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Dairy Products, Dairy Fatty Acids, and the Prevention of Cardiometabolic Disease: a Review of Recent Evidence

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Abstract

Purpose of Review To examine recent literature on dairy products, dairy fatty acids, and cardiometabolic disease. Primary questions of interest include what unique challenges researchers face when investigating dairy products/biomarkers, whether one should consume dairy to reduce disease risk, whether dairy fatty acids may be beneficial for health, and whether one should prefer low- or high-fat dairy products.

Recent Findings Dairy composes about 10% of the calories in a typical American diet, about half of that coming from fluid milk, half coming from cheese, and small amounts from yogurt. Most meta-analyses report no or weak inverse association between dairy intake with cardiovascular disease and related intermediate outcomes. There is some suggestion that dairy consumption was inversely associated with stroke incidence and yogurt consumption was associated with lower risk of type 2 diabetes. Odd chain fatty acids (OCFAs) found primarily in dairy (15:0 and 17:0) appear to be inversely associated with cardiometabolic risk, but causation is uncertain. Substitution analyses based on prospective cohorts suggested that replacing dairy fat with vegetable fat or polyunsaturated fat was associated with significantly lower risk of cardiovascular disease.

Summary Current evidence suggests null or weak inverse association between consumption of dairy products and risk of cardiovascular disease. However, replacing dairy fat with polyunsaturated fat, especially from plant-based foods, may confer health benefits. More research is needed to examine health effects of different types of dairy products in diverse populations.

Keywords Dairy · Saturated fat · Yogurt · Cardiovascular disease · Odd chain fatty acids

Introduction

In an era where many food categories have been deemed healthy or unhealthy, dairy remains controversial. Its relationship with cardiometabolic disease, particularly cardiovascular disease (CVD), which includes coronary heart disease (CHD), stroke, heart failure, and peripheral artery disease, has long been a subject of investigation, and despite many publications, no consensus has been reached. Dairy products are based on milk from mammals and include milk itself, cream, butter, cheese, yogurt, frozen desserts, and whey and contain a varied collection of micro- and macronutrients, namely saturated fatty acids (SFAs) [1]. While researchers have recommended the reduction in total SFAs in the diet for the prevention of CVD [2], the relationship between dairy fat and disease is still unsettled. Thus, it is important to pose several questions: do dairy SFAs decrease CVD risk? Should one eat more dairy for a healthier heart? Is low fat or high fat preferred? The present review of dairy and dairy SFAs will consider these questions through a review of available evidence, outline several challenges in the field, and present gaps in knowledge that may be filled by future research.

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Metabolism and Measurement of Dairy Products and Biomarkers

Dairy is a major part of the Western diet and composes 10% of daily calories in the USA [3]. Dairy products are diverse in both variety and composition, but all are derived from milk. The lipid profile of milk consists of dozens of types of acylglycerols, cholesterols, and fatty acids [4]. Saturated fats compose the majority of the total fat content in milk [5], although the specific composition of milk varies considerably according to animal feeding method, genetics, environment, lactation stage, and processing method [6, 7]. Table 1 lists the fatty acid composition of retail milk from the USA in 2008 [8]. Proposed biomarkers of dairy include fatty acids 14:0, 14:1, 15:0, 17:0, 17:1, and trans 16:1n-7 [9], but most research efforts have focused on the odd chain fatty acids (OCFAs) 15:0 (pentadecanoic acid) and 17:0 (heptadecanoic acid). Historically, OCFAs were of little scientific interest due to their relatively low physiological concentrations compared to even chain fatty acids (ECFAs) [10] and were used primarily as internal standards in chromatographic analyses [11]. In the body, the majority of OCFAs undergo β-oxidation to produce acetyl-CoA, NADH, and FADH2 [12]. Since β-oxidation involves shortening fatty acid chains two carbons at a time, metabolism of OCFAs ends with propionyl CoA, whereas ECFAs end with acetyl CoA [13]; whether or not this makes a difference in incidence of clinical endpoints has yet to be reported. In addition to fat, milk also typically contains about 3.5% protein, 80% of which is in the form of casein and 20% in whey protein [14]. Existing studies of milk protein consumption point to some potential benefit for metabolic health, but the data are inconclusive [15]. Carbohydrates dominated primarily by lactose constitute approximately 4.6% of milk by weight [16]. Although the cardiovascular effects of lactose are poorly characterized, lactose intolerance may affect individual willingness to consume dairy products [17].

Table 1 Fatty acid (FA) composition of retail milk samples in the USA [8]

Variable (g/100 g of FA)	Mean	SEM
C4:0	4.15	0.017
C6:0	2.13	0.008
C8:0	1.19	0.006
C10:0	2.59	0.015
C12:0	2.87	0.018
C14:0	9.53	0.039
C14:1	0.82	0.007
C15:0	0.89	0.004
C16:0	28.08	0.078
C16:1	1.48	0.011
C17:0	0.52	0.002
C18:0	11.68	0.078
C18:1, trans-6	0.32	0.002
C18:1, trans-9	0.29	0.002
C18:1, trans-10	0.55	0.007
C18:1, trans-11	1.48	0.013
C18:1, trans-12	0.54	0.004
C18:1, cis-9	23.58	0.074
C18:2, cis-9, cis-12	3.19	0.019
C20:0	0.09	0.001
C18:3	0.38	0.004
C18:2, cis-9, trans-11	0.55	0.004
C18:2, trans-10, cis-12	ND	–
Other	3.09	0.021

ND, not detected (< 0.01% of total fatty acids); SEM, standard error of the mean

Reprinted with permission from O'Donnell-Megaro AM, Barbano DM, Bauman DE. Survey of the fatty acid composition of retail milk in the United States including regional and seasonal variations. Journal of Dairy Science. 2011;94 (1):59–65

Analysis of dairy products and biomarkers presents several challenges to researchers, the most important being the accurate measurement of exposure. Reliable measurements of food intake and nutrients have been a long-standing challenge in the field of nutritional epidemiology. For most large-scale observational studies, semiquantitative food frequency questionnaires (FFQs) are the preferred method of assessment for intake. FFQs such as the Willett [18] and the Block [19] have been validated for both accuracy and reproducibility. Dairy intake as reported by FFQs tends to exhibit a relatively high degree of correlation with diet records. Byers et al. reported a Spearman correlation of 0.53 for dairy products compared with 0.41 for fruits, 0.41 for vegetables, and 0.39 for meats [20]; van Liere et al. reported a correlation of 0.67 for dairy [21]; the EPIC group of Spain reported a correlation of 0.90 [22]. Regarding biomarkers, 15:0 and 17:0 remain the most popular candidates [23]. Assessment of these OCFAs typically consists of analyzing blood samples with gas chromatography-mass spectrometry after storage at – 80 °C. The concentration of OCFAs found in the adipose tissue is highly correlated with dairy intake assessed by diet record (Spearman's $r = 0.59$ and 0.45 for 15:0 and 17:0, respectively) [23, 24], although trace amounts may also be found in beef, fish, and other animal ruminants [23], leading to doubts as to whether OCFAs may be used as a valid biomarker in populations consuming heavy amounts of these meats [25]. As such, caution must be exercised when deciding whether the nominal exposure of interest in biomarker studies is dairy products (which contain a multitude of micro- and macronutrients) or dairy fats (a single component derived from multiple potential sources). Recent publications have also speculated on the possibility of de novo synthesis of OCFAs in humans via α-oxidation, the details of which are beyond the scope of this review [26–28]. Roberts et al. observed conversion of 16:0 to 15:0 during adipocyte differentiation, raising the possibility

that plasma OCFA concentrations may be regulated [29]. Weitkunat et al. further reported that gut-derived propionate may be used to synthesize OCFAs in the liver [30].

Dairy Products and Cardiometabolic Disease

Numerous observational and experimental studies of dairy intake and cardiovascular disease or related secondary outcomes have been conducted, most having been published after 2010. In the USA, the vast majority of dairy intake consists of fluid milk (51%) and cheese (45%), which presents challenges since cheese is most often consumed as an ingredient in other foods [31]. Thus, results from prospective studies of total dairy intake most likely represent a combination of milk and cheese intake and also capture correlations of CVD with other components consumed with cheese such as pizza and sandwiches.

Total Dairy

Figure 1 summarizes the results of several meta-analyses with various cardiometabolic endpoints. The most recent meta-analysis of dairy products by Guo et al. covered all cohort studies through September 2016 [32]. Using data from 29 studies accruing 28,419 cases of CHD and 25,416 cases of composite CVD, the authors found an inverse association between total dairy intakes for CVD (relative risk (RR) = 0.98, 95% confidence interval (CI) = 0.97, 0.99 per 20 g/day) but not CHD (RR = 0.99, 95% CI = 0.98, 1.01 per 20 g/day), although there was a large degree of heterogeneity in both outcomes. The results were similar for stroke: de Geode et al. indicate that a 200-g/day increase in milk intake was associated with a RR = 0.93, 95% CI = 0.88, 0.98; this association appeared to be stronger in East Asian (RR = 0.82, 95% CI = 0.75, 0.90) compared to Western countries (RR = 0.98, 95% CI = 0.95, 1.01) [33]. Soedamah-Muthu et al. report a similar magnitude of association for total dairy intake and hypertension in a meta-analysis of nine cohort studies (RR = 0.97, 95% CI = 0.95, 0.99 per 200 g/day) [34], although a publication using Mendelian randomization techniques did not support this finding (OR = 1.04, 95% CI = 0.88, 1.24 comparing high vs. low consumer allele) [35]. Kim and Je found an inverse association of dairy intake with metabolic syndrome (RR = 0.85, 95% CI = 0.73, 0.98 per 1 serving/day) [36], and a small benefit was observed for type 2 diabetes mellitus (T2DM) (RR = 0.97, 95% CI = 0.95, 1.00 per 200 g/day) [37].

Although no randomized trials have been conducted for clinical endpoints, a meta-analysis of nine trials for lipid profile (Fig. 2) found no significant association for the effects of high dairy intake (≥ 3 servings/day) vs. low dairy (< 3 servings/day) on high-density lipoprotein cholesterol (HDL-c), or triglycerides, and a small significant increase in low-density lipoprotein cholesterol (LDL-c) [38], and another systematic review of eight trials conducted among overweight/obese adults reported seven neutral studies and one report of improved inflammatory marker profile among those randomized to dairy consumption [39].

Subgroups of Dairy

Figure 3 summarizes meta-analyses of cheese, milk, yogurt, and butter with various cardiometabolic outcomes. There was a modest inverse association between consumption of cheese and CHD (RR = 0.90, 95% CI = 0.84, 0.95 per 50 g/day) [40], but no significant association for yogurt and CVD (RR = 1.03, 95% CI = 0.97, 1.09 per 50 g/day) [32]. A large recent study not included in previous meta-analyses reported that yogurt and cheese consumption were strongly associated with lower risk of overall and CVD-specific mortality [41]. Although questions of type

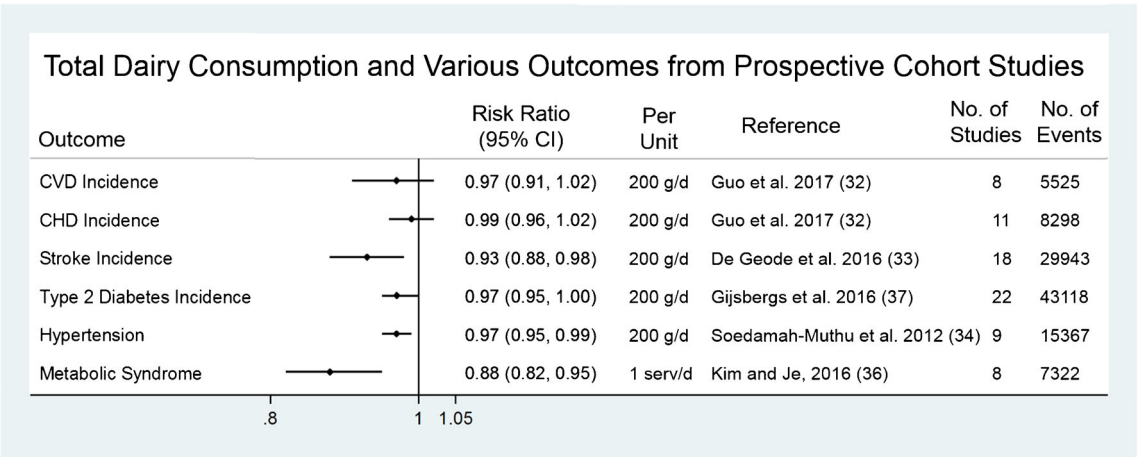

Fig. 1 Summary of recent meta-analyses of total dairy consumption with cardiometabolic endpoints from prospective cohort studies. CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; g/d, grams per day; MetS, metabolic syndrome; RR, risk ratio; serv/d, servings per day

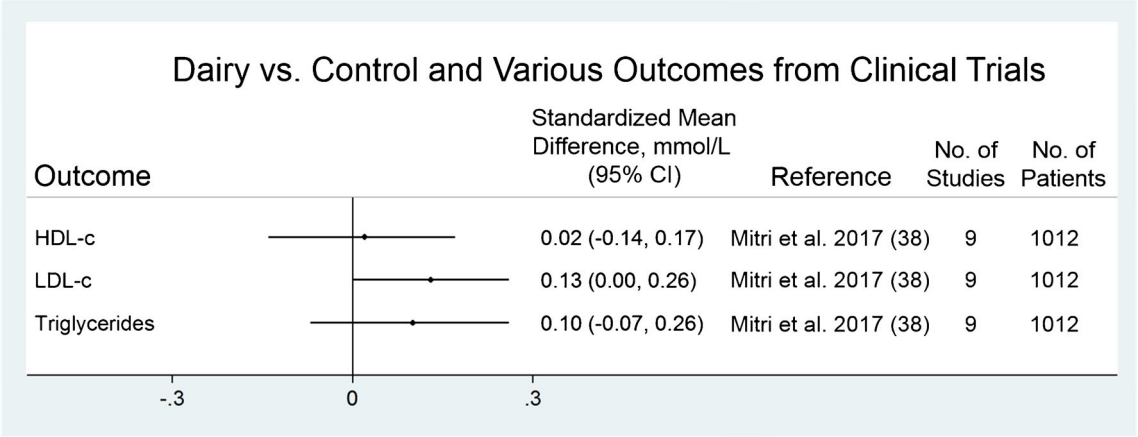

Fig. 2 Summary of dairy intervention vs. controls with cardiovascular risk factors from clinical trials. CI, confidence interval; CVD, HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; mmol/L, millimoles per liter

of cheese (high fat vs. low fat) remain unanswered, the finding that cheese seems to be inversely associated with CVD is surprising, given that cheese is seldom eaten by itself and is usually included in mixed dishes such as pizza, burgers, pasta, and other grain-based dishes [42]. These foods constitute a typical Western dietary pattern [43] that has been shown to increase risk of CHD [44, 45] and is associated with unhealthy lifestyle factors such as lower multivitamin use, smoking, low physical activity, and heavy drinking [46]. Yogurt is also a food of particular interest, given its potential to stimulate gut microbiota [47] and existing studies which suggest benefit for body weight and type 2 diabetes [37, 48]. Probiotic bacteria in yogurt and cheese, mainly members in the *Lactobacillus* and *Bifidobacterium* genera [49], have also shown favorable effects on immunity, inflammation, diarrhea prevention, and cardiovascular risk factors in clinical trials [50]. Thus, specific attention should be given to cheese and yogurt in future studies.

Total Dairy Fat Intake and Cardiometabolic Disease

Fat composes the majority of the energy content and weight of dairy (Table 1). Among fat subtypes, even chained saturated fatty acids 14:0, 16:0, and 18:0 constitute the majority of milk fat content. A case-control study conducted by Biong et al. indicated no significant association of 14:0 concentration in adipose tissue and later myocardial infarction [51]. Goldbohm et al. reported no association of milk fat intake with CVD mortality in men but a slight positive association of milk fat intake and CHD mortality (RR = 1.11, 95% CI = 1.01, 1.21) in a cohort of 120,852 participants [52]. de Oliveira Otto et al. reported that higher intake of dairy SFAs was associated with a lower CVD risk (RR = 0.79, 95% CI = 0.68, 0.92 for 5 g/day) but that higher intake of meat SFAs was associated with a higher risk (RR = 1.26, 95% CI = 1.02, 1.54 for 5 g/day) [53].

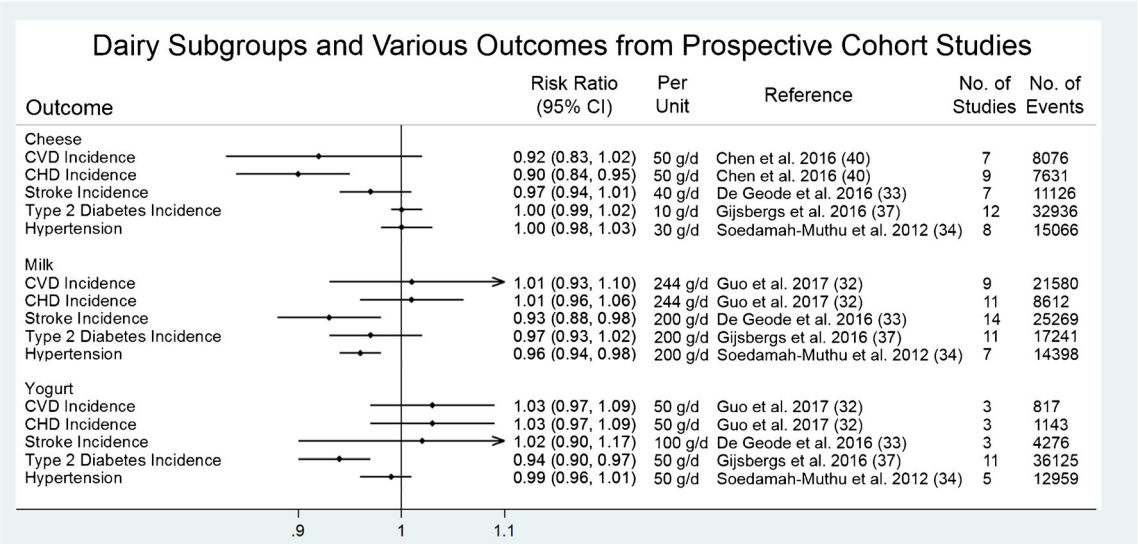

Fig. 3 Summary of recent meta-analyses of cheese, milk, and yogurt with cardiometabolic endpoints from prospective cohort studies. CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; g/d, grams per day; RR, risk ratio

However, these results can be misleading because it is virtually impossible to separate the effects of SFAs from dairy or meats from other components of these foods.

Chen et al. [54] found that dairy fat intake was not significantly associated with incident CVD, CHD, or stroke, but that substitution of 5% daily calories from dairy fat with polyunsaturated fat or vegetable fat was associated with a 24% (RR = 0.76, 95% CI = 0.71, 0.81) and 10% reduction (RR = 0.90, 95% CI = 0.87, 0.93) in CVD, respectively (Fig. 4). On the other hand, substitution of dairy fat with animal fat (primarily from red meat) was associated with an increased risk of CVD (RR = 1.06, 95% CI = 1.02, 1.09). These results are in line with the general observation that replacement of saturated fat with polyunsaturated fat, especially from plant sources, is associated with a reduced risk of CHD [55].

Odd Chain Fatty Acids and Cardiometabolic Disease

Although the number of studies relating circulating OCFAs to cardiometabolic disease is sparse, existing data point to a possible protective effect. A meta-analysis of 13 studies found a non-significant association of 15:0 with CVD (RR = 0.94,

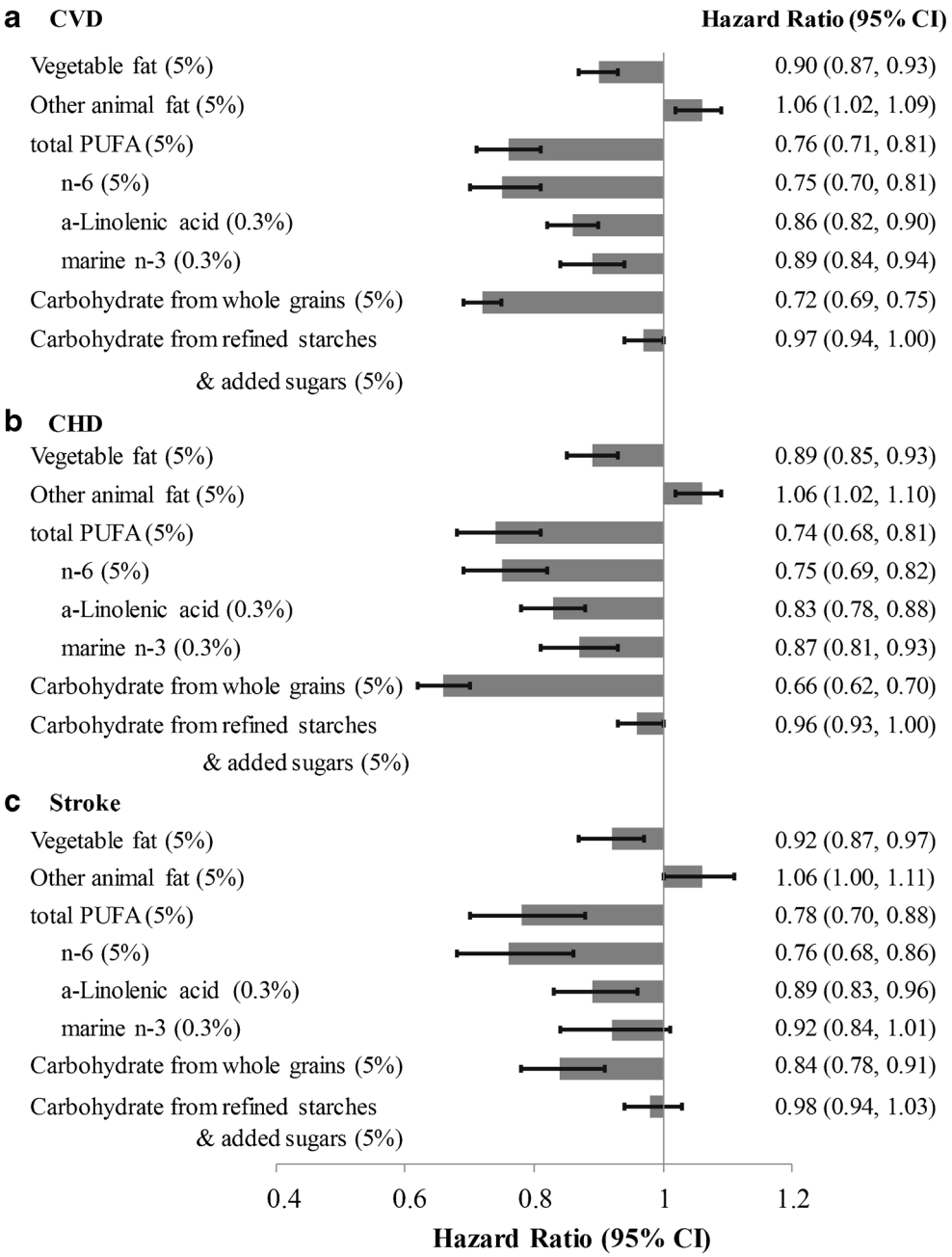

Fig. 4 From Chen et al.: RR (95% CIs) for CVD (A), CHD (B), and stroke (C) associated with isocaloric substitutions of vegetable fat, other animal fat, PUFA, and carbohydrate for dairy fat in the NHS I, II, and HPFS. The 95% CIs are represented by horizontal lines, and gray bars represent overall estimates. Reproduced with permission from Frank B. Hu [54]. From Chen M, Li Y, Sun Q, Pan A, Manson JE, Rexrode KM, et al. Dairy fat and risk of cardiovascular disease in three cohorts of US adults. Am J Clin Nutr. 2016 Nov;104(5):1209–1217

95% CI = 0.77, 1.15), but an inverse association for 17:0 (RR = 0.82, 95% CI = 0.68, 0.99) comparing top vs. bottom tertiles [56]. No meta-analysis has been published for T2DM, but the largest study from the EPIC-InterAct cohort reported a negative association for 15:0 (RR = 0.79, 95% CI = 0.73, 0.85 per standard deviation (S.D.)) and 17:0 (RR = 0.67, 95% CI = 0.63, 0.71 per S.D.) [57]. Similar results were observed in a case-control study from Northern Sweden [58], the Melbourne Collaborative Cohort Study [59], the Nurses' Health Study and Health Professionals' Follow-up Study [60], and the Insulin Resistance Atherosclerosis Study [61]. The EPIC-Norfolk cohort confirmed protective associations only for 17:0 [62]. Data from the Cardiovascular Health Study [63], EPIC-Potsdam [64], and Multi-Ethnic Study of Atherosclerosis [65] suggested non-significant inverse associations.

The totality of evidence to date suggests an inverse association of 15:0 and to a larger extent, 17:0, with CVD and T2DM, but questions remain. Are OCFAs truly proxies for dairy intake or are they themselves a causal factor for cardiometabolic risk reduction? If so, is it plausible that small amounts of OCFAs could have large effect sizes? One salient discrepancy is that the effect sizes of dairy biomarkers are much larger than those of dairy intake measured from consumption data. Attenuated risk ratios could arise due to methodological issues associated with FFQs, such as within-person variation or non-differential misclassification [66]. Another explanation is the relationship between OCFAs and cardiometabolic outcomes could be confounded by healthy lifestyle [67]. In the EPIC-InterAct study, OCFAs showed the highest correlation with dairy intake, they were also significantly correlated with intakes of fruits/vegetables and nuts [57]. Rosell et al. note that 15:0 and 17:0 levels were associated with low alcohol consumption, high physical activity [68], and high fiber intake [30]. Finally, the possibility that OCFAs, particularly 17:0 [69], are imperfect markers of dairy or that they may be synthesized de novo and therefore regulated [13, 31] cannot be ruled out. One must also keep in mind that dairy fat contains only trace amounts of OCFAs by weight and that the majority of SFAs in milk is composed of 14:0, 16:0, and 18:0 [70], with 16:0 exhibiting the strongest positive associations with CHD [54].

High Fat or Low Fat?

The USDA currently recommends that Americans should consume fat-free and low-fat dairy instead of high-fat alternatives, citing that "increasing the proportion of fat-free milk consumed to meet Dairy Group recommendations would ... decrease amounts of sodium, cholesterol, and saturated fatty acids" [31]. Current evidence of high-fat vs. low-fat dairy do not conclusively point to a benefit one way or the other [71]. Guo et al. report that neither low-fat (RR = 0.98, 95% CI = 0.95, 1.01 per 200 g/day) nor high-fat dairy (RR = 0.93, 95% CI = 0.84, 1.03 per 200 g/day) was significantly associated with CVD [32]; similarly, Gijsbers et al. indicate similar associations for low-fat (RR = 0.96, 95% CI = 0.92, 1.00 per 200 g/day) and high-fat dairy (RR = 0.98, 95% CI = 0.93, 1.04 per 200 g/day) with type 2 diabetes [37]. Current experimental data are also inconclusive. A meta-analysis of 21 randomized trials revealed that both low-fat and high-fat dairies significantly increase body weight, but that there were no differences for waist circumference, HOMA-IR, fasting glucose, LDL-c, HDL-c, systolic blood pressure, diastolic blood pressure, or C-reactive protein [72]. In a comprehensive Finnish study of 34,525 participants over 40 years, population-level shifts from high-fat to low-fat dairy sources were critical in dramatic decreases in CHD mortality (overall 83% decreased mortality rate) [73]. On the other hand, low-fat dairy, cheese, and yogurt may contribute to the prevention of T2DM according to a meta-analysis of eight prospective studies (RR = 0.88, 95% CI = 0.84, 0.93 per 200 g/day) [74]. Thus, while advocated by some, current evidence does not suggest that high-fat dairy (such as whole milk) is superior to low-fat dairy in terms of disease risk [75].

In light of the lack of robust evidence for the differential health effects of low vs. high-fat dairy, the primary motivation to recommend low-fat products therefore comes from the anticipated reduction in consumed SFAs. A great deal of controversy surrounds the issue of SFAs and cardiovascular disease, and much of the misunderstanding stems from poorly conducted studies that fail to consider replacement nutrient for saturated fat. In free-living populations, a person consuming more SFAs typically replaces something else from their diet, usually carbohydrates [76]. Thus, in most epidemiological analyses, saturated fat is often compared to total carbohydrates (comprised of refined starch and added sugars in significant amounts) [77]. When saturated fats are replaced with unsaturated fats, an inverse association with CVD is observed [55]. Consideration of these substitution studies led to the American Heart Association (June 2017) recommending the replacement of SFAs with unsaturated fats, especially polyunsaturated fat [2].

Conclusions

To date, several large meta-analyses found null or weak inverse associations between dairy consumption and risk of CVD. Currently, the 2015–2020 Dietary Guidelines for Americans recognize that low- or reduced fat dairy can be part of a healthy diet [32], based on dietary pattern analyses, observational evidence, and the fact that dairy products provide significant amounts of under-consumed nutrients in the US

population such as calcium, potassium, and vitamin D. Current evidence does not support consuming high-fat dairy products to improve metabolic health. Despite some evidence that minor components of dairy fat such as odd chain fatty acids were associated with lower risk of diabetes and cardiometabolic risk factors, dairy fat as a whole is not considered an optimal type of fat due to high saturated fatty acid content, and there is some evidence that replacing dairy fat with polyunsaturated fat, especially from plant-based foods may confer health benefits. Whether fermented dairy products such as different types of cheese and yogurt have unique metabolic benefits requires further investigations.

Several methodological issues need to be considered when interpreting the current evidence. First, despite reasonable validity of FFQs in assessing dairy intake, measurement errors are inevitable, especially for individual types of dairy. Random errors may have attenuated the observed associations. Therefore, it is important to collect repeated measures of diet, which can be used to reduce within-person random errors and represent long-term dietary habits. It is also important to continue to identify reliable biomarkers of dairy intake. Second, sources of heterogeneity in population characteristics must be considered. For example, there is a biological reason to believe that dairy may have different health effects on individuals from East Asia compared to other countries, since lactose, a major component of dairy, cannot be metabolized by most East Asians [78]. Effect modifications by sex [79], obesity [80], and baseline hypertension [81] have also been observed. Third, studies should continue to report the relative risks of specific dairy products with health outcomes. Specific foods such as milk, cheese, and yogurt may show different effects on cardiometabolic health due to different amounts of nutrients, bioactive compounds, and fermentation methods for different dairy products. Therefore, more research is needed to examine health effects of different types of dairy products in diverse populations. Lastly, substitution analyses should be employed to investigate the replacement of dairy with other foods, especially plant-based items such as soy and nuts. It is more desirable to make practical dietary recommendations based on substitution analyses.

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Compliance with Ethical Standards

Conflict of Interest Dr. Frank Hu has received research support from the California Walnut Commission and an honorarium from Metagenics. Dr. Edward Yu declares no conflict of interest.

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