**Calcium and vitamin D supplementation are not associated with risk of incident ischaemic cardiac events or death: findings from the UK Biobank cohort**

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**Abstract**

We investigated associations between calcium/vitamin D supplementation and incident cardiovascular events/deaths in a UK population-based cohort. UK Biobank is a large prospective cohort comprising 502,637 men and women aged 40-69 years at recruitment. Supplementation with calcium/vitamin D was self-reported, and information on incident hospital admission (ICD-10) for ischaemic heart disease (IHD), myocardial infarction (MI) any cardiovascular event, and subsequent death, was obtained from linkage to national registers. Cox Proportional Hazards models were used to investigate longitudinal relationships between calcium/vitamin D supplementation and hospital admission for men/women, controlling for covariates. 475,255 participants (median age 58years, 55.8% women) had complete data on calcium/vitamin D supplementation. 33,437 participants reported taking calcium supplements; 19,089 vitamin D; 10,007 both. In crude and adjusted analyses, there were no associations between use of calcium supplements and risk of incident hospital admission with either IHD, MI or any cardiovascular event, or subsequent death. Thus, for example, in unadjusted models, the hazard ratio (HR) for admission with myocardial infarction was 0.97 (95%CI:0.79,1.20; p=0.79) amongst women taking calcium supplementation. Corresponding HR for men: 1.16 (95%CI:0.92,1.46;p=0.22). After full adjustment, HR(95%CI) were 0.82 (0.62,1.07), p=0.14 amongst women and 1.12 (0.85,1.48), p=0.41 amongst men. Adjusted HR(95%CI) for admission with IHD were 1.05 (0.92,1.19), p=0.50 amongst women and 0.97 (0.82,1.15), p=0.77 amongst men. Results were similar for any cardiovascular admission and for vitamin D and combination supplementation. There were no associations with death, and in women, further adjustment for HRT use did not alter the associations. In this very large prospective cohort, there was no evidence that use of calcium/vitamin D supplementation was associated with increased risk of hospital admission or death following ischaemic or non-ischaemic cardiovascular events.

**Keywords:** Epidemiology; ischaemic heart disease; cardiovascular; calcium; vitamin D; osteoporosis

**Introduction**

Calcium supplementation given with or without vitamin D supplementation is widely used, particularly in the elderly, and has been shown to modestly reduce the risk of new fragility fracture,([1](#_ENREF_1)) particularly in those older individuals in residential care.([2](#_ENREF_2)) Calcium and vitamin D supplementation is given routinely as adjunctive therapy with anti-osteoporosis medications, all of which are licenced to be taken in the context of calcium and vitamin D repletion.([3](#_ENREF_3)) Calcium supplementation either alone or in combination with vitamin D was viewed as extremely safe, other than gastrointestinal side effects and a slightly increasing risk of renal stones,([4](#_ENREF_4)) until a publication in the BMJ by Bolland et al. in 2008. In this New Zealand based trial of calcium supplementation in older women, increased risk of myocardial infarction with calcium supplementation was demonstrated.([5](#_ENREF_5)) Subsequent meta-analyses and a re-analysis of the Women’s Health Initiative trial by the same group again demonstrated modest associations between calcium, or calcium and vitamin D, supplementation and increased risk of myocardial infarction but not cardiovascular death.([6](#_ENREF_6),[7](#_ENREF_7)) In contrast, no statistically significant associations between calcium and vitamin D supplementation and cardiac outcomes were found in a similar meta-analysis by Lewis et al.([8](#_ENREF_8)) or by investigators studying the Women’s Health Initiative.([9-11](#_ENREF_9)) However, in the Lewis paper, a sub-analysis amongst the much smaller number of individuals randomised to calcium alone did suggest an increased risk of myocardial infarction with use of calcium supplements alone vs placebo. Observational cohort data have led to similarly conflicting findings([12-18](#_ENREF_12)), particularly with regard to dietary calcium intake compared with supplement use. More recently work has documented differences in the endothelial response to prevailing calcium concentration between healthy and uraemic patients,([19-21](#_ENREF_19)) and novel Mendelian randomisation approaches have indicated an association between lifelong genetically determined calcium concentrations and ischaemic heart disease.([22](#_ENREF_22),[23](#_ENREF_23)) Given the high incidence of osteoporotic fracture,([24](#_ENREF_24)) cardiovascular side-effects of treatments used to improve bone health, such as calcium/vitamin D supplementation, could potentially have major implications for public health.([25](#_ENREF_25)) Across the intervention and observational data there is substantial heterogeneity amongst both exposure and outcome definitions, and there is a marked dearth of evidence pertaining to men. We therefore undertook a study of sex-specific associations between calcium and/or vitamin D supplementation and risk of hospitalisation for ischaemic heart disease, or subsequent mortality in a very large, population-based cohort of men and women with uniform ascertainment of both exposure and outcomes: the UK Biobank. The large study population also permitted investigation of whether associations might vary according to baseline cardiovascular risk factors.

**Methods**

*Study subjects*

We conducted a prospective analysis using data collected in the UK Biobank study, linked to outcome data derived from National Health Service records. Details of the UK Biobank methodology have been published previously.([26](#_ENREF_26)) UK National Health Service (NHS) registers maintain records of almost everybody in the general population (excluding the small number of individuals not legally registered as resident). The protocol is available publicly (<http://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf?phpMyAdmin=trmKQlYdjjnQIgJ%2CfAzikMhEnx6>). Using these records, around 9.2 million primary invitations were sent to individuals aged 40­ to 69 years living within a reasonable travelling distance of a total of 22 assessment centres across Great Britain 2007­10.([27](#_ENREF_27),[28](#_ENREF_28)) This age range was chosen to allow time for a wide range of incident disease events to accrue, permitting case-control studies to be undertaken with the aim of investigating the determinants of chronic non-communicable diseases of middle and later life.

*Data collection*

Participants completed a series of touch-screen computer-based questionnaires followed by a face to face interview with trained research staff. Details of the assessments and variables are publicly available (<http://biobank.ctsu.ox.ac.uk/crystal/>), and a transcript of the touchscreen questionnaire may be downloaded (<http://www.ukbiobank.ac.uk/wp-content/uploads/2011/06/Touch_screen_questionnaire.pdf?phpMyAdmin=trmKQlYdjjnQIgJ%2CfAzikMhEnx6>). The information collected included: socio-demographics (age, gender, ethnicity, educational attainment), and lifestyle factors (including cigarette smoking, diet, physical activity and alcohol use), medication and supplement use. Physical activity was documented through the question: “In a typical WEEK, how many days did you do 10 minutes or more of vigorous physical activity? (these are activities that make you sweat or breathe hard such as fast cycling, aerobics, heavy lifting).” Height and weight were measured in all participants by trained data collectors during the clinic attendance using standard operating procedures, and body mass index (BMI) subsequently calculated (kg/m2). We obtained information on incident hospital admission coded using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) for ischaemic heart disease (IHD: I20-­I25), myocardial infarction (MI: I21), any cardiovascular event (I63/I64 or I20-­I25) and death following these events, through linkage to Hospital Episode Statistics and death registry data (Office for National Statistics) with data included up to 10 years after baseline assessment.

This study was conducted under generic approval from the NHS National Research Ethics Service (17th June 2011, Ref 11/NW/0382). Participants provided electronic consent for the baseline assessments.

*Statistical analysis*

We performed all analyses in men and women separately. We documented baseline characteristics with the mean (standard deviation) or median (interquartile range) for continuous variables and number (percent) for categorical variables, and testing for differences between those using and not using calcium supplements. We explored associations between calcium and/or vitamin D supplementation and incident hospital admission with ischaemic heart disease/ myocardial infarction/ any cardiovascular event using Cox proportional hazard models, with results expressed as Hazard Ratios (HRs) and 95% Confidence Interval (95%CI). The small proportion of individuals who had reported prior cardiovascular events at baseline, or had linked information on such events prior to baseline, were excluded, as there were insufficient numbers to permit meaningful sub-analyses. Results are reported firstly unadjusted and then adjusted for age, BMI, family history of cardiac disease, smoking, alcohol, educational level, vigorous physical activity, systolic blood pressure, diabetes medications and cholesterol medications. For women, we also additionally adjusted for use of hormone replacement therapy (HRT). Covariates were considered based on known associations with cardiovascular outcomes, and included in the models following testing for associations with exposure and outcomes. Analyses were replicated using death from ischaemic heart disease/ myocardial infarction/ any cardiovascular event as outcomes. In a sensitivity analysis, we limited the cohort to those women not taking HRT at baseline.

In order to further explore whether a healthy user effect might have influenced the findings, we investigated whether there was any interaction between calcium supplementation and either age, BMI, systolic blood pressure, smoking, alcohol, medication for cholesterol, medication for diabetes, medication for hypertension, and dietary calcium intake, for the outcome of admission with myocardial infarction.

All analyses were carried out with Stata v 14.2 (StataCorp LP, College Station, Texas).

**Results**

*Characteristics of the study participants*

A total of 502,637 men and women completed the baseline questionnaire and had complete data on calcium and vitamin D intake. Figure 1 summarises flow through the cohort from recruitment to analysis. We excluded people who either had hospital admission records for cardiovascular diseases before completing the baseline questionnaire according to the Hospital Episode Statistics or, when recruited, reported to have been diagnosed by a doctor with myocardial infarction or angina. This resulted in a final dataset containing 475,255 participants (264,984 women and 210,271 men), all of whom had complete data for the exposure and outcome variables. The average follow-up time was 7 years and the maximum 10 years. Table 1 shows the characteristics of the study participants at the baseline assessment, and compares those individuals who were taking calcium supplements with those who were not. Overall, the median (IQR) age was 57 (50 to ­63) years amongst women and 57 (50 to ­63) years amongst men, and mean (SD) BMI 27.0 (5.2) and 27.7 (4.2) kg/m² respectively. 59.6% of women and 50.1% of men had never smoked, and 10.6% of women and 2.6% of men took calcium supplements; the use of vitamin D supplements was 5.2% and 2.6% respectively, with 3.5% women and 0.8% men reporting use of both supplements. Men and women taking calcium supplements as opposed to non-users tended to be older and are more likely to be taking also vitamin D supplements (Table 1). Medical and lifestyle factors differed very modestly between those taking calcium supplements and those not using them; however, given the very large number of individuals, these differences are statistically significant in most cases. As expected, use of calcium/vitamin D supplementation was positively associated with past history of fracture, with incidence rate ratios (Poisson regression) between 1.2 and 1.8, all p < 0.001.

*Use of calcium, vitamin D or combined supplementation and incident hospital admission for cardiac events*

In total 7,106 men and 3,407 women were admitted with ischaemic heart disease (IHD); 2,456 men and 929 women with myocardial infarction (MI); 8,378 men and 4,312 women were admitted with any cardiovascular disease (CVD). Table 2A summarises the hazard ratios for admission with either IHD, MI or CVD amongst men and women separately, associated with use of calcium and/or vitamin D supplementation. The results were broadly similar across all patterns of supplementation. Thus whether unadjusted or adjusted, the hazard ratio for any outcome, with any of the three exposure variables, was not statistically significant. For example, in unadjusted models, the hazard ratio (HR) for admission with myocardial infarction was 0.97 (95%CI: 0.79, 1.20; p=0.79) amongst women taking calcium supplementation. The corresponding HR for men was 1.16 (95%CI: 0.92, 1.46; p=0.22). After full adjustment (age, BMI, family history of cardiac disease, smoking, alcohol, educational level, vigorous physical activity, systolic blood pressure, diabetes medications and cholesterol medications), the HRs (95% CI) were 0.82 (0.62, 1.07), p=0.14 amongst women and 1.12 (0.85, 1.48), p=0.41 amongst men. The adjusted HRs (95% CI) for admission with IHD were 1.05 (0.92, 1.19), p=0.50 amongst women and 0.97 (0.82, 1.15), p=0.77 amongst men. Figure 1A summarises these relationships for the fully adjusted data. In women, these null findings remained similar after further adjustment for HRT use; amongst the 137,750 women who were not using HRT (Table 3) the unadjusted HR (95%CI) for IHD with calcium supplementation was 1.23 (1.05, 1.45), p=0.01 but with full adjustment this became 1.18 (0.97, 1.43), p=0.11. However the HR (95%CI) for acute myocardial infarction with calcium supplementation was 1.02 (0.73, 1.43), p=0.89 and on full adjustment this became 0.90 (0.60, 1.36), p=0.63.

*Use of calcium, vitamin D or combined supplementation and death from cardiac events*

Table 2B documents risk of death from IHD, MI or any CVD among men and women using calcium, vitamin D or both supplements. Consistent with the lack of any statistically significant associations between calcium, vitamin D or combined supplementation and hospital admission for cardiovascular events, there was no evidence of any association between these exposures and death from either cause. This lack of association was consistent regardless of adjustment, and remained robust in women after inclusion of HRT in the models. Figure 1B summarises these associations, using the fully adjusted models.

*Interactions between cardiovascular risk factors and calcium supplementation for admission with myocardial infarction*

Tests for interactions between calcium supplementation and baseline characteristics are demonstrated in Table 4 for men and women separately, revealing no statistically significant interactions for the outcome of admission with myocardial infarction.

**Discussion**

We have demonstrated in this large prospective population-based cohort of women and men, that use of calcium and/or vitamin D supplementation was not statistically significantly associated with increased risk of hospital admission or death following ischaemic or non-ischaemic cardiovascular events, specifically after myocardial infarction. This lack of association was robust to adjustment for a range of confounders, and similar in both men and women.

Our findings contrast with those of Bolland et al., in which an increased risk of myocardial infarction was seen in the post-hoc analysis of safety reporting in a trial of calcium supplementation in elderly New Zealand women,([5](#_ENREF_5)) through a subsequent meta-analysis of calcium supplementation trials,([6](#_ENREF_6)) and then calcium and/or vitamin D supplementation trials,([7](#_ENREF_7)) including the Women’s Health Initiative (WHI). In the majority of these analyses,([29](#_ENREF_29)) the associations are of borderline statistical significance and inconsistent across vascular outcomes. Indeed analysis of the WHI by its own investigators, accounting for personal calcium/vitamin D supplementation as did the New Zealand group, did not demonstrate adverse cardiovascular effects.([11](#_ENREF_11)) Consistent with this finding, in the present analysis, we did not observe any interaction between calcium/vitamin D supplementation and background dietary intake. In our analysis, it is notable that the upper bound of the 95% confidence interval for the association between calcium with or without vitamin D and myocardial infarction was 1.07 for women and 1.48 for men (calcium alone), and 0.95 for women and 2.08 for men (combined supplementation). In the Bolland meta-analysis([30](#_ENREF_30)) including WHI, the relative risk of myocardial infarction ranged from 1.21 to 1.26; given that the vast majority of participants in this meta-analysis were women, it is apparent that the point estimate is outside the 95% CI for associations amongst women in our study, although does fall within the 95% CI for men.

Importantly, the reporting of safety outcomes is heterogeneous between the trials included in the Bolland meta-analysis and not consistently verified in all.([31](#_ENREF_31)) This is critical because of the well-documented upper gastrointestinal side-effects of calcium supplementation, which may result in misclassification of gastrointestinal as cardiovascular events.([32](#_ENREF_32)) In the present study, outcomes were identified through hospital discharge data, and uniformly reported across the whole cohort. Although Bolland et al.([33](#_ENREF_33)) reported similar findings when self-reported outcomes were excluded, no effect of calcium and vitamin D supplementation on cardiovascular outcomes were found by Lewis et al. in a further meta-analysis using only events verified by clinical review, hospital record or death certificates.([8](#_ENREF_8)) A weak association between calcium supplementation alone and myocardial infarction was observed in a secondary analysis, consistent with the meta-analyses of Bolland et al. However this is based on a much smaller number of individuals (n=6,333) than the calcium and vitamin D analysis (n=45,796). In the present study, we observed a non-significant 18% increase in risk of IHD admission with calcium supplementation in non-users of HRT. Importantly, there was no corresponding trend for myocardial infarction, the outcome most frequently associated with calcium supplementation in previous studies.([29](#_ENREF_29)) Although a recent study suggested associations between calcium supplementation and total cholesterol levels in a relatively small human cross-sectional study, and that in an ovariectomised rat model a high calcium diet increased serum total cholesterol,([14](#_ENREF_14)) to our knowledge there are no human data suggesting that HRT use modifies relationships between calcium supplementation and ischaemic heart disease outcomes. Indeed in the WHI, importantly a trial rather than an observational study, there was no difference in the risk of myocardial infarction/coronary heart disease death by calcium/vitamin D supplementation versus placebo when stratified by use of HRT.([9](#_ENREF_9)) An important consideration in the comparison of these meta-analyses is that WHI participants were permitted personal use of calcium and vitamin D supplements.([11](#_ENREF_11)) Whilst Lewis et al. did not specifically test for an interaction with personal calcium and vitamin D supplement use in the WHI study, a sensitivity analysis in which the WHI participants using personal supplementation at baseline were excluded yielded very similar null results overall.([8](#_ENREF_8)) This is consistent with the analysis from the WHI investigators,([11](#_ENREF_11)) and contrasts with the finding from Bolland et al. of a specific effect within the participants who were not taking personal calcium and vitamin D supplementation.([30](#_ENREF_30))

The existing trial data are very largely based on women, and thus the present study complements these findings with a very large cohort of men, who are generally observed to be at higher cardiovascular risk than women of similar ages. Other population-based cohort studies have derived conflicting findings. The largest existing study including men used the AARP Diet and Health study cohort in which a total of 388,229 men and women aged 50 to 71 years were followed over 12 years.([18](#_ENREF_18)) Here, increasing background intake of dietary calcium was associated with lower risk of death from heart disease. In contrast supplemental calcium was associated with a 19% increase in heart disease death amongst men, but not women. The US Nurses’ Health Study of 74,245 women followed over 24 years, consistent with our present findings, demonstrated no independent associations between intake of calcium supplements and risk of new coronary heart disease events([12](#_ENREF_12)). Conversely, in the Heidelberg cohort participants from the European Prospective Investigation into Cancer and nutrition study (EPIC),([13](#_ENREF_13)) amongst 23,980 men and women aged 35-64 years there appeared to be an increased risk of myocardial infarction (based on only 7 events), but not cardiovascular death, with the use of calcium-only supplements but not supplements containing calcium plus other nutrients. A smaller study using the Multi-Ethnic Study of Atherosclerosis (MESA) cohort of 5448 adults again indicated a decreased risk of incident atherosclerosis with greater dietary calcium intake, but a positive association between calcium supplement use and incident coronary artery disease.([17](#_ENREF_17)) A study from Finland demonstrated positive associations between calcium/vitamin D supplementation and coronary heart disease amongst women, but did not consider the baseline intake.([15](#_ENREF_15)) Increased risk of death from all causes and cardiovascular disease but not stroke with increasing calcium intake was observed in a large Swedish cohort.([16](#_ENREF_16)) Conversely, in a large meta-analysis of calcium/vitamin D trials, this intervention appeared to have a protective effect on mortality.([34](#_ENREF_34)) Given the greater number of individuals in UK Biobank than in these cohorts, we were able to investigate interactions between calcium supplementation and cardiovascular risk factors, in men and women separately. Thus the lack of association did not appear dependent upon any baseline covariates, and importantly, the population who took calcium supplements seemed broadly similar to non-users, and if anything might be at slightly higher cardiovascular risk given their greater age, making a “healthy-user” effect unlikely.

Mechanistic data present a similarly inconclusive picture to those findings from observational cohort and randomised trials. Whilst several studies have demonstrated associations between serum calcium concentrations and markers of coronary atherosclerosis, the major differences in study design, definition of exposure (e.g. calcium, phosphorus or calcium phosphorus product) and outcome (coronary artery calcification, clinical event), and differences in associations by sex between studies make these data difficult to interpret.([29](#_ENREF_29)) Two recent Mendelian Randomisation studies have demonstrated positive associations between genetically raised serum calcium concentrations and myocardial infarction.([22](#_ENREF_22),[23](#_ENREF_23)) However the genetic instruments only explained around 0.8% of the variance in calcium concentrations, and these analyses are strongly dependent on the underlying assumptions.([35](#_ENREF_35)) They also represent lifelong exposure to calcium concentration and this design cannot be used to imply that dietary supplementation in older age, or transient increases in calcium concentration lead to these outcomes. Furthermore, it is undocumented, to our knowledge, whether the transient rise in serum calcium concentration following ingestion of a calcium load (which is modest and remains below the saturation point of the calcium x phosphate product) is specifically associated with adverse cardiovascular events.([29](#_ENREF_29)) Given that biological mechanisms sense calcium ions rather than their source, it would seem unlikely that dietary calcium would behave differently to supplements in associations with cardiac outcomes.

Coronary calcification begins with pathological intimal thickening and atherosclerotic plaques forming at sites of endothelial damage.([36](#_ENREF_36)) Calcification of plaques appears to be an active process related to macrophage apoptosis leading to microcalcifications which may coalesce, rather than dependent upon the prevailing serum calcium concentration([36](#_ENREF_36)) Whilst there is evidence from meta-analyses that calcium-containing phosphate binders increase ischaemic cardiac outcomes in end-stage renal failure,([20](#_ENREF_20),[21](#_ENREF_21)) there is also evidence that the vascular endothelial behaves very differently in this context.([19](#_ENREF_19)) Thus exposure to raised calcium concentrations leads to calcification of vessels in vascular tissue taken from chronic renal failure patients, but not in vascular tissue taken from healthy controls.([19](#_ENREF_19)). Although a recent study demonstrated a potential mechanism of calcium supplementation increasing serum triglycerides in ovariectomized rats,([14](#_ENREF_14)) human studies examining links between calcium supplementation and outcomes such as blood pressure and lipid profile have generally indicated protective relationships([37-41](#_ENREF_37)).

We studied a very large population-based cohort assessed in detail and with uniform methodology, with outcome events linked through hospital records. However there are limitations that should be considered in the interpretation of our results. Firstly, calcium and vitamin D supplementation was assessed by self-report. However, as UK Biobank is not predicated on any individual disease, there is no reason why individuals might preferentially report use of such supplements. Notwithstanding, in the setting of an observational cohort study, residual confounding remains a possibility, and an appropriately powered randomised trial with validated endpoints would ultimately be needed to definitively answer the question. Secondly, we relied on hospital event linkage for outcome data and therefore may have incomplete capture of non-acute presentations of cardiovascular disease. However, hospital admission for myocardial infarction is a clearly defined and thus more reliable endpoint than its antecedents. Thirdly, we cannot exclude the possibility of selection bias towards a healthy population, as is common with such studies, and which is likely to have reduced the incidence of cardiovascular events. Conversely, a healthy population bias is likely to increase use of the exposure, calcium and vitamin D supplementation, and in relation to other studies, this is an extremely large cohort. However, we did not have information on duration of supplement use and therefore could not reliably investigate temporal relationships between the exposure and outcome. Finally, this was not a population of frail elderly individuals, and therefore we cannot exclude associations between supplementation and cardiovascular events in the oldest population.

In conclusion, in this very large prospective UK cohort of around half a million individuals, use of calcium supplementation, with or without vitamin D supplementation, was not associated with increased risk of hospital admission or death following ischaemic or non-ischaemic cardiovascular events.

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**References**

1. DIPART-Group. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. BMJ. 2010;340:b5463. Epub 2010/01/14.

2. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med. 1992;327(23):1637-42.

3. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. Jan 2013;24(1):23-57. Epub 2012/10/20.

4. Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, et al. Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev. 2014;1:CD007470. Epub 2014/01/15.

5. Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. BMJ. Feb 2 2008;336(7638):262-6. Epub 2008/01/17.

6. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ. 2010;341:c3691. Epub 2010/07/31.

7. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ. 2011;342:d2040. Epub 2011/04/21.

8. Lewis JR, Radavelli-Bagatini S, Rejnmark L, Chen JS, Simpson JM, Lappe JM, et al. The effects of calcium supplementation on verified coronary heart disease hospitalization and death in postmenopausal women: a collaborative meta-analysis of randomized controlled trials. J Bone Miner Res. Jan 2015;30(1):165-75. Epub 2014/07/22.

9. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, et al. Calcium/vitamin D supplementation and cardiovascular events. Circulation. 2007;115(7):846-54.

10. LaCroix AZ, Kotchen J, Anderson G, Brzyski R, Cauley JA, Cummings SR, et al. Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial. The journals of gerontology Series A, Biological sciences and medical sciences. May 2009;64(5):559-67. Epub 2009/02/18.

11. Prentice RL, Pettinger MB, Jackson RD, Wactawski-Wende J, Lacroix AZ, Anderson GL, et al. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporos Int. Feb 2013;24(2):567-80. Epub 2012/12/05.

12. Paik JM, Curhan GC, Sun Q, Rexrode KM, Manson JE, Rimm EB, et al. Calcium supplement intake and risk of cardiovascular disease in women. Osteoporos Int. Aug 2014;25(8):2047-56. Epub 2014/05/08.

13. Li K, Kaaks R, Linseisen J, Rohrmann S. Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). Heart. Jun 2012;98(12):920-5. Epub 2012/05/26.

14. Li S, Li Y, Ning H, Na L, Niu Y, Wang M, et al. Calcium supplementation increases circulating cholesterol by reducing its catabolism via GPER and TRPC1-dependent pathway in estrogen deficient women. International journal of cardiology. Oct 03 2013;168(3):2548-60. Epub 2013/04/23.

15. Pentti K, Tuppurainen MT, Honkanen R, Sandini L, Kroger H, Alhava E, et al. Use of calcium supplements and the risk of coronary heart disease in 52-62-year-old women: The Kuopio Osteoporosis Risk Factor and Prevention Study. Maturitas. May 20 2009;63(1):73-8. Epub 2009/04/28.

16. Michaelsson K, Melhus H, Warensjo Lemming E, Wolk A, Byberg L. Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. BMJ. Feb 12 2013;346:f228. Epub 2013/02/14.

17. Anderson JJ, Kruszka B, Delaney JA, He K, Burke GL, Alonso A, et al. Calcium Intake From Diet and Supplements and the Risk of Coronary Artery Calcification and its Progression Among Older Adults: 10-Year Follow-up of the Multi-Ethnic Study of Atherosclerosis (MESA). Journal of the American Heart Association. Oct 11 2016;5(10). Epub 2016/10/13.

18. Xiao Q, Murphy RA, Houston DK, Harris TB, Chow WH, Park Y. Dietary and supplemental calcium intake and cardiovascular disease mortality: the National Institutes of Health-AARP diet and health study. JAMA internal medicine. Apr 22 2013;173(8):639-46. Epub 2013/02/06.

19. Shroff RC, McNair R, Skepper JN, Figg N, Schurgers LJ, Deanfield J, et al. Chronic mineral dysregulation promotes vascular smooth muscle cell adaptation and extracellular matrix calcification. Journal of the American Society of Nephrology : JASN. Jan 2010;21(1):103-12. Epub 2009/12/05.

20. Floege J. Phosphate binders in chronic kidney disease: a systematic review of recent data. Journal of nephrology. Jun 2016;29(3):329-40. Epub 2016/01/24.

21. Jamal SA, Vandermeer B, Raggi P, Mendelssohn DC, Chatterley T, Dorgan M, et al. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. Lancet. Oct 12 2013;382(9900):1268-77. Epub 2013/07/23.

22. Larsson SC, Burgess S, Michaelsson K. Association of Genetic Variants Related to Serum Calcium Levels With Coronary Artery Disease and Myocardial Infarction. JAMA. Jul 25 2017;318(4):371-80. Epub 2017/07/26.

23. Xu L, Lin SL, Schooling CM. A Mendelian randomization study of the effect of calcium on coronary artery disease, myocardial infarction and their risk factors. Scientific reports. Feb 14 2017;7:42691. Epub 2017/02/15.

24. Harvey N, Dennison E, Cooper C. Osteoporosis: impact on health and economics. NatRevRheumatol. nrrheum.2009.260 pii ;10.1038/nrrheum.2009.260 doi 2010;6(2):99-105.

25. Abrahamsen B. The calcium and vitamin D controversy. Therapeutic Advances in Musculoskeletal Disease. 2017;9(5):107-14.

26. Walker-Bone K, Harvey NC, Ntani G, Tinati T, Jones GT, Smith BH, et al. Chronic widespread bodily pain is increased among individuals with history of fracture: findings from UK Biobank. Archives of osteoporosis. 2016;11:1. Epub 2015/12/19.

27. Ollier W, Sprosen T, Peakman T. UK Biobank: from concept to reality. Pharmacogenomics. Sep 2005;6(6):639-46. Epub 2005/09/07.

28. Harvey NC, Matthews P, Collins R, Cooper C. Osteoporosis epidemiology in UK Biobank: a unique opportunity for international researchers. Osteoporos Int. Dec 2013;24(12):2903-5. Epub 2013/09/24.

29. Harvey NC, Biver E, Kaufman JM, Bauer J, Branco J, Brandi ML, et al. The role of calcium supplementation in healthy musculoskeletal ageing : An expert consensus meeting of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Foundation for Osteoporosis (IOF). Osteoporos Int. Feb 2017;28(2):447-62. Epub 2016/10/21.

30. Bolland MJ, Grey A, Gamble GD, Reid IR. Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set. Am J Clin Nutr. Oct 2011;94(4):1144-9. Epub 2011/09/02.

31. Harvey NC, Biver E, Kaufman JM, Bauer J, Branco J, Brandi ML, et al. The role of calcium supplementation in healthy musculoskeletal ageing : An expert consensus meeting of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Foundation for Osteoporosis (IOF). Osteoporos Int. Oct 20 2016. Epub 2016/10/21.

32. Lewis JR, Zhu K, Prince RL. Adverse events from calcium supplementation: relationship to errors in myocardial infarction self-reporting in randomized controlled trials of calcium supplementation. J Bone Miner Res. Mar 2012;27(3):719-22. Epub 2011/12/06.

33. Bolland MJ, Grey A, Reid IR. Calcium supplements and cardiovascular risk: 5 years on. Therapeutic advances in drug safety. Oct 2013;4(5):199-210. Epub 2014/08/13.

34. Rejnmark L, Avenell A, Masud T, Anderson F, Meyer HE, Sanders KM, et al. Vitamin D with Calcium Reduces Mortality: Patient Level Pooled Analysis of 70,528 Patients from Eight Major Vitamin D Trials. J Clin Endocrinol Metab. May 17 2012. Epub 2012/05/19.

35. Katikireddi SV, Green MJ, Taylor AE, Davey Smith G, Munafo MR. Assessing causal relationships using genetic proxies for exposures: an introduction to Mendelian randomization. Addiction (Abingdon, England). Sep 18 2017. Epub 2017/09/19.

36. Otsuka F, Yasuda S, Noguchi T, Ishibashi-Ueda H. Pathology of coronary atherosclerosis and thrombosis. Cardiovascular diagnosis and therapy. Aug 2016;6(4):396-408. Epub 2016/08/09.

37. Reid IR, Mason B, Horne A, Ames R, Clearwater J, Bava U, et al. Effects of calcium supplementation on serum lipid concentrations in normal older women: a randomized controlled trial. Am J Med. Apr 1 2002;112(5):343-7. Epub 2002/03/21.

38. Reid IR, Ames R, Mason B, Bolland MJ, Bacon CJ, Reid HE, et al. Effects of calcium supplementation on lipids, blood pressure, and body composition in healthy older men: a randomized controlled trial. Am J Clin Nutr. Jan 2010;91(1):131-9. Epub 2009/11/13.

39. Denke MA, Fox MM, Schulte MC. Short-term dietary calcium fortification increases fecal saturated fat content and reduces serum lipids in men. J Nutr. Jun 1993;123(6):1047-53. Epub 1993/06/01.

40. Bell L, Halstenson CE, Halstenson CJ, Macres M, Keane WF. Cholesterol-lowering effects of calcium carbonate in patients with mild to moderate hypercholesterolemia. Arch Intern Med. Dec 1992;152(12):2441-4. Epub 1992/12/01.

41. Griffith LE, Guyatt GH, Cook RJ, Bucher HC, Cook DJ. The influence of dietary and nondietary calcium supplementation on blood pressure: an updated metaanalysis of randomized controlled trials. American journal of hypertension. Jan 1999;12(1 Pt 1):84-92. Epub 1999/03/13.

**Figure legends**

**Figure 1:** Flowchart of cohort participation.

**Figure 2:** Fully adjusted hazard ratios for A) hospital admission with ischaemic heart disease (IHD), any cardiovascular disease (CVD), or myocardial infarction (MI) amongst men and women supplemented with calcium, vitamin D or both; and B) death from ischaemic heart disease or any cardiovascular disease, amongst men and women supplemented with calcium, vitamin D or both. The data are the hazard ratio point estimate and 95% CI adjusted for age, BMI, smoking, alcohol, educational level, vigorous physical activity, systolic blood pressure and diabetes/cholesterol medication.

**Table 1:** Characteristics of the participants

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|   | **Women not using calcium supplements** | **Women using calcium supplements** | **p†** | **Men not using calcium supplements** | **Men using calcium supplements** | **p†** | **cardiovascular risk factor** |
| **Demographic characteristics** | n=237,020 | n=27,964 |  | n=204,798 | n=5,473 |  |  |
| Age [median(IQR)], years | 57.0 (49.0,62.0) | 60.0 (54.0,64.0) | <0.001 | 57.0 (50.0,63.0) | 60.0 (52.0,65.0) | <0.001 |  |
| BMI [mean(SD)], kg/m2 | 27.1 (5.2) | 26.0 (4.7) | <0.001 | 27.7 (4.2) | 27.1 (4.2) | <0.001 | ≥30 |
| Ethnicity (%) |  |  |  |  |  |  |  |
| White | 94.7% | 92.1% | <0.001 | 94.3% | 89.7% | <0.001 |  |
| Qualification (%) |  |  |  |  |  |  |  |
| College or University degree | 37.9% | 41.6% | <0.001 | 42.0% | 45.2% | <0.001 |  |
| A levels/AS levels | 14.4% | 15.1% | 12.6% | 12.9% |  |
| O levels/GCSEs | 28.5% | 26.8% | 22.6% | 20.1% |  |
| CSEs or equivalent | 6.8% | 4.5% | 6.8% | 5.3% |  |
| NVQ or HND or HNC | 5.5% | 4.5% | 10.8% | 10.6% |  |
| Other professional qualification | 6.9% | 7.5% | 5.2% | 5.9% |  |
| **Lifestyle factors** |  |  |  |  |  |  |  |
| Alcohol consumption (%) |  |  |  |  |  |  |  |
| At least 3 times per week | 37.1% | 38.1% | 0.001 | 52.3% | 46.4% | <0.001 |  |
| Smoking (%) |  |  |  |  |  |  |  |
| Never | 59.6% | 59.7% | <0.001 | 50.1% | 49.1% | 0.007 |  |
| Ex | 30.7% | 33.4% | 36.9% | 38.9% |  |
| Current | 9.1% | 6.6% | 12.5% | 11.4% |  |
| Not known | 0.6% | 0.3% | 0.6% | 0.7% |  |
| On vitamin D supplements [n (%)] | 5358 (2.3) | 8373 (29.9) | <0.001 | 3724 (1.8) | 1634 (29.9) | <0.001 |  |
| Physical activity [median (IQR)], days a week+ | 1.0 (0,3.0) | 1.0 (0,3.0) | <0.001 | 2.0 (0,3.0) | 2.0 (0,4.0) | <0.001 |  |
| Systolic blood pressure [mean(SD)], mmHg | 135.2 (19.2) | 135.6 (19.2) | 0.005 | 141.2 917.4) | 140.3 (17.9) | <0.001 |  |
| Diastolic blood pressure [mean(SD)], mmHg | 80.9 (10.0) | 80.0 (9.9) | <0.001 | 84.5 (9.9) | 83.5 (10.3) | <0.001 |  |
| High blood pressure (>140/90 mmHg) (%) | 36.1% | 37.2% | <0.001 | 48.2% | 46.6% | 0.02 |  |
| Taking medication for cholesterol [n (%)] | 25387 (10.7) | 3308 (11.8)% | <0.001 | 35403 (17.3) | 1026 (18.8) | 0.005 |  |
| Taking medication for diabetes [n (%)] | 1712 (0.7) | 194 (0.7) | 0.59 | 2368 (1.1) | 100 (1.8) | <0.001 |  |
| Taking medication for hypertension [n (%)] | 38603 (16.3) | 4350 (15.6) | 0.002 | 41790 (20.4) | 1154 (21.1) | 0.22 |  |
| Family history of cardiovascular events (%) | 53.4% | 56.1% | <0.001 | 48.5% | 49.7% | 0.08 |  |
| Mean number cardiovascular risk factors | 1.5 (1.2) | 1.4 (1.1) | <0.001 | 1.7 (1.3) | 1.7 (1.2) | 0.12 |   |

†p-difference in the baseline characteristic between women or men using calcium supplements and women not using supplements; No missing data for these baseline variables. Final column indicates variables included in the count of cardiovascular risk factors; +In a typical WEEK, how many days did you do 10 minutes or more of vigorous physical activity? (these are activities that make you sweat or breathe hard such as fast cycling, aerobics, heavy lifting).

**Table 2:** Associations between calcium, vitamin D or combined supplementation and A) incident hospital admission for ischaemic heart disease, myocardial infarction or any cardiovascular event; and B) death from ischaemic heart disease or any cardiovascular event.

A)

|  |  |  |
| --- | --- | --- |
|  | **Women** | **Men** |
| **Hospitalisation with ischaemic heart disease**  | *HR (95% CI)* | *p* | *HR (95% CI)* | *p* |
| **N**  | 3,407 |  | 7,106 |  |
| *Calcium* |  |  |  |  |
| Unadjusted | 1.09 (0.98,1.21) | 0.12 | 1.05 (0.91,1.21) | 0.48 |
| Fully adjusted | 1.05 (0.92,1.19) | 0.50 | 0.97 (0.82,1.15) | 0.77 |
| *Vitamin D* |  |  |  |  |
| Unadjusted | 1.02 (0.88,1.18) | 0.82 | 1.02 (0.88,1.18) | 0.82 |
| Fully adjusted | 1.05 (0.89,1.25) | 0.56 | 0.95 (0.80,1.13) | 0.58 |
| *Combined* |  |  |  |  |
| Unadjusted | 0.92 (0.75,1.12) | 0.41 | 0.86 (0.64,1.14) | 0.30 |
| Fully adjusted | 1.01 (0.81,1.27) | 0.93 | 0.93 (0.68,1.28) | 0.66 |
|  |  |  |  |  |
| **Hospitalisation with any cardiovascular event**  | *HR (95% CI)* | *p* | *HR (95% CI)* | *p* |
| **N**  | 4,312 |  | 8,378 |  |
| *Calcium* |  |  |  |  |
| Unadjusted | 1.05 (0.95,1.15) | 0.33 | 1.09 (0.96,1.24) | 0.20 |
| Fully adjusted | 0.99 (0.88,1.11) | 0.88 | 1.01 (0.86,1.17) | 0.93 |
| *Vitamin D* |  |  |  |  |
| Unadjusted | 1.00 (0.87,1.14) | 0.97 | 1.02 (0.90,1.17) | 0.73 |
| Fully adjusted | 1.05 (0.90,1.23) | 0.51 | 0.96 (0.82,1.13) | 0.63 |
| *Combined* |  |  |  |  |
| Unadjusted | 0.91 (0.76,1.09) | 0.30 | 0.88 (0.68,1.15) | 0.35 |
| Fully adjusted | 1.01 (0.82,1.23) | 0.96 | 0.98 (0.74,1.30) | 0.89 |
|  |  |  |  |  |
| **Hospitalisation with acute myocardial infarction** | *HR (95% CI)* | *p* | *HR (95% CI)* | *p* |
| **N**  | 929 |  | 2,456 |  |
| *Calcium* |  |  |  |  |
| Unadjusted | 0.97 (0.79,1.20) | 0.79 | 1.16 (0.92,1.46) | 0.22 |
| Fully adjusted | 0.82 (0.62,1.07) | 0.14 | 1.12 (0.85,1.48) | 0.41 |
| *Vitamin D* |  |  |  |  |
| Unadjusted | 0.86 (0.63,1.17) | 0.33 | 1.08 (0.85,1.38) | 0.53 |
| Fully adjusted | 0.77 (0.53,1.13) | 0.18 | 1.08 (0.81,1.43) | 0.61 |
| *Combined* |  |  |  |  |
| Unadjusted | 0.62 (0.39,0.99) | 0.05 | 0.96 (0.60,1.52) | 0.85 |
| Fully adjusted | 0.54 (0.30,0.95) | 0.03 | 1.31 (0.82,2.08) | 0.26 |

B)

|  |  |  |
| --- | --- | --- |
|  | **Women** | **Men** |
| **Death for Ischaemic heart disease**  | *HR (95% CI)* | *p* | *HR (95% CI)* | *p* |
| **N** | 125 |  | 518 |  |
| *Calcium* |  |  |  |  |
| Unadjusted | 0.74 (0.39,1.41) | 0.36 | 1.05 (0.62,1.78) | 0.87 |
| Fully adjusted | 0.44 (0.16,1.22) | 0.12 | 0.62 (0.28,1.40) | 0.25 |
| *Vitamin D* |  |  |  |  |
| Unadjusted | 1.09 (0.51,2.33) | 0.83 | 0.83 (0.46,1.51) | 0.55 |
| Fully adjusted | 0.70 (0.22,2.23) | 0.55 | 0.63 (0.28,1.42) | 0.27 |
| *Combined* |  |  |  |  |
| Unadjusted | 0.99 (0.37,2.68) | 0.98 | 0.50 (0.12,2.00) | 0.33 |
| Fully adjusted | 0.72 (0.18,2.97) | 0.65 | 0.36 (0.05,2.54) | 0.30 |
|  |  |  |  |  |
| **Death for any cardiovascular event** |  |  |  |
| **N** | 156 |  | 588 |  |
| *Calcium* |  |  |  |  |
| Unadjusted | 0.90 (0.53,1.54) | 0.71 | 1.05 (0.64,1.73) | 0.83 |
| Fully adjusted | 0.75 (0.36,1.56) | 0.44 | 0.65 (0.31,1.37) | 0.26 |
| *Vitamin D* |  |  |  |  |
| Unadjusted | 0.99 (0.49,2.02) | 0.98 | 0.94 (0.55,1.59) | 0.81 |
| Fully adjusted | 0.75 (0.28,2.06) | 0.58 | 0.75 (0.37,1.52) | 0.43 |
| *Combined* |  |  |  |  |
| Unadjusted | 1.01 (0.41,2.45) | 0.99 | 0.44 (0.11,1.77) | 0.25 |
| Fully adjusted | 0.91 (0.29,2.90) | 0.88 | 0.32 (0.04,2.27) | 0.25 |
|  |  |  |  |  |
| **Death for acute myocardial infarction** |  |  |  |
| **N** | 68 |  | 206 |  |
| *Calcium* |  |  |  |  |
| Unadjusted | 0.67 (0.27,1.67) | 0.40 | 1.72 (0.88,3.36) | 0.11 |
| Fully adjusted | 0.39 (0.09,1.65) | 0.20 | 0.78 (0.25,2.45) | 0.67 |
| *Vitamin D* |  |  |  |  |
| Unadjusted | 1.14 (0.42,3.14) | 0.79 | 0.96 (0.39,2.32) | 0.92 |
| Fully adjusted | 0.85 (0.20,3.56) | 0.82 | 0.79 (0.25,2.50) | 0.69 |
| *Combined* |  |  |  |  |
| Unadjusted | 0.91 (0.22,3.71) | 0.89 | 0.64 (0.09,4.58) | 0.66 |
| Fully adjusted | 0.64 (0.09,4.69) | 0.66 | - | - |

Fully adjusted models include age, BMI, smoking, family history of cardiac disease, alcohol, educational level, vigorous physical activity, systolic blood pressure, diabetes medications and cholesterol medications.

**Table 3:** Amongst women not taking HRT: Associations between calcium, vitamin D or combined supplementation and A) incident hospital admission for ischaemic heart disease, myocardial infarction or any cardiovascular event; and B) death from ischaemic heart disease or any cardiovascular event.

|  |  |
| --- | --- |
|  | **Women** |
| **Hospitalisation with Ischaemic heart disease**  | *HR (95% CI)* | *p* |
| **N**  | 1,525 |  |
| *Calcium* |  |  |
| Unadjusted | 1.23 (1.05,1.45) | 0.01 |
| Fully adjusted | 1.18 (0.97,1.43) | 0.11 |
| *Vitamin D* |  |  |
| Unadjusted | 1.02 (0.80,1.31) | 0.86 |
| Fully adjusted | 0.99 (0.74,1.32) | 0.94 |
| *Combined* |  |  |
| Unadjusted | 1.14 (0.84,1.54) | 0.39 |
| Fully adjusted | 1.16 (0.82,1.64) | 0.39 |
|  |  |  |
| **Hospitalisation with any cardiovascular event**  | *HR (95% CI)* | *p* |
| **N**  | 1,957 |  |
| *Calcium* |  |  |
| Unadjusted | 1.15 (0.99,1.34) | 0.06 |
| Fully adjusted | 1.04 (0.87,1.25) | 0.66 |
| *Vitamin D* |  |  |
| Unadjusted | 0.96 (0.77,1.20) | 0.72 |
| Fully adjusted | 0.93 (0.72,1.21) | 0.61 |
| *Combined* |  |  |
| Unadjusted | 1.02 (0.77,1.35) | 0.87 |
| Fully adjusted | 1.07 (0.78,1.46) | 0.69 |
|  |  |  |
| **Hospitalisation with acute myocardial infarction** | *HR (95% CI)* | *p* |
| **N**  | 427 |  |
| *Calcium* |  |  |
| Unadjusted | 1.02 (0.73,1.43) | 0.89 |
| Fully adjusted | 0.90 (0.60,1.36) | 0.63 |
| *Vitamin D* |  |  |
| Unadjusted | 0.98 (0.61,1.57) | 0.94 |
| Fully adjusted | 0.70 (0.37,1.32) | 0.27 |
| *Combined* |  |  |
| Unadjusted | 0.92 (0.49,1.72) | 0.78 |
| Fully adjusted | 0.69 (0.31,1.54) | 0.36 |

**Table 4:** p-values for interactions between calcium supplementation and baseline covariates for admission with myocardial infarction in males and females (unadjusted for other covariates).

|  |  |  |
| --- | --- | --- |
| **Baseline characteristic** | **Women** | **Men** |
|  | **p** | **p** |
| Age (years) | 0.41 | 0.37 |
| BMI (kg/m2) | 0.09 | 0.15 |
| Smoking (never, ex, current) | 0.18 | 0.18 |
| Dietary calcium intake (mg/day) | 0.94 | 0.43 |
| Alcohol (≥3 times per week) | 0.49 | 0.65 |
| Medication for cholesterol (Y/N ) | 0.43 | 0.57 |
| Medication for diabetes (Y/N) | - | 0.86 |
| Medication for hypertension (Y/N ) | 0.37 | 0.68 |
| Systolic blood pressure (mmHg) | 0.92 | 0.98 |
| HRT use (yes/no) | 0.52 | - |

Tables show p-values for the test of interaction between calcium supplementation versus no supplementation and baseline covariates for the outcome of admission with myocardial infarction.