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Fermented dairy food and CVD risk

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Abstract
Fermented dairy foods such as yoghurt and cheese are commonly found in the Mediterranean diet. Recent landmark research has confirmed the effect of the Mediterranean diet on reducing the CVD risk, but the relative contributions of fermented dairy foods have not been fully articulated. The present study provides a review of the relationship between fermented dairy foods consumption and CVD risk in the context of the whole diet. Studies show that people who eat healthier diets may be more likely to consume yoghurt, so there is a challenge in attributing separate effects to yoghurt. Analyses from large population studies list yoghurt as the food most negatively associated with the risk of weight gain (a problem that may lead to CVD). There is some suggestion that fermented dairy foods consumption (yoghurt or cheese) may be associated with reduced inflammatory biomarkers associated with the development of CVD. Dietary trials suggest that cheese may not have the same effect on raising LDL-cholesterol levels as butter with the same saturated fat content. The same might be stated for yoghurt. The use of different probiotic cultures and other aspects of study design remain a problem for research. Nevertheless, population studies from a range of countries have shown that a reduced risk of CVD occurs with the consumption of fermented dairy foods. A combination of evidence is necessary, and more research is always valuable, but indications remain that fermented dairy foods such as cheese and yoghurt are integral to diets that are protective against CVD.

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Fermented dairy food and cardiovascular disease risk

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Abstract

Fermented dairy foods such as cheese and yoghurt are integral to cultural eating patterns across the globe. There are many types of food in the dairy category, but in observational studies there is emerging evidence that fermented dairy foods are significant, and other forms of research add support for this position. There are challenges with reviewing the evidence for reduced disease risk that can be seen from reviews to date. For example, the natural interdependence between nutrients, foods and whole diets is relevant in critiquing research questions and designs. This paper addresses the issue of fermented dairy foods and CVD risk from the critical perspective of foods, nutrients and whole diets. The review describes the position of fermented dairy foods in the context of two recent reports: the review supporting the 2013 Australian Dietary Guidelines and a systematic review on effects of fermented dairy foods published in 2012. The review summarises commentary on proposed mechanisms of action and then identifies research issues related to research on cuisine patterns. Reviews of observational studies have consistently shown that a regular intake of milk, cheese and yoghurt may be associated with a reduced risk of cardiovascular disease, but more needs to be known on the type of food, particularly fermented dairy foods. The background diet or cuisine remains an important factor in terms of energy and nutrient balance, food variety and amounts of foods consumed. The indications are that moderate amounts of fermented dairy foods may play a significant role in dietary patterns that protect against cardiovascular disease but more targeted research is required.

Introduction

Fermented dairy foods such as cheese and yoghurt are commonly found in the Mediterranean diet. Recent research has confirmed that consuming a Mediterranean diet reduces the risk of cardiovascular disease (CVD) (Estruch et al 2013), but the relative contribution of fermented dairy foods has not been articulated. One of the mechanisms by which fermented dairy foods may attenuate CVD risk is via effects on the gut microbiota. Animal model experiments suggest value in supporting the integrity of the gut wall to reduce the development of basal inflammation associated with metabolic disease (Lam). Indeed, the secretion of inflammatory cytokines from fat cells implicates central obesity and the development of CVD (Grundy). In the first instance, observational studies provide indications that yoghurt consumption may help to protect against weight gain. One analysis of 3 large prospective studies of 22,557 men and 98,320 women in the USA examined changes in food and beverage consumption and changes in weight over a 4 y period. Yoghurt was the food most negatively associated with weight gain (Mozaffarian) [8]. The association with cheese consumption was less clear.

Another proposed pathway is the effect of fermented dairy foods intake on cardiovascular disease risk. The main concern is the saturated fat content of dairy foods and the evidence linking saturated fat to high LDL levels and an increased risk of cardiovascular disease. In a review of this area Hu and Park (2012) found that most observational studies had failed to find an association between intake of dairy products and an increased risk of CVD. Short term trials were proving informative in differentiating between dairy products, with some showing a difference in effects on LDL cholesterol between butter and cheese. It is interesting to note that cheese is a fermented dairy food.

These observations suggests that fermented dairy foods may have a particular role to play in the prevention of CVD risk, either directly or via effects on body weight or other risk factors for CVD. This paper reviews recent research examining the associations and effects of fermented dairy foods on CVD risk.

Fermented dairy foods, body weight and inflammation

The consumption of fermented dairy foods may have a primary preventive effect on CVD by supporting the development of a healthy gut microbiota. In a review on this topic, Marette and Picard-Deland (2014) argued that the early introduction of yoghurt into the diets of children was important in establishing a microbial community that supports long term health.

More research is needed in this area, but in the first instance, yoghurt was seen to deliver essential nutrients with high bioavailability and relatively low energy density. The energy value of yoghurt may be considered problematic with high fat varieties and with added ingredients, particular sugar. In a randomised crossover trial of 45 young adults whose diets were supplemented with whole fat or low fat dairy products (milk and yoghurt) during 8 week periods, providing the whole fat dairy supplement increased weight significantly compared to the low fat supplements (1.2kg 95% CI=0.5-1.8. P=0.007). (Alonso 2009). While the crossover design used in this study is powerful in determining treatment effects, it should be noted that these students from Spain were asked to consume usual diets (substituting dairy foods) and additional efforts were not made for reducing energy intake. Nevertheless, this study did show how fat content may serve as a passive source of energy when other parts of the diet are not considered.

Put in a broader context, observational studies tell us something about people who eat specific foods as a normal part of their diet. In a cross sectional analysis of data from two cohorts related to the Framingham Study (n=6526 older adults), yoghurt consumers were found to have a higher diet quality score and higher intakes of key micronutrients than non-consumers (Wang et al 2013). This places usual yoghurt consumption in the context of a healthy diet. Combined with the analysis showing yoghurt in a negative association with 4 yr weight gain in a similar population (Mozaffarian), the position of yoghurt in CVD prevention becomes clearer.

Basal inflammation associated with obesity is a further consideration, and there are indications that fermented dairy products may have protective effects. For example, in a cross sectional analysis of the ATTICA study (n=3042 adults) inverse associations were found between markers of inflammation (C-reactive protein, CRP; interleukin-6, IL-6 and tumour necrosis factor-alpha, TNF-α) and consumption of dairy products (Panagiotakos 2013). Compared to those consuming fewer than 8 servings per week, significant reductions were found between those consuming between 11-14 serves per week ($P<0.05$) and the differences were even greater for those consuming more than 14 servings per week ($P<0.01$). Although the analysis focused on dairy foods as a group, the cohort reported consumption of white cheese such as feta (93%), hard yellow cheese (92%), full fat yoghurt and/or milk (65%), low fat yoghurt (50%) and low fat milk (46%). A greater focus on fermented dairy foods has been suggested in clarifying the research effort (Nestle 2013). In a more powerful 3 week crossover study comparing effects of low fat (milk/yoghurt) with fermented (yoghurt /

cheese) or non-fermented (butter/cream/ice cream) dairy foods, the concentrations of IL-6 was significantly lower on low fat or fermented diet than on the non -fermented diet ($P<0.05$). This study reported on a number of cardiovascular biomarkers in overweight adults, and the overall conclusion was that fermented dairy products appeared more favourable (Nestel 2013). The comprehensive approach demonstrated may be more informative, bearing in mind that a single biomarker is insufficient for addressing CVD risk, rather, multiple biomarkers and studies with clinical endpoints are required (Astrup 2013).

Fermented dairy foods and CVD

In a review of epidemiological research Huth and Park [6] found no association between dairy product consumption and increased risk of CVD in the majority of studies. Cheese intake and risk of CVD was reported in 6 prospective cohort studies from 5 countries, almost all showing no association between consumption and risk, but this could indicate a high degree of residual confounding. Nine trials were identified examining the effects of cheese on blood lipid levels. These showed that a lower LDL-cholesterol (LDL-C) was achieved in diets providing cheese vs butter with the same dietary fat and saturated fatty acid (SFA) content. Thus cheese may not increase LDL-C compared with a lower SFA diet (Hugh and Park). An earlier review by German (2009) came to a similar conclusion that eating hard cheese may have a lesser LDL raising effect than consuming butter or milk (German) [4]. Fifteen studies were identified examining the effects of fermented milk and yoghurt. These produced little evidence that conventional starter cultures (*L. Bulgaricus, S, Thermophilus*) lower LDL-C or TG or raise HLD-C. Again, there are problems with controls and confounding, and in this case, the use of different probiotic bacterial strains making comparisons difficult (Huth and Park). The conclusions were similar to a previous critique (nestle) [9] that there is a need to control for energy and macronutrient intakes, to determine appropriate bacterial concentrations, and to consider the blood lipid status of subjects.

In a more recent review, Astrup concluded that observational studies show the consumption of yoghurt and other dairy products is associated with a reduced risk of obesity and CVD, with some support from RCTs. Treating the risk associated with saturated fat intakes and blood cholesterol in isolation of food sources is now seriously challenged. This is particularly the case for cheese, where studies do not concur with anticipated effects based on saturated fat content. In addition, foods delivering a probiotic effect such as yoghurt may afford additional protection at the gut level.

Thus despite the lack of definitive results in reviews examining the relationship between dairy foods and CVD reported earlier (Gibson et al) the situation is becoming more clear. Problems have included bias in study design, in particular the lack of adjustments for socio-economic and educational factors Gibson et al. These may reflect cultural differences in the use of dairy foods. Dietary assessment methods are particularly problematic. Food categorisation remains a problem, particularly with continuing changes in available dairy products. Further research on fermented dairy foods still needs to consider dietary fat, (including saturated fat), the types of foods in the diets, and the total background diet, in addition to carefully delineating study populations and disease risk status. At least one study involving a dose response meta-analysis has confirmed no significant associations between consumption of dairy food products (per200g/day) and coronary heart disease (Muthu). Future research may well focus on individual dairy products, and in particular cheese and yoghurt given their presence in the protective Mediterranean diet.

Plausibility of potential effects

While not direct evidence of effects, research on proposed mechanisms adds to the plausibility of results from clinical studies and population surveys and can further inform study designs. The potential mechanisms by which fermented dairy foods may act on gut health and CVD risk have been discussed in the literature. In a review on fermented milk [15], a number of studies were found to show beneficial effects of milk fermented with *L., helveticus* on hypertension, with effects postulated as due to ACE inhibition from peptides in the fermented milk products. Different bacterial strains were seen to have different cholesterol lowering properties, but the bacteria needed to be able to survive the gut and colonise the intestine (probiotic effect). The effect of cheese was suggested as a response to the calcium content or peptides produced during fermentation [15]. It has also been argued that fermentation is the likely mediator for the relatively smaller effects of consuming cheeses on raising LDL seen in studies in Norway, Denmark and Australia [9]. An hypothesised mechanism for the effects of yoghurt relates to a reduced cholesterol synthesis (via increased short chain fatty acids) or reduced reabsorption of bile acids [9].New biomarkers of CVD also contribute to the developing science behind the evidence base. For example, the measurement of arterial stiffness (using pulse wave velocity and pulse pressure) was able to expose a negative linear relationship with intakes of dairy food in the Main Syracuse cohort (n=587).

The dairy food consumption likely reflected dietary patterns (mostly milk, mostly reduced fat, then cheese 2-4/wk, but rarely yoghurt) [1]. In contrast a related study examining common carotid artery intima media thickness (CCA-IMT) in1080 women over 70yrs in Perth, Australia, found a negative association with yoghurt consumption, but not with cheese, milk, or total dairy food intake [7]. Because every study has unique characteristics, it remains difficult to integrate the results. Nevertheless, potential mechanistic understandings are informative in developing hypotheses and interpreting the results of human studies.

Fermented dairy foods in cultural cuisines

Mechanistic studies tend to focus on nutrients, and RCTs on single foods, but in reality foods are consumed in the context of whole diets, often defined by cuisines. There is limited reporting in the scientific literature on cultural cuisines, with the exception of the Mediterranean Dietary pattern. Indeed the evidence supporting the health qualities of the Mediterranean diet pattern have led to global recognition via an inclusion on UNESCO's Intangible Cultural Heritage list, expanding the appreciation of the dietary pattern to that of 'treasured elements of culture with local and global value'(Reguant-Aleix) [16]. Recently the PREDIMED study demonstrated the highly significant impact of a Mediterranean style diet on preventing cardiovascular disease in older adults in Spain [2]. Adherence to the Mediterranean diet was based on a pattern of traditional cultural food choices (Table 1)

The key foods utilised in the assessment of the PREDIMED Mediterranean cuisine appeared silent on dairy foods, but did emphasise avoidance of soft drinks and bakery goods. This likely reflects the cultural cuisine of the Spanish region, and in this sense contrasts with the Greek style Mediterranean dietary pattern in which yoghurt, cheese and milk are recognised as traditional foods [17]. The interdependence between individual foods, their significant nutritional components and the dietary pattern in which they are all consumed [11] may be significant (Fig 1). With the addition of fermented dairy foods in particular, a consideration of the impact of dairy peptides and probiotics may be included

Bearing in mind the contextual nature of cuisine patterns, there is some evidence that fermented dairy foods consistently appear in a positive health frame across the globe. While further research is needed, data from a number of major cohort studies have provided interesting results. In Europe (EPIC-Interact) an inverse association was found with consumption of cheese and fermented dairy food and risk of type 2 diabetes, a risk factor for CVD [13], and in the Netherlands (NCLS cohort) an inverse association was found between

consumption of fermented full-fat dairy food and all-cause mortality [5]. In Sweden (Malmo cohort), with a Nordic cuisine, a 15% reduction in CVD risk (P=0.003) was found comparing the highest vs lowest intakes of fermented milk. There was also a decreased risk CVD with cheese intake in women (P=0.03) but not men [14]. In another Swedish study of women undergoing mammography [10] total cheese intake was inversely associated with MI risk (HR=0.74; 0.60-0.91). In this report the authors stressed the need to differentiate between different foods in the dairy category, and to not treat all dairy foods as the same. They also acknowledged the limitations for research inherent in the cultural use of dairy foods. While a Japanese cuisine may be seen in stark contrast to European cuisines, dietary pattern research using factor analysis and data from the Osaka NHI cohort found a lower CVD risk with the Japanese pattern (fish, seaweed, vegetables, fruit, green tea) and an increased risk with the animal food pattern. Notably, a third pattern (DFA) defined by high dairy food, high fruit and vegetables and low alcohol intake was not associated with increased CVD risk [12]. Interestingly, the Japanese pattern was associated with a high sodium intake and greater risk of hypertension, so the findings of the analysis need to be considered in total. The translation of scientific research on diets clearly has multiple implications, particularly with the globalisation of the food supply and fusion of cuisines that is seen with cultural integration. In addition to local vs global issues, there are other indicators from environmental conditions which could be described as more extreme. For example, no association was found between dairy food intake and the incidence of CVD in a cross sectional study of 14 villages of the Nunavik in Canada [3]. Even though this was a small study (n=543), the intake of dairy food was small (120-290g/day), compared to that found in the Swedish study previously referred to, of 180-673g/day [10], for example. This cluster of studies from various regions suggests that studying the effects of fermented dairy foods would need to address the degree of dietary exposure alongside broader dietary and other environmental factors.

Conclusion

Reviews of observational studies have consistently shown that a regular intake of milk, cheese and yoghurt may be associated with a reduced risk of cardiovascular disease, but more needs to be known on the type of food, in particular fermented dairy foods such as cheese and yoghurt. The background diet or cuisine remains an important factor in terms of energy and nutrient balance, food variety and amounts of foods consumed. The indications are that moderate amounts of fermented dairy foods may play a significant role in dietary patterns that protect against cardiovascular disease but more targeted research is required. There are

many challenges; in particular careful consideration is required of the study designs, classification of individual dairy foods, serving sizes and the cuisine patterns in which they are consumed.

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