ASSOCIATION BETWEEN GAIT SPEED WITH MORTALITY, CARDIOVASCULAR DISEASE AND CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS OF PROSPECTIVE COHORT STUDIES

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ABSTRACT

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 15th 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-analysed with a random-effects model.

Results: Among 7,026 papers, 44 articles corresponding to 48 independent cohorts were eligible. The studies followed-up 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 14% 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. Since 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.

Key words: gait speed; mortality; cardiovascular disease; cancer; meta-analysis.

INTRODUCTION

The speed at which someone walks (gait speed) is an important indicator of a 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]. Since 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 five studies. In a seminal paper, which was not informed by a systematic review, data pooled from nine 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. Whilst these studies have advanced our knowledge regarding gait speed and mortality, one was limited to only older people [12], whilst another only adjusted for three potential confounders [10] a further 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, to understand if slow gait speed is associated with higher incidence of CVD and cancer could be of interest. To the best of our knowledge, only one 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 in 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 pre-conceived, but not published and is available upon request to 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 15th, 2018. The search strategies were established using a combination of standardized terms and key words. The search strategy used in PubMed was reported in **Supplementary Table 1** and run in the other databases (Embase, PsycINFO and the Cochrane Library). Two investigators (NV, BS) independently conducted an electronic literature search and inconsistencies were resolved by consensus with a third author (SM).

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 four times over a month period to enable inclusion and acquire the variables of interest.

Study selection

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

Studies were excluded if they: a) did not report data regarding gait speed or the outcomes of interest; b) reported data regarding transitions in gait speed over a follow-up period and outcomes of interest; c) reported gait speed as self-reported information; d) reported data as odds ratios, OR (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 (NV, EC) independently recorded data extracted from the selected studies into a standardized Microsoft Excel spreadsheet. Any disagreement was resolved by consensus with a third author (BS).

The following information was extracted: i) study characteristics; ii) study setting (e.g., community); iii) main condition (e.g. frailty, general, CVD , etc.); iv) demographic characteristics of the whole population (percentage of women and mean age); v) type and number of adjustments used in the multivariate analyses; vi) duration of follow-up; vii) distance (in meters) over which gait speed was recorded. When two 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 settings and any medical conditions present at baseline. The incidence of composite CVD (fatal or non-fatal 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 three quality parameters: selection, comparability, and outcome, with a cut-off of ≤ 5 being indicative of high risk of bias [19]. NOS scores were initially assessed by two investigators (NV, BS), and discrepancies were addressed by a joint re-evaluation of the article with a third author (EC).

Statistical analysis

Analyses were performed by one investigator (NV) and checked by another researcher (EC) using Comprehensive Meta-Analysis (CMA) 2 (http://www.meta-analysis.com).

Pooled risks of all study endpoints (all-cause mortality and incident CVD and cancer) were computed for per -0.1 m/s reduction in gait speed 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 $p<0.10$ 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 pre-specified 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, i.e.=9), distance walked in the gait speed assessment ($\leq$ vs. > 4 meters), and quality of the studies (by the median value, i.e.=9). For incident CVD we also stratified analysis for fatal or non-fatal events.

Publication bias was assessed by visual inspection of funnel plots and using the Egger bias test [24]. When ≥3 studies were available, we used the Duval and Tweedie non-parametric 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 7,026 non-duplicated, potentially eligible studies. After excluding 6,927 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 (**eFigure 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 a total of 101,945 participants over a median of 5.4 years (range: 0.5-13.5) (**eTable 1**). 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 three studies which reported data only on incident CVD [26,42,57], and one 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 general population (n=26), followed by specific clinical conditions (e.g. 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 scale (median=9), with only six studies at high risk of bias (NOS $\leq$ 5) (**eTable 1**).

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 (=27.1% of the baseline population). Death was ascertained through medical/administrative data in 23 studies and through death certificates in five 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<0.0001; I^2=90%). The Egger's test suggested a presence of significant publication bias (=2.21±0.60; p=0.0007). 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 7,646, 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<0.0001; I^2=92%; 31 studies) was lower than those conducted in other settings (i.e. outpatients, nursing home, hospital) (HR=1.19; 95%CI: 1.14-1.24; p<0.0001; I^2=53%; 14 studies) **(Table 1)**. There was some indication of publication bias in settings other than community (Egger's test=2.23±0.36; p=0.0005). 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 2,219 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=0.03; I^2=87%; 3 studies) in people affected by cancer to a HR=1.15 (95%CI: 1.11-1.17; p<0.0001; 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's test=0.08±0.63; p=0.90) 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], two a composite outcome [31,44], one the onset of coronary heart disease [26], one stroke [42] and one 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 non-fatal (composite) CVD by 13% (HR=1.13; 95%CI: 1.08-1.18; p<0.0001; I^2=81%). There was some evidence of publication bias (Egger's test: 2.92±0.76; p=0.003) 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 a 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 (three regarding overall cancer mortality [41,62,64] and one regarding incident breast cancer [47]) including a total of 20,717 participants and 1,087 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=0.97; I^2=15%; **Figure 2**). For this outcome, publication bias was not evident (Egger's test: 1.53±0.88; p=0.22).

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 increased risk of earlier mortality, incident CVD, whilst 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 required 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 two papers, but our study added many other studies published in recent years and is the largest meta-analysis on this topic containing over 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 of our meta-analysis are supported by consistent findings of individual studies since we found a higher risk of death across 44/48 (=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 epidemiological and clinical interest, such as cancer or CVD, were not considered. Another meta-analysis regarding gait speed and mortality included only three potential confounders [10], whilst, 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 which 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 co-morbidities (e.g. 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] and all these factors are associated with higher risk of death [74-76]. Next to this, gait speed may indicate difficulties with activities of daily living and engaging in physical activity, restrictions within each of these 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 early capture 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 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 sub-clinical 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), we recommend that other studies using people free from CVD or at least adjusting for this relevant factor at baseline are required.

On the contrary, we did not find any association between slow gait speed and incident cancer. Whilst 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 as due to inadequate statistical power, as this analysis was limited to four 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]. Since cancer 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.

Whilst our paper 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. Whilst we attempted to reduce this by attempting to include conference abstracts and we adjusted 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 could influence our findings. Third, people not able to walk were not considered in these cohort studies, but it is widely known that are at higher risk of mortality. However, this source of bias cannot be addressed. Finally, we had only four studies eligible for cancer and other works are needed for this outcome.

In conclusion, slow gait speed is a significant predictor of mortality and of the onset of CVD, whilst no significant association was found for cancer. Since gait speed is a quick and inexpensive measure to obtain, also in older and vulnerable 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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FIGURE LEGEND

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

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