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Impact of lifestyle factors on fracture risk in older patients with cardiovascular disease: a prospective cohort study of 26,335 individuals from 40 countries

RASHA KHATIB1,2, SALIM YUSUF1,3, JOSHUA I. BAZILAY4, ALEXANDRA PAPAIOANNOU3, LEHANA THABANE1,2, PEGGY GAO1, PHILIP G. JOSEPH1,3, KOON TEO1,3, ANDREW MENTE1,2

1Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada
2Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada
3Department of Medicine, McMaster University, Hamilton, Ontario, Canada
4Endocrinology, Kaiser Permanente of Georgia and Emory University School of Medicine, Atlanta, Georgia, USA

Address correspondence to: R. Khatib. Tel. 905-527-432 ext. 40683; Fax: 905-297-3781. Email: rasha.khatib@phri.ca

Abstract

Background: fractures are a major health concern among the elderly. People at risk for cardiovascular disease (CVD) are at an increased risk for fractures. The aim of this study was to assess the individual and combined effect of the CVD risk factors of smoking, alcohol consumption and physical activity on fracture risk in a large sample of older individuals with CVD or diabetes with end-organ damage.

Methods: we analysed data for 26,335 adults, aged 55 years or older, who participated in two large antihypertensive drug treatment trials and who had no previous fracture at baseline. Lifestyle factors were assessed by the standardised questionnaire and their individual and combined effects on incident fracture risk were modelled using Cox proportional hazard regression.

Results: during the 56-month follow-up, 1,079 incident fractures occurred; 508 (6.51%) among women and 571 (3.08%) among men. Smoking [hazard ratio (HR) 1.52, 95% confidence interval (CI) 1.27–1.82] and low physical activity (HR: 1.19, 95% CI: 1.05–1.36) were associated with an increased risk of any fracture, while high alcohol intake showed a directional, but non-significant, relationship with fracture risk (HR: 1.09, 95% CI: 0.64–1.84). Compared with participants with no lifestyle risk factors, those having one, two, or three risk factors had an increased risk of a future fracture (HR: 1.17, 95% CI: 1.03–1.34 for one risk factor; HR: 1.73, 95% CI: 1.38–2.16 for two risk factors; and HR: 2.37, 95% CI: 0.88–6.36 for three risk factors; P for trend <0.001).

Conclusions: a healthier lifestyle advocated to reduce the risk of CVD is associated with a significant and graded reduction in fracture risk.

Keywords: lifestyle, risk factors, modifiable, fracture risk, cardiovascular disease, prospective, cohort, international
Introduction

Lifestyle modification is the cornerstone of preventive management for people with cardiovascular disease (CVD), or at high risk for CVD. In the past decade, it has become increasingly clear that people with CVD have an increased risk for osteoporosis and for fractures [1, 2]. The mechanisms underlying this association are multi-factorial, including factors common to both conditions. Both conditions increase with age, and share common pathophysiological abnormalities including increased inflammation [3] and metabolic disorders [1], such as diabetes mellitus [4]. Fractures and osteoporosis risk are also associated through common lifestyle factors such as smoking, low physical activity and high alcohol consumption [5–7].

Previous observational studies of modifiable lifestyle factors and fractures were conducted in single geographic regions, on participants with relatively homogenous lifestyles, focused predominantly on women, considered lifestyle factors singly rather than in combination, or accrued a limited number of fracture events. The effect of lifestyle factors on fracture risk in CVD patients has not yet been explored. Given the large number of people with CVD in the population, it would be of interest to examine what impact, if any, lifestyle interventions could have on fracture risk in people with CVD. Such information could not only serve to inform medical care but also broaden the indications for lifestyle changes.

In the current study, we determined the impact of common modifiable risk factors on total fracture risk in a cohort of 26,335 individuals with pre-existing CVD or diabetes who were followed prospectively in the Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEDE) trials [8].

Methods

Cohort

Participants in ONTARGET and TRANSCEDE trials were included in this analysis [8]. ONTARGET was a randomised controlled, double-blind trial comparing the effects of the combination of telmisartan plus ramipril with telmisartan or ramipril daily alone in 25,620 patients. TRANSCEDE similarly enrolled 5,926 participants who were intolerant to ACE inhibitors comparing telmisartan with placebo. In both trials, patients aged ≥55 years with a history of either CV disease such as coronary artery disease, peripheral artery disease, cerebrovascular disease, or diabetes mellitus with end-organ damage but free of heart failure were included. Trial exclusion criteria was limited to inability to discontinue ACE inhibitors and ARB, intolerance to ACE inhibitors or ARB, or significant CVD or other chronic disease, and inability or unwillingness to provide written informed consent. Participants were recruited from 733 collaborating centres in 40 countries between November 2001 and May 2004, assessed for weight and height in the clinic, and were followed at 6 month intervals for a median of 56 months. Approval was obtained from the Institutional Ethics Committee of each centre and all participants provided written informed consent [8].

Assessment of modifiable risk factors

We identified smoking, alcohol consumption and physical inactivity as potential predictors of future fracture risk [5–7]. These risk factors are targeted by healthcare providers in strategies to reduce CVD events. We considered dietary factors in secondary analyses only, due to weak evidence relating diet to fracture risk [9]. The risk factors were assessed by questionnaire during a baseline clinic visit.

Participants were asked whether they regularly consumed alcohol and the frequency of consumption. Regular alcohol consumption was defined as at least one drink per week of one standard glass of beer (355 mL), wine (150 mL), or shot of hard liquor (45 mL). High alcohol consumption was defined as >2 drinks per day for women and >3 drinks per day for men [10]. Participants were also asked if they ever, formerly, or currently used any tobacco products including cigarettes, beedies, pipes/cigars and sheesa (water pipe). To assess the combined effect of lifestyle factors, smoking was defined as current smokers. Participants were asked about how often they engaged in any physical activity. Response options included ‘mainly sedentary’, ‘once per week’, ‘2–4 times per week’, ‘5–6 times per week’ and ‘every day of the week’. For the combined effects of lifestyle factors, low physical activity was defined as engaging in any activity for >5 days per week [11]. Usual food intake in the past year was recorded using a validated qualitative food frequency questionnaire that contained 20 food items, originally used in the INTERHEART study [12]. We considered intake of dairy products (>1 time daily), fruit and vegetables (>3 times daily) in assessing effects on fracture risk.

Outcome measures

The primary outcome of the study was any incident fracture. The secondary outcome was any incident osteoporotic fracture. Participants were asked at baseline, 2 years and the penultimate visit (year 4.6 of follow-up) whether they had sustained a fracture in the preceding 2 years (vertebral, hip, or ‘other’). If ‘other’, they were asked the fracture location. Osteoporotic fractures were defined as sites that are age dependent and show a graded relationship with bone density (vertebral, rib, pelvic, humeral, forearm, hip, femoral, clavicle, scapula and sternum) [13]. Tibia and fibula fractures were considered osteoporotic if they occurred in women [13]. Fractures of the skull, face, hands, fingers, feet, toes, ankle, patella and in men, tibia and fibula were not considered osteoporotic fractures [13].

For these analyses, we excluded 5,008 individuals with any previous fracture prior to enrolment. This was done to examine the impact of lifestyle on fracture risk in de novo
cases, as the focus of the study was on primary prevention by improving modifiable risk factors. An additional 203 individuals were excluded who did not have baseline information on lifestyle. These exclusions left 26,335 participants for analysis (Figure 1).

**Statistical analysis**

The baseline characteristics of the participants are reported as mean [standard deviation (SD)] for continuous variables, and count (%) for categorical variables. Each of the three lifestyle factors was coded as 0 (beneficial response) or 1 (harmful response). The combined effect was calculated as the unweighted sum of each of the three factors with an overall scores range from 0 to 3 (with 3 being the most harmful). Multivariable Cox regression models were used to estimate the single and combined effects of the lifestyle variables on the risk of any fracture (all sites included) and osteoporotic fractures. The results are reported as hazard ratios (HR), corresponding 95% confidence intervals (CI) and associated P-values. All models were adjusted for age, sex, region, BMI diet quality [using the alternative Healthy Eating Index (aHEI) but excluding alcohol] and the use of hormone replacement therapy in women. Given the high-risk study population, we also adjusted for a history of diabetes, stroke, coronary artery disease, hypertension and hypertension medications. In secondary analyses of CV events, we modelled the effects of lifestyle factors on the composite outcome of CV death, myocardial infarction, stroke, or hospitalisation for heart failure, adjusting for potential confounders. The population attributable risk (PAR) of any fractures and 95% CI was calculated for the lifestyle factors considered in combination from full-adjusted multivariable models using Levin’s formula [14].

The criterion for statistical significance was set at alpha = 0.05 (two-sided). Analyses were done using STATA statistical package version 10.0.

![Figure 1](image-url). Flow diagram for participants included in the current analysis.

**Results**

**Study sample**

During a median of 5.6 years of follow-up, 1,079 participants experienced at least one fracture. The mean age of the study population was 66.5 (SD 7.2) years and was similar for men and women. The mean baseline body mass index for women was 28.6 kg/m$^2$ and for men it was 27.7 kg/m$^2$. A total of 37% of participants reported having diabetes, with a higher proportion among women. Seventy-four per cent of the population had a history of coronary heart disease, 21% reported a previous stroke and 5.4% reported having had cancer (Table 1).

The distribution of baseline characteristics of lifestyle factors is presented in Table 1. Twelve per cent of the population reported being current smokers, and 1.5% were heavy alcohol consumers. More than half of the population (58%) was physically inactive (i.e. being physically active for >2–4 days a week). When compared with men, women smoked less often and consumed less alcohol, but were less physically active (Table 1).

**Individual effects of lifestyle risk factors**

Table 2 presents the 5-year risk of fracture based on lifestyle factors. After adjustment for age, sex, body mass index and region, current smoking (HR: 1.51, 95% CI: 1.26–1.81) and low physical activity (HR: 1.20, 95% CI: 1.06–1.36) were each associated with an increased risk of fracture. The results were similar after further adjustment for diet quality using the aHEI index, medical history of coronary artery disease, stroke or transient ischaemic attack, hypertension, diabetes, use of statin and treatment allocation in the trials (current smoking: HR: 1.52, 95% CI: 1.27–1.82; and low physical activity: HR: 1.19, 95% CI: 1.05–1.36). A test for linear trend showed a significant positive and graded association between smoking and any fracture (for current smokers, HR: 1.68, 95% CI: 1.38–2.04; for former smokers, HR: 1.21, 95% CI: 1.05–1.39; P-trend ≤ 0.001). Alcohol consumption showed a directional but non-significant-graded relationship with fractures (P-trend = 0.595).

For osteoporotic fractures, smoking was significantly associated with fracture risk following minimal adjustment (HR: 1.56, 95% CI: 1.26–1.94) and in the fully adjusted model (HR: 1.58, 95% CI: 1.27–1.97). Low physical activity was also significantly associated with osteoporotic fractures with minimal adjustment (HR: 1.18, 95% CI: 1.01–1.37) but showed a non-significant trend in the adjusted model (HR: 1.17, 95% CI: 1.00–1.36). High alcohol intake was directionally but not significantly associated with osteoporotic fractures (HR: 1.24, 95% CI: 0.65–2.34) in the full-multivariable model.

In secondary analyses exploring the influence of diet, in full-multivariable models we found no significant association between increased dairy product (greater than one time daily) or fruit and vegetable (greater than three times daily) intake and risk of any fracture (dairy products: HR: 1.09, 95% CI: 0.93–1.27; fruit and vegetables: HR: 1.02, 95% CI: 0.91–1.16) or osteoporotic fracture (dairy products: HR: 1.01, 95% CI: 0.83–1.22; fruit and vegetables: HR: 1.02, 95% CI: 0.88–1.18).
Combined effects of modifiable risk factors

Table 3 shows the adjusted combined estimates of fracture risk. Compared with participants with no lifestyle risk factors, those having one (HR: 1.17, 95% CI: 1.03–1.34) two (HR: 1.73, 95% CI: 1.38–2.16), or three (HR: 2.37, 95% CI: 0.88–6.36) risk factors had an increased risk ($P$ for trend <0.001), after full adjustment. In the analysis of number of risk factors as a quantitative variable, each one-point increase was associated with a 23% increase in fracture risk (HR: 1.27, 95% CI: 1.14–1.40). For osteoporotic fractures, compared with individuals with no previous fracture...
lifestyle risk factors, those having two (HR: 1.79, 95% CI: 1.36–2.35) or three (HR: 2.75, 95% CI: 0.85–8.92) risk factors had an increased risk of future fracture (P for trend <0.001), after full adjustment. As a quantitative predictor, each one-point increase was associated with a 26% increase in osteoporotic fracture risk (HR: 1.27, 95% CI: 1.12–1.44).

The estimated PAR indicated that 100 fracture events occurring in the population, an estimated 11.30% (95% CI: 3.51–18.73) could be prevented if every person had no lifestyle risk factors. Three-hundred and forty-five participants without any of the three lifestyle risk factors experienced a fracture—3.58% of the total population and 32% of those who experienced a fracture.

**Subgroup analyses**

In subgroup analyses, the combined effect of lifestyle factors showed similar associations with risk of incident fracture by age, sex, obesity, diabetes and coronary artery disease status. No significant effect modification by baseline factors was found.

**Effect of lifestyle risk factors on cardiovascular events**

The composite outcome of cardiovascular death, myocardial infarction, stroke, or hospitalisation for heart failure occurred in 4286 (16.3%) participants. In the full-multivariable model, the presence of one additional lifestyle risk factor was associated with a 26% (HR: 1.26, 95% CI: 1.20–1.32; P-trend <0.001) increase in composite outcome events.

**Discussion**

In this large international cohort study of older patients with CVD or diabetes, individuals with two lifestyle risk factors were 76% more likely to have an incident fracture compared individuals leading a healthy lifestyle with no risk factors. The greater the number of lifestyle risk factors present, the higher was the risk of any form of fracture. Further, these effects on fracture risk were consistent with the effects on the CVD composite outcome. Taken together, our findings indicate that lifestyle changes in CVD patients have benefits extending to other common conditions including fractures.

The robust association of smoking with future fractures and osteoporotic fractures is consistent with the findings of a previous international cohort of individuals without CVD [15]. There is evidence that physical activity may reduce bone loss in postmenopausal women [16], though the association among men is shown to be weaker [17]. We found a weak non-significant relationship between heavy drinking and fractures. Previous studies showed a significant increased fracture risk with heavy alcohol intake [18], while a few studies have suggested a more complex J-shaped relationship, with moderate intake being protective against fractures [6, 19], which we did not find. Alcohol intake in older individuals has been linked to falls and injury [20], which further supports a more complex relationship between alcohol and fracture risk across populations.

Fracture risk scores are currently being used to predict fracture incidence [21]. These scores use clinical (history of fractures, glucocorticoid use and rheumatoid arthritis) and lifestyle (smoking, alcohol) risk factors combined into one score. In our study, we focused on lifestyle risk factors to quantify the magnitude of risk reduction attributable to modifiable factors and consequently the potential for disease prevention. We estimated that, for every 100 events of incident fracture occurring in the population with multiple risk factors, 11.3 fractures (95% CI: 3.5–18.7) could be prevented if every person followed a healthy lifestyle. Thus investigation of other modifiable risk factors and approaches to prevention (e.g., drug therapy) may be warranted.
Recent prospective data have shown that people with CVD have an increased risk for osteoporosis and fractures [1, 22]. Coronary angiographic studies have shown that there is an association between low bone mineral density and atherosclerotic vascular disease [23, 24]. Both conditions share common abnormalities including increased inflammation [3] and metabolic disorders [1], such as diabetes mellitus [4], hypertension, dyslipidaemia and homocysteinaemia [25]. It has been suggested that common molecular, cellular and biochemical processes are implicated in their pathogenesis, but further work is needed to understand the precise physiological derangements linking these conditions, beyond shared lifestyle risk factors [26].

The observed similar trend between any fracture and osteoporotic fractures indicates validity for this analysis. Other advantages of this study include its prospective design, the large sample size, the large number of events, worldwide participants with diversity in lifestyles, the availability of detailed covariates that could be used to adjust for a broad range of potential confounders and high completeness of systematically collected data.

Limitations of this study should be noted. Fractures were self-reported and not adjudicated during the follow-up. Previous work has shown, however, that self-reported fractures are accurate but vary by the site of fracture [27]. Measurement error in fracture assessment was likely random and would dilute associations towards the null. Vertebral fractures rarely present to healthcare and may thus be underreported. Lifestyle factors were self-reported at baseline but were not assessed during the follow-up. Any lifestyle changes over time would not have been captured. Although the overall sample size for this study was large, there were not enough participants to conduct the analysis by different sites of fractures. Also, since the primary focus of the original study was CVD, it includes more men compared with women and the number of women with some of the risk factors (e.g. smoking and high alcohol intake) was small. Data on glucocorticoid use and other drugs related to osteoporosis were not collected and therefore could not be adjusted for. All of the participants were taking an ACE inhibitor or Angiotensin II receptor blockers, which may limit the generalisability of the findings to patients who are prescribed other medications.

In conclusion, common modifiable risk factors are associated with a significant-graded increased incidence of fractures in a large international sample of patients with CVD. Modifying lifestyle in patients with CVD would have benefits that extend to fracture risk reduction.

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**Conflicts of interest**

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