoglycemia (Fig. 2). After additional adjustment for cardiovascular risk factors and medications, only *Tandem* remained worse (difference in Z-score −0.20, 95% CI −0.33; −0.07) in participants with diabetes compared to participants with normogly-

Table 1
Population characteristics.

Characteristic	Normoglycemia, N = 1782	Impaired fasting glucose, N = 921	Diabetes, N = 316
Age, years	66.1 (9.2)	68.6 (8.7)*	70.0 (8.2)*,†
Female sex, n	1,085 (60.9)	416 (45.2)*	137 (43.4)*
Height, cm	168.6 (9.3)	169.9 (9.4)	169.5 (9.0)
Weight, kg	75.3 (13.1)	82.0 (14.4)*	84.9 (14.5)*,†
Current cigarette smoking, n	284 (16.0)	135 (14.7)	43 (13.6)
Alcohol, grams per day	6.1 (6.7)	8.1 (8.4)*	5.8 (7.5)†
Diastolic blood pressure, mmHg	82.9 (11.0)	85.4 (11.0)*	84.6 (10.9)
Systolic blood pressure, mmHg	138.2 (21.7)	145.5 (21.9)*	148.2 (21.8)*
Antihypertensive medication, n	502 (28.2)	404 (43.9)*	215 (68.3)*,†
Total cholesterol, mmol/L	5.6 (1.1)	5.5 (1.0)	4.8 (1.1)*,†
HDL-cholesterol, mmol/L	1.5 (0.4)	1.4 (0.4)*	1.3 (0.4)*,†
Lipid lowering medication, n	367 (20.6)	266 (28.9)*	172 (54.6)*,†
Glucose, mmol/L	5.1 (0.4)	6.0 (0.4)*	8.1 (2.3)*,†

Values are mean (SD) or number (%). Percentages were calculated without missing values. Missing values occurred in less than 1%.

* p-value < 0.05, impaired fasting glucose and diabetes compared to normoglycemia, age- and sex adjusted (if applicable).

† p-value < 0.05, diabetes compared to impaired fasting glucose, age- and sex adjusted (if applicable).

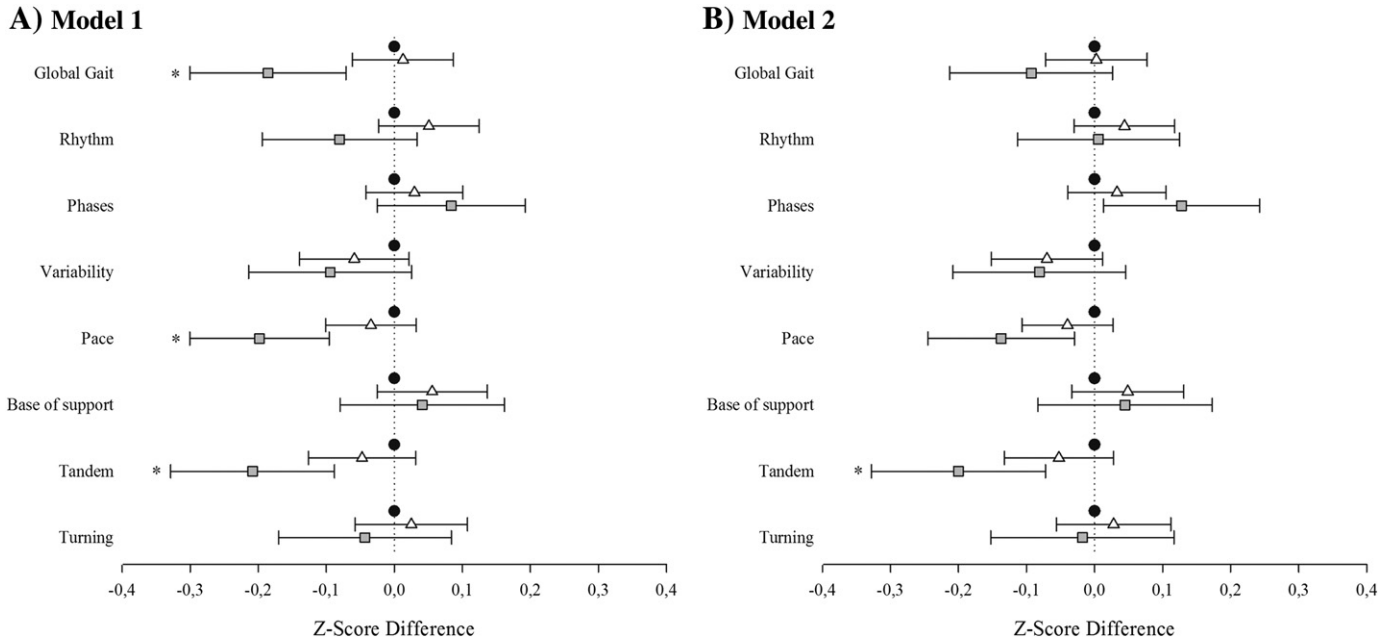

Fig. 2. Difference in Z-scores of global gait and gait domains across different glycemic stages. The symbols represent the difference in Z-score of gait for participants with diabetes (gray squares) and impaired fasting glucose (white triangles) compared to normoglycemia (black circles, reference). Error bars represent the 95% confidence intervals around the difference. Asterisks mark the associations that survived Bonferroni correction for 7 tests ($p < 0.007$). Model 1 is adjusted for age, sex, height, weight. Model 2 is additionally adjusted for smoking, alcohol, mean diastolic blood pressure, mean systolic blood pressure, antihypertensive medication, total cholesterol, HDL-cholesterol, lipid lowering medication.

cemia (Fig. 2). The attenuation of the association with *Pace* and *Global Gait* was mainly driven by the inclusion of antihypertensive medication and total cholesterol into the analyses.

Impaired fasting glucose was not associated with *Global Gait*, nor with any of the specific gait domains. However, for several domains the effect estimates for impaired fasting glucose were between those of diabetes and normoglycemia. This was especially noticeable for the domains *Pace* and *Tandem* (Fig. 2).

Higher glucose levels were not associated with gait within participants with normoglycemia nor within individuals with normoglycemia or impaired fasting glucose combined (Table 2). There were some indications for a non-linear relation of glucose with *Rhythm*, *Turning* and *Global Gait*, but these associations did not survive correction for multiple testing. We did not observe a consistent pattern of effect modification by sex in any of the analyses.

4. Discussion

In this population-based study diabetes mellitus was associated with worse *Global Gait*, which was mainly accounted for by worse *Pace* and *Tandem*. The association for *Tandem* remained significant after adjustment for cardiovascular risk factors. In persons with impaired fasting glucose or a glucose level below the threshold for diabetes there was no association with gait.

The strengths of our study include the large population-based sample, assessment of both diabetes mellitus and earlier stages of diabetes, defined as impaired fasting glucose, and the extensive and objective assessment of gait in different walking conditions using an electronic walkway. Our study also has some limitations. The analyses are cross-sectional, making it difficult to draw firm conclusions on causality. Gait was assessed in persons that visited the research center, which might have prevented persons with severe physical disability to participate, leading to a relatively healthy study population. We did not have data on impaired glucose tolerance, which is also part of the definition of prediabetes. Impaired glucose tolerance may be stronger associated with complications of diabetes, especially neuropathy, than impaired fasting glucose (Tabak et al., 2012). We were not able to assess how different diabetes treatment types and diabetes duration would affect our results. This would be interesting, since both insulin treatment and diabetes duration have been associated with mobility impairment (Bruce, Davis, & Davis, 2005). Another limitation is that we did not evaluate the presence of polyneuropathy, peripheral artery disease, diabetic feet and retinopathy and therefore were not able to assess how these conditions influence the associations.

Gait is a complex motor function that depends on the interplay of multiple systems, such as intact structure and functioning of the central and peripheral nervous system, the vestibular system, intact vascularization of both the brain and the extremities and intact functioning of the musculoskeletal system. All of these systems can be affected by diabetes. We found that participants with diabetes had significantly worse *Global Gait*, *Pace* and *Tandem* compared to persons with normoglycemia. Previous, smaller studies that investigated the association of diabetes with spatiotemporal variables of gait found an association with a decrease in cadence (constituting the domain *Rhythm*) (Allet et al., 2010, 2009; Ko, Hughes, & Lewis, 2012) and with lower gait velocity and shorter stride length (both constituting the domain *Pace*) (Allet et al., 2009, 2008; Kalyani et al., 2013; Ko et al., 2012; Lalli et al., 2013; Raspovic, 2013; Sawacha, Guarneri, Avogaro, & Cobelli, 2010; Sawacha et al., 2009; Volpato et al., 2012; Wrobel & Najafi, 2010). In our study, we also found an association with *Pace*, which might result from damage to the vasculature of the legs or feet or be due to damage of the proprioceptive system in case of neuropathy. After adjusting for cardiovascular risk factors the association with *Pace* attenuated, mainly due to inclusion of total cholesterol and antihypertensive medications. Adjusting for cardiovascular risk factors also attenuated the association of diabetes with *Global Gait*, suggesting that a large part of the effect of diabetes on gait is due to vascular comorbidity.

Our study is among the first to investigate the effect of diabetes mellitus on tandem walk in a community-dwelling population. We found a strong independent association of diabetes with errors in tandem walking. Tandem walk represents a complex heel-to-toe type of walk that requires very fine and precise motor function, preserved

Table 2
Difference in Z-score of gait per mmol/L change in glucose level in people without diabetes.

Gait domains	Normoglycemia, N = 1766 (serum glucose <5.6 mmol/L)		Normoglycemia and impaired fasting glucose, N = 2675 (serum glucose <7.0 mmol/L)	
	Model 1	Model 2	Model 1	Model 2
Global gait	0.05 (−0.06; 0.16)	0.04 (−0.07; 0.15)	0.02 (−0.04; 0.08)	0.01 (−0.06; 0.07)
Rhythm	0.05 (−0.06; 0.16)	0.03 (−0.08; 0.14)	0.03 (−0.03; 0.09)	0.02 (−0.05; 0.08)
Phases	0.09 (−0.01; 0.20)	0.10 (−0.01; 0.20)	0.06 (−0.00; 0.12)	0.06 (−0.00; 0.12)
Variability	−0.02 (−0.13; 0.09)	−0.03 (−0.15; 0.08)	−0.04 (−0.11; 0.03)	−0.05 (−0.12; 0.02)
Pace	−0.07 (−0.17; 0.02)	−0.10 (−0.20; −0.01)	−0.05 (−0.10; 0.01)	−0.06 (−0.12; −0.01)
Base of Support	0.03 (−0.08; 0.14)	0.04 (−0.07; 0.16)	0.06 (−0.01; 0.13)	0.06 (−0.01; 0.13)
Tandem[a]	−0.03 (−0.14; 0.08)	−0.03 (−0.14; 0.08)	−0.04 (−0.11; 0.03)	−0.04 (−0.11; 0.03)
Turning	0.08 (−0.04; 0.20)	0.10 (−0.02; 0.22)	0.03 (−0.04; 0.10)	0.03 (−0.04; 0.11)

Values represent the difference in Z-score of gait with 1 mmol/L change in glucose level.
Model 1: age, sex, height, weight.
Model 2: model 1 + smoking, alcohol, mean diastolic blood pressure, mean systolic blood pressure, antihypertensive medication, total cholesterol, HDL-cholesterol, lipid lowering medication.
None of the results survived Bonferroni adjustment for 7 tests (p-value = 0.007).
[a] Additionally adjusted for step length and step count in tandem walk.

balance and integration of various other systems, including the eyes, in order to be performed correctly. Even subtle changes in the feet and lower limbs, as well as ocular pathology that can occur due to diabetes mellitus may affect successful performance in tandem walk.

In our study, there was no association of diabetes with *Rhythm*. The most likely explanation for this is that in our study cadence (*Rhythm*) is made independent from stride length (*Pace*) with the principle component analysis. Hence, associations with cadence in previous studies may have been (partly) driven by an association with stride length, which in our study is a component of *Pace*. Moreover, we adjusted the analyses for several cardiovascular risk factors, which is not performed in most studies that found an effect on cadence (part of the domain *Rhythm*). The results of these studies might have been due to confounding. We did not find an association of diabetes with *Variability*, which is the domain from the normal walk that is most strongly related to falls (Verlinden et al., 2014, 2013). Previous studies that reported this association could only find an effect while walking in challenging circumstances or on irregular surface, which makes comparison with our study difficult (Allet et al., 2009, 2008). A perhaps surprising result was the inverted association of diabetes with *Phases*, even though it did not survive correction for multiple testing. Post-hoc analysis revealed that this was possibly due to overadjustment for weight, which is a strong determinant of both diabetes and *Phases*. Indeed, if we ran models without weight as covariate, the effect size of diabetes for *Phases* was −0.17 (95% CI −0.29; −0.04). This suggests that the association of diabetes with "better" gait was likely a spurious result. Whether our findings of gait impairment are specific to diabetes, or specific to certain complications of diabetes such as polyneuropathy, needs to be further investigated.

Since microvascular pathology occurs early in the development of diabetes we hypothesized that this already leads to subtle changes in gait characteristics in patients with earlier stages of diabetes. However, in our study gait was not significantly different in participants with impaired fasting glucose than in participants with normoglycemia, though we did find a pattern of the strength of the associations with impaired fasting glucose being in between those of normoglycemia (reference) and diabetes. This suggests an early decline in gait when moving away from the normal glucose range and was especially noticeable in the domains *Pace* and *Tandem*. Yet, a counterargument against this reasoning is the finding that a glucose level within the normal range was not associated with gait domains when investigated continuously.

To conclude, in our community-dwelling population, the presence of diabetes mellitus was associated with worse *Global Gait*, *Pace* and *Tandem*. This relationship is mainly mediated by cardiovascular risk factors. Impairment in gait seems to occur early in the process of developing diabetes mellitus. It may be beneficial to detect and treat abnormal fasting glucose levels and diabetes in early stages in order to prevent future gait impairment in middle-aged and elderly people. Furthermore, within diabetes care, tight regulation of blood pressure and cholesterol levels might be important to prevent or reduce the development of gait problems.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jdiacomp.2015.10.006.

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ORIGINAL ARTICLE

The associations of alcohol, coffee and tobacco consumption with gait in a community-dwelling population

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BACKGROUND/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.
SUBJECTS/METHODS: Two thousand forty-six 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, coffee and tobacco consumption was assessed by questionnaires. With analysis of covariance, we investigated associations of consumption of alcoholic beverages, coffee consumption and smoking with Global Gait, gait velocity and the seven individual gait domains.
RESULTS: In all, 81.9% of participants drank alcohol, 92.4% drank coffee, 17.3% were current smokers and 50.9% were past smokers. Moderate alcohol consumption (1–3 glasses per day) associated with better gait, as measured by Global Gait (0.20 standard deviations (s.d.) (95% confidence interval: 0.10; 0.31)), gait velocity (2.65 cm/s (0.80; 4.50)), Rhythm and Variability. Consuming high amounts of coffee (>3 cups per day) associated with better Global Gait (0.18 s.d. (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 s.d. (−0.21; 0.00)), gait velocity (−3.47 cm/s (−5.33; −1.60)), Rhythm and Pace, compared with non-smokers.
CONCLUSIONS: In a community-dwelling population, consuming >1 cup of coffee and 1–3 glasses of alcohol relate to better gait, whereas 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.

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INTRODUCTION

Alcohol, coffee and tobacco are widely consumed and have addictive properties.[1–6] These substances contain many different components, which have various effects on health with chronic use.[1–5,7–9] Although excessive consumption is usually considered detrimental, beneficial effects of coffee and moderate alcohol consumption have been described.[1,3,5,6,9,10] However, substance consumption reflects lifestyle and socioeconomic status, which may obscure biological effects.[2,11–13]

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 these systems may impair gait, which in turn can severely impair daily functioning and increase risk of falling, morbidity and mortality.[14,21–24] Conventionally, gait is assessed as gait velocity. However, gait is a complex concept consisting of many domains (Figure 1), which reflect different abilities, for example, physical strength and cognition, and relate distinctively to various health aspects.[18–20,25] Investigating alcohol, coffee and tobacco consumption in relation to gait may provide additional insight into overall beneficial or detrimental effects of these substances on general health, delineating possible interventions to improve gait and thereby health.

Previous studies were restricted to substance abuse and therefore uninformative on the associations of overall alcohol, coffee and tobacco consumption with gait in the general population.[26]

We investigated associations of alcohol, coffee and tobacco consumption with gait in a community-dwelling population.

MATERIALS AND METHODS

Setting

The study was embedded in the Rotterdam Study, a population-based cohort study in Ommoord, a suburb of Rotterdam, the Netherlands.[27] This study included three recruitment periods, or subcohorts, two initiated in 1990 and 2000, inviting all inhabitants of Ommoord aged $\geqslant 55$ years, and one in 2006, inviting inhabitants aged $\geqslant 45$ years. Participants undergo home interviews and extensive medical examinations at the research centre. From March 2009 onwards, gait assessment was included in the study protocol. The current study includes all participants who 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. Written informed consent was obtained from all participants.

Assessment of alcohol, coffee and tobacco consumption

Alcohol and coffee consumption was assessed as part of a 389-item semiquantitative food frequency questionnaire (FFQ), based on a validated

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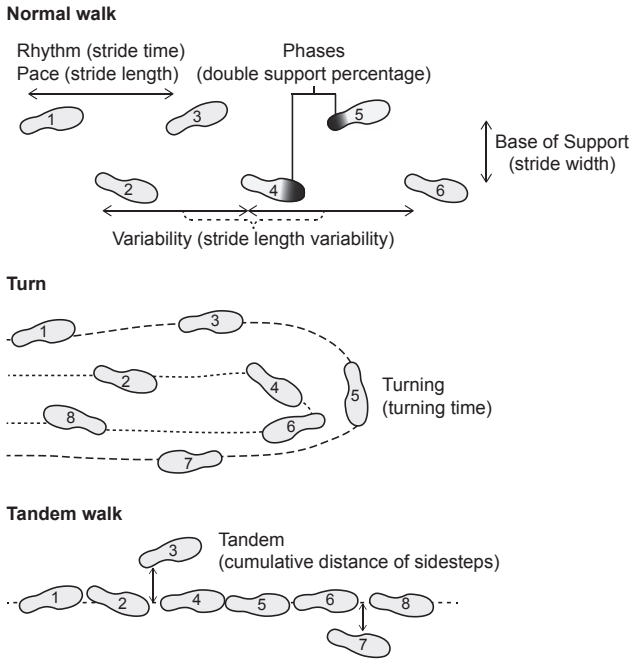

Figure 1. The three walking conditions including the seven gait domains. The gait domains are represented by highly correlated original gait parameters, as specified between parentheses.

FFQ for Dutch adults.[28,29] Questions included consumption frequency of food items over the past month, their amount, type and preparation. Portion sizes were estimated using standardised household measures for glasses and cups.[30] Initially, grams of alcohol or coffee consumed were calculated, from which number of glasses (10 g per glass) or cups (125 g per cup) were estimated. Dietary data were converted into daily nutrient intake (total energy) using the Dutch Food Composition Table of 2011.[31] Every visit, home interviews included questions on whether participants smoked cigarettes, cigars or pipe, or whether they had smoked previously. 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 20. Missing data on smoking were imputed using a last observation carried forward method.

Questions on alcohol, coffee and tobacco consumption are provided in Supplementary Methods 1.

Gait assessment

Gait was assessed using a 5.79-m-long electronic walkway (4.88 m active area; GAITRite Platinum; CIR systems, Sparta, NJ, USA).[25] Participants performed three walking conditions: normal walk, in which participants walked at regular pace; turn, in which people turned 180°; and tandem walk, in which people walked heel-to-toe over a line.

Principal component analysis was used to summarise gait into seven independent gait domains, as described previously:[25] Rhythm, reflecting stride time; Phases, reflecting double support as a percentage of the stride time; Variability, reflecting variability in stride length; Pace, reflecting stride length; Tandem, reflecting errors in tandem walking; Turning, reflecting turning time; and Base of Support, reflecting stride width (Figure 1). As gait domains are *z*-scores (scores with mean 0 and standard deviation (s.d.) 1), the unit of the gait domains is s.d. For interpretation of effect sizes, s.d. of gait domains can be compared with s.d. of correlated parameters, provided in Supplementary Table 1. Global Gait was calculated by summing the gait domains and dividing by seven and subsequently restandardised into a *z*-score.[20] Additionally, we investigated gait velocity as a general gait measure, which is the most commonly used gait parameter and strongly associates with mortality.[24]

Gait assessment was blinded to FFQ assessment and vice versa.

Covariates

At home interviews and examinations at the research centre, height, weight, education, working status, marital status, Mini-Mental State Examination (MMSE), blood pressure, total cholesterol, high-density lipoprotein and glucose level, use of blood pressure lowering medication for indication hypertension, use of antidiabetic medication and functioning on activities of daily living (ADL) were assessed. Education was assessed as the highest attained degree of participants. Diabetes mellitus was defined as a fasting blood glucose level $\geqslant 7.0$ mmol/l, non-fasting glucose level $\geqslant 11.1$ mmol/l or use of antidiabetic medication. ADLs were assessed using the disability index from the Stanford Health Assessment Questionnaire.[32]

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 (computer problems or water leakage), 19 for refusal and 2 for other reasons.

Of the remaining 3369 participants, 239 were excluded for technical reasons (e.g. feet falling outside the walkway, poor electronic registration, computer crashes, errors during parameter calculation or other reasons), 34 for performing fewer than 16 steps in normal walk, lowering validity of measurements,[33] 27 for not following instructions and 3 for using walking aids. Dementia was assessed as described previously.[34] As demented participants are more likely to erroneously answer the FFQ because of memory problems, we excluded 45 people for having dementia or missing dementia data. Of 3021 remaining participants, 475 missed FFQ data. Finally, 2546 participants were included in the analyses. Sex-specific exclusion criteria are provided in Supplementary Table 2.

Statistical analysis

Education was categorised into: 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: never married, married, widowed, divorced or Living Apart Together relationship. To properly adjust for marital status, we recoded marital status into four separate dichotomous dummy variables, each reflecting a different marital status. Missing values on covariates were imputed using five imputations, based on age, sex and other covariates. In all, 0.8% of variables were imputed in this way and for categorical variables were rounded to the nearest integer.

Sex differences in population characteristics were determined using binary logistic regression analyses, adjusted for age.

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

Second, alcohol consumption was categorised into consuming no, 0–1, 1–3 or >3 glasses of alcohol daily.[9] Coffee consumption was similarly categorised, but because of few people consuming no coffee, we collapsed the first two categories. Hence, coffee consumption was categorised into three categories: consuming $\leqslant 1$, 1–3 or >3 cups of coffee daily.

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

Analysis of covariances were used to investigate associations of consumption of alcoholic beverages, coffee consumption and smoking with Global Gait, gait velocity and gait domains.

As quadratic relationships have been reported for alcohol consumption, we also investigated quadratic relationships with gait by including daily alcohol consumption and its quadratic term in linear analyses.[5]

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 step length and step count in tandem walking. Analyses on pack-years of smoking were adjusted for ever smoking cigars or pipe.

To investigate the influence of consumption of the other substances, cardiovascular risk factors and cognition on associations, analyses were repeated while adjusting for consumption of other substances, cardiovascular risk factors and MMSE.

To investigate whether relations were driven by general well-being, we performed sensitivity analyses by additionally adjusting for ADL.

We explored effect modification by sex by including sex × substance consumption interaction terms in analyses on Global Gait and gait velocity.

Residuals of analyses were approximately normally distributed.

Analyses were performed using IBM SPSS version 21.0.0.1 for Windows.

RESULTS

Median age of participants was 68.1 years (interquartile range 13.1, minimum 50.0, maximum 93.9) and 55.7% were women (Table 1). In all, 92.4% consumed coffee, 81.9% consumed alcoholic beverages, 17.3% were current smokers and 50.9% were past smokers. All population characteristics (except diastolic blood pressure) differed significantly by sex. Median ages per category of substance consumption are provided in Supplementary Table 3. On average, gait was assessed 1.8 years (s.d. 2.0) after the FFQ. Mean gait velocity was 121.8 cm/s (s.d. 17.8).

Variance in gait was similar across categories of substance consumption.

Associations with Global Gait and gait velocity

Consuming alcoholic beverages associated with higher Global Gait (0.13 s.d. (95% confidence interval: 0.04; 0.22)) and gait velocity (2.04 cm/s (0.41; 3.66)) (Table 2). Consuming 1–3 glasses of alcohol daily associated with higher Global Gait and gait velocity compared with consuming no alcohol. Additionally, consuming >3 glasses of alcohol daily associated with higher Global Gait. We found a significant quadratic association between daily consumption of alcoholic beverages and Global Gait, with highest Global Gait for consuming moderate amounts of alcohol.

We found no significant associations of consuming coffee versus not consuming coffee. However, consuming 1–3 and >3 cups of coffee daily did associate with higher Global Gait and gait velocity, compared with consuming ⩽1 cups of coffee.

Table 1. Population characteristics, the Rotterdam Study

Characteristic	*Total (n = 2546)*	*Men (n = 1128)*	*Women (n = 1418)*[a]
Age (years)[b]	68.1 (13.1)	68.9 (13.5)	67.4 (12.8)
Height (cm)	169.0 (9.2)	176.2 (6.8)	163.2 (6.3)
Weight (kg)	77.9 (13.7)	84.7 (11.9)	72.4 (12.6)
Education[b]	3 (3)	3 (3)	2 (2)
Current paid work (*n*)	786 (30.9%)	385 (34.1%)	401 (28.3%)
Energy intake (1000 kcal per day)	2.2 (0.8)	2.3 (0.8)	2.0 (0.7)
Total cholesterol (mmol/l)	5.5 (1.1)	5.2 (1.0)	5.7 (1.0)
High-density lipoprotein (mmol/l)	1.5 (0.4)	1.3 (0.3)	1.6 (0.4)
Systolic blood pressure (mm Hg)	142.4 (22.1)	145.3 (21.3)	140.2 (22.6)
Diastolic blood pressure (mm Hg)	84.1 (11.0)	84.6 (10.8)	83.6 (11.1)
Blood pressure lowering drug use (*n*)	848 (33.3%)	411 (36.4%)	430 (30.3%)
Diabetes mellitus (*n*)	264 (10.4%)	146 (12.9%)	118 (8.3%)
MMSE 15–20 (*n*)	8 (0.3%)	6 (0.5%)	2 (0.1%)
MMSE 20–25 (*n*)	133 (5.2%)	73 (6.5%)	60 (4.2%)
MMSE >25 (*n*)	2405 (94.5%)	1049 (93.0%)	1356 (95.6%)
Coffee drinkers (*n*)	2353 (92.4%)	1059 (93.9%)	1294 (91.3%)
Coffee intake (cups per day)	3.0 (2.0)	3.3 (2.1)	2.8 (1.9)
Alcohol drinkers (*n*)	2085 (81.9%)	980 (86.9%)	1105 (77.9%)
Alcohol intake (glasses per day)	1.2 (1.5)	1.6 (1.7)	0.9 (1.2)
Past smokers (*n*)	1296 (50.9%)	680 (60.3%)	616 (43.4%)
Current smokers (*n*)	441 (17.3%)	219 (19.4%)	222 (15.7%)
Cigarette smoking (pack-years)	13.2 (18.5)	16.7 (20.1)	10.4 (16.6)

Abbreviations: MMSE, Mini-Mental State Examination; s.d., standard deviations. Values are means (s.d.) or numbers (percentages). [a]All population characteristics, except diastolic blood pressure, differed significantly between the sexes, after adjustment for age ($P < 0.05$). [b]Median (interquartile range).

Table 2. Associations of alcohol, coffee and tobacco consumption with Global Gait and gait velocity, the Rotterdam Study

	Global Gait (s.d.)	*Gait velocity (cm/s)*
Alcohol consumption		
0 glasses per day (*n* = 461)	0	0
0–1 glasses per day (*n* = 1025)	0.08 (−0.02; 0.18)	1.62 (−0.12; 3.35)
1–3 glasses per day (*n* = 808)	**0.20 (0.10; 0.31)**	**2.65 (0.80; 4.50)**
>3 glasses per day (*n* = 252)	**0.15 (0.00; 0.29)**	2.15 (−0.37; 4.66)
Coffee consumption		
⩽1 cups per day (*n* = 363)	0	0
1–3 cups per day (*n* = 584)	**0.13 (0.01; 0.25)**	**2.74 (0.67; 4.80)**
>3 cups per 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)**

Abbreviation: s.d., standard deviations. Values are differences in s.d. of gait (95% confidence interval) for the respective category of alcohol or coffee consumption versus the reference category or per 10 pack-years of smoking. 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.

Current smoking associated with lower Global Gait (−0.11 s.d. (−0.21; 0.00)) and gait velocity (−3.47 cm/s (−5.33; −1.60)), compared with never smoking. We found no associations for past smoking. More pack-years of smoking associated with lower gait velocity.

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

After further adjustment for ADL, only the association of consuming any alcohol versus none with gait velocity became borderline nonsignificant ($P = 0.06$).

We found no significant sex interactions.

Associations with gait domains

Consuming any alcohol associated with higher Phases (Table 3). Additionally, consuming 0–1 glasses of alcohol daily associated with higher Phases but lower Base of Support compared with consuming no alcohol. Consuming 1–3 glasses of alcohol daily associated with higher Rhythm.

We found no associations of consuming coffee compared with not consuming coffee with any gait domain (Table 4). However, consuming 1–3 cups of coffee daily associated with higher Pace and consuming >3 cups with higher Variability, Pace and Turning, compared with consuming ⩽1 cups of coffee.

Current smoking associated with lower Rhythm and Pace (Table 5). We found no associations for past smoking. More pack-years of smoking associated with lower Phases and Pace.

Additional adjustment for consumption of other substances, cardiovascular risk factors and MMSE attenuated results. Yet, associations of consumption of alcoholic beverages with Rhythm, Phases and Base of Support; consuming >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, consuming coffee and moderate amounts of alcohol associate with better gait, whereas smoking associates with worse gait. These findings remained after adjustment for other substance consumption, cardiovascular risk factors, MMSE and ADL. Consumption of alcoholic beverages additionally associated with better Rhythm and Phases; consuming coffee with better Variability, Pace and Turning; and smoking with worse Rhythm, Phases and Pace.

Study strengths include the large population-based sample, assessing alcohol, coffee and tobacco consumption, and objective assessment of gait in three walking conditions. Our study also has limitations. Most importantly, its semi cross-sectional design precludes investigation of causality. Although conceptually the more likely direction would be substance consumption affecting gait, especially since substance consumption was assessed before gait, such directionality cannot be proven in this study. Additionally, we did not ask participants not consuming alcohol or coffee in the past month whether they consumed alcohol or coffee earlier and for how long they have quit. Hence, associations may have suffered from reverse causality, that is, people changing substance consumption because of health problems that also affect gait. Nonetheless, the small change in associations after adjustment for the general health indicator ADL indicates that such reverse causality may not be severe. Conceptually, ADL adjustment may even be over adjustment, as gait, or walking, is included as part of ADL and many activities require walking to be performed. Another important issue is confounding by

Table 3. Associations of alcohol consumption with individual gait domains, the Rotterdam Study

	Rhythm, s.d.	*Phases, s.d.*	*Variability, s.d.*	*Pace, s.d.*	*Tandem*[a]*, s.d.*	*Turning, s.d.*	*Base of Support, s.d.*
Any 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 per day	0	0	0	0	0	0	0
0 – 1 glasses per 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 per 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 per 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)

Abbreviation: s.d., standard deviations. Values are differences in standard deviations of gait (95% confidence interval) for consuming any alcohol or the respective category of alcohol consumption compared with not consuming 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 coffee consumption with individual gait domains, the Rotterdam Study

	Rhythm, s.d.	*Phases, s.d.*	*Variability, s.d.*	*Pace, s.d.*	*Tandem*[a] *, s.d.*	*Turning, s.d.*	*Base of Support, s.d.*
Any 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 per day	0	0	0	0	0	0	0
1–3 cups per 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 per 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)

Abbreviation: s.d., standard deviations. Values are differences in s.d. of gait (95% confidence interval) for consuming any coffee or the respective category of coffee consumption compared with not consuming any coffee or the reference category of consuming less than one cup of 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, the Rotterdam Study

	Rhythm, s.d.	*Phases, s.d.*	*Variability, s.d.*	*Pace, s.d.*	*Tandem*[a] *, s.d.*	*Turning, s.d.*	*Base of Support, s.d.*
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)

Abbreviations: Packyrs, pack-years; s.d., standard deviations. Values are differences in s.d. of gait (95% confidence interval) for past or current smoking compared with never smoking and per 10 pack-years of smoking. 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.

sociobehavioural factors, that is, a healthier lifestyle may relate to a different substance consumption and gait pattern.[2,11–13] To account for these factors, we adjusted analyses for working status, marital status, education and energy intake. The associations remaining after these adjustments suggest that our findings are not entirely explained by sociobehavioural factors. Still, there remains the possibility of residual confounding, including due to unmeasured confounders. Another problem is that substance consumption was assessed by questionnaires, which are subject to reporting bias, especially underreporting.[35] Furthermore, our FFQ only covered the past month. Although we expect these amounts to reflect consumption over a longer period, we cannot be certain. Yet, as strongest effects are expected for long-term alcohol or coffee consumption, such misclassification will most likely lead to an underestimation of the true associations. Finally, generalisability of the findings may be restricted to a relatively healthy population.

We investigated associations of alcohol, coffee and tobacco consumption with the gait pattern in the general population. In contrast, previous studies investigated the relation of substance abuse and used different gait measures, complicating comparison of our findings to theirs.[26]

We found that consuming 1–3 glasses of alcohol daily associates with better Global Gait and gait velocity. Additionally, we found a quadratic relationship of alcohol consumption with Global Gait, corresponding to its relationship with cardiovascular disease, disability and mortality.[3,5] The concept of positive health effects for moderate alcohol consumption has recently been challenged, especially by findings from Mendelian randomisation studies.[36–38] These studies found no or even protective associations for genetic variants, related to less alcohol consumption, with cardiovascular and cognitive health.[37,38] However, as these genetic variants may have affected health through other pathways compared with the amount of alcohol consumption, the discussion on the true effect of alcohol consumption on health remains inconclusive.[39–41] Our findings, if anything, support a positive effect of moderate alcohol consumption on health.

Consuming >1 cup of coffee daily associated with better Global Gait and gait velocity. However, the weak associations of consuming any coffee versus none suggest a threshold effect, with only consuming >1 cup of coffee daily 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, which may be because of 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 possible relationship of alcohol, coffee and tobacco consumption with gait may be explained by several pathways and mechanisms. Both epidemiological and animal studies found alcoholic beverages, coffee and smoking or their components, for example, alcohol, polyphenols, caffeine and nicotine, to affect many organs, including the cardiovascular, nervous and musculoskeletal system.[1–10] Better functioning in all of these systems may provide pathways linking substance consumption with 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 after adjustments indeed suggests involvement of these organ systems. However, remaining associations suggest that other organ systems or mechanisms are also involved. Future research should investigate possible pathways for the relationship of substance consumption with gait in more detail, including mediation by other organ systems.

The clinical importance of our findings is best exemplified by our results for gait velocity, a strong predictor of survival.[24] Consuming 1–3 glasses of alcohol and >1 cup of coffee associated with nearly 3 cm/s faster gait velocity, with an even stronger negative association for current smoking. These associations remained even after mutual adjustment. Around our mean velocity of 122 cm/s and age of 68 years, a previous study has shown such differences to relate to almost 0.7 years longer survival.[24]

When investigating gait domains, consumption of alcoholic beverages weakly associated with better Rhythm (quicker steps) and Phases (less double support) at light to moderate amounts. These associations indicate that consumption of alcohol increases gait velocity because of taking quicker steps and spending less time in double support. However, because all domain-specific associations were relatively weak, moderate consumption of alcohol most likely has a general association with gait, which is spread across domains.

Consuming 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 consumption mainly increases gait velocity through larger step size.

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.

The effect size of associations in our study were generally small, for example, effect sizes of consuming >1 cup of coffee corresponded to around 1.6 cm longer stride length and of consuming >3 cups of coffee with around 0.2 cm less variability in stride length. However, most differences correspond to over 1% of mean values in these parameters. Such effects may not be strong on an individual level, but may have important implications on the risk of falling at a population level.[23,42,43]

CONCLUSIONS

Consuming coffee and moderate amounts of alcoholic beverages associates with better gait, whereas smoking relates to worse gait.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

MAI, JCK-dJ, AH, OHF and JNvdG designed the study. VJAV collected and analysed the data. VJAV, AM, MAI and JNvdG drafted the manuscript. All authors had an important role in interpreting the results and critically revised the manuscript for important intellectual content. All authors have approved the final version of the manuscript. The corresponding author confirms that he has had full access to the data in the study and final responsibility for the decision to submit the manuscript for publication.

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Original Article

The impact of restless legs syndrome on physical functioning in a community-dwelling population of middle-aged and elderly people

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ABSTRACT

Objective: To investigate whether restless legs syndrome (RLS) is associated with impaired physical functioning using subjective and objective assessments.
Methods: From 2006–2013, 5,960 participants (mean age 67.2; 57.5% females) of the prospective population-based Rotterdam Study, aged 45 years and over, 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 13.7% of the participants. Persons with restless legs had more impairment in basic (difference in score 0.65, 95% CI 0.41;0.90) and instrumental activities of daily living (difference in score 0.28, 95% CI 0.09;0.48) 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 1.69, 95% CI 1.28;2.09). The association between restless legs syndrome and activities of daily living attenuated after adjusting for sleep quality or depressive symptoms. There was no association with the Purdue Pegboard Test score nor with gait.
Conclusions: Individuals with restless legs syndrome experienced significantly more impairment in activities of daily function than persons without restless legs. This seemed to be (partly) mediated by poor sleep quality and depressive symptoms. No association was found with objectively assessed physical functioning.

1. 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

Abbreviations: RLS, restless legs syndrome; BMI, body mass index; ADL, activities of daily living; IRLSSG, international restless legs syndrome study group; BADL, basic activities of daily living; IADL, instrumental activities of daily living; PSQI, Pittsburgh Sleep Quality Index; CES-D, Center for Epidemiologic Studies Depression scale; PCA, Principle component analysis; GFR, Glomerular Filtration Rate (estimated).

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involves both arms and legs [2,7,11,13–21]. 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 [22,23], while functioning of the arms can be assessed with tests for manual dexterity, such as the Purdue Pegboard Test [24]. Indeed, several studies have shown these objective measurements to capture various aspects of self-reported physical functioning [25–30]. However, little is known on the association of RLS with these objective measurements. The underlying mechanism linking RLS with motor performance includes dopamine dysregulation and altered circuitry of the motor cortex [3,4,31]. Additionally, whether impaired performance of daily tasks in patients with RLS is a result of often accompanied sleep or mood disorders, or is a direct result of the pathophysiological changes in RLS leading to diminished motor function remains unclear.

We investigated the associations of RLS with subjectively assessed daily functioning, using activities of daily living (ADL) questionnaires and with objectively assessed motor performance using tests for gait and manual dexterity.

2. Material and methods

2.1. Study 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 [32]. The study started in 1990 and was expanded in 2000 and 2006. Over the years, 14,926 participants have been enrolled in the Rotterdam Study. All inhabitants of the Ommoord district of Rotterdam who were 55 years or older were selected from the municipal population register and invited to participate in the study. In 2006, people above the age of 45 years were invited. There were no other selection criteria. At baseline and every three to four years of follow-up, all participants undergo a home interview and a comprehensive set of examinations at the research center. Participants are invited for these follow-up assessments in a random order. 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.

2.2. Population for analysis

Between August 2006 and May 2013 6,431 participants were interviewed. We excluded participants who had missing data concerning either the RLS (106 participants) or the ADL questionnaires (72 participants). We excluded 71 participants because they were demented and 204 participants because they were not sufficiently screened for dementia. The final study population consisted of 5,960 participants. Gait was only assessed between March 2009 and December 2011, after implementation of an electronic walkway. Of the 5,960 participants with RLS and ADL data, 2,548 had complete gait data available. Data on the Purdue Pegboard Test was available in 5,125 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.

2.3. Assessment of restless legs syndrome

RLS was assessed with a questionnaire, based on the International Restless Legs Syndrome Study Group (IRLSSG) 2003 criteria [1], which are commonly used in epidemiological studies [6,33]. 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. The urge to move the legs was not assessed with the questionnaire.

2.4. 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 [34] was used to assess basic activities of daily living (BADL) and a Dutch version of the Instrumental Activities of Daily Living scale [35] was used to evaluate instrumental activities of daily living (IADL).

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 [34,36]. 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 [36].

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 [35]. 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.

2.5. 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 [22]. 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 (PCA) 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), which were averaged into Global Gait. When necessary, factors were inverted so that lower values indicate "poorer" gait. The PCA yielded standardized factors (Z-scores) that were uncorrelated to each other. Details about the PCA and the different domains have been described elsewhere [22,25].

The Purdue Pegboard Test was used to assess fine motor skills of the upper extremities, also called manual dexterity [24]. 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 [27,37,38]. 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.

2.6. Additional measurements

The home interview comprised information about alcohol and coffee consumption, smoking status, level of education, self-reported osteoarthritis, depressive symptoms (assessed with the Center for Epidemiologic Studies Depression scale, CES-D [39]) and sleep quality (assessed with the Pittsburgh Sleep Quality Index [40], PSQI). 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). Medication use was assessed by self-report and by going through the medication cabinets in the house. The examinations at the research center included blood sampling (glucose and creatinine) and measurement of height, weight and blood pressure. Body mass index was calculated by dividing a person's weight by the square of their height. Cardiovascular diseases (coronary heart disease and stroke) were assessed through active follow-up and adjudicated using standardized definitions [41,42]. Diabetes mellitus was defined as a fasting glucose level >7.0 mmol/L, or use of anti-diabetic therapy. Hypertension was defined as a mean systolic blood pressure (average from two readings) above 140 mmHg, diastolic blood pressure above 90 mmHg, or use of antihypertensive medication. Use of lipid lowering medication was documented and medication that is frequently prescribed in RLS syndrome was also documented and combined into one variable. This includes anti-Parkinson medication, such as dopamine agonist, and anti-epileptics, such as pregabalin and gabapentin.

2.7. 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 analysis of covariance (ANCOVA). Last, we performed sensitivity analysis, investigating the association of RLS with ADL restricting to participants with both gait and manual dexterity data. The associations of RLS (presence and frequency) with objective gait domains and the Purdue Pegboard Test were investigated with multiple linear regression analysis and analysis of covariance. We additionally performed an analysis of covariance for the strongest correlated gait variables within each gait domain. These variables can be easier to interpret than the Z-scores that yielded from the PCA. Results for this analysis are provided as supplement.

All analyses were adjusted for age, sex, body mass index, alcohol use, smoking, coffee intake, diabetes mellitus, hypertension, stroke, coronary heart disease, kidney function, osteoarthritis, lipid lowering medication, education, and RLS medication. Additionally, we explored the effect of sleep and depressive symptoms by adjusting the ADL analyses separately for these two factors. 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).

3. Results

In total 5,960 participants (57.5% females) were included in the analyses. Age ranged from 46 to 98 years (46–55 years: 1048 subjects, 18%; 56–65 years: 1445 subjects, 24%; 66–75 years: 1840 subjects, 31%; >75 years: 1627 subjects, 27%). RLS was present in 816 participants (13.7%). Prevalence of RLS was higher in females than in males (18.3% compared to 7.5%). Age specific prevalence showed a peak at age 55–60 of 17.0%. Participants with RLS were younger and had worse scores on the PSQI and the CES-D than those without RLS (Table 1). The mean BADL score in the entire population was 3.06 (95% confidence interval (CI) 2.97;3.16, range 0–24) and the mean IADL score was 1.91 (95% CI 1.83;1.99, range 0–24).

3.1. Restless legs syndrome and subjectively assessed physical functioning (Table 2)

When adjusting for multiple potential confounders, RLS was associated with higher BADL scores (0.65 points higher, 95% CI 0.41;0.90) and a higher probability of having impairment in BADL (odds ratio 1.85, 95% CI 1.35;2.53), while RLS related to only small differences in IADL score (0.28 points higher, 95% CI 0.09;0.48). No association was found between RLS and having IADL impairment (odds ratio 0.97, 95% CI 0.55;1.72). After adjusting for sleep quality or depressive symptoms the associations between RLS and ADL attenuated, both in BADL and IADL score and in BADL impairment (Table 2). The effect of sleep quality was stronger for BADL, while adjusting for depressive symptoms had a larger effect on IADL.

Individuals with RLS were more severely disabled in all components of BADL and in the following three IADL components: shopping, housekeeping, and transportation (see Supplementary Table S1). However, after adjusting for sleep quality, most of these associations attenuated strongly.

The associations were stronger for persons who experienced RLS symptoms two or more times a week (Fig. 1 and Supplementary

Table 1
Characteristics of the study population.

	Without restless legs syndrome n = 5,144	With restless legs syndrome n = 816	p-value
Age, years	67.3 (11.1)	66.6 (11.2)	0.02
Females, *n*	2798 (54.4)	627 (76.8)	<0.01
Body mass index, kg/m^2	27.5 (4.4)	27.8 (4.4)	0.23
Alcohol use, grams/day	6.9 (7.8)	5.8 (7.1)	0.64
Current smoking, *n*	788 (15.3)	137 (16.8)	0.63
Diabetes mellitus, *n*	575 (11.8)	84 (10.7)	0.88
Hypertension, *n*	3544 (70.2)	525 (65.0)	0.16
Prevalent coronary heart disease, *n*	227 (4.5)	25 (3.1)	0.94
Prevalent stroke, *n*	184 (3.6)	25 (3.1)	0.88
Self-reported osteoarthritis, *n*	812 (15.8)	170 (20.8)	0.04
Lipid lowering medication, *n*	1451 (28.3)	222 (27.3)	0.39
Kidney function, GFR, ml/min/1.73 m^2	77.6 (17.1)	76.8 (18.0)	<0.01
Coffee intake, cups/day	2.9 (2.0)	2.9 (2.0)	0.18
Primary education only, *n*	432 (8.5)	83 (10.3)	0.18
PSQI score	3.6 (3.4)	5.4 (4.1)	<0.01
CES-D score	4.9 (6.8)	6.8 (7.7)	<0.01
RLS medication[a], *n*	102 (2.0)	21 (2.6)	0.34

Values are number (%) for categorical variables or mean (standard deviation) for continuous variables. Percentages are calculated without missing values.
PSQI: Pittsburgh Sleep Quality Index, higher score indicates poorer sleep quality.
CES-D: Center for Epidemiological Studies Depression Scale, higher scores reflect more depressive symptoms.
P-values are age and sex adjusted (if applicable).
[a] RLS medication includes use of anti-Parkinson medication and/or anti-epileptics.

Table S2). Individuals with RLS symptoms more than two days a week scored 1.69 points higher on BADL score (95% CI 1.28;2.09) than participants without RLS and 0.77 points higher on IADL score (95% CI 0.44;1.09). Adjustment for sleep quality and depressive symptoms slightly attenuated these associations too, but the results remained significant (Supplementary Table S2).

When restricting these analyses to the 2,341 participants with all data available (RLS, ADL, gait and manual dexterity) similar associations were found (Supplementary Table S3).

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

3.2. Restless legs syndrome and objectively assessed physical functioning (Table 3)

The prevalence of RLS in the subsample of participants with gait assessment was 13.4%. RLS did not associate with any of the gait domains, nor with the strongest correlated gait variable within each gait domain (Supplementary Table S4). Higher frequency of RLS symptoms was also not associated with gait (Supplementary Table S2). Similarly, no associations were found between RLS and Purdue Pegboard Test scores (Table 3 and Supplementary Table S2).

4. 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 after adjusting for sleep quality or depressive symptoms. RLS was not associated with either gait or scores on the Purdue Pegboard Test.

We found an association between RLS and subjective impairment in physical functioning, even after adjusting for multiple potential confounders. 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 [2,7,11,13–20]. 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 these associations remains unclear. It is possible that sleep disturbance and depressive symptoms, which are often seen in RLS patients and are associated with impairment in physical functioning, are acting as intermediates. Indeed, when adjusting for these variables, the associations between RLS and ADL weakened. Still, this adjustment did not explain away the whole effect, suggesting other potential explanations.

Other proposed explanations linking RLS with ADL include the 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 generation and modulation [21,43,44]. 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 objective measurements 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 [45]. This implies that the association of RLS with self-reported disability in activities of daily living has no apparent pathophysiological explanation. However, we note that this would only hold for the aspects of physical functioning we captured with the assessment of gait and manual dexterity. In other words, it remains possible that a pathophysiological substrate explains the association of RLS with physical function, but is not reflected in gait and manual dexterity.

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	0.57 (0.32;0.82)**	1.38 (1.08;1.78)*	0.23 (0.02;0.44)*	0.90 (0.60;1.33)
Model 2	0.65 (0.41;0.90)**	1.85 (1.35;2.53)**	0.28 (0.09;0.48)**	0.97 (0.55;1.72)
Model 3	0.30 (0.04;0.55)*	1.30 (0.90;1.88)	0.21 (0.01;0.41)*	0.91 (0.47;1.75)
Model 4	0.45 (0.21;0.69)**	1.61 (1.15;2.25)**	0.16 (-0.03;0.35)	0.70 (0.37;1.33)

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 and sex.
Model 2: adjusted for age, sex, body mass index, alcohol use, smoking, diabetes mellitus, education, hypertension, coronary heart disease, stroke, lipid lowering medication, osteoarthritis, coffee intake, GFR and RLS medication.
Model 3: Model 2, additionally adjusted for PSQI score.
Model 4: Model 2, additionally adjusted for CES-D score.
* $p < 0.05$, ** $p < 0.01$.

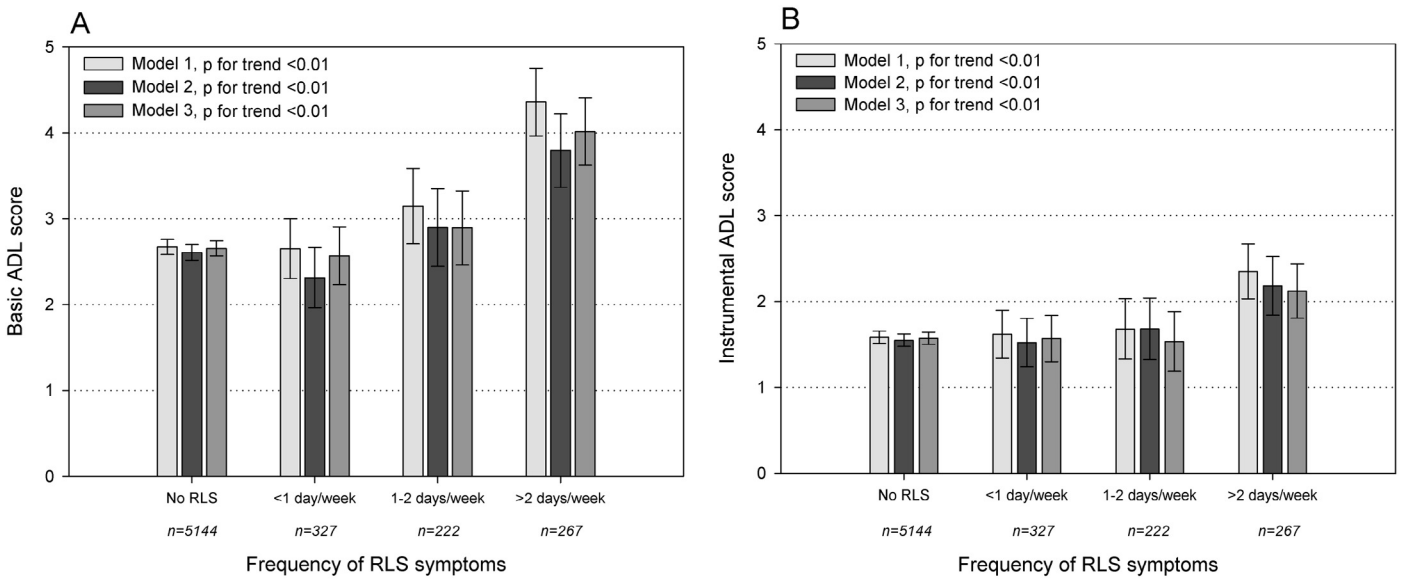

Fig. 1. Frequency of RLS symptoms and activities of daily living scores.
Mean adjusted ADL scores per frequency of RLS symptoms. Error bars represent the 95% confidence interval around the mean.
A: Basic activities of daily living.
B: Instrumental activities of daily living
Model 1: adjusted for age, sex, body mass index, alcohol use, smoking, diabetes mellitus, education, hypertension, coronary heart disease, stroke, lipid lowering medication, osteoarthritis, coffee intake, GFR and RLS medication
Model 2: model 1, additionally adjusted for sleep quality (PSQI)
Model 3: model 1, additionally adjusted for depressive symptoms (CES-D)

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. Moreover, the objective assessments were performed only once, and since RLS symptoms occur intermittently, it is possible that the assessment was not performed during a symptomatic period. 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 [46]. The associations of RLS with gait and manual dexterity may thus be more reliable as they are measured independently.

We found that the association of RLS with physical functioning attenuated after adjustment for CES-D and sleep quality. This suggests that the associations we found for RLS with self-reported disability are at least partly a reflection of a person's general well-being or quality of life. The lack of sleep and presence of depressive symptoms accompanying RLS may influence an individual's perception of his physical functioning. This highlights the importance of recognition of both RLS and the accompanying sleep or mood disturbances. Improving sleep quality and treating mood disorders in patients with RLS may have a 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

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]	Global Gait	Purdue Pegboard
Model 1	–0.05 (–0.15;0.06)	0.02 (–0.09;0.13)	0.06 (–0.05;0.18)	–0.05 (–0.15;0.05)	0.04 (–0.07;0.16)	0.00 (–0.12;0.11)	0.06 (–0.06;0.19)	0.02 (–0.08;0.13)	0.18 (–0.15;0.52)
Model 2	0.01 (–0.11;0.12)	0.01 (–0.11;0.14)	0.09 (–0.01;0.20)	0.00 (–0.10;0.10)	–0.01 (–0.14;0.11)	0.02 (–0.11;0.14)	0.04 (–0.10;0.18)	0.05 (–0.06;0.17)	0.24 (–0.13;0.61)

Values for gait domains represent difference in Z-score (with 95% confidence interval) between restless legs syndrome (RLS) compared to no RLS. Lower values indicate poorer gait.
Values for the Purdue Pegboard Test represent difference in correctly placed pins between RLS compared to no RLS.
Higher numbers represent better performance.
Model 1: adjusted for age, sex.
Model 2: adjusted for age, sex, height, weight, alcohol use, smoking, diabetes mellitus, education, hypertension, coronary heart disease, stroke, lipid lowering medication, osteoarthritis, coffee intake, GFR and RLS medication.
[a] Additionally adjusted for step length and step count in tandem walk.
In all the analyses p-values were above 0.05.

limitations to our work. An important limitation of our study is that the questionnaire did not incorporate the urge to move the legs, which is an essential criterion for the diagnosis of RLS. We assessed presence of uncomfortable sensation in the legs, which are not always present in patients with RLS. People who do not feel the urge, but do have these sensations may have been considered as RLS positives. This might have led to an overestimation of the prevalence. Prevalence can also be underestimated, because people with the urge but without these sensations are considered as RLS negative. This misclassification could have led to a dilution of the association. Other essential RLS criteria are met in our case definition. Another limitation of the questionnaire is that it did not assess the severity of RLS symptoms. 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 only investigated the associations between RLS and physical functioning cross-sectionally. 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 or leg cramps, could not be excluded with our questionnaire. This may have led to an overestimation of the prevalence. The prevalence of RLS in our study is high, but corresponds to prevalence reported in some other studies investigating an aged population, especially in countries from Northern Europe [2,47]. Information regarding other potential confounders like Parkinson's Disease, and medications that might be associated with RLS were not systematically assessed, so we could not investigate whether this influenced our results. We used gait and manual dexterity as tests to quantify motor performance, but this probably covers only part, and possibly other aspects of physical functioning. 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. Moreover, our sensitivity analysis yielded similar results as the main analysis.

To conclude, in our community-dwelling population of middle-aged and older people, we found RLS to associate with self-reported impairment in daily functioning. We did not find an association between RLS and gait or manual dexterity. This indicates that impairment in basic ADL does not originate from a pathophysiological mechanism that affects motor performance. However, there may be processes involved that are not covered by our measurements of gait and manual dexterity. Moreover, we found that the association between RLS attenuated after adjusting for sleep or mood disturbance, indicating that at least part of the association can be explained by a person's general well-being or quality of life.

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Conflicts of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.11.013.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.sleep.2014.11.013.

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Curriculum Vitae

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Gender	Female

Education and training

Dates	December 2020
Title of qualification awarded	**Dr. med. (Rigorosum expected)**
Principal subjects/occupational skills covered	Epidemiology, Neuropsychiatry, Gait and Mobility, Sleep, Diabetes, Addiction
Name and type of organisation providing education and training	**University of Lübeck, Germany**

Dates	August 2012- August 2014
Title of qualification awarded	**Master of Science (MSc)**
Principal subjects/occupational skills covered	Clinical Epidemiology, Health Sciences, Behaviour and Neuroscience

Name and type of organisation providing education and training	**Erasmus University Rotterdam, Netherlands** **Erasmus University Medical Center Rotterdam, Netherlands** **Netherlands Institute for Health Sciences (NIHES)**
Dates	October 2005 – July 2012
Title of qualification awarded	**Doctor of Medicine (MD)**
Principal subjects/occupational skills covered	General and Overall Medical Practice
Name and type of organisation providing education and training	**University of Belgrade, Faculty of Medicine, Belgrade, Serbia**
Working experience	**Centogene AG, Rostock, Germany (March 2016 to present)** **Medical Advisor for Clinical Genetics** **Prenatal genetic evaluation specialist**
	Erasmus University Medical Center Rotterdam, Netherlands (2014-2016) **Doctoral Researcher**
Languages	
Mother tongue(s)	**Serbian, Croatian, Bosnian**

Other language(s)
Self-assessment

	Understanding			**Speaking**				**Writing**	
European level (*)	Listening		Reading	Spoken interaction		Spoken production			
English	C2	Proficient user	C2	Proficient user	C2	Proficient user	C2	Proficient user	C1	Proficient user
French	B2	Independent user	B2	Independent user	B2	Independent user	B2	Independent user	B2	Independent user
Italian	B2	Independent user	B2	Independent user	B2	Independent user	B2	Independent user	B2	Independent user
Spanish	B2	Independent user	B2	Independent user	B2	Independent user	B2	Independent user	B2	Independent user
German	A2	Basic user	A2	Basic user	A2	Basic user	A2	Basic user	A2	Basic User

(*) Common European Framework of Reference for Languages

Technical skills and competences	Genetics diagnostics softwares Big databases analyzing SPSS Alamut Gepado ClinVar HGMD Professional CentoMD IGV
Driving licence	Holder of Driving Licence for B category vehicles
Annexes	**List of Publications:** **1.** "The impact of Restless legs syndrome and sleep quality on daily functioning", published in *Sleep medicine* (*http://www.sciencedirect.com/science/article/pii/S138994571500026X*) **2.** "The associations of alcohol, coffee and tobacco consumption with gait in a community-dwelling population", published in *European Journal of Clinical Nutrition* *(http://www.nature.com/ejcn/journal/vaop/ncurrent/full/ejcn2015120a.html)* **3.** "Depression is associated with gait domains in community dwelling population" under review in *Psychology and Aging* **4.** "Gait characteristics in older adults with diabetes and impaired fasting glucose: the Rotterdam Study" published in *Journal of Diabetes and its complications* (*http://www.sciencedirect.com/science/article/pii/S1056872715003967*)

Annexes

Diplomas and Certificates obtained:

American Society of Human Genetics Annual Meeting, October 2020- poster presentation (Prenatal genetics)

World Congress of Perinatal Medicine, Belgrade, Serbia (October 2017) - lecturer

American Society of Human Genetics Annual Meeting, Orlando, USA (October 2017) – platform presenataion

European Congress of Epidemiology, Maastricht, Netherlands (June 2015)

Erasmus Summer programe, Erasmus University Medical Center Rotterdam, Netherlands (August 2013)

Chronic Disease Epidemiology, University of Cambridge, United Kingdom (February 2013)

Erasmus Summer Programme, Erasmus University Medical Center Rotterdam, Netherlands (August 2012)

Spring School of Healthy Ageing, University of Groningen, Netherlands (May 2012)

The Sixth Young European Scientist Meeting, Porto, Portugal
The best presentation in Internal Medicine session (September 2011)

AIESEC 6-week- internship at "Colors of Society" project in Izmir, Turkey (July to September 2011)

Summer School of Global Health; Universal aspects of Reproductive health, University of Groningen, The Netherlands (July 2011)

International Student Congress of Medical Sciences, University of Groningen, The Netherlands
Active participant with scientific research in the field of Psyciatry (June 2011)

Leiden International Medical Student Conference, Leiden University, The Netherlands
The Best presenatation of the scientific research in the field of Psychiatry awarded (March 2011)

Clinical leadership workshop, Belgrade, Serbia (February 2011)

The 8th International Congress of Medical Sciences, Sofia, Bulgaria (May 2009)
The 2nd Award for Scientific reasearch in the field of Public Health

The 10th Craiova International Medical Student Conference, Cariova, Romania (November 2008) oral presentation
Seminar in the field of Experimental Laparoscopy completed

The 7th International Congress of Medical Sciences, Sofia, Bulgaria (May 2008)
The 1st Award for Scientific reasearch in the field of Public Health

The 6th International Congress of Medical Sciences, Sofia, Bulgaria (May 2007)
The 3rd Award for Scientific reasearch in the field of Public Health

The 5th International Congress of Medical Sciences, Sofia, Bulgaria (May 2006)
The 1st Award for Scientific reasearch in the field of Public Health

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