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REVIEW

The relationship between high-fat dairy consumption and obesity, cardiovascular, and metabolic disease

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Abstract
Purpose To comprehensively review the data on the relationship between the consumption of dairy fat and high-fat dairy foods, obesity, and cardiometabolic disease.
Methods We have conducted a systematic literature review of observational studies on the relationship between dairy fat and high-fat dairy foods, obesity, and cardiometabolic disease. We have integrated these findings with data from controlled studies showing effects of several minor dairy fatty acids on adiposity and cardiometabolic risk factors, and data on how bovine feeding practices influence the composition of dairy fat.
Results In 11 of 16 studies, high-fat dairy intake was inversely associated with measures of adiposity. Studies examining the relationship between high-fat dairy consumption and metabolic health reported either an inverse or no association. Studies investigating the connection between high-fat dairy intake and diabetes or cardiovascular disease incidence were inconsistent. We discuss factors that may have contributed to the variability between studies, including differences in (1) the potential for residual confounding; (2) the types of high-fat dairy foods consumed; and (3) bovine feeding practices (pasture- vs. grain-based) known to influence the composition of dairy fat.
Conclusions The observational evidence does not support the hypothesis that dairy fat or high-fat dairy foods contribute to obesity or cardiometabolic risk, and suggests that high-fat dairy consumption within typical dietary patterns is inversely associated with obesity risk. Although not conclusive, these findings may provide a rationale for future research into the bioactive properties of dairy fat and the impact of bovine feeding practices on the health effects of dairy fat.

Keywords Milk fat · Dairy fat · Obesity · Adiposity · Diabetes · Cardiovascular disease

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Introduction

Most dietary guidelines recommend the consumption of milk and dairy products as an important part of a healthy, well-balanced diet [1, 2]. The rationale most often provided for this recommendation is that milk and dairy products are rich sources of protein, calcium, and added nutrients such as vitamins A and D [1]. In both public perception and the scientific community, dairy fat is typically portrayed as a negative component of milk and dairy products, largely because it is energy dense and a rich source of cholesterol and saturated fatty acids (SFA). Therefore, typical dietary advice recommends fat-reduced milk and dairy products. For example, the US Department of Agriculture "Dietary Guidelines for Americans 2010" recommends to "[…] increase the intake of fat-free or low-fat milk and milk products" [1]. These guidelines also specifically recommended replacing butter with plant-derived oils rich in

monounsaturated fatty acids (MUFA) and/or polyunsaturated fatty acids (PUFA). One rationale behind these recommendations is the finding that both dietary cholesterol and SFA raise total serum cholesterol concentrations, and the ratio of low-density lipoprotein (LDL) to high-density lipoprotein (HDL) cholesterol when compared to MUFA or PUFA [3, 4]. As total cholesterol and the ratio of LDL-to-HDL cholesterol are risk factors for cardiovascular disease (CVD), it is thought that reducing the intake of fats rich in cholesterol and SFA will lower the risk of CVD. Another rationale is the higher energy density of full-fat milk and dairy products. Energy density has been proposed to affect calorie intake and body weight gain [5]. Partially as a result of these guidelines, the pattern of dairy fat intake has changed considerably over the last 40 years, a time frame during which the modern obesity epidemic has developed in the United States (US) and the US diet has become increasingly industrialized. Butter consumption declined 75 % over the course of the twentieth century, while low-fat and skim milk, uncommon in 1970, have largely supplanted whole milk since that time [6]. In parallel, dairy fat consumption from other sources has increased, most notably in ice cream and cheese associated with prepared foods such as pizza [1, 6]. The fat content of commercial whole milk in the United States has declined from 3.75 to 3.26 % over the last century [6].

In contrast to most animal models of atherosclerosis, dietary cholesterol does not appear to elevate the risk of CVD in the majority of humans [4]. A recent meta-analysis of observational studies concluded that the consumption of SFA is also not associated with an increased risk of CVD [3], while both this and a recent Cochrane Collaboration meta-analysis conclude that replacing SFA with unsaturated fatty acids is likely to provide some benefit [3, 7]. A recent meta-analysis of randomized controlled trials suggests, however, that replacing SFA with unsaturated fats reduces cardiovascular disease risk only if the unsaturated fat includes n-3-PUFA [8]. In addition, research conducted over the past two decades has produced a large amount of information on the composition of dairy fat, demonstrating that dairy fat is a complex substance containing fatty acids with suspected health benefits such as conjugated linoleic acids (CLA), *cis* and *trans* palmitoleic acid, butyric acid, phytanic acid, and alpha-linolenic acid (ALA). These findings call for a detailed evaluation of the evidence concerning the relationship between dairy fat consumption and human health, which to our knowledge does not currently exist. In this article, we summarize the available data on the relationship between dairy fat consumption and the risk of CVD, obesity, and type 2 diabetes mellitus (T2DM). Based on these studies, we propose that dairy fat is unlikely to increase the risk of obesity or cardiometabolic disease, and may even be a valuable component of the human diet. New data from studies on the relationship between dairy cow feeding practices and dairy fat composition suggest that this may be particularly true when dairy cows are raised on pasture.

Dairy fat and high-fat dairy consumption and chronic disease: data from observational studies

Several recent meta-analyses and reviews have examined the association between dairy consumption, adiposity, and cardiovascular and metabolic disease risk [9, 10]. We will focus on studies that have attempted to shed light on the specific health effects of dairy fat. Three approaches have been used to examine the health effects of dairy fat, as opposed to other components in dairy: (1) studies on disease associations that differentiate between full-fat and skim/low-fat milk and dairy products, as assessed by food frequency questionnaire (FFQ) or dietary record; (2) studies that have estimated dairy fat intake directly from these questionnaires and records; and (3) studies using validated biomarkers of dairy fat intake. FFQ and other forms of dietary assessment allow the estimation of food intake in large observational studies. The major caveat with FFQs is that while they capture the intake of some foods relatively accurately, for other foods, such as whole milk, they capture less than half the inter-individual variability in consumption [11]. More troubling, the remaining variability may be related to under- and over-reporting that depends on the social value associated with individual foods, raising the possibility that populations with specific demographic characteristics may have a tendency to preferentially misreport certain foods and therefore introduce bias into subsequent calculations [11]. As we will discuss in more detail below, the strong cultural stigma against foods rich in SFA in the United States over the last 30–40 years may have caused full-fat dairy products to be under- and skim milk products to be over-reported, particularly by health-conscious individuals. An objective measure of dairy fat intake may therefore be considered preferable. Such biomarkers have indeed been validated, taking advantage of the fact that dairy contains several fatty acids that are uncommon in other food sources in prevailing diet patterns, and which are the result of microbial fermentation in the rumen [12]. These include the odd-numbered saturated fatty acids pentadecanoic acid (C15:0) and heptadecanoic acid (C17:0), as well as *trans* palmitoleic acid (*trans* C16:1), all of which have been validated as markers of dairy fat intake [13–15]. Although serum and adipose tissue fatty acid markers eliminate bias and variability due to misreporting, there are unique caveats that must be considered when interpreting results based on them. First, although they derive primarily from

dairy in most prevailing diet patterns, these fatty acids can also reflect the consumption of other forms of ruminant fat, for example that contained in beef or lamb, or fatty fish [16, 17]. Second, serum measurements of dairy-derived fatty acids are not necessarily a more accurate measure of dairy fat intake than FFQs, although their concentration in adipose tissue is a relatively accurate reflection of long-term dairy fat consumption [13, 14]. Third and perhaps most problematic, certain serum fatty acids may be altered by metabolic status. For example, the findings of Hodge et al. [18] suggest that the pre-diabetic state itself alters the concentration of linoleic acid in plasma phospholipids. While plasma phospholipid linoleic acid was inversely related to diabetes risk, dietary linoleic acid trended in the opposite direction. Serum and adipose tissue C15:0, C17:0, and *trans* palmitoleic acid are relatively good dietary biomarkers; however, it remains possible that these fatty acids are influenced by metabolic factors. Despite these caveats, studies that used fatty acid biomarkers to assess the relationship between dairy fat intake and adiposity or disease end points were broadly consistent with those that assessed dairy fat intake by other means.

It is important to note that although these three approaches have been used widely in the literature to study the disease relationships of dairy fat or high-fat as opposed to low-fat dairy, they are not without limitations. Dairy fat intake, whether calculated from a FFQ/dietary record or assessed by a plasma or adipose tissue biomarker, is hard to isolate from the food in which it is consumed. Aside from butter, dairy products contain numerous other components such as protein or micronutrients that could affect disease outcomes. Measurements of the intakes of these other components are inaccurate and typically incomplete, and it is rarely possible to fully adjust for their effect. When reviewing the evidence, one therefore needs to consider that any disease association found for dairy fat intake may be explained by dairy fat or another dairy component. Potentially insightful may therefore be to study the disease association for pure dairy fat, that is, butter. Some authors have indeed listed associations for specific dairy foods including butter separately as will be seen below. Otherwise, the strongest of the above approaches is to compare the disease associations of high-fat as compared to low-fat dairy. One could reason that if a disease association was seen for high-fat or low-fat dairy, but not the other, then that difference may be attributable to the primary difference between these product classes, that is, the dairy fat. A limitation of this approach lies in how dairy foods are commonly categorized. Often, ice cream is categorized as a high-fat dairy product, while yogurt is usually categorized as a low-fat dairy product. A sugary desert like ice cream as well as fermented dairy products may have effects on disease outcomes independent of its dairy fat content. Another limitation of this approach is that the statistical power to detect associations may differ for high-fat versus low-fat dairy products. In most recent studies conducted in Western societies, the number of servings of high-fat dairy consumed is much lower than the number of servings of low-fat dairy, and n-tiles formed on the basis of low-fat dairy product consumption typically cover a much wider range of intake levels than those formed on the basis of high-fat dairy intakes. Lastly, an obvious concern is residual confounding due to the fact that the consumption of high-fat or low-fat dairy may be associated with other health behaviors, as we will discuss in more detail below.

We have decided to systematically review the literature, rather than conduct a meta-analysis of all studies done in this area. As will be discussed in much detail below, the health effects of dairy fat or high-fat dairy may be dependent on a number of factors, including bovine feeding practices or the type of dairy product consumed. Bovine feeding practices differ by country, as do traditions and dietary preferences relating to milk and dairy. It may be an opportunity to consider such differences in the interpretation of the data, particularly as the associations found between dairy fat, obesity, and cardiometabolic disease risk show substantial variation between countries, as described below. It is a central hypothesis of this paper that milk and dairy are not standardized foods, and that considering each study carefully by itself may further our understanding of the role of dairy fat and high-fat dairy products more than examining pooled data.

Dairy fat and high-fat dairy consumption and obesity

Dairy fat is commonly thought to contribute to the development of obesity due to its high energy density. To evaluate the association between dairy fat consumption and obesity, we performed a literature search to identify observational studies examining the relationship between these two variables (Table 1). We identified 16 studies that directly measured dairy fat consumption, or variables related to dairy fat consumption, spanning the years 1999–2011, of which ten were prospective, five cross-sectional, and one retrospective. Seven studies were conducted in the United States, and nine in Europe, seven of which originated in Northern Europe. All but one of the studies determined dairy fat and/or high-fat dairy intake using dietary assessment questionnaires, and in addition, five used serum and/or adipose tissue fatty acid markers.

Overall, 11 of the 16 studies found that participants who consumed more dairy fat and/or high-fat dairy foods at baseline were leaner and/or gained less weight over time than participants who consumed less [14, 19–29]. None of the 16 studies reported a positive association between baseline consumption of dairy fat or high-fat dairy foods and measures of adiposity at baseline or over time.

Table 1 Relationship between dairy fat and high-fat dairy intakes and adiposity

References	Type	Subjects	Assessment method	Covariates	Outcome
Smedman et al. [14]	Cross-sectional	70-year-old Swedish men ($n = 62$)	7-day dietary recall; plasma C15:0	Physical activity, intakes of meat, beer, potatoes, vegetables, and root crops	Dairy fat intake, as assessed by diet recall, and serum cholesterol ester C15:0 were inversely associated with BMI
Pereira et al. [19]	Prospective (cohort)	18–30-year-old black and white US men and women ($n = 3,157$)	Baseline FFQ (28 day recall)	Age, sex, race, baseline BMI, energy intake, education, smoking, physical activity, supplement use, and intakes of alcohol, polyunsaturated fat, caffeine, fiber, grains, meat, fruit, vegetables, soda, magnesium, calcium, and vitamin D	High-fat dairy intake, but not low-fat dairy intake, was inversely associated with the risk of developing obesity among the overweight at baseline
Phillips et al. [33]	Prospective (cohort)	8–12-year-old US girls ($n = 196$)	Annual FFQ (1-year recall)	Energy intake, parental overweight, and intakes of fruit, vegetables, soda, and protein	Neither full-fat nor low-fat dairy consumption was associated with BMI change over time
Rosell et al. [20]	Cross-sectional	63-year-old Swedish men ($n = 301$)	7-day food record; C15:0 and C17:0 in serum phospholipids and adipose tissue	Physical activity, and intakes of alcohol and calcium	Dairy fat intake, phospholipid C15:0 and C17:0, and adipose tissue C17:0 were inversely associated with abdominal obesity
Warensjo et al. [21]	Prospective (case–control)	Adult Swedish men and women ($n = 234$)	Baseline C15:0 and C17:0 in serum lipids	None	The sum of C15:0 and C17:0 in serum lipids was inversely associated with BMI at baseline. Prospective changes in BMI were not investigated
Barba et al. [22]	Cross-sectional	3–11-year-old Italian boys and girls ($n = 884$)	Baseline FFQ (1-year recall)	Age, sex, birth weight, parental overweight, physical activity, parental education, and intakes of fish, cereals, meat, fruit, vegetables, sweet beverages, and snacks	The prevalence of overweight was inversely associated with the consumption of whole milk. When whole milk and skim milk consumption were pooled, the association was no longer statistically significant
Berkey et al. [30]	Prospective (cohort)	9–14-year-old US boys and girls ($n = 12,829$)	Baseline FFQ	Age, race, ethnicity, change in height during follow-up, baseline BMI, tanner stage, menstrual history, and physical activity	Whole milk intake was not associated with BMI change; 1 % and skim milk intake were positively associated with BMI increase in boys and girls, respectively
Rajpathak et al. [23]	Prospective (cohort)	40–75-year-old US men ($n = 23,504$)	FFQ (1-year recall) at baseline and every 4 years	Age, baseline weight, smoking, physical activity, glycemic load, and intakes of alcohol, calories, total fat, cereal fiber, whole grains, fruit, vegetables, caffeine, *trans* fat, and soda	Baseline high-fat dairy intake was inversely associated with weight gain before and after multivariate adjustment, whereas low-fat diary was not. An increase in high-fat dairy consumption over time was positively associated with weight gain, while low-fat dairy was not
Rosell et al. [24]	Prospective (cohort)	40–55-year-old Swedish women ($n = 19,352$)	Baseline and 10-year FFQ (6-month recall)	Age, baseline height and weight, education, parity, baseline intakes of energy, fat, carbohydrate, protein, fiber, and alcohol, and change in intakes of energy, fat, carbohydrate, protein, fiber, and alcohol	Baseline intake of whole milk and butter were inversely associated with baseline BMI, while low-fat milk was not. Higher intake of whole milk was inversely associated with weight gain before and after multivariate adjustment, while low-fat milk was not

Table 1 continued

References	Type	Subjects	Assessment method	Covariates	Outcome
Snijder et al. [25]	Cross-sectional	50–75-year-old Dutch men and women ($n = 2,064$)	FFQ	Age, sex, smoking, physical activity, education, antihypertensive medication use, and intakes of energy, fiber, and alcohol	Waist circumference was inversely associated with high-fat dairy intake before and after multivariate adjustment; waist circumference and BMI were positively associated with low-fat dairy intake before and after multivariate adjustment
Beydoun et al. [31]	Cross-sectional	18 + year old US men and women ($n = 14,618$)	FFQ (24 h recall)	Age, sex, ethnicity, socioeconomic status, physical activity, and intakes of energy, fruit, vegetables, grains, legumes, nuts/seeds, soy, meat/poultry/fish, eggs, added fats and oils, added sugars, alcohol, and caffeine	Dairy fat intake as a percentage of total fat was not associated with obesity or central obesity. Whole milk intake was inversely associated with central obesity while low-fat milk was positively associated with central obesity
Mozaffarian et al. [26]	Prospective (cohort)	65+ year old US men and women ($n = 3,736$)	Baseline FFQ; plasma phospholipid trans palmitoleate	Age, sex, race, education, enrollment site, diabetes, coronary heart disease, smoking, physical activity, and intakes of alcohol, carbohydrates, protein, red meat, total fat, whole-fat dairy, low-fat dairy, and energy	Waist circumference was inversely associated with plasma phospholipid trans palmitoleate. Prospective changes in waist circumference were not reported
Warensjo et al. [27]	Prospective (case–control)	30–60-year-old Swedish men and women ($n = 1,000$)	Baseline FFQ; C15:0 and C17:0 in serum phospholipids	None	Serum phospholipid C15:0 and C17:0 were inversely associated with BMI at baseline. Prospective changes in BMI were not investigated
Duffey et al. [32]	Prospective (cohort)	18–30-year-old US men and women ($n = 2,774$)	Baseline and 7-year FFQ (one-month recall)	Age, sex, race, exam center, weight, smoking, physical activity, intakes of energy, fruit juice, sugar-sweetened beverages, and alcohol	The incidence of elevated waist circumference was not associated with whole or low-fat milk intake
Te Velde et al. 2011 [28]	Retrospective	13–36-year-old Dutch men and women ($n = 374$)	8 dietary history interviews over 23 years (1-month recall)	Physical activity, smoking, and energy intake	Participants who were not overweight at 36 years of age had consumed more full-fat dairy and less low-fat dairy 15 years earlier than participants who were overweight at 36
Noel et al. 2011 [29]	Prospective (cohort)	10–13-year-old British children ($n = 2,245$)	3-day diet records at baseline and end of study	Age, sex, height, pubertal status, maternal BMI, maternal education, and intakes of total fat, cereal, sugar-sweetened beverages, fruit juice, calcium, and energy	In cross-sectional analysis at age 13, full-fat milk, but not low-fat milk consumption was inversely associated with percent body fat. In prospective analysis, neither baseline full-fat nor low-fat milk consumption assessed at age 10 was associated with percent body fat at age 13

BMI body mass index, *FFQ* food frequency questionnaire

Rajpathak et al. [23] reported changes in body weight over 12 years in 16,471 US male health professionals aged 42–75 years, divided by quintiles of high-fat dairy intake as measured by FFQ. After adjustment for age, baseline weight, demographic factors, lifestyle factors, and a variety of dietary factors, baseline high-fat dairy intake was inversely associated with weight gain over 12 years (0.38 kg difference between quintiles 1 and 5). In contrast, neither total dairy intake nor low-fat dairy intake at baseline were associated with weight gain. FFQ were collected every 4 years, which also permitted the investigation of associations between changes in dairy intake and weight gain. In this analysis, Rajpathak et al. found that increased consumption of high-fat dairy, and total dairy, but not low-fat dairy, was associated with weight gain over 12 years (0.57 kg difference between quintiles 1 and 5). It is not clear why participants with a high baseline intake of high-fat dairy gained less weight over time, while participants who increased high-fat dairy intake over time gained more weight. The authors suggest residual confounding as one possible explanation for the latter finding, stating that "the weight change associated with increased dairy intake may represent changes in other dietary and lifestyle factors."

All five of the studies that estimated dairy fat intake objectively via fatty acid markers found an inverse relationship between dairy fat intake and measures of adiposity [14, 20, 21, 26, 27]. However, caution must be exercised in interpreting these studies, because all five reported cross-sectional rather than prospective associations, and two of them did not adjust for possible confounding factors.

Smedman et al. [14] reported cross-sectional associations between the consumption of dairy fat and measures of adiposity in 70-year-old Swedish men. Dairy fat consumption was estimated both by 7-day dietary records and C15:0 in serum cholesterol esters, making it perhaps the most careful dietary assessment of any similar investigation. Cholesterol ester C15:0 was positively associated with the intake of specific high-fat dairy foods as well as total dairy fat, as assessed by food record. Total dairy fat consumption as assessed by food record was inversely associated with body weight, body mass index (BMI), and waist-to-hip ratio, while assessment by cholesterol ester C15:0 revealed inverse associations with body weight, BMI, and waist circumference.

In the majority of the studies that compared high-fat dairy to low-fat dairy, consumption of high-fat dairy was associated with more favorable weight outcomes, while in four studies, low-fat dairy consumption was positively associated with the risk of weight gain over time [25, 28, 30, 31]. None of the 16 studies found that low-fat dairy consumption was inversely associated with obesity risk. Therefore, observational studies do not support the hypothesis that dairy fat is obesogenic, nor do they support the hypothesis that low-fat dairy protects against obesity. Rather, they suggest the hypothesis that dairy fat and/or high-fat dairy products, in the context of prevailing dietary patterns, may protect against weight gain.

There are several potential confounding factors that must be considered when evaluating these findings. The first is the possibility that dairy fat is inversely associated with baseline weight or weight change because it is preferentially consumed by individuals who are lean at baseline, whereas individuals who are overweight at baseline and are already on a trajectory of fat gain tend to favor low-fat dairy because it is commonly perceived as less obesogenic (reverse causation). One way to interrogate this possibility is to consider only prospective studies that have adjusted for baseline weight or BMI. Of the six studies that fall into this category [19, 23, 24, 29, 30, 32], four reported inverse associations between dairy fat intake and obesity risk [19, 23, 24, 29]. Therefore, although it may still be considered a plausible confounding factor, reverse causation cannot fully explain this association.

Examining Table 1, it is clear that location has a major influence on the studies' outcomes. Of the nine studies that were conducted in Europe, eight found that dairy fat intake is inversely associated with adiposity [14, 20–22, 24, 25, 27–29]. Of the seven that were conducted in the United States, three found an inverse association, while four did not [19, 23, 26, 30–33]. Three factors stand out as possible explanations for this discrepancy. The first is the high potential for residual and unmeasured confounding in US cohorts. Since the 1980s, there has been a public health campaign in the United States to lower the consumption of SFA-rich foods such as animal fats. As a result, dairy fat is perceived as unhealthy in the United States, and one would expect its consumption to be associated with other behaviors that are perceived as unhealthy. Indeed, Liu et al. [34] reported that US women in the highest quintile of high-fat dairy intake were 62 % more likely to be current smokers than women in the lowest quintile, whereas women in the highest quintile of low-fat dairy intake were 62 % less likely to smoke than the lowest quintile. Similarly, dietary fiber intake was 21 % lower in the highest quintile of high-fat dairy intake compared to the lowest [34]. Comparable trends were reported by Margolis et al., including substantially higher physical activity and income level in the top quintile of low-fat dairy intake, and substantially lower physical activity and income level in the top quintile of high-fat dairy intake [35]. This demonstrates the cultural stigma attached to dairy fat consumption in the United States, and casts doubt upon the ability of observational studies to fully adjust for the unhealthy lifestyle patterns that associate with dairy fat consumption in this environment. Although data are limited, the potential for residual confounding may be lower in European studies. Rosell

et al. [24] reported only small differences in fiber intake and educational status among individuals consuming different amounts of dairy fat in Sweden.

A second factor that may influence the association between dairy fat consumption and obesity differently in the United States and Europe is the form in which it is consumed. In the modern United States, a large proportion of dairy fat is consumed in the form of sweet or savory commercial foods such as ice cream and pizza [1, 6]. Although this is increasingly true throughout the industrialized world, Europe retains a stronger tradition of consuming full-fat traditional dairy products such as plain cheeses, plain butter, and unsweetened yogurt. It is difficult to disentangle the effects of dairy fat from the substrate within which it was consumed using observational methods. Therefore, this may be considered a potential confounding factor.

A third factor that may explain the differences between US and European studies is dairy fat quality. Typical dairy farming in the United States is highly industrialized, with a focus on maximizing yield per dairy cow. Average milk production per cow is higher in the US than in European countries, and stocking rate (cows per hectare) is also higher, implying lower access to pasture [36]. High milk production is achieved using high-yielding Holstein breeds, treatment with growth hormones (such as rBGH, banned in the EU since 2000 [37]), and heavy reliance on corn and soybean-based feed concentrates rather than fresh pasture. While there is an accelerating trend for similar industrialization of milk production throughout the world, other countries have been slower to adopt these practices, and dairy farming in select countries such as Ireland or New Zealand is still much less industrialized, exposing dairy cows to more fresh pasture or even exclusively pasture-feeding animals [38]. This has substantial, and potentially biologically important, implications for dairy fat composition, as will be discussed in more detail below. In addition, the long fermentation that takes place during the production of many traditional cheeses produces bioactive fat-soluble compounds with potential health impacts, and these types of cheeses are more commonly consumed in Europe [39]. As discussed below, dairy fat quality, in addition to quantity, could plausibly influence human health. Because neither prevailing FFQ nor serum measurements of odd-numbered fatty acids determine the provenance of dairy products, it is currently difficult to assess the relationship between animal husbandry practices and health outcomes in observational studies.

Dairy fat and high-fat dairy consumption and metabolic health

On the heels of the obesity epidemic has followed an epidemic of metabolic dysfunction and diabetes in affluent nations, with the US Centers for Disease Control reporting a diabetes prevalence of 11.3 % of US adults in 2010 [40]. Elevated fasting insulin, fasting blood glucose, and elevated blood glucose during an oral glucose tolerance test (OGTT) are considered risk factors for T2DM, although they do not always progress to overt disease. To determine the relationship between the consumption of dairy fat and metabolic health, we performed a literature search for observational studies that interrogated this question (Table 2). We identified eleven studies, nine of which overlap with those in Table 1 [14, 19, 21, 25–28, 32, 41]. Six of the eleven studies reported that dairy fat consumption was associated with markers of better metabolic health at baseline or over time [19, 21, 26, 27, 42], one study was partially supportive of this association [41], three found no association at all [25, 31, 32], and one reported that higher full-fat dairy intake was associated with one marker of poorer metabolic health [28]. The latter study employed an unusual design, dividing participants into two groups based on the median glycated hemoglobin value measured at the end of the study and basing its conclusions on a retrospective examination of high-fat dairy consumption in the two groups over the previous 23 years [28]. Overall, the observational evidence does not support the hypothesis that dairy fat promotes metabolic dysfunction. Rather, it is somewhat consistent with the alternative hypothesis that dairy fat may protect against metabolic dysfunction.

These data should again be interpreted with the important confounders discussed above in mind. Specifically, these may again explain in part the tendency for studies conducted in the United States to report less favorable metabolic outcomes linked to dairy fat intake than those conducted in Europe. Another factor that should be considered is the potential for overadjustment by incorporating measures of adiposity into multivariate models. As dairy fat intake is inversely associated with adiposity in most studies, adjusting for this variable effectively removes any protective metabolic effects of dairy fat that are mediated indirectly through effects on adiposity. Therefore, studies that adjust for adiposity may tend to underestimate the association between dairy fat intake and metabolic health. For example, Snijder et al. [25] reported that high-fat dairy intake was inversely associated with fasting insulin after multivariate adjustment; however, this association lost statistical significance after further adjustment for BMI. Warensjo et al. [21] reported that the inverse association between the sum of C15:0 and C17:0 in serum phospholipids and fasting insulin was attenuated after adjustment for BMI [21], and Warensjo et al. [27] reported a similar finding for fasting glucose [27]. Although weakened, the two latter findings retained statistical significance after adjustment for BMI, suggesting that dairy fat may protect against metabolic dysfunction by a mechanism that is partially independent of effects on adiposity.

Table 2 Relationship between dairy fat and high-fat dairy intakes and biomarkers of metabolic health

References	Type	Subjects	Assessment method	Covariates	Outcome
Smedman et al. [14]	Cross-sectional	70-year-old Swedish men ($n = 62$)	7-day dietary recall; plasma phospholipid and cholesterol ester C15:0	Physical activity, intakes of meat, beer, potatoes, vegetables, and root crops	Intake of fat from milk and cream, as assessed by diet recall, was inversely associated with the glucose area under the curve during an oral glucose tolerance test and fasting plasma glucose. Intake of fat from ice cream was positively associated with insulin sensitivity index. Plasma phospholipid and cholesterol ester C15:0 were not associated with these variables
Pereira et al. [19]	Prospective (cohort)	18–30-year-old black and white US men and women ($n = 3,157$)	Baseline FFQ (28 day recall)	Age, sex, race, baseline BMI, energy intake, education, smoking, physical activity, supplement use, and intakes of alcohol, polyunsaturated fat, caffeine, fiber, grains, meat, fruit, vegetables, soda, magnesium, calcium, and vitamin D	High-fat dairy intake was inversely associated with abnormal glucose homeostasis and the insulin resistance syndrome. Reduced fat dairy intake was inversely associated with the insulin resistance syndrome but not abnormal glucose homeostasis
Warensjo et al. [21]	Prospective (case–control)	Adult Swedish men and women ($n = 234$)	Baseline C15:0 and C17:0 in serum lipids	BMI and smoking	The sum of C15:0 and C17:0 in serum lipids was inversely associated with fasting insulin at baseline, before and after adjusting for BMI. Prospective changes were not investigated
Snijder et al. [25]	Cross-sectional	50–75-year-old Dutch men and women ($n = 2,064$)	FFQ	Age, sex, smoking, physical activity, education, antihypertentive medication use, and intakes of energy, fiber, and alcohol	After multivariate adjustment, high-fat dairy intake was inversely associated with fasting insulin, but not glucose tolerance or fasting glucose. This was not observed before adjustment. The association lost significance after additional adjustment for BMI. Low-fat dairy was positively associated with fasting glucose but not fasting insulin or glucose tolerance both before and after multivariate adjustment
Beydoun et al. [31]	Cross-sectional	18+ year old US men and women ($n = 14,618$)	FFQ (24 h recall)	Age, sex, ethnicity, socioeconomic status, physical activity, and intakes of energy, fruit, vegetables, grains, legumes, nuts/seeds, soy, meat/poultry/fish, eggs, added fats and oils, added sugars, alcohol, and caffeine	No associations were observed between the intake of dairy fatty acids as a percentage of total fat, whole milk, low-fat milk, skim milk, and the metabolic syndrome
Mozaffarian et al. [26]	Prospective (cohort)	65+ year old US men and women ($n = 3,736$)	Baseline FFQ; plasma phospholipid *trans* palmitoleate	Age, sex, race, education, enrollment site, diabetes, coronary heart disease, smoking, physical activity, and intakes of alcohol, carbohydrates, protein, red meat, total fat, whole-fat dairy, low-fat dairy, and energy	Fasting insulin and insulin resistance were inversely associated with plasma phospholipid *trans* palmitoleate after adjustment for BMI, waist circumference and dietary factors including dairy food and red meat intake
Warensjo et al. [27]	Prospective (case–control)	30–60-year-old Swedish men and women ($n = 1,000$)	Baseline FFQ; C15:0 and C17:0 in serum phospholipids	BMI and smoking	The sum of C15:0 and C17:0 in serum phospholipids was inversely associated with fasting glucose before and after adjustment for BMI and smoking. Prospective changes were not investigated
Duffey et al. [32]	Prospective (cohort)	18–30-year-old US men and women ($n = 2,774$)	Baseline and 7-year FFQ (one-month recall)	Age, sex, race, exam center, weight, smoking, physical activity, intakes of energy, fruit juice, sugar-sweetened beverages, and alcohol	Neither whole-fat milk intake nor low-fat milk intake was associated with high fasting glucose or the metabolic syndrome

Table 2 continued

References	Type	Subjects	Assessment method	Covariates	Outcome
Iggman et al. [41]	Cross-sectional	71-year-old Swedish men ($n = 795$)	C15:0 and C17:0 in adipose tissue	BMI, smoking, physical activity, and alcohol intake	Insulin sensitivity measured by euglycemic clamp was positively related to adipose C17:0, and HOMA-IR was negatively related to adipose C17:0. No relationship was found with C15:0
Sonestedt et al. [42]	Prospective (cohort)	44–74-year-old Swedish men and women ($n = 26{,}445$)	Baseline diet history questionnaire	Age, sex, season, BMI, physical activity, education, and intakes of energy and alcohol	Butter consumption was inversely associated with HOMA-IR in the fully adjusted model
Te Velde et al. [28]	Retrospective	13–36-year-old Dutch men and women ($n = 374$)	8 dietary history interviews over 23 years (one-month recall)	Physical activity, smoking, and energy intake	Participants who had an HbA1c above the median at 36 years of age had consumed more full-fat dairy 15 years earlier than participants who had an HbA1c below the median

BMI body mass index, *FFQ* food frequency questionnaire

Dairy fat and high-fat dairy consumption and type 2 diabetes mellitus

Eight observational studies have investigated the prospective relationship between dairy fat consumption and the incidence of T2DM (Table 3) [18, 26, 34, 35, 43–46]. Of the eight, three reported that diabetes incidence is inversely associated with high-fat dairy intake or markers of dairy fat intake at baseline [26, 43, 45], one found inconsistent evidence for an inverse association [18], while four found no association [34, 35, 44, 46]. In one of these latter studies, incident diabetes was associated neither with high-fat nor with low-fat dairy intake [46]; the other three reported an inverse association between low-fat dairy intake and diabetes incidence [34, 35, 44], while full-fat dairy was not associated with diabetes risk. The findings of these latter three studies may suggest that the fat component of dairy has a negative impact on diabetes risk, and thus we conclude that the studies as a whole offer conflicting evidence. It is notable that all three of these latter studies were conducted in the United States.

Choi et al. [44] reported prospective associations between the consumption of dairy products and T2DM incidence in 41,254 male US health professionals over 12 years. After adjustment for age, BMI, demographic factors, lifestyle factors, hypertension, hypercholesterolemia, and a variety of dietary factors, high-fat dairy intake as measured by FFQ was not associated with diabetes incidence. In contrast, low-fat dairy intake was inversely associated with diabetes risk, and this association was driven in large part by low-fat and skim milk.

Mozaffarian et al. [26] reported prospective associations between dairy fat intake and T2DM incidence in 3,736 US adults over 14 years. Dairy fat intake was estimated by plasma phospholipid *trans* palmitoleic acid and FFQ. Among dietary variables, high-fat dairy consumption was the most strongly associated with plasma phospholipid *trans* palmitoleic acid. After adjustment for age, BMI, waist circumference, demographic factors, lifestyle factors, and dietary factors, plasma phospholipid *trans* palmitoleic acid showed a strong inverse relationship with incident diabetes. This association was scarcely attenuated by adjusting for six categories of whole-fat dairy foods. This may suggest that differences in the endogenous processing or blood clearance of *trans* palmitoleic acid are associated with diabetes risk. Alternatively, it may suggest an association between dairy fat quality, rather than quantity, and diabetes risk. As we will see below, the content of *trans* palmitoleic acid is several-fold higher in milk from pasture-fed as compared to grain concentrate-fed dairy cows. The authors also found that the consumption of high-fat dairy foods as assessed by FFQ was inversely associated with T2DM incidence in this paper.

Table 3 Relationship between dairy fat and high-fat dairy intakes and diabetes incidence

Reference	Type	Subjects	Assessment method	Covariates	Outcome
Choi et al. [44]	Prospective (cohort)	40–75-year-old US men ($n = 41,254$)	Baseline FFQ (1-year recall)	Age, BMI, follow-up time, diabetes, smoking, hypercholesterolemia, hypertension, physical activity, glycemic load, and intakes of energy, alcohol, cereal fiber, *trans* fats, and the ratio of polyunsaturated to saturated fat	Neither high-fat dairy nor whole milk intake was associated with diabetes incidence. Low-fat dairy and skim/low-fat milk intake were inversely associated with diabetes incidence
Liu et al. [34]	Prospective (cohort)	Middle-aged US women ($n = 37,183$)	Baseline FFQ (1-year recall)	Age, diabetes, smoking, BMI, hypercholesterolemia, hypertension, physical activity, hormone use, glycemic load, and intakes of energy, alcohol, fiber, total fat, calcium, vitamin D, and magnesium	High-fat dairy intake was not associated with diabetes incidence. Low-fat dairy intake was inversely associated with diabetes incidence
Hodge et al. [18]	Prospective (case-cohort)	36–72-year-old Australian men and women ($n = 3,737$)	Baseline FFQ and plasma phospholipid C15:0	Age, sex, BMI, waist-to-hip ratio, country of birth, diabetes, physical activity, and alcohol intake	Plasma phospholipid C15:0 was inversely associated with diabetes incidence. Although cases consumed significantly less C15:0 than controls, dietary C15:0 was not associated with diabetes incidence across quintiles after adjustment
Krachler et al. [45]	Prospective (case–control)	Middle-aged Swedish men and women ($n = 450$)	Erythrocyte membrane C15:0 and C17:0	BMI, HbA1c, and alcohol intake	Erythrocyte membrane C15:0 and C17:0 were inversely associated with diabetes incidence
Mozaffarian et al. [26]	Prospective (cohort)	65+ year old US men and women ($n = 3,736$)	Baseline FFQ; plasma phospholipid *trans* palmitoleic acid	Age, sex, race, education, enrollment site, smoking, BMI, waist circumference, coronary heart disease, physical activity, and intakes of energy, alcohol, carbohydrates, protein, red meat, whole-fat dairy, and low-fat dairy	Plasma phospholipid, *trans* palmitoleic acid, and whole-fat dairy intake were inversely associated with diabetes incidence
Malik et al. [43]	Prospective (cohort)	34–53-year-old US women ($n = 37,038$)	Retrospective and baseline FFQ; additional FFQ every 4 years	Age, baseline BMI, physical activity, smoking, family history of diabetes, hormone use, polyunsaturated to saturated fat ratio, glycemic load, and intakes of baseline energy intake, sugar-sweetened beverages, alcohol, coffee, processed meat, *trans* fat, and cereal fiber,	Adolescent intake of high-fat, but not low-fat dairy was inversely associated with diabetes incidence. This association became nonsignificant after adjustment for adult dairy intake and weight change. Adult intake of both high-fat and low-fat dairy was inversely associated with diabetes incidence
Margolis et al. [35]	Prospective (cohort)	50–79-year-old US women ($n = 82,076$)	Baseline FFQ (3-month recall)	Age, race, ethnicity, income, education, smoking, family history of diabetes, hormone use, blood pressure, BMI, physical activity, and intakes of energy, and alcohol	High-fat dairy intake was not associated with diabetes incidence before or after adjustment. Low-fat dairy intake was inversely associated with diabetes incidence before and after adjustment
Soedamah-Muthu et al. [46]	Prospective (cohort)	35–55-year-old British men and women ($n = 4,186$)	Baseline FFQ	Age, ethnicity, employment grade, smoking, BMI, physical activity, family history, and intakes of alcohol, fruit, vegetables, bread, meat, fish, coffee, tea, and total energy	Neither high-fat nor low-fat dairy intake was significantly associated with incident diabetes during 10 years of follow-up

BMI body mass index, *FFQ* food frequency questionnaire

These studies must take into consideration the same caveats mentioned above, namely the potential for residual confounding, the substrate in which the dairy fat was consumed, and differences in fatty acid composition due to animal husbandry practices. In particular, in both studies of Liu et al. and Margolis et al. [34, 35], high-fat dairy consumption was strongly and positively associated with a pattern of unhealthy lifestyle factors such as smoking, while low-fat dairy consumption showed a strong negative association with these variables. In addition, all six studies adjusted for BMI. As excess body fat is a dominant risk factor for T2DM, this certainly seems appropriate. However, it also presents the possibility that this adjustment may have attenuated a negative association between dairy fat intake and diabetes incidence. Hodge et al. and Malik et al. [18, 43] were the only two studies out of seven that reported the association both before and after adjustment for measures of adiposity alone. Both found that the inverse association between high-fat dairy intake (as judged by plasma phospholipid C15:0 or FFQ) and diabetes incidence was attenuated after adjustment for measures of adiposity, supporting the point discussed above that adjustment for BMI may have minimized beneficial effects of dairy fat mediated by an influence on body fatness.

Dairy fat and high-fat dairy consumption and cardiovascular disease

We identified fifteen manuscripts from twelve different studies that provide insight into the relationship between the consumption of dairy fat and cardiovascular disease risk (Table 4). Six studies assessed dairy fat intake by measuring the concentration of specific fatty acids in plasma or adipose tissue [21, 27, 47–50].

The first such study, by Warensjö et al. [21] reported an inverse association between dairy fat intake and risk factors for CVD including triglycerides, total cholesterol, and insulin in fasting serum, as well as BMI. This relatively small ($n = 234$) prospective case–control study in Swedish men and women showed an inverse association between dairy fat intake and the risk of myocardial infarction in univariate analysis. This relationship was barely attenuated by adjusting for classical CVD risk factors (serum total cholesterol, smoking habits, systolic and diastolic blood pressure), while the association was completely removed by adjusting for metabolic risk factors including serum fasting triglycerides, fasting insulin, and BMI. One potential explanation may therefore be that dairy fat intake reduces the risk of myocardial infarction through a mechanism that involves reducing adiposity and triglycerides and improving metabolic health. In a later publication of findings from the same study that included more cases and controls [27], the authors again found a trend for an inverse association between plasma phospholipid C15:0 + C17:0 and myocardial infarction that was statistically significant in women, but not in men. Again, the association became nonsignificant after adjustment for factors that were inversely associated with plasma C15:0 + C17:0 including BMI, systolic blood pressure, and the ratio of apolipoprotein B to apolipoprotein A-I [27]. In a similar analysis, Biong et al. [47] assessed the relationship between dairy fat biomarkers in adipose tissue and myocardial infarction in a retrospective case control study ($n = 197$) conducted in Norway. In the model adjusted for age, sex, waist-to-hip ratio, smoking, family history, and education, adipose tissue C14:1, C15:0, and C17:1 were each inversely associated with the risk of a first myocardial infarction. A major weakness of two of these studies was that they were adjusted for neither other dietary or lifestyle factors. It may be possible that dairy fat intake was associated with other protective lifestyle or dietary factors in these Scandinavian countries; residual confounding can therefore not be excluded. Another study that used plasma biomarkers to assess dairy fat intake investigated the relationship between dairy fat and stroke risk using a case–control design ($n = 386$) [49]. In Swedish men and women, the sum of C15:0 + C17:0 in plasma phospholipids was inversely associated with the risk of stroke. Adjusting for other dietary variables showed little effect on the model. A retrospective case–control study conducted in Costa Rica found a strong inverse relationship between 9-*cis*, 11-*trans* CLA in adipose tissue and the risk of myocardial infarction [50]. This relationship was present in the crude analysis and in the model fully adjusted for CVD risk factors, dietary factors, and other fatty acids in adipose tissue. Adipose tissue 9-*cis*, 11-*trans* CLA was strongly related to the intake of dairy products in this study. In additional analyses, these authors found that in a model adjusted only for demographic and lifestyle factors, dairy intake was not significantly associated with the risk of myocardial infarction. When adjusting for SFA intake (per FFQ) and adipose tissue *trans* fatty acids excluding 9-*cis*, 11-*trans* CLA, dairy intake was inversely associated with myocardial infarction ($p = 0.03$), suggesting that dairy fat components other than SFA and/or *trans* fatty acids may be cardioprotective. After adjustment for adipose tissue 9-*cis*, 11-*trans* CLA, the association between dairy fat intake and myocardial infarction became nonsignificant, suggesting that CLA (or something associated with it) may be the protective factor in dairy. Although the retrospective nature of this study may be considered a limitation, it is strengthened by the fact that the exposure was assessed by an objective measure of long-term intake of dairy fat.

These data are in contrast to those from the Nurses' Health Study. Measuring dairy fat biomarkers in both plasma and erythrocytes in a case–control design, Sun et al.

Table 4 Relationship between dairy fat and high-fat dairy intakes and cardiovascular disease incidence

References	Type	Subjects	Assessment method	Covariates	Outcome
Hu et al. [51]	Prospective (cohort)	Adult US women ($n = 80{,}082$)	Repeated FFQ	Age, BMI, smoking, menopausal status, hormone use, family history, vitamin E supplement use, hypertension, aspirin use, vigorous exercise, and intakes of energy and alcohol	In the fully adjusted model, neither high-fat dairy intake nor low-fat dairy intake was associated with coronary heart disease risk. However, the ratio of high-fat to low-fat dairy products was associated with coronary heart disease risk
Ness et al. [57]	Prospective (cohort)	35–64-year-old Scottish men ($n = 5{,}765$)	Baseline FFQ and a second FFQ in $\sim$ half the study population	Age, smoking, blood pressure, serum cholesterol, BMI, social class, education, forced expiratory volume, angina, ischemia, bronchitis, alcohol consumption, and social factors	In the fully adjusted model, the consumption of milk was strongly and inversely associated with death from cardiovascular disease (and all causes). Although the fat content of the milk consumed was not assessed, the authors note that during the study period (1970-1995), the majority of milk consumed in Scotland was full-fat milk
Warensjö et al. [21]	Prospective (case–control)	Adult Swedish men and women ($n = 234$)	Baseline C15:0 and C17:0 in serum lipids	Serum cholesterol, smoking, blood pressure, serum triglycerides, serum fasting insulin and leptin, BMI, plasminogen activator inhibitor-1, tissue-type plasminogen activator, and von Willebrandt factor	The sum of C15:0 and C17:0 in serum phospholipids was inversely associated with the risk of acute myocardial infarction, and adjustment for "classical" risk factors including serum cholesterol, smoking, and blood pressure barely attenuated that relationship. Adjustment for "metabolic" risk factors (serum triglycerides, insulin, leptin, BMI), however, eliminated the association
Biong et al. [47]	Retrospective (case–control)	45–75-year-old Norwegian men and post-menopausal women, aged ($n = 197$)	C14:0, C14:1, C15:0, C17:0, and C17:1 in adipose tissue	Age, sex, waist-to-hip ratio, smoking, family history of coronary heart disease, and education	In the fully adjusted model, adipose tissue C14:1, C15:0, and C17:1 were each inversely associated with the risk of a first myocardial infarction
Lockheart et al. [56]	Retrospective (case–control)	45–75-year-old Norwegian men and postmenopausal women ($n = 211$)	FFQ	Age, marital status, education, family history, smoking, and energy intake.	No association between the risk of myocardial infarction and the following food groups: cheese and yogurt, low-fat dairy, and high-fat milk
Sun et al. [48]	Prospective (case–control)	Adult US women ($n = 493$)	C15:0, trans C16:1, and C17:0 in plasma and erythrocytes	Age, smoking, fasting status, BMI, postmenopausal status hormone use, physical activity, aspirin intake, family history, hypertension, hypercholesterolemia, diabetes, plasma/erythrocyte C18:2 and *trans* fatty acid content, and alcohol intake	Plasma C15:0 was positively associated with the risk of ischemic heart disease in the fully adjusted model. None of the other fatty acids were significantly associated with ischemic heart disease in the fully adjusted model
Larson et al. [52]	Prospective (cohort)	50–69-year-old Finnish smokers ($n = 26{,}556$)	FFQ	Age, supplementation group, education, smoking, BMI, serum cholesterol, diabetes, heart disease, physical activity, intakes of total energy, caffeine, sugar, red meat, poultry, fish, fruit, fruit juices, vegetables, potatoes, whole grains, and refined grains.	Whole milk intake, but not low-fat milk intake, was associated with an increased risk for cerebral infarction and intracerebral hemorrhage. However, cheese and cream were inversely associated with cerebral infarction, while butter intake did not show an association with any type of stroke

Table 4 continued

References	Type	Subjects	Assessment method	Covariates	Outcome
Warensjö et al. [49]	Prospective (nested case–control)	Adult Swedish men and women ($n = 386$)	C15:0 and C17:0 in plasma phospholipids	BMI, serum cholesterol, tobacco use, and blood pressure	The sum of C15:0 and C17:0 was inversely associated with the risk of stroke in the fully adjusted model. Additional analyses adjusting for other foods (assessed by FFQ) including fish, fruits, vegetables, and alcohol intake had little effect on the model
Warensjö et al. [27]	Prospective (nested case–control)	Adult Swedish men and women ($n = 1{,}000$)	C15:0 and C17:0 in plasma phospholipids	Physical activity, BMI, smoking, ratio of apolipoprotein B to A-I, systolic blood pressure, diabetes, and intakes of fruit and vegetables	In women, plasma phospholipid C17:0 and the sum of C15:0 + C17:0 were inversely associated with the risk for myocardial infarction. This association became nonsignificant after adjusting for classic risk factors for cardiovascular disease. Among men, the trend was similar without reaching statistical significance
Smit et al. [50]	Retrospective (case–control)	Adult Costa Rican men and women ($n = 3{,}626$)	9-*cis*, 11-*trans* conjugated linoleic acid in adipose tissue	Age, sex, area of residence, physical activity, income, smoking, waist-to-hip ratio, family history, adipose tissue content of α-linolenic acid and *trans* fatty acids, and intakes of alcohol and saturated fatty acids	Adipose tissue content of 9-*cis*, 11-*trans* conjugated linoleic acid was inversely associated with risk of myocardial infarction
Bonthuis et al. [54]	Prospective (cohort)	25–78-year-old Australian men and women ($n = 1{,}529$)	Repeated FFQ	Age, energy intake, BMI, school education, physical activity, smoking, supplement use, β-carotene treatment, medication use, and intakes of alcohol and calcium	Dairy intake was not assessed with all-cause mortality. Full-fat dairy intake was inversely associated with cardiovascular disease mortality in the multivariate model
Sonestedt et al. [42]	Prospective (cohort)	44–74-year-old Swedish men and women ($n = 26{,}445$)	Baseline diet history questionnaire	Age, sex, season, BMI, smoking, physical activity, education, and intakes of energy, alcohol, vegetables, fruit, berries, fish, shellfish, meat, coffee, and whole grains	Neither low-fat or high-fat milk, nor cheese, butter, or cream consumption was associated with cardiovascular disease. Intake of fermented milk products was inversely associated with cardiovascular disease in the crude as well as the fully adjusted models
Goldbohm et al. [53]	Prospective (cohort)	55–69-year-old Dutch men and women ($n = 120{,}852$)	Baseline FFQ	Age, education, smoking, physical activity, BMI, multivitamin use, and intakes of alcohol, energy, mono- and polyunsaturated fatty acids, vegetables, and fruits	Dairy fat intake was inversely associated with the risk of death from ischemic heart disease in men, but positively in women. Dairy fat intake was not associated with the risk of death due to stroke in men or women
Soedamah-Muthu et al. [46]	Prospective (cohort)	35–55-year-old British men and women ($n = 4{,}255$)	Baseline FFQ	Age, ethnicity, employment grade, smoking, BMI, physical activity, family history, and intakes of alcohol, fruit, vegetables, bread, meat, fish, coffee, tea, and total energy	Neither high-fat nor low-fat dairy intake was significantly associated with incident coronary heart disease during 10 years of follow-up
Dalmeijer et al. [55]	Prospective (cohort)	21–64-year-old Dutch men and women ($n = 33{,}625$)	Baseline FFQ	Gender, age, physical activity, smoking, education, BMI, intakes of energy, alcohol, coffee, fruit, vegetables, fish, meat, and bread	Neither high-fat nor low-fat dairy intake was significantly associated with incident coronary heart disease or stroke during 13 years of follow-up

BMI body mass index, *FFQ*: food frequency questionnaire

[48] found that plasma C15:0 was positively associated with the risk of ischemic heart disease in a model including a wide range of CVD risk factors (Table 4). The data, however, did not strongly support the conclusion that dairy fat is associated with the risk of ischemic heart disease. The authors measured three different fatty acids that are considered biomarkers of dairy fat intake (C15:0, C17:0, and *trans* C16-1) in plasma and erythrocytes. A significant association with ischemic heart disease was seen only for C15:0, and only in plasma. The relative risks associated with higher levels of the other fatty acids such as *trans* C16:1 in plasma and erythrocytes, or C17:0 in erythrocytes, suggested an inverse relationship, albeit a nonsignificant one. Another aspect to consider in this (and most other studies in this area) is that if dairy fat intake is indeed inversely associated with adiposity, body weight, plasma triglycerides, insulin resistance, and the risk for type 2 diabetes as the studies discussed above suggest, then adjusting for these factors may underestimate the true effect of dairy fat on CVD risk as it would eliminate variables that lie in the pathway by which dairy fat may modify CVD risk.

Among the first studies that used FFQs to assess the intake of both full-fat and skim/low-fat milk and dairy products was the Nurses' Health Study, a prospective cohort study that included more than 80,000 women (note that this is the same cohort that the case–control study by Sun et al. [51] discussed above was based on). Hu and colleagues concluded that a higher ratio of high-fat to low-fat dairy consumption was associated with significantly greater risk of coronary heart disease (CHD). In their study, the intake of SFA was strongly associated with lifestyle and dietary risk factors for CHD, including a positive correlation with smoking and *trans* fatty acid intake, and an inverse correlation with physical activity and fiber intake. While in a crude analysis, SFA intake was associated with CHD risk, adjustment for these risk factors removed the association. Notably, in their analysis of the relationship between major dietary sources of SFA, meat and dairy, the authors did not adjust for all of these confounding factors. As dairy products were among the main dietary sources for SFA in this population, it seems possible that adjusting for these dietary variables would have attenuated the association between the ratio of high-fat to low-fat dairy products and CHD. The second point to emphasize is that Hu et al. included ice cream in the "high-fat dairy" category. While for their manuscript this may have been appropriate given that ice cream is undoubtedly a major source of dairy fat, it makes their data hard to interpret for our analysis given that ice cream is also a major source of sugar and potentially other fats, which may give ice cream an effect on disease risk independent of its dairy fat content. This is also related to the discussion above that, particularly in the United States, dairy fat is increasingly consumed as part of processed foods such as ice cream and pizza. It may therefore be hard to disentangle the effects of dietary dairy fat from those of a diet rich in processed foods. The last potential limitation of the study by Hu et al. is that their main finding was based on a ratio (high-fat dairy to low-fat dairy intake); a ratio does not reflect absolute intakes, and as such could be very high even at quite low absolute consumption of high-fat dairy. As there is no plausible biological mechanism by which the relative consumption of high-fat and low-fat dairy foods could affect disease risk, independent of the total amounts consumed, this approach seems questionable.

Five other prospective cohort studies investigated the relationship between dairy fat and CVD. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study enrolled 26,556 Finnish male smokers, asked them to complete a FFQ at baseline, and followed them for an average of 13.6 years [52]. Whole milk intake, but not low-fat milk intake, was associated with an increased risk for cerebral infarction and intracerebral hemorrhage. However, two other major dietary sources of dairy fat, cheese and cream, were inversely associated with cerebral infarction, while dairy fat in its pure form, butter, did not show any association with any type of stroke. This study therefore does not provide consistent evidence that dairy fat consumption is related to stroke incidence. In the Netherlands Cohort Study in 120,852 men and women, dairy fat intake was inversely associated with the 10-year risk of death from ischemic heart disease in men, but positively in women [53]. No association between dairy fat intake and the risk of death due to stroke was found in men or women.

In a prospective cohort study conducted in Australia, Bonthuis et al. [54] found that while dairy intake was not associated with all-cause mortality, full-fat dairy intake was inversely associated with CVD mortality over the 14.4-year follow-up period. In two prospective cohort studies conducted in Great Britain and The Netherlands, respectively, neither high-fat nor low-fat dairy intake was associated with incident CHD or, in the Dutch study, stroke [46, 55]. Lockheart and colleagues, using a retrospective case-cohort design ($n = 211$), assessed the relationship between different food groups and the risk of myocardial infarction [56]. No association was found between the food groups "cheese and yogurt," "low-fat dairy," and "high-fat milk" on the one hand and myocardial infarction on the other. An obvious limitation of this study was the dietary assessment method (FFQ) in combination with the retrospective design. Another study of interest is that by Ness et al., who observed that among 5,765 Scottish men, consumption of milk was strongly and inversely associated with death from CVD (and all causes). In that study, the authors did not specifically collect data on the fat content

of the milk consumed, but noted that "consumption of reduced fat milks was unusual" in Scotland during the study period [57].

Taken together, the available studies do not support the widely held sentiment that dairy fat consumption is associated with an increased risk for CVD. The inconsistencies between studies, as well as within studies between different dietary sources of dairy fat, may be due to residual confounding by associated dietary factors. It may well be, however, that dairy fat may indeed have different health effects dependent on the specific food in which it is consumed. This idea is supported by a recent study in which Hjerpsted et al. [58] showed differential effects of cheese and butter (with equal fat content) on LDL cholesterol concentrations. It is remarkable that the only study that found a consistently positive relationship between dairy fat consumption and CVD was conducted in the United States (the Nurses' Health Study) [48, 51], while of the nine studies conducted in Europe, four reported an inverse association [21, 49, 52, 57], four no association [46, 52, 55, 56], and one an inverse association in men, but a positive association in women [53]. The two studies conducted in Costa Rica and Australia suggest an inverse association between dairy fat and CVD [50, 54]. It therefore seems possible that the three factors discussed above (residual confounding due to strong association of dairy fat intake with other dietary and lifestyle factors, particularly in the United States; differences in the food sources of dairy fat; and differences in husbandry practices) may explain the differences between US and non-US data.

A number of studies have assessed the relationship between ruminant *trans* fat intake and CVD risk. As dairy fat is a major source for ruminant *trans* fat, these studies may provide further information on the relationship between dairy fat and CVD. Laake and colleagues found in a prospective Norwegian cohort study that the consumption of ruminant *trans* fatty acids was associated with an increased risk of death from CVD [59]. Ruminant *trans* fat intake was strongly associated with numerous other dietary variables; when the models were adjusted for these associated dietary factors, the relationship between ruminant *trans* fat and CVD risk became nonsignificant. As the authors correctly point out, it is unclear whether adjustment for a strongly associated dietary factor such as SFA is appropriate in these studies. The intake of ruminant *trans* fats is strongly correlated with the intake of SFA; therefore, adjustment for a possibly CVD-relevant factor such as SFA seems prudent to assess the effect of ruminant *trans* fatty acids separately. At the same time, because the foods with which ruminant *trans* fats and SFA are consumed are largely the same, it may cause the issue of overadjustment where the effects of these foods are adjusted for, effectively making it impossible to detect the isolated effect of one or the other. This may be a strong argument for studying the relationship between whole foods and disease in such studies, rather than factors associated with foods. Other studies on the relationship between ruminant *trans* fatty acids and CVD have been summarized in a review by Mozaffarian and colleagues [60]. They concluded that "of four prospective studies […], none identified a significant positive association, whereas three identified a nonsignificant trend towards an inverse association." They further speculated that this may be due to "the presence of other factors in dairy and meat products that balance any effects of the small amount of *trans* fats they contain" [60].

Mechanisms by which dairy fat may affect adiposity and cardiometabolic health

It is important to consider the limitations of these studies. As discussed above, it is difficult to separate dairy fat from other dairy components in observational studies. It would therefore be reasonable to conclude that none of the studies conducted thus far were truly able to isolate the health effect of the dairy fat *per se*, making it impossible to draw any conclusions about whether the consumption of high-fat or low-fat dairy may be more beneficial. If we consider, however, that in spite of their limitations, these studies have some merit, then data summarized above show that dairy fat consumption is not associated with an increased risk of obesity and cardiometabolic disease. Another important limitation of most studies reviewed herein is that they assessed dairy intake by FFQ. As discussed above, FFQ is not an accurate assessment tool for certain foods, and it seems reasonable to hypothesize that this may be particularly the case for foods that are perceived as unhealthy such as whole milk, butter, and cream [11]. It is therefore possible that the studies underestimated the actual relationship between dairy fat and health outcomes. This seems unlikely, however, considering that in a relatively large number of studies dairy fat consumption was associated with lower body weight and no increase in cardiometabolic risk. This would suggest the possibility that the purported negative cardiovascular health effects of the well-described, SFA-triggered increase in the LDL-to-HDL cholesterol ratio in controlled trials of diets rich in dairy fat [3] may be countered by other components of dairy fat. One potential mechanism by which dairy fat may exert beneficial effects on cardiometabolic risk is by reducing chronic inflammation and lipid peroxidation, as suggested by a recent study that found that dairy fat intake, as assessed by serum biomarkers, was inversely related to measures of low-grade inflammation and oxidative stress in overweight adolescents [61]. In this section, we will summarize some data from animal studies as well as

observational or small-scale interventional human studies that have looked into the health effects of some of the minor fatty acids in dairy fat. As we will see, dairy fat is rich not only in C12-C16 SFA, but in fatty acids that may have beneficial effects on adiposity and metabolic health, thereby potentially providing an explanation for why dairy fat consumption has been found to be inversely associated with obesity, metabolic risk factors, and—in some studies—CVD.

Ruminant fat is the most complex fat in the human diet, consisting of more than 400 distinct fatty acid species [62], including many that are not found in our diets in significant amounts elsewhere. In particular, dairy fat is a rich source of butyric acid (C4:0), CLA, *cis* and *trans* palmitoleic acid (C16:1), and the branched-chain fatty acid phytanic acid (C20:0). While all of these constitute only a small percentage of the fatty acids present in dairy fat, there are data to suggest that these small amounts may still be biologically relevant, alone or within the context of other fatty acids.

Conjugated linoleic acids

Of the fatty acids mentioned above, CLAs have been studied most extensively. CLAs are dienoic isomers of linoleic acid (C18:2). Primary dietary sources are fats from ruminants, that is, cows, sheep, and goats, as CLAs are formed from C18-precursors, mostly linoleic acid and vaccenic acid (*trans* C18:1) by bacteria in the rumen [63]. The primary CLA in dairy fat is *cis*-9, *trans* 11 CLA (rumenic acid), typically accounting for 70–90 % of all CLA in dairy fat, while the second most abundant CLA is *trans* 10, *cis*-12 CLA [63]. The total content of CLA in the human diet from all sources has been estimated to be between 0 and 440 mg per day [64]. As will be discussed in more detail below, the total amount of CLA in dairy fat varies greatly, largely as a result of the amount of grass and linoleic acid-containing seeds and grains in the dairy cow's feed [63].

Considerable interest in CLA has been triggered by animal studies suggesting beneficial effects of different CLA isomers or mixtures of CLA on body weight and adiposity, serum lipids, insulin sensitivity and glucose tolerance, hepatic triglyceride content, and measures of inflammation [summarized in [63]]. We will focus here on the available human studies. Several groups have studied the effect of CLA on these end points in humans in recent years. Most of these studies have used supplements containing mixed CLAs or isolated CLA isomers, in doses of 1–5 g per day.

Body weight and adiposity

Most human studies showed no effect of CLA on body weight or adiposity, independent of whether mixed CLA was administered (most often consisting of ~50 % *cis*-9, *trans* 11 CLA and ~50 % *trans* 10, *cis*-12 CLA) [65–68] or whether either of the isomers was administered in purified form [66, 69, 70]. The doses administered in these studies ranged from 0.6 to 3.9 g/day, and length of treatment ranged from 6 to 18 weeks. Subject populations were most commonly overweight to obese, healthy men and women. Several studies have shown a modest reduction in body weight and fat mass [71–76]. Most of the studies that showed an effect of CLA on body weight or fat mass used relatively high doses (in excess of 3.2 g/day), often administered over an extended period of time (in excess of 12 weeks) [77]. Thus, while CLA supplementation with a high dose of mixed CLA for an extended period of time seems to have a modest effect on body weight and fat mass, it seems unlikely that the much lower CLA content in dairy fat will have a similar effect, particularly because dairy fat CLA is mostly in the *cis*-9, *trans* 11 CLA form that is thought to have less of an impact on fat mass than the *trans* 10, *cis*-12 CLA isomer. A study of potential interest in this regard was conducted by Tricon et al. [78]. These authors asked 32 healthy male subjects aged 34–60 years to consume milk, butter and cheese that were naturally enriched in CLA (mostly *cis*-9, *trans* 11) and control milk, butter, and cheese low in CLA for 6 weeks each, in randomized order. Only these test foods were provided, in relatively large quantities, while all other foods were chosen freely by the subjects and consumed ad libitum. Neither the control nor CLA study phase affected body weight or BMI [78]. Potential limitations of this study were that the duration may have been too short for this end point, that the dairy products differed with regard to many other fatty acids as well in addition to CLA, and that many of the subjects in this study were lean, making it harder to induce significant changes in body weight or adiposity. It is important to note that the 9-*cis*, 11-*trans* CLA enrichment was achieved not by pasture-feeding the dairy cows, but by adding a mixture of fish oil and sunflower oil to the total mixed ration (TMR). As we will discuss further below, feeding fresh grass as compared to TMR based on forage, grains, and soy has substantial effects on the dairy fat composition. Adding oils rich in unsaturated fatty acids can be expected to lead to some enrichment in certain fatty acids in milk, such as CLA, but an overall fatty acid composition that is still substantially different from that of pasture-fed animals.

Serum lipids

With regard to serum lipids, a particularly interesting study was conducted by Tricon et al. [69]. Forty-nine healthy men with a BMI between 18 and 34 kg/m^2 consumed 0.6 g/d, 1.2 g/d, and 2.4 g/d sequentially of either *cis*-9,

trans 11 CLA or *trans* 10, *cis*-12 CLA for 8 weeks, followed by a 6-week washout phase and a crossover to the other isomer. The *cis*-9, *trans* 11 CLA lowered the total-to-HDL cholesterol ratio compared to baseline, while the *trans* 10, *cis*-12 CLA isomer raised it. Similarly, triglycerides were higher during the *trans* 10, *cis*-12 CLA isomer phase than during the *cis*-9, *trans* 11 CLA isomer phase [69]. In another study by the same group, 32 healthy male subjects aged 34–60 years consumed naturally CLA-enriched milk, butter, and cheese as well as control milk, butter, and cheese low in CLA for 6 weeks each, in randomized order (as discussed above). The only serum lipid-related difference between the two phases was a slightly elevated LDL-to-HDL cholesterol ratio at the end of the CLA-enriched diet phase [78]. Moloney et al. [79] found that 3 g/d of mixed CLA for 8 weeks increased HDL cholesterol and lowered the LDL-to-HDL cholesterol ratio compared to placebo. Otherwise, there were no statistically significant effects on fasting lipid concentrations, LDL density, and LDL susceptibility to oxidation, leading the authors to conclude that "increased consumption of full-fat dairy products and naturally derived *trans* fatty acids did not cause significant changes in cardiovascular risk variables" [78]. In two other well-controlled dietary intervention studies, no significant effects of mixed CLA preparations or a purified *cis*-9, *trans* 11 CLA preparation on serum lipid concentrations were observed [65, 66]. Taken together, the available human data suggest that CLA has little or no effect on serum lipid concentrations. It appears unlikely that the relatively small amount of CLA in dairy fat would have any clinically significant effect on the serum lipid profile.

Insulin sensitivity and glucose tolerance

Studies conducted by Riserus et al. [80] have shown that ~3 g/day of purified preparations of either the *cis*-9, *trans* 11 CLA or the *trans* 10, *cis*-12 CLA isomer reduce insulin sensitivity, as assessed by the gold standard euglycemic clamp method [80, 81]. Interestingly, in these studies, a mixed CLA preparation consisting of both isomers in equal amounts did not affect insulin sensitivity or glucose tolerance. The 24-month study by Gaullier discussed above that showed a reduced body weight and fat mass in individuals taking 3.4 g/day of mixed CLA also showed slightly, but significantly increased fasting glucose and insulin concentrations, which is surprising given the loss of fat mass [72]. A similar dose of mixed CLA administered for 8 weeks also increased fasting glucose and the 3-hour OGTT glucose area under the curve compared to placebo [79]. Other studies did not find any effect of mixed CLA or the purified isomers (*cis*-9, *trans* 11 or *trans* 10, *cis*-12) to have an effect on insulin sensitivity or glucose tolerance [69, 82, 83], although only one of these assessed the end points by the gold standard euglycemic clamp [82]. One study even found the opposite effect. Lambert et al. [65] administered 3.9 g/d of mixed CLA or placebo to 62 nonobese, healthy men and women for 12 weeks, and found that the insulin and plasma free fatty acids were lower during an OGTT in women after CLA, suggesting improved insulin sensitivity. A study that may again be of particular relevance is again that of Tricon et al. [78] mentioned above where subjects consumed dairy products that were either low in CLA or naturally enriched in CLA. Consuming 141 mg/d vs. 1,421 mg/d of *cis*-9, *trans* 11 CLA from dairy did not differentially affect fasting glucose, insulin, or measures of insulin sensitivity, suggesting that the amount and type of CLA commonly consumed from dairy fat has no or little impact on insulin sensitivity and glucose tolerance.

Inflammation

Two studies reported increased CRP concentrations in subjects receiving either mixed CLA or purified *trans* 10, *cis*-12 CLA supplements [84, 85]. In contrast, consuming dairy products rich or low in *cis*-9, *trans* 11 CLA did not affect biomarkers of inflammation or endothelial dysfunction [78]. Another small study found a reduction in serum markers of inflammation (IL-6, IL-8, TNFα) in healthy subjects aged 30–65 years consuming cheese naturally rich in *cis*-9, *trans* 11 CLA for 10 weeks each, compared to when these people were eating cheese with a low CLA content (control) [86]. In this study, the authors did not specifically produce cheese with low and high CLA contents, respectively. Instead, they identified commercially available cheeses that were naturally low versus high in CLA content, in this case likely as a result of different degrees of pasture feeding. It should be noted, however, that the two cheeses differed with regard to numerous fatty acids, and it is possible that the differential effects were, at least partly, due to other differences in the fatty acid composition or other components of these cheeses.

Taken together, the effects of CLA in humans differ substantially from those observed in rodents. This may be related to generally lower doses used in the human studies or because of species differences. Either way, the dose used in most studies (2–4 g/day) as well as the type of CLA (mostly mixed CLA with a substantial portion of *trans* 10, *cis*-12) is not very informative to gauge the health effects of CLA in dairy fat. The best estimate based on the available data is that the relatively small amount of predominantly *cis*-9, *trans* 11 CLA in dairy fat has little or no effect on body weight, adiposity, serum lipids, insulin sensitivity, glucose tolerance, and measures of inflammation.

Butyric acid (C4:0)

Dairy fat is unusual in that it is one of very few dietary sources of short-chain fatty acids, including butyric acid (C4:0). Short-chain fatty acids are produced in the gastrointestinal tract of all animal species by microbial fermentation of carbohydrates, specifically fibers [87]. Butyrate plays an important role in gut health by providing energy to enterocytes and inhibiting NFκB-mediated upregulation of inflammatory pathways [88]. More recently, it has also been shown in an in vitro model that butyrate reduces translocation of pathogenic bacteria across the epithelial cell layer, at least partly by inhibiting NFκB-mediated pro-inflammatory pathways in the epithelial cells [89]. These beneficial effects seem to be present not only when butyrate is produced by the gastrointestinal microbiota, but also when butyrate is taken up orally. In a small clinical study, oral butyrate reduced the expression of pro-inflammatory cytokines in the gastrointestinal mucosa and improved disease symptoms in human subjects suffering from Crohn's disease [90]. The effect of 4 g of butyrate per day for 8 weeks was so strong that total remission was observed in more than half the patients [90].

Extra-gastrointestinal health benefits of butyrate have also been reported. In a mouse model of diet-induced obesity, adding 5 % (by weight) of butyrate to the animals' diet prevented the development of both obesity and insulin resistance [91]. Of note, the addition of butyrate to the diet had numerous unanticipated effects, including an increase in oxidative muscle fibers, increased mitochondrial function and fat oxidation, increased uncoupling protein expression, and increased adenosine monophosphate-activated protein kinase (AMPK) activity. Butyrate also increased leptin production in an adipocyte cell line in vitro through a mechanism involving the G protein coupled receptor 41 (GPR41). Oral administration of butyrate also increases circulating leptin levels in mice [92]. The systemic effects of oral butyrate in some of these studies are somewhat surprising, given that most butyrate is removed from portal blood when it passes the liver, with peripheral blood butyrate levels being generally low and mostly unaffected by diet composition [87].

Taken together, through anti-inflammatory effects and possibly effects on energy expenditure, it seems plausible to hypothesize that dietary butyrate in the concentrations present in dairy fat (∼4 %) may have clinically relevant effects on body weight and metabolic health. It also seems possible that dietary butyrate consumption may have beneficial effects on chronic inflammatory conditions in the gastrointestinal tract.

Palmitoleic acid (C16:1)

Interest in palmitoleic acid has emerged recently from work performed in mice deficient in the two major fatty acid binding proteins (FABP) in adipocytes [93, 94]. In these animals, de novo lipogenesis in adipocytes is not inhibited by a high-fat diet, supposedly because the adipocyte cannot appropriately sense the long-chain fatty acids taken up with the diet in the absence of the two primary FABP [93]. The resulting phenotype was surprising in that these mice were resistant to weight gain and the development of insulin resistance on a high-fat diet, which was partly explained by increased hepatic fat oxidation and increased energy expenditure [93]. The authors observed a distinct elevation of *cis* palmitoleic acid in adipose tissue as well as the free fatty acid fraction in plasma, and hypothesized that *cis* palmitoleic acid may be formed in adipocytes during lipogenesis and may function as a "lipokine" released by adipocytes to stimulate fat oxidation and inhibit lipogenesis in the liver [94]. According to this hypothesis, the balance between adipocyte lipogenesis and lipolysis on the one hand, and hepatic lipogenesis and β-oxidation on the other, is highly coordinated, in part by adipocyte-derived palmitoleic acid and of crucial importance for both energy homeostasis and metabolic control of insulin sensitivity and glucose tolerance [94]. These considerations may be of relevance to the health effects of dairy fat given that dairy fat (and other ruminant fats) are among the very few dietary sources of palmitoleic acid. If palmitoleic acid indeed plays an important role in the regulation of hepatic versus adipocyte lipogenesis, then consuming dietary fats rich in this fatty acid may beneficially affect both energy homeostasis and metabolic health. Another indication that this may be the case is provided by an in vitro study showing that while palmitic acid (C16:0) distinctly impaired insulin signaling and insulin-stimulated glucose transport in muscle cells, palmitoleic acid substantially enhanced glucose uptake, glucose oxidation, and glycogen synthesis [95]. In humans, the *cis* palmitoleate content of the fasting free fatty acid fraction, that is, fatty acids released from adipose tissue, was found to be strongly and independently associated with insulin sensitivity, as measured by OGTT or euglycemic–hyperinsulinemic clamp [96]. In 3,736 adults participating in the prospective Cardiovascular Health Study, Mozaffarian et al. [26] found that higher plasma phospholipid *trans* palmitoleic acid levels "were associated with lower adiposity, and, independently, with higher high-density lipoprotein cholesterol levels, lower triglyceride levels, lower C-reactive protein levels, and lower insulin resistance." Plasma phospholipid *trans* palmitoleic acid was also associated with a lower incidence of diabetes, by 62 % in the highest quintile of plasma phospholipid *trans* palmitoleic acids versus the lowest [26]. Notably, whole-fat dairy consumption was most strongly associated with *trans* palmitoleic acid concentrations in multivariate analyses [26]. It should be noted, however, that the association between

plasma phospholipid *trans* palmitoleic acid and diabetes risk held even after adjusting for all potential dietary sources of *trans* palmitoleic acid, that is, red meat and full-fat dairy products [26], which may suggest that endogenous regulation of the phospholipid composition rather than diet composition may be linked to diabetes risk. Another explanation may be that full-fat dairy intake, as assessed by FFQ, indeed explains only a small portion of the variation in plasma palmitoleic acid content because of the inherent limitations of that assessment method, specifically the fact that the quality of dairy fat cannot be taken into account. As we will see below, the *trans* palmitoleic acid content of dairy fat is strongly related to the dairy cow feed. In a separate paper, these same authors found that plasma phospholipid *cis* palmitoleic acid was associated with risk factors for cardiometabolic disease [97]. However, the directions of these associations were not consistent, possibly related to the fact that phospholipid *cis* palmitoleic acid could be derived from either ruminant fat or hepatic de novo lipogenesis. Taken together, the available data suggest that *trans* palmitoleic acid may benefit adiposity and metabolic health; however, future research will be required to test this directly. The same may be true for dairy fat *cis* palmitoleic acid. However, the relationship between *cis* palmitoleic acid, obesity, and cardiometabolic disease is more difficult to study because humans can synthesize this fatty acid endogenously.

Phytanic acid

Another fatty acid of potential interest is the branched-chain fatty acid phytanic acid (C20:0). This fatty acid is characterized by a C16 chain with four methyl side chains attached in positions 3,7,11, and 15 [98]. While at this time, no controlled feeding studies have been conducted with purified phytanic acid, and there are a number of in vitro experiments that suggest that dietary phytanic acid from dairy fats may be relevant to energy and glucose homeostasis. Specifically, phytanic acid, in concentrations available in the human circulation, binds to and activates the transcription factors retinoid-X-receptor (RXR) and peroxisome proliferator activated receptor α (PPARα) [99–102]. In the liver, this is thought to stimulate peroxisomal α- and β-fatty acid oxidation, which is necessary because the side chain at position 3 prevents typical mitochondrial β-oxidation [98]. In rodent models, phytanic acid feeding reduces hepatic triglyceride content [102], which would be expected to improve hepatic insulin sensitivity and reduce VLDL-lipoprotein assembly and plasma circulating triglycerides. This consideration is consistent with the observation that phytanic acid regulates glucose metabolism in hepatocytes in vitro [103]. In adipose tissue, phytanic acid has been shown to stimulate adipogenesis of metabolically active brown fat in cell culture experiments [104]. And finally, phytanic acid has been shown to be a strong inducer of uncoupling protein 1 and may therefore affect energy homeostasis [104]. In conclusion, although no definitive evidence exists that phytanic acid affects energy and glucose homeostasis in humans, the available literature suggests that this hypothesis is worth investigating in future research.

Taken together, while there has been much interest in CLA as a potential beneficial fatty acid in dairy fat, the existing evidence suggests that CLA in the amounts and form present in dairy fat is unlikely to have a significant effect on end points relevant to chronic disease, such as energy expenditure, adiposity, liver fat content, inflammation, insulin sensitivity, and glucose tolerance. In contrast, although inconclusive, it appears possible that butyric acid, phytanic acid, and palmitoleic acid in the amounts present in dairy fat could affect these end points. Importantly, these are by no means the only lipid components in milk that may have health effects; however, we intended to provide these as examples to illustrate that dairy fat is more than C12-C16 SFA. It should further be considered that these (and other) fatty acids may act differently or synergistically when consumed together.

Dairy fat composition: effect of feeding practices

Milk production practices have changed dramatically since the Second World War, particularly in the United States. Today, the majority of dairy originates from highly specialized industrialized farms. In 1940, milk cows were present on 76 % of all US farms, a total of 4.6 Million, 99 % of which had a herd size of less than 30 cows [105]. Between 1940 and 2004, the number of dairy operations in the United States declined by 98 % [105], while the number of cows per operation increased from an average of 5 in 1940 to an average of 88 in 1997 [105]. It seems likely that that number has increased further since. The industrialization process has had a number of consequences. First, dairies have increasingly focused on high-yield bovine genetics such as Holsteins. Second, to increase yields to more than 40 kg of milk per day per animal, dairy cows are fed fodders with a high density of digestible energy and protein. To standardize energy and nutrient intakes, modern dairy cows are typically maintained indoors and are fed with a constant ratio of fodders known as TMR, which are largely based on conserved forage, grains, soy, and added micronutrients. This management based on high-yielding dairy cows kept indoors during the year is very different from the season-based production of the 1940 and 1950 s where cows were grazed during the spring and summer.

As discussed above, dairy fat can be a significant source of biologically active fatty acids. The content of these fatty acids in milk is directly linked to the feed of the dairy cow, a fact not often considered in dietary studies evaluating the health effects of dairy foods. Several fatty acids reflect the intake of fresh, growing green fodder, particularly CLAs, rumenic acid as well as its precursors *trans* 11 C18:1 (vaccenic acid) and *trans* 9 C16:1 (palmitoleic acid), phytanic acid, the omega-3 fatty acid α-linolenic acid, the n-6/n-3-polyunsaturated fatty acid ratio, and the contents of C12-C16 SFA (Table 5). With regard to CLAs, there is a rich literature describing the numerous factors affecting its concentration in milk, including breed, season, seeds, or seed oils in the fodder, and most importantly the degree to which the animals have access to fresh, growing grass [summarized in [64]]. Due to the fact that dried fodders do not support the same level of CLA production as fresh fodders, even milk from organic farms aiming to feed only grass and hay will have substantially less CLA in winter than in spring and summer. Phytanic acid is derived by microbial processing of phytol, the side chain of chlorophyll. The phytanic acid content of dairy fat is therefore directly related to the amount of green fodder, ranging from ~0.15 to ~0.45 % [106, 107]. Green, growing leaves are also fairly rich in ALA. In the rumen, over 95 % of the ALA is biohydrated and saturated (to C18:0); only a small portion is absorbed as ALA and enters the milk. Nevertheless, the ALA content of milk from grass-fed cows is considerably higher than that of grain-fed cows (Table 5), also affecting the n-6/n-3-polyunsaturated fatty acid ratio. The health relevance of the relatively small amount of ALA in dairy fat (<1 %) is currently unclear. For that reason, it is not possible to gauge whether the difference in the ALA content in pasture-fed versus grain-fed milk has an impact on disease risk. Similarly, it is unclear whether the small amounts of *trans* palmitoleic acid and phytanic acid that are found even in milk from pasture-fed animals is biologically relevant. However, there is good reason to believe that these fatty acids are highly biologically active even at low concentrations in the body, as outlined above. The contents of the primary cholesterol-raising SFA (C12:0–C16:0) are typically lower in pasture-fed milk [106, 108]. The dairy fat content of butyric acid, however, seems to be relatively unaffected by the cow's feed, typically accounting for ~3.5–4 % of all dairy fat [106, 108].

Table 5 Relationship between dairy fat content of selected fatty acids and dairy cow feed

Fatty acid	Pasture- or grass-based (%)	Grain-based	References
Butyric acid (C4:0)	3.4	3.6	[108]
	3.6	3.3	[106]
Palmitoleic acid (C16:1)			
trans	0.14	0.06	[109]
cis	1.28	1.53	[109]
Conjugated linoleic acids (C18:2)			
Rumenic acid (cis-9 trans 11)	1.61	0.45	[108]
	1.34	0.55	[106]
Phytanic acid (C20:0)	0.45	0.15	[106]
Vaccenic acid (*trans* 11 C18:1)	3.1	0.7	[106]
Oleic acid (C18:1)	24.1	20.2	[106]
α-linolenic acid (C18:3n-3)	0.78	0.16	[108]
	1.15	0.54	[106]
Total C12-C16 saturated fatty acids	39.4	54.1	[108]
	36.0	47.5	[106]

All data in % of total dairy fat

While we have focused thus far on selected fatty acids for which current evidence suggests biological activity, perhaps a more important point is that the composition of dairy fat as a whole shows complex patterns that shift greatly with changes in the cows' feed. In a two-dimensional principal component analysis, Ferlay et al. [109] showed that a wide range of major and minor fatty acids were correlated with grazing on fresh grass, whereas others were related to rations based on conserved fodders. A cluster of stearic, oleic, vaccenic, rumenic and linolenic acids, cis-9, cis-11 CLA, trans 11, cis-14 and *cis*-9, *trans* 13 linoleic acid, *trans* 9 C16:1, and trans and cis isomers of C18:1 are related to diets from fresh grass, whereas SFA (C10:0, C12:0, C13:0, C14:0 and C16:0) and cis-monounsaturated fatty acids (*cis*-9 C10:1, *cis*-9 C14:1 and *cis*-9 C16:1) were characterizing diets based on grass silage plus concentrates.

In summary, milk from cows fed predominantly pasture has a substantially different fatty acid profile than milk from cows fed typical feed concentrates. Major differences are observed in CLA, vaccenic acid, *trans* palmitoleic acid, phytanic acid, ALA and C12-C16 SFA concentrations.

Summary and conclusion

We have summarized the evidence from observational studies demonstrating that, in contrast to the prevailing scientific and public sentiment, dairy fat consumption is not typically associated with an increased risk of weight gain, CVD, or T2DM. This is also in contrast to most current dietary guidelines recommending the consumption of fat-reduced milk and dairy products. The primary rationale for these recommendations to limit dairy fat intake has been (1) to reduce intakes of C12-C16 SFA, due to their effect on serum lipids and putative negative effects on CVD risk,

and (2) to reduce energy density, which is thought to promote excessive caloric intake and fat gain. However, the potential health benefits of other bioactive fatty acids including butyric acid, phytanic acid, *cis*- and *trans* palmitoleic acid, CLA, and ALA have rarely been considered. This is particularly relevant as the contents of these fatty acids in milk vary greatly, largely as a function of dairy cow feed. The currently available literature does not permit any definitive conclusions on the overall health effects of dairy fat, or the differences between dairy fat from cows fed a grass-based versus grain-based diet. However, the evidence does not offer any compelling reason to avoid dairy fat and furthermore suggests that it may be worthwhile to consider milk and dairy as complex foods with effects on health that may be difficult to predict based on prevailing diet-health models that are often focused on isolated dietary factors (e.g., SFA content) and isolated biomarkers of disease risk (e.g., serum lipids).

The United States has seen a dramatic change in the husbandry practices of dairy cows from pasture-based to concentrate-based fodder. As dairy fat is a rare source of certain fatty acids such as butyric acid, phytanic acid, *cis*- and *trans* palmitoleic acid, the shift to high-yielding breeds with a lower milk fat content, the removal of fat from many dairy products, and novel feeding practices has likely led to a substantial reduction in the overall consumption of these fatty acids in many individuals. Given that the available evidence suggests a possible effect of these fatty acids on end points such as energy expenditure, adiposity, liver fat content, insulin sensitivity, and glucose tolerance, it seems prudent to reconsider the common recommendation to consume milk and dairy products in their fat-reduced form. Further, well-controlled intervention studies on the health effects of milk produced by traditional pasture-based versus grain-based husbandry practices should be an important research priority in this area.

Methods

Investigators performed systematic literature searches in MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed/) and Google Scholar (scholar.google.com) databases for observational studies investigating the link between high-fat dairy and/or dairy fat consumption and obesity, metabolic health, and cardiovascular disease risk. Search terms used were "dairy" or "milk" in combination with "obesity," "adiposity," "body weight," "diabetes," "metabolic," "insulin sensitivity," "insulin resistance," "glucose tolerance," "cardiovascular," "coronary," "myocardial," or "stroke." References of all papers identified were examined for additional relevant studies. The "related articles" function in Google Scholar was used to search for additional studies that may have been overlooked by other methods. All identified studies that specifically addressed high-fat dairy and/or dairy fat were included, while those that related to dairy consumption but did not specifically address high-fat dairy and/or dairy fat were not included.

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Conflict of interest None of the authors has any conflicts of interest to disclose.

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