



Prospective associations of cardiovascular disease with physical performance and disability

A longitudinal cohort study in the Osteoarthritis Initiative

Nicola Veronese · Brendon Stubbs · Sarah E Jackson · Ai Koyanagi · Vania Noventa · Francesco Bolzetta · Alberto Cester · Pinar Soysal · Stefania Maggi · Guillermo F. López-Sánchez · Mike Loosemore · Jacopo Demurtas · Lee Smith

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Summary

Background Literature regarding cardiovascular disease (CVD) and incident physical performance limitations and disability in older people is equivocal.

Aims This study aimed to investigate whether CVD is longitudinally associated with incident physical performance limitations and disability in a large population-based sample.

Methods This was an 8-year prospective study using data collected as part of the Osteoarthritis Initiative. Participants were community-dwelling adults

with knee osteoarthritis or at high risk for this condition. Diagnosed CVD was self-reported. Physical performance was assessed with measures of chair stand time and gait speed, whereas disability was assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Longitudinal associations between CVD and changes in physical performance tests (chair stand time and gait speed) and

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N. Veronese · S. Maggi
 Aging Branch, Neuroscience Institute, National Research Council, Padova, Italy

Department of Geriatric Care, Orthogeriatrics and Rehabilitation, E. O. Galliera Hospital, National Relevance & High Specialization Hospital, Genoa, Italy

B. Stubbs
 Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London, SE5 8AF, UK

S. E. Jackson
 Department of Behavioural Science and Health, University College London, London, UK

A. Koyanagi
 Research and Development Unit, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Parc Sanitari Sant Joan de Déu, Carrer Del Dr. Antoni Pujadas 42, Barcelona, Spain

V. Noventa
 Primary Care Department, Azienda ULSS (Unità Locale Socio Sanitaria) 3 “Serenissima”, 30031 Dolo, Mirano District, Italy

F. Bolzetta · A. Cester
 Medical Department, Geriatric Unit, Azienda ULSS (Unità Locale Socio Sanitaria) 3 “Serenissima”, 30031 Dolo, Mirano District, Italy

P. Soysal
 Department of geriatric Medicine, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey

G. F. López-Sánchez
 Faculty of Sport Sciences, University of Murcia, Murcia, Spain

M. Loosemore
 Institute of Sport Exercise and Health Sciences, University College London Hospital, London, UK

J. Demurtas
 Primary Care Department, Azienda USL Toscana Sud Est, 58100 Grosseto, Italy

L. Smith (✉)
 The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK
lee.smith@anglia.ac.uk

disability score were analyzed using generalized linear models with repeated measurements.

Results The analyzed sample comprised 4796 adults (mean age 61.2 years, 58.5% female), of whom 313 people (6.5%) reported CVD at baseline. During 8 years of follow-up, after adjustment for 11 potential confounders measured at baseline, those with CVD experienced a worse profile in chair stand time over the 8-year follow-up period than those without CVD ($p=0.006$).

Conclusion In a cohort of middle-aged and older adults with knee osteoarthritis or at high risk for this condition those with CVD experienced a worse profile in chair stand time over the 8-year follow-up period than those without CVD; however, CVD was not significantly associated with an increased incidence of poor gait speed and disability over 8 years of follow-up. Importantly, no associations were observed when utilizing propensity score matching.

Keywords Cardiovascular disease · Chair stand time · Gait Speed · WOMAC · Osteoarthritis

Introduction

Global population ageing is a leading public health concern given the increased risk of chronic conditions associated with older age. Cardiovascular conditions are common and their consequences are of clinical importance [1]. Cardiovascular conditions are a major cause of sick leave, and diseases of the circulatory system are estimated to be the fourth most common basis for long-term disability insurance claims [2]. Cardiovascular disease (CVD) is also a leading cause of premature mortality, killing approximately 610,000 people in the USA each year (<https://www.cdc.gov/heartdisease/facts.htm>). The presence of CVD may confer additional risks for older people. Studies have suggested a potential association between CVD and incident frailty; a condition characterized by diminished resistance to stressful events [3]. In the Women's Health Initiative Observational Study, people with coronary artery disease (CAD) had an increased risk of frailty during 6 years of follow-up [4]. Important precursors of developing frailty are difficulties in completing objective physical performance tests (e.g. slowness of gait, difficulty rising from a chair) and disability [5, 6]. The evidence suggests that the presence of CVD could worsen physical performance in older people, leading to frailty [7]. A study of 786 women in the Women's Health and Aging Studies I and II found the risk of disability over a 3-year follow-up was 16 times higher in people with CVD than those without [8]. Another recent longitudinal study in 392 older participants indicated that CVD can lead to disability through different functional trajectories [9]. Taken together, these early findings suggest that older people with CVD may be at increased risk of (physical) frailty and potentially disability [10]; however,

the extant literature has some important limitations, in particular a lack of adjustment for important potential confounders (such as physical activity level, depression, number of medications), short follow-up periods, and relatively small samples. Thus, there is a need for further investigation addressing these limitations to provide a better understanding of the association between CVD and physical performance and risk of disability. For these reasons, this study aimed to investigate whether the presence of CVD can affect (i) physical performance tests (chair stand time and gait speed) that are predictive of mortality and other negative outcomes and (ii) disability in a large cohort of middle-aged and older people at increased risk or having knee osteoarthritis, with outcomes assessed over 8 years of follow-up.

Patients, material and methods

Data source and subjects

Data were obtained from the Osteoarthritis Initiative (OAI) database. Participants were recruited across four clinical sites in the USA (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH) between February 2004 and May 2006. Participants were included if they: (1) had knee osteoarthritis (OA) with knee pain for a 30-day period in the past 12 months or (2) were at high risk of developing knee OA, e.g. were overweight or obese with a body mass index (BMI) ≥ 25 kg/m² or had a family history of knee OA [11]. Data were collected at baseline and during subsequent evaluations at 1, 2, 3, 4, 6 and 8 years. All participants provided written informed consent. The OAI study was given full ethical approval by the institutional review board of the OAI Coordinating Center, at the University of California in San Francisco.

Exposure: cardiovascular disease (CVD)

The presence of CVD was determined based on self-reports of one or more of the following at baseline: heart attack, heart failure, operation to unclog or bypass arteries in legs, stroke, cerebrovascular accident, blood clot or bleeding in brain, or transient ischemic attack (TIA) [12].

Outcomes: physical performance tests and disability

Assessment of outcomes were made at baseline and during the V01 (12 months), V03 (24 months), V05 (36 months), V06 (48 months), V08 (72 months) and V10 (96 months) follow-up assessments. The following outcomes were considered:

- (i) Chair stand time: each participant was asked to complete five stands from a chair without using the assistance of their arms. A total of two attempts were made (separated by a break of 2 min) and the

best value between the two attempts was used for analyses.

- (ii) Gait speed: each participant was asked to walk for 20 m. The use of a cane was allowed and two attempts were made and the fastest time recorded was used for the analyses.
- (iii) Disability, assessed through the WOMAC index [13] disability subscale score, which includes 17 different activities of daily living (e.g. ability to walk down stairs, upstairs, and walking per se).

The range of possible scores on this scale is 0–68. Scores were calculated for the right and left knee separately and the highest (reflecting greater disability) was used for analyses.

Covariates

Several covariates at baseline (other than age and sex) were identified as potential confounding factors. These included: ethnicity (white vs. other), education (college or higher vs. other), BMI (as continuous), yearly income (< vs ≥ \$50,000), depressive symptoms assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) [14], smoking habits (never vs. current/former), physical activity evaluated using the total score for the Physical Activity Scale for the Elderly (PASE) [15], Charlson Comorbidity Index score [16], excluding the CVD of interest and the number of medications used and some medications of cardiovascular interest such as betablockers, ACE/ARB, diuretics, antiplatelet drugs and anticoagulants, re-

ported as descriptive information. Scores on the relevant outcome at baseline were also included as covariates.

Statistical analyses

Data on continuous variables were normally distributed according to the Kolmogorov-Smirnov test. Data were presented as means and standard deviation (SD) for quantitative measures, and percentages for all categorical variables. The *P*-values were calculated using independent t-tests for continuous variables and χ^2 -tests for categorical variables.

To assess the relationship between CVD at baseline and changes in physical performance tests (chair stand time and gait speed) and disability score over 8-year follow-up, generalized linear models (GLM) with repeated measurements were carried out. First, GLM with repeated measures were carried out, adjusting for factors that significantly differed between people with and without CVD at baseline ($p < 0.05$), forced in the model. Second, propensity scores [17] were used. This method better accounts for significant differences between two groups, including correspondent tests of interest at baseline significantly different between people vs. without CVD ($p < 0.05$) [17]. Propensity scores were then divided in quintiles and finally matched between the 313 people with CVD to 313 without CVD (controls) for each outcome of interest. Finally, outcomes of interest were the inability to execute chair stands or walking during follow-up. These last data were reported as odds ratio

Table 1 Descriptive findings of the participants by presence or not of cardiovascular disease

	CVD (<i>n</i> = 313)	No CVD (<i>n</i> = 4483)	<i>P</i> value
Age (years)	66.5 (8.8)	60.8 (9.1)	<0.0001
PASE (points)	139 (76)	162 (83)	<0.0001
CESD (points)	8.7 (8.8)	6.5 (6.8)	<0.0001
Females (<i>n</i> , %)	149 (47.6)	2655 (59.2)	<0.0001
White race (<i>n</i> , %)	233 (74.7)	3557 (79.4)	0.052
Smoking (previous/current)	170 (54.7)	2062 (46.6)	0.007
Graduate degree (<i>n</i> , %)	71 (22.7)	1365 (30.7)	0.003
Yearly income (<50,000 \$)	129 (43.9)	2666 (62.3)	<0.0001
BMI (kg/m ²)	29.6 (4.7)	28.6 (4.8)	<0.0001
Charlson comorbidity index (points)	1.8 (1.1)	0.3 (0.7)	<0.0001
Number of medications	4.96 (3.16)	2.80 (2.60)	<0.0001
Use of beta-blockers (<i>n</i> , %)	98 (33.0)	505 (14.1)	<0.0001
Use of ACE/ARB (<i>n</i> , %)	105 (35.4)	835 (23.4)	<0.0001
Use of diuretics (<i>n</i> , %)	19 (6.4)	39 (1.1)	<0.0001
Use of antiplatelet drugs (<i>n</i> , %)	16 (5.4)	15 (0.4)	<0.0001
Use of anticoagulants (<i>n</i> , %)	22 (7.4)	30 (0.8)	<0.0001
Chair stands time (seconds)	11.77 (4.22)	10.54 (3.55)	<0.0001
Walking time (seconds)	16.42 (3.58)	15.05 (2.83)	<0.0001
WOMAC disability score (points)	7.55 (11.97)	4.47 (8.12)	<0.0001

The data are presented as means (with standard deviations) for continuous variables and number (with percentage) PASE Physical Activity Scale for the Elderly, BMI body mass index, CESD Center for Epidemiological Studies Depression, WOMAC Western Ontario and McMaster Universities Osteoarthritis Index, ACE angiotensin converting enzyme inhibitors, ARB angiotensin-receptor blockers, CVD cardiovascular disease

(ORs) with 95% confidence intervals (CIs). A $p < 0.05$ was deemed statistically significant. Analyses were performed using STATA® software version 14.1 (Stata Corp LP, College station, TX, USA).

Results

Baseline characteristics

The cohort included 4796 participants, of whom 2804 (58.5%) were women. The mean age was 61.2 years (± 9.3 years; range: 45–79 years). The 313 people with CVD reported in 94 cases a heart attack, 98 heart failure, 46 operation to unclog or bypass arteries in legs and 139 a cerebrovascular event, with 64 participants reporting more than one CVD. Table 1 summarizes the baseline characteristics in relation to the presence of CVD at baseline. Participants with CVD at baseline ($n = 313$; prevalence = 6.5%) were significantly older, less physically active, more depressed and more likely to be male than those without CVD (controls; $n = 4483$) ($p < 0.0001$ for all comparisons). Moreover, people with CVD were more frequently smokers, less educated, had a lower yearly income and more likely to be obese than controls. People with CVD reported more comorbidities and used more medications than the control group and, as expected, they used medications of cardiovascular interest more frequently. Finally, people with CVD performed worse than controls at baseline regarding chair stand time and walking time and were more likely to be disabled, as investigated by the WOMAC disability score (Table 1).

CVD and physical performance/disability during follow-up

Several significant differences were observed between people with CVD (cases) and those without (controls). After adjusting for 11 potential baseline confounders, people with CVD experienced a significantly worse profile in chair stand time over the 8-year follow-up period (12.37 ± 4.00 vs. 10.31 ± 3.27 at the last follow-up; $p = 0.006$), but no significant differences were observed for gait speed ($p = 0.29$) or disability ($p = 0.81$). The weighting of covariates other than CVD presence and changes of the outcomes of interest over time, are reported in supplementary tables 1–3 (in the electronic supplementary material). A propensity score approach was applied in order to reduce the significant differences at baseline between the two groups. After matching the 313 people with CVD to a sample of 313 without CVD, but with similar baseline characteristics, no differences were observed between people with or without CVD during the 8 years of follow-up ($p = 0.51$) in chair stand time (Fig. 1a), gait speed ($p = 0.46$; Fig. 1b) or disability ($p = 0.28$; Fig. 1c).

Finally, the inability to execute chair stands or the walking task during follow-up were considered as outcomes. Again, people with CVD did not experience

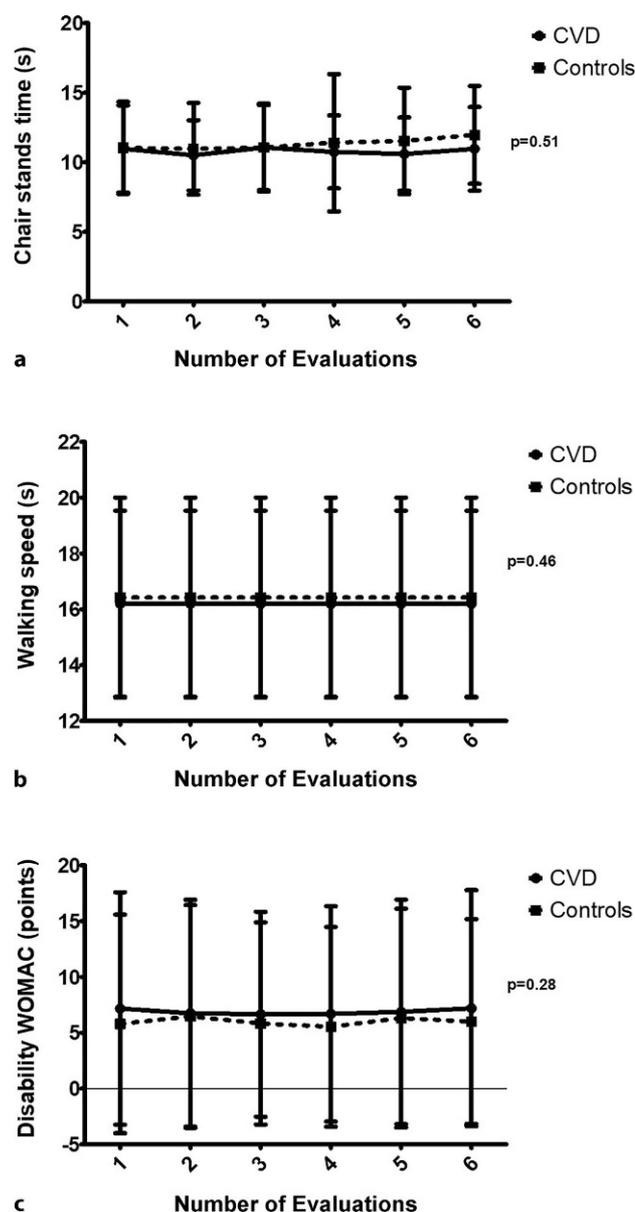


Fig. 1 a Differences between people with or without CVD during the 8 years of follow-up in chair stand time. b Differences between people with or without CVD during the 8 years of follow-up in gait speed. c Differences between people with or without CVD during the 8 years of follow-up in disability

any increased risk of being unable to complete chair stands (OR = 1.12; 95%CI: 0.81–1.55; $p = 0.51$) or walking (OR = 0.97; 95%CI: 0.62–1.53; $p = 0.91$). After removing people with CVD (stroke/transient ischemic attack, TIA), the results remain similar in adjusted analyses, using the propensity score matching or using inability to execute chair stands or the walking task as outcomes (other details can be requested upon request to the corresponding author).

Discussion

In this longitudinal study with an 8-year follow-up period, people with CVD at baseline reported more unfavorable outcomes in chair stand time, after adjusting for several potential confounders, whilst the association between the presence of CVD and walking speed was not significant. Using propensity score matching, CVD was not significantly associated with any significant worsening in physical performance and disability over 8 years of follow-up. Finally, CVD was not associated with any significant increased risk of inability to complete the chair stand or walking tests that can be considered as surrogates of disability.

Previous literature has suggested a potential bidirectional association between CVD and disability/poor physical performance; however, even though there is a large body of literature showing that poor physical performance [18] and frailty [19], can be associated with incident CVD, the reverse association has been less explored [7–9]. For example, in a middle-aged population (25–60 years) it was reported that coronary heart disease (CHD) was significantly associated with worse disability [20], suggesting that these conditions can greatly impact on disability; however, taken together, the present results are in contradiction to the majority of previous literature that has suggested that CVD plays an important role in the onset of poor physical performance and disability [7–9]. These findings can be justified through several explanations. First, adjustment was made for a wider range of covariates and used propensity score matching. It is possible that the presence of other conditions or characteristics, more than CVD per se, are responsible for developing disability and poor physical performance in people with CVD. In support of these findings, a recent study reported that having CVD at baseline was likely not related to higher risk of developing disability and poor physical performance. Moreover, the study found that people with CVD had different trajectories leading to disability, mainly depending on other potential confounders, such as age, sex, education and comorbidity [9]. Second, the OAI does not include people having symptomatic CVD (e.g. class III–IV New York Heart Association [NYHA] heart failure) or significant CVD (such as coronary artery disease, previous percutaneous intervention, arterial hypertension), therefore including only people having subclinical or stable CVD [21] that can affect physical performance less than symptomatic forms. Finally, it is likely that CVD causes disability immediately therefore the findings of the present study may also suggest that disability trajectories in older adults are the same between those with and without CVD over time.

These findings should be interpreted in light of the study's limitations. First, the sample population was restricted to individuals who already had or were at high risk of knee OA. Thus, the results might not

be representative of the general population. Second, the OAI does not include people having symptomatic CVD (e.g. class III–IV NYHA heart failure) or significant CVD (such as coronary artery disease, previous percutaneous intervention, arterial hypertension). This study relied on self-reported measures of CVD, although some validation studies have shown good agreement between self-reports and medical records with ischemic heart disease [22] more recent data on stroke has not [23]. Indeed, a recent systematic review concluded that self-report stroke is unlikely to be helpful for identifying cases without subsequent confirmation but may be useful for case ascertainment in combination with other data sources [23]. Moreover, no information regarding severity of CVD was recorded, but severity of CVD could have affected baseline functional status. The data used in this study are 5-years old and may not reflect present reality. Future studies are now required with more recent data. Finally, we were not able to explore the effect of singular CVD events on the outcomes of our interest (e.g. stroke), but larger populations should identify the effect of singular cardiovascular events on disability and poor physical performance.

In conclusion, in this cohort of people with knee osteoarthritis or at high risk for this condition, the presence of CVD was not significantly associated with the incidence of poor physical performance or disability over 8 years of follow-up. Since CVD is continuously increasing in prevalence in older people, future studies are needed to better understand the role of CVD in determining frailty and disability.

Compliance with ethical guidelines

Conflict of interest N. Veronese, B. Stubbs, S.E. Jackson, A. Koyanagi, V. Noventa, F. Bolzetta, A. Cester, P. Soysal, S. Maggi, G.F. López-Sánchez, M. Loosemore, J. Demurtas, and L. Smith declare that they have no competing interests.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all individual participants included in the study.

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