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Cardiovascular disease, muscle function, and long-term falls risk: The Perth Longitudinal Study of Ageing Women

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Running title:

Clinical CVD and long-term falls

Abstract

Background

A few cross-sectional studies have highlighted inconsistent associations between cardiovascular disease (CVD) and musculoskeletal conditions. We sought to investigate the relationship between clinical CVD including subtypes, compromised muscle function, as well as incident self-reported and injurious falls in older women.

Materials and methods

1431 community-dwelling older women (mean age ± SD 75.2 ± 2.7 years) were included in over 14.5 years of a prospective study, the Perth Longitudinal Study of Ageing in Women. CVD (up to 18-years prior to the baseline visit) and injurious fall hospitalizations over 14.5 years were obtained from linked health records. Self-reported falls for 5 years were obtained via a written adverse event diary posted every four months. Timed-Up-and-Go (TUG) test and hand grip strength were used to assess mobility and muscle strength, respectively. Mobility impairment was defined as TUG performance >10.2 s and muscle weakness characterized as grip strength <22 kg.

Results

Over 5-years, 411 (28.7%) women reported falls; while 567 (39.6%) were hospitalized due to injurious falls over 14.5 years. Prior CVD events were associated with 32% (HR 1.32 95%CI, 1.06-1.64) and 29% (HR 1.29 95%CI, 1.07-1.56) increased risk of self-reported and injurious falls, respectively, in multivariable-adjusted models. When considering subtypes of CVD, only cerebrovascular disease was related to self-reported (HR 1.77; 95%CI, 1.15-2.72) and injurious falls requiring hospitalizations (HR 1.51; 95%CI, 1.00-2.27). CVD was also associated with cross-sectional and prospective mobility impairments. However, no evidence for such relationships was observed for muscle weakness.

Conclusions

Prevalent CVD events, particularly cerebrovascular disease, are related to an increased risk of long-term falls. These findings highlight the need to recognise increased fall risk in patients with CVD. Further, there is a need to understand whether incorporating prevalent CVD into falls screening tools improves risk stratification or affects model calibration.

Keywords: CVD, muscle weakness, mobility impairment, self-reported falls, fall-related hospitalization.

1. Introduction

Falls are associated with an estimated 684,000 deaths and approximately 38 million disability-adjusted life years lost annually, making it one of the leading causes of injury-related mortality and morbidity [1]. The burden of falls and fall-related injuries increases with age, with the highest impact in older women [2, 3]. Approximately 32% to 42% of people aged 70 years and over fall at least once each year [4]. Of note, up to 40% of fallers experience recurrent falls and fall-related injuries such as fractures, which often contribute towards functional decline and subsequent institutionalization [5].

Cardiovascular disease (CVD) is the most common cause of mortality and a significant contributor to disability worldwide with an increasing trend among older people [6]. A few studies reported an association between CVD and compromised musculoskeletal health [7, 8], including a decline in muscle strength [9] and mobility impairment [10], both of which are independent predictors of falls [11, 12]. Although the available evidence is largely inconsistent, a few cross-sectional studies have also reported an association between CVD and falls [13-17], particularly self-reported falls. CVD is also related to several fall risk factors including cognitive [18] and neuromuscular impairments [19]. Atherosclerosis, the leading cause of CVD, is associated with increased transient events [20-22] (e.g., hypotension and syncope),

which are independently associated with increased falls risk [23, 24]. Cerebrovascular disease is also thought to impair cerebral perfusion leading to neuromuscular dysfunction and subsequently impairments in balance and gait, which can contribute towards increased risk of falls [25].

CVD can also impact an individual's ability to engage in regular exercise, which in turn may lead to a greater functional decline and poorer capacity to counteract falling [26]. Furthermore, markers of asymptomatic CVD such as abdominal aortic calcification (AAC) and biomarkers (such as high sensitivity cardiac troponin T and N-terminal pro B-type natriuretic peptide) are related to falls [27, 28], overall implying a possible link between CVD and falling. Despite such evidence supporting an association between CVD and falls, the majority of studies to date are cross-sectional and report inconsistent findings [24, 29]. To our knowledge, no study has investigated a relationship between clinical CVD (requiring one or more hospitalisations), long-term measures of muscle function (e.g. muscle weakness and mobility impairment) and falls. Therefore, we sought to investigate the relationship between clinical CVD, including its subtypes, with long-term measures of muscle function (muscle weakness and mobility impairment), self-reported and injurious falls requiring hospitalizations in a cohort of older women.

2. Materials and Methods

2.1. Study population

The study included ambulant community-dwelling older women aged 70 years and over who were recruited in 1998 to a 5-year (1998-2003) prospective, randomised controlled trial of oral calcium supplements to prevent osteoporotic fractures [Calcium Intake Fracture Outcome Study (CAIFOS)]. In brief, the participants were recruited by mail from the Western Australian general population of women, using the electoral roll as a requirement of citizenship. Over 99% of Australians of this age are on the electoral roll. Among the 5,586 women who responded to

an invitation to participate, 1,510 were willing and eligible, and 1,500 were recruited for the study. The study's participants had no medical conditions that would have an impact on their 5-year survival. They were ineligible if they were taking a bone-active agent, such as hormone replacement therapy. In terms of disease burden and medication use, the women included were comparable to whole populations their age, but they were more likely to be from higher socioeconomic groups [30]. Following the completion of CAIFOS, participants were enrolled in an additional 10 years (2003-2013) of observational follow-up; both of these studies, totalling over 14.5 years of follow-up, are known as the Perth Longitudinal Study of Ageing Women (PLSAW). 69 participants with missing fall risk factors were excluded, leaving 1431 for the final analysis of CVD and long-term falls (**Supplementary Figure 1**).

2.2. Ethics approval

Ethics approval was provided by the Human Research Ethics Committee of the University of Western Australia. PLSAW was retrospectively registered on the Australian New Zealand Clinical Trials Registry, with trial registration number #ACTRN12617000640303, and complied with the Declaration of Helsinki. Ethics approval for the use of linked data was granted by Ethics Committee of the Western Australian Department of Health (project number #2009/24). Written informed consent, including future access to the Western Australian Department of Health data, was obtained from all participants.

2.3. Baseline Characteristic Assessment

Body weight (kg) and height (cm), which were taken using digital scales and a wall-mounted stadiometer, respectively, were used to calculate body mass index (kg/m^2). Participants in the CAIFOS were randomly assigned to receive either a placebo or 1.2 g/day of calcium carbonate for the first five years (1998-2003). Insulin or the use of oral hypoglycemic medications were used to determine the prevalence of diabetes. When possible, participants' primary care physician verified their use of statins and antihypertensive medication. These data were coded

(T89001-T90009) using the International Classification of Primary Care-Plus (ICPC-Plus) method, which enables the grouping of various terms for comparable pathologic entities as defined by the ICD-10 coding system. When it came to smoking history, individuals were classified as never smoked, or previous/current smokers if they had ever smoked more than one cigarette per day for more than three months. Abdominal aortic calcification (AAC) was identified using digitally enhanced lateral single-energy images of the thoraco-lumbar spine using a Hologic 4500A bone densitometer (Hologic, Bedford, MA, USA) and scored out of 24 (AAC24) [27]. Plasma 25-hydroxyvitamin D concentration was measured using a validated LC–MS/MS (Liquid Chromatography Tandem Mass Spectrometry) method at the RDDT Laboratories (Bundoora, VIC, Australia) as previously described [31]. Previous falls and physical activity were assessed for the three months prior to participants baseline clinical visit in 1998 using questionnaires. Specifically, women were asked if they had experienced a fall in the last three months (yes/no). Falls were defined as "unintentionally coming to rest on the ground, floor, or other lower level" [32]. Physical activity level of each participant was assessed by being questioned about their involvement in sports, leisure, and/or regular physical activities. The level of activity was then computed in kcal/day considering body weight and energy costs of listed activities [30]. Fear of falling at baseline was assessed by asking participants to reply yes or no to the following questions: ''Are you afraid of falling?'', ''Do you limit any household activities because you are frightened you may fall?'' and ''Do you limit any outside activities because you are frightened you may fall?'' If they answered yes to any of the three questions, the participant was classified as having a fear of falling [33]. The study design according to the CONSORT guidelines is described in **Supplementary Figure 1.** All participant baseline characteristics, including the covariates included in the analyses, were collected in 1998 during the baseline clinical visit.

2.4. Prevalent CVD

Prevalent CVD (1980 to 1998) was defined as one or more hospitalizations with primary discharge diagnosis codes from the International Classification of Diseases, Injuries and Causes of Death Clinical Modification (ICD-9-CM)[34] and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10- AM) [35]. These codes included: disease of the circulatory system (ICD-9-CM codes 390-459 and ICD-10-AM codes I00-I99) and specific CVD hospitalizations such as cerebrovascular disease excluding hemorrhage (ICD-9-CM codes 433-438 and ICD-10-AM codes I63-69, G45.9) and Ischaemic Heart Disease (ICD-9-CM codes 410-414 and ICD-10-AM codes I20-I25). Hospitalization data were retrieved from the Western Australian Data Linkage System for each of the study participants, which provides a complete validated record of every participant's primary diagnosis at hospital discharge using coded data from all hospitals in Western Australia.

2.5. Measures of muscle function

Hand grip strength (measured with a Jamar hand dynamometer─Lafayette Instrument Company, USA) and TUG performance were used to assess muscle strength and mobility, respectively, at the baseline clinical visit (1998) and after 5-years (2003). For TUG performance, the participant is timed while rising from a chair, walking three meters, turning, and returning to sit on the chair. Muscle weakness and mobility impairment were considered when the participant recorded hand grip strength of <22 kg and TUG >10.2 sec at baseline or in 2003 (5 years), respectively. Those cut-points were adopted from previous reports of the same or different cohorts that have established a relationship with various clinical outcomes in older adults [36-40]. Incident muscle weakness was used to represent a participant with a normal baseline (1998) hand grip strength (n=457) who presented with a hand grip strength of <22 kg (n=255) five years later. The same concept was applied to define incident mobility

impairment (n=319), in which women with normal TUG at baseline (n=766) that presented with TUG performance < 10.2 sec after five years were included (Supplementary **Figure 1)**.

2.6. Incident Falls

2.6.1. 5-years self-reported falls

Self-reported falls were collected via a written adverse event diary posted every four months and followed up by a telephone interview conducted by a team member. However, data was collected in person if the four-month follow-up coincided with a previously scheduled clinic visit as part of the 5-year RCT [41], thereby enabling calculation of time to event. Participants were advised to keep a daily record of any fall incidents in their diaries to minimize recall bias.

2.6.2. 14.5-years fall-related hospitalizations

Fall-related hospitalizations were captured through Western Australian Data Linkage System (Department of Health Western Australia, East Perth, Australia) and retrieved from the Western Australia Hospital Morbidity Data Collection. Falls from standing height or less, not resulting from external force were considered using the following ICD- 10 codes: W01-Fall on same level from slipping, tripping and stumbling; W05-Fall involving a non-moving wheelchair or scooter; W06-Fall from bed; W07-Fall from chair; W08-Fall from furniture, W10-fall from stairs and steps, W18-other fall on the same level, and W19-unspecified fall. Follow-up was available for each of the participants starting from their baseline visit in 1998 until the first fall, death, loss to follow-up or end of the study.

2.7. Statistical analysis

To obtain a summary of baseline characteristics of participants with and without CVD at baseline, independent t-tests, chi-square tests, and Mann-Whitney U non-parametric tests where appropriate were used. Using Cox proportional hazards regression, the association between CVD, including subtypes (cerebrovascular and ischaemic heart disease), and long-

term falls was examined using three models: i) unadjusted, ii) minimally-adjusted: age, BMI and treatment (calcium/placebo), and iii) multivariable-adjusted: minimally-adjusted plus smoked ever (yes/no), diabetes (yes/no), statin (yes/no), antihypertensive medication use (yes/no), physical activity (yes/no) and previous falls (yes/no). The aforementioned covariates were identified a priori, primary guided by their relationship with the exposure (CVD) or the outcome (long-term falls). Of note, we used similar covariates in previous reports to investigate the associations between measures of subclinical CVD and long-term falls from the same cohort and found reasonably precise effect estimates [27, 37]. The assumptions for Cox proportional hazards models were examined based on Schoenfeld residuals. The fact that all analyses, including the covariates, had p-values >0.05 indicates that the proportional hazards assumptions were not violated. In order to evaluate the univariate relationship between prevalent CVD and long-term falls, Kaplan-Meier survival analysis were used.

The cross-sectional and prospective relationships between prevalent CVD, muscle weakness and mobility impairment were examined using binary logistic regression model. Multivariable-adjusted model for this analysis included minimally-adjusted (Age, BMI, and treatment) plus prevalent diabetes mellitus (yes/no), smoking (yes/no), statin use (yes/no) and physical activity at baseline. Additionally, multinominal logistic regression was used to investigate the association between CVD and quartiles of TUG performance. Generalized linear model repeated measures analyses were used to determine whether estimated marginal mean of grip strength and TUG performance differed over 5-years and across prevalent CVD in the minimally-adjusted model. All analysis were undertaken using SPSS version 28.0 (IBM Corp., Armonk, NY).

2.8. Additional analyses

We acknowledge that the observed associations may be influenced by the fact that we have only considered the baseline values of the covariates not a time-varying covariates. To try and address this, we undertook additional analyses where we truncated the follow up period to 3 years for self-reported falls and 10 years for injurious fall-related hospitalization. Given the multifactorial nature of falls, we also conducted additional analyses to see if the association between prevalent CVD and falls persists after accounting for several additional falls risk factors. These analyses demonstrate the robustness of the observed association as well as the underlying mechanism (s) explaining the association between CVD and long-term falls. Specifically, AAC, an advanced marker of CVD, has been associated to loss of muscle strength [36] as well as injurious falls [27]. In order to determine whether the association between CVD and long-term falls still exists, we looked into it after including AAC-24 score into the multivariable-adjusted model. The relationships between CVD and long-term falls were also evaluated, after taking into account measures of muscle functions (baseline hand grip strength and TUG performance), which are independent predictors of falls risk [42]. As low vitamin D is associated with injurious falls [31], we conducted further analyses after adding total plasma 25-hydroxy vitamin D to the multivariable-adjusted model. We also investigated an association between CVD and fear of falling, which is directly related to the causal pathways of falls, using a binary logistic regression model. In our study, CVD was linked to poor TUG performance as well as to injurious falls risk. Thus, the proportion of the association between prevalent CVD and fall-related hospitalizations in the multivariable-adjusted model that was mediated by TUG performance at baseline was determined using mediation analysis with a Cox proportional hazards model in the Medflex package for R [43]. The point estimates and 95% CIs were determined by bootstrapping (1000 iterations).

3. Results

Clinical CVD was recorded in 342 (23.9%) women at baseline. Compared to women without CVD, women with CVD were older, more likely to fear falling, and take lipid and antihypertensive drugs (**Table 1**). These women also presented with slower TUG, but their grip strength, previous falls, and physical activity levels were comparable to women without CVD.

3.1.Muscle function

Older women with CVD had higher risks for mobility impairment cross-sectional (at baseline) (OR 1.32 95%CI, 1.01-1.70) and prospectively (5 years later) (OR 1.65 95%CI, 1.18-2.31) compared to those without CVD. Those with CVD had also greater risk of incident mobility impairment (OR 1.49 95%CI, 1.03-2.16) in a multivariable-adjusted model. Furthermore, women with CVD had greater odds of having TUG performance in quartile 3 (OR 2.13 95%CI, 1.36-3.33) and quartile 4 (OR 1.88 95%CI, 1.22-2.90), both of which indicate mobility impairment, than in quartile 1 (highest TUG performance) (**Supplementary Table 1**). However, no cross-sectional and prospective relationship was observed between CVD, and muscle weakness (**Table 2**). Over 5-years, there was a significant reduction in the estimated mean TUG performance (1.64 95%CI 1.46-1.81 sec) and grip strength (-3.25 95%CI, -3.49 to -3.02 kg). Of note, older women with CVD experienced a greater decline in estimated marginal mean of TUG performance (0.60 sec 95% CI, 0.22-0.99) compared to those without CVD. However, no change was observed between groups when considering grip strength (-0.07 kg 95% CI, -66 to 0.52).

3.2. Incident falls

3.2.1. Self-reported falls

Over the 5-years (6258 person-years) of follow-up (mean ± SD; 4.2 ± 1.4 years), 411/1431 (28.7%) women reported a fall. Women with CVD had increased risk for a self-reported fall

compared to those without CVD (**Figure 1 A**). In the multivariable-adjusted model, CVD was associated with a 32% greater relative hazard for self-reported fall (**Table 3**).Additionally, CVD was associated with a higher risk of self-reported falls (HR 1.47 95%CI, 1.12-1.94) when data was truncated to three years. Of the CVD subtypes considered, only cerebrovascular disease (HR 1.77 95%CI, 1.15-2.73) was associated with an increased relative hazard for self-reported falls. No such relationship was observed when considering ischaemic heart disease (HR 1.21 95%CI, 0.87-1.68) (**Table 3**).

3.2.2. Fall-related hospitalization

Over the 14.5-years (16,261 person years) of follow-up (mean ± SD; 10.8 ± 4.2 years), 567/1431 (39.6%) women were hospitalized due to an injurious fall. Women with CVD were more likely to be hospitalized due to falls compared to those without CVD (**Figure 1 B)**. Those with CVD had a 29% (HR 1.29 95%CI, 1.07-1.56) increased risk for a fall-related hospitalization in the multivariable-adjusted model (**Table 3**). CVD was also associated with increased risk when considering fall-related hospitalization over 10 years (HR 1.33 95%CI, 1.04-1.70). For CVD subtypes, only cerebrovascular disease was related to a higher risk of a fall-related hospitalization (HR 1.51 95%CI 1.00-2.27). No evidence for such a relationship was observed for ischaemic heart disease (HR 1.22 95%CI, 0.92-1.62).

3.3. Additional analysis

The associations between clinical CVD and long-term falls remained significant after adjustment for AAC-24 score, measures of baseline muscle function (e.g., grip strength and TUG performance) and 25-hydroxyvitamin D (**Table 4**). Clinical CVD was also associated with increased odds for presenting with a fear of falling in the minimally (OR 1.40 95%CI, 1.07-1.83) and multivariable-adjusted models (OR 1.41 95%CI, 1.07-1.86). Finally, baseline

TUG performance appeared to mediate 8.0% (95%CI, 0.02-44.2%) of the observed association between CVD and fall-related hospitalization.

4. Discussion

CVD is associated with a large healthcare burden in older people and may contribute towards a higher long-term falls risk [44]. Understanding its relationship with falls may serve to improve falls risk prediction and develop primary prevention interventions. This is important because it may prompt clinicians to recognise that patients with CVD may also have poor musculoskeletal health. We observed associations between CVD and greater relative hazards for long-term self-reported incident falls and fall-related hospitalization in older women. HRs for self-reported falls after 5 years were similar to HRs for fall-related hospitalizations, obtained from linked health records, after 14.5 years. A similar pattern was observed when falls outcomes were truncated (e.g., 3-years for self-reported and 10 years of injurious falls), indicating that our findings have good internal validity. According to our understanding for some of the main causes of falls (e.g., neuromuscular, cognitive impairment, gait and balance issues in this age group), the link between CVD and long-term falls appeared to be driven mostly by cerebrovascular disease [25]. Additionally, we also found an association between CVD, mobility impairment, and fear of falling. Collectively, this work provides evidence for the link between vascular disease and poor musculoskeletal health, implying that CVD should be considered when assessing falls risk.

To our knowledge, this is the first study to highlight the association between CVD and long-term falls. Interestingly, the associations were independent of measures of muscle function, and subclinical vascular disease, suggesting prognostic importance of CVD for falls. Previously, cross-sectional studies have reported a relationship between cardiovascular conditions and falls, although the findings are largely inconsistent [24, 45]. For example, in a

study of 2456 hospitalized patients with CVD (mean age~71 years, 45% female), 60% of the patients had moderate or high falls risk score [46]. Secondary analyses of cross-sectional studies have also shown an association between prevalent CVD and falls [14, 17]. On the contrary, other studies have reported no association between CVD and falls [47, 48]. Collectively, the present study along with the existing literature largely supports an association between CVD and falls. When considering subtypes of CVD, besides cerebrovascular disease, we found no relationship between ischaemic heart disease, self-reported falls and fall-related hospitalization, and inconsistent findings have been reported previously [24, 49]. As such, further well-powered studies are warranted. It is also important to note that there were significant differences in baseline characteristics between women with and without CVD, implying that the observed association could have been affected by confounding factors. To try and minimize the influence of such differences and other confounders, several CVD and musculoskeletal factors were accounted in our analyses.

There are several putative mechanisms that may explain why clinical CVD is related to falls. CVD is associated with transient events such as syncope, hypotension and bradyarrhythmia, which are established precipitants for falls and falls-related injuries [8]. CVD is also associated with frailty [50], which in turn is related to increased falls propensity [51]. Further, CVD is linked with decreased exercise tolerance [26], which may restrict involvement in physical activity, thus explaining why we found fear of falling to be more evident in people with CVD. A lack of physical activity is related to poor musculoskeletal health and increasing the risk of chronic diseases such as diabetes, sarcopenia and osteoporosis [52], which are all related to increased falls propensity [53]. In this study, it is noteworthy that that we found women with CVD had a higher risk of prevalent and incident mobility impairment as well as fear of falling, which are related to a lack of physical activity and increased falls risk [54, 55]. The observed relationship between CVD and injurious falls also appeared to be partially explained by

baseline TUG performance. Large longitudinal studies conducted in the past also found a link between poor TUG performance and incident CVDs [56, 57]. CVD, presumably by affecting cerebral blood flow, is associated with impairments of cognitive, neuromuscular, and sensory functions (e.g., executive function, mental processing speed, vision, balance, gait etc) [58] contributing towards increased falls risk. This relationship between CVD and slower TUG may be explained in part by such neuromuscular impairment [19]. Additionally, medications used to treat CVD, such as statins [59] and digitalis [60] may be associated with a higher risk of falling. This may be reflective of the multiple interrelated pathways leading to falls [60]. It important to note that relatively little research exists on the effects of CVD medications on musculoskeletal health and the risk of falling, particularly in the context of multimorbidity [61]. On the other hand, certain medications such statins have well-recognized albeit rare musculoskeletal side effects (e.g., myopathy) [62]. Clearly, the association between CVD medications and falls requires cautious investigation, as they could prevent or improving CVD-related complications.

The study has a number of strengths and limitations. Firstly, PLSAW is a prospective cohort with a long-term follow-up, 5-years for self-reported fall and 14.5-years for fall-related hospitalization. This is important as it allows exploration of long-term clinically important outcomes. Secondly, prevalent CVD (including specific events) and fall-related hospitalization were obtained from validated linked health records that would maximize the accuracy of the data. Alternatively, when considering self-reported incident falls, these were collected via a written adverse event diary posted every four months and followed up by a telephone interview [41], so the accuracy of the data pertaining to those falls may have been affected by the ability of the participants to report their falls experience accurately. Nonetheless, to minimize recall bias, participants were instructed to record a fall incident (s) (if any) on a daily basis

Thirdly, considerable falls/musculoskeletal (e.g., muscle function measures), and CVD (e.g., AAC) risk factors were considered while examining the relationship between CVD and falls, which minimizes the potential residual confounding. Nevertheless, due to the observational nature of this work, no causal inferences can be made, and the risk of bias due to unmeasured confounders cannot be excluded. Additionally, given the study's long-term follow-up and the fact that our covariates were only measured at baseline, not their changes over time, the impact of the included covariates on the observed association cannot be fully accounted. However, the Cox proportional hazards assumption was not violated for both the 5 years of self-reported and 14.5-years of injurious falls-related hospitalization analyses, implying that the relative hazards were similar, at least theoretically, throughout the follow-up period, regardless of any changes to covariates considered. Moreover, the study population were older women aged ≥70 years, so the findings of the present study may not be generalized to younger populations and older men. It is also important to acknowledge half of the study population was on calcium intervention during the first five years of the study despite it was accounted in the current analyses. Of note, calcium supplementation was not related to either 5-year self-reported (HR 1.07 95% CI,0.88-1.30 p=0.502) or injurious falls (HR 1.09 95% CI, 0.93-1.29, p=0.302) in our study. Finally, the statistical power for CVD subtypes may be insufficient, implying that the observed association between CVD types, particularly cerebrovascular disease, and long-term fall prognosis should be interpreted with caution, necessitating additional large epidemiological studies.

5. Conclusions

Clinical CVD, and in particular cerebrovascular disease, is related to long-term falls in community-dwelling older women independent of well-established falls risk factors. Such findings imply that falls screening in patients with CVD may be necessary given the significant burden of CVD and its related consequences. The inclusion of prevalent CVD as risk factor in

falls assessment tools may contribute towards improved detection of those at high risk of falls and targeting of prevention interventions.

Author contributions

AKG, MS, JRL and RLP contributed to study concept and design. AKG analysed the data. AKG, wrote the draft of the manuscript under the supervision of MS and JRL. All authors contributed to critical revision of the manuscript. All authors read and approved the final version of the manuscript. AKG, MS and JRL have the primary responsibility for the final content.

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Conflict of interest

None of authors have any conflicts of interest to disclose.

Data availability

The data that support the findings of this study are available upon reasonable request from the corresponding author.

Table 1: Baseline characteristics of the participants across clinical CVD

	All participants	CVD	
		Absent	**Present**
Number	1431	1089 (76.1)	342 (23.9)
Demographics			
Age, years	75.2 ± 2.7	**75.0 ± 2.7**	**75.5 ± 2.8**
Calcium treatment group, yes (%)	717 (50.1)	**565 (51.9)**	**152 (44.4)**
Body mass index (BMI), kg/m	27.2 ± 4.8	27.2 ± 4.7	27.3 ± 4.9
Smoked ever, yes (%)	529 (37.0)	405 (37.2)	124 (36.3)
Prevalent diabetes mellitus, yes (%)	94 (6.6)	64 (5.9)	30 (8.8)
Lipid lowering medications, yes (%)	274 (19.1)	**176 (16.2)**	**98 (28.7)**
Antihypertensive medications, yes (%)	623 (43.5)	**443 (40.7)**	**180 (52.6)**
Fear of falling[1], yes (%)	403 (28.3)	**288 (26.5)**	**115 (33.9)**
Physical function			
Physical activity, kcal/day	110 (26-203)	109 (0-202)	114 (39-204)
Grip strength[2], kg	20.5 ± 4.7	20.5 ± 4.7	20.3 ± 4.6
Timed-up-and-go[3], sec	10.0 ± 3.0	**9.9 ± 2.9**	**10.4 ± 3.4**
Previous falls, yes (%)	169 (11.8)	121 (11.1)	48 (14.0)

Data presented as mean ± SD, median (IQR) or number *n* (%). Bolded numbers indicate $p<0.05$ and are a comparison between the presence and absence of cardiovascular disease (CVD); [1](n=1087), [2](n=1423), [3](n=1428).

Table 2: The effect of CVD on muscle weakness (GS < 22 kg) and mobility impairment (TUG >10.2 s)[†]

Outcome measures	CVD (OR 95%CI)	
	Absent	**Present**
Cross-sectional (baseline in 1998)		
Muscle weakness[1] (n=872)	660 (60.9)	212 (62.4)
Minimally-adjusted	Referent	1.01 (0.78-1.30)
Multivariable-adjusted	Referent	0.98 (0.76-1.27)
Mobility impairment[2] (n=531)	**384 (35.5)**	**147 (43.1)**
Minimally-adjusted	Referent	**1.33 (1.03-1.72)**
Multivariable-adjusted	Referent	**1.32 (1.01-1.71)**
Prospective (5-year in 2003)		
Muscle weakness[3]***** (n=891)	686 (77.9)	205 (79.2)
Minimally-adjusted	Referent	1.02 (0.72-1.44)
Multivariable-adjusted	Referent	1.08 (0.70-1.64)
Mobility impairment[4#] (n=631)	461 (52.2)	170 (65.4)
Minimally-adjusted	Referent	**1.66 (1.23-2.24)**
Multivariable-adjusted	Referent	**1.65 (1.18-2.31)**
Prospective incident only (5-year in 2003)		
Muscle weakness[5] (n=255)	197 (55.6)	58 (56.3)
Minimally-adjusted	Referent	0.98 (0.63-1.55)
Multivariable-adjusted	Referent	0.96 (0.60-1.53)
Mobility impairment[6] (n=319)	243 (39.8)	76 (48.7)
Minimally-adjusted	Referent	1.42 (0.98-2.04)
Multivariable-adjusted	Referent	**1.49 (1.03-2.16)**

GS: Grip strength; TUG: Timed up go test: Minimally-adjusted: age, BMI and treatment (calcium/placebo); Multivariable-adjusted: minimally-adjusted plus prevalent diabetes mellitus, smoking, statin use and physical activity at baseline; [†]data was presented as n (%);*baseline (in 1998) grip strength (kg) was included in the multivariable adjusted model; [#]baseline (in 1998) timed-up-and-go (sec.) was included in the multivariable adjusted model; Muscle weakness and mobility impairment were defined as hand grip strength <22 kg and timed-up-and-go performance >10.2 seconds respectively. Bolded numbers indicate p <0.05. Assessment was undertaken in [1]N=1423; [2] N=1428; [3] N=1140; [4]N=1143; [5]N=457; and [6] N=766.

Table 3: Hazard ratios (HR) for the association between clinical CVD, specific CVD events and long-term falls

Outcomes	Prevalent conditions					
	CVD		Cerebrovascular disease (n=49)		Ischaemic heart disease (n=127)	
	Absent (n=1089)	Present (n=342)	Absent (n=1382)	Present (n=49)	Absent (n=1304)	Present (n=127)
Self-reported incident falls over 5 y						
Events, n (%)	293 (26.9)	118 (34.5)	388 (28.1)	23 (46.9)	368 (28.2)	43 (33.9)
Unadjusted	**Ref.**	**1.39 (1.12-1.67)**	**Ref.**	**2.04 (1.34-3.10)**	**Ref.**	1.29 (0.94-1.76)
Minimally-adjusted	**Ref.**	**1.37 (1.11-1.70)**	**Ref.**	**2.04 (1.34-3.11)**	**Ref.**	1.22 (0.89-1.68)
Multivariable-adjusted	**Ref.**	**1.32 (1.06-1.64)**	**Ref.**	**1.77 (1.15-2.72)**	**Ref.**	1.21 (0.87-1.67)
Fall-related hospitalization over 14.5 y						
Events, n (%)	411(37.7)	156 (45.6)	542 (39.2)	25 (51.0)	511 (39.2)	56 (44.1)
Unadjusted	**Ref.**	**1.40 (1.17-1.69)**	**Ref.**	**1.75 (1.17-2.61)**	**Ref.**	**1.36 (1.03-1.80)**
Minimally-adjusted	**Ref.**	**1.32 (1.09-1.60)**	**Ref.**	**1.60 (1.07-2.39)**	**Ref.**	1.25 (0.95-1.66)
Multivariable-adjusted	**Ref.**	**1.29 (1.07-1.56)**	**Ref.**	**1.51 (1.00-2.27)**	**Ref.**	1.22 (0.92-1.62)

Ref.; Referent: CVD: Cardiovascular disease; Hazard ratios (95% CI) analyzed using Cox-proportional hazard models; Models adopted: unadjusted; minimally-adjusted: age, BMI, and treatment code (calcium/placebo); Multivariable-adjusted: minimally-adjusted plus smoked ever (yes/no), prevalent diabetes (yes/no), statin use (yes/no), antihypertensive medication use (yes/no), physical activity (kcal/day) and previous falls (yes/no); Bolded numbers indicate $p < 0.05$.

Table 4: Multivariable-adjusted hazard ratios (HR) for long-term falls in individuals with clinical CVD after inclusion of falls risk factors

	HR 95%CI	
Covariates	**Self-reported falls over 5 y**	**Fall-related hospitalization over 14.5 y**
Multivariable-adjusted[1]	**1.32 (1.06-1.64)**	**1.29 (1.07-1.56)**
+AAC-24 score[2]	**1.29 (1.01-1.66)**	**1.25 (1.00-1.56)**
+Grip strength[3]	**1.32 (1.06-1.64)**	**1.29 (1.07-1.56)**
+ timed-up-and-go[4]	**1.32 (1.06-1.64)**	**1.27 (1.05-1.53**
+Grip strength and timed-up-and-go[5]	**1.31 (1.05-1.63)**	**1.26 (1.04-1.52)**
+25 hydroxyvitamin D at baseline[6]	**1.32 (1.05-1.66)**	**1.30 (1.07-1.58)**

Multivariable adjusted: minimally-adjusted plus smoked ever, prevalent diabetes, statin use, antihypertensive medication use, physical activity at baseline and previous falls; AAC-24 score: Abdominal aortic calcification-24 score; timed-up-and-go; [1](n=1424), [2](n=1031), [3](n=1412), [4](n=1421),[5](n=1411), and [6](n=1319); Bolded numbers indicate $p < 0.05$.

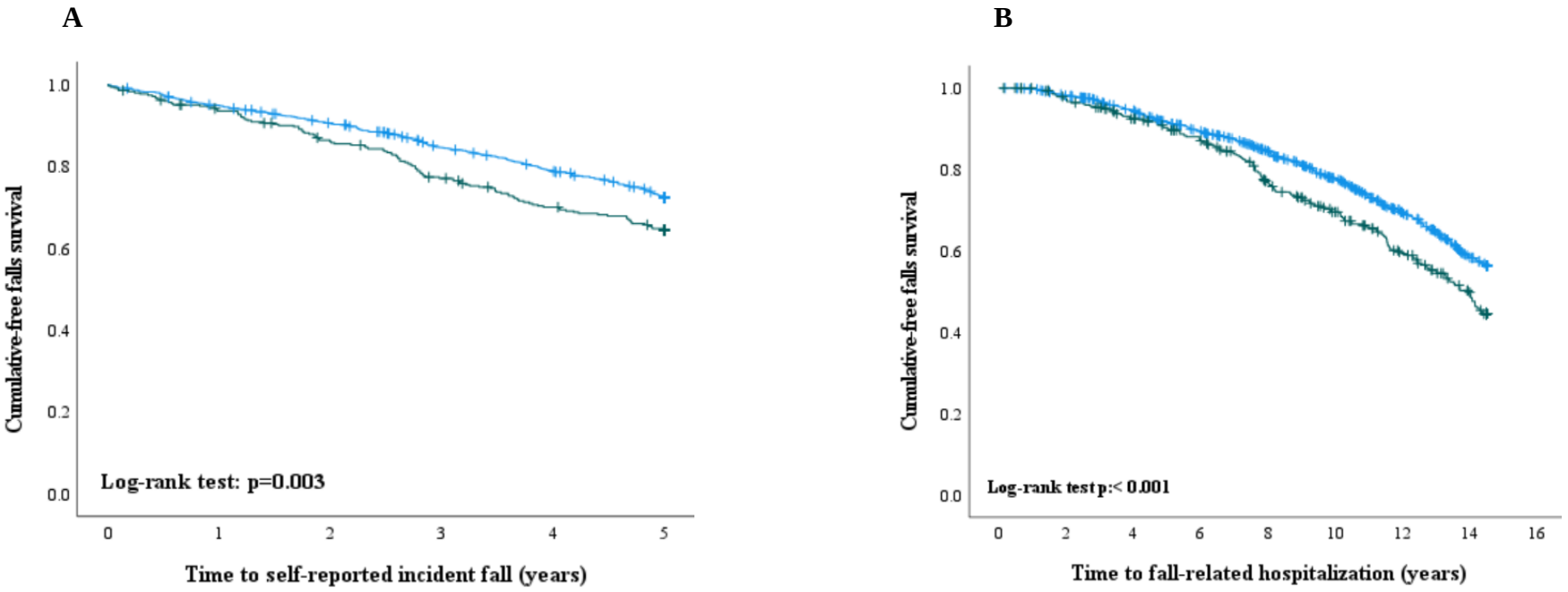

Figure 1: Kaplan-Meier survival curve for the association between prevalent CVD, **A)** self-reported incident fall for 5-years, **B)** fall-related hospitalization over 14.5 years. CVD present and absent are represented by green and blue lines respectively.

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CRediT authorship contribution statement

AKG, MS, JRL and RLP contributed to study concept and design. AKG analysed the data. AKG, wrote the draft of the manuscript under the supervision of MS and JRL. All authors contributed to critical revision of the manuscript. All authors read and approved the final version of the manuscript. AKG, MS and JRL have the primary responsibility for the final content.

Cardiovascular disease, muscle function, and long-term falls risk: The Perth Longitudinal Study of Ageing Women

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Running title:

Clinical CVD and long-term falls

Abstract

Background

A few cross-sectional studies have highlighted inconsistent associations between cardiovascular disease (CVD) and musculoskeletal conditions. We sought to investigate the relationship between clinical CVD including subtypes, compromised muscle function, as well as incident self-reported and injurious falls in older women.

Materials and methods

1431 community-dwelling older women (mean age ± SD 75.2 ± 2.7 years) were included in over 14.5 years of a prospective study, the Perth Longitudinal Study of Ageing in Women. CVD (up to 18-years prior to the baseline visit) and injurious fall hospitalizations over 14.5 years were obtained from linked health records. Self-reported falls for 5 years were obtained via a written adverse event diary posted every four months. Timed-Up-and-Go (TUG) test and hand grip strength were used to assess mobility and muscle strength, respectively. Mobility impairment was defined as TUG performance >10.2 s and muscle weakness characterized as grip strength <22 kg.

Results

Over 5-years, 411 (28.7%) women reported falls; while 567 (39.6%) were hospitalized due to injurious falls over 14.5 years. Prior CVD events were associated with 32% (HR 1.32 95%CI, 1.06-1.64) and 29% (HR 1.29 95%CI, 1.07-1.56) increased risk of self-reported and injurious falls, respectively, in multivariable-adjusted models. When considering subtypes of CVD, only cerebrovascular disease was related to self-reported (HR 1.77; 95%CI, 1.15-2.72) and injurious falls requiring hospitalizations (HR 1.51; 95%CI, 1.00-2.27). CVD was also associated with cross-sectional and prospective mobility impairments. However, no evidence for such relationships was observed for muscle weakness.

Conclusions

Prevalent CVD events, particularly cerebrovascular disease, are related to an increased risk of long-term falls. These findings highlight the need to recognise increased fall risk in patients with CVD. Further, there is a need to understand whether incorporating prevalent CVD into falls screening tools improves risk stratification or affects model calibration.

Keywords: CVD, muscle weakness, mobility impairment, self-reported falls, fall-related hospitalization.

1. Introduction

Falls are associated with an estimated 684,000 deaths and approximately 38 million disability-adjusted life years lost annually, making it one of the leading causes of injury-related mortality and morbidity [1]. The burden of falls and fall-related injuries increases with age, with the highest impact in older women [2, 3]. Approximately 32% to 42% of people aged 70 years and over fall at least once each year [4]. Of note, up to 40% of fallers experience recurrent falls and fall-related injuries such as fractures, which often contribute towards functional decline and subsequent institutionalization [5].

Cardiovascular disease (CVD) is the most common cause of mortality and a significant contributor to disability worldwide with an increasing trend among older people [6]. A few studies reported an association between CVD and compromised musculoskeletal health [7, 8], including a decline in muscle strength [9] and mobility impairment [10], both of which are independent predictors of falls [11, 12]. Although the available evidence is largely inconsistent, a few cross-sectional studies have also reported an association between CVD and falls [13-17], particularly self-reported falls. CVD is also related to several fall risk factors including cognitive [18] and neuromuscular impairments [19]. Atherosclerosis, the leading cause of CVD, is associated with increased transient events [20-22] (e.g., hypotension and syncope),

which are independently associated with increased falls risk [23, 24]. Cerebrovascular disease is also thought to impair cerebral perfusion leading to neuromuscular dysfunction and subsequently impairments in balance and gait, which can contribute towards increased risk of falls [25].

CVD can also impact an individual's ability to engage in regular exercise, which in turn may lead to a greater functional decline and poorer capacity to counteract falling [26]. Furthermore, markers of asymptomatic CVD such as abdominal aortic calcification (AAC) and biomarkers (such as high sensitivity cardiac troponin T and N-terminal pro B-type natriuretic peptide) are related to falls [27, 28], overall implying a possible link between CVD and falling. Despite such evidence supporting an association between CVD and falls, the majority of studies to date are cross-sectional and report inconsistent findings [24, 29]. To our knowledge, no study has investigated a relationship between clinical CVD (requiring one or more hospitalisations), long-term measures of muscle function (e.g. muscle weakness and mobility impairment) and falls. Therefore, we sought to investigate the relationship between clinical CVD, including its subtypes, with long-term measures of muscle function (muscle weakness and mobility impairment), self-reported and injurious falls requiring hospitalizations in a cohort of older women.

2. Materials and Methods

2.1. Study population

The study included ambulant community-dwelling older women aged 70 years and over who were recruited in 1998 to a 5-year (1998-2003) prospective, randomised controlled trial of oral calcium supplements to prevent osteoporotic fractures [Calcium Intake Fracture Outcome Study (CAIFOS)]. In brief, the participants were recruited by mail from the Western Australian general population of women, using the electoral roll as a requirement of citizenship. Over 99% of Australians of this age are on the electoral roll. Among the 5,586 women who responded to

an invitation to participate, 1,510 were willing and eligible, and 1,500 were recruited for the study. The study's participants had no medical conditions that would have an impact on their 5-year survival. They were ineligible if they were taking a bone-active agent, such as hormone replacement therapy. In terms of disease burden and medication use, the women included were comparable to whole populations their age, but they were more likely to be from higher socioeconomic groups [30]. Following the completion of CAIFOS, participants were enrolled in an additional 10 years (2003-2013) of observational follow-up; both of these studies, totalling over 14.5 years of follow-up, are known as the Perth Longitudinal Study of Ageing Women (PLSAW). 69 participants with missing fall risk factors were excluded, leaving 1431 for the final analysis of CVD and long-term falls (**Supplementary Figure 1**).

2.2. Ethics approval

Ethics approval was provided by the Human Research Ethics Committee of the University of Western Australia. PLSAW was retrospectively registered on the Australian New Zealand Clinical Trials Registry, with trial registration number #ACTRN12617000640303, and complied with the Declaration of Helsinki. Ethics approval for the use of linked data was granted by Ethics Committee of the Western Australian Department of Health (project number #2009/24). Written informed consent, including future access to the Western Australian Department of Health data, was obtained from all participants.

2.3. Baseline Characteristic Assessment

Body weight (kg) and height (cm), which were taken using digital scales and a wall-mounted stadiometer, respectively, were used to calculate body mass index (kg/m^2). Participants in the CAIFOS were randomly assigned to receive either a placebo or 1.2 g/day of calcium carbonate for the first five years (1998-2003). Insulin or the use of oral hypoglycemic medications were used to determine the prevalence of diabetes. When possible, participants' primary care physician verified their use of statins and antihypertensive medication. These data were coded

(T89001-T90009) using the International Classification of Primary Care-Plus (ICPC-Plus) method, which enables the grouping of various terms for comparable pathologic entities as defined by the ICD-10 coding system. When it came to smoking history, individuals were classified as never smoked, or previous/current smokers if they had ever smoked more than one cigarette per day for more than three months. Abdominal aortic calcification (AAC) was identified using digitally enhanced lateral single-energy images of the thoraco-lumbar spine using a Hologic 4500A bone densitometer (Hologic, Bedford, MA, USA) and scored out of 24 (AAC24) [27]. Plasma 25-hydroxyvitamin D concentration was measured using a validated LC–MS/MS (Liquid Chromatography Tandem Mass Spectrometry) method at the RDDT Laboratories (Bundoora, VIC, Australia) as previously described [31]. Previous falls and physical activity were assessed for the three months prior to participants baseline clinical visit in 1998 using questionnaires. Specifically, women were asked if they had experienced a fall in the last three months (yes/no). Falls were defined as "unintentionally coming to rest on the ground, floor, or other lower level" [32]. Physical activity level of each participant was assessed by being questioned about their involvement in sports, leisure, and/or regular physical activities. The level of activity was then computed in kcal/day considering body weight and energy costs of listed activities [30]. Fear of falling at baseline was assessed by asking participants to reply yes or no to the following questions: ''Are you afraid of falling?'', ''Do you limit any household activities because you are frightened you may fall?'' and ''Do you limit any outside activities because you are frightened you may fall?'' If they answered yes to any of the three questions, the participant was classified as having a fear of falling [33]. The study design according to the CONSORT guidelines is described in **Supplementary Figure 1.** All participant baseline characteristics, including the covariates included in the analyses, were collected in 1998 during the baseline clinical visit.

156 *2.4. Prevalent CVD*

157 Prevalent CVD (1980 to 1998) was defined as one or more hospitalizations with primary
158 discharge diagnosis codes from the International Classification of Diseases, Injuries and
159 Causes of Death Clinical Modification (ICD-9-CM)[34] and the International Statistical
160 Classification of Diseases and Related Health Problems, 10th Revision, Australian
161 Modification (ICD-10- AM) [35]. These codes included: disease of the circulatory system
162 (ICD-9-CM codes 390-459 and ICD-10-AM codes I00-I99) and specific CVD hospitalizations
163 such as cerebrovascular disease excluding hemorrhage (ICD-9-CM codes 433-438 and ICD-
164 10-AM codes I63-69, G45.9) and Ischaemic Heart Disease (ICD-9-CM codes 410-414 and
165 ICD-10-AM codes I20-I25). Hospitalization data were retrieved from the Western Australian
166 Data Linkage System for each of the study participants, which provides a complete validated
167 record of every participant's primary diagnosis at hospital discharge using coded data from all
168 hospitals in Western Australia.

169 *2.5. Measures of muscle function*

170 Hand grip strength (measured with a Jamar hand dynamometer─Lafayette Instrument
171 Company, USA) and TUG performance were used to assess muscle strength and mobility,
172 respectively, at the baseline clinical visit (1998) and after 5-years (2003). For TUG
173 performance, the participant is timed while rising from a chair, walking three meters, turning,
174 and returning to sit on the chair. Muscle weakness and mobility impairment were considered
175 when the participant recorded hand grip strength of <22 kg and TUG >10.2 sec at baseline or
176 in 2003 (5 years), respectively. Those cut-points were adopted from previous reports of the
177 same or different cohorts that have established a relationship with various clinical outcomes in
178 older adults [36-40]. Incident muscle weakness was used to represent a participant with a
179 normal baseline (1998) hand grip strength (n=457) who presented with a hand grip strength of
180 <22 kg (n=255) five years later. The same concept was applied to define incident mobility

impairment (n=319), in which women with normal TUG at baseline (n=766) that presented with TUG performance < 10.2 sec after five years were included (Supplementary **Figure 1)**.

2.6. Incident Falls

2.6.1. 5-years self-reported falls

Self-reported falls were collected via a written adverse event diary posted every four months and followed up by a telephone interview conducted by a team member. However, data was collected in person if the four-month follow-up coincided with a previously scheduled clinic visit as part of the 5-year RCT [41], thereby enabling calculation of time to event. Participants were advised to keep a daily record of any fall incidents in their diaries to minimize recall bias.

2.6.2. 14.5-years fall-related hospitalizations

Fall-related hospitalizations were captured through Western Australian Data Linkage System (Department of Health Western Australia, East Perth, Australia) and retrieved from the Western Australia Hospital Morbidity Data Collection. Falls from standing height or less, not resulting from external force were considered using the following ICD- 10 codes: W01-Fall on same level from slipping, tripping and stumbling; W05-Fall involving a non-moving wheelchair or scooter; W06-Fall from bed; W07-Fall from chair; W08-Fall from furniture, W10-fall from stairs and steps, W18-other fall on the same level, and W19-unspecified fall. Follow-up was available for each of the participants starting from their baseline visit in 1998 until the first fall, death, loss to follow-up or end of the study.

2.7. Statistical analysis

To obtain a summary of baseline characteristics of participants with and without CVD at baseline, independent t-tests, chi-square tests, and Mann-Whitney U non-parametric tests where appropriate were used. Using Cox proportional hazards regression, the association between CVD, including subtypes (cerebrovascular and ischaemic heart disease), and long-

term falls was examined using three models: i) unadjusted, ii) minimally-adjusted: age, BMI and treatment (calcium/placebo), and iii) multivariable-adjusted: minimally-adjusted plus smoked ever (yes/no), diabetes (yes/no), statin (yes/no), antihypertensive medication use (yes/no), physical activity (yes/no) and previous falls (yes/no). The aforementioned covariates were identified a priori, primary guided by their relationship with the exposure (CVD) or the outcome (long-term falls). Of note, we used similar covariates in previous reports to investigate the associations between measures of subclinical CVD and long-term falls from the same cohort and found reasonably precise effect estimates [27, 37]. The assumptions for Cox proportional hazards models were examined based on Schoenfeld residuals. The fact that all analyses, including the covariates, had p-values >0.05 indicates that the proportional hazards assumptions were not violated. In order to evaluate the univariate relationship between prevalent CVD and long-term falls, Kaplan-Meier survival analysis were used.

The cross-sectional and prospective relationships between prevalent CVD, muscle weakness and mobility impairment were examined using binary logistic regression model. Multivariable-adjusted model for this analysis included minimally-adjusted (Age, BMI, and treatment) plus prevalent diabetes mellitus (yes/no), smoking (yes/no), statin use (yes/no) and physical activity at baseline. Additionally, multinominal logistic regression was used to investigate the association between CVD and quartiles of TUG performance. Generalized linear model repeated measures analyses were used to determine whether estimated marginal mean of grip strength and TUG performance differed over 5-years and across prevalent CVD in the minimally-adjusted model. All analysis were undertaken using SPSS version 28.0 (IBM Corp., Armonk, NY).

2.8. Additional analyses

We acknowledge that the observed associations may be influenced by the fact that we have only considered the baseline values of the covariates not a time-varying covariates. To try and address this, we undertook additional analyses where we truncated the follow up period to 3 years for self-reported falls and 10 years for injurious fall-related hospitalization. Given the multifactorial nature of falls, we also conducted additional analyses to see if the association between prevalent CVD and falls persists after accounting for several additional falls risk factors. These analyses demonstrate the robustness of the observed association as well as the underlying mechanism (s) explaining the association between CVD and long-term falls. Specifically, AAC, an advanced marker of CVD, has been associated to loss of muscle strength [36] as well as injurious falls [27]. In order to determine whether the association between CVD and long-term falls still exists, we looked into it after including AAC-24 score into the multivariable-adjusted model. The relationships between CVD and long-term falls were also evaluated, after taking into account measures of muscle functions (baseline hand grip strength and TUG performance), which are independent predictors of falls risk [42]. As low vitamin D is associated with injurious falls [31], we conducted further analyses after adding total plasma 25-hydroxy vitamin D to the multivariable-adjusted model. We also investigated an association between CVD and fear of falling, which is directly related to the causal pathways of falls, using a binary logistic regression model. In our study, CVD was linked to poor TUG performance as well as to injurious falls risk. Thus, the proportion of the association between prevalent CVD and fall-related hospitalizations in the multivariable-adjusted model that was mediated by TUG performance at baseline was determined using mediation analysis with a Cox proportional hazards model in the Medflex package for R [43]. The point estimates and 95% CIs were determined by bootstrapping (1000 iterations).

3. Results

Clinical CVD was recorded in 342 (23.9%) women at baseline. Compared to women without CVD, women with CVD were older, more likely to fear falling, and take lipid and antihypertensive drugs (**Table 1**). These women also presented with slower TUG, but their grip strength, previous falls, and physical activity levels were comparable to women without CVD.

3.1.Muscle function

Older women with CVD had higher risks for mobility impairment cross-sectional (at baseline) (OR 1.32 95%CI, 1.01-1.70) and prospectively (5 years later) (OR 1.65 95%CI, 1.18-2.31) compared to those without CVD. Those with CVD had also greater risk of incident mobility impairment (OR 1.49 95%CI, 1.03-2.16) in a multivariable-adjusted model. Furthermore, women with CVD had greater odds of having TUG performance in quartile 3 (OR 2.13 95%CI, 1.36-3.33) and quartile 4 (OR 1.88 95%CI, 1.22-2.90), both of which indicate mobility impairment, than in quartile 1 (highest TUG performance) (**Supplementary Table 1**). However, no cross-sectional and prospective relationship was observed between CVD, and muscle weakness (**Table 2**). Over 5-years, there was a significant reduction in the estimated mean TUG performance (1.64 95%CI 1.46-1.81 sec) and grip strength (-3.25 95%CI, -3.49 to -3.02 kg). Of note, older women with CVD experienced a greater decline in estimated marginal mean of TUG performance (0.60 sec 95% CI, 0.22-0.99) compared to those without CVD. However, no change was observed between groups when considering grip strength (-0.07 kg 95% CI, -66 to 0.52).

3.2. Incident falls

3.2.1. Self-reported falls

Over the 5-years (6258 person-years) of follow-up (mean ± SD; 4.2 ± 1.4 years), 411/1431 (28.7%) women reported a fall. Women with CVD had increased risk for a self-reported fall

compared to those without CVD (**Figure 1 A**). In the multivariable-adjusted model, CVD was associated with a 32% greater relative hazard for self-reported fall (**Table 3**).Additionally, CVD was associated with a higher risk of self-reported falls (HR 1.47 95%CI, 1.12-1.94) when data was truncated to three years. Of the CVD subtypes considered, only cerebrovascular disease (HR 1.77 95%CI, 1.15-2.73) was associated with an increased relative hazard for self-reported falls. No such relationship was observed when considering ischaemic heart disease (HR 1.21 95%CI, 0.87-1.68) (**Table 3**).

3.2.2. Fall-related hospitalization

Over the 14.5-years (16,261 person years) of follow-up (mean ± SD; 10.8 ± 4.2 years), 567/1431 (39.6%) women were hospitalized due to an injurious fall. Women with CVD were more likely to be hospitalized due to falls compared to those without CVD (**Figure 1 B)**. Those with CVD had a 29% (HR 1.29 95%CI, 1.07-1.56) increased risk for a fall-related hospitalization in the multivariable-adjusted model (**Table 3**). CVD was also associated with increased risk when considering fall-related hospitalization over 10 years (HR 1.33 95%CI, 1.04-1.70). For CVD subtypes, only cerebrovascular disease was related to a higher risk of a fall-related hospitalization (HR 1.51 95%CI 1.00-2.27). No evidence for such a relationship was observed for ischaemic heart disease (HR 1.22 95%CI, 0.92-1.62).

3.3. Additional analysis

The associations between clinical CVD and long-term falls remained significant after adjustment for AAC-24 score, measures of baseline muscle function (e.g., grip strength and TUG performance) and 25-hydroxyvitamin D (**Table 4**). Clinical CVD was also associated with increased odds for presenting with a fear of falling in the minimally (OR 1.40 95%CI, 1.07-1.83) and multivariable-adjusted models (OR 1.41 95%CI, 1.07-1.86). Finally, baseline

TUG performance appeared to mediate 8.0% (95%CI, 0.02-44.2%) of the observed association between CVD and fall-related hospitalization.

4. Discussion

CVD is associated with a large healthcare burden in older people and may contribute towards a higher long-term falls risk [44]. Understanding its relationship with falls may serve to improve falls risk prediction and develop primary prevention interventions. This is important because it may prompt clinicians to recognise that patients with CVD may also have poor musculoskeletal health. We observed associations between CVD and greater relative hazards for long-term self-reported incident falls and fall-related hospitalization in older women. HRs for self-reported falls after 5 years were similar to HRs for fall-related hospitalizations, obtained from linked health records, after 14.5 years. A similar pattern was observed when falls outcomes were truncated (e.g., 3-years for self-reported and 10 years of injurious falls), indicating that our findings have good internal validity. According to our understanding for some of the main causes of falls (e.g., neuromuscular, cognitive impairment, gait and balance issues in this age group), the link between CVD and long-term falls appeared to be driven mostly by cerebrovascular disease [25]. Additionally, we also found an association between CVD, mobility impairment, and fear of falling. Collectively, this work provides evidence for the link between vascular disease and poor musculoskeletal health, implying that CVD should be considered when assessing falls risk.

To our knowledge, this is the first study to highlight the association between CVD and long-term falls. Interestingly, the associations were independent of measures of muscle function, and subclinical vascular disease, suggesting prognostic importance of CVD for falls. Previously, cross-sectional studies have reported a relationship between cardiovascular conditions and falls, although the findings are largely inconsistent [24, 45]. For example, in a

study of 2456 hospitalized patients with CVD (mean age~71 years, 45% female), 60% of the patients had moderate or high falls risk score [46]. Secondary analyses of cross-sectional studies have also shown an association between prevalent CVD and falls [14, 17]. On the contrary, other studies have reported no association between CVD and falls [47, 48]. Collectively, the present study along with the existing literature largely supports an association between CVD and falls. When considering subtypes of CVD, besides cerebrovascular disease, we found no relationship between ischaemic heart disease, self-reported falls and fall-related hospitalization, and inconsistent findings have been reported previously [24, 49]. As such, further well-powered studies are warranted. It is also important to note that there were significant differences in baseline characteristics between women with and without CVD, implying that the observed association could have been affected by confounding factors. To try and minimize the influence of such differences and other confounders, several CVD and musculoskeletal factors were accounted in our analyses.

There are several putative mechanisms that may explain why clinical CVD is related to falls. CVD is associated with transient events such as syncope, hypotension and bradyarrhythmia, which are established precipitants for falls and falls-related injuries [8]. CVD is also associated with frailty [50], which in turn is related to increased falls propensity [51]. Further, CVD is linked with decreased exercise tolerance [26], which may restrict involvement in physical activity, thus explaining why we found fear of falling to be more evident in people with CVD. A lack of physical activity is related to poor musculoskeletal health and increasing the risk of chronic diseases such as diabetes, sarcopenia and osteoporosis [52], which are all related to increased falls propensity [53]. In this study, it is noteworthy that that we found women with CVD had a higher risk of prevalent and incident mobility impairment as well as fear of falling, which are related to a lack of physical activity and increased falls risk [54, 55]. The observed relationship between CVD and injurious falls also appeared to be partially explained by

baseline TUG performance. Large longitudinal studies conducted in the past also found a link between poor TUG performance and incident CVDs [56, 57]. CVD, presumably by affecting cerebral blood flow, is associated with impairments of cognitive, neuromuscular, and sensory functions (e.g., executive function, mental processing speed, vision, balance, gait etc) [58] contributing towards increased falls risk. This relationship between CVD and slower TUG may be explained in part by such neuromuscular impairment [19]. Additionally, medications used to treat CVD, such as statins [59] and digitalis [60] may be associated with a higher risk of falling. This may be reflective of the multiple interrelated pathways leading to falls [60]. It important to note that relatively little research exists on the effects of CVD medications on musculoskeletal health and the risk of falling, particularly in the context of multimorbidity [61]. On the other hand, certain medications such statins have well-recognized albeit rare musculoskeletal side effects (e.g., myopathy) [62]. Clearly, the association between CVD medications and falls requires cautious investigation, as they could prevent or improving CVD-related complications.

The study has a number of strengths and limitations. Firstly, PLSAW is a prospective cohort with a long-term follow-up, 5-years for self-reported fall and 14.5-years for fall-related hospitalization. This is important as it allows exploration of long-term clinically important outcomes. Secondly, prevalent CVD (including specific events) and fall-related hospitalization were obtained from validated linked health records that would maximize the accuracy of the data. Alternatively, when considering self-reported incident falls, these were collected via a written adverse event diary posted every four months and followed up by a telephone interview [41], so the accuracy of the data pertaining to those falls may have been affected by the ability of the participants to report their falls experience accurately. Nonetheless, to minimize recall bias, participants were instructed to record a fall incident (s) (if any) on a daily basis

Thirdly, considerable falls/musculoskeletal (e.g., muscle function measures), and CVD (e.g., AAC) risk factors were considered while examining the relationship between CVD and falls, which minimizes the potential residual confounding. Nevertheless, due to the observational nature of this work, no causal inferences can be made, and the risk of bias due to unmeasured confounders cannot be excluded. Additionally, given the study's long-term follow-up and the fact that our covariates were only measured at baseline, not their changes over time, the impact of the included covariates on the observed association cannot be fully accounted. However, the Cox proportional hazards assumption was not violated for both the 5 years of self-reported and 14.5-years of injurious falls-related hospitalization analyses, implying that the relative hazards were similar, at least theoretically, throughout the follow-up period, regardless of any changes to covariates considered. Moreover, the study population were older women aged ≥70 years, so the findings of the present study may not be generalized to younger populations and older men. It is also important to acknowledge half of the study population was on calcium intervention during the first five years of the study despite it was accounted in the current analyses. Of note, calcium supplementation was not related to either 5-year self-reported (HR 1.07 95% CI,0.88-1.30 p=0.502) or injurious falls (HR 1.09 95% CI, 0.93-1.29, p=0.302) in our study. Finally, the statistical power for CVD subtypes may be insufficient, implying that the observed association between CVD types, particularly cerebrovascular disease, and long-term fall prognosis should be interpreted with caution, necessitating additional large epidemiological studies.

5. Conclusions

Clinical CVD, and in particular cerebrovascular disease, is related to long-term falls in community-dwelling older women independent of well-established falls risk factors. Such findings imply that falls screening in patients with CVD may be necessary given the significant burden of CVD and its related consequences. The inclusion of prevalent CVD as risk factor in

falls assessment tools may contribute towards improved detection of those at high risk of falls and targeting of prevention interventions.

Author contributions

AKG, MS, JRL and RLP contributed to study concept and design. AKG analysed the data. AKG, wrote the draft of the manuscript under the supervision of MS and JRL. All authors contributed to critical revision of the manuscript. All authors read and approved the final version of the manuscript. AKG, MS and JRL have the primary responsibility for the final content.

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Conflict of interest

None of authors have any conflicts of interest to disclose.

Data availability

The data that support the findings of this study are available upon reasonable request from the corresponding author.

Table 1: Baseline characteristics of the participants across clinical CVD

	All participants	**CVD**	
		Absent	**Present**
Number	1431	1089 (76.1)	342 (23.9)
Demographics			
Age, years	75.2 ± 2.7	**75.0 ± 2.7**	**75.5 ± 2.8**
Calcium treatment group, yes (%)	717 (50.1)	**565 (51.9)**	**152 (44.4)**
Body mass index (BMI), kg/m	27.2 ± 4.8	27.2 ± 4.7	27.3 ± 4.9
Smoked ever, yes (%)	529 (37.0)	405 (37.2)	124 (36.3)
Prevalent diabetes mellitus, yes (%)	94 (6.6)	64 (5.9)	30 (8.8)
Lipid lowering medications, yes (%)	274 (19.1)	**176 (16.2)**	**98 (28.7)**
Antihypertensive medications, yes (%)	623 (43.5)	**443 (40.7)**	**180 (52.6)**
Fear of falling[1], yes (%)	403 (28.3)	**288 (26.5)**	**115 (33.9)**
Physical function			
Physical activity, kcal/day	110 (26-203)	109 (0-202)	114 (39-204)
Grip strength[2], kg	20.5 ± 4.7	20.5 ± 4.7	20.3 ± 4.6
Timed-up-and-go[3], sec	10.0 ± 3.0	**9.9 ± 2.9**	**10.4 ± 3.4**
Previous falls, yes (%)	169 (11.8)	121 (11.1)	48 (14.0)

Data presented as mean ± SD, median (IQR) or number *n* (%). Bolded numbers indicate $p<0.05$ and are a comparison between the presence and absence of cardiovascular disease (CVD); [1](n=1087), [2](n=1423), [3](n=1428).

Table 2: The effect of CVD on muscle weakness (GS < 22 kg) and mobility impairment (TUG >10.2 s)[†]

Outcome measures	CVD (OR 95%CI)	
	Absent	**Present**
Cross-sectional (baseline in 1998)		
Muscle weakness[1] (n=872)	660 (60.9)	212 (62.4)
Minimally-adjusted	Referent	1.01 (0.78-1.30)
Multivariable-adjusted	Referent	0.98 (0.76-1.27)
Mobility impairment[2] (n=531)	**384 (35.5)**	**147 (43.1)**
Minimally-adjusted	Referent	**1.33 (1.03-1.72)**
Multivariable-adjusted	Referent	**1.32 (1.01-1.71)**
Prospective (5-year in 2003)		
Muscle weakness[3]***** (n=891)	686 (77.9)	205 (79.2)
Minimally-adjusted	Referent	1.02 (0.72-1.44)
Multivariable-adjusted	Referent	1.08 (0.70-1.64)
Mobility impairment[4#] (n=631)	461 (52.2)	170 (65.4)
Minimally-adjusted	Referent	**1.66 (1.23-2.24)**
Multivariable-adjusted	Referent	**1.65 (1.18-2.31)**
Prospective incident only (5-year in 2003)		
Muscle weakness[5] (n=255)	197 (55.6)	58 (56.3)
Minimally-adjusted	Referent	0.98 (0.63-1.55)
Multivariable-adjusted	Referent	0.96 (0.60-1.53)
Mobility impairment[6] (n=319)	243 (39.8)	76 (48.7)
Minimally-adjusted	Referent	1.42 (0.98-2.04)
Multivariable-adjusted	Referent	**1.49 (1.03-2.16)**

GS: Grip strength; TUG: Timed up go test: Minimally-adjusted: age, BMI and treatment (calcium/placebo); Multivariable-adjusted: minimally-adjusted plus prevalent diabetes mellitus, smoking, statin use and physical activity at baseline; [†]data was presented as n (%);*baseline (in 1998) grip strength (kg) was included in the multivariable adjusted model; [#]baseline (in 1998) timed-up-and-go (sec.) was included in the multivariable adjusted model; Muscle weakness and mobility impairment were defined as hand grip strength <22 kg and timed-up-and-go performance >10.2 seconds respectively. Bolded numbers indicate p <0.05. Assessment was undertaken in [1]N=1423; [2] N=1428; [3] N=1140; [4]N=1143; [5]N=457; and [6] N=766.

Table 3: Hazard ratios (HR) for the association between clinical CVD, specific CVD events and long-term falls

Outcomes	Prevalent conditions					
	CVD		Cerebrovascular disease (n=49)		Ischaemic heart disease (n=127)	
	Absent (n=1089)	Present (n=342)	Absent (n=1382)	Present (n=49)	Absent (n=1304)	Present (n=127)
Self-reported incident falls over 5 y						
Events, n (%)	293 (26.9)	118 (34.5)	388 (28.1)	23 (46.9)	368 (28.2)	43 (33.9)
Unadjusted	**Ref.**	**1.39 (1.12-1.67)**	**Ref.**	**2.04 (1.34-3.10)**	**Ref.**	1.29 (0.94-1.76)
Minimally-adjusted	**Ref.**	**1.37 (1.11-1.70)**	**Ref.**	**2.04 (1.34-3.11)**	**Ref.**	1.22 (0.89-1.68)
Multivariable-adjusted	**Ref.**	**1.32 (1.06-1.64)**	**Ref.**	**1.77 (1.15-2.72)**	**Ref.**	1.21 (0.87-1.67)
Fall-related hospitalization over 14.5 y						
Events, n (%)	411(37.7)	156 (45.6)	542 (39.2)	25 (51.0)	511 (39.2)	56 (44.1)
Unadjusted	**Ref.**	**1.40 (1.17-1.69)**	**Ref.**	**1.75 (1.17-2.61)**	**Ref.**	**1.36 (1.03-1.80)**
Minimally-adjusted	**Ref.**	**1.32 (1.09-1.60)**	**Ref.**	**1.60 (1.07-2.39)**	**Ref.**	1.25 (0.95-1.66)
Multivariable-adjusted	**Ref.**	**1.29 (1.07-1.56)**	**Ref.**	**1.51 (1.00-2.27)**	**Ref.**	1.22 (0.92-1.62)

Ref.; Referent: CVD: Cardiovascular disease; Hazard ratios (95% CI) analyzed using Cox-proportional hazard models; Models adopted: unadjusted; minimally-adjusted: age, BMI, and treatment code (calcium/placebo); Multivariable-adjusted: minimally-adjusted plus smoked ever (yes/no), prevalent diabetes (yes/no), statin use (yes/no), antihypertensive medication use (yes/no), physical activity (kcal/day) and previous falls (yes/no); Bolded numbers indicate $p < 0.05$.

Table 4: Multivariable-adjusted hazard ratios (HR) for long-term falls in individuals with clinical CVD after inclusion of falls risk factors

	HR 95%CI	
Covariates	**Self-reported falls over 5 y**	**Fall-related hospitalization over 14.5 y**
Multivariable-adjusted[1]	**1.32 (1.06-1.64)**	**1.29 (1.07-1.56)**
+AAC-24 score[2]	**1.29 (1.01-1.66)**	**1.25 (1.00-1.56)**
+Grip strength[3]	**1.32 (1.06-1.64)**	**1.29 (1.07-1.56)**
+ timed-up-and-go[4]	**1.32 (1.06-1.64)**	**1.27 (1.05-1.53**
+Grip strength and timed-up-and-go[5]	**1.31 (1.05-1.63)**	**1.26 (1.04-1.52)**
+25 hydroxyvitamin D at baseline[6]	**1.32 (1.05-1.66)**	**1.30 (1.07-1.58)**

Multivariable adjusted: minimally-adjusted plus smoked ever, prevalent diabetes, statin use, antihypertensive medication use, physical activity at baseline and previous falls; AAC-24 score: Abdominal aortic calcification-24 score; timed-up-and-go; [1](n=1424), [2](n=1031), [3](n=1412), [4](n=1421),[5](n=1411), and [6](n=1319); Bolded numbers indicate $p < 0.05$.

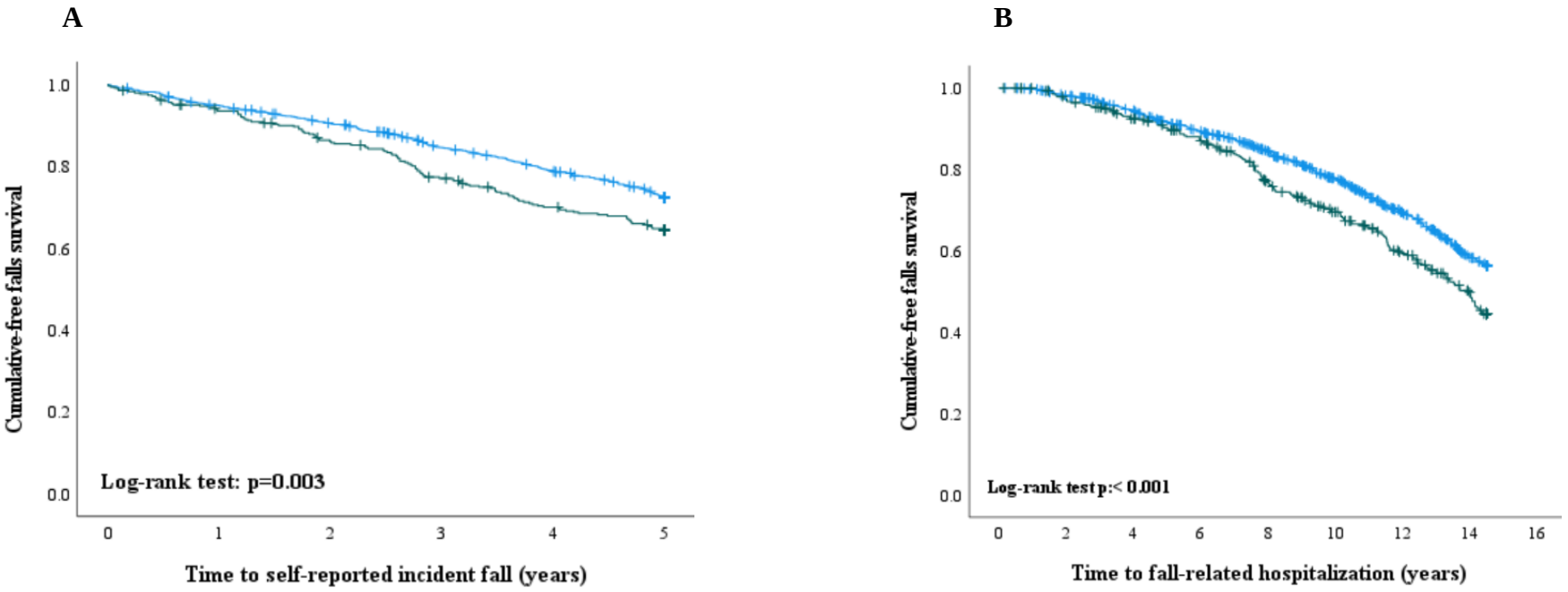

Figure 1: Kaplan-Meier survival curve for the association between prevalent CVD, **A)** self-reported incident fall for 5-years, **B)** fall-related hospitalization over 14.5 years. CVD present and absent are represented by green and blue lines respectively.

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