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Self-reported walking pace and 10-year cause-specific mortality: A UK biobank investigation

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ABSTRACT

Objective: To investigate associations of self-reported walking pace (SRWP) with relative and absolute risks of cause-specific mortality.

Patients and methods: In 391,652 UK Biobank participants recruited in 2006–2010, we estimated sex- and cause-specific (cardiovascular disease [CVD], cancer, other causes) mortality hazard ratios (HRs) and 10-year mortality risks across categories of SRWP (slow, average, brisk), accounting for confounders and competing risk. Censoring occurred in September 30, 2021 (England, Wales) and October 31, 2021 (Scotland).

Results: Over a median follow-up of 12.6 years, 22,413 deaths occurred. In women, the HRs comparing brisk to slow SRWP were 0.74 (95% CI: 0.67, 0.82), 0.40 (0.33, 0.49), and 0.29 (0.26, 0.32) for cancer, CVD, and other causes of death, respectively, and 0.71 (0.64, 0.78), 0.38 (0.33, 0.44), and 0.29 (0.26, 0.32) in men. Compared to CVD, HRs were greater for other causes (women: 39.6% [6.2, 72.9]; men: 31.6% [9.8, 53.5]) and smaller for cancer (−45.8% [−58.3, −33.2] and − 45.9% [−54.8, −36.9], respectively). For all causes in both sexes, the 10-year mortality risk was higher in slow walkers, but varied across sex, age, and cause, resulting in different risk reductions comparing brisk to slow: the largest were for other causes of death at age 75 years [women: −6.8% (−7.7, −5.8); men: −9.5% (−10.6, −8.4)].

Conclusion: Compared to slow walkers, brisk SRWP was associated with reduced cancer (smallest reduction), CVD, and other (largest) causes of death and may therefore be a useful clinical predictive marker. As absolute risk reductions varied across age, cause, and SRWP, certain groups may particularly benefit from interventions to increase SRWP.

Introduction

Higher levels of physical activity (PA) are associated with a lower risk of all-cause mortality, cardiovascular disease (CVD), and some site-specific cancers.[1,2] Additionally, self-reported walking pace (SRWP) – a measure of physical function – has been shown to be associated with objectively measured walking speed, functional mobility, and cardiorespiratory fitness (CRF),[3–5] and is a powerful discriminator and predictor of CVD- and all-cause mortality,[6–8] with associations also observed for cancer and COVID-19 mortality.[8,9] Importantly SRWP has also shown to be causally associated with cardiometabolic health and biological ageing,[10,11] making it a potentially modifiable predictor of future health risks and an important target for public health campaigns and interventions.

Abbreviations: BIC, Bayesian Information Criterion; BMI, body mass index; CI, confidence interval; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; HR, hazard ratio; IQR, interquartile range; LDL, low-density lipoprotein; LTPA, leisure time physical activity; MET, metabolic equivalent; PA, physical activity; SBP, systolic blood pressure; SRWP, self-reported walking pace.

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Little is known, however, about whether differences in cause-specific mortality across levels of SRWP, and PA/function measures more generally, vary in relation to the cause of death. Only one identified study thus far has directly compared associations across various underlying causes of deaths to explore whether a greater PA/function would induce physiological changes that may be more advantageous to certain bodily systems or disease processes.[12] Furthermore, associations are rarely described in terms of absolute risk – which is more relevant from a public health perspective compared to relative measures (e.g., hazard ratios[HR])[13] – and there is a lack of research accounting for the competing risk of different causes of death, which vary in relation to age.

To understand the possible benefits of a risk-reducing effect of PA and physical function, and the subsequent impact on individual prognosis and public health, both relative and absolute risk measures are therefore important. In this context, we set out to detail the relative and absolute risk of death related to CVD, cancer, and other causes across levels of SRWP in the UK Biobank participants.

Methods

This study followed a pre-specified protocol (UK Biobank application number 33266) and has been conducted and reported in line with the STROBE guidelines (checklist in the Supplementary Material). Ethical approval for the UK Biobank study was obtained from the North West Centre for Research Ethics Committee (MREC, 11/NW/0382). In Scotland, UK Biobank has approval from the Community Health Index Advisory Group (CHIAG). The study complies with the Declaration of Helsinki and written consent was obtained from all participants.

Cohort definition

UK Biobank is an ongoing prospective cohort study whose baseline data have been collected in women and men aged 38 to 73 years between March 2006 and July 2010. Participants were recruited from family practices within 40 km of 22 assessment centres in England, Wales, and Scotland. From the initial sample of 502,413 participants, we excluded those who, at baseline: were pregnant; had missing data on the main exposure or confounders; self-reported a previous doctor diagnosis of cancer or CVD; or whose cause of death was unknown, leaving 391,652 participants for the analyses. The cohort definition flowchart, confounders, and UK Biobank data-field (DF) codes to identify previous cancer or CVD are reported in Supplementary Fig. S1.

Self-reported walking pace

Information on the main exposure – usual walking pace – was collected at baseline via a touchscreen questionnaire: participants were asked to answer the following question: "How would you describe your usual walking pace? Slow; Steady/Average; Brisk; None of the above; Prefer not to answer". Participants who did not answer or answered "None of the above" were excluded from the analyses ($n = 4673$). Further information was available to participants to define a slow pace as <3 miles per hour (mph); a steady/average pace as 3–4 mph; and a brisk pace as >4 mph.

Outcomes

The date and underlying cause of death were available through the linkage of UK Biobank with NHS Digital, in participants from England and Wales; and with NHS Central Register, in participants from Scotland. Participants were followed up from the study entry (baseline UK Biobank visit) until the occurrence of death or censoring (September 30, 2021 for England and Wales; October 31, 2021 for Scotland). We included cancer-related and CVD-related deaths, as they represent the most common causes of death,[14] as well as non-cancer- or non-CVD-related deaths, defined as deaths due to "other" causes; the International Classification of Diseases 9th and 10th revision codes to identify the underlying cause of death are reported in the Supplementary Excel file. As COVID-19-related deaths accounted for around 9% of all other causes of death, we assessed the robustness of the results in a sensitivity analysis excluding deaths reporting COVID-19 as the underlying cause.

Confounding variables

Data were captured on the following confounders in the association between walking pace and cause-specific death: age, sex, deprivation (Townsend deprivation index, with higher values indicating greater degrees of deprivation), systolic blood pressure (SBP), smoking status, body mass index (BMI), low-density lipoprotein (LDL) cholesterol, and leisure time PA volume (LTPA). LTPA was estimated by combining the duration and frequency of self-reported LTPA behaviours over one week, including walking, strenuous sports, other exercises, and heavy "do-it-yourself", and assigning a metabolic equivalent (MET) to each PA as previously reported.[15]

Statistical analysis

All analyses were stratified by sex. Descriptive values are reported as median and interquartile range (IQR) for continuous variables and number and percentage for categorical ones. We used the Royston-Parmar parametric survival model,[16] with study entry to death as time scale, to estimate cause-specific death HRs across walking pace categories (slow [reference], average, and brisk); models were adjusted for the continuous variables age, Townsend deprivation, SBP, serum LDL, BMI, and LTPA; and for the categorical variable smoking status (current/former/never). We firstly explored the shape of the association between age and cause-specific HRs, confirming log-linearity (Fig. S2). For each cause of death, we then compared two survival models, with and without an interaction term between linear age and walking pace, using the Bayesian Information Criterion (BIC). As BIC values indicated that models without interactions fitted the data better (i.e., lower BIC) than those with interactions, all survival models included a linear term for age without an interaction with walking pace. The same survival models were employed to estimate the standardized (i.e., adjusted) 10-year cumulative incidence of each cause of death accounting for competing risk: incidences were obtained for each individual and averaged across levels of walking pace for ages 45, 55, 65, and 75 years.[17] In a sensitivity analysis, we excluded deaths reporting COVID-19 as underlying cause and re-estimated cause-specific death HRs.

Stata routines, *stpm2*, *merlin*, and *standsurv* commands were used in Stata/BE Version 17.0 (StataCorp. 2021. College Station, TX, USA). Results are reported with 95% confidence interval (CI) and graphs were prepared in Stata and Inkscape Version 1.2.1. The statistical codes are publicly available on GitHub (frazac82) and at UK Biobank, in line with UK Biobank regulations. All aggregate results are reported in the Supplementary Excel file.

Results

Cohort characteristics

Table 1 shows the baseline characteristics of the 214,259 (54.7%) women and 177,393 (45.3%) men included in the analysis. Overall, the median (IQR) age was 57.3 (49.7–63.0) years. 25,727 (6.6%) reported that they were slow walkers, 206,126 (52.6%) average-pace walkers, and 159,799 (40.8%) brisk walkers; this distribution of walking paces was similar between women and men (Supplementary Table S1). Compared to average and brisk walkers, slow walking women and men had a lower LTPA volume and higher age, SBP (particularly women), BMI, Townsend deprivation index, and prevalence of smoking (Table S1).

Table 1
Characteristics stratified by walking pace.

	Women	Men	All cohort
No. of people	214,259	177,393	391,652
Age (years)	57.2 (49.8, 62.9)	57.4 (49.6, 63.2)	57.3 (49.7, 63.0)
Systolic blood pressure (mmHg)	133 (121, 147)	140 (129, 152)	136 (125, 149)
LDL cholesterol (mmol/l)	3.6 (3.0, 4.2)	3.5 (3.0, 4.1)	3.6 (3.0, 4.1)
Body mass index (kg/m^2)	26.0 (23.4, 29.5)	27.2 (24.9, 29.9)	26.6 (24.1, 29.7)
Townsend deprivation index	−2.2 (−3.7, 0.4)	−2.2 (−3.7, 0.5)	−2.2 (−3.7, 0.4)
Leisure time physical activity volume, MET-min/week	450.0 (148.5, 1039.5)	668.3 (210.0, 1504.7)	535.3 (158.8, 1216.9)
Smoking status			
Never	129,598 (60.5)	90,329 (50.9)	219,927 (56.2)
Former	66,047 (30.8)	65,113 (36.7)	131,160 (33.5)
Current	18,614 (8.7)	21,951 (12.4)	40,565 (10.4)
Usual walking pace			
Slow pace	15,111 (7.1)	10,616 (6.0)	25,727 (6.6)
Steady average pace	113,319 (52.9)	92,807 (52.3)	206,126 (52.6)
Brisk pace	85,829 (40.1)	73,970 (41.7)	159,799 (40.8)

Numbers are reported as median (interquartile range) or n (%).
A greater Townsend index indicates a greater degree of deprivation.
LDL: Low density lipoprotein; MET: Metabolic equivalent of task.

Over a median (IQR) follow-up of 12.6 (11.9–13.3) years, 22,413 (5.7%) deaths occurred: 9270 (4.3%) in women (1046 [0.49%] CVD, 5242 [2.4%] cancer; 2982 [1.4%] other causes) and 13,143 (7.4%) in men (2329 [1.3%] CVD, 6209 [3.5%] cancer; 4605 [2.6%] other causes; Table S2). There were a broad range of other causes of death, with COVID-19 representing 9.4% of the total deaths in this group, over twice than the next prevalent cause of death (Fig. S3): other than COVID-19, the most frequent other causes included dementia and neurological and respiratory diseases.

The crude mortality rates varied by sex, cause of death, and SRWP (Table S2), with the lowest being 0.2 (95% CI: 0.2, 0.3) CVD-related deaths per 1000 person-years in brisk walking women and the highest 7.4 (6.9, 7.9) other-cause-related deaths per 1000 person-years in slow walking men.

HRs of cause-specific mortality

Fig. 1 shows that, in both sexes and after adjustment for confounders, compared to slow walkers both brisk and average walkers had lower mortality rates due to cancer, CVD, and other causes, with the greatest reduction in brisk walkers: in women and men, respectively, brisk walkers had a HR of 0.40 (95% CI: 0.33, 0.49) and 0.38 (0.33, 0.44) for CVD mortality compared to slow walkers; corresponding HRs for cancer mortality were 0.74 (0.67, 0.82) and 0.71 (0.64, 0.78), respectively. The magnitude of the associations for cancer-related death was significantly lower than that observed for CVD death: in women, a HR from 0.40 (CVD) to 0.74 (cancer) equated to a reduction of −45.8% (95% CI: −58.3, −33.2) in the strength of the association; the corresponding reduction in men was virtually identical: −45.9% (−54.8, −36.9; Fig. 1). Conversely, comparing brisk to slow walkers the HR of mortality related to other causes was 0.29 (95% CI: 0.26, 0.32) in women and 0.29 (0.26,0.32) in men; these estimates were of greater magnitude than those seen for CVD death for the same comparison brisk vs slow walkers:

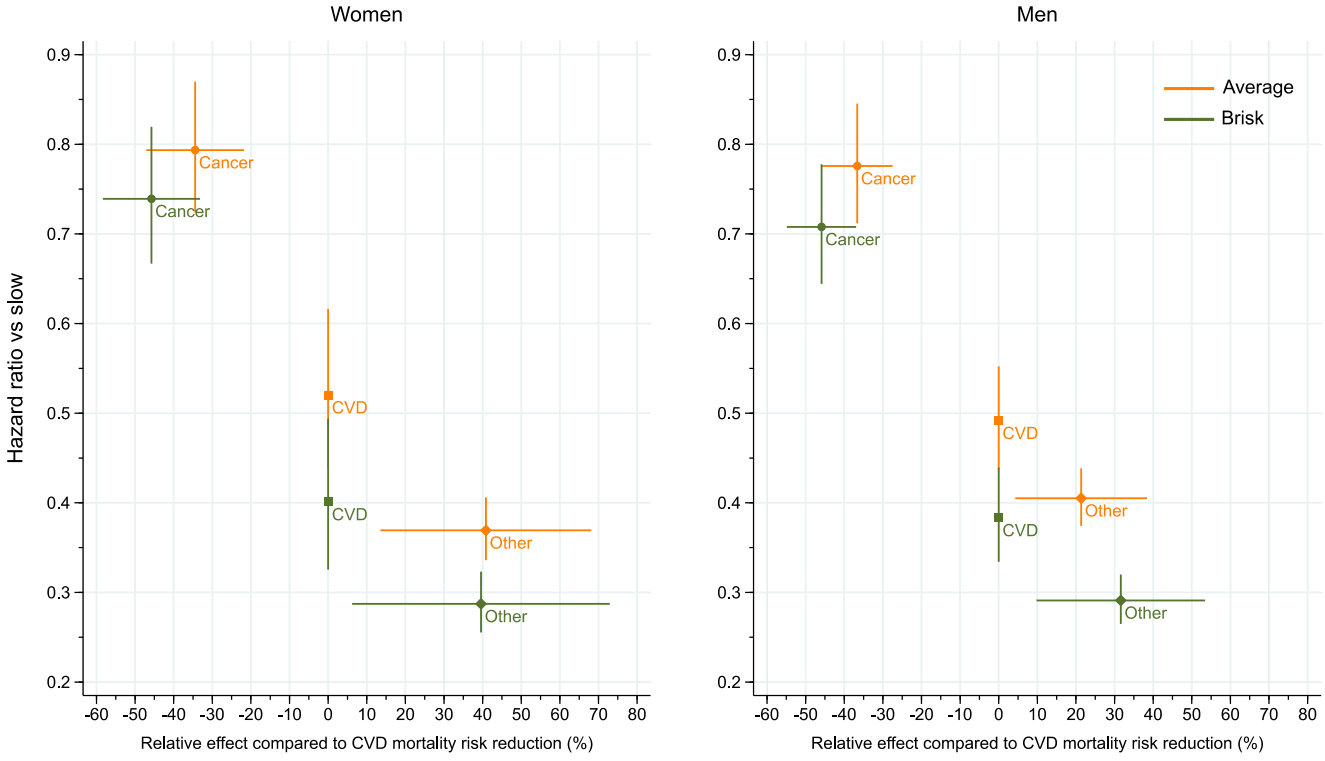

Fig. 1. Relative hazards of cause-specific death.
Legend: Estimates adjusted for age, systolic blood pressure, low density lipoprotein cholesterol, smoking status, Townsend deprivation index, body mass index, and leisure time physical activity volume. The plot shows the hazard ratios of average (orange) and brisk (green) vs slow (reference) pace (y-axis) as well as the relative (%) difference between the hazard ratios across competing causes of deaths (x-axis): for example, in women comparing brisk vs slow, the hazard ratio is 0.40 (95% CI: 0.33, 0.49) for cardiovascular (CVD) and 0.74 (0.67, 0.82) for cancer mortality; therefore, the association is of smaller magnitude for cancer than CVD, and equates to a relative (0.40–0.74)/0.74 = −45.8% compared to CVD, as indicated on the x-axis (reference, 0% for CVD). Bars indicate 95% confidence interval.
CVD: Cardiovascular disease. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

+39.6% (6.2, 72.9) in women and + 31.6% (9.8, 53.5) in men. Albeit to a lesser extent, the differences in the strengths of the associations remained when comparing average to slow walkers (Fig. 1).

Absolute risk of cause-specific mortality

Fig. 2 shows the cause-specific absolute risk of death up to 10 years of follow-up by sex, age, and SRWP. The risks of cancer, CVD, and other-cause-related mortality were higher for those that were older and in men, with the highest risk seen in slow-walking men aged 75 years; this translated into a greater risk of all-cause mortality in this group (Fig. S4). At 10 years, across all ages the absolute risk reduction comparing either brisk or average-speed walkers to slow walkers was lower in women compared to men and, regardless of sex, the reductions were always higher for other causes of death than for cancer- or CVD-related death (Fig. 3). The largest 10-year absolute risk reduction in cause-specific death was seen for both sexes in mortality from other causes at the age of 75 years: −6.8% (95% CI: −7.7, −5.8) in women and − 9.5% (−10.6, −8.4) in men when comparing brisk walkers to slow walkers.

Sensitivity analysis: removing COVID-19 related deaths

After removing the individuals with COVID-19 as underlying cause of death, the HRs of cause-specific death (Fig. S5) were virtually identical to those obtained in the main analysis (Fig. 1).

Discussion

In this large, population-based cohort study of middle-aged adults, the mortality rates for CVD, cancer, and other causes were lower in participants with brisk or average than slow SRWP. After adjusting for possible confounders, the greatest reduction was observed for the mortality rates related to other causes, followed by CVD- and cancer-related; sensitivity analyses confirmed this pattern after removing COVID-19 related deaths. Accounting for the competing risk of cause-specific deaths, which varies while ageing, our findings also showed absolute risk reductions in all three causes of death associated with brisk or average SRWP compared to slow; these reductions, however, were greater in older individuals, men, and for other causes of death.

The relative reductions in the mortality rates (i.e., HRs) across levels of SRWP are consistent with previous findings.[5,8] In a pooled analysis of 11 prospective UK studies including 50,225 walkers,[18] compared to slow, those reporting brisk walking had reduced all-cause (HR: 0.76 [95% CI: 0.67, 0.87]) and CVD (0.79 [0.62, 0.99]) but not cancer (1.02 [0.81, 1.29]) mortality rates.[8] Our study complements these findings by showing that, for the same comparisons (brisk or average vs slow SRWP), the reductions in the mortality rates were smaller for cancer than for CVD mortality, whilst greater for other causes of death. Heterogeneity in relative reductions across competing causes of death was investigated in a previous study exploring the relationship between self-reported PA volume and cause-specific mortality: in a competing risk analysis of 50,112 participants in the Nurses' Health cohort study. The

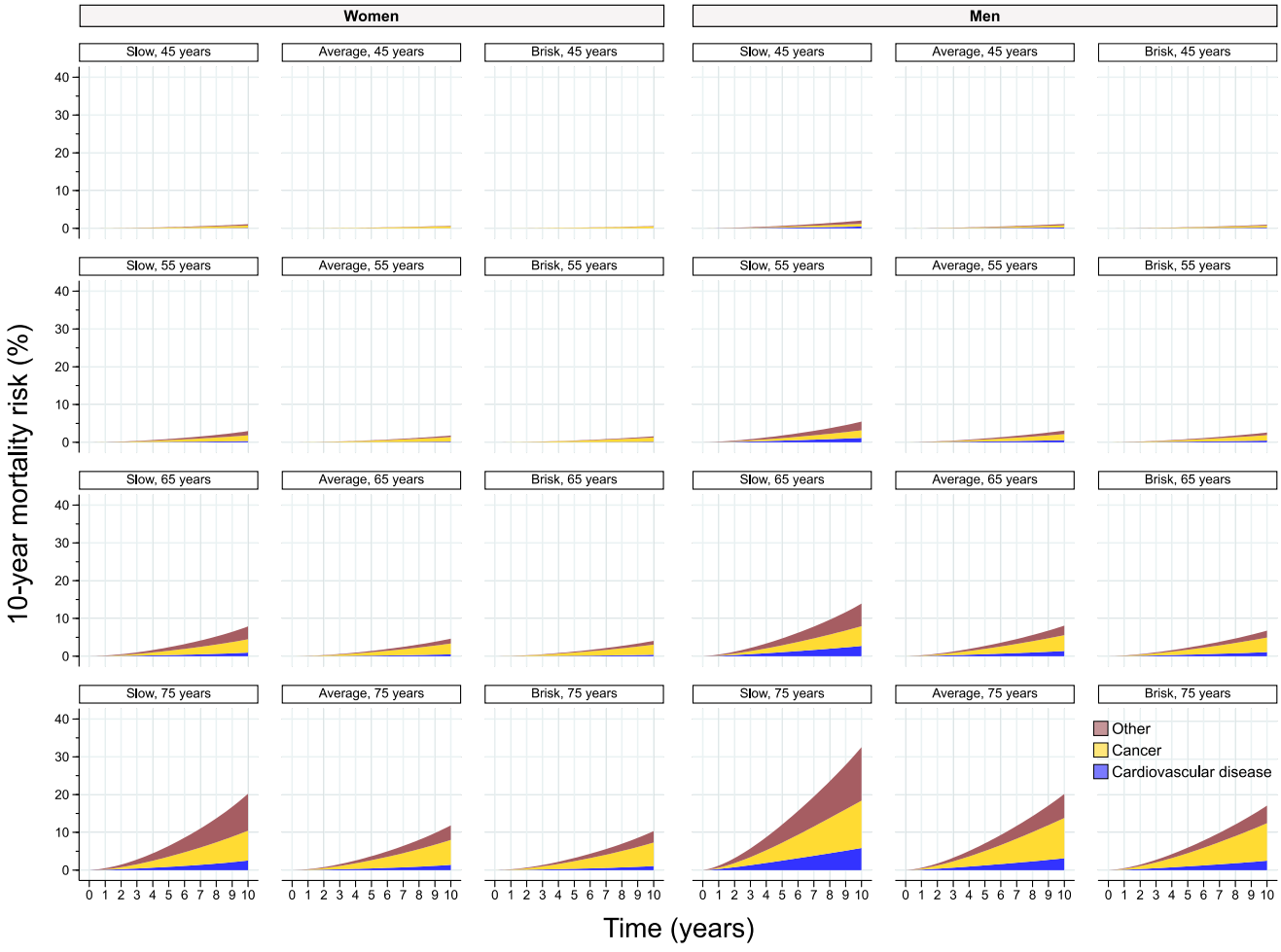

Fig. 2. Cumulative incidences by sex, age, and walking pace.
Legend: Estimates adjusted for age, systolic blood pressure, low density lipoprotein cholesterol, smoking status, Townsend deprivation index, body mass index, and leisure time physical activity volume.

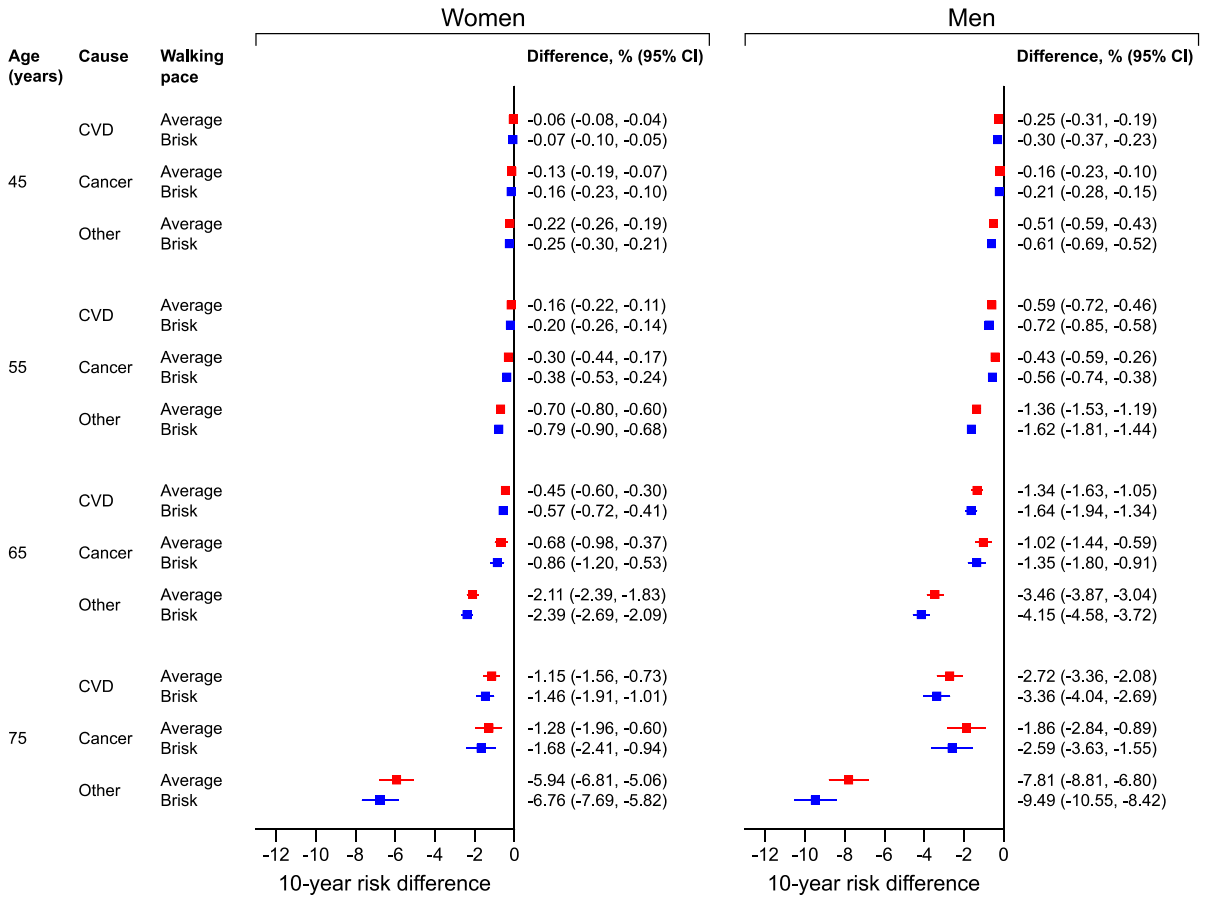

Fig. 3. Cumulative incidence differences at 10 years.
Legend: The reference is "slow" walking pace. Estimates adjusted for age, systolic blood pressure, low density lipoprotein cholesterol, smoking status, Townsend deprivation index, body mass index, and leisure time physical activity volume. Red: Average brisk; Blue: Brisk walking.
CVD: Cardiovascular disease. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

authors found that each increase of 33 MET hours/week of self-reported PA was associated with a HR of 0.88 (95% CI: 0.75, 1.03), 0.97 (0.83, 1.14), 0.91 (0.81, 1.04), and 0.76 (0.66, 0.86) in the mortality related to CVD, smoking-related cancer, other cancers, and other-causes, respectively, concluding that these four cause-specific reductions were different ($p = 0.07$ using a threshold of 0.1).[12] Although not directly comparable with our findings (e.g., different measures of physical activity/function, population characteristics, and outcomes), this study similarly identified a nominal, largest reduction in the mortality rates related to other-cause.

To our knowledge, relative reductions in the competing risk of CVD, cancer, and other causes of death across levels of SRWP have not been directly and formally compared before, albeit previous studies have reported reductions of greater magnitude for CVD than cancer mortality.[5,8] Furthermore, increasing levels of (variably defined) PA have been associated with larger relative reductions in the mortality rates for CVD, cancer, and other causes; yet, these reductions have not been formally compared across causes.[19–21] The different relative reductions across SRWP observed in our study raise aetiological questions as to why a faster SRWP may offer more protection to certain causes of death than others. This variation may be explained by the potentially larger benefits of a higher CRF – which is closely associated to SRWP[5] – to cardiovascular than other bodily systems. A higher CRF has been associated with an improved cardiac output, ventilation, maximal oxygen uptake, and peripheral muscle oxygen extraction,[22,23] all physiological mechanisms that may be more relevant in the development of CVD than cancer. A recent meta-analysis has also shown different associations with causes of death, although such differences have not been formally tested: for the same increase in CRF (1-MET), the pooled relative reduction was of greater magnitude for CVD (HR 0.87) than for cancer (HR 0.93),[24] further suggesting that SRWP may be more reflective of cardiovascular health. Furthermore, while some studies have reported an inverse association between levels of physical fitness and cancer mortality rates,[25–28] this finding is not observed consistently.[29–31]

The reason behind the greater relative reduction in the rates of death related to other causes is, conversely, less clear, particularly as the causes of death within this outcome were highly heterogeneous in our population, yet the most common causes were dementia and respiratory diseases. A previous study has reported progressively lower rates of chronic obstructive pulmonary disease, which represents a large proportion of other deaths in our study, for higher CRF.[32] Similarly, the incidence of, and the mortality related to, Alzheimer's dementia – another common cause of death in our population – have been inversely associated with CRF[33,34]; these observations are further supported by the relationships between a higher CRF and improved cognition as well as physiological and radiological markers of brain health.[35–39]

It should also be noted that SRWP is a subjective measure and, therefore, may also reflect psychological factors such as a poor self-perception of health or low self-confidence, which may additionally affect the risk of acquiring and dying from diseases; similar points have been made previously.[40] Furthermore, it is important to highlight that there is the possibility of reverse causality, whereby participants with non-CVD and non-cancer related chronic diseases were slow walkers because of an underlying (subclinical) disease process, as we only excluded those with CVD or cancer at baseline and not those with other diseases. Lastly, CVD- and cancer-related deaths represent composite

endpoints, and these may impact on the observed differences when compared to specific cancers or causes of CVD death that are particularly associated with PA behaviours.

Estimates of competing, cause-specific absolute risks of death and their differences, including by sex and age, have not been reported so far across levels of SRWP. Even in the broader PA literature, absolute risk reductions are rarely the focus, with a preference for relative risk estimates,[1,41,42] and occasional exceptions where absolute risks are reported.[43,44] One such study was limited only to estimations of absolute risk differences using adjusted relative risk differences from meta-analysis and an unadjusted crude mortality rate.[44] The quantification of the absolute risks, and their differences, across age, sex, and causes of death is particularly novel and helps in the identification of groups with absolute risk differences far higher than population-level differences estimated previously, such as when comparing slow and brisk SRWP in men aged 75 years. This highlights potentially cost-effective and high-impact targets for public health interventions, particularly as changes in CRF are associated with changes in mortality risk,[45,46] which may also be true for self-reported walking pace. While appropriately-adjusted relative measures (i.e., HRs) give more insights into which causes of death may be more/less associated with PA/function, allowing postulation of aetiological mechanisms, absolute risks are indeed more useful to understand and communicate an individual's risk of disease and to postulate possible reductions in outcomes from population-level intervention, should a risk factor be causally related to an outcome and modifiable. Of note, the absolute risk differences reflect the HR, the incidence of the outcome, and the follow-up time; thus, a large relative reduction (e.g., HR 0.5) could translate into a small absolute risk difference if the incidence rates are small and/or the follow-up is short.[13] As such, the observed larger absolute risk reductions with increasing age across cause-specific mortality may reflect the higher rates of mortality in older participants, even if the relative reductions across SRWP are similar between older and younger participants.

Finally, a strong argument has been made for the importance of CRF as a routinely measured clinical predictive marker due to the strong and consistent negative associations observed with all-cause mortality.[45–50] However, gold-standard measures of CRF within routine clinical practice remains practically difficult. SRWP may provide an easier alternative for use in clinical practice as it is readily available and a low-cost proxy of CRF,[5] particularly as a predictive marker of CVD and other-cause related death as this analysis has demonstrated.

The strengths of this analysis lie in the large, contemporary, and well-phenotyped cohort. We also investigate risks across sex and age, two strong predictors of mortality, providing more information on specific population groups. Furthermore, we accounted for competing risk: this is essential when calculating the risk of cause-specific death.[51] This method fits with the biological argument that causes of death are mutually exclusive; therefore, if a participant has died of cancer, for example, they should not be considered anymore at risk of CVD death. As mentioned, the use of SRWP, a readily available and low-cost measure for CRF which does not require expensive assessment facilities: combined with the absolute risk estimates, our results have meaningful and interpretable implications for public health intervention. Like all prospective studies, we are limited by the observational nature whereby unmeasured confounders may affect associations, or indeed measured confounders with error (residual bias). Despite excluding subjects with a diagnosis of cancer or CVD at baseline, there may be both undiagnosed disease, and non-cancer, non-CVD diseases, that could influence both SRWP and mortality risk and result in reverse causality, particularly in the risk of death related to other causes. Furthermore, participants within UK Biobank tend to be healthier and more affluent than the general UK population, which limits generalisability.[52]

In conclusion, compared to slow, both brisk and average SRWP are associated with lower rates of deaths related to CVD, cancer, and other causes, with smaller and larger reductions in cancer-related and other-cause-related deaths, respectively, when compared to CVD-related death. Therefore, SRWP could be used in routine clinical practice as a predictive marker for CVD and other-cause related mortality in particular. Further clinical and pre-clinical studies are required to investigate the mechanisms behind these differences. Absolute risk reductions across SRWP categories were larger with increasing age, in males, and for deaths not related to CVD or cancer. If causal, our findings highlight that some groups may particularly benefit from behavioural interventions to increase walking speed.

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Authors' contributions

FZ, AR, PCD, CR, JH, JG, and TY formed the core working group and developed the research question. FZ developed the analysis code. JG and FZ drafted the manuscript. All authors contributed to the interpretation and revised the manuscript for important intellectual content.

Declaration of Competing Interest

The authors had financial support from the funders listed above for the submitted work. The authors declare that they have no competing interests.

Data availability

Research was conducted using the UK Biobank Resource under Application #33266. The UK Biobank resource can be accessed by researchers on application. Variables derived for this study have been returned to the UK Biobank for future applicants to request. No additional data are available.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pcad.2023.09.003.

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