Received: 23 August 2021 | Revised: 18 October 2021 | Accepted: 25 October 2021

DOI: 10.1111/cen.14632

ORIGINAL ARTICLE

WILEY

The acute effects of milk intake on calcium homeostasis and cardiovascular outcome: A randomized crossover trial in postmenopausal women

Rasmus Espersen[1,2] | Lars Rejnmark[1,2]

[1]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark

[2]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

Correspondence
Rasmus Espersen, Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Palle Juul-Jensens Blvd 99, 8200 Aarhus, Denmark.
Email: rasesp@clin.au.dk

Funding information
Innovationsfonden, Grant/Award Number: 4105-00008B

Abstract

Objective: The importance of calcium intake from dairy in regard to cardiovascular health has been investigated in several studies with discrepant results. Hence, we aim to investigate the immediate effects of milk intake on cardiovascular function.

Design: A randomized crossover study with at least 10 days for washout between the two interventions, 500 ml of water with 200 µg of cholecalciferol or 500 ml of semi-skimmed milk containing approximately 600 mg of calcium with 200 µg of cholecalciferol.

Patients: Twenty community-based postmenopausal women aged 60–80 years.

Measurements: Parathyroid hormone and ionized calcium were measured at baseline and after 2 and 4 h on each study day. Pulse wave analysis and velocity were measured at baseline and after 4 h on each study day.

Results: Compared to water, milk intake increased ionized calcium levels by 0.02 mmol/L ($p = .029$) and decreased parathyroid hormone levels by 1.78 pmol/L ($p < .001$). The two interventions caused no changes as measured 4 h after the intervention in the following indices of cardiovascular health; pulse wave velocity, brachial diastolic or systolic blood pressure, central diastolic or systolic blood pressure, mean arterial pressure, pulse pressure, augmentation pressure, augmentation index, heart rate or pulse transit time.

Conclusions: Despite significant changes in calcium homeostasis with increased levels of ionized calcium following milk intake, no acute effects seem to occur on measures of cardiovascular health.

KEYWORDS
blood pressure, calcium, cross-over studies, milk, parathyroid hormone, pulse wave analysis, vascular stiffness

1 | INTRODUCTION

Over the past decade, the importance of calcium intake in general and calcium intake from milk products and supplementation in particular has been investigated in a number of studies showing discrepant results. A Cochrane meta-analysis suggested an overall beneficial effect of increased calcium intake from milk products and calcium supplements.[1] Another meta-analysis found an increased risk of myocardial infarction among participants in randomized trials receiving calcium supplements.[2] Likewise, a Swedish community-based cohort study

found that a high intake of calcium (>1400 mg/day) in women was associated with higher death rates from all causes and cardiovascular disease (CVD) but not from stroke.[3] A recent randomized crossover trial has suggested a relative increase in blood pressure in the hours following intake of 1000 mg of calcium citrate compared with placebo.[4] In contrast, Burt et al.[5] found no effect on arterial stiffness and a decrease in arterial wave reflection (augmentation index [Aix]) in the hours following intake of 1000 mg of calcium as citrate.[5] So far, it has not been investigated whether milk intake has similar effects on indices of cardiovascular health. The current discrepancy in research on the cardiovascular effect of calcium intake is concerning given the status milk consumption enjoys in today's western societies.

Arterial stiffness is a strong predictor of CVD, future cardiovascular events and all-cause mortality.[6,7] It can be measured non-invasively by pulse wave velocity (PWV), which is considered the gold standard.[8,9] Carotid-femoral PWV reflects the arterial stiffness in aorta,[9] but it is also a dynamic measure that can change within 90 min after administration of antihypertensiva.[10] An increase in PWV by 1 m/s corresponds to an age-, sex-, and risk factor–adjusted risk increase of 14% in cardiovascular events.[6]

The aim of this study was to investigate the immediate effects of milk intake on cardiovascular indices by measuring arterial stiffness. Our null hypothesis was that cardiovascular indices are not affected by milk intake.

2 | MATERIALS AND METHODS

We enroled 20 postmenopausal women, aged between 60 and 80 years. Exclusion criteria were daily use of calcium and/or vitamin D supplementation, current treatment with beta-blockers and/or overt CVD such as known severe heart failure (NYHA III-IV), previous major heart surgery, pacemaker or arrhythmias (e.g., atrial fibrillation or flutter, second- and third-degree atrioventricular block), chronic kidney or liver disease, cancer, treatment for rheumatoid arthritis, treatment with oral corticosteroids or lithium, allergy or intolerance towards milk, juice or vitamin D supplementation and use of sun beds.

Participants were recruited from the general background population by direct mailing using a list of randomly selected individuals living in the area of Aarhus, Denmark. In total, 8977 letters were sent out. Of 774 respondents, 243 were eligible for a blood test. Seventy-one had vitamin D insufficiency. Among these, 30 wanted to participate in the study of whom one dropped out, six were cancelled due to the COVID-19 pandemic and maintenance of equipment, and PWV measurements were impossible in three participants (Figure 1).

The study was conducted at Aarhus University Hospital, Denmark, during the winter and spring of 2019 and 2020 as part of a larger study investigating the influence of food matrix delivery system on the bioavailability of vitamin D_3 (www.clinicaltrials.gov ID: 1107213017). The study was performed in accordance with the Helsinki II declaration. Participation was preceded by written consent and the protocol was approved by the ethical committee in the Central Denmark Region (1-10-72-130-17).

2.1 | Design

Analyses are based on data from a larger randomized multiple crossover study (five treatment arms) investigating the influence of different food matrix delivery systems on the bioavailability of vitamin D_3. Before inclusion, 25(OH)D levels were measured to allow for the inclusion of only women with vitamin D insufficiency (Figure 1). The current analyses includes only two of the treatment arms during which cardiovascular indices were measured in response to either 500 ml of water or 500 ml of semi-skimmed milk (Arla® Letmælk 1.5%) (calcium content: 123.8 mg, calcium/100 g milk, i.e., a total dose of approximately 619 mg of calcium was given) with 200 µg of cholecalciferol added to both liquids. Treatment sequences were randomized (using the sealed envelope method) with each treatment being investigated on two separate days. If a participant received water on the first study day, milk was served on the second study day and vice versa. A washout period of at least 10 days was interposed between the two study days. Before the treatment arms in question, some of the participants had been allocated to other treatment arms (also including a single dose of 200 µg of cholecalciferol) and accordingly, not all participants were strictly vitamin D insufficient during current measurements.

Together with the intervention, a light breakfast meal composed of bread, jam and coffee or tea was served. No smoking, food or caffeine intake was allowed between the intervention and the second PWV measurement. Antihypertensive medications were paused during the day of examinations. No talking or sleeping was allowed during measurements. The right arm, leg and coronary artery were used in all participants except one, whose right leg was amputated.

In the present analyses, PWV was considered the primary outcome, whereas changes in office blood pressure, pulse wave analysis (PWA) and indices of calcium homeostasis were prespecified as secondary outcomes.

2.2 | Measurements

We performed PWA, including measurements of PWV, twice during each study day using the SphygmoCor® XCEL (AtCor Medical): Once in the morning with the participants in a fasting state before the intervention, and again 4 h after the intervention. Blood samples were taken trice: Before the intervention and 2 and 4 h after the intervention.

The PWA and PWV measurements were performed in a quiet room with a stable room temperature. After at least 10 min of rest and with the participants in a supine position, brachial blood pressure was measured thrice and the mean value was used for PWV measurements. The SphygmoCor XCEL System derives central aortic pressure waveforms from cuff pulsations recorded at the brachial artery. The built-in PWA software provides central diastolic blood pressure (cDBP), central systolic blood pressure (cSBP), pulse pressure (PP), mean arterial pressure (MAP) and indices of arterial stiffness such as augmentation pressure (AP) and Aix.[11]

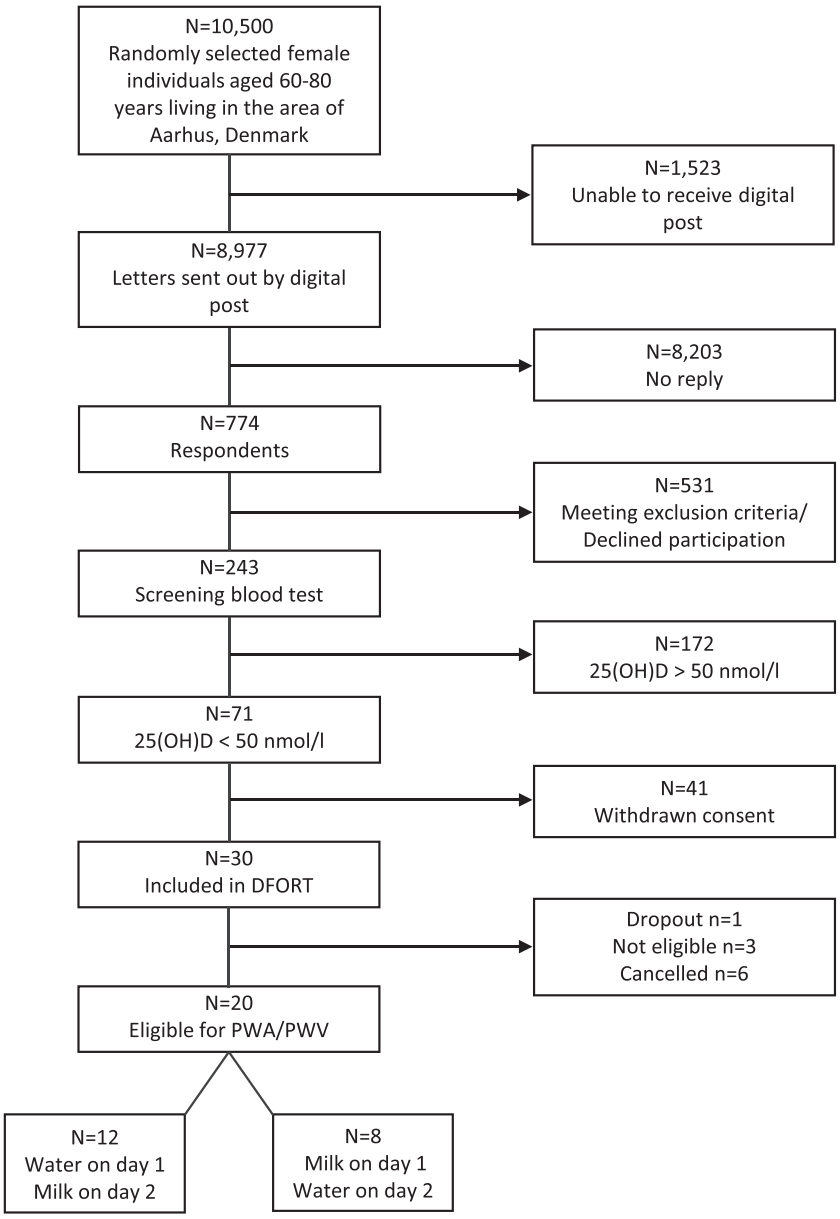

FIGURE 1 Flow chart of recruitment. 25(OH)D, 25-hydroxy vitamin D; DFORT, the Influence of food matrix delivery system on the bioavailability of vitamin D_3; PWA, pulse wave analysis, PWV, pulse wave velocity

For measurements of PWV, the direct distance between the common carotid artery and the femoral cuff was measured using a calliper. The distance between the femoral cuff and the common femoral artery was measured using a tape measure. The measures were taken at least twice until no in-between difference was seen.

At each time point of measurement, PWV was measured twice if the difference was <0.5 m/s and the mean was taken for further analyses. If the difference was >0.5 m/s, a third measurement was performed and the median was taken for further analyses. The build-in quality control was used to verify the measurements. Only measurements with approved quality control were used in further analyses.

All measurements were performed by a single investigator (R. E.), who was not blinded to the intervention. After ensuring parameters being within the quality control, the reproducibility of the techniques was tested by duplicate measurements by the operator showing good agreement using Bland–Altman plots.

Plasma levels of venous ionized calcium (Ca^{2+}) were measured immediately by an automated electrochemical method (Nova 8), and levels were adjusted to a pH value of 7.4 with a coefficient of variation [CV] of 5.4% at 1.19 mmol/L (reference range: 1.18–1.32 mmol/L). Serum 25(OH)D_2 + D_3 was measured by tandem mass spectrometry and analysed by high-performance liquid chromatography (LS-MS/MS) with a CV of 5.4% at 33 nmol/L and 10% at 113 nmol/L. Plasma creatinine was measured by absorption photometry and analysed using a chromogenic enzymatic reaction (Chemistry XPT) with a CV of 8.9% at 68 µmol/L (reference range: 45–90 µmol/L). Plasma samples were refrigerated at −80°C until analysed in a single batch for analysis of levels of parathyroid hormone (PTH) using a chemiluminescent microparticle immunoassay (Centaur XPT automated analyser) with a CV of 25.3% at 5.5 pmol/L (reference range: 2.0–8.5 pmol/L).

Height and weight were measured without shoes and clothes except underwear. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

2.3 | Statistics

Period effects were investigated comparing baseline values at Days 1 and 2 independently of whether water or milk was provided on Days 1 or 2, using the paired *t*-test. Carry-over effects were investigated by comparing differences in baseline values between Days 1 and 2 when milk was given on Day 1 to differences between baseline values at the two study days when water was given on Day 1, using the Student's *t*-test.

We calculated the relative difference in percentage between the baseline and the second measurement of PWA and PWV. Aix was not adjusted for heart rate. We compared the differences by using paired *t*-test, reporting the estimated mean and standard error of the mean.

Levels of Ca^{2+} and PTH were analysed using a mixed-effects regression model with intervention and time along with the interaction between them, order and day as fixed effects. Subject and day within subject were included in the analyses as random effects. Model validation was performed by inspecting QQ plots for the standardized residuals and plots of standardized residuals against the fitted values. Results are presented as estimated mean and mean differences with 95% confidence intervals (CIs).

Sample size calculations showed that 20 subjects would be needed to be able to detect a minimum difference of 1 m/s in PWV between the two interventions (paired samples) assuming a common standard deviation of 1.5 m/s with a statistical power of 80% ($\beta = .20$) and a 5% risk of a statistical type I error ($\alpha = .05$).

Data were collected and managed using REDCap electronic data capture tools hosted at Aarhus University, Denmark,[12,13] and analysed using Stata version 16.1 and IBM SPSS Statistics version 27. A two-tailed *p*-value below .05 was considered statistically significant.

3 | RESULTS

Twenty women with a mean age of 69.4 years were included in the study. Of these, 12 had water as an intervention on Day 1. Analyses did not suggest carry-over effect or period effect. Table 1 shows the characteristics of the participants. Mean 25(OH)D levels were 38 nmol/L at screening (data not shown), 40 nmol/L at baseline on Day 1 and 48 nmol/L at baseline on Day 2.

3.1 | Changes in Ca^{2+} and PTH levels

Figure 2A shows changes in Ca^{2+} levels in response to the two interventions. At the start of each of the two interventions, plasma Ca^{2+} levels did not differ (mean difference = −0.00, 95% CI: −0.02, 0.01 mmol/L; $p = .56$). The test for parallel mean curves for the two interventions showed a borderline significant difference ($p = .07$). The change in plasma Ca^{2+} levels was significantly different between the two interventions from baseline to 4 h ($p = .030$). After 4 h, drinking milk resulted in significantly higher plasma Ca^{2+} levels than water intake (mean difference = 0.02, 95% CI: 0.00, 0.03 mmol/L; $p = .029$).

Figure 2B shows changes in PTH levels in response to the two interventions. At the start of each of the two interventions, plasma PTH levels did not differ (mean difference = −0.54, 95% CI: −1.13, 0.05 pmol/L; $p = .07$). The test for parallel mean curves for the two interventions showed a significant difference ($p < .004$). The change in plasma PTH was significantly different between the two interventions from baseline to 4 h ($p = .001$). After 2 h, drinking milk

TABLE 1 Characteristics of included women

		N	Reference interval	Mean (SD)
Age, years		20	NA	69.41 (4.37)
BMI, kg/m^2		20	NA	27.71 (7.78)
Plasma				
Screening	Creatinine, μmol/L	20	45–90	60 (11.85)
Screening	eGFR/1.73 m^2, ml/min	20	>60	86 (11.80)
Day 1	25-Hydroxy vitamin D, nmol/L	19	>50	40 (9.20)
Day 2	25-Hydroxy vitamin D, nmol/L	20	>50	48 (10.18)
Day 1	Ionized calcium, mmol/L	19	1.18–1.32	1.22 (0.03)
Day 2	Ionized calcium, mmol/L	20	1.18–1.32	1.21 (0.04)
Day 1	PTH, pmol/L	20	2.0–8.5	5.4 (2.22)
Day 2	PTH, pmol/L	20	2.0–8.5	5.3 (1.93)

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; NA, not applicable; PTH, parathyroid hormone.

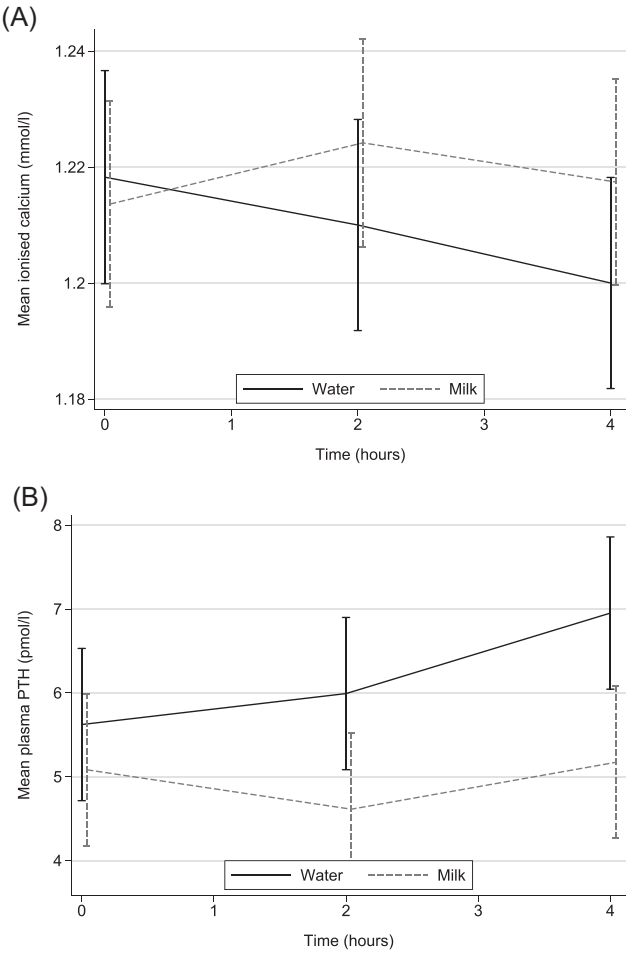

FIGURE 2 (A) Changes in serum ionized calcium in response to the two interventions. (B) Changes in plasma parathyroid hormone (PTH) in response to the two interventions

resulted in significantly lower plasma PTH levels than water intake (mean difference = −1.38, 95% CI: −1.97, −0.79 pmol/L; $p < .001$). The same was true after four hours (mean difference = −1.78, 95% CI: −2.37, −1.19 pmol/L; $p < .001$).

3.2 | PWA and PWV

PWV was performed in 19 participants as it was not possible to perform tonometry on Day 2 (water as intervention) for one participant. Furthermore, for three participants, PWA was impossible to perform on one of the study days (one with water as intervention, two with milk as intervention) due to problems with the brachial cuff.

The two types of intervention did not cause changes as measured 4 h after the intervention in indices of cardiovascular health in terms of PVW, brachial diastolic blood pressure), brachial systolic blood pressure (brSBP), cDBP, cSBP, MAP, PP, AP, Aix, heart rate and pulse transit time (Table 2).

Eight participants had self-reported hypertension. If we excluded these patients from the analyses, no effect on any parameter except for brSBP and PP was seen. BrSBP increased by 4.0% 4 h after water intake and decreased by 2.1% 4 h after milk intake ($p = .02$). PP increased by 8.6% 4 h after water intake and decreased by 2.7% 4 h after milk intake ($p = .02$).

TABLE 2 Difference in percentage between baseline and 4 h after the intervention

		Water		Milk		
	N	Mean	SEM	Mean	SEM	*p*-Value
ΔPWV (%)	19	−0.7	1.3	−1.8	1.6	.56
ΔbrDBP (%)	19	1.4	2.0	−0.8	1.5	.43
ΔbrSBP (%)	19	3.5	1.4	0.8	1.8	.21
ΔcDBP (%)	16	0.6	1.6	−0.7	1.7	.60
ΔcSBP (%)	16	2.8	1.8	0.9	1.9	.40
ΔMAP (%)	16	0.7	1.5	−0.3	1.8	.67
ΔPP (%)	16	6.8	3.0	4.0	3.2	.44
ΔAP (%)	16	−5.5	5.6	−6.2	5.0	.92
ΔAIx (%)	16	−11.9	3.8	−10.6	3.0	.78
ΔHeart rate (%)	19	−4.9	1.9	−2.9	1.0	.34
ΔPulse transit time (%)	19	−0.0	1.3	−0.1	1.8	.99

Abbreviations: AIx, aortic augmentation index; AP, aortic augmentation; brDBP, brachial diastolic blood pressure; brSBP, brachial systolic blood pressure; cDBP, central diastolic blood pressure; cSBP, central systolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; PWV, pulse wave velocity.

4 | DISCUSSION

Despite small, but significant changes in the calcium homeostasis with increased levels of ionized calcium following milk intake, the detrimental effects observed by some investigators on cardiovascular health after intake of calcium as tablets do not seem to occur after milk intake.

In a prior crossover trial by Billington et al.,[4] postmenopausal women were randomized to treatment with 1000 mg of calcium as citrate or placebo. Office blood pressure and serum calcium concentrations were measured immediately before, and 2, 4 and 6 h after each intervention. The study showed an increase in ionized calcium levels of approximately 0.05 mmol/L and an attenuated postprandial decrease in brSBP following calcium intake compared with placebo. In our study, we found no difference in brSBP from baseline to 4 h after the intervention in either of the two intervention groups. However, our study showed an increase in ionized calcium levels of 0.02 mmol/L 4 h after milk intake compared with water intake. This increase may not be large enough to cause the same negative effects as seen by Billington et al.[4] However, it may be questioned whether an acute rise in calcium levels actually affects cardiovascular health in

an adverse manner. In a study by Burt et al.,[5] administration of a single oral dose of 1000 mg calcium citrate did not increase arterial stiffness (PVW), but decreased AIx, despite increasing ionized calcium levels by 0.1 mmol/L. This raises the question on whether acute calcium-mediated changes in vascular function are associated with CVD.

The Swedish mammography cohort found that a daily calcium intake above 1400 mg was associated with increased death rates from all causes and CVD except for stroke.[3] Thus, the lower calcium intake in the present study may explain why we found no effect on cardiovascular parameters. Five hundred millilitres of semi-skimmed milk contains approximately 600 mg calcium. However, Bristow et al.[14] have shown that 500 mg of calcium in a dairy meal causes a smaller increase in serum calcium than 500 mg of calcium citrate as a tablet in a fasting state, whereas the increase in serum ionized calcium was similar when comparing 500 and 1000 mg of calcium citrate as tablets. This supports that in addition to dose, administration form, as well as indices such as gastric acid secretion/fasting/use of proton pump inhibitors, are of importance, as well as the net effect of milk intake on CVD risk also is influenced by numerous additional factors, including intake of calories etc.

Indeed, most meta-analyses have shown beneficial effects of dairy intake on cardiovascular health with an inverse association between intake and CVD,[15–18] while others have found no consistent association.[19] Therefore, milk as a calcium source could contain protective ingredients counteracting the detrimental effects of calcium. Bioactive peptides and lipid compounds, as well as fatty acids, amino acids and dairy phosphorus, have been proposed as possible beneficial contributors.[15,16,20] Alonso et al.[20] found that a high intake of phosphorus from dairy products, but not from other sources, was associated with lower blood pressure and a lower risk of developing hypertension than a low intake of phosphorus. On the other hand, Foulkes et al.[21] found no effect of calcium and vitamin D_3 fortified milk on blood pressure in healthy Australian men. Even though the angiotensin-converting enzyme-inhibiting effect of casein-derived peptides has been reported,[22,23] we have no clear picture of the mechanism by which milk or dairy products may protect against developing CVD. This underlines the importance of focusing on foods in addition to their nutrients.[15,20]

The effects of dairy intake on cardiovascular health do not seem to occur acutely. Thus, the inverse relationship between dairy intake and CVD seen in previous studies might be owing to long-term intake.

Billington et al.[4] included solely healthy postmenopausal women without hypertension in their study. In our study, eight women reported having hypertension. When we excluded them from our analyses, we found a difference in brSBP between the two intervention groups with a decrease following milk intake and an increase following water intake. This finding points towards a protective effect of milk in spite of its calcium content.

A major strength of this study is its crossover design, which reduces the risk of confounding from interindividual variation. While a potential issue with crossover trials can be that of carry-over effects, no evidence of carry-over effect was detected, suggesting that a washout period of at least 10 days was sufficient. Another strength of this study is its homogenous population of Caucasian postmenopausal women. Accordingly, our results cannot necessarily be generalized to men, younger women or women of different ethnicity.

A limitation to our study is the 4-h gap between the first and the second PWA and PWV measurement. The change in plasma Ca^{2+} and PTH was significantly different between the two interventions after 4 h. This difference seems to be driven more by the first 2 h than the last two. Therefore, it could have been interesting to perform the tonometry as early as after 2 h. However, it is recommended to wait at least 3 h after a meal before measurements.[9]

All participants were vitamin D insufficient at baseline and received a supplementation of 200 µg of cholecalciferol to both interventions as this present study is a part of a larger study investigating the influence of food matrix delivery system on the bioavailability of vitamin D_3. Since the same amount of vitamin D_3 was added to both interventions, we do not believe that this has had any significant influence on our findings. However, the possibility of a different absorption exists.

In conclusion, any potentially harmful as well as beneficial effects on cardiovascular health measurable by PWA and PWV did not occur in spite of acute effects on calcium homeostasis detected within the first 4 h after intake.

Based on this study, there does not appear to be an acute impact on the cardiovascular physiology of milk ingestion.

ACKNOWLEDGEMENTS

The authors would like to thank Klavs Würgler Hansen for lending us his SphygmoCor equipment, and Liv Vernstrøm and Diana Grove-Laugesen for their support and training in the use of this equipment. The authors would also like to thank the staff at the Osteoporosis Clinic, Aarhus University Hospital for their help with DXA scans and blood samples during study days, and Bo Martin Bibby for statistical support. Finally, the authors would like to thank all the participants for their contribution. This study was part of the DFORT project supported by Innovation Fund Denmark (Grant No. 4105-00008B).

CONFLICT OF INTERESTS

Rasmus Espersen and Lars Rejnmark declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Rasmus Espersen http://orcid.org/0000-0001-7464-6785
Lars Rejnmark https://orcid.org/0000-0002-2152-4247

REFERENCES

1. Cormick G, Ciapponi A, Cafferata ML, Belizan JM. Calcium supplementation for prevention of primary hypertension. *Cochrane Database Syst Rev*. 2015;(6):CD010037.
2. Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ*. 2010;341:c3691.
3. 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*. 2013;346:f228.
4. Billington EO, Bristow SM, Gamble GD, et al. Acute effects of calcium supplements on blood pressure: randomised, crossover trial in postmenopausal women. *Osteoporos Int*. 2017;28(1):119-125.
5. Burt MG, Mangelsdorf BL, Srivastava D, Petersons CJ. Acute effect of calcium citrate on serum calcium and cardiovascular function. *J Bone Miner Res*. 2013;28(2):412-418.
6. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55(13):1318-1327.
7. Ben-Shlomo Y, Spears M, Boustred C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol*. 2014;63(7):636-646.
8. Williams B, Mancia G, Spiering W, et al. ESC/ESH guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens*. 2018;36(10):1953-2041.
9. Van Bortel LM, Laurent S, Boutouyrie P, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens*. 2012;30(3):445-448.
10. Berkhout J, Stone JA, Verhamme KM, Danhof M, Post TM. Disease systems analysis of bone mineral density and bone turnover markers in response to alendronate, placebo, and washout in postmenopausal women. *CPT Pharmacometrics Syst Pharmacol*. 2016;5(12):656-664.
11. Operator's Manual SphygmoCor XCEL System v1.
12. PA Harris RT, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.
13. PA Harris RT, Minor BL, Elliott V, et al. REDCap Consortium, The REDCap consortium: building an international community of software partners. *J Biomed Inform*. 2019;95:103208.
14. Bristow SM, Gamble GD, Stewart A, Kalluru R, Horne AM, Reid IR. Acute effects of calcium citrate with or without a meal, calcium-fortified juice and a dairy product meal on serum calcium and phosphate: a randomised cross-over trial. *Br J Nutr*. 2015;113(10):1585-1594.
15. Fontecha J, Calvo MV, Juarez M, Gil A, Martinez-Vizcaino V. Milk and dairy product consumption and cardiovascular diseases: an overview of systematic reviews and meta-analyses. *Adv Nutr*. 2019;10(suppl_2):S164-S189.
16. Soedamah-Muthu SS, Ding EL, Al-Delaimy WK, et al. Milk and dairy consumption and incidence of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. *Am J Clin Nutr*. 2011;93(1):158-171.
17. Sonestedt E, Wirfält E, Wallström P, Gullberg B, Orho-Melander M, Hedblad B. Dairy products and its association with incidence of cardiovascular disease: the Malmö diet and cancer cohort. *Eur J Epidemiol*. 2011;26:609-618.
18. Qin LQ, Xu JY, Han SF, Zhang ZL, Zhao YY, Szeto IM. Dairy consumption and risk of cardiovascular disease: an updated meta-analysis of prospective cohort studies. *Asia Pac J Clin Nutr*. 2015;24(1):90-100.
19. Larsson SC, Crippa A, Orsini N, Wolk A, Michaelsson K. Milk consumption and mortality from all causes, cardiovascular disease, and cancer: a systematic review and meta-analysis. *Nutrients*. 2015;7(9):7749-7763.
20. Alonso A, Nettleton JA, Ix JH, et al. Dietary phosphorus, blood pressure, and incidence of hypertension in the atherosclerosis risk in communities study and the multi-ethnic study of atherosclerosis. *Hypertension*. 2010;55(3):776-784.
21. Foulkes S, Kukuljan S, Nowson CA, Sanders KM, Daly RM. Effects of a multi-modal resistance exercise program and calcium-vitamin D3 fortified milk on blood pressure and blood lipids in middle-aged and older men: secondary analysis of an 18-month factorial design randomised controlled trial. *Eur J Nutr*. 2021;60(3):1289-1299.
22. Bougle D, Bouhallab S. Dietary bioactive peptides: human studies. *Crit Rev Food Sci Nutr*. 2017;57(2):335-343.
23. Marcone S, Belton O, Fitzgerald DJ. Milk-derived bioactive peptides and their health promoting effects: a potential role in atherosclerosis. *Br J Clin Pharmacol*. 2017;83(1):152-162.

How to cite this article: Espersen R, Rejnmark L. The acute effects of milk intake on calcium homeostasis and cardiovascular outcome: a randomized, crossover trial in postmenopausal women. *Clin Endocrinol (Oxf)*. 2022;96:812-818. doi:10.1111/cen.14632