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# Dairy consumption and circulating levels of inflammatory markers among Iranian women

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## Abstract

*Objective:* Although recent studies have shown an inverse relationship between dairy consumption and metabolic abnormalities, we are aware of no study evaluating the association between dairy consumption and circulating levels of inflammatory markers. The current study was undertaken to assess the association between the consumption of high-fat and low-fat dairy products and circulating levels of inflammatory markers among Tehrani women aged 40–60 years.

*Design:* In a cross-sectional study of 486 apparently healthy women aged 40–60 years, we assessed usual dietary intakes by means of an FFQ. Anthropometric measurements were made and fasting blood samples were taken for measuring inflammatory markers.

*Results:* The reported mean (SD) daily intake of low- and high-fat dairy consumption was 85 (SD 23) and 101 (SD 29) g/d, respectively. After control for age, BMI, waist circumference and other potential confounders, low-fat dairy consumption was inversely associated with C-reactive protein ($\beta = -0.04$), IL-6 ($\beta = -0.02$) and soluble vascular cell adhesion molecule-1 ($\beta = -0.06$); with further adjustment for dietary intakes, the associations remained significant just for soluble vascular cell adhesion molecule-1 ($\beta = -0.03$). High-fat dairy intake was positively associated with log-transformed values of serum amyloid A ($\beta = 0.08$) and soluble vascular cell adhesion molecule-1 ($\beta = 0.05$), both before and after adjustment for all potential confounding variables. No overall significant associations were found between total dairy consumption and inflammation.

*Conclusions:* The current study indicates an independent relationship between high-fat as well as low-fat dairy consumption, not total dairy intake, and some markers of inflammation and endothelial dysfunction. Further studies are required to identify responsible components of dairy products and related mechanisms of action.

**Keywords**
Dairy consumption
Inflammation
Cardiovascular risk factors
Endothelial dysfunction

Inflammation has been postulated to have a pivotal role in the pathogenesis of many chronic conditions, such as obesity, CVD, diabetes and metabolic syndrome[1–5]. Harvard investigators[6] have introduced inflammation as a key driver of these chronic conditions. Circulating levels of inflammatory markers such as C-reactive protein (CRP) and TNF-$\alpha$ are considered to be involved in the development of ischaemic events[7,8]. Moreover, recent evidence supports the association between inflammation and endothelial dysfunction[9]. Overall, these data indicate that identifying determinants of markers of systemic inflammation and endothelial dysfunction is of great importance in the field of cardiology.

The exact underlying factors of elevated circulating levels of inflammatory markers remain to be identified. Although recent studies have reported obesity[10], smoking[11], hypercholesterolaemia[12] and physical inactivity[13] as major predictors of inflammation, data on dietary determinants of circulating levels of inflammatory biomarkers are scarce. Moreover, limited data available in this field have mainly focused on nutrients[14–17] or dietary patterns[18–20], and little attention has been given to foods, particularly dairy products. Some investigations have reported the relationship between consumption of vegetable oils[21], red meat[22], fruits and vegetables[23,24] and soya[25] with inflammatory biomarkers, but we are aware of no study evaluating the association between dairy consumption and circulating levels of inflammatory markers. On the other hand, recent studies have shown an inverse relationship between dairy consumption and metabolic abnormalities, such as obesity[26–28], diabetes[29,30], metabolic syndrome[31,32] and insulin resistance[33], but the mechanisms have not been fully understood. Dairy products are a rich

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source of Ca; a nutrient seems to be responsible for dairy's beneficial effect[34]. Supplementation with Ca and vitamin D, two major ingredients of dairy products, for 3 years could affect glycaemia and insulin resistance, but not inflammatory markers, among older adults[35]. Besides Ca, dairy products contain other nutrients, such as conjugated linoleic acid (CLA), riboflavin and high-quality proteins, that may affect systemic inflammatory levels[36,37]. The current study was, therefore, undertaken to assess the association between consumption of high- and low-fat dairy products and circulating levels of inflammatory markers among female teachers aged 40–60 years living in Tehran.

## Subjects and methods

### *Subjects*

The current cross-sectional study was conducted among a representative sample of female teachers aged 40–60 years living in Tehran selected by a multistage cluster random sampling method. A random sample of 583 female teachers were invited to participate in the current study and 521 women agreed to do so. Participants with a prior history of CVD, diabetes, cancer and stroke were excluded because of possible changes in diet. We also excluded those with possible inflammation. We also excluded subjects who had left >70 items blank on the FFQ, who reported a total daily energy intake outside the range of 3347·2–17 522·8 kJ (800–4200 kcal) and those taking medications that would affect serum lipoprotein, blood pressure and carbohydrate metabolism. These exclusions resulted in 486 subjects for present analysis. All participants provided an informed written consent.

### *Assessment of dietary intake*

Usual dietary intake was assessed using a validated 168-item semi-quantitative FFQ[28,31]. Briefly, our validation study included randomly chosen participants of 132 subjects (not included in the current study) by comparing nutrient consumption determined using responses to the FFQ on two occasions 1 year apart. Comparative validity was determined by comparison with intake estimated from the average of twelve 24 h dietary recalls (one for each month of the year). The findings from the current validation study can be found elsewhere[28,31]. We concluded from the validation study that the FFQ provides reasonably valid and reliable measures of the average long-term dairy intake.

All the questionnaires were administered by a trained dietitian. The FFQ consisted of a list of foods with standard serving sizes commonly consumed by Iranians. Participants were asked to report their frequency of consumption of a given serving of each food item during the previous year on a daily (e.g. bread), weekly (e.g. rice and meat) or monthly (e.g. fish) basis. The reported frequency for each food item was then converted to a daily intake. Portion sizes of consumed foods were converted to grams using household measures. Total energy intake was calculated by summing up energy intakes from all foods[38].

We considered low-fat (<2 %) dairy as skim or low-fat milk and low-fat yoghurt. High-fat dairy (≥2 %) was considered as high-fat milk, whole milk, chocolate milk, cream, high-fat yoghurt, cream yoghurt, cream cheese, other cheeses and ice cream. Before performing separate analysis for low- and high-fat dairy, we considered the total dairy intake as an independent variable. But, we did not reach significant finding for any of the inflammatory markers. So, decided to separately analyse for low- and high-fat dairy intake.

### *Assessment of biomarkers*

Detailed information about the measurement of inflammatory biomarkers could be found elsewhere[18]. Briefly, a blood sample was drawn between 07.00 and 09.00 h into Vacutainer tubes from all study participants after >12 h overnight fasting. Blood samples were centrifuged within 30–45 min of collection, and plasma was frozen at −70°C until analysis. CRP concentrations were measured by using an ultrasensitive latex-enhanced immunoturbidimetric assay (Randox Laboratories Ltd, Crumlin, UK). Circulating levels of serum amyloid A (SAA), E-selectin, soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular adhesion molecule-1 (sVCAM-1) were measured by commercially available ELISA and standards (Biosource International Ltd, Camarillo, CA, USA and Bender Med Ltd, Vienna, Austria). TNF-$\alpha$ and IL-6 were assayed by enzyme-linked immunoassay assay (Bender Medsystem kits). Inter- and intraassay CV for all markers were <10 %. Blood lipid levels were assessed according to the standard methods[39].

### *Assessment of other variables*

Weight and height were measured, and BMI was calculated accordingly[39]. Waist circumference (WC) was measured at the narrowest level over light clothing using an unstretched tape measure. Data on family history of diabetes were collected as the participants' oral responses to the pre-tested questionnaire. The criterion for family history of diabetes was having at least one first-degree relative with a diagnosis of diabetes after 30 years of age. Data on physical activity were obtained using the subjects' oral responses to a pre-tested questionnaire and expressed as metabolic equivalent hours per week (MET × h/week)[18]. Additional covariate information regarding age, smoking habits, menopausal status, medical history and current use of medications was obtained using validated questionnaires. Participants' blood pressure was also assessed according to a standard protocol[40].

### *Statistical methods*

Cut-off points for quintiles of high- and low-fat dairy intakes were calculated and subjects were categorised based on quintile cut-off points. Significant differences in general

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characteristics across quintiles of high- and low-fat dairy intakes were assessed using a one-way ANOVA with Tukey *post hoc* test. Chi-square test was used to detect significant differences in the distribution of subjects across quintiles of high- and low-fat dairy intakes with regard to categorical variables. We determined age- and energy-adjusted means for dietary variables across quintiles of high- and low-fat dairy intakes by using a general linear model. Analysis of covariance was used to compare these means.

Before statistical analyses, we looked at outliers in each variable and excluded them from the final analysis. The distribution of inflammatory markers was highly skewed. Therefore, logarithmically transformed values of these markers were used in all analyses. Geometric means of inflammatory markers across quintiles of high- and low-fat dairy intakes were computed by using analysis of covariance in three different models. In the first model, we adjusted for age (continuous), BMI (continuous) and WC (continuous). In the second model, we additionally adjusted for smoking (yes or no), physical activity (continuous), total energy intake (continuous), use of oestrogen (yes or no), menopausal status (yes or no) and family history of diabetes or stroke (yes or no), systolic and diastolic blood pressure (continuous), fasting plasma glucose, serum TAG concentrations, total cholesterol and HDL and LDL cholesterol. Finally, we added dietary variables into the model including cholesterol intake, consumption of meats and fish, fruit and vegetables, whole and refined grains, hydrogenated and non-hydrogenated vegetable oils, percentage of energy from fat and mutual effects of high- and low-fat dairy intakes (all as continuous). Analysis of covariance was used for comparison of inflammatory markers across quintiles.

To determine the association of high- and low-fat dairy consumption with inflammatory markers, we used multiple linear regression analysis. In these models, log-transformed plasma concentrations of inflammatory markers were used to achieve normal distributions. We looked at the mentioned associations in three different models with covariates as those used in the above-mentioned models. The Statistical Package for Social Science statistical software package version 9·05 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

## Results

The reported mean (SD) daily intake of low- and high-fat dairy consumption was 85 (SD 23) and 101 (SD 29) g/d, respectively. The food items that contributed most to low-fat dairy intakes were low-fat yoghurt and those that contributed most to high-fat dairy intake were high-fat yoghurt and cheeses.

Participants' general characteristics and dietary intakes across quintiles of dairy consumption are shown in Table 1. Compared to participants in the lowest quintile, those in the upper quintile of low-fat dairy consumption had lower BMI and WC, were older, more physically active and more likely to be current oestrogen users. Individuals in the top quintile of high-fat dairy consumption had lower means of BMI and WC, were older, and more likely to be current oestrogen users than those in the third quintile. No significant difference was seen regarding the distribution of current smokers and those with family history of diabetes or stroke across quintiles of either low- or high-fat dairy consumption. Higher intakes of low-fat dairy were associated with a healthier diet; those subjects in the upper category consumed more fruit, vegetables, whole grains, non-hydrogenated vegetable oils, dietary fibre, vitamin $B_2$, Mg and Ca and less hydrogenated vegetable oils, high-fat dairy and energy from fat. Individuals in the top category of high-fat dairy intakes consumed more fruit, hydrogenated vegetable oils, cholesterol, vitamin $B_2$, Ca and energy from fat and less whole grains, refined grains, low-fat dairy, non-hydrogenated vegetable oils, Mg and energy from carbohydrate.

Geometric means of circulating inflammatory marker levels across quintile categories of dairy consumption are given in Table 2. Compared to those in the lowest quintile, individuals in the top quintile of low-fat dairy consumption had lower circulating levels of CRP, TNF-$\alpha$, IL-6, E-selectin, sICAM-1 and sVCAM-1. Adjustment for potential confounding variables attenuated these associations. However, after further control for dietary intakes, a significant association between low-fat dairy consumption and circulating levels of IL-6 and sVCAM-1 was found; those in the highest category had lower circulating levels of these markers. There was a significant association between high-fat dairy consumption and serum levels of TNF-$\alpha$, SAA, E-selectin and sVCAM-1. Adjustment for age, BMI and WC made the association with E-selectin disappear. Additional control for other potential confounders attenuated the association with TNF-$\alpha$. However, the associations with SAA and sVCAM-1 remained significant even after further control for dietary intakes; individuals in the highest quintile had higher levels of these inflammatory markers than those in the lowest quintile.

Findings from multiple linear regression models, with low- and high-fat dairy consumption as independent and log-transformed values of inflammatory markers as dependent variables, are shown in Table 3. After control for age, BMI, WC and other potential confounders, low-fat dairy consumption was inversely associated with CRP, IL-6 and sVCAM-1; with further adjustment for dietary intakes, the associations remained significant just for sVCAM-1. High-fat dairy intake was positively associated with log-transformed values of SAA and sVCAM-1, both before and after adjustment for all potential confounding variables. No overall significant associations were found between total dairy consumption, markers of inflammation and endothelial function.

**Table 1** General characteristics and dietary intakes of participants by quintiles of low- and high-fat dairy consumption*

| | Low-fat dairy consumption quintiles | | | | | | | High-fat dairy consumption quintiles | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 (lowest) | | 3 | | 5 (highest) | | | 1 (lowest) | | 3 | | 5 (highest) | | |
| | Mean | SD | Mean | SD | Mean | SD | *P* value† | Mean | SD | Mean | SD | Mean | SD | *P* value† |
| Age (years) | 47 | 5 | 44 | 6 | 54 | 6 | <0·01 | 51 | 6 | 42 | 5 | 55 | 6 | <0·01 |
| BMI (kg/m$^2$) | 28·1 | 3·1 | 27·8 | 3·9 | 26·4 | 3·8 | <0·05 | 27·4 | 3·6 | 28·8 | 3·3 | 27·0 | 3·7 | <0·05 |
| Waist girth (cm) | 96 | 13 | 92 | 10 | 90 | 12 | <0·05 | 93 | 11 | 96 | 12 | 91 | 11 | <0·05 |
| Physical activity (MET × h/week) | 13·4 | 11·6 | 12·9 | 9·8 | 17·2 | 11·1 | <0·01 | 15·6 | 10·8 | 14·9 | 9·7 | 15·7 | 11·7 | 0·80 |
| Family history of diabetes (%) | 9 | | 9 | | 11 | | 0·39 | 7 | | 12 | | 9 | | 0·11 |
| Family history of stroke (%) | 0 | | 2 | | 2 | | 0·24 | 1 | | 2 | | 1 | | 0·87 |
| Current daily smokers (%) | 0 | | 0 | | 2 | | 0·11 | 1 | | 2 | | 0 | | 0·52 |
| Current oestrogen use (%) | 19 | | 31 | | 28 | | <0·05 | 25 | | 17 | | 27 | | <0·05 |
| Nutrients | | | | | | | | | | | | | | |
| Total energy (kcal/d) | 2316 | 29 | 2765 | 19 | 2477 | 22 | <0·05 | 2511 | 26 | 2589 | 23 | 2493 | 28 | 0·67 |
| Carbohydrate (% total energy) | 57 | 1 | 59 | 1 | 59 | 1 | 0·18 | 60 | 1 | 58 | 1 | 55 | 1 | <0·01 |
| Protein (% total energy) | 12·7 | 0·5 | 11·8 | 0·4 | 14·1 | 0·4 | <0·05 | 13·1 | 0·6 | 13·6 | 0·4 | 14·3 | 0·5 | 0·36 |
| Fat (% total energy) | 30·1 | 0·7 | 29·4 | 0·6 | 27·0 | 0·8 | <0·05 | 26·6 | 0·8 | 28·2 | 0·5 | 29·9 | 0·6 | <0·05 |
| Cholesterol (mg/d) | 190 | 10 | 203 | 9 | 181 | 11 | 0·09 | 174 | 9 | 194 | 10 | 208 | 11 | <0·05 |
| Dietary fibre (g/d) | 14 | 1 | 15 | 1 | 18 | 1 | <0·05 | 16 | 1 | 15 | 1 | 18 | 1 | 0·26 |
| Vitamin $B_2$ (mg/d) | 0·41 | 0·02 | 0·96 | 0·01 | 1·61 | 0·02 | <0·01 | 0·53 | 0·02 | 1·02 | 0·02 | 1·56 | 0·01 | <0·01 |
| Ma (mg/d) | 137 | 2 | 154 | 3 | 149 | 2 | <0·05 | 164 | 3 | 140 | 3 | 121 | 2 | <0·05 |
| Ca (mg/d) | 183 | 2 | 413 | 2 | 786 | 3 | <0·01 | 211 | 3 | 373 | 3 | 715 | 3 | <0·01 |
| Foods (g/d) | | | | | | | | | | | | | | |
| Fruit | 204 | 8 | 227 | 6 | 263 | 7 | <0·01 | 235 | 6 | 222 | 9 | 251 | 8 | <0·05 |
| Vegetables | 186 | 6 | 178 | 5 | 194 | 5 | <0·05 | 182 | 5 | 189 | 6 | 192 | 6 | 0·18 |
| Meat and fish | 85 | 3 | 97 | 3 | 91 | 2 | <0·05 | 90 | 3 | 88 | 3 | 94 | 3 | 0·39 |
| Whole grains | 96 | 2 | 127 | 3 | 117 | 3 | <0·05 | 133 | 3 | 110 | 3 | 87 | 3 | <0·05 |
| Refined grains | 205 | 4 | 192 | 9 | 209 | 6 | 0·28 | 217 | 7 | 201 | 8 | 184 | 6 | <0·05 |
| Low-fat dairy | 33 | 2 | 88 | 2 | 152 | 3 | <0·01 | 112 | 3 | 73 | 2 | 86 | 3 | <0·01 |
| High-fat dairy | 98 | 3 | 91 | 3 | 82 | 2 | <0·05 | 27 | 2 | 97 | 3 | 165 | 3 | <0·01 |
| Hydrogenated fats | 37 | 1 | 24 | 1 | 17 | 1 | <0·01 | 12 | 1 | 20 | 1 | 43 | 1 | <0·01 |
| Non-hydrogenated fats | 12 | 1 | 19 | 1 | 29 | 1 | <0·01 | 22 | 1 | 35 | 1 | 10 | 1 | <0.01 |

MET, metabolic equivalent task.
*Data are mean and SD unless indicated. Dietary data are mean and SE that have been adjusted for age and energy intakes.
†By using ANOVA for continuous variables (analysis of covariance for dietary variables) and the $\chi^2$ test for categorical variables.

**Table 2** Multivariate-adjusted geometric means (SD) of circulating inflammatory marker levels across quintile categories of dairy consumption

| | Low-fat dairy consumption quintiles | | | | | | | High-fat dairy consumption quintiles | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 (lowest) | | 3 | | 5 (highest) | | | 1 (lowest) | | 3 | | 5 (highest) | | |
| | Mean | SD | Mean | SD | Mean | SD | *P* value* | Mean | SD | Mean | SD | Mean | SD | *P* value* |
| CRP (mg/l) | | | | | | | | | | | | | | |
| Crude | 2·32 | 2·09 | 1·75 | 2·19 | 1·53 | 1·78 | <0·001 | 1·88 | 1·95 | 2·01 | 2·10 | 1·85 | 2·02 | 0·19 |
| Model I† | 2·08 | 1·95 | 1·71 | 2·03 | 1·61 | 1·70 | <0·01 | 1·90 | 1·91 | 1·99 | 2·05 | 1·82 | 1·99 | 0·27 |
| Model II‡ | 1·91 | 1·93 | 1·70 | 2·00 | 1·69 | 1·68 | <0·05 | 1·89 | 1·90 | 1·99 | 2·05 | 1·83 | 1·98 | 0·29 |
| Model III§ | 1·78 | 1·89 | 1·72 | 1·94 | 1·81 | 1·63 | 0·14 | 1·87 | 1·88 | 1·98 | 2·04 | 1·83 | 1·98 | 0·38 |
| TNF-$\alpha$ (ng/l) | | | | | | | | | | | | | | |
| Crude | 5·41 | 2·31 | 4·19 | 1·84 | 3·46 | 1·79 | <0·01 | 4·63 | 1·90 | 4·89 | 1·97 | 4·21 | 1·89 | <0·05 |
| Model I | 4·28 | 2·14 | 4·03 | 1·81 | 3·50 | 1·65 | <0·05 | 4·56 | 1·88 | 4·70 | 1·94 | 4·35 | 1·86 | <0·05 |
| Model II | 3·93 | 2·12 | 3·78 | 1·68 | 3·56 | 1·61 | <0·05 | 4·51 | 1·88 | 4·62 | 1·93 | 4·33 | 1·85 | 0·09 |
| Model III | 3·54 | 1·88 | 3·69 | 1·57 | 3·64 | 1·58 | 0·09 | 4·46 | 1·85 | 4·54 | 1·91 | 4·38 | 1·85 | 0·22 |
| SAA (mg/l) | | | | | | | | | | | | | | |
| Crude | 5·00 | 2·75 | 4·89 | 3·75 | 4·95 | 3·12 | 0·67 | 4·33 | 3·02 | 5·17 | 3·26 | 5·04 | 3·29 | <0·05 |
| Model I | 4·84 | 2·67 | 4·93 | 3·66 | 4·99 | 2·99 | 0·53 | 4·25 | 2·99 | 5·06 | 3·16 | 5·11 | 3·25 | <0·01 |
| Model II | 4·80 | 2·64 | 4·90 | 3·68 | 5·03 | 2·94 | 0·26 | 4·24 | 2·99 | 5·05 | 3·14 | 5·10 | 3·22 | <0·01 |
| Model III | 4·78 | 2·61 | 4·88 | 3·62 | 5·01 | 2·92 | 0·21 | 4·22 | 2·96 | 5·01 | 3·14 | 5·12 | 3·20 | <0·01 |
| IL-6 (ng/l) | | | | | | | | | | | | | | |
| Crude | 2·42 | 1·76 | 2·01 | 2·03 | 1·38 | 1·94 | <0·01 | 2·04 | 1·88 | 2·20 | 2·14 | 1·88 | 1·90 | 0·20 |
| Model I | 1·98 | 1·68 | 1·94 | 1·98 | 1·66 | 1·89 | <0·01 | 1·92 | 1·80 | 2·05 | 2·10 | 1·91 | 1·88 | 0·38 |
| Model II | 1·91 | 1·60 | 1·95 | 1·94 | 1·73 | 1·88 | <0·05 | 1·90 | 1·80 | 2·04 | 2·09 | 1·90 | 1·89 | 0·43 |
| Model III | 1·84 | 1·57 | 1·91 | 1·90 | 1·79 | 1·85 | <0·05 | 1·88 | 1·82 | 2·02 | 2·08 | 1·91 | 1·87 | 0·49 |
| E-selectin (ng/l) | | | | | | | | | | | | | | |
| Crude | 56·6 | 17·4 | 50·3 | 18·9 | 47·1 | 21·7 | <0·01 | 49·7 | 19·1 | 52·6 | 19·9 | 50·3 | 18·7 | <0·05 |
| Model I | 53·4 | 17·6 | 49·1 | 18·1 | 49·5 | 20·4 | <0·05 | 50·1 | 18·8 | 50·8 | 19·3 | 51·5 | 18·9 | 0·18 |
| Model II | 51·7 | 17·1 | 49·8 | 17·6 | 49·9 | 19·9 | 0·08 | 50·0 | 18·7 | 50·9 | 19·5 | 51·2 | 18·8 | 0·26 |
| Model III | 50·5 | 16·8 | 49·4 | 17·5 | 50·3 | 19·6 | 0·21 | 49·3 | 18·6 | 50·5 | 19·8 | 51·9 | 19·1 | 0·07 |
| sICAM-1 ($\mu$g/l) | | | | | | | | | | | | | | |
| Crude | 252 | 49 | 249 | 58 | 238 | 51 | <0·05 | 249 | 53 | 250 | 55 | 242 | 50 | 0·14 |
| Model I | 248 | 48 | 247 | 56 | 243 | 50 | 0·12 | 251 | 51 | 246 | 54 | 246 | 51 | 0·23 |
| Model II | 246 | 48 | 248 | 56 | 244 | 51 | 0·46 | 250 | 51 | 247 | 53 | 246 | 51 | 0·29 |
| Model III | 242 | 47 | 247 | 55 | 247 | 50 | 0·26 | 248 | 50 | 244 | 51 | 248 | 50 | 0·41 |
| sVCAM-1($\mu$g/l) | | | | | | | | | | | | | | |
| Crude | 553 | 121 | 541 | 139 | 519 | 126 | <0·01 | 537 | 129 | 531 | 133 | 547 | 136 | <0·05 |
| Model I | 545 | 119 | 537 | 137 | 526 | 125 | <0·01 | 530 | 127 | 525 | 131 | 555 | 134 | <0·01 |
| Model II | 543 | 120 | 535 | 138 | 528 | 123 | <0·01 | 531 | 129 | 525 | 131 | 557 | 133 | <0·01 |
| Model III | 540 | 120 | 531 | 138 | 531 | 123 | <0·05 | 529 | 128 | 523 | 130 | 557 | 135 | <0·01 |

CRP, C-reactive protein; SAA, serum amyloid A; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM, soluble vascular adhesion molecule-1.
*By using analysis of covariance.
†Model I: Adjusted for age, BMI and waist circumference.
‡Model II: Additionally adjusted for smoking, physical activity, total energy intake, use of oestrogen, menopausal status and family history of diabetes or stroke, systolic and diastolic blood pressure, fasting plasma glucose, serum TAG concentrations, total cholesterol and HDL and LDL cholesterol.
§ Model II: Further adjusted for dietary variables including cholesterol intake, consumption of meats and fish, fruit and vegetables, whole and refined grains, hydrogenated and non-hydrogenated vegetable oils, percentage of energy from fat and mutual effects of high- and low-fat dairy intakes.

## Discussion

The current study, performed among women in Iran, found a significant inverse association of low-fat dairy consumption with sVCAM-1 and a positive association of high-fat dairy consumption with SAA and sVCAM-1. These associations persisted in multivariate models after known potential confounders were accounted for. Therefore, the relationships we reached are not likely to be attributed to other lifestyle variables associated with dairy consumption. To our knowledge, this is the first study reporting the epidemiological association between dairy consumption and circulating levels of inflammatory markers.

Although inflammation has recently obtained considerable attention as an important contributor to the development of many chronic diseases, little data are available relating food intakes to systemic inflammation. In the current study, the associations between dairy consumption and most inflammatory biomarkers were not significant; however, in some cases, such as sVCAM-1 (for both low- and high-fat dairy intakes) and SAA (just for high-fat dairy intake), we reached significant associations, even after control for dietary intakes. This finding is in accord with a recently reported cross-sectional study among a group of Spanish adults at high risk of CVD, in which a higher intake of dairy products was associated with lower concentrations of CRP and sICAM-1, even after adjustment for BMI[41]. However, findings from clinical trials indicated opposite results. Tricon *et al.*[42], in a cross-over trial among healthy middle-aged men, showed that consumption of full-fat dairy products enriched with CLA did not affect inflammatory markers such as IL-6, sVCAM-1, sICAM-1, E-selectin or serum CRP concentrations. Compared to a diet with moderate dairy products, a hypoenergetic diet, high in dairy products, could not influence CRP levels among obese patients[43]. Supplementation with a milk drink for 12 weeks in hypertensive adults had no significant impact on inflammatory marker levels like CRP and IL-6[44]. Not only dairy consumption[40–43], but also supplementation with Ca and vitamin D (two major components of dairy products) for 3 years could not affect systemic inflammation[35]. However, in two recent clinical trials[45,46], vitamin D supplementation markedly reduced the serum levels of CRP and IL-6. In addition, low serum 25 (OH) vitamin D concentrations have cross-sectionally been associated with high serum CRP[47]. It should be kept in mind that none of these trials has been designed to assess the effect of dairy consumption on inflammation, and most have reported such an effect as their accessory finding. Therefore, specifically designed clinical trials are required to assess dairy consumption's effect on systemic inflammation.

At this stage, no one can guess the mechanisms by which dairy consumption might affect systemic inflammation. However, findings from earlier studies might provide some clues. The Ca content of dairy

**Table 3** Regression coefficients ($\beta$) for the relationship between dairy consumption and log-transformed inflammatory biomarkers

| | Low-fat dairy consumption | | | | | | | | High-fat dairy consumption | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Model I* | | | Model II† | | | Model III‡ | | Model I* | | | Model II† | | | Model III‡ | |
| | $\beta$ | SE | $P$ | $\beta$ | SE | $P$ | $\beta$ | SE | $P$ | $\beta$ | SE | $P$ | $\beta$ | SE | $P$ | $\beta$ | SE | $P$ |
| CRP (mg/l) | −0·07§ | 0·02 | 0·008 | −0·04 | 0·02 | 0·048 | 0·004 | 0·02 | 0·463 | 0·003 | 0·02 | 0·227 | 0·00 | 0·021 | 0·348 | 0·000 | 0·02 | 0·419 |
| TNF-$\alpha$ (ng/l) | −0·03 | 0·01 | 0·041 | −0·008 | 0·01 | 0·197 | 0·006 | 0·01 | 0·337 | −0·009 | 0·02 | 0·153 | −0·003 | 0·02 | 0·197 | 0·001 | 0·01 | 0·341 |
| SAA (mg/l) | 0·001 | 0·01 | 0·636 | 0·006 | 0·01 | 0·419 | 0·007 | 0·01 | 0·397 | 0·11 | 0·01 | <0·001 | 0·09 | 0·01 | <0·001 | 0·08 | 0·01 | 0·016 |
| IL-6 (ng/l) | −0·05 | 0·03 | 0·018 | −0·03 | 0·03 | 0·039 | −0·001 | 0·03 | 0·141 | 0·001 | 0·03 | 0·421 | 0·000 | 0·03 | 0·679 | 0·000 | 0·03 | 0·693 |
| E-selectin (ng/l) | −0·001 | 0·03 | 0·317 | 0·000 | 0·03 | 0·687 | 0·000 | 0·03 | 0·741 | 0·000 | 0·03 | 0·526 | 0·000 | 0·03 | 0·579 | 0·001 | 0·03 | 0·381 |
| sICAM-1 (μg/l) | −0·003 | 0·02 | 0·214 | 0·001 | 0·02 | 0·336 | 0·002 | 0·02 | 0·349 | −0·001 | 0·02 | 0·315 | −0·001 | 0·02 | 0·387 | −0·000 | 0·02 | 0·511 |
| sVCAM-1 (μg/l) | −0·08 | 0·02 | 0·005 | −0·06 | 0·02 | 0·019 | −0·03 | 0·02 | 0·042 | 0·06 | 0·02 | 0·014 | 0·06 | 0·02 | 0·021 | 0·05 | 0·02 | 0·030 |

CRP, C-reactive protein; SAA, serum amyloid A; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM, soluble vascular adhesion molecule-1.
*Model I: Adjusted for age, BMI and waist circumference.
†Model II: Additionally adjusted for smoking, physical activity, total energy intake, use of oestrogen, menopausal status and family history of diabetes or stroke, systolic and diastolic blood pressure, fasting plasma glucose, serum TAG concentrations, total cholesterol and HDL and LDL cholesterol.
‡Model III: Further adjusted for dietary variables including cholesterol intake, consumption of meats and fish, fruit and vegetables, whole and refined grains, hydrogenated and non-hydrogenated vegetable oils, percentage of energy from fat and mutual effects of high- and low-fat dairy intakes.

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products has been reported to be responsible for dairy's favourable association with obesity and other metabolic abnormalities[26,31,34]; however, it does not seem to play a role in inflammation. Adjustment for Ca intake in a study by Salas-Salvado *et al.*[41] could not explain the inverse association of dairy consumption with some inflammatory biomarkers. Our current analysis also indicated that total dairy intake had no significant associations with inflammation. Therefore, Ca does not seem to play a significantly role in the inflammation story. However, further studies are required to examine the relationship between Ca intake and systemic inflammation. Dairy's whey protein might be a contributing factor; however, milk drink supplemented with whey protein had no significant impact on inflammatory marker levels compared to a control dairy drink among hypertensive adults[44]. Also consumption of milk protein in conjunction with a high-fat meal did not acutely modify postprandial inflammation in young healthy men[37]. Besides Ca and protein, fat content of dairy might be an influencing factor for inflammation. In addition to saturated fats (SFA), dairy products contain CLA and *trans* fats (TFA). Some human and cell culture studies[36] have suggested that CLA intake might attenuate the proinflammatory state. However, others indicated that daily consumption of 3 g of different isomers of CLA did not affect plasma CRP levels[48,49]. TFA intake has been related to elevated levels of inflammatory biomarkers[14,50]. Significant positive association between high-fat dairy intake and some inflammatory biomarkers in the current study could be attributed to SFA and TFA content of these products. The hypothesis that TFA from dairy products might affect human health differently from those in hydrogenated fats[51] should also be kept in mind. Further studies are needed to examine this hypothesis. Other components of dairy products, such as vitamin $B_2$ and bioactive compounds, have not yet been examined for their effects on systemic inflammation.

## Conclusion

Several limitations need to be considered in the interpretation of our findings. The major concern is the cross-sectional design of the study that does not allow us to infer causal relationships. However, the appropriate analysis of cross-sectional data represents a valuable initial step in identifying relationships between diet and disease. Possible misclassifications of participants due to the use of an FFQ for assessing dietary intakes should also be considered. This is particularly relevant for the inclusion of cheese and other dairy products in the same category, because each 100 g of Iranian cheese gives very seldom less than 30 g of fat, most often much more, while other products in the high-fat dairy category, such as yoghurt, give almost 6–7 g fat/100 g. Unfortunately, our database did not include fat intake contributed from dairy products and it just had a variable on total fat intake. We tried to control for known lifestyle variables associated with dairy consumption; however, residual confounding (like lack of data on family history of stroke and heart diseases) in our study, as in all epidemiological studies, is inevitable. We used a single blood measurement of inflammation, but that may not accurately reflect long-term inflammatory status. Lack of control for glycaemic load, a dietary agent that has been shown to correlate with inflammation[52], should also be kept in mind. However, the associations we observed are unlikely to be confounded significantly by dietary glycaemic load, because the extensive adjustments we made had minimal impacts on correlations.

Given the aforementioned limitations, we have found evidence indicating an independent relationship between dairy consumption and some markers of inflammation and endothelial dysfunction. Further studies are required to identify responsible components of dairy products and related mechanisms of action.

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