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Association of dairy product consumption and cardiovascular diseases

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Abstract: Although it has often been postulated that the consumption of dairy products is associated with a high risk of coronary heart disease, study results have been conflicting. This review summarizes recent observational and human intervention trial findings on dairy products and cardiovascular disease. It is unclear whether specific dairy products are associated with risk of cardiovascular disease (CVD). We examine the association between intake of milk, cheese, cream and butter, and incidence of CVD. Overall consumption of dairy products was inversely associated with risk of CVD. The main finding was that a high intake of fermented milk may reduce the risk of CVD. This study suggests that it is important to examine dairy products separately when investigating their health effects. High-fat milk was positively associated with CHD and cheese was inversely associated with CHD. Milk was inversely associated with ischemic stroke in high versus low meta-analysis only. In conclusion, total dairy consumption was associated with a modestly lower risk of hypertension, CHD, and stroke.
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Review of literature

Cardiovascular disease (CVD) is the most common cause of death in the US and worldwide, with an estimated 0.84 million and 17.90 million cardiovascular deaths in 2016, respectively (Benjamin et al. 2019). The American Heart Association has released the 2030 Impact Goal for improving cardiovascular health and preventing CVD, and one of approaches achieving this goal may be through targeting modifiable CVD risk factors (Angell et al. 2020). It is now well known that diet can directly and strongly affect the occurrence and development of CVD (Brandhorst and Longo 2019; Yu et al. 2018). A number of modifiable risk factors for CVD have been identified including high blood cholesterol, hypertension, diabetes, obesity/overweight, and a/n atherogenic diet. A high intake of saturated fat (SF) and industrial sources of *trans* fatty acids (TFA) have been linked to an increased risk of CVD, and this effect is thought to be mediated predominantly by increased blood levels of LDL cholesterol (LDL-C). Decreasing the consumption of SF, particularly C12:0, C14:0, and C16:0, as well as industrial sources of TFA is the primary dietary recommendation for decreasing the risk of CVD. The WHO and the 2010 Dietary Guidelines for Americans recommended consuming <10% of total energy from SF, and the American Heart Association recommended consuming <7% energy to reduce CVD risk. However, despite the well-established evidence in humans that high intake of SF increases plasma levels of LDL-C (Mensink et al. 2003), along with pharmacological evidence showing that interventions that reduce LDL-C result in decreased ischemic heart disease (IHD) events and stroke (Law et al. 2003), a causal relationship between the intake of SF and CVD risk remains controversial (Hooper et al. 2011; Siri-Tarino et al. 2010). Milk and dairy products play critical roles in providing multiple essential nutrients and energy for humans (Drewnowski and Fulgoni III 2008) and are listed as a core part of dietary recommendations around the world (Society 2016). The Dietary Guideline for Americans recommended intake of fat-free and low-fat milk and dairy products is three servings/day (about 710 mL/day) for adults. Chinese Dietary Guidelines in 2016 (CDG–2016) has a recommended consumption of 300 g of milk and dairy products every day to maintain adequate nutrition (Society 2016). Dairy products are a diverse food group, some are non-fermented (eg, milk) and others are fermented (eg, yoghurt and cheese), and these different foods could have varying effect on cardiovascular diseases and mortality. For example, a meta-analysis of cohort studies suggested a lower risk of hypertension with increasing milk consumption (Soedamah-Muthu et al. 2012), with a neutral effect on cardiovascular disease (Mozaffarian 2016). Dairy products containing milk fat are major food sources of SF, accounting for ~21% of total SF intake in the U.S. diet (Huth and Park 2012). Dairy products are a major source of saturated fats, which have been presumed to adversely affect blood lipids and increase cardiovascular disease and mortality. Using this framework, dietary guidelines recommend minimising consumption of whole-fat dairy products for cardiovascular disease prevention in populations (Alexander et al. 2016). In particular, there is emerging evidence regarding the role of dairy fats and CVD. While increased intake of saturated fat from dairy is expected to increase low-density lipoprotein (LDL) cholesterol, recent human clinical studies found that such effects differ depending on the type of dairy products as well as the processing methods (Mozaffarian and Wu 2018; Rosqvist et al. 2015). An unhealthy diet, physical inactivity and excess weight are of major importance in the development of type 2 diabetes, and many cases can be prevented with lifestyle modifications (Zheng et al. 2018). Dairy products can be an interesting preventive target in maintaining cardiometabolic health, as they are a rich source of calcium, potassium and vitamins. Furthermore, dairy proteins have been associated with favorable body composition and improved insulin sensitivity. Advice regarding the inadvisability of consuming dairy food arose from a general guidance to avoid fatty foods with high-saturated fatty acid content. Such foods included fatty meats especially processed meats and fried foods with the focus on "total fat". The approximate fat content of cow's milk is 3–4% and the fatty acid composition of dairy fat varies with the breed and nutrition. Only recently has advice regarding dairy intake taken into account the whole food and the compositional variety in the matrix of individual products. Such recognition has modified attitudes while not entirely dismissing the importance of the fat content. The evidence relating to differing interpretations and guidance is the substance of this review. Well researched meta-analyses of the association of dairy foods with cardiovascular health have been published with increasing frequency. Fontecha et al. have analyzed 12 meta-analyses involving RCTs as well as the updated meta-analyses of RCTs (Fontecha et al. 2019). Based on data from 31 cohort studies, Alexander et al. reported an inverse trend between total dairy consumption and CVD and fatal and non-fatal coronary heart disease (CHD), which appears to have been driven by intake of cheese (Hazzard Ratio, HR of 0.86 for each 600 g/day of total dairy and 0.86 for each 50 g/day cheese intake) (Alexander et al. 2016). High-fat dairy food tended to be positively associated with CHD contrasting with the inverse association with low-fat total dairy (HR 0.90). Gholami et al. reporting on 27 cohort studies found an inverse association between total dairy intake and CVD (HR 0.90) (Gholami et al. 2017). Surprisingly, the effect of total dairy on stroke was more striking than on CHD. Alexander et al. showed total dairy intake, including full-fat and low-fat dairy, was associated significantly and inversely with total stroke (HR 0·91) (Alexander et al. 2016). Similarly, Gholami et al. reported a significant inverse association between total dairy intake, mainly attributable to low-fat dairy products, and stroke (HR 0.88) (Gholami et al. 2017). As with CHD, cheese intake was significantly inversely associated with total stroke (HR 0·87) (Alexander et al. 2016). Cheese intake was also generally inversely associated with stroke in each of the 5 meta-analyses quoted by Fontecha et al. that had been published since 2014 (Fontecha et al. 2019). Butter showed no association with CVD but the amounts consumed were small, interpretations based on increments of 10–14 g/day. The conclusions indicate little association in either direction between total dairy consumption and CHD, but possibly an inverse association with stroke. Since the risk factors for CVD generally apply to both CHD and stroke, there may have been unrecognised confounding factors. In one of the largest meta-analyses, Guo et al. reported on 29 prospective cohort studies including 928,465 participants of whom about one-tenth died, 28,419 suffered incident CHD events and 25,416 CVD events. No associations were observed with total dairy or milk intake whether of low-fat or high-fat variety. This meta-analysis differed from those reported above in that it showed a modest but significant inverse association between total fermented dairy products (yogurt, cheese, and fermented milk; per 20 g/day) with mortality (HR 0.98) and CVD risk (HR 0.98) but not for CHD (Guo et al. 2017). Further analyses showed cheese associated with a lower risk of CVD (HR 0.98 per 10 g/day), but not yogurt. In contrast, a recent report suggests a protective link between yogurt consumption and CVD. Cruijsen et al. have recently reported that during a 12-year follow-up of the Alpha Omega Cohort from the Netherlands that included 48,473 person-years and 2035 deaths, yogurt consumption was inversely associated with CVD mortality (HR 0.96 per 25 g/day) and all-cause mortality (HR 0.98 per 25 g/day) in patients with a history of myocardial infarction (Cruijsen et al. 2021). The present study includes an overview of systematic reviews and meta-analyses of follow-up studies, an overview of meta-analyses involving RCTs, and an update on meta-analyses of RCTs (2013–2018) aiming to synthesize the evidence regarding the influence of dairy product consumption on the risk of major cardiovascular-related outcomes and how various doses of different dairy products affect the responses, as well as on selected biomarkers of cardiovascular disease risk, i.e., blood pressure and blood lipids. The search strategies for both designs were conducted in the MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Web of Science databases from their inception to April 2018. From the 31 full-text articles retrieved for cohort studies, 17 met the eligibility criteria. The pooled risk ratio estimated for the association between the consumption of different dairy products at different dose-responses and cardiovascular outcomes (CVD, CHD, and stroke) showed a statistically significant negative association with RR values <1, or did not find evidence of significant association. The overview of 12 meta-analyses involving RCTs as well as the updated meta-analyses of RCTs did not result in significant changes on risk biomarkers such as systolic and diastolic blood pressure and total cholesterol and LDL cholesterol. Therefore, the present study states that the consumption of total dairy products, with either regular or low fat content, does not adversely affect the risk of CVD (Fontecha et al. 2019).

20 studies with 1677 participants with a median duration of dietary change of 26 (IQR 10-39) weeks and mean increase in dairy food intake of 3.6 (SD 0.92) serves/day were included. There was an increase in weight with low (+0.82, 0.35 to 1.28 kg, p<0.001) and whole fat dairy food (+0.41, 0.04 to 0.79kg, p=0.03), but no significant change in waist circumference (-0.07 , -1.24 to 1.10 cm) ; HOMA – IR (-0.94 , -1.93 to 0.04 units); fasting glucose (+1.32 , 0.19 to 2.45 mg/dl) ; LDL-c (1.85 ,-2.89 to 6.60 mg/dl); HDL-c (-0.19 , -2.10 to 1.71 mg/dl); systolic BP (-0.4, -1.6 to 0.8 mmHg); diastolic BP (-0.4 , -1.7 to 0.8 mmHg) or CRP (-1.07 , -2.54 to 0.39 mg/L). Changes in other cardio-metabolic risk factors were similar for low and whole fat dairy interventions. Increasing whole fat and low fat dairy food consumption increases weight but has minor effects on other cardio-metabolic risk factors. Increase in both whole and low fat dairy food, without other dietary interventions, is associated with a modest weight gain, with no or minor effects on other cardio-metabolic risk factors. These observations suggest that for most healthy individuals it is reasonable to include both low and whole fat dairy food as part of a healthy diet (Benatar et al. 2013). De Goede et al (2015) conducted meta-analysis to evaluate randomized controlled trials that examined the effect of cheese consumption compared with another food product on blood lipids and lipoproteins. A total of 12 randomized controlled trials (RCTs) were identified that examined the effect of cheese consumption on blood lipids and lipoproteins in healthy adults. Compared with butter intake, cheese intake (weighted mean difference: 145.0 g/d) reduced low-density lipoprotein cholesterol (LDL-C) by 6.5% (−0.22 mmol/l; 95%CI: −0.29 to −0.14) and high-density lipoprotein cholesterol (HDL-C) by 3.9% (−0.05 mmol/l; 95%CI: −0.09 to −0.02) but had no effect on triglycerides. Compared with intake of tofu or fat-modified cheese, cheese intake increased total cholesterol or LDL-C, as was expected on the basis of the P/S ratio of the diets. There was insufficient data to compare intake of cheese with intake of other foods. Despite the similar P/S ratios of hard cheese and butter, consumption of hard cheese lowers LDL-C and HDL-C when compared with consumption of butter. Whether these findings can be attributed to calcium, specific types of saturated fatty acids, or the food matrix of cheese warrants further research *(De Goede et al. 2015).*

We aimed to investigate the association of serum pentadecanoic acid (15:0), a biomarker of dairy fat intake, with incident cardiovascular disease (CVD) and all-cause mortality in a Swedish cohort study. We also systematically reviewed studies of the association of dairy fat biomarkers (circulating or adipose tissue levels of 15:0, heptadecanoic acid [17:0], and *trans*-palmitoleic acid [*t*16:1n-7]) with CVD outcomes or all-cause mortality. In a meta-analysis of 18 observational studies including our new cohort study, higher levels of 15:0 and 17:0 were associated with lower CVD risk. Our findings support the need for clinical and experimental studies to elucidate the causality of these relationships and relevant biological mechanisms (Trieu et al. 2021). The milk fat enclosed by MFGM does not raise plasma cholesterol in overweight but otherwise healthy adults. The MFGM component is potentially responsible for preventing the marked increase in plasma lipids observed in the control diet. These results highlight the importance of the food matrix, in addition to fermentation, and suggest that the effects of single components in dairy foods (e.g., saturated fat) do not necessarily correspond to the effects of all dairy foods that contain these components. The current results may also explain some of the inconsistent associations between dairy consumption (e.g., butter compared with cream or cheese) and CVD risk previously reported in cohort studies (Rosqvist et al. 2015). The LDL-cholesterol–raising effect of butter is well known, and limiting the use of butter has led to major reductions of both serum cholesterol and CVD (Puska and Metabolism 2009). As expected, the butter oil in the control diet caused a marked impairment of the lipoprotein profile not only by raising LDL cholesterol by 13% but also by increasing related CVD risk factors, including non-HDL cholesterol and the apolipoprotein B: apolipoprotein A-I ratio (Pischon et al. 2005; Ridker et al. 2005), compared with the MFGM diet. A cholesterol-raising effect of butter oil compared with whipping cream (including MFGM) is in keeping with previous controlled studies that compared butter and cheese (Hjerpsted et al. 2011; Tholstrup et al. 2004) although, apart from being high in MFGM, the latter is fermented. After 6 wk, the cheese intervention resulted in lower serum total, LDL-, and HDL-cholesterol concentrations and higher glucose concentrations than did the butter intervention. Cheese intake did not increase serum total or LDL-cholesterol concentrations compared with the run-in period, during which total fat and saturated fat intakes were lower. Fecal fat excretion did not differ between the cheese and butter periods. Cheese lowers LDL cholesterol when compared with butter intake of equal fat content and does not increase LDL cholesterol compared with a habitual diet (Hjerpsted et al. 2011). The findings of (Huth and Park 2012) indicate that the majority of observational studies have failed to find an association between the intake of dairy products and increased risk of CVD, coronary heart disease, and stroke, regardless of milk fat levels. Results from short-term intervention studies on CVD biomarkers have indicated that a diet higher in SF from whole milk and butter increases LDL cholesterol when substituted for carbohydrates or unsaturated fatty acids; however, they may also increase HDL and therefore might not affect or even lower the total cholesterol:HDL cholesterol ratio. The results from the review also indicate that cheese intake lowers LDL cholesterol compared with butter of equal milk fat content. In addition, the review highlights some significant gaps in the research surrounding the effects of full-fat dairy on CVD outcomes, pointing to the need for long-term intervention studies.

The association of milk intake with cardiovascular disease (CVD) and cause-specific mortality remained controversial and evidence among the Chinese population was limited. We aimed to study the relationship between milk intake and CVDs among general Chinese adults. Among the 91,757 participants with a median follow-up period of 5.8 years, we documented 3877 CVD cases and 4091 all-cause deaths. Compared with participants who never consumed milk, the multivariate-adjusted HRs (95% CIs) of CVD incidence for 1 to 150 g/day, 151 to 299 g/day, and ≥300 g/day were 0.94 (0.86-1.03) ($P > 0.05$), 0.77 (0.66-0.89) ($P < 0.05$), and 0.59 (0.40-0.89) ($P < 0.05$), respectively; each 100 g increase of daily milk intake was associated with 11% lower risk of CVD incidence (HR, 0.89; 95% CI: 0.85-0.94; $P < 0.001$), and 11% lower risk of CVD mortality (HR, 0.89; 95% CI: 0.82-0.97; $P = 0.008$) after adjustment for age, sex, residential area, geographic region, education level, family history of CVD, smoking, alcohol drinking, physical activity level, body mass index, and healthy diet status (ideal or not). RCS analyses also showed a linear dose-response relationship with CVD (P for overall significance of the curve <0.001; P for non-linearity = 0.979; P for linearity <0.001) and stroke (P for overall significance of the curve = 0.010; P for non-linearity = 0.998; P for linearity = 0.002) incidence, and CVD mortality (P for overall significance of the curve = 0.045; P for non-linearity = 0.768; P for linearity = 0.014) within the current range of daily milk intake. Daily milk intake was associated with lower risk of CVD incidence and mortality in a linear inverse relationship. The findings provide new evidence for dietary recommendations in CVD prevention among Chinese adults and people with similar dietary pattern in other countries (Wang et al. 2020). One study in Taiwan of China showed favorable effects of milk intake on stroke and mortality,(Huang et al. 2014) while the association of milk with a composite of mortality or major cardiovascular events reported in the mainland of China was only modest or null (Dehghan et al. 2018). (Dehghan et al. 2018) aimed to assess the associations between total dairy and specific types of dairy products with mortality and major cardiovascular disease. Between Jan 1, 2003, and July 14, 2018, we recorded 10 567 composite events (deaths [n=6796] or major cardiovascular events [n=5855]) during the 9·1 years of follow-up. Higher intake of total dairy (>2 servings per day compared with no intake) was associated with a lower risk of the composite outcome (HR 0·84, 95% CI 0·75–0·94; p_{trend}=0·0004), total mortality (0·83, 0·72–0·96; p_{trend}=0·0052), non-cardiovascular mortality (0·86, 0·72–1·02; p_{trend}=0·046), cardiovascular mortality (0·77, 0·58–1·01; p_{trend}=0·029), major cardiovascular disease (0·78, 0·67–0·90; p_{trend}=0·0001), and stroke (0·66, 0·53–0·82; p_{trend}=0·0003). No significant association with myocardial infarction was observed (HR 0·89, 95% CI 0·71–1·11; p_{trend}=0·163). Higher intake (>1 serving *vs* no intake) of milk (HR 0·90, 95% CI 0·82–0·99; p_{trend}=0·0529) and yogurt (0·86, 0·75–0·99; p_{trend}=0·0051) was associated with lower risk of the composite outcome, whereas cheese intake was not significantly associated with the composite outcome (0·88, 0·76–1·02; p_{trend}=0·1399). Butter intake was low and was not significantly associated with clinical outcomes (HR 1·09, 95% CI 0·90–1·33; p_{trend}=0·4113). During the 24-year follow-up period, there were 893 CVD deaths, 174 deaths from coronary heart disease (CHD), and 417 stroke deaths among 9243 participants. For women, the HRs for death from CVD, CHD, and stroke in the low consumption group were 1.27 (95% CI: 0.99–1.58; *P* for trend = 0.045), 1.67 (0.99–2.80; *P* = 0.02), and 1.34 (0.94–1.90; *P*= 0.08), respectively, after adjustment for age, body mass index, smoking status, alcohol drinking habits, history of diabetes, use of antihypertensives, work category, and total energy intake. With each 100-g / day increase in consumption of milk and dairy products, HRs tended to decrease for deaths from CVD (HR, 0.86; 95% CI, 0.74–0.99), CHD (0.73; 0.52–1.03), and stroke (0.81; 0.65–1.01) in women. was observed in men. Consumption of milk and dairy products was inversely associated with CVD death among women in Japan (Kondo et al. 2013). (Jakobsen et al. 2021) conducted a systematic review and meta-analysis of cohort studies to summarize findings on the associations between total dairy product intake and intake of dairy product subgroups and the risk of major atherosclerotic CVDs in the general adult population. Our protocol was registered in PROSPERO (CRD42019125455). PubMed and Embase were systematically searched through 15 August 2019. For high versus low intake and dose–response meta-analysis, random-effects modelling was used to calculate summary risk ratios (RR). There were 13 cohort studies included for coronary heart disease (CHD), 7 for ischemic stroke and none for peripheral artery disease. High-fat milk was positively associated with CHD (RR 1.08 (95% confidence interval 1.00–1.16) per 200 g higher intake/day) and cheese was inversely associated with CHD (RR 0.96 (95% confidence interval 0.93–0.98) per 20 g higher intake/day). Heterogeneity, however, was observed in high versus low meta-analyses. Milk was inversely associated with ischemic stroke in high versus low meta-analysis only. In conclusion, this systematic review indicates a positive association of high-fat milk and an inverse association of cheese with CHD risk. The findings should be interpreted in the context of the observed heterogeneity.

The effect of dairy consumption on cholesterolaemia has exhibited varied results. An early study demonstrated that high milk intake in an African Maasai ethnic group was inversely correlated with blood cholesterol levels (Mann and Spoerry 1974). Later, these observations were confirmed by others and it was hypothesised that that this effect was a result of intestinal microbial fermentation of indigestible carbohydrates, that could alter cholesterol synthesis and disrupt enterohepatic circulation, thus lowering cholesterolaemia (St-Onge et al. 2000). Studies eventually expanded to various dairy products; one examined the effects of an isoenergetic (20% of total calories, normalised for casein and lactose) provision of milk (2164 mL), butter (93 g) and cheese (305 g) administered in three sessions over three weeks. The authors found that cheese did not significantly raise LDL levels. In contrast, whole milk raised serum LDL levels similarly to butter (Tholstrup et al. 2004); results that were subsequently confirmed by Biong et al. who also demonstrated that consumption of cheese induced a lower increase of serum LDL cholesterol levels in 22 participants, in contrast to an identical mass of butter (42 g) consumed (Biong et al. 2004). It was hypothesised that the different effects were a result of different calcium contents between the dairy products. Another study fed 40 g/day of either butter or mature cheddar cheese to 19 mildly hypercholesterolaemic participants four weeks in a randomised crossover trial (Nestel et al. 2005). They observed that total cholesterol and LDL cholesterol increased significantly in the butter group ($p < 0.05$) versus cheese, which has been observed previously (Nestel et al. 2005). The authors suggested that dietary advice surrounding cheese consumption should be revised. This was also questioned by Tholstrup et al. who suggested that modest amounts of cheese should be included in the diets of mildly hypercholesterolaemic participants (St-Onge et al. 2000). After 6 weeks of the intervention, cheese resulted in higher amounts of calcium excreted in faeces compared to butter. However, no difference was observed in faecal bile acid output despite lower serum total, LDL and HDL cholesterol concentrations observed with cheese intake. Although well designed, it is unfortunate that the mechanisms responsible for the lowering of cholesterol concentrations with cheese compared to butter intake remain unresolved. It is also thought that the protein and probiotic content of cheese may contribute to the observed neutral effect on serum cholesterol (Hjerpsted et al. 2016). Butter consumption has been consistently associated with negative cardiovascular risk outcomes due to the focus on cholesterol levels, however the long-term effects of butter consumption on other major endpoints, such as all-cause mortality and CVD, are also not well-established. In 2014, a systematic review and meta-analysis that examined the effect of butter consumption in 636,151 subjects from 15 country-specific cohorts on the risk of CVD, type II diabetes mellitus (T2DM), and total mortality was published (Pimpin et al. 2016). Pimpin and colleagues discovered that butter was weakly associated with all-cause mortality in (N = 9 country-specific cohorts; per 14 g/day: relative risk (RR) = 1.01, 95% confidence interval (CI) = 1.00–1.03, p = 0.045); was not significantly associated with any CVD (N = 4; RR = 1.00, 95% CI = 0.98–1.02; p =

0.704), coronary heart disease (*N* = 3; RR = 0.99, 95% CI = 0.96–1.03; *p* = 0.537), or stroke (*N* = 3; RR = 1.01, 95% CI = 0.98–1.03; *p* = 0.737) and was inversely associated with incidence of diabetes (*N* = 11; RR = 0.96, 95% CI = 0.93–0.99; *p* = 0.021) (Pimpin et al. 2016).

Conclusions:

Evidence regarding increased risk of consuming dairy food for future CVD remains uncertain. The risk is minor if at all for healthy individuals without CVD risk factors. The complex nature of dairy foods justifies distinguishing between butter that has the highest fat content and is frequently associated positively with increased CVD risk, and other dairy foods. Fermented dairy foods, fermented milk, yogurt, and cheese are more often than not negatively associated with CVD risk.

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