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Relations between dairy product intake and blood pressure: the INTERNational study on MACro/micronutrients and blood Pressure

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Abstract

Background: Epidemiologic evidence suggests that low-fat dairy consumption may lower risk of hypertension. Dairy products may be distinctly linked to health, because of differences in nutritional composition, but little is known about specific nutrients that contribute to the dairy-blood pressure (BP) association, nor to underlying kidney function.

Methods: We examined cross-sectional associations to BP of dairy product intakes, total and by type, from the INTERNational study on MACro/micronutrients and blood Pressure (INTERMAP) including 2694 participants aged 40–59 years from the UK and the USA. Eight BP, four 24-h dietary recalls and two 24-h urine samples were collected during four visits. Linear regression models adjusted for lifestyle/dietary factors to estimate BP differences per 2SD higher intakes of total-and-individual-types of dairy were calculated.

Results: Multivariable linear regression coefficients were estimated and pooled. In contrast to total and whole-fat dairy, each 195 g/1000 kcal (2SD) greater low-fat dairy intake was associated with a lower SBP –2.31 mmHg and DBP –2.27 mmHg. Significant associations attenuated with adjustment for dietary phosphorus, calcium, and lactose, but strengthened with urinary calcium adjustment. Stratification by median albumin–creatinine ratio (ACR; high ACR indicates impaired kidney function) showed strong associations between low-fat dairy and BP in participants with low ACR (SBP: –3.66; DBP: –2.15 mmHg), with no association in participants with high ACR.

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Conflicts of interest

There are no conflicts of interest.

Conclusion: Low-fat dairy consumption was associated with lower BP, especially among participants with low ACR. Dairy-rich nutrients including phosphorus and calcium may have contributed to the beneficial associations with BP.

Keywords

albumin–creatinine ratio; blood pressure; dairy products; dietary factors

BACKGROUND

High blood pressure (BP; SBP of at least 140 mmHg and DBP of at least 90 mmHg) is a major risk factor for myocardial infarction and stroke and remains a significant global health concern [1]. The World Health Organization has classified high BP as the greatest single preventable cause of death [2], due mainly to environmental factors, including diet and other aspects of lifestyle [3]. The landmark Dietary Approaches to Stop Hypertension (DASH) trial was the first study that demonstrated additional SBP and DBP-lowering effects of 2.7 and 1.9 mmHg after 8 weeks of eating three servings of low-fat dairy products per day in 459 adults with elevated BP [4]. Subsequent randomized controlled intervention studies showed inconsistent results on the BP-lowering effects of total dairy products, possibly because of using different dairy products with varied nutritional composition, and to differences in study design (e.g. short trial duration and lack of power) [5–10]. Meta-analyses of prospective studies showed a 16% lower risk of elevated BP and a 3% lower risk of hypertension (HTN) for each 200 g/day greater of total dairy intake, predominantly consumed as low-fat dairy [11,12]. Methodological limitations in these studies include absence of detailed dietary assessment methods [13–16], self-reported risk of HTN, inadequate frequency of BP measurement [13–15], and limited or absent investigation of the role of nutrients in dairy products that may be contributing to lower BP [13–16].

Dairy products are abundant in nutrients, including high-quality protein, calcium, magnesium, and phosphorus, that may contribute to a lower BP and lower risk of HTN [12]. There is, however, limited evidence available on which nutrients are the main contributors to the dairy–BP association. In addition, limited evidence is available on differences in association between low-fat and whole-fat dairy products with BP [17,18]. Also, little is known on the mechanisms by which such dairy foods may improve BP, but it has been suggested that the BP-lowering effects of low-fat dairy products may be attributed to electrolytes such as calcium, potassium, and magnesium [11]. These nutrients may influence vascular resistance, promote vasodilation, and reduce renal retention [11,17,19]. Evidence also suggests that digestive enzymes result in the release of bioactive peptides from dairy protein, which modulate endothelial function and result in vasodilatation [20]. Recent prospective cohort studies found that higher consumption of low/reduced fat dairy foods is associated with a lower risk of chronic kidney disease (CKD) and less annual decline in the estimated glomerular filtration rate (eGFR) [21,22]. However, there is limited evidence on the role of kidney function in the dairy–BP relation.

In the present study, we investigated cross-sectional relations to SBP and DBP of dairy product consumption, total, by type, and by fat content, including influence of individual

and combined nutrients abundant in dairy products using isocaloric multivariable regression models. We also investigated the role of renal function in the dairy–BP associations, demonstrated by urinary albumin (mg/ml)-tocreatinine (mg/ml) ratio (ACR), as high levels of ACR indicate impaired kidney function [23]. We used high-quality dietary data from four multipass 24-h dietary recalls, eight BP measurements, and data from two 24-h urine collections on 4680 men and women from the People’s Republic of China (PRC), Japan, the UK, and the USA samples of the INTERnational study of MACro/micro-nutrients and blood Pressure (INTERMAP).

METHODS

Study population

The INTERMAP included 4680 men and women aged 40–59 years from Japan, PRC, UK, and the USA. Participants were randomly recruited from community and workforce populations between 1996 and 1999, totalling 17 population samples [24]. Collection of dietary and nondietary data underwent extensive quality control with regular local, national, and international checks to ensure completeness and precision. Institutional ethics committees approved the study at all sites, and each participant provided written consent. This observational study was registered at www.clinicaltrials.gov/ as NCT00005271.

Of 4895 individuals initially surveyed, those who did not attend all four study visits ($n = 110$) were excluded; whose dietary data were considered unreliable ($n = 7$); with a total energy intake from any 24-h recall less than 500 or greater than 5000 kcal/day for women and less than 500 or greater than 8000 kcal/day for men ($n = 37$ total); with unavailable urine samples; or with other data, incomplete, missing, or indicating protocol violation ($n = 61$). This resulted in a study population of 4680 participants (2359 men and 2321 women).

Clinic visits

Participants were measured on four clinic visits, two on consecutive days and two on consecutive days approximately 3 weeks later. During each clinic visit, BP was measured twice and 24-h dietary recalls were obtained once. Two-timed 24-h urine samples were collected on the second and fourth visits. Height and body weight were measured on the first and third visits. A health history questionnaire to collect information on medical history, medication intake, smoking, and physical activity was collected on the first visit. Information on vita-min and supplement intakes was on each of the four visits.

Dietary assessment

A standardized multipass method was used to collect four 24-h dietary recalls from each participant as reported previously in detail [25]. Dietary data including foods, beverages, and supplements consumed in the past 24-h, were collected by trained interviewers.

In the USA, all dietary data were transferred to software (the Nutrition Data System (NDS), Nutrition Coordinating Centre (NCC), version 2.91, University of Minnesota) for on-screen coding during an interview [25]. The NDS for Research version 4.01 was used to obtain daily nutrient intakes. For other countries, standard forms were used, coded, and

computerized. Nutrient intake was calculated using country-specific food tables, standardized across countries by the NCC [25,26]. Dietary recall data were compared with urinary excretion data for quality control assessment. Pearson partial correlation coefficients adjusted for sample and sex between dietary and urinary total protein, sodium, and potassium were 0.51, 0.42, 0.55, respectively [25].

We classified sources of dietary dairy products reported by participants as follows. Total dairy products (sum of milk, yogurt, and cheese intakes); by total fat content: whole-fat and low-fat (including fat-free) dairy products; by type: milk, yogurt and cheese; by type and total fat content: whole-fat milk (<3.0% fat), whole-fat yogurt (<3.0% fat), whole-fat cheese (>17% fat), low-fat milk (with <2% fat), low-fat yogurt (with <2% fat), and low-fat cheese(10–17% fat) [27].

The reliability of dairy intake for individuals was estimated using the following formula: $1/[1+(\text{ratio}/2)] \times 100$. The ratio is intra-individual variance divided by inter-individual variance, estimated separately by sex, and combined. The averages of the first two and second two visits were used to account for higher correlation between dietary intakes on consecutive days. This gives an indication of the effect of random error (day-to-day variability) on the associations with BP [28].

Blood pressure

Trained staff measured SBP and DBP using a random-zero sphygmomanometer. All participants refrained from food, drink, smoking, and physical activity for 30 min. They were seated in a quiet room, with their bladder emptied, feet flat on the floor for at least 5 min. BP was measured twice on the right arm at each of four clinic visits, using first and fifth Korotkoff sounds, with a total of eight BP readings.

Other variables

During two visits, weight and height measurements were collected twice, participants without shoes or heavy clothing, total of four readings, and BMI (kg/m^2) was calculated. Lifestyle factors were assessed using interviewer-guided questionnaires including: smoking, education, hours of physical activity, adherence to a weight reduction diet, use of antihypertensive and lipid-lowering drugs, individual and family history of cardiovascular diseases and diabetes mellitus, and daily alcohol intake during the past 7 days.

Urinary data

Two timed 24-h urine specimens were collected between consecutive visits for measurement of urinary albumin, sodium, potassium, creatinine, and other metabolites. Timed collections were started at the research centre on the first and third visits and completed at the centre the next day. Urine aliquots were stored frozen at -20°C before being shipped frozen to the Central Laboratory in Leuven, Belgium, where analyses were performed using strict internal and external quality control. Urinary samples were thawed to room temperature, homogenized manually, and pretested for albumin with Albustix (Bayer, Brussels, Belgium). Urinary albumin was quantitatively determined by means of immunoturbidimetric assay using automated clinical chemistry analyzers (Roche/Hitachi 717; Roche Diagnostics,

Indianapolis, Indiana, USA). The lowest detectable level of albumin was 1 mg/l. Urinary sodium and potassium were measured by means of emission flame photometry; creatinine, by the modified Jaffé method. Individual excretion values were calculated as the product of concentrations in urine and urinary volumes corrected to 24 h. The average of the two excretion values was used.

Statistical analysis

Statistical analyses were applied using SAS software version 9.3 (SAS Institute Inc., Cary, North Carolina, USA). Dietary intake was estimated as a mean of the four dietary recalls. The mean value of eight BP measurements was used in the analyses. Averaged urinary data across the two 24-h urinary collections were used.

Baseline characteristics of participants are presented by median intakes (68 g/1000 kcal) of low-fat dairy products. To assess linearity of associations, participants were categorized into quintiles of dairy intake and *P* for trend was calculated using a generalized linear model adjusted for age, sex, and population sample. Multivariable linear regression analyses were used to examine associations between total, whole-fat, and low-fat dairy products and BP per 2SD of intake. Three sequential models were used, adjusted extensively for potential lifestyle and dietary confounders of the association of dairy products intake and BP, including models mutually adjusted for whole-fat or low-fat dairy, BMI, and urinary sodium excretion.

Additionally, we sequentially investigated the role of individual nutrients abundant in dairy products that may contribute to lower BP including urinary calcium and potassium, dietary magnesium, calcium, phosphorus, lactose, and galactose. We further investigated the role of combinations of these nutrients, as well as several food groups.

Stratified analyses and inclusion of interaction terms showed no evidence for potential effect modification by age, sex, or smoking. Due to observed interaction, we further investigated the association of intakes of types of low-fat dairy products and milk with BP stratified by ACR. Participants with one or both albumin concentration values below the detection limit of the assay (1 mg/l) [29] were excluded; the analyses were carried out for 1027 participants.

We repeated the analyses in three subcohorts with characteristics excluded that might bias the dairy–BP association: a subcohort excluding participants with diagnosed HTN and users of antihypertensive drugs ($n = 1836$), a subcohort of nonhypertensive participants ($n = 1755$), and a subcohort free of major chronic diseases ($n = 1570$). Two-tailed probability values ($P < 0.05$) were considered statistically significant.

RESULTS

Descriptive statistics

Average $\pm$ SD dairy intakes (g/1000 kcal) were negligible in Japanese 12 ± 9 and in Chinese 2 ± 3 populations; analyses were, therefore, performed in Western participants only. Average daily consumption of total, whole-fat, low-fat dairy products was 129 ± 253 , 29 ± 47 , 97 ± 100 g/1000 kcal in the USA and 136 ± 84 , 35 ± 52 , 100 ± 84 g/1000 kcal in the UK. In the UK and

the USA, whole-fat dairy intake was constituted mainly of cheese (69%) and milk (27%), whereas milk (67%) and cheese (23%) contributed predominantly to lowfat dairy product intake (data not shown).

Participants with higher intake of low-fat dairy (>68 g/1000 kcal) more often took dietary supplements, were less likely to smoke, consumed less alcohol, had lower BMI and SBP, less often had a previous diagnosis or family history of cardiovascular disease/diabetes, consumed more whole grains and less meat compared with those with lower intakes of low-fat dairy products (Table 1).

Intakes of whole-fat dairy and low-fat dairy were not correlated ($r = -0.07$). Low-fat dairy intake was positively correlated with intakes of dietary calcium ($r = 0.74$), phosphorus ($r = 0.61$), and lactose ($r = 0.68$). Dietary calcium was strongly correlated with phosphorus ($r = 0.77$) and lactose ($r = 0.67$), and phosphorus was strongly correlated with lactose ($r = 0.53$) (Supplemental Table S1, <http://links.lww.com/HJH/A939>). Weighted average nutritional composition was calculated per 100 g of low-fat and full-fat milk, and results showed that low-fat milk contained similar amounts of calcium, but higher amounts of phosphorus and lactose whenever compared with full-fat milk (Supplemental Table S2, <http://links.lww.com/HJH/A939>). Analyses of linearity showed that participants in the highest quintile of low fat dairy intake (± 231 g/1000 kcal) had more years of education, less intake of alcohol and lower levels of BP and ACR compared with those in the lowest quintile (± 8 g/1000 kcal; Table S3, <http://links.lww.com/HJH/A939>).

Overall, the reliability estimate of total dairy products in the UK and USA was 80%, 79% in the UK and 81% in the USA for whole-fat dairy products, 78% in the UK and 79% in the USA for low-fat dairy products. For types of dairy products, reliability estimates ranged from 77 to 84%.

Associations of dairy product consumption with blood pressure

In Western participants, and after adjustment for lifestyle and dietary factors (Model 3), higher consumption of low-fat dairy products by 195 g/1000 kcal (2SD) was associated with a lower SBP of -2.31 mmHg (95% confidence interval (CI) -3.31 to -1.32) and DBP of -2.27 mmHg (95% CI -3.64 to -0.90) (Table 2). These findings were independent of BMI, urinary excretion of sodium, potassium, magnesium, and dietary galactose. Additional, but separate adjustments for dietary intakes of calcium, phosphorus, and lactose attenuated the association between low-fat dairy products and BP. In contrast, adjustment for urinary calcium excretion strengthened the inverse association of low-fat dairy with SBP (-3.03 mmHg, 95% CI -4.04 to -2.02) and DBP (-2.63 mmHg, 95% CI -3.01 to -1.24), suggesting possible interaction.

We further investigated the influence of combinations of nutrients that attenuated the low-fat dairy–BP association using four models: dietary calcium and lactose; dietary calcium and phosphorus; phosphorus and lactose; dietary calcium, phosphorus, and lactose. The combination of dietary calcium and lactose attenuated the association between low-fat dairy and BP: SBP (-0.07 mmHg, 95% CI -3.86 to 3.72). The combination of dietary calcium and phosphorus showed compatible results, but with less attenuation: SBP (-0.59 mmHg,

95% CI –3.84 to 2.31). The combination of phosphorus and lactose showed similar results to combining dietary calcium and lactose: SBP (0.28 mmHg, 95% CI –3.40 to 3.95). Total and whole-fat dairy product consumption was not related to BP (Table 2).

Associations of dairy product consumption by type and fat content with blood pressure

Low-fat milk consumption higher by 140 g/1000 kcal was associated with lower SBP of –2.62 mmHg (95% CI –3.20 to –1.13) and DBP of –1.91 mmHg (95% CI 3.31 to –0.51) (Table 3). Adjustment for urinary phosphorus, dietary calcium, and dietary lactose attenuated the low-fat dairy–BP association, with comparable findings on the influence of combinations of nutrients. We investigated associations between individual types of dairy products, namely total milk, total cheese, and total yogurt, and BP, but found no significant associations (results not shown). Whenever dairy products were analysed by fat content, no significant findings with BP were found for intakes of whole-fat milk and cheese, and for low-fat cheese and yogurt (Table 3).

Associations of dairy consumption with blood pressure stratified by median albumin–creatinine ratio

Additional adjustment for urinary calcium excretion showed stronger inverse associations with BP of low-fat dairy products and low-fat milk (Tables 2 and 3), suggesting effect modification (P for interaction <0.0001). To further investigate this, we stratified the cohort by the median ACR (0.05 mg/g) (Table 4). In participants with low ACR ($n = 514$), higher intake of low-fat dairy products by (200 g/1000 kcal) was associated with lower levels of SBP by –3.66 mmHg (95% CI –6.54 to mmHg –0.77) and DBP by –2.15 (95% CI –4.15 to –0.13). This inverse relationship was independent of BMI, urinary excretion of sodium and potassium, but attenuated with adjustments for dietary phosphorus and lactose, and their combination. Similar results were found for higher low-fat milk intake and SBP [156 g/1000 kcal: –2.85 mmHg (95% CI –5.68 to –0.01)]. Consumption of low-fat dairy products/milk was not associated with BP in participants with high ACR ($n = 513$).

Associations of dairy intakes with blood pressure in healthy subcohorts

We repeated the regression analyses between low-fat dairy and low-fat milk with BP in subcohorts of participants after excluding characteristics that might bias the relations between dairy intake and BP; three subcohorts were included: a subcohort excluding participants with diagnosed HTN and users of antihypertensive drugs, a subcohort of nonhypertensive participants, and a subcohort free of major chronic diseases. Findings on the association between low-fat dairy with BP and low-fat milk with BP in all three subcohorts were consistent and comparable with the results of the main analyses (Table 5).

DISCUSSION

Main findings in this study was higher intake of low-fat dairy products was associated with lower BP; attributable to the observed inverse association between low-fat milk and BP. These inverse associations were independent of BMI and urinary excretion of sodium and potassium, as markers of diet quality. Associations attenuated with adjustment for dietary phosphorus and calcium but strengthened with urinary calcium adjustment. Sensitivity

analyses for three subcohorts excluding participants with health conditions that might bias associations between low-fat dairy and BP showed similar significant inverse associations. Further investigation of the role of specific nutrients that are most abundant in dairy products suggest that dietary intakes of phosphorus and calcium are key nutrients that may explain these inverse associations with BP. To our knowledge, this is the first such study to include a detailed assessment of the role of dairy-specific nutrients (individual/combined) in explaining the dairy–BP relation.

Furthermore, adjustment for urinary calcium strengthened the inverse associations of low-fat dairy products and milk with BP. We stratified participants by ACR, where high ACR indicates impaired kidney function, and found that inverse relationships of low-fat dairy products and milk with BP were present only in participants with low ACR. This suggests that low-fat dairy and milk intake may protect against renal dysfunction. Evidence on the link between dairy intake, renal dysfunction, and BP is limited. A recent prospective cohort study among 1185 older adults (≥ 65 years) showed that participants in the highest quintile of low/reduced-fat dairy food intake had a 36% reduced odds of 10-year incidence of CKD compared with those in the lowest quintile [21]. Also, analyses of data from the Doetinchem Cohort study including 3798 participants (≥ 65 years) showed that decline in the eGFR was less per year in the middle (198 g/day) and highest (411 g/day) tertiles of low-fat dairy intake [22]. Similarly, results from the Multi-Ethnic Study of Atherosclerosis (MESA) showed that those in the highest versus lowest quartile of low-fat dairy intake had 37% lower odds of microalbuminuria and 13% lower ACR [30]. Previous investigation of the association of calcium excretion and BP in the INTERMAP study showed that altered calcium homeostasis, as demonstrated by increased urinary calcium, is related to higher BP [31]. Altered calcium homeostasis, and thus increased urinary calcium excretion, has been found in individuals with higher salt intakes [32], elevated intestinal calcium absorption, increased bone resorption, and decreased renal tubular calcium reabsorption [33]. A genetic link exists between higher urinary calcium excretion and kidney stone disease in those with familial hypertension [34]. Higher calcium excretion results from changes in renal glomerular membrane permeability and alterations in glomerular hydrostatic pressures and leads to excess albumin excretion, suggesting impaired kidney function [35]. An ACR of 25–355 mg/g in men or 17–250 mg/g in women, known as microalbuminuria, is also an indicator of endothelial dysfunction [23] and is common in diabetic and hypertensive individuals [36]. As increased oxidative stress and inflammation are pathways to renal dysfunction [37], these findings suggest that low-fat dairy products may protect against oxidative stress and endothelial dysfunction, and thereby may reduce the risk of developing CKD [38].

Our results showed total and whole-fat dairy product consumption were not related to BP. These findings are compatible with previous systematic reviews of prospective cohort studies showing no association of total dairy intake with CVD mortality [39,40], but an inverse association with risk of nonfatal CVD [41]. With regard to HTN, meta-analyses of prospective cohort studies with 45 000 and 57 000 participants reported a 3% risk reduction of HTN for each 200 g/day increase of total dairy intake, and a 16% risk reduction of elevated BP [11,12], whereas high-fat dairy intake was not associated with the risk of HTN or elevated BP suggesting the inverse association is explained by lowfat dairy intake [11,12].

Previously reported cross-sectional findings of dairy intake and BP, however, showed either inverse [42,43] or no associations [13–16]. The inconsistent results may be explained by methodological differences such as absence of detailed urinary assessment methods [13–16] as most studies calculated dairy intake from single food frequency questionnaires [42,44–46], self-reported risk of HTN [13–16], and the frequency of BP measurements was typically low [13–15]. Most cross-sectional studies did not distinguish different associations for low-fat and whole-fat dairy [17,47] or to extensively investigate the role of dairy-rich nutrients [11,12]. The results of the present study are derived from eight averaged BP measurements and four high-quality 24-h multipass dietary recalls, collected over four visits. In comparison to other studies, we found stronger correlations between dietary and urinary variables from two timed 24-h urinary collections [48]. The availability of urinary data allowed us to adjust multivariable models for objective measures of sodium, potassium, and calcium, which in most other studies is not available. In addition, Willet [49] recently concluded that another limitation is that the two fundamental concepts in nutritional epidemiology, the isocaloric principle and the importance of substitution were not addressed in primary studies on the role of dairy product intake on cardiovascular health. We addressed this limitation by applying isocaloric models in all our analyses, and adjusted for whole-fat dairy intake whenever considering low-fat dairy intake, and low-fat dairy intake was included in the multivariable model whenever considering whole-fat dairy.

Our comprehensive assessment of the role of nutrients abundant in dairy products showed a number of nutrients attenuated the dairy–BP association, with the attenuation strongest when adding lactose to calcium or phosphorus, suggesting that lactose is an important nutrient in this analysis. We analysed the nutritional composition per 100 g of full-fat and low-fat milk, and results showed that low-fat milk contains higher amounts of phosphorus compared with full-fat milk, which may explain our findings. It should, however, be noted that inclusion of these nutrients in one model may have resulted in over-adjustment given the high inter-correlations. These nutrients are beneficial in that they work in combination with sodium and magnesium to regulate ionic balance and vascular resistance, promote vasodilation, and reduce renal retention [11,17].

Limited information is available on the potential mechanisms by which low-fat dairy products may improve BP [17,47]. Evidence suggests that digestive enzymes result in the release of bioactive peptides from dairy protein, which modulate endothelial function and result in vasodilatation [20]. The Maine Syracuse Longitudinal Study also suggested an inverse association between measures of arterial stiffness, as assessed by pulse wave velocity, and dairy product intake [50]. Possible relative benefits of consuming low-fat dairy compared with whole-fat dairy include decreased intake of saturated fatty acids that are associated with greater ACR in diabetic individuals, endothelial dysfunction and inflammation, and atherosclerosis [51]. Furthermore, certain dairy products may be distinctly linked to health benefits because of their unique food matrix [18], as a dietary pattern high in low-fat dairy is rich in nutrients that may work synergistically in lowering BP [52]. Low-fat dairy intake may also be an indicator of other healthy eating patterns and lifestyle behaviours that may independently impact BP and CVD risk.

Limitations of our study include its cross-sectional design, regression dilution bias related to imprecise measures, and the possibility of residual confounding. However, extensive efforts were applied to minimize those limitations (continuous observer training, repeated measurements of BP, standardized methods in dietary collection and BP measures, open-end questions, and on-going quality control). In addition, although four multipass 24-h dietary recalls were performed, the dietary data may not be representative of a participant's long-term habitual intake. Finally, although significant, when participants were stratified by median ACR, the smaller sample size in the stratified groups may have led to reduction of statistical power, as indicated by the wider confidence intervals, suggesting that larger scale studies are warranted.

In summary, in this cross-sectional study, higher intake of low-fat dairy products was associated with lower BP, especially among participants with low ACR. Data on the influence of dairy and differential associations by low-fat and high-fat dairy on BP and renal function are limited, emphasizing the need for confirmation from intervention studies and large-scale, prospective population studies with high-quality dietary data, urinary, and BP measurements.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ACR	albumin–creatinine ratio
BP	blood pressure
CI	confidence interval
CKD	chronic kidney disease
DASH	Dietary Approaches to Stop Hypertension

eGFR estimated	glomerular filtration rate
HTN	hypertension
INTERMAP	the INTERnational study on MACro/micronutrients and blood Pressure
NCC	Nutrition Coordinating Centre
NDS	Nutrition Data System
PRC	People's Republic of China

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TABLE 1.

Baseline characteristics of the INTERnational study on MACro/micronutrients and blood Pressure participants from Western countries stratified by median intake of low-fat dairy products (68 g/1000 kcal) ^a

Variable	Less than 68 g	At least 68 g
N	1354	1342
Men (n)	54.2 (734)	47.3 (635)
Age (years)	49.0 (5.4)	49.3 (5.4)
Education (years)	14.4(3.2)	14.7(3.2)
Current smokers (%)	20.2 (274)	13.6(182)
Alcohol intake (g/day)	9.6 (17.6)	7.2(12.1)
Engagement in moderate and heavy physical activity (hours/day)	3.2 (3.2)	2.9 (2.9)
Taking dietary supplements (%)	45.2 (612)	53.3 (715)
BMI (kg/m ²)	29.1 (6.0)	28.2 (5.4)
SBP(mmHg)	120.1 (14.3)	117.8 (13.7)
DBP (mmHg)	74.5 (10.0)	73.8 (9.6)
History of cardiovascular disease or diabetes mellitus (%)	15.2 (206)	14.2 (191)
Use of antihypertensive treatment (%)	22.9(310)	17.8(239)
Family history of hypertension (%)	65.6 (888)	63.0 (845)
Adhering to energy restricted diet (%)	15.8(214)	21.8(193)
Total energy intake (kcal/24 h)	2264(711)	2196 (662)
Total carbohydrates (% kcal)	48(9)	50(8)
Total sugar (% kcal)	25(9)	26(7)
Lactose (% kcal)	2(2)	4(3)
Galactose (% kcal)	0.1 (0.2)	0.1 (0.2)
Total dietary fiber (g/1000 kcal)	9(4)	10(4)
Total protein (% kcal)	15(3)	16(3)
Animal protein (% kcal)	10(3)	11 (3)
Vegetable protein (% kcal)	5(2)	5(2)
Total fat (% kcal)	34(7)	32(7)
Dietary calcium (g/1000 kcal)	453 (142)	453 (142)
Dietary phosphorus (g/1000 kcal)	549 (94)	659(133)
Food group intakes (g/1000kcal)		
Total dairy products	68 (75)	185 (198)
Total milk	35 (58)	119(120)
Total cheese	20 (20)	35 (29)
Total yogurt	13(23)	31 (82)
Whole-fat dairy products	39 (52)	28 (34)
Whole-fat milk	19 (41)	8(22)
Whole-fat cheese	14(19)	11 (30)
Whole-fat yogurt	6(16)	9(12)

Variable	Less than 68 g	At least 68 g
Low-fat dairy products	29(19)	1 57 (94)
Low-fat milk	16(14)	111 (78)
Low-fat cheese	6(16)	24 (33)
Low-fat yogurt	7(14)	22(19)
Whole grains	25 (32)	33 (32)
Refined grains	1 62 (74)	153 (69)
Vegetables	163 (88)	156 (88)
Fruit	87 (96)	99 (90)
Fish and shellfish	16(22)	14(24)
Meat	141 (64)	118 (62)
Urinary sodium (mmol/24h)	162.5 (60.6)	156.2 (55.4)
Urinary calcium (mmol/24h)	3.9(2.1)	4.4 (2.2)
Urinary potassium (mmol/24h)	54.9 (19.8)	64.4(21.5)
Urinary magnesium (mmol/24h)	4.0(1.5)	4.3(1.6)
N^b	475	552
Urinary volume (dl)	20.8(8.8)	21.7(9.1)
24-h albumin excretion (g)	47.1 (241.8)	41.7 (299.8)
Albumin concentration (g/dl)	2.3 (10.0)	2.0 (12.6)
Creatinine concentration (mg/dl)	6.7 (3.2)	6.3 (2.9)
Albumin-creatinine ratio (mg/g)	0.4(2.2)	0.4 (2.6)

^aMean (SD) or percentage (number).

^bExcluding those with one or both albumin concentration values below the detection limit of the assay (1 mg/l).

TABLE 2.

Estimated mean difference in blood pressure associated with 2SD higher intakes of total, whole-fat, and low-fat dairy products in Western International study on MAcro/micronutrients and blood Pressure participants ($n = 2696$)^a

Model	SBP		DBP	
	Difference (95% CI)	P	Difference (95% CI)	P
	mmHg		mmHg	
Total dairy products				
Model 1	-0.33 (-1.47 to 0.81)	0.57	-0.30 (-1.08 to 0.47)	0.44
Model 2	-0.13 (-1.21 to 0.95)	0.82	-0.06 (-0.81 to 0.68)	0.87
Model 3a	-0.24 (-1.28 to 0.80)	0.65	-0.13 (-0.85 to 0.60)	0.73
Whole-fat dairy products				
Model 1	-0.83 (-1.84 to 1.18)	0.42	-0.59 (-1.95 to 0.77)	0.40
Model 2	-0.43 (-1.53 to 1.49)	0.66	-0.28 (-1.60 to 1.04)	0.68
Model 3	-0.67 (-1.60 to 1.28)	0.50	-0.41 (-1.74 to 0.93)	0.55
Model 3a	-0.64 (-1.51 to 1.24)	0.51	-0.41 (-1.72 to 0.89)	0.54
Low-fat dairy products				
Model 1	-3.92 (-4.97 to -2.87)	<0.0001	-3.20 (-4.58 to -1.81)	<0.0001
Model 2	-2.13 (-3.11 to -1.15)	0.002	-2.20 (-3.56 to -0.84)	0.002
Model 3	-2.31 (-3.31 to -1.32)	0.001	-2.27 (-3.64 to -0.90)	0.001
Model 3a	-1.91 (-3.84 to -0.98)	0.003	-2.07 (-3.40 to -0.72)	0.003
Model 3b	-1.24 (-3.61 to -0.86)	0.001	-2.23 (-3.61 to -0.86)	0.001
Model 3c	-3.03 (-4.04 to -2.02)	0.0001	-2.63 (-3.01 to -1.24)	0.0002
Model 3d	-2.77 (-3.84 to -0.96)	0.01	-1.95 (-3.38 to -0.52)	0.007
Model 3e	-3.27 (-3.28 to -1.26)	0.001	-2.18 (-3.56 to -0.80)	0.002
Model 3f	-0.92 (-3.77 to 1.92)	0.52	-1.59 (-3.55 to 0.37)	0.11
Model 3g	-1.58 (-3.10 to 0.93)	0.21	-0.98 (-2.72 to 0.74)	0.26
Model 3h	-0.34 (-3.80 to 3.11)	0.85	-0.67 (-3.05 to 1.71)	0.58
Model 3i	-3.01 (-3.02 to -1.00)	0.003	-2.19 (-3.57 to -0.81)	0.002
Model 3j	-0.07 (-3.86 to 3.72)	0.97	-0.54 (-3.16 to 2.07)	0.68
Model 3k	-0.59 (-3.48 to 2.31)	0.69	-1.17 (-3.16 to 0.82)	0.25
Model 3l	0.28 (-3.40 to 3.95)	0.88	-0.20 (-2.72 to 2.33)	0.88

Model	SBP		DBP	
	Difference (95% CI)	P	Difference (95% CI)	P
	mmHg		mmHg	
Model 3m	0.28 (−3.40 to 3.95)	0.88	−0.20 (−2.72 to 2.33)	0.89
Model 3n	−2.14 (−3.51 to −0.76)	0.002	−2.13 (−3.51 to −0.76)	0.002

Model 1 was adjusted for age (years), sex (male or female), and population sample (i.e. centre). Model 2 was adjusted as Model 1 with total energy intake (kcal/24 h), alcohol intake (g/24 h), smoking (never, former, or current), years of education (years completed), physical activity during leisure time (a lot, moderate, little, or none), dietary supplement use (yes or no), adherence to a special diet (yes or no), history of cardiovascular disease or diabetes mellitus (yes or no), family history of cardiovascular disease (yes or no), and use of medications for CVD/high BP (yes or no). Model 3 was adjusted as Model 2 with either (whole-fat or low-fat dairy products) (g/1000 kcal). Models 3a–3n were adjusted as Model 3 but additionally for: Model 3a: BMI, Model 3b: urinary sodium (mmol/24 h), Model 3c: urinary calcium (mmol/24 h), Model 3d: urinary potassium (mmol/24 h), Model 3e: urinary magnesium (mmol/24 h), Model 3f: dietary calcium (g/1000 kcal), Model 3g: dietary phosphorus (g/1000 kcal), Model 3h: dietary lactose (% kcal), Model 3i: dietary galactose (% kcal), Model 3j: dietary calcium and lactose (% kcal), Model 3k: dietary calcium and phosphorus (g/1000 kcal), Model 3l: phosphorus and lactose (% kcal), Model 3m: dietary calcium, phosphorus (g/1000 kcal), and lactose (% kcal), Model 3n: meat, refined grains, and whole grains.

^a2SD (g/1000 kcal) total dairy products = 450, whole-fat dairy products = 96, low-fat dairy products = 195.

TABLE 3.

Estimated mean difference in blood pressure associated with 2SD higher intakes of individual dairy products in Western INTERnational study on MAcro/
micronutrients and blood Pressure participants ($n = 2696$)^a

Model	SBP		DBP	
	Difference (95% CI)	P	Difference (95% CI)	P
	mmHg		mmHg	
Whole-fat milk				
Model 1	-1.05 (-3.01 to 0.92)	0.30	-0.55 (-1.86 to 0.77)	0.42
Model 2	-0.63 (-2.51 to 1.24)	0.51	-0.24 (-1.52 to 1.05)	0.72
Model 3	-1.33 (-3.32 to 0.64)	0.19	-0.53 (-1.89 to 0.83)	0.45
Model 3c	-1.35 (-3.54 to 0.84)	0.23	-0.57 (-2.08 to 0.93)	0.46
Low-fat milk				
Model 1	-3.70 (-4.21 to -2.20)	<0.0001	-2.69 (-4.05 to -1.34)	<0.0001
Model 2	-2.96 (-3.88 to -1.04)	0.002	-1.97 (-3.23 to -0.65)	0.003
Model 3	-2.62 (-3.20 to -1.13)	0.002	-1.91 (-3.31 to -0.51)	0.007
Model 3a	-2.17 (-3.59 to -0.66)	0.01	-1.63 (-3.00 to -0.26)	0.02
Model 3b	-2.90 (-3.09 to -1.03)	0.003	-1.86 (-3.26 to -0.46)	0.009
Model 3c	-3.64 (-3.78 to -1.71)	0.0003	-2.22 (-3.61 to -0.82)	0.002
Model 3d	-2.76 (-3.85 to -0.66)	0.01	-1.66 (-3.10 to -0.22)	0.02
Model 3e	-3.11 (-3.16 to -1.08)	0.003	-1.83 (-3.23 to -0.43)	0.01
Model 3f	-2.39 (-3.15 to 0.36)	0.09	-1.93 (-3.83 to -0.04)	0.05
Model 3g	-2.20 (-3.65 to 0.25)	0.08	-0.99 (-2.68 to 0.68)	0.24
Model 3h	-1.52 (-3.92 to 1.88)	0.38	-0.85 (-3.18 to 1.49)	0.48
Model 3i	-2.05 (-3.08 to -1.02)	0.003	-1.88 (-3.28 to -0.48)	0.008
Model 3j	-2.71 (-3.80 to 1.35)	0.19	-1.21 (-4.01 to 1.60)	0.40
Model 3k	-2.05 (-3.88 to 0.78)	0.16	-1.45 (-3.39 to 0.49)	0.14
Model 3l	-1.20 (-3.94 to 2.54)	0.53	-0.35 (-2.91 to 2.22)	0.79
Model 3m	-2.37 (-3.50 to 1.80)	0.26	-0.88 (-3.72 to 1.95)	0.54
Model 3n	-2.74 (-3.78 to -0.70)	0.009	-1.64 (-3.04 to -0.23)	0.02
Whole-fat cheese				
Model 1	3.30 (-5.39 to -1.21)	0.001	-0.06 (-0.82 to 0.70)	0.88

Model	SBP		DBP	
	Difference (95% CI)	P	Difference (95% CI)	P
	mmHg		mmHg	
Model 2	0.35 (−0.61 to 1.52)	0.39	−0.09 (−0.82 to 0.64)	0.81
Model 3	0.60 (−0.97 to 2.57)	0.22	−0.36 (−1.57 to 0.86)	0.57
Model 3g	0.43 (−0.96 to 2.58)	0.71	−0.35 (−1.57 to 0.87)	0.57
Low-fat cheese				
Model 1	−2.06 (−4.13 to 0.01)	0.05	−1.52 (−2.93 to −0.13)	0.03
Model 2	−0.47 (−1.37 to 1.83)	0.63	−0.71 (−2.06 to 0.65)	0.31
Model 3	−0.40 (−1.68 to 2.24)	0.71	−0.11 (−1.55 to 1.32)	0.88
Model 3g	−0.81 (−1.34 to 2.96)	0.46	−0.25 (−1.23 to 1.73)	0.73

CI, confidence interval.

^a2SD (g/1000 kcal) whole-fat milk = 66, low-fat milk = 140, whole-fat cheese = 64, low-fat cheese = 100. Adjusted as footnote in Table 2, except Model 3, where it was adjusted variables in Model 2 with either (whole-fat milk or low-fat , milk, whole-fat or low-fat cheese, whole-fat or low-fat yogurt) (g/1000 kcal).

Estimated mean difference in blood pressure associated with 2SD higher intakes of low-fat dairy products and low-fat milk stratified by median albumin-to-creatinine ratio in Western INTERnational study on Macro/micronutrients and blood Pressure participants ($n = 1027$)^a

TABLE 4.

Model	SBP		DBP	
	Difference (95% CI)	P	Difference (95% CI)	P
Low-fat dairy products				
Albumin-creatinine ratio 0.05 mg/g or less ($n = 514$)				
Model 1	-4.21 (-7.66 to -1.70)	0.002	-2.57 (-4.57 to -0.58)	0.01
Model 2	-3.58 (-6.46 to -0.70)	0.02	-2.06 (-4.09 to -0.04)	0.05
Model 3	-3.66 (-6.54 to -0.77)	0.01	-2.15 (-4.15 to -0.13)	0.04
Model 3a	-3.13 (-5.90 to -0.37)	0.03	-1.82 (-3.78 to 0.13)	0.07
Model 3b	-3.64 (-6.51 to -0.76)	0.01	-2.14 (-5.07 to 0.06)	0.04
Model 3c	-2.78 (-5.84 to 0.28)	0.08	-1.84 (-3.99 to 0.30)	0.09
Model 3e	-3.65 (-6.56 to -0.75)	0.01	-2.09 (-4.13 to -0.06)	0.04
Model 3f	-1.47 (-5.74 to 2.79)	0.50	-1.61 (-4.60 to 1.38)	0.29
Model 3g	-3.75 (-7.42 to -0.08)	0.05	-2.51 (-5.07 to 0.06)	0.06
Model 3h	-0.55 (-6.91 to 5.81)	0.87	-0.91 (-5.37 to 3.54)	0.69
Model 3i	-3.49 (-6.37 to -0.61)	0.02	-2.05 (-4.07 to -0.03)	0.05
Model 3j	-0.34 (-6.72 to 6.04)	0.92	-0.88 (-5.36 to 3.58)	0.70
Model 3k	-1.85 (-6.21 to 2.52)	0.41	-1.86 (-4.92 to 1.21)	0.24
Model 3l	-0.69 (-7.10 to 5.72)	0.83	-1.07 (-5.56 to 3.42)	0.64
Model 3m	-0.58 (-6.99 to 5.82)	0.86	-1.04 (-5.54 to 3.45)	0.65
Model 3n	-3.81 (-6.87 to -0.75)	0.02	-2.25 (-4.40 to -0.10)	0.04
Albumin-creatinine ratio greater than 0.05 mg/g ($n = 513$)				
Model 1	-3.14 (-6.26 to -0.02)	0.05	-2.92 (-4.91 to -0.92)	0.004
Model 2	-2.12 (-5.25 to 1.01)	0.19	-2.29 (-4.29 to -0.29)	0.03
Model 3	-2.07 (-5.22 to 1.08)	0.20	-2.17 (-4.18 to -0.15)	0.04
Model 3a	-2.24 (-5.36 to 0.89)	0.16	-2.21 (-4.23 to -0.20)	0.03
Low-fat milk				
Albumin-creatinine ratio 0.05 mg/g or less ($n = 514$)				

Model	SBP		DBP	
	Difference (95% CI)	P	Difference (95% CI)	P
	mmHg		mmHg	
Model 1	-3.57 (-6.41 to -0.73)	0.01	-1.68 (-3.58 to 0.22)	0.08
Model 2	-2.95 (-5.66 to -0.25)	0.03	-1.34 (-3.24 to 0.55)	0.17
Model 3	-2.85 (-5.68 to -0.01)	0.05	-1.05 (-3.03 to 0.93)	0.30
Model 3a	-2.78 (-5.49 to -0.07)	0.04	-1.01 (-2.93 to 0.90)	0.30
Model 3b	-2.73 (-5.56 to 0.10)	0.06	-1.01 (-2.99 to 0.98)	0.32
Model 3c	-2.05 (-5.01 to 0.91)	0.18	-0.75 (-2.82 to 1.33)	0.48
Model 3e	-2.83 (-5.67 to 0.01)	0.05	-1.02 (-3.01 to 0.97)	0.32
Model 3f	-0.90 (-4.64 to 2.84)	0.64	-0.61 (-3.24 to 2.02)	0.65
Model 3g	-2.78 (-6.14 to 0.59)	0.11	-1.24 (-3.59 to 1.11)	0.30
Model 3h	0.08 (-5.57 to 5.73)	0.98	0.31 (-2.82 to 1.33)	0.88
Model 3i	-2.81 (-5.64 to 0.01)	0.05	-1.03 (-3.01 to 0.95)	0.31
Model 3j	0.36 (-5.31 to 6.03)	0.90	0.35 (-3.63 to 4.32)	0.86
Model 3k	-1.18 (-5.01 to 2.65)	0.55	-0.78 (-3.47 to 1.92)	0.57
Model 3l	0.01 (-5.70 to 5.72)	1.00	0.19 (-3.81 to 4.19)	0.93
Model 3m	0.15 (-5.55 to 5.86)	0.96	0.22 (-3.79 to 4.22)	0.91
Model 3n	-2.73 (-5.62 to 0.16)	0.07	-1.04 (-3.07 to 0.99)	0.32
Albumin-creatinine ratio greater than 0.05 mg/g (n = 513)				
Model 1	-2.26 (-5.46, 0.94)	0.17	-2.85 (-4.90, -0.81)	0.01
Model 2	-1.24 (-4.40 to 1.92)	0.44	-2.10 (-4.12 to -0.08)	0.04
Model 3	-0.73 (-4.28 to 2.82)	0.69	-2.35 (-4.63 to -0.08)	0.04
Model 3a	-1.06 (-4.59 to 2.46)	0.55	-2.46 (-4.73 to -0.19)	0.03

CI, confidence interval.

^aMedian albumin-creatinine ratio = 0.05 (mg/g), 2SD (g/1000 kcal) low-fat dairy products = 200, low-fat milk = 156. Adjusted as footnote in Table 2, except Model 3 in low-fat milk, where it was adjusted for variables in Model 2 with whole-fat milk (g/1000 kcal).

TABLE 5.

Estimated mean difference in blood pressure associated with 2SD higher intakes of low-fat dairy products and low-fat milk in Western INTERnational study on MAcro/micronutrients and blood Pressure subcohorts

Model	SBP		DBP	
	Difference (95% CI)	P	Difference (95% CI)	P
	mmHg		mmHg	
Excluding participants with a diagnosis of hypertension and users of antihypertensive drugs (<i>n</i> = 1836) ^a				
Low-fat dairy products				
Model 1	-3.61 (-5.68 to -1.55)	0.001	-2.11 (-3.60 to -0.63)	0.005
Model 2	-2.60 (-4.68 to -0.53)	0.01	-1.53 (-3.03 to -0.03)	0.05
Model 3	-2.61 (-4.71 to -0.53)	0.02	-1.61 (-3.12 to -0.10)	0.04
Model 3c	-3.20 (-4.30 to -1.09)	0.003	-1.99 (-3.50 to -0.44)	0.01
Low-fat milk				
Model 1	-3.53 (-4.69 to -1.52)	0.001	-1.92 (-3.35 to -0.49)	0.01
Model 2	-2.68 (-3.68 to -0.68)	0.01	-1.42 (-2.85 to 0.02)	0.05
Model 3	-3.08 (-4.22 to -0.94)	0.01	-1.60 (-3.15 to -0.06)	0.04
Model 3c	-3.53 (-4.66 to -1.37)	0.001	-1.88 (-3.41 to -0.31)	0.02
Nonhypertensive participants (<i>n</i> = 1755) ^b				
Low-fat dairy products				
Model 1	-2.11 (-3.98 to -0.25)	0.03	-1.33 (-2.72 to -0.11)	0.07
Model 2	-1.18 (-3.05 to -0.11)	0.04	-0.76 (-2.18 to 0.36)	0.28
Model 3	-1.13 (-3.05 to -0.08)	0.04	-0.45 (-1.25 to 0.36)	0.28
Model 3c	-1.67 (-2.54 to -0.31)	0.03	-0.59 (-1.40 to -0.23)	0.04
Low-fat milk				
Model 1	-2.44 (-3.22 to -0.65)	0.01	-1.44 (-2.79 to -0.09)	0.04
Model 2	-2.38 (-3.28 to -0.42)	0.02	-0.97 (-2.33 to 0.38)	0.16
Model 3	-2.34 (-3.25 to -0.44)	0.02	-1.37 (-2.82 to 0.08)	0.06
Model 3c	-2.70 (-3.61 to 0.79)	0.01	-1.60 (-3.05 to -0.15)	0.03
Excluding participants with cardiovascular diseases or diabetes mellitus (<i>n</i> =1570) ^c				
Low-fat dairy products				
Model 1	-2.67 (-3.50 to -0.86)	0.005	-1.31 (-2.70 to 0.13)	0.07

Model	SBP		DBP	
	Difference (95% CI)	P	Difference (95% CI)	P
	mmHg		mmHg	
Model 2	-1.82 (-3.78 to -0.10)	0.04	-0.86 (-2.30 to 0.59)	0.25
Model 3	-1.84 (-3.77 to -0.13)	0.04	-0.99 (-2.49 to 0.48)	0.18
Model 3c	-2.31 (-3.30 to -0.32)	0.02	-1.33 (-2.80 to 0.14)	0.07
Low-fat milk				
Model 1	-2.66 (-3.52 to -0.81)	0.005	-1.20 (-2.57 to 0.18)	0.09
Model 2	-1.96 (-3.82 to -0.11)	0.04	-0.91 (-2.30 to 0.48)	0.20
Model 3	-2.34 (-3.35 to -0.37)	0.02	-1.12 (-2.60 to 0.37)	0.14
Model 3c	-2.68 (-3.67 to -0.69)	0.01	-1.35 (-2.84 to 0.14)	0.07

CI, confidence interval.

^a₂SD (g/1000 kcal) low-fat dairy products = 204, low-fat milk = 136.

^b₂SD (g/1000 kcal) low-fat dairy products = 206, low-fat milk = 136.

^c₂SD (g/1000 kcal) low-fat dairy products = 202, low-fat milk = 132. Adjusted as footnote in Table 2, except Model 3 in low-fat milk, where it was adjusted for variables in Model 2 with whole-fat milk (g/1000 kcal).