Calcium supplementation and cardiovascular disease in postmenopausal women: a study in South Brazil

Suplementação de cálcio e doença cardiovascular em mulheres na pós-menopausa: um estudo no Sul do Brasil

Ronaldo Nunes Godinho[1], Thales Santa Helena Iha[1], Pietra Zorzo[1], Rafaela Martinez Copês[1], Fabio Vasconcellos Comim[2], Melissa Orlandin Premaor[2]

ABSTRACT

Objective: To evaluate the link between calcium supplementation and cardiovascular disease in postmenopausal women (aged 55 years or older). **Methods:** A standardized questionnaire was employed to collect data about calcium supplements, eart disease, and demographic of women attended at Primary Care in the South Region of Brazil. Generalized linear regression models were performed to evaluate the association and adjust for potential confounders. **Results:** Overall, 1,057 women completed the questionnaire. Information about calcium supplementation was present in 1,035 questionnaires. The mean ± standard deviation of the age of participants was 67.2±7.6 years. The frequency of calcium supplementation was 18.6%. There was no association between heart failure, stroke, and ischemic heart disease and calcium supplementation (prevalence ratio; 95% confidence interval of 0.3; -0.9-0.4, -0.2; -0.8-0.4 and -0.5; -1.0-0.02, respectively. **Conclusions:** Our study did not find an association of higher risk of cardiovascular disease in women using calcium supplementation at Primary Care in South Brazil.

Keywords: Calcium carbonate; Cardiovascular diseases; Fractures, bone; Postmenopause; Dietary supplement

RESUMO

Objetivo: Avaliar a ligação entre a suplementação de cálcio e doença cardiovascular em mulheres na pós-menopausa (com 55 anos ou mais). **Métodos:** Um questionário padronizado foi empregado para coletar dados sobre suplementos de cálcio, doenças cardíacas e demográficos de mulheres que frequentavam a Atenção Primária na Região Sul do Brasil. Modelos de regressão linear generalizada foram realizados para avaliar a associação e ajustar os potenciais fatores de confusão. **Resultados:** No total, 1.057 mulheres responderam ao questionário. As informações sobre suplementação de cálcio estavam presentes em 1.035 questionários. A média ± desvio-padrão da idade dos participantes foi de 67,2 ± 7,6 anos. A frequência de suplementação de cálcio foi de 18,6%. Não houve associação entre insuficiência cardíaca, acidente vascular cerebral e doença cardíaca isquêmica e suplementação de cálcio (razão de prevalência; intervalo de confiança de 95% de -0,3; -0,9-0,4, -0,2; -0,8-0,4 e -0,5; -1,0-0,02, respectivamente). **Conclusão:** Nosso estudo não encontrou associação de maior risco de doença cardiovascular em mulheres em uso de suplementação de cálcio na Atenção Primária no Sul do Brasil.

Descritores: Carbonato de cálcio; Doenças cardiovasculares; Fraturas ósseas; Pós-menopausa; Suplementos nutricionais

[1] Departamento de Clínica Médica, Universidade Federal de Santa Maria, Santa Maria, RS, Brazil.
[2] Departamento de Clínica Médica, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil.
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Corresponding author: Melissa Orlandin Premaor. Departamento de Clínica Médica, Universidade Federal de Minas Gerais, Avenida Professor Alfredo Balena, 190, sala 246 – Santa Efigênia. Zip code: 30130-100 – Belo Horizonte, MG, Brazil – Phone: 55 (31) 3409-9746 – E-mail: premaor@ufmg.br
Authors contributions:
Project conception and design: RNG, PZ and MOP.
Data collection, analysis, and interpretation: PZ, RMC, FVC, RNG, TSHI and MOP.
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INTRODUCTION

Calcium supplementation is recommended by several practice guidelines to prevent fractures in people at risk to develop or with established osteoporosis.[1-3] Besides its actions on the bone, calcium plays many other vital roles, being involved in the coagulation pathway, intracellular signaling, nervous system function and muscle contraction. Calcium is also associated with some pathologic processes related to the cardiovascular system, such as soft-tissue calcifications and atheromatous plaques. Evidence in the literature has suggested that calcium supplementation could be adverse to the cardiovascular system.[4,5] Bolland et al., in their meta-analysis, reported that the use of calcium supplementation elevated the cardiovascular risk, particularlyacute myocardial infarction (MI).[5,6] In a German cohort, Li et al.[7] also found associations between calcium intake (dietary or supplemented) and MI, stroke risk, and overall cardiovascular disease mortality. In contrast, the data from the 2006 Women Health Initiative (WHI) study reported that calcium intake was a protective factor for cardiovascular disease.[8,9] Similarly, Paik et al. did not report differences in calcium intake in the rates of stroke or coronary artery disease in a North American cohort.[10] Thus, the exact association of calcium supplementation and cardiovascular disease remains unclear in the current literature. Therefore, our study aimed to look at the association between calcium supplementation and cardiovascular diseases in postmenopausal women.

METHODS

Study design and population

A cross-sectional study was carried out in the municipality of Santa Maria, 29º parallel, South Brazil, from March 1 to August 31, 2013. These study details are described in Copes et al.[11,12] In brief, female participants of 55 years of age and above who were registered at the Brazilian Primary Care in the municipality of Santa Maria were included in the study. The women should have had at least a single appointment at the Primary Care facility in the 24 months previous to the study enrolment. Women who had cognitive deficits, or had communication difficulties, or still had their periods were excluded from the research.

This work was authorized by the *Núcleo Permanente de Educação em Saúde* (492/2012/SMS/NEPeS) of the *Secretaria de Saúde de Santa Maria* and by the Ethics Committee of the *Universidade Federal de Santa Maria* (CAAE 11166012.6.0000.5346). All study procedures followed the Declaration of Helsinki and Brazilian Resolution 466/12. Free and informed consent was obtained from all participants.

Measurements

Information on socio-demographic characteristics (age, sex, and schooling), health-related life habits (physical activities, alcoholism, and smoking), history of a previous fracture, family history of fractures, the age of menarche, the age of menopause, use of medications, history of comorbidities was obtained through a standardized questionnaire.[11] This questionnaire was translated into Portuguese with the permission of GLOW researchers and The Center for Outcomes Research, University of Massachusetts Medical School.[13] To reduce bias, the interviewers were trained and all procedures involving data collection were standardized.[11,12] The outcomes were self-reported for heart failure (HF), stroke, and ischemic heart disease.

Weight was measured with the patient using only light clothes, without footwear, with scales of the health unit itself. All the scales used were validated by the National Institute of Metrology, Quality and Technology (Inmetro).[14] Height was addressed according to the recommendations of the World Health Organization (WHO).[15] Regarding body mass index (BMI), the WHO criteria were used.[16]

The study factor was considered present in the volunteers who were taking any amount of calcium supplement in any form (carbonate, citrate or phosphate) at the moment of the application of the questionnaire.

Statistical analysis

Data obtained were reported as mean (standard deviation), prevalence rate (PR; percent), and proportional distribution. The associations between cardiovascular outcomes and use of supplements were assessed using Fisher's exact test. Generalized linear regression models with Poisson distribution were performed to evaluate the associations between cardiovascular disease and the use of calcium supplements. The models were adjusted for age, smoking, dyslipidemia, diabetes mellitus, systemic arterial hypertension, and bone fractures. The results of these models were presented as PR and 95% confidence interval (95%CI). Differences between groups were assumed when $p<0.05$. Statistical analysis was performed using version 19.0 of the IBM software Statistical Package for the Social Sciences (SPSS) for Windows.

RESULTS

Of the 1,057 recruited, 1,035 provided information about calcium supplementation and therefore were included in this analysis (Figure 1). Table 1 shows the features of the study population regarding their mean age and BMI. The use of calcium supplement and vitamin D

supplement were described in percentages of participants who used it. Arterial hypertension was the most frequent comorbidity, followed by diabetes mellitus and fractures.

Figure 2 shows the association of cardiovascular diseases (self-reported implantable cardioverter-defibrillato, stroke, and HF) in patients who did or did not use calcium supplement. It was not possible to observe a statistically significant difference between the groups, although we may notice fewer events in the group that used calcium supplementation.

Generalized linear regression analysis showed no association between calcium supplement use and the cardiovascular outcomes in question (Table 2).

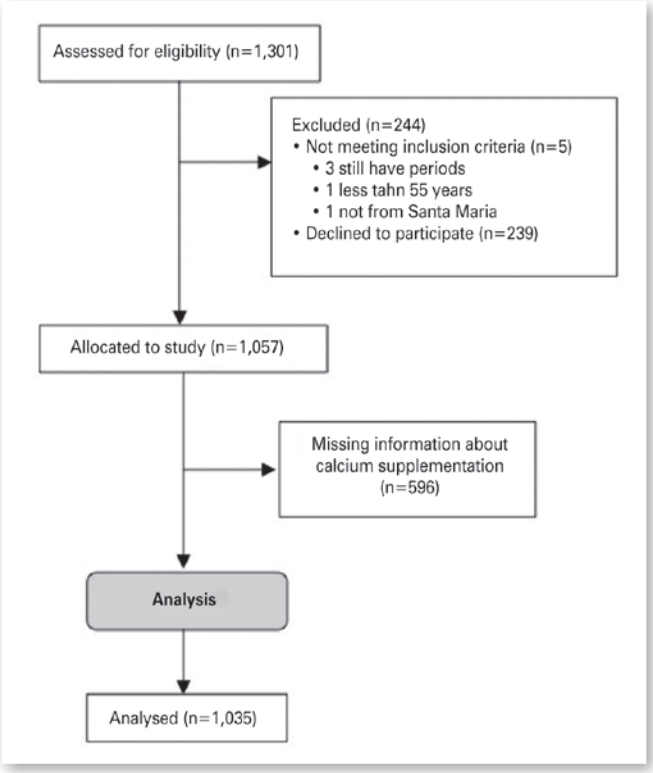


Figure 1. Flow-chart of the study.

DISCUSSION

This cross-section study included 1,035 postmenopausal women from a Southern Brazilian city. The results did not show a deleterious effect on the use of calcium supplementation concerning stroke, ischemic heart disease, and HF outcomes. These results remained neutral both in the models without adjustment for comorbidities and in models adjusted for comorbidities, age, smoking, dyslipidemia, diabetes mellitus, systemic arterial hypertension, and fractures.

The impact of calcium supplementation on the cardiovascular disorders is controversial in previous studies.[6,8,17,18] The quality of assessment of cohorts, different geographic and dietetic characteristics, and unmeasured confounders could be responsible for these discrepancies. Indeed, the co-existence of other morbidities and traditional risk factors for cardiovascular disease have been present in most cohort assessmenst.[19] Several studies adjusted their data for cardiovascular risk, and naturally their indices of risk and cardiovascular events associated with calcium reduced.[4] However, bias remains, mainly in observational studies, consequently creating noise in some meta-analyses.

In contrast to our data, a meta-analysis[4] of observational studies found a positive association between serum calcium and mortality, with a hazard ratio (HR) of 1.13 (95%CI 1.09-1.18) and heterogeneity (I^2) of 64%. Similarly, HF risk was associated with higher calcium concentrations 1.48 (95%CI 1.29-1.70), and an increase of cardiovascular events of 1.08 (95%CI 1.04-1.13). However, the study used mainly studies from Europe, United States, Australia, and China, countries with generally different social, economic conditions and nutritional habits when compared to Brazil. Furthermore, the variety of food types and the calcium concentration in each food may vary with weather, ground, and other geogra-

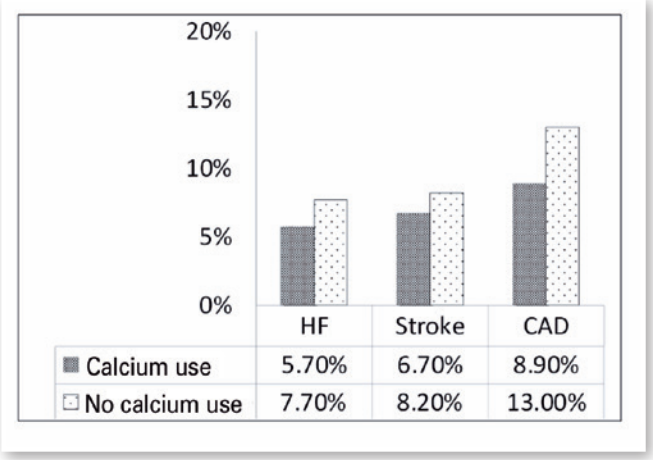
Table 1. Characteristics of the women studied

Characteristic	Without calcium	With calcium	p-value
Age, years	67.2±7.6	69.3±7,5	<0.0001
BMI	29.3±5.5	29.2±6,0	0.903
Vitamin D supplements use	21/843	89/191	<0.0001
Tobacco use	104/834	18/191	0.267
Dyslipidemia	476/816	119/189	0.251
Hypertension	534/823	121/189	0.866
Diabetes mellitus	186/840	38/192	0.499
Coronary artery disease	110/842	17/192	0.115
Stroke	69/843	13/193	0.307
Heart failure	65/843	11/192	0.443
Fracture	124/806	41/179	0.020

Results expressed as mean ± standard deviation or n/total n.
BMI: body mass index.

phic conditions. Brondani et al.[20] showed that, in Brazil, the daily intake of dietary calcium is below the dietary reference intake (DRI) recommended by the Institute of Medicine (IOM). Thus, the total ingestion of calcium in dietary may have contributed to the differences found.

Some studies found an association between cardiovascular events and calcium supplementation.[5,21] The increase of circulating calcium levels is related to the increase of vessels calcification.[5,22] The calcium citrate supplement, when compared with dairy-rich meal, demonstrates increased and sustained effects of the supplement on the calcium serum levels.[23] Bolland et al.[5] reported the relative risk (RR) of MI of 1.27 (95%CI 1.01-1.59) with calcium supplementation in their meta-analysis. However, similar to our study, most studies assessed by the authors did not mention basal daily dietary calcium intake. In another study, Bolland et al. demonstrated similar data with an increased hazard ratio for MI (HR of 1.21; 95%CI 1.01-1.44) and stroke (HR of 1.2; 95%CI 1.00-1.43).[6] Nevertheless, in addition to the bias in the analyzing method, there are inconsistent cardiovascular outcome and associations with borderline statistical significance in their analyses.[19]



HF: heart failure; CAD: coronary artery disease.

Figure 2. Frequency of self-reported cardiovascular diseases according to the use of calcium supplementation. There are no significant differences between the groups.

On the other hand, in accordance with our present findings, Harvey et al.,[18] in a UK population-based cohort with 475,255 participants, did not find an association between calcium supplementation, with or without vitamin D, andincreased risk of hospital admission or death following ischaemic or non-ischaemic cardiovascular events. A US Nurses' Health Study showed no independent associations between intake of calcium supplements and risk of new coronary heart disease events and stroke in 74,245 women followed over 24 years. The authors still found a protective effect reducing the event of an episode of coronary heart disease (RR of 0.71; 95%CI 0.61-0.83; p<0.001) but no effect against the risk of stroke (RR of 1.03; 95%CI 0.87-1.21; p=0.61).[10] Similarly, a study from London following 9,910 women, between 60 and 89 years of age, for two years,[24] demonstrated no relationship between calcium intake and increase in cardiovascular disease or death.[24] Furthermore, based on the literature published until 2016, the National Osteoporosis Foundation and American Society for Preventive Cardiology considered the use of calcium with or without vitamin D of no benefit or harm to cardiovascular and cerebrovascular disease, mortality, or all-cause mortality in generally healthy patients.[25] They graded this evidence as of moderate quality.[18]

Another important issue is the relationship between calcium and vitamin D. Several studies have suggested the beneficial effects of vitamin D on cardiovascular endpoints, including decreased mortality.[8-10,24,26] Low levels of 25-hydroxyvitamin D [25(OH) D] have been associated with cardiovascular disease in epidemiologic studies.[27] Patients with hypertension, metabolic syndrome, HF, and stroke showed lower 25(OH) D concentrations when compared with persons without these disorders. Ford et al.[28] found that vitamin D supplementation has a protective effect against cardiac failure but not on MI or stroke in older people. In the same article, the authors conducted a systematic review and meta-analysis, and the results did not show significant reductions in MI, stroke or cardiac failure. Although the causality of these relations is uncertain, vitamin D seems to be beneficial

Table 2. Generalized linear regression analysis for the use of calcium as a factor associated with cardiovascular diseases in postmenopausal women

Factor	Model		
	Unajusted	Adjusted*	Adjusted†
Heart failure	-0.3 (-0.9-0.3); 0.359	-0.3 (-0.9-0.4); 0.390	-0.3 (-0.9-0.4); 0.388
Stroke	-0.2 (-0.7-0.4); 0.579	-0.2 (-0.8-0.4); 0.422	-0.2 (-0.8-0.4); 0.435
Coronary artery disease	-0.4 (-0.96-0.09); 0.105	-0,5 (-1.0-0.04); 0.069	-0.5 (-1.0-0,02); 0.060

Results expressed as prevalence ratio (95% confidence interval); p-value

*Model adjusted for age, smoking, dyslipidemia, diabetes mellitus, and hypertension; † model adjusted for age, smoking, dyslipidemia, diabetes mellitus, hypertension and fractures.

to the cardiovascular system. In the clinical practice, several calcium supplements prescriptions are combined with vitamin D, which could influence the real effect of calcium. In the same way, the non-separation of calcium supplementation and vitamin D supplementation in observational studies may have influenced the results, as a bias of confusion. The beneficial effect of vitamin D could be protecting individuals from the malefic effect of calcium. However, in our study, the number of subjects using both calcium and vitamin D was too small to evaluate this hypothesis.

Despite many studies indicated that higher calcium supplementation could be linked to an increased risk of cardiovascular mortality, Raffield et al., in a Multi-Ethnic Study of Atherosclerosis (MESA), showed individuals using a low dose of calcium supplements (1 to 499mg) had lower risk of MI than individuals with no calcium supplements (HR of 0.69; 95%CI 0.48-0.98; p=0.039).[29,30] Furthermore, Chung et al. suggest that calcium intake (2,000 to 2,500mg/d) is not associated with cardiovascular disease risk in healthy persons.[31] Unfortunately, it was not possible to evaluate the total, dietary, and supplemental calcium intake levels in our cohort. Thus, we could not estimate dose-response relationships between calcium levels and possible cardiovascular outcomes.

This study has some limitations that should be considered in the interpretation of our results. It is a cross-sectional study and some confounding factors could be present in this type of analysis. Moreover, calcium and vitamin D supplementation, as well as cardiovascular outcomes, were collected through self-report. Also, we assessed women of 55 years of age with at least one appointment at the Primary Care. Thus, we could not exclude the possibility of observational studies bias. Healthy people, or even memory recall bias, could reduce our cardiovascular outcomes data. Notwithstanding there is no reason to believe that the possible inaccuracies in self-reports were different between women taking and not taking calcium. Our study also has some strength. We believe the sample is fully representative of the postmenopausal women population attending Primary Care services. All Primary Care facilities in our municipality were included.[11,32]

CONCLUSION

Our data did not show an association between the increase in the risk of cardiovascular diseases and calcium supplementation in women treated at Primary Care in the municipality of Santa Maria. However, further controlled studies are required to identify the possible dose-response relation between calcium supplementation and cardiovascular disease, and to clarify the influence of geographic and genetic factors on this issue.

REFERENCES

1. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, et al.; National Osteoporosis Guideline Group (NOGG). UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos. 2017;12(1):43. doi: https://doi.org/10.1007/s11657-017-0324-5
2. Black DM, Rosen CJ. Postmenopausal Osteoporosis. N Engl J Med. 2016;374(21):2096-7. doi: https://doi.org/10.1056/NEJMc1602599
3. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al.; National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int. 2014;25(10):2359-81. doi: https://doi.org/10.1007/s00198-014-2794-2. Erratum in: Osteoporos Int. 2015;26(7):2045-7.
4. Reid IR, Gamble GD, Bolland MJ. Circulating calcium concentrations, vascular disease and mortality: a systematic review. J Intern Med. 2016;279(6):524-40. doi: https://doi.org/10.1111/joim.12464
5. 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. doi: https://doi.org/10.1136/bmj.c3691
6. 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. doi: https://doi.org/10.1136/bmj.d2040
7. 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. 2012;98(12):920-5. doi: https://doi.org/10.1136/heartjnl-2011-301345
8. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, et al.; Women's Health Initiative Investigators. Calcium/vitamin D supplementation and cardiovascular events. Circulation. 2007;115(7):846-54. doi: https://doi.org/10.1161/CIRCULATIONAHA. 106.673491. Erratum in: Circulation. 2007;115(19):e466.
9. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al.; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354(7):669-83. doi: https://doi.org/10.1056/NEJMoa055218. Erratum in: N Engl J Med. 2006;354(10):1102.
10. 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. 2014;25(8):2047-56. doi: https://doi.org/10.1007/s00198-014-2732-3
11. Copês RM, Comim FV, Langer FW, Codevilla AA, Sartori GR, de Oliveira C, et al. Obesity and Fractures in Postmenopausal Women: A Primary-care Cross-Sectional Study at Santa Maria, Brazil. J Clin Densitom. 2015;18(2):165-71. doi: https://doi.org/10.1016/j.jocd.2014.09.005
12. Copês RM, Dal Osto LC, Langer FW, de Vieira AR, Codevilla AA, Sartori GR, et al. Low health related quality of life associated with fractures in obese postmenopausal women in Santa Maria, Brazil. Bone Rep. 2017;6:70-3. doi: https://doi.org/10.1016/j.bonr.2017.02.005
13. Hooven FH, Adachi JD, Adami S, Boonen S, Compston J, Cooper C, et al. The Global Longitudinal Study of Osteoporosis in Women (GLOW): rationale and study design. Osteoporos Int. 2009;20(7):1107-16. doi: https://doi.org/10.1007/s00198-009-0958-2

14. Instituto Nacional de Metrologia, Qualidade e Tecnologia (Inmetro). Solicitar verificação de instrumento de medição em Goiás, Distrito Federal e Rio Grande do Sul. 2022 [citado 2022 Jul. 22]. Disponível em: https://www.gov.br/pt-br/servicos/solicitar-verificacao-de-instrumento-de-medicao-em-goias-distrito-federal-e-rio-grande-do-sul
15. World Health Organization (WHO). The WHO STEPS Surveillance Manual. WHO STEPwise Approach to Chronic Disease Risk-Factor surveillance. Geneve: WHO; 2008 [cited 2022 Jul 5]. Available from: https://www.paho.org/hq/dmdocuments/2009/STEPSmanual.pdf
16. Sager MA, Rudberg MA, Jalaluddin M, Franke T, Inouye SK, Landefeld CS, et al. Hospital admission risk profile (HARP): identifying older patients at risk for functional decline following acute medical illness and hospitalization. J Am Geriatr Soc. 1996;44(3):251-7. doi: https://doi.org/10.1111/j.1532-5415.1996.tb00910.x
17. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, et al.; Women's Health Initiative Investigators. Calcium/vitamin D supplementation and cardiovascular events. Circulation. 2007;115(7):846-54. doi: https://doi.org/10.1161/CIRCULATIONAHA.106.673491. Erratum in: Circulation. 2007;115(19):e466.
18. Harvey NC, D'Angelo S, Paccou J, Curtis EM, Edwards M, Raisi-Estabragh Z, et al. Calcium and Vitamin D Supplementation Are Not Associated With Risk of Incident Ischemic Cardiac Events or Death: Findings From the UK Biobank Cohort. J Bone Miner Res. 2018;33(5):803-11. doi: https://doi.org/10.1002/jbmr.3375
19. 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. 2017;28(2):447-62. doi: https://doi.org/10.1007/s00198-016-3773-6
20. Brondani J. Consumo alimentar de cálcio, fósforo, magnésio, proteínas e estado nutricional em mulheres hospitalizadas por fraturas osteoporóticas em um Hospital Universitário [Mestrado]. Santa Maria: Universidade Federal de Santa Maria; 2015.
21. 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. 2008;336(7638):262-6. doi: https://doi.org/10.1136/bmj.39440.525752.BE
22. Li S, Na L, Li Y, Gong L, Yuan F, Niu Y, et al. Long-term calcium supplementation may have adverse effects on serum cholesterol and carotid intima-media thickness in postmenopausal women: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr. 2013;98(5):1353-9. doi: https://doi.org/10.3945/ajcn.113.062844. Erratum in: Am J Clin Nutr. 2014;99(5):1143.
23. Bristow SM, Gamble GD, Stewart A, Horne AM, Reid IR. Acute effects of calcium supplements on blood pressure and blood coagulation: secondary analysis of a randomised controlled trial in post-menopausal women. Br J Nutr. 2015;114(11):1868-74. doi: https://doi.org/10.1017/S0007114515003694
24. Shah SM, Carey IM, Harris T, DeWilde S, Cook DG. Calcium supplementation, cardiovascular disease and mortality in older women. Pharmacoepidemiol Drug Saf. 2010;19(1):59-64. doi: https://doi.org/10.1002/pds.1859
25. Kopecky SL, Bauer DC, Gulati M, Nieves JW, Singer AJ, Toth PP, et al. Lack of Evidence Linking Calcium With or Without Vitamin D Supplementation to Cardiovascular Disease in Generally Healthy Adults: A Clinical Guideline From the National Osteoporosis Foundation and the American Society for Preventive Cardiology. Ann Intern Med. 2016;165(12):867-8. doi: https://doi.org/10.7326/M16-1743
26. Zhang R, Li B, Gao X, Tian R, Pan Y, Jiang Y, et al. Serum 25-hydroxyvitamin D and the risk of cardiovascular disease: dose-response meta-analysis of prospective studies. Am J Clin Nutr. 2017;105(4):810-9. doi: https://doi.org/10.3945/ajcn.116.140392
27. Beveridge LA, Witham MD. Vitamin D and the cardiovascular system. Osteoporos Int. 2013;24(8):2167-80. doi: 10.1007/s00198-013-2281-1
28. Ford JA, MacLennan GS, Avenell A, Bolland M, Grey A, Witham M; RECORD Trial Group. Cardiovascular disease and vitamin D supplementation: trial analysis, systematic review, and meta-analysis. Am J Clin Nutr. 2014;100(3):746-55. doi: https://doi.org/10.3945/ajcn.113.082602
29. 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 Intern Med. 2013;173(8):639-46. doi: https://doi.org/10.1001/jamainternmed.2013.3283
30. Raffield LM, Agarwal S, Hsu FC, de Boer IH, Ix JH, Siscovick D, et al. The association of calcium supplementation and incident cardiovascular events in the Multi-ethnic Study of Atherosclerosis (MESA). Nutr Metab Cardiovasc Dis. 2016;26(10):899-907. doi: https://doi.org/10.1016/j.numecd.2016.07.007
31. Chung M, Tang AM, Fu Z, Wang DD, Newberry SJ. Calcium intake and cardiovascular disease risk: an updated systematic review and meta-analysis. Ann Intern Med. 2016;165(12):856-66. doi: https://doi.org/10.7326/M16-1165. Erratum in: Ann Intern Med. 2017;166(9):687.
32. Langer FW, da Silveira Codevilla AA, Bringhenti R, Dal Osto LC, Campos TR, Martins TT, et al. Low self-awareness of osteoporosis and fracture risk among postmenopausal women. Arch Osteoporos. 2016;11(1):27. doi: https://doi.org/10.1007/s11657-016-0266-3