Title page

Improvements in walking speed reduce mortality in patients with cardiovascular disease during exercise-based secondary prevention: findings from the ITER registry

Running head: Improved walking speed reduces mortality risk

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Abstract

Aim: To investigate associations between walking speed (WS) and mortality among patients with stable cardiovascular disease (CVD). Additionally, it sought to analyse the impact of a long-term

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exercise intervention on physical function by analysing the relationship between changes in WS and mortality over a decade of observation.

Methods: Of the 3,328 patients included in the ITER registry (NCT05817305) between 1997 and 2023, 2,858 (aged 65±11 years) were analysed. Walking speed was measured using the 1-km treadmill walking test (1k-TWT). Patients were initially categorized into tertiles based on baseline WS and subsequently divided into six categories by associating baseline WS with changes over time. Cox proportional hazard models were used to examine associations between WS, all-cause and disease-specific mortality, adjusting for demographic and clinical confounders.

Results: A total of 1,031 patients died over a median follow-up of 11 years. Higher baseline WS was inversely associated with mortality with magnitudes ranging from 23% (95% CI: 0.56,1.06) lower risk for cancer to 58% (95% CI: 0.32,0.54) lower risk for CVD. A similar trend resulted in WS improvements over time, particularly among the LowWS-improved group, with a 38% (95% CI: 0.52, 0.74) lower risk for all-cause mortality, which was comparable to the HighWS-decreased patients.

Conclusions: The 1k-TWT is an effective predictor of mortality among CVD patients and a valuable educational tool for exercise-based interventions in secondary prevention. These findings highlight the efficacy of exercise-based programs to improve physical function and reduce mortality, underscoring the importance of promoting exercise as part of long-term CVD management.

Keywords: cardiovascular disease, walking speed, physical exercise, cardiac rehabilitation, secondary prevention, epidemiology

Lay summary

The present study provides evidence about the effectiveness of stable walking speed improvement in modifying all-cause and disease specific mortality in a large cohort of cardiac outpatients during a secondary prevention program.

- Walking speed measured over longer distances throughout a submaximal treadmill test is a reliable indicator of exercise capacity and overall endurance. Improvements in walking speed over time are associated to a significant reduction in all-cause and disease-specific mortality.

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- This may provide a valuable strategy of intervention in the context of exercise prescription and training. It also offers helpful insights for the long-term management of patients involved in exercise-based secondary prevention programs.

Introduction

Cardiovascular disease (CVD) continues to be the greatest cause of morbidity and mortality globally, accounting for about 17 million deaths annually [1]. Advancements in intervention strategies and medications have resulted in more people surviving initial events, leading to a greater number of patients requiring long-term cardiovascular risk management [2–4]. In this context, international guidelines have emphasized the importance of cardiac rehabilitation and secondary prevention programs in order to mitigate the health and economic burden of CVD and manage the long-term continuum of care for patients with CVD [5,6]. One of the major components of these programs is the determination of exercise capacity, typically represented by cardiorespiratory fitness [7–10]. There is strong evidence regarding the relationship of exercise capacity with walking speed (WS), suggesting that an age-associated reduction in exercise capacity reflects an increased perception of exertion and a slower speed during habitual walks [11]. Walking speed has therefore been recognized as a potential additional "vital sign" [12], as it reflects the overall health of multiple organs and systems, and is positively related to independence and quality of life [13,14]. In support of this, it has been widely demonstrated that WS is inversely associated with hospitalization and mortality rates among older adults in epidemiological studies [15–17].

Previous studies have investigated the relationship of WS with mortality, but WS is usually self-reported [18], or assessed through short walking tests that focused on the estimation of gait speed [19]. Although gait and walking speeds are often considered synonymous, a specific distinction should be made. Gait speed assessed by walking over a short distance reflects an individual's functional mobility, health status, or risk of falls, but is not a measure of endurance [20,21]. In contrast, WS measured over longer distances, is likely a more reliable indicator of exercise capacity and overall endurance. However, most of the existing submaximal tests have been primarily validated on healthy participants and require walking as quickly as possible or covering as much ground as possible within a set time frame. This can impact their adaptability in the evaluation of older or frail individuals potentially increasing the risk of bias. To address these limits, the 1-km treadmill walking test (1k-TWT) has been validated on patients with CVD. Consequently, a growing body of evidence has demonstrated that WS

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maintained during the 1km-TWT was a practical measure of physical function and demonstrated strong prognostic value in patients with CVD [22–25]. Nonetheless, there is a lack of studies examining the long-term impact of exercise-based interventions on physical function applying changes in WS over time and its association with mortality outcomes. One study was conducted investigating variations in WS after three years of follow-up. Although the results supported the value of WS, it was conducted in a small sample of female patients [24].

Thus, the aim of the current study was to examine the relationship between WS and disease-specific causes of mortality, and how changes in WS impact all-cause mortality in a large cohort of outpatients with CVD involved in an exercise-based prevention program.

Methods

Source and study population

Data derived from the ITER study (InTegrating exERcise into lifestyle of cardiac outpatients) were analysed. ITER is a patient-registry observational study that aims to investigate the effectiveness of an exercise-based secondary prevention program on patients with stable CVD (ClinicalTrials.gov. NCT05817305). The initial sample was composed of 3,328 participants referred by their general practitioner or specialist doctor to the Center for Exercise Science and Sport, University of Ferrara, Italy, between 1997 and 2023. Cardiovascular disease history was defined as follows: acute myocardial infarction (AMI), percutaneous coronary intervention (PCI), coronary artery bypass graft, or heart valve repair or replacement. Coronary bypass graft surgery superseded other reasons for hospitalization. If the admitting diagnosis was AMI and a subsequent PCI was or was not performed, it was coded as an AMI. If a PCI was performed in the absence of AMI, it was coded as PCI without AMI. If valvular replacement was performed in the absence of AMI, it was coded as valvular replacement. Admitting diagnosis of cardiac tumours, coronary artery anomalies, or heart transplantation were coded as others. Specific diagnoses were identified according to the International Classification of Diseases coding system, version 10 (ICD-10). The study was approved by the Ethics Committee of the University of Ferrara, cod. 105/2023/Oss/UniFe. Written informed consent was obtained from all participants at the time of enrolment.

Measures

During each follow-up visit, patients underwent a clinical evaluation including medical history, fasting blood chemical analysis and risk factor control. Body mass index and blood pressure were

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measured, and hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg [27]. During centre-based sessions, all patients performed a submaximal, moderate, and perceptually regulated 1km-TWT [22,28]. Specifically, patients started the test at a WS of 2.0 km/h, with a progressive increase of 0.3 km/h every 30 seconds up to a WS corresponding to a perceived exercise intensity of 11-13/20 on the Borg scale (6-20). The WS reached during this phase was maintained relatively constant for 1000m. During the walk, WS could be adjusted to maintain a steady level of perceived effort allowing the patient to complete the test. The time taken to complete the 1000m, along with heart rate and average and maximum WS were recorded. Heart rate was monitored continuously using a Polar RS100 heart rate monitor (Polar Electro, Kempele, Finland). Patients unable to complete the test at a WS ≥3.0 km/h performed a validated "short form" over 500m or 200m [29–31]. In order to investigate the efficacy of the intervention over time by analysing WS changes, the difference between first and last observation was calculated, and results were categorized into three tertiles: Decreased (< 0.1 km/h), Stable (0.1 – 0.8 km/h) and Improved (> 0.8 km/h) walking speed.

Exercise intervention

During each visit, kinesiologists and physicians conducted an educational intervention aimed at reinforcing the idea of being physically active [32]. In addition, based on the results of the test, a home-based exercise program was designed. The 1km-TWT plays an important educational role as patients are able to experience the proper intensity and duration of walking in such a way to reach a certain learning effect [32]. The training program was continuously individualized, aiming for 30 to 60 minutes of moderate-intensity aerobic activity such as brisk walking, at least 5 days, and preferably 7 days per week. Less fit or less motivated patients were encouraged to accumulate the daily recommended volume in shorter bouts of at least 10 minutes. Given the importance of generating a long-term improvement in exercise habits, patients were invited to perform any other type of parallel leisure time physical activity.

Follow-up

Participants were followed for all-cause and disease-specific mortality. Information on deaths were provided by the regional Health Service Registry of the Emilia-Romagna region, or by contacting the patient's general practitioner or relatives to determine vital status. Time from baseline to death was calculated in months.

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Data analysis

Patients were initially categorized into three tertiles (Slower, Medium, or Faster) based on their baseline WS, adjusting for age and sex to create homogeneous groups. For the second analysis, two new age-sex-specific quantiles of baseline WS were created (HighWS and LowWS) and subsequently associated with change in WS tertiles, resulting in six categories (LowWS-decreased, LowWS-stable, LowWS-improved, HighWS-decreased, HighWS-stable, HighWS-improved). All-cause and disease-specific mortality were the endpoints for the first analysis while WS changes were analysed in relation to all-cause mortality. Descriptive statistics for continuous variables are presented as mean and standard deviation or as frequency and percentage for categorical variables. Normal distribution was verified through a Kolmogorov-Smirnov test. Differences between groups in terms of demographics, risk factors, medical history and medications were determined by one way ANOVA or χ^2 test for trend if variables were categorical. For each patient, the follow-up ended on the date of death or the end of follow-up (31st December 2023). Differences in survival across the tertiles were assessed using Kaplan-Meier curves. All the associations were subsequently investigated performing Cox proportional hazard models, and all results were reported as hazard ratios (HR) and 95% confidence intervals (CI). Slower and LowWS-decreased groups were considered as reference categories. All the associations were adjusted for confounders with three models that included an increasing number of covariates. Model 0 was unadjusted. Model 1 (minimally adjusted model) was adjusted for age, sex, marital status and education. Model 2 (clinical variables model) was adjusted for all variables in model 1 plus myocardial infarction, coronary artery bypass graft, family history, hypertension, diabetes, and dyslipidaemia. Confounders were selected by investigating relationships between outcome, exposure and covariates through a Directed Acyclic Graph (DAG) model [33]. Based on the assumptions described in the diagram (**Supplementary material online, Figure S1**), the minimal adjustment set was identified following the backdoor criterion [34]. Schoenfeld residual analysis was performed to assess the assumption of proportionality. The proportional hazard assumption was met for all models. To reduce the potential influence of reverse causality, sensitivity analyses were performed, excluding all participants who died in the first three years. The level of statistical significance was set at $p < 0.05$. Statistical analyses were performed using R Statistical Software [R Core Team. A language and environment for statistical computing. Published online 2021. https://www.R-project.org/].

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Results

Of the 3,328 patients, 2,858 were included in the study. 470 patients (12%) were excluded for the following reasons: (1) inability to complete the test; (2) heart failure classified as class III or higher according to the New York Heart Association [35]; (3) other physical or psychological conditions that interfered with walking ability; or (4) missing data for measures or covariates considered in the analysis. A detailed flowchart of participants included in the analysis is provided in **Supplementary material online, Figure S2**. The 1km-TWT was performed by all the patients without any major complication. The average walking speed measured throughout the test was 4.1 ± 1.2 km/h. The median follow-up period was 11 years (interquartile range 5.8 to 17.8, or 16,432 person-years) during which a total of 1,031 people died from any cause (469 due to CVD and 266 due to cancer), with an average annual mortality of 6.1%. Demographic and clinical characteristics of the patients stratified by tertiles of measured WS are presented in **Table 1**. Compared to Slower patients, participants in the Faster group were relatively younger. In terms of medical history, they presented a higher percentage of AMI diagnoses as well as a higher percentage of PCI. Finally, they had a lower overall percentage of medication use.

Association of baseline WS with all-cause and disease-specific mortality

Survival, represented by Kaplan-Meier curves, is reported in **Supplementary figure 1**. Survival was progressively lower as the estimated WS decreased. After adjusting for confounders, a decreased risk of all-cause mortality was detected for Medium (HR 0.54 [95% CI: 0.44, 0.61; p<0.0001]), and Faster (HR 0.53 [95% CI: 0.46, 0.61; p<0.0001]) patients as compared with the reference group. A similar magnitude was observed for CVD mortality (HR 0.43 [95% CI: 0.34, 0.53; p<0.0001]; HR 0.42 [95% CI: 0.32, 0.54; p<0.0001]), while there were no significant differences for cancer mortality (HR 0.81 [95% CI: 0.61, 1.09; p=0.177]; HR 0.77 [95% CI: 0.56, 1.06; p=0.115]) (**Figure 1** and **Supplementary material online, Table S1**). Moreover, each 1 km/h increment in average WS was associated with a 27% reduction in all-cause mortality (HR 0.73 [95% CI: 0.69, 0.78; p<0.0001]), 36% in CVD mortality (HR 0.64 [95% CI: 0.59, 0.70; p<0.0001]), and 12% in cancer mortality (HR 0.88 [95% CI: 0.78, 0.99; p<0.05]) (**Figure 1**). Finally, when patients who died during the first three years of follow-up were removed from the analysis, associations remained unchanged (**Supplementary material online, Table S3**).

Joint associations of WS changes with all-cause mortality

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Detailed information of average WS at baseline and at the end of the follow-up, for each category, is shown in **Table 2**. Results show a gradual decrease in mortality risk that can be observed among groups if compared with the reference, with HighWS-improved group reporting the lowest risk ratio (HR 0.24 [95% CI: 0.15, 0.33; p<0.001]) (**Figure 2** and **Supplementary material online, Table S2**). Interestingly, a slight difference was evidenced between LowWS-improved and HighWS-decreased categories, where slower patients who increased WS over time had a lower mortality risk (HR 0.62 [95% CI: 0.52, 0.74; p<0.001]) compared to faster individuals who reduced their speed (HR 0.69 [95% CI: 0.58, 0.82; p<0.001]). Sensitivity analysis showed an attenuation in the difference between the mortality risk in LowWS-improved patients, compared with the HighWS-decreased group (**Supplementary material online, Table S4**).

Discussion

The current study included a cohort of 2,858 patients with stable CVD over a wide range of age and functional capacity, across a total of 25 years of in an exercise-based secondary prevention program. The primary finding of this study was the inverse association between WS estimated through the 1km-TWT and mortality (**see graphic abstract, Figure 3**). We also aimed to determine whether these findings were consistent with previous research. In a recent meta-analysis of prospective cohort studies, the relationship between gait speed and mortality was investigated. From more than 44 articles, each reduction of 0.1 m/s in gait speed was associated with a 14% increased risk of mortality (HR 1.12 [95% CI: 1.09; 1.14]) [19]. However, the majority of the analyses were performed among healthy participants. Taking into account only those conducted on patients with CVD, each 0.1 m/s was associated with an overall HR ranging from 0.67 to 0.87 [36–38]. Among 1474 older patients with CVD, the improvement in WS was associated with a 23% reduction in all-cause mortality (HR 0.87 [95% CI: 0.81; 0.93]) [36]. A similar relationship was found among 338 US older patients with AMI, where lower speed was associated with increased mortality risk (HR 1.23 [95% CI: 0.74; 2.04]) [37]. Finally, among 472 Japanese participants with ST-segment elevation myocardial infarction, higher WS values were associated with both lower all-cause (HR 0.71 [95% CI: 0.62; 0.82]) and CVD (HR 0.67 [95% CI: 0.55; 0.81]) mortality risks [38]. To the best of our knowledge, no studies have reported on the association between gait speed and cancer mortality in patients with CVD.

A second notable finding of the current study was the inverse association of changes in walking speed with all-cause mortality. Based on these results, the greatest benefits were observed among faster walkers who were able to increase their speed. Also notable was the observation that slow walkers who

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improved walking speed over time (mean increase of 1.8 km/h), had a risk ratio that became comparable to the not improved faster walkers. This analysis is consistent with previous studies conducted in female patients. Among 176 women with CVD re-evaluated three years after baseline, hospitalization or mortality risk was progressively lower across tertiles for moderate (HR 0.79 [95% CI: 0.46, 1.34]) and high improvement in WS (HR 0.47 [95% CI: 0.25, 0.88], respectively [24]. Thus, the improvement may be attributed to an effective exercise intervention strategy that likely led to increased overall physical activity levels. According to the literature, exercise positively impacts several established CVD risk factors, such as fibrinolysis, coagulability, inflammation, and autonomic function. It also mitigates age-related declines in myocardial blood flow and endothelial-dependent vasodilation [39,40]. These factors may contribute to modifying walking speed and help explain the association between WS changes and mortality.

These findings reinforce the usefulness of the 1km-TWT. In addition to its demonstrated prognostic contribution in epidemiological studies, this test is valuable as an educational tool for exercise-based interventions within secondary prevention programs compared to other common walking tests, which tend to be too short or are performed at a near maximum intensity. Moreover, the test is simple to perform, safer and suitable for cardiac patients, and adaptable to older participants with limited mobility or mild cognitive deficits. Finally, the broad inclusion criteria used in this study are likely to reflect real-world clinical practice.

Limitations of the study

This study has several limitations. First, social, behavioural, and psychological factors independently associated with reduced WS were not available. Second, given that the cohort presented a mean preserved systolic function, the findings may not be directly generalizable to populations with reduced left ventricle ejection fraction. Third, since adherence rates were not determined, establishing a causal relationship between changes in physical activity and WS was not possible. Fourth, given the significant loss of statistical power after categorization, the analysis of WS changes was only based on all-cause mortality. Finally, the results were obtained from patients interested in participating in a secondary prevention program, indicating a need for external validation to generalize the findings.

Conclusions

Average WS estimated from a moderate and perceptually regulated treadmill walk test predicts mortality and helps to quantify long-term improvements in physical function among patients with

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stable CVD. Overall, these findings emphasize the health benefits of regular exercise and underscore the critical role of healthcare providers in promoting exercise prescriptions as part of secondary prevention programs.

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Conflict of interest

All the authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. All authors have read and approved the submission of the manuscript

Authors' contribution

SM, TP and AR had access to all of the data and took full responsibility for the integrity of the data and the accuracy of the data analysis. AR, SM and TP performed statistical analyses. SM, GM, EM and VZ drafted the manuscript. AR, SM, VZ, RL, and TP contributed with acquisition of the data. GM, GG, and JM contributed with conceptual design. JM contributed with analyses and interpretation of the results. All authors contributed in drafting the article or reviewing it for significant intellectual content. All authors gave final approval for the version to be submitted.

Availability of data and materials

The datasets used and/or analysed during the current study will be available from the corresponding author on reasonable request.

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Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the University of Ferrara, cod. 105/2023/Oss/UniFe and was conducted in accordance with the principles of the Declaration of Helsinki. Patients were informed that their participation was voluntary, and all of them gave written informed consent.

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Figure 1: Associations of walking speed tertiles with all-cause and cause-specific mortality

Data presented as HR and their 95% CI. The reference group was people reporting lower walking speed values. Walking speed was analysed both as a categorical variable and as a continuous variable. A hazard ratio for trend was estimated and expressed as risk per one unit increment in walking speed. Analyses were adjusted for age, sex, marital status, education, myocardial infarction, coronary artery bypass graft, family history, hypertension, diabetes, and dyslipidaemia.

Figure 2: Joint associations of walking speed and variation of walking speed tertiles with all-cause mortality

Data presented as HR and their 95% CI. The reference group was people reporting lower and decreased walking speed values. A hazard ratio for trend was estimated and expressed as risk per one category increment in walking speed. Analyses were adjusted for age, sex, marital status, education, myocardial infarction, coronary artery bypass graft, family history, hypertension, diabetes, and dyslipidaemia.
WS, walking speed

Figure 3: Graphical abstract

Table 1: Baseline characteristics of the 2,858 patients examined by age- and sex-specific tertiles of measured walking speed

Variable	**All patients (n=2 858)**	**Slower (n=986)**	**Medium (n=923)**	**Faster (n=949)**	**p-value**
Measured walking speed (km/h)					
Mean (SD)	4.1 (1.2)	2.8 (0.6)	4.2 (0.3)	5.4 (0.6)	<0.0001
Range (min/max)	0.8 – 8.0	0.8 – 3.6	3.7 – 4.6	4.7 – 8.0	
Demographics					
Age (yr)	65 (11)	67 (10)	64 (10)	63 (11)	<0.001
Sex (women, n, %)	501 (18)	254 (26)	125 (14)	122 (13)	<0.001
BMI (Kg/m^2)	27.4 (4.0)	27.6 (4.2)	27.5 (3.8)	27.2 (4.0)	0.207
LV ejection fraction (%)	58 (9)	57 (8)	58 (9)	58 (11)	<0.01
Marital status (married, %)	2 287 (80)	764 (77)	764 (83)	759 (80)	<0.05
Education (high school, %)	1 307 (46)	416 (42)	428 (46)	463 (49)	<0.05
Risk factors					
Family history (n, %)	1 199 (42)	374 (38)	375 (41)	450 (47)	<0.001
Hypertension (n, %)	1 737 (61)	656 (67)	517 (56)	564 (59)	<0.001
Diabetes (n, %)	498 (17)	199 (20)	133 (14)	166 (17)	<0.01
Current smoking (n, %)	635 (22)	197 (20)	200 (22)	238 (25)	<0.05
Haemoglobin (mg/dl)	13.5 (1.9)	13.4 (1.9)	13.5 (1.9)	13.6 (1.8)	<0.05
Total cholesterol (mg/dl)	183 (48)	185 (51)	184 (45)	180 (46)	0.064
HDL cholesterol (mg/dl)	49 (15)	49 (15)	49 (16)	49 (14)	0.888
Serum triglycerides (mg/dl)	132 (69)	131 (71)	133 (66)	133 (70)	0.814

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Serum creatinine (mg/dl)	1.07 (0.32)	1.09 (0.31)	1.08 (0.32)	1.05 (0.34)	<0.05
Medical history					
Myocardial infarction (n, %)	931 (33)	296 (30)	305 (33)	330 (35)	0.090
PCI (n, %)	799 (28)	214 (22)	260 (28)	325 (34)	<0.001
CABG (n, %)	1 110 (39)	427 (43)	365 (40)	318 (34)	<0.001
Valvular replacement (n, %)	481 (17)	205 (21)	143 (15)	133 (14)	<0.01
Other (n, %)	534 (19)	182 (18)	149 (16)	203 (21)	<0.001
Medications					
ACE inhibitor or ARB (n, %)	1 669 (58)	570 (58)	535 (58)	564 (59)	0.753
Aspirin (n, %)	2 095 (73)	650 (66)	678 (73)	767 (81)	<0.001
β-blocker (n, %)	1 931 (68)	648 (66)	648 (70)	635 (67)	0.092
Calcium antagonist (n, %)	526 (18)	215 (22)	162 (18)	149 (16)	<0.01
Statin (n, %)	1 778 (62)	531 (54)	582 (63)	665 (70)	<0.001
Diuretic (n, %)	666 (23)	359 (36)	188 (20)	119 (13)	<0.001

Values are presented as mean (SD) or percentage. Differences between groups were determined through One way ANOVA for continuous variables or χ^2 test for categorical variables

ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; HDL, high-density lipoprotein; LV, left ventricular; PCI, percutaneous coronary intervention, stenting, or both.

Table 2: Mean difference between average walking speed at baseline and at the end of the follow-up, for walking speed joint associations

Categories	Baseline AvgWS	Final AvgWS
LowWS-decreased	3.3 (0.8) [0.6 - 4.3]	3.0 (0.8) [0.4 - 4.3]
LowWS-stable	3.3 (0.7) [1.7 - 5.1]	3.7 (0.8) [1.2 - 4.3]
LowWS-improved	3.2 (0.8) [0.8 - 4.3]	5.0 (0.9) [5.3 - 7.5]
HighWS-decreased	5.3 (0.6) [4.4 - 8.0]	4.6 (1.1) [0.6 - 7.7]
HighWS-stable	5.1 (0.5) [4.4 - 6.6]	5.5 (0.5) [4.6 - 6.8]
HighWS-improved	4.8 (0.3) [4.4 - 6.2]	6.2 (0.5) [5.3 -7.5]

Data are presented as mean (SD). Cut-offs are presented as [min-max].

AvgWS, average walking speed

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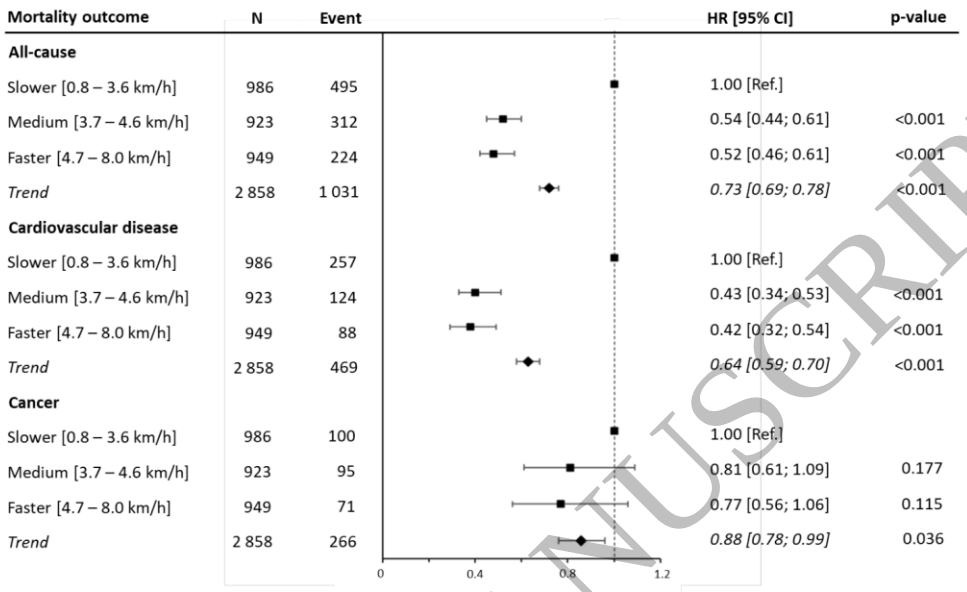


Figure 1
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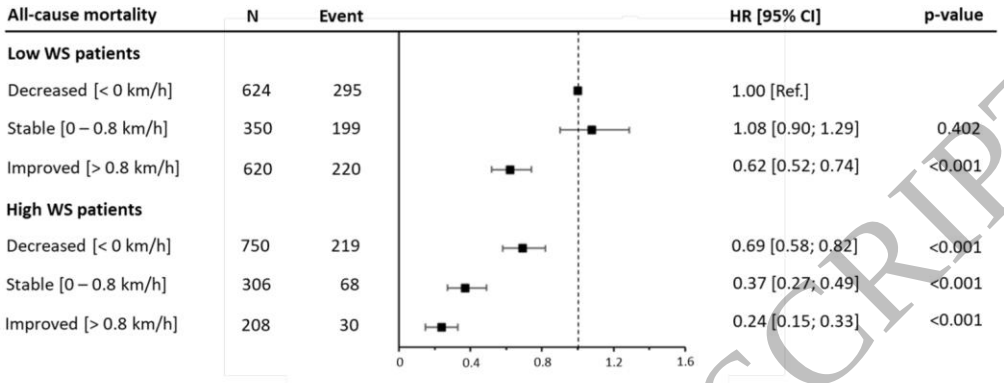
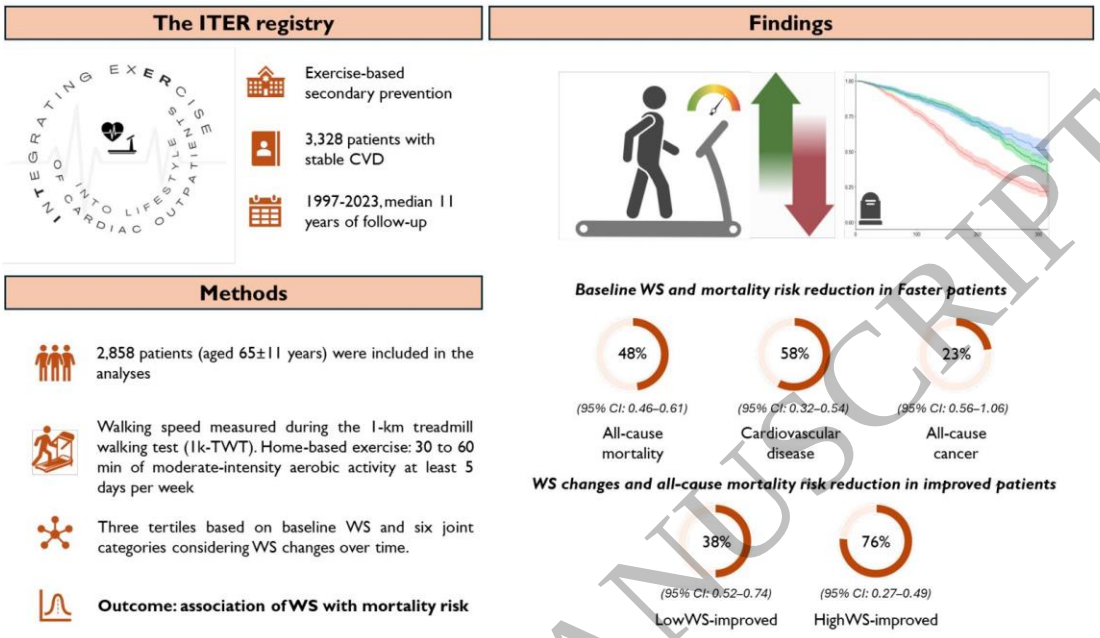


Figure 2
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Graphical Abstract
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