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Original Study

Association Between Gait Speed With Mortality, Cardiovascular Disease and Cancer: A Systematic Review and Meta-analysis of Prospective Cohort Studies

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A B S T R A C T

Objectives: Slow gait speed may be associated with premature mortality, cardiovascular disease (CVD), and cancer, although a comprehensive meta-analysis is lacking. In this systematic review and meta-analysis, we explored potential associations between gait speed and mortality, incident CVD, and cancer.
Design: A systematic search in major databases was undertaken from inception until March 15, 2018 for prospective cohort studies reporting data on gait speed and mortality, incident CVD, and cancer.
Setting and Participants: All available.
Measures: The adjusted hazard ratios (HRs) and 95% confidence intervals (CIs), based on the model with the maximum number of covariates for each study between gait speed (categorized as decrease in 0.1 m/s) and mortality, incident CVD, and cancer, were meta-analyzed with a random effects model.
Results: Among 7026 articles, 44 articles corresponding to 48 independent cohorts were eligible. The studies followed up on a total of 101,945 participants (mean age 72.2 years; 55% women) for a median of 5.4 years. After adjusting for a median of 9 potential confounders and the presence of publication bias, each reduction of 0.1 m/s in gait speed was associated with a 12% increased risk of earlier mortality (45 studies; HR = 1.12, 95% CI: 1.09-1.14; $I^2 = 90\%$) and 8% increased risk of CVD (13 studies; HR = 1.08, 95% CI: 1.03-1.13; $I^2 = 81\%$), but no relationship with cancer was observed (HR = 1.00, 95% CI: 0.97-1.04; $I^2 = 15\%$).
Conclusion/implications: Slow gait speed may be a predictor of mortality and CVD in older adults. Because gait speed is a quick and inexpensive measure to obtain, our study suggests that it should be routinely used and may help identify people at risk of premature mortality and CVD.

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The speed at which someone walks (gait speed) is an important indicator of their functional status.[1] An increasing body of research suggests that among older people slow gait speed is an important predictor of a range of adverse health outcomes.[2–6] Because gait speed is a quick, inexpensive, and reliable measure of functional capacity,[7] it is widely recorded by physical therapists and other clinicians[8] to assess the functioning of healthy[1] or disease-affected[9] individuals.

There is a particular interest in the relationship between gait speed and mortality. Cooper et al[10] reported that slow gait speed was associated with a significantly increased mortality risk in 5 studies. In a seminal paper, which was not informed by a systematic review, data pooled from 9 cohorts showed that faster gait speed was consistently associated with later survival in older adults.[11] More recently, a systematic review of the literature with meta-analysis[12] reported that slow gait speed was associated with a significant higher risk of death in 12,901 participants older than 65 years. Although these studies have advanced our knowledge regarding gait speed and mortality, one was limited to only older people,[12] another only adjusted for 3 potential confounders,[10] and a further one was not informed by a systematic review,[11] thus offering an incomplete picture of the total evidence base on this topic.

In addition, an increasing body of research highlighted the importance of slow gait speed as prognostic factor for other outcomes such as cancer[13] or cardiovascular disease (CVD).[14] Both CVD and cancer are the most important (and partially preventable) causes of death in industrialized countries.[15] Thus, understanding if slow gait speed is associated with higher incidence of CVD and cancer could be of interest. To our knowledge, only 1 systematic review and meta-analysis has reported data regarding slow gait speed and CVD, but these findings were limited to patients affected by peripheral artery disease at baseline.[16] In addition, no data are available regarding the association between slow gait speed and incident cancer, but it could be of importance to know if gait speed may provide additional prognostic information to improve life expectancy estimation and management decisions in cancer patients.

Given this background, we aimed to investigate the association between slow gait speed and mortality, taking into account different population settings and conditions. Moreover, we aimed to investigate the potential association between gait speed and incident CVD and cancer.

Methods

This systematic review was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria[17] and the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[18] The protocol of this systematic review and meta-analysis is pre-conceived, but not published, and is available upon request from the corresponding author.

Search Strategy

The published literature was searched using key words for the concepts of gait speed, risk, mortality/death/survival, CVD, and cancer until March 15, 2018. The search strategies were established using a combination of standardized terms and key words. The search strategy used in PubMed is reported in Supplementary Table 1 and run in the other databases (Embase, PsycINFO, and the Cochrane Library). Two investigators (N.V., B.S.) independently conducted an electronic literature search, and inconsistencies were resolved by consensus with a third author (S.M.).

References of articles included in the analysis and of others relevant to the topic were hand-searched to identify additional, potentially relevant publications. Conference abstracts were also considered. If we encountered a conference abstract with potentially relevant data, we contacted the authors up to 4 times over a month to enable inclusion and acquire the variables of interest.

Study Selection

We only considered studies that (1) had a prospective design; (2) reported information regarding gait speed measured by trained health personnel; and (3) reported data on incident mortality, CVD, or cancer determined via medical records, hospital records, confirmed via physician-based diagnosis or via self-report, or confirmed by relatives in the case of death.

Studies were excluded if they (1) did not report data regarding gait speed or the outcomes of interest; (2) reported data regarding transitions in gait speed over a follow-up period and outcomes of interest; (3) reported gait speed as self-reported information; or (4) reported data as odds ratios [ORs; in this case, the authors were contacted at least 4 times in a month to obtain the corresponding hazard ratios (HRs)].

Data Extraction

To be included in the quantitative synthesis, studies had to provide data on risk estimates for death, any type of CVD, or for specific CVD or cancer as HRs, together with precision estimates (95% confidence interval [95% CI]). Two authors (N.V., E.C.) independently recorded data extracted from the selected studies into a standardized Microsoft Excel spreadsheet. Any disagreement was resolved by consensus with a third author (B.S.).

The following information was extracted: (1) study characteristics; (2) study setting (eg, community); (3) main condition (eg, frailty, general, CVD, etc); (4) demographic characteristics of the whole population (percentage of women and mean age); (5) type and number of adjustments used in the multivariate analyses; (6) duration of follow-up; and (7) distance (in meters) over which gait speed was recorded. When 2 or more studies represented the same cohort, the largest study was included.

Outcomes

The primary outcome was all-cause mortality analyzed through the adjusted HRs from the model with the maximum number of covariates in each study. This outcome was also analyzed according to the setting and any medical conditions present at baseline. The incidence of composite CVD (fatal or nonfatal events) and cancer were considered as secondary outcomes.

Assessment of Study Quality

The Newcastle-Ottawa Scale (NOS)[19,20] was used to assess study quality. The NOS assigns a maximum of 9 points based on 3 quality parameters: selection, comparability, and outcome, with a cut-off of $\leq$5 being indicative of high risk of bias.[19] NOS scores were initially assessed by 2 investigators (N.V., B.S.), and discrepancies were addressed by a joint reevaluation of the article with a third author (E.C.).

Statistical Analysis

Analyses were performed by one investigator (N.V.) and checked by another researcher (E.C.) using Comprehensive Meta-Analysis 2 (http://www.meta-analysis.com).

Pooled risks of all study endpoints (all-cause mortality and incident CVD and cancer) were computed for reduction in gait speed per −0.1 m/s using fully adjusted HRs. If these estimates were not

reported in the original studies, they were calculated as the inverse variance-weighted mean of the logarithm of HR.[21]

The random effects model was used to account for anticipated between-study heterogeneity.[22] This was assessed using the chi-squared and I-squared statistics, assuming that a $P < .10$ for the former and a value $\geq 50\%$ for the latter were indications of significant heterogeneity.[23] Whenever significant heterogeneity existed and ≥4 studies were available, a meta-regression analysis was performed examining the following prespecified moderators: setting (community-dwelling vs others), condition (general population, presence of cancer/CVD or other medical conditions at baseline), type of ascertainment (categorized as death certificates, medical/administrative data, phone calls, not reported), mean age (categorized as less or more than 75 years, median value), percentage of females (by the median value, 55%), number of covariates (by the median value, ie, 9), distance walked in the gait speed assessment (≤4 vs > 4 m), and quality of the studies (by the median value, ie, 9). For incident CVD, we also stratified the analyses for fatal or nonfatal events.

Publication bias was assessed by visual inspection of funnel plots and by using the Egger bias test.[24] When ≥3 studies were available, we used the Duval and Tweedie nonparametric trim-and-fill method to account for potential publication bias. Based on the assumption that the effect sizes of all the studies are normally distributed around the center of a funnel plot, in the event of asymmetries, this procedure adjusts for the potential effect of unpublished (trimmed) studies.[25]

Results

The search identified 7026 nonduplicated, potentially eligible studies. After excluding 6927 papers on the grounds of a review of their titles and abstracts, 99 full-text articles were examined, and 44 articles[11,26–69] were finally included in our meta-analysis (Supplementary Figure 1), with one paper[11] giving information for 5 cohorts in our analyses. Thus, 48 cohorts were included in the meta-analysis.

Study and Patient Characteristics

The 48 cohorts followed-up on a total of 101,945 participants over a median of 5.4 years (range: 0.5-13.5) (Supplementary Table 2). These participants were on average 72.2 years old (95% CI: 59.1-85.0) and mainly women (55%, 95% CI: 52.0%-55.6%). All the studies reported data regarding mortality, except for 3 studies that reported data only on incident CVD,[26,42,57] and 1 only on incident cancer.[47]

The studies were mainly conducted in Europe (n = 22). The most common setting was the community (n = 35). The study samples were primarily from the general population (n = 26), followed by specific clinical conditions (eg, dementia, heart failure, cancer) (n = 22). The studies mainly investigated gait speed over 4 m (n = 21). The quality of the studies was generally high, as shown by the median value of the NOS score (median = 9), with only 6 studies at high risk of bias (NOS score ≤ 5) Supplementary Table 2.

All-Cause Mortality

Figure 1 shows the association between a reduction of 0.1 m/s in gait speed and mortality, including 45 cohorts with 71,308 participants and 19,294 deaths (ie, 27.1% of the baseline population). Death was ascertained through medical/administrative data in 23 studies and through death certificates in 5 studies.

After adjusting for a median of 9 potential confounders (range: 0-22) and pooling data from 45 cohorts, a reduction of 0.1 m/s in gait speed was associated with an increased risk of mortality of 14% (HR = 1.14, 95% CI: 1.11-1.17; $P < .0001$; $I^2 = 90\%$). The Egger test suggested a presence of significant publication bias (2.21 ± 0.60; $P = .0007$). The recalculated HR was 1.12 (95% CI: 1.09-1.14), after trimming 9 studies to the left of the mean. The fail-safe number was 7646, indicating a large number of negative studies would be required to nullify the finding.

Table 1 reports the association between gait speed and mortality stratified by some possible confounders. In the studies among community-dwellers the association between a reduction in 0.1 m/s and mortality (HR = 1.12, 95% CI: 1.09-1.15; $P < .0001$; $I^2 = 92\%$; 31 studies) was lower than those conducted in other settings (ie, outpatients, nursing home, hospital) (HR = 1.19, 95% CI: 1.14-1.24; $P < .0001$; $I^2 = 53\%$; 14 studies) (Table 1). There was some indication of publication bias in settings other than community (Egger test = 2.23 ± 0.36; $P = .0005$). After trimming 6 studies to the left of the mean, the adjusted HR was 1.21 (95% CI: 1.10-1.32). The fail-safe number was 2219 for studies conducted among community dwellers and 507 in the other settings investigated.

When stratified by conditions, a reduction of 0.1 m/s in gait speed was associated with a higher mortality rate ranging from a HR = 1.10 (95% CI: 1.01-1.20; $P = .03$; $I^2 = 87\%$; 3 studies) in people affected by cancer to a HR = 1.15 (95% CI: 1.11-1.17; $P < .0001$; $I^2 = 71\%$; 23 studies) in the general population (Table 1). Studies conducted in the general population did not show evidence of any publication bias (Egger test = 0.08 ± 0.63; $P = .90$) and the fail-safe number for this outcome was 1897.

The meta-regression showed that none of the confounders (mean age, percentage of females, type of ascertainment, distance walked, number of covariates or quality) affected our results (Table 1).

Cardiovascular Diseases

The association between decreasing gait speed and incident CVD is reported in Figure 2. Of the 13 studies included, 8 reported CVD-related mortality as an outcome,[27,41,43,57,62–65] 2 a composite outcome,[31,44] 1 the onset of coronary heart disease,[26] 1 stroke,[42] and 1 hospitalization for heart failure.[38]

After adjusting for a median of 14 potential confounders (range: 9-22), each reduction of 0.1 m/s in gait speed was associated with a higher risk of fatal or nonfatal (composite) CVD by 13% (HR = 1.13, 95% CI: 1.08-1.18; $P < .0001$; $I^2 = 81\%$). There was some evidence of publication bias (Egger test: 2.92 ± 0.76; $P = .003$), and after trimming 4 studies to the left of the mean, the recalculated HR was 1.08 (95% CI: 1.03-1.13). The fail-safe number for this outcome was 371.

Among the moderators for the incidence of CVD investigated, studies using CVD-related death as the outcome reported an HR of 1.19 (95% CI: 1.10-1.29), even if no moderator (setting, main condition, mean age, quality, number of covariates, type of outcome) explained any heterogeneity of our findings.

Cancer

Four studies reported data regarding a reduction in gait speed and incidence of cancer (3 regarding overall cancer mortality[41,62,64] and 1 regarding incident breast cancer[47]) including a total of 20,717 participants and 1087 events (5.2%). After adjusting for a median of 17 potential confounders (range: 13-21), each reduction in 0.1 m/s in gait speed was not associated with the risk of cancer (HR = 1.00, 95% CI: 0.97-1.04; $P = .97$; $I^2 = 15\%$; Figure 2). For this outcome, publication bias was not evident (Egger test: 1.53 ± 0.88; $P = .22$).

Similar findings were evident for cancer-related mortality (3 studies; HR = 1.02, 95% CI: 0.95-1.09; $I^2 = 35\%$).

Discussion

In this meta-analysis, including 48 cohorts and more than 100,000 participants, we found that slow gait speed was associated with an

Study name	Sample size	Hazard ratio	Lower limit	Upper limit	p-Value
Arnau, 2016	315	1.210	1.052	1.392	0.008
Cesari, 2009	934	1.170	1.066	1.285	0.001
Cesari, 2013	200	1.350	1.071	1.702	0.011
Chen, 2012	558	1.230	1.089	1.389	0.001
Cheung, 2016	2841	1.150	1.082	1.222	<0.0001
Dallmeier, 2016	1166	1.150	1.050	1.260	0.003
Dodson, 2016	338	1.030	0.944	1.123	0.504
Dulaney,2017	85	1.570	1.201	2.052	0.001
Dumurgier, 2009	3208	1.050	1.001	1.101	0.045
Elbaz, 2013	6266	1.070	1.012	1.132	0.018
Hernández-Luis, 2018	298	1.320	1.042	1.673	0.022
Hsu, 2018	1705	1.450	1.293	1.626	<0.0001
Idland, 2013	300	1.160	1.069	1.259	<0.0001
Kamiya, 2016	599	1.220	1.058	1.407	0.006
Kano, 2017	1256	1.240	1.086	1.415	0.001
Kittiskulnam, 2017	645	1.140	1.101	1.180	0.000
Klepin, 2010	429	1.050	0.919	1.199	0.472
Kon, 2015	402	1.100	1.009	1.199	0.030
Kutner, 2015	752	1.090	1.022	1.162	0.009
Lee, 2017	911	1.030	0.939	1.129	0.529
Lipnicki, 2016	1007	1.190	1.090	1.300	0.000
Lo, 2015	1119	1.020	0.976	1.066	0.377
Matsuzawa, 2013	472	1.410	1.227	1.620	0.000
McDermott, 2008	444	1.110	1.006	1.225	0.038
Nofuji, 2016	1085	1.080	1.017	1.147	0.012
Pamoukdjan, 2017	190	1.330	1.079	1.639	0.007
Piovezan, 2016	958	1.130	1.016	1.257	0.025
Pulignano, 2016	331	1.170	0.994	1.377	0.059
Rodríguez-Pascual, 2017	497	1.180	1.066	1.307	0.001
Rolland, 2008	7250	1.190	1.076	1.316	0.001
Rosano, 2008	3168	1.020	1.010	1.030	<0.0001
Roshanravan, 2012	309	1.190	1.041	1.361	0.011
Roshanravan,2013	385	1.160	1.011	1.331	0.035
Sanders, 2016	1559	1.090	1.056	1.125	<0.0001
Sergi, 2015	2565	1.150	1.082	1.222	<0.0001
Sigvardsen, 2017	116	1.080	0.998	1.168	0.055
Studenski, 2011 (EPESE)	2128	1.200	1.151	1.251	<0.0001
Studenski, 2011 (HEPESE)	1905	1.050	1.016	1.085	0.004
Studenski, 2011 (Osteoporotic Fractures in Men)	5833	1.200	1.156	1.246	<0.0001
Studenski, 2011 (PEF)	491	1.180	1.160	1.200	<0.0001
Studenski, 2011 (SOF)	10349	1.150	1.121	1.180	<0.0001
Taekema, 2012	599	1.020	0.971	1.071	0.429
Toots, 2013	772	1.120	1.052	1.192	<0.0001
van der Holst, 2016	494	1.170	1.083	1.264	<0.0001
von Bonsdorff, 2013	4074	1.090	1.056	1.125	<0.0001
Overall effect *(I^2=91% [p<0.001])*		**1.138**	**1.110**	**1.167**	**<0.0001**

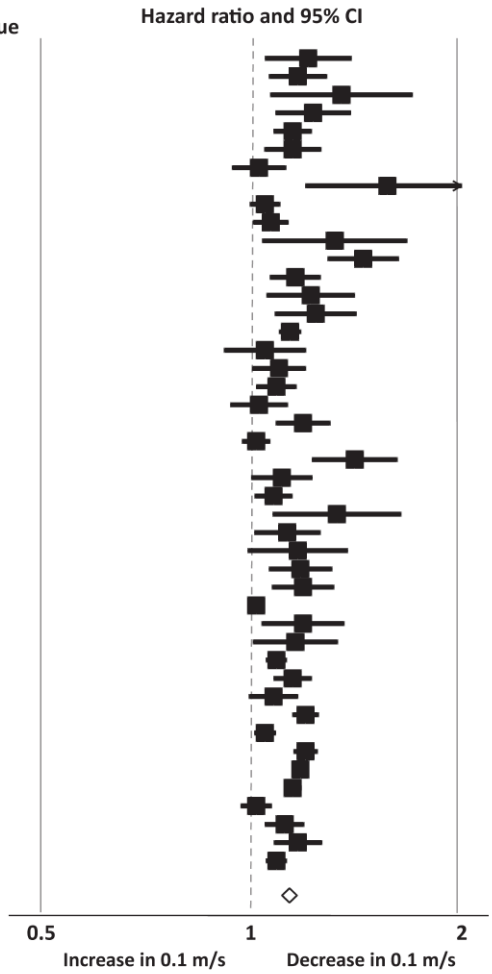

Fig. 1. Meta-analysis of pooled hazard ratios (HRs) of gait speed and mortality.

increased risk of earlier mortality and incident CVD, whereas we did not observe a relationship between gait speed and incident cancer. After adjusting for multiple confounders, the risk-effect associated with a reduction of 0.1 m/s in gait speed was consistent with death and the onset of CVD, which was present after adjusting for publication bias, and our additional analysis indicated that a high number of studies would be needed to nullify the effects (particularly for death).

Two previous meta-analyses have previously reported a significant association between slow gait speed and mortality.[10,11] Our findings are substantially in agreement with these 2 papers, but our study added many other studies published in recent years and is the largest meta-analysis on this topic containing more than 100,000 people. In addition, our meta-analysis included all people independently from their baseline conditions and after a systematic review of the literature. The significant overall effects found in our meta-analysis are supported by consistent findings of individual studies; we found a higher risk of death across 44 of 48 (92%) studies. When compared to the previous literature regarding gait speed and mortality, we would like to report several novel/important points from our meta-analysis. First, a previous large systematic review and meta-analysis was limited to only older people,[12] and other outcomes of great epidemiologic and clinical interest, such as cancer or CVD, were not considered. Another meta-analysis regarding gait speed and mortality included only 3 potential confounders,[10] whereas a seminal meta-analysis regarding gait speed and mortality was not supported by a systematic review of the literature,[11] potentially introducing a bias. Finally, we have for the first time conducted numerous subgroup analyses such as according to the setting, population, mean age, and percentage of females to better explain the findings and provide a more meaningful, targeted clinical message that was previously not available. Unfortunately, despite the large number of stratification, no moderator was able to explain the heterogeneity of our findings, suggesting that other factors could influence our results.

The reason why slow gait speed is associated with premature death is unclear but may be explained through several pathways. First, a common contributor to slow gait speed is the presence of other comorbidities (eg, diabetes, osteoarthritis) which have also been associated with premature mortality.[15,70] However, the original papers included in our pooled analyses were adjusted for many of these confounders. Second, slow gait speed is commonly associated with endocrine dysfunction (such as low testosterone levels),[71] inflammation,[72] and oxidative stress,[73] all of which are associated with a higher risk of death.[74–76] Furthermore, gait speed may indicate difficulties with activities of daily living and engaging in physical activity; restrictions within each of these activities have been associated with increased risk of earlier death.[77] Finally, as supported by a recent meta-analysis on function and mortality,[78] gait speed is a powerful predictor of death, being able to capture early on the multisystemic impairment associated with aging and multimorbidity. Therefore, gait speed might be an indicator of functional reserve and resilience.

A similar argument can be proposed for the relationship between slow gait and CVD. Higher inflammatory and oxidative stress levels

Table 1
Stratification for Some Potential Confounders for the Association Between Slow Gait Speed and Mortality

Moderator	Strata	Analysis Details	Mortality
Setting	Community	Pooled estimate, HR (95% CI)	1.12 (1.09-1.15)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	92 (<.0001)
		Number of studies	31
	Others	Pooled estimate, HR (95% CI)	1.19 (1.14-1.24)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	53 (.01)
		Number of studies	14
		P value*	.03
Condition	General population	Pooled estimate, HR (95% CI)	1.15 (1.11-1.18)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	86 (<.0001)
		Number of studies	23
	Cancer	Pooled estimate, HR (95% CI)	1.10 (1.01-1.20)
		P value for estimate	.03
		Heterogeneity, I^2 (*P* value)	87 (.001)
		Number of studies	3
	CVD	Pooled estimate, HR (95% CI)	1.11 (1.05-1.17)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	91 (<.0001)
		Number of studies	9
	Other medical conditions	Pooled estimate, HR (95% CI)	1.14 (1.09-1.19)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	76 (<.0001)
		Number of studies	10
		P value*	.64
Type of ascertainment	Death certificates	Pooled estimate, HR (95% CI)	1.10 (1.03-1.18)
		P value for estimate	.005
		Heterogeneity, I^2 (*P* value)	75 (.004)
		Number of studies	5
	Medical/administrative data	Pooled estimate, HR (95% CI)	1.12 (1.07-1.16)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	95 (<.0001)
		Number of studies	23
	Phone calls	Pooled estimate, HR (95% CI)	1.20 (1.12-1.28)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	0 (.74)
		Number of studies	4
	Not reported	Pooled estimate, HR (95% CI)	1.21 (1.13-1.26)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	45 (.089)
		Number of studies	13
		P value*	.08
Mean age	<75 y	Pooled estimate, HR (95% CI)	1.123 (1.09-1.16)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	93 (<.0001)
		Number of studies	28
	≥75 y	Pooled estimate, HR (95% CI)	1.16 (1.11-1.20)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	75 (<.0001)
		Number of studies	17
		P value*	.22
Percentage of females	<55%	Pooled estimate, HR (95% CI)	1.14 (1.11-1.18)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	77 (<.0001)
		Number of studies	26
	≥55%	Pooled estimate, HR (95% CI)	1.13 (1.09-1.17)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	90 (<.0001)
		Number of studies	19
		P value*	.49
Number of covariates	<9	Pooled estimate, HR (95% CI)	1.15 (1.13-1.18)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	71 (<.0001)
		Number of studies	22
	≥9	Pooled estimate, HR (95% CI)	1.11 (1.08-1.15)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	84 (<.0001)
		Number of studies	23
		P value*	.09

(*continued on next page*)

Table 1 (*continued*)

Moderator	Strata	Analysis Details	Mortality
Distance walked in the assessment (meters)	≤4	Pooled estimate, HR (95% CI)	1.12 (1.09-1.16)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	92 (<.0001)
		Number of studies	25
	>4	Pooled estimate, HR (95% CI)	1.15 (1.12-1.19)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	86 (<.0001)
		Number of studies	20
		P value*	.27
Quality	NOS score <9	Pooled estimate, HR (95% CI)	1.14 (1.09-1.18)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	94 (<.0001)
		Number of studies	20
	NOS score = 9	Pooled estimate, HR (95% CI)	1.14 (1.11-1.17)
		P value for estimate	<.0001
		Heterogeneity, I^2 (*P* value)	77 (<.0001)
		Number of studies	25
		P value*	.86

*P value represents the interaction between strata.

are known risk factors for the onset of CVD,[79] and people with endocrine abnormalities often have slow gait speed.[80] Some researchers have reported that slow gait speed is associated also with subclinical atherosclerotic lesions.[81] This may explain the higher incidence of CVD in people with slow gait speed. Moreover, the results of our work are in agreement with recent evidence highlighting frailty as a potential CVD risk factor[82] and suggesting that frailty, sarcopenia, malnutrition and disability are inter-connected domains.[83] However, a possible limitation of the studies investigating fatal CVD events as outcomes is that they did not adjust for the presence at baseline of previous CVD. Even if the adjustment for other factors is probably sufficient (minimum 9), further studies using people free from CVD or at least adjusting for this relevant factor at baseline are required.

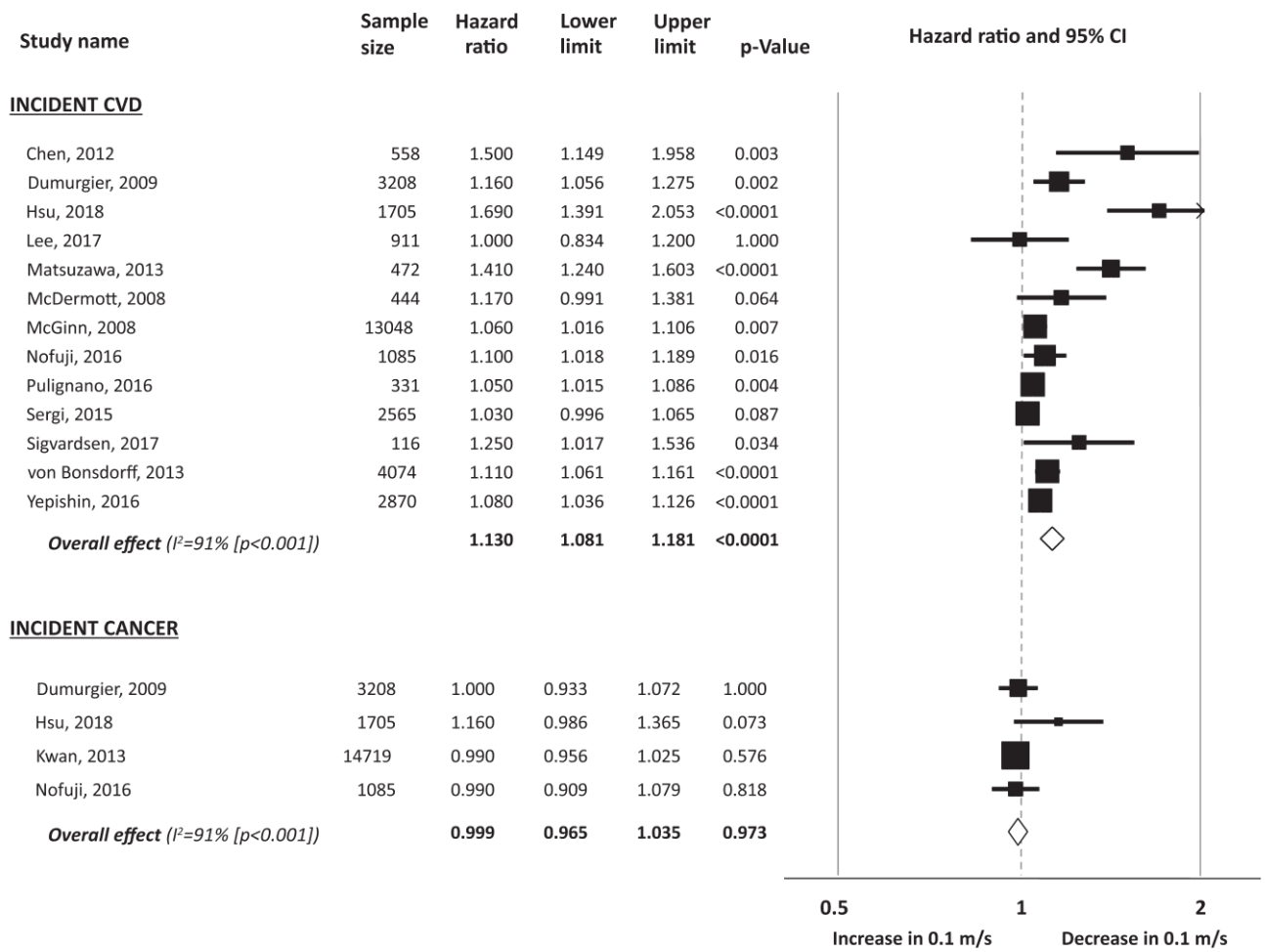

Fig. 2. Meta-analysis of pooled hazard ratios (HRs) of gait speed and incident cardiovascular disease and incident cancer.

On the contrary, we did not find any association between slow gait speed and incident cancer. Although it may be true that there is no relationship between gait speed and cancer incidence, it is also possible that we failed to identify a relationship due to inadequate statistical power, as this analysis was limited to 4 studies and only 5.2% of the baseline population developed cancer during the follow-up period, raising the possibility of type II error. Similarly to our findings, Wu et al found, in a large meta-analysis in community dwellers, that low handgrip strength is associated with a higher incidence of death and CVD but not cancer.[84] Because cancer incidence is increasing worldwide,[85] to elucidate whether slow gait speed is associated with higher incidence of cancer is of importance, and consequently other studies with larger populations and longer follow-ups are needed to clarify this issue.

Although our article represents a comprehensive meta-analysis of the relationship between gait speed and these outcomes, it should be interpreted within its limitations. First, gait speed was assessed differently across the studies included. Second, as mentioned before, we were not able to explain the high level of heterogeneity found regarding mortality and CVD. Moreover, some outcomes were affected by publication bias. Although we attempted to reduce this by including conference abstracts and adjusting our results for publication bias using the trim and fill analysis, we cannot exclude the possibility that studies reporting negative or null findings may not have been published and that could influence our findings. Third, people not able to walk were not considered in these cohort studies, but it is widely known that such people are at a higher risk of mortality. However, this source of bias cannot be addressed. Finally, we had only 4 studies eligible for cancer, and additional works are needed for verifying the cancer-related outcome.

In conclusion, slow gait speed is a significant predictor of mortality and of the onset of CVD, although no significant association was found for cancer. Because gait speed is a quick and inexpensive measure to obtain even in older people, our work suggests that it should be routinely used. Future studies on the association between slow gait speed and cancer are warranted.

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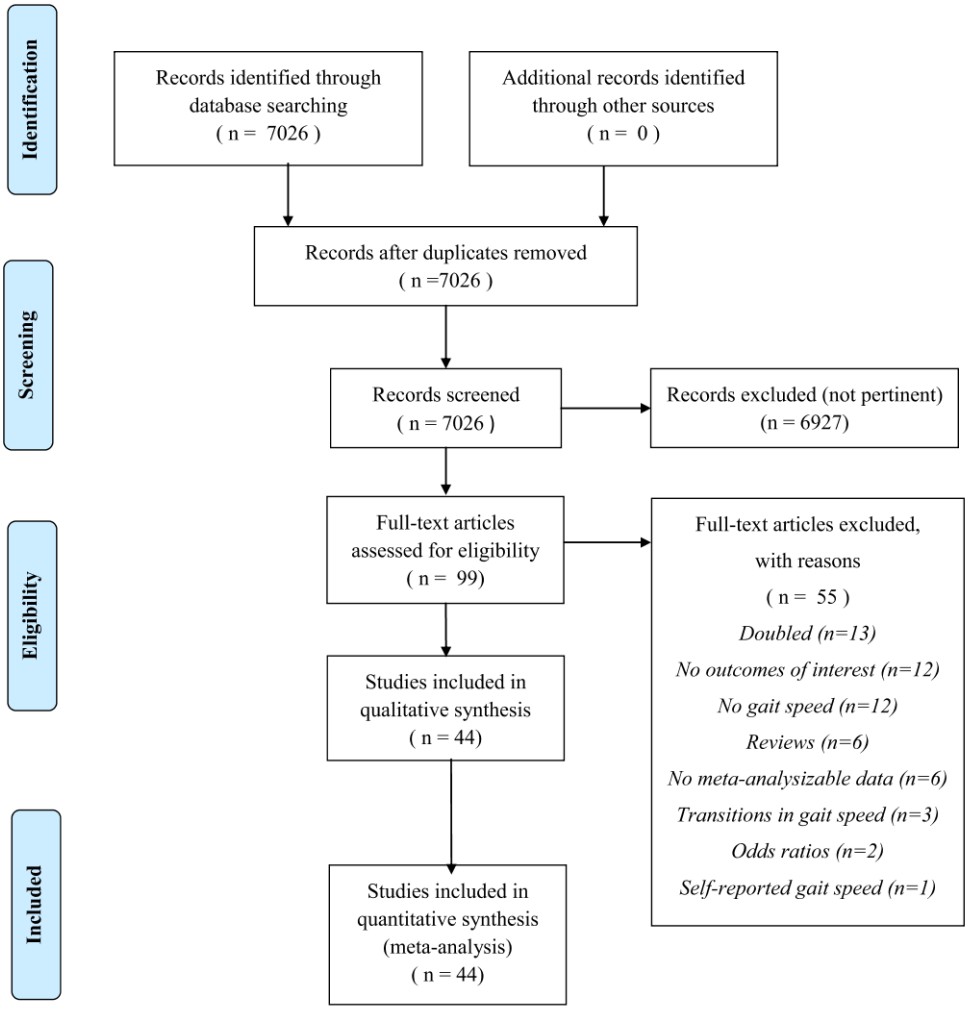
Appendix



Supplementary Figure 1. PRISMA flow-chart.

Supplementary Table 1
Search Strategy

(gait OR gait speed OR walking speed OR walking pace OR walking) AND (cardiovascular OR stroke OR cerebrovascular OR transient ischemic attack OR transient ischaemic attack OR peripheral vascular OR myocardial infarction OR coronary heart disease OR coronary artery disease OR ischemic heart disease OR ischaemic heart disease OR hypertensive heart disease OR angina OR cardiac failure OR heart failure OR congestive heart failure OR cardiovascular mortality OR cancer OR tumor OR neoplasia OR mortality OR survival OR death) AND (longitudinal OR prospective OR cohort OR risk ratio OR RR OR hazard ratio OR HR OR follow up OR follow-up). A similar search (adapted to the requirements of each database).

Supplementary Table 2
Descriptive Findings of the Studies Included

Author, Year	Country	Setting	Main Condition	No. of Participants	Mean Age (SD)	Percentage of Females	No. of Events	Follow-up Duration, y	Distance Walked in Gait Speed Testing, m	Quality	Covariates (n)
Arnau, 2016	Spain	Community	General population (≥75 y, no disabled)	315	81.9 (4.7)	60.6	209	10	4	8	Age, gender, number of drugs, cognitive status, BMI, visual sharpness (6)
Cesari, 2009	Italy	Community	General population	934	74.5 (7)	54.9	263	5.1	7	9	Height, weight, age, gender, site, education, Mini-Mental State Examination score, Center for Epidemiological Studies—Depression scale score, physical activity, congestive heart failure, CAD, hypertension, peripheral artery disease, respiratory disease, osteoarthritis, stroke, IL-6 (log value), CRP (log value), tumor necrosis factor alpha (19)
Cesari, 2013	Italy	Outpatients	Gynecologic cancer	200	73.5 (6.2)	100	23	1	4	7	Age, BMI, Mini-Mental State Examination, quality of life, cancer stage (5)
Chen, 2012	Taiwan	Nursing home	Residents in nursing home	558	82.4 (5.7)	0	99	2.5	6	7	Age, height, BMI, waist circumference, current smoking, exercise, hypertension, diabetes mellitus, proteinuria, handgrip strength, hemoglobin, platelet, neutrophil count, lymphocyte count, HbA_{1C}, alanine transaminase, creatinine, albumin, uric acid, serum triglyceride, serum total cholesterol, serum high-density lipoprotein (22)
Cheung, 2016	United States	Community	General population	2841	73 (3)	39.2	330	5	6	9	Age, sex, race/ethnicity, BMI, alcohol drinking, aspartate aminotransferase, alkaline phosphatase, microalbuminuria/ albuminuria (8)
Dallmeier, 2016	Germany	Community	General population	1166	NA	NA	6	4	NA	3	Age (1)
Dodson, 2016	United States	Community	Previous acute myocardial infarction (<1 mo)	338	73.3 (6)	40	93	1	5	7	Age, sex, race, atrial fibrillation, heart failure, hypertension, peripheral vascular disease, diabetes mellitus, chronic lung disease, advanced renal dysfunction (10)
Dulaney, 2017	United States	Outpatients	Brain metastases	85	61.5 (10.3)	57.6	57	1.5	4	6	Graded prognostic assessment (1)

Dumurgier, 2009	France	Community	General population	3208	73.2 (4.6)	65	209	5.1	4	9	Age, sex, BMI, height, education level, Mini-Mental State Examination, physical activity, diabetes mellitus, hypertension, use of NSAIDs for joint pain, psychotropic drug use, alcohol, smoking, dyslipidemia, exertional dyspnea, peripheral artery disease, dependence for at least 1 IADL, depressive symptoms, homocysteine concentration (19)
Elbaz, 2013	United Kingdom	Community	General population	6266	61.1 (6)	29.2	227	6.4	2.44	9	Age, sex, smoking history, alcohol consumption, physical activity, fruit and vegetable consumption, systolic and diastolic blood pressure, blood cholesterol, heart rate, history of diabetes, coronary heart disease, self-reported stroke, arthritis, respiratory diseases, antidepressant use at phase 7, AH4-I test, IL-6, CRP (18)
Hernández-Luis, 2018	Spain	Hospital	Any cause of hospitalization	298	76.6	49	109	2.02	10	9	Global Subjective Nutritional Score, Fried Frailty Index, Clinical Frailty Scale of the Canadian Study of Health and Aging (12)
Hsu, 2018	Australia	Community	General population	1705	76.9 (5.5)	0	519	7	6	9	Age, comorbidity, smoking status, alcohol, BMI, ethnicity, education, CVD, diabetes, self-rated health, ADL disability, depression, walking duration (13)
Idland, 2013	Norway	Community	Older women (≥75 y)	300	80.9 (4.1)	100	213	13.5	29	8	TUG test, living alone, self-rated health, number of medications, number of diseases general health questionnaire scores (6)
Kamiya, 2016	Japan	Hospital	Hospitalized for CVD	599	75 (6)	35	72	1.9	10	3	Not declared (0)
Kano, 2017	Japan	Hospital	Transcatheter aortic valve replacement	1256	NA	72.3	116	1	5	9	Age, male sex, New York Heart Association class III/IV, diabetes mellitus, previous coronary artery bypass grafting, STS score, B-type natriuretic peptide, serum creatinine, hemoglobin, transfemoral approach, peripheral artery disease, liver disease (12)
Kittiskulnam, 2017	United States	Outpatients	Hemodialysis	645	56.7 (14.5)	41.4	78	1.9	4	9	Age, sex, race, comorbidities, serum albumin (5)

(*continued on next page*)

Supplementary Table 2 (*continued*)

Author, Year	Country	Setting	Main Condition	No. of Participants	Mean Age (SD)	Percentage of Females	No. of Events	Follow-up Duration, y	Distance Walked in Gait Speed Testing, m	Quality	Covariates (n)
Klepin, 2010	United States	Community	Cancer	429	77.2 (3.3)	36.1	308	6	20	8	Demographics, smoking status, physical activity, major disability at baseline, cognitive screen (modified Mini-Mental State Examination score), diabetes mellitus, CVD, COPD, cancer type (9)
Kon, 2015	United Kingdom	Community	COPD	402	69 (NA)	43	266	3	4	3	Not declared (0)
Kutner, 2015	United States	Outpatients	Hemodialysis	752	53.4 (14.1)	64	109	3.5	4	7	Age, sex, race, education, participant clinic, smoking status, BMI, end-stage renal disease vintage, diabetes, COPD, cancer, cardiovascular comorbid conditions, hemoglobin level, cognitive function score, history of recent falls (15)
Kwan, 2013	United States	Community	General population	14719	50-79	100	762	12.4	4	9	Age, ethnicity, income, general health status, smoking status, alcohol use, mammogram in the last 2 y, prior use and duration of estrogen plus progestin, BMI, and Gail 5-y risk for breast cancer (10)
Lee, 2017	Taiwan	Community	General population	911	65.3 (9.3)	44.7	67	4.1	3	9	Age, sex, systolic blood pressure, use or nonuse of antihypertensive medication, total cholesterol, HDL, use or nonuse of lipid lowering medication, presence or absence of diabetes, smoking status (9)
Lipnicki, 2016	Australia	Community	General population	1007	62.7 (14.1)	66.7	201	5.8	6	9	Waist-to-hip ratio, CVD, cancer, mean systolic blood pressure, mean diastolic blood pressure, kidney disease, arthritis, Parkinson disease, alcohol drinking, smoking, depression, age, sex (12)
Lo, 2015	United States	Community	General population	1119	74 (6)	51	740	10	4	9	Age, gender, race, marital status, education, income, depression score, Mini-Mental State Examination score, hypertension, CAD, chronic kidney disease (11)

Matsuzawa, 2013	Japan	Hospital	Primary PCI after an ST elevated myocardial infarction	472	62 (11)	18.2	64	5.5	200	8	Framingham Risk Score, height, weight, comorbidity index, eGFR, BNP, Killip class, LVEF, HMG-CoA RI, ACE-I/ARB, use of cane or walker, days in bed, days from admission to measurement of gait speed, number of times of rehabilitation (14)
McDermott, 2008	United States	Community	Peripheral artery disease	444	71.9 (8.4)	40.1	127	4.8	4	7	Age, gender, race, comorbidities, cigarette smoking, BMI, ankle brachial index, blocks walked during the past week, stair flights climbed during the past week (9)
McGinn, 2008	United States	Community	General population	13048	65 (7.1)	100	264	7.3	6	9	Age, race/ethnicity, BMI, waist-hip ratio, depression, arthritis, hypertension, smoking, systolic blood pressure, history of coronary heart disease, treated diabetes at baseline, hormone use, NSAID use, aspirin use, self-reported general health (14)
Nofuji, 2016	Japan	Community	General population	1085	71 (5.7)	55.5	324	10	5	9	Age, sex, study area, education, BMI, stroke, heart disease, hypertension, diabetes mellitus, cystatin C, IL-6, high-sensitivity CRP, albumin, hemoglobin, total cholesterol, self-rated health, depressive mood, smoking, alcohol, physical activity, grip strength, balance (21)
Pamoukdjan, 2017	France	Outpatients	Cancer	190	80.6 (5.6)	49.5	32	0.5	4	7	CRP, Eastern Cooperative Oncology Group performance status, Cumulative Illness Rating Scale Geriatric, ADL, IADL (5)
Piovezan, 2016	Multicontinent	Not declared	Dementia	958	NA	NA	NA	3.5	10	5	Sociodemographic characteristics, physical impairments, cardiovascular risk factors, nutritional status, depression, dementia severity, dementia subtypes (7)
Pulignano, 2016	Italy	Community	Heart failure	331	78 (5.2)	42.3	80	1	4	7	Age, ejection fraction <20%, systolic blood pressure, anemia, absence of beta-blocker therapy (5)
Rodríguez-Pascual, 2017	Spain	Outpatients	Heart failure	497	85.2 (7.3)	61	99	1	4	5	None (0)

(*continued on next page*)

Supplementary Table 2 (*continued*)

Author, Year	Country	Setting	Main Condition	No. of Participants	Mean Age (SD)	Percentage of Females	No. of Events	Follow-up Duration, y	Distance Walked in Gait Speed Testing, m	Quality	Covariates (n)
Rolland, 2008	France	Community	General population (womenaged ≥75 y)	7250	80.5 (3.8)	100	NA	3.8	6	8	IADL, diabetes, cancer, Pfeiffer Cognitive Test, smoking, self-reported assessment of health, obesity, inability to walk outdoors, hospitalization during the year (9)
Rosano, 2008	United States	Community	General population	3168	70.4 (4.6)	57	704	8.4	4	9	Subclinical disease, congestive heart failure, hypertension, diabetes mellitus, myocardial infarction, physical activity, modified Mini-Mental State Examination score, grip strength, MRI lesions (9)
Roshanravan, 2012	United States	Community	Chronic kidney disease (not in dialysis)	309	58.9 (13)	NA	31	2.7	4	4	Age, sex, race, study site, smoking, BMI, eGFRCysC, diabetes, prevalent coronary disease (9)
Roshanravan, 2013	United States	Outpatients	Chronic kidney disease	385	61 (13)	16	34	3	4	7	Age, sex, race, study site, smoking, BMI, diabetes, prevalent CAD, eGFR (9)
Sanders, 2016	The Netherlands	Community	General population	1559	74.9 (5.8)	50	1318	13	6	9	Gender, age, educational level, household composition, alcohol use, processing speed, Center for Epidemiologic Studies—Depression scale (7)
Sergi, 2015	Italy	Community	General population	2565	75.6 (7.5)	58.6	460	4.4	4	8	Age, sex, BMI, diabetes, hypertension, CVD at baseline, fractures, COPD, cancer, cognitive impairment, education, smoking, income, physical activity level, ADL score (15)
Sigvardsen, 2017	Denmark	Hospital	Asymptomatic aortic valve stenosis	116	72 (8)	27	23	5.5	6MWT	9	COPD (1)
Studenski, 2011 (EPESE)	United States	Community	General population	2128	78.9 (5.5)	66	1955	10	2	7	Age (1)
Studenski, 2011 (HEPESE)	Spain	Community	General population	1905	74.7 (6)	57.6	972	10	2	7	Age (1)
Studenski, 2011 (Osteoporotic Fractures in Men)	United States	Community	General population	5833	73.6 (5.8)	0	1073	10	6	7	Age (1)
Studenski, 2011 (PEF)	United Kingdom	Community	General population	491	74.1 (5.7)	44	283	10	4	6	Age (1)
Studenski, 2011 (SOF)	United States	Community	General population	10349	71.8 (5.2)	100	5512	10	6	7	Age (1)

Taekema, 2012	The Netherlands	Community	General population (≥85 y)	599	NA	66.1	542	12.2	6	9	Summed score chronic diseases, systolic blood pressure, BMI, smoking status, self-reported health, physical activity score, walking aid use, Geriatric Depression Scale, Mini-Mental State Examination, IADL (10)
Toots, 2013	Sweden	Community	General population (>=85 y)	772	89.6 (4.6)	70.2	464	5	2.44	9	Age, age* follow-up time, sex, care facility resident, lives alone, education, education* follow-up time, depression, cerebrovascular disease, myocardial infarction, heart failure, hip fracture, diabetes, malignancy, benzodiazepines, antidepressants, diuretics, analgesics, neuroleptics, number of prescribed drugs, systolic blood pressure, diastolic blood pressure, vision impairment, hearing impairment, BMI, Mini-Mental State Examination (26)
van der Holst, 2016	The Netherlands	Community	Cerebral Small Vessel Disease	494	65.7 (8.8)	44.6	78	8	4	8	Age, sex, smoking, diabetes mellitus, hypertension (5)
von Bonsdorff, 2013	Iceland	Community	General population	4074	76 (5.5)	62.8	645	5.4	4	9	Age, gender, education, smoking, physical activity, BMI, total cholesterol, prevalent hypertension, diabetes, arthritis, COPD (11)
Yepishin, 2016	United States	Community	General population	2870	NA	NA	NA	8	4	6	Age, BMI, hypertension, diabetes, pack-years smoking, physical activity, cholesterol, HDL, alcohol intake (9)
Total	Europe: n = 22; North America: n = 18; Asia: n = 5; Oceania: n = 2; multicontinent: n = 1	Community: n = 35; outpatients: n = 7; hospital: n = 4; nursing home: n = 1; not declared:n = 1	General population: n = 26; specific conditions: n = 22; nursing home residents: n = 1	101,945	72.2 (7.1)	55	20,160	Median = 5.4 (range: 0.5-13.5)	4 m: n = 21; <4 m: 5; >4 m: 21; not declared: n = 1	Median = 9 (range: 3-9)	Median = 9 (range: 0-26)

ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers; ADL, activities of daily living; BMI, body mass index; BNP, brain natriuretic peptide; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; eGFRCysC, eGFR by cystatin C; EPESE, established populations for epidemiologic studies of the elderly; HbA_{1C}, glycosylated hemoglobin; HDL, high-density lipoprotein; HEPESE, Hispanic Established Populations for the Epidemiologic Study of the Elderly; HMG-CoA RI, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; IADL, instrumental activities of daily living; IL, interleukin; LVEF, left ventricular ejection function; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention; PEF, predicting elderly performance; 6MWT, 6-minute walk test; SOF, Study of Osteoporotic Fractures; SD, standard deviation; STS, Society of Thoracic Surgeons; TUG, timed up and go test.