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The Impact of Dairy Products in the Development of Type 2 Diabetes: Where Does the Evidence Stand in 2019?

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ABSTRACT

The prevalence of type 2 diabetes (T2D) has increased rapidly. Adopting a healthy diet is suggested as one of the effective behaviors to prevent or delay onset of T2D. Dairy consumption has been recommended as part of a healthy diet, but there remains uncertainty in both the scientific community and the public about the effect of different dairy products on T2D risk. In a recent workshop, the evidence on dairy products and T2D risk was presented and discussed by a group of experts. The main conclusions from the workshop are presented in this position paper and are as follows. 1) Available evidence from large prospective cohort studies and limited randomized controlled trials (RCTs) suggests that total dairy consumption has a neutral or moderately beneficial effect on T2D risk. 2) Increasing evidence from prospective cohort studies indicates that yogurt is most strongly associated with a lower T2D risk, but evidence from RCTs is scarce. 3) Fatty acids from dairy (medium-chain, odd, and very long-chain SFAs as well as *trans*-palmitoleic acid) are associated with lower T2D risk and improved metabolic health, but more research is needed on studies that explore cause and effect relations to exclude the possibility that the dairy fatty acids simply serve as markers of overall dairy consumption. 4) The food matrix can be a stronger determinant of health effects than SFA content. This review further identifies research gaps in the existing knowledge and highlights key research questions that need to be addressed to better understand the impact of dairy consumption on future T2D risk. *Adv Nutr* 2019;10:1066–1075.

Keywords: dairy, type 2 diabetes, milk, yogurt, cheese

Introduction

The prevalence of diabetes has increased rapidly in recent times, and globally 425 million people were affected by diabetes in 2017, mainly type 2 diabetes (T2D), which comprises ~91% of all cases of diabetes (1). It is expected that the worldwide number of people with T2D will rise to 629 million by 2045 and a further 352 million people with impaired glucose tolerance will have a high risk of developing diabetes (1). Diabetes is a serious medical condition that often requires the use of oral antidiabetic medication or insulin injections to maintain glycemic control (2). In 2017, the global healthcare cost of diabetes, including treatment and related complications, reached US\$850 billion (1). Lifestyle interventions, particularly reducing sedentary behavior, increasing exercise, energy intake restriction to

promote weight loss, and adopting a healthy diet, are usually effective for reducing insulin resistance, and may partially restore pancreatic β -cell function, thereby reducing the need for glucose-lowering medication, and preventing or delaying the onset of T2D (3–9). The pathophysiology of T2D is complex and not the same for each individual, but insulin resistance and β -cell dysfunction are key factors in the development of T2D. It is well established that adipose tissue dysfunction (impaired adipose tissue expandability, adipocyte hypertrophy, altered lipid metabolism, and local inflammation), which may partly be explained by altered adipose tissue oxygenation, is a central player in obesity-related insulin resistance (10–12). Abdominal fat accumulation and low lean body mass are associated with insulin resistance and increased T2D risk, whereas lower-body fat storage seems

protective against the development of T2D and cardiovascular disease, when adjusted for total adipose tissue mass (13–15). Evidence from a recent meta-analysis of randomized controlled trials (RCTs) suggested dairy products may have modest benefits in assisting weight loss in short-term or energy-restricted RCTs (16), with some specific evidence showing that yogurt consumption is associated with a lower risk of obesity, lower risk of increased body weight, and lower risk of elevated waist circumference (17). In addition, a recent meta-analysis of RCTs indicated that increased dairy consumption as part of energy-restricted diets resulted in greater loss in body weight and fat mass, while preventing excessive loss of lean body mass in 18- to 50-y-old adults (18). Furthermore, as one of the important food groups in guidelines for a healthy diet (19, 20), there are components in dairy which have been suggested to be beneficial for T2D, such as flavonoids, calcium, medium-chain and odd-chain saturated fats, unsaturated fats, branched-chain amino acids (BCAAs), *trans*-palmitoleic acid (*trans* 16:1n-7), probiotics, and phylloquinone (vitamin K-1) and menaquinones (vitamin K-2) (21, 22). However, dairy products also contain saturated fats, *trans* fats, and sodium, which could be harmful for T2D (23–26). In addition, the recent study of Liu et al. (27) investigated the association between dietary SFAs and T2D risk by following 37,421 participants for 10 y, and found milk and milk products and butter-derived SFAs were not statistically significantly associated with T2D risk, except for cheese-derived SFAs which were associated with a lower T2D risk (HR 0.90; 95% CI: 0.83, 0.98). Furthermore, the recent review of Thorning et al. (28) indicated that cheese intake generally results in a lower LDL-cholesterol response than

that from the same amount of dairy fat as butter, which is suggestive that fat consumed in isolation (butter) is more bioavailable than fat that is carried in the cheese matrix (29).

US dietary guidelines recommend daily consumption of 3 cups of fat-free or low-fat (1%) milk and milk products for individuals aged ≥ 9 y (30). In line with the United States, low-fat and low-sugar dairy products have been recommended as part of the Eatwell Guide in the United Kingdom, although without quantity recommendations (31). However, very little evidence exists on the adverse impact of high-fat compared with low-fat dairy consumption on T2D risk. The most recent meta-analysis of 13 prospective cohort studies found no association between high-fat dairy and T2D risk (32). In addition, although sugar improves the palatability of dairy foods like yogurt (33), there is little evidence on whether there is any differential effect of sweetened and unsweetened or artificially sweetened yogurt on human health.

The current article is based on presentations, discussions, and conclusions from a workshop on the effect of dairy foods on the risk of T2D. The closed consensus workshop of invited scientists was held at Wageningen University (Wageningen, Netherlands) on 20–21 November, 2017. A total of 8 experts (DIG, AA, SJLB, GHG, MK, AM, HP, SSS-M) were selected based on their previous published work on dairy products and diabetes-related topics, representing different scientific areas related to dairy foods and health. Before the workshop, each expert was asked to prepare a presentation summarizing the evidence in his/her area of expertise. Each presentation was challenged during an extensive discussion.

Evidence from Prospective Cohort Studies on Dairy Products and T2D Risk

A number of systematic reviews and meta-analyses (32, 34–37) have published evidence on the association between dairy products and T2D. The most recent meta-analysis of Gijsbers et al. (32) in 2016 performed a dose–response meta-analysis to quantify the associations of incident T2D with total dairy and types of dairy consumption at different amountsof intake. The meta-analyses of Gao et al. (35) and Aune et al. (34) were both dose–response meta-analyses and of similar design to Gijsbers et al. (32), and will therefore be discussed in the following sections. Using similar search strategies and inclusion and exclusion criteria for study selection as Gijsbers et al. (32), 4 new prospective cohort studies (38–41) were identified with data on dairy and incident diabetes. All the cohort studies mentioned in the meta-analyses of Gijsbers et al. (32), Aune et al. (34), Gao et al. (35), and more recently published studies (38–41) are summarized in **Supplemental Table 1**.

Total dairy

Previous meta-analyses by Gao et al. (35) and Aune et al. (34) in 2013 both reported a significant inverse association between total dairy consumption and T2D risk. The summary RRs were 0.93 (95% CI: 0.87, 0.99) per 400 g/d

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Abbreviations used: BCAA, branched-chain amino acid; HbA1c, glycated hemoglobin; OGTT, oral-glucose-tolerance test; RCT, randomized controlled trial; T2D, type 2 diabetes.

and 0.94 (95% CI: 0.91, 0.97) per 200 g/d for Aune et al. (34) and Gao et al. (35), respectively. The meta-analysis by Gijsbers et al. (32) summarized data from 16 studies and the main finding was a linear inverse association for total dairy intake, with a 3% lower T2D risk per 200 g/d higher intake (RR: 0.97; 95% CI: 0.95, 1.00), which was in line with findings of earlier studies (34, 35). Most studies included in these meta-analyses were from Europe and America (32, 34, 35). In subgroup analyses, a stronger inverse association was found in Asian populations (RR: 0.85, 95% CI: 0.65, 1.12), but no association in European populations (32). The results of a recently published study based on data of a Chinese prospective cohort (39) were consistent with previous meta-analyses (32, 34, 35). In the Chinese cohort study, a total of 45,411 Chinese men and women were followed for 12 y (39) and total dairy was associated with a significantly lower T2D risk, with high dairy consumers having a significant 10% reduction in T2D risk compared with low consumers (39). Another 3 recent studies (38, 40, 41) found no association between total dairy consumption and T2D risk, but these studies had relatively small sample sizes ranging from 1867 to 2974 subjects. By adding 4 new studies (38–41) into the most recent meta-analysis of Gijsbers et al. (32), the updated results of Soedamah-Muthu and de Goede (42) showed a similar result, that total dairy (per 200 g/d) was borderline significantly associated with a 3% lower T2D risk (RR: 0.97; 95% CI: 0.95, 1.00), although with significant heterogeneity existing between studies ($I^2 = 62.8\%$).

Liquid milk

For the associations between liquid milk consumption and T2D risk, the most up-to-date meta-analysis by Gijsbers et al. (32) summarized 11 studies and showed that total milk consumption was not associated with T2D risk (RR: 0.97; 95% CI: 0.93, 1.02—per 200 g/d), which is in line with previous meta-analyses (34, 35). Recently published prospective cohort studies (38, 40, 41) have also confirmed a null association between milk consumption and T2D. On the contrary, a recent Chinese prospective cohort study (39) followed 45,411 participants for 12 y and found that daily intake of milk was associated with a lower T2D risk (HR: 0.88; 95% CI: 0.81, 0.96—comparing daily drinkers with nondrinkers; P for trend = 0.01), although the majority of participants (67.4%) never or hardly drank milk and only 15% of participants were daily milk consumers. This inverse association was in line with the subgroup analysis by Gijsbers et al. (32), which also indicated an inverse association of milk consumption and T2D risk (RR: 0.87; 95% CI: 0.72, 1.05—per 200 g/d) in Asian populations. In addition, Bergholdt et al. (43) addressed the question of whether there could be a causal association between milk consumption and T2D by milk intake observationally and genetically via lactase persistence, using a Mendelian Randomization design in 97,811 subjects of the Danish general population. This found that high milk intake was not associated with T2D risk.

Fermented dairy

Fermented dairy products are the milk products prepared by lactic acid fermentation or a combination of this and yeast fermentation, mainly consisting of yogurt and cheese (44). For yogurt, the most recent meta-analysis by Gijsbers et al. (32) reported a nonlinear inverse association between yogurt consumption and T2D risk at 80 g/d (RR: 0.86; 95% CI: 0.83, 0.90—compared with 0 g/d), although with significant heterogeneity existing between studies ($I^2 = 73\%$), which was consistent with previous meta-analyses reporting yogurt consumption to be inversely associated with lower T2D risk (34, 35). Evidence of the association between yogurt consumption and T2D risk was only available in 2 (38, 40) out of the 4 recently published prospective cohort studies (38–41), and they reported neutral associations between yogurt intake and T2D risk; however, these 2 studies (38, 40) were based on cohorts with small sample sizes (1867–2974 participants) compared with the meta-analysis by Gijsbers et al. (32) (22 cohort studies, 579,832 participants). The study by Soedamah-Muthu and de Goede (42) updated the meta-analysis of Gijsbers et al. (32) by adding the 2 new studies (38, 40) and found a similar result: that of a nonlinear inverse significant association of yogurt consumption with T2D risk (RR: 0.86; 95% CI: 0.83, 0.90; $I^2 = 69\%$, at 80 g/d compared with 0 g/d). For the associations between yogurt of different fat contents and T2D risk, to our knowledge, evidence is only available from the PREDIMED study (45, 46), which followed 3349 individuals free of T2D but at high cardiovascular disease risk for 4 y and found both whole-fat yogurt and low-fat yogurt to be associated with a lower T2D risk.

An inverse association between cheese consumption and T2D risk was found by the earlier meta-analyses by Aune et al. (34) and Gao et al. (35) with pooled RRs of 0.92 per 50 g/d (95% CI: 0.86, 0.99; 8 studies; $I^2 = 0\%$) and 0.80 per 30 g/d (95% CI: 0.69, 0.93; 7 studies; $I^2 = 59\%$), respectively. The more recent meta-analysis by Gijsbers et al. (32) reported a neutral association between cheese intake and T2D risk (RR: 1.00 per 10 g/d; 95% CI: 0.99, 1.02; 12 studies), although significant heterogeneity was present ($I^2 = 62\%$). The findings of 2 new published cohort studies (40, 41) were in accordance with Gijsbers et al. (32), showing that cheese intake was not associated with T2D risk.

Butter

There has been an increasing controversy around the effect of butter on human health (47), because butter has the highest fat and saturated fats concentrations of all dairy products. The meta-analyses by Aune et al. (34), Gao et al. (35), and Gijsbers et al. (32) did not analyze data separately for butter. Interestingly, a recent meta-analysis by Pimpin et al. (47) summarized 4 studies (46, 48–50) and reported that butter (per 14 g/d) consumption tended to be inversely associated with a lower risk of T2D (RR: 0.96; 95% CI: 0.93, 0.99). Furthermore, Mozaffarian (51) and Pimpin et al. (47) indicated the existence of potential publication bias for the

relations between butter intake and T2D risk. Therefore, the evidence on butter from cohort studies overall suggests, if anything, a slightly inverse association with T2D risk, but more studies are needed.

Cream and ice cream

There are a limited number of cohort studies which have investigated the associations between cream or ice cream intake and T2D risk. Three meta-analyses (32, 34, 35) showed consistent results that cream was not associated with T2D risk and there were no significant heterogeneities existing between studies. Ice cream was significantly associated with lower T2D risk in 2 meta-analyses (32, 34) and significant heterogeneity ($I^2 = 86\%$) was present in the study of Gijsbers et al. (32) but not in that of Aune et al. (34). There has been no further updated evidence on the association between cream or ice cream and T2D risk.

Dairy fat content

For high-fat and low-fat dairy, the meta-analysis by Gijsbers et al. (32) summarized 13 studies and reported a borderline significant linear inverse association between low-fat dairy and T2D (RR: 0.96; 95% CI: 0.92, 1.00; $P = 0.072$; $I^2 = 68\%$ —per 200 g/d) and no association between high-fat dairy and T2D (RR: 0.98; 95% CI: 0.93, 1.04; $P = 0.52$; $I^2 = 52\%$ —per 200 g/d). The results by Gijsbers et al. (32) agreed with earlier meta-analyses by Gao et al. (35) and Aune et al. (34), which both also reported low-fat but not high-fat dairy to be inversely associated with T2D risk. Although the recent prospective cohort study of Brouwer-Brolsma et al. (40), involving 2974 participants with a mean follow-up of 9.5 y, reported no association between both high-fat and low-fat dairy consumption and T2D risk, Hruby et al. (38) reported that greater high-fat dairy consumption was associated with 70% lower T2D risk in 925 subjects with prediabetes. The other 2 recently published prospective cohort studies (39, 41) did not separate high-fat or low-fat dairy from total dairy consumption, which precludes drawing conclusions concerning differential associations for low-fat compared with high-fat dairy. Recently, the study of Soedamah-Muthu and de Goede (42) pooled the data of the new studies (38, 40) with the previous meta-analysis of Gijsbers et al. (32) and reported a similar result: that low-fat dairy was borderline significantly associated with a 4% lower T2D risk (RR: 0.96; 95%: 0.92, 1.00; $I^2 = 60.3\%$).

Prediabetes

For incident prediabetes, the Framingham Heart Study Offspring Cohort study (38) found an inverse association between total dairy intake and incident prediabetes, with higher total dairy intake associated with a 37% lower risk of incident prediabetes (HR: 0.63; 95% CI: 0.49, 0.80), which may indicate early-phase effects of dairy consumption potentially delaying and/or preventing the onset of T2D. Furthermore, there are a few cross-sectional studies (52, 53) which also studied the associations between dairy consumption and prediabetes. The study by Eussen et al. (53) found

that high consumption of skimmed dairy and fermented dairy was associated with a lower risk of impaired glucose metabolism, whereas high intake of high-fat dairy was not related to impaired glucose metabolism. The findings of Brouwer-Brolsma et al. (52) were in line with those of Eussen et al. (53), with similar inverse associations of skimmed dairy and fermented dairy with prediabetes, although positive associations were observed for high-fat and nonfermented dairy consumption. However, a limitation of these studies was a nonconsistent definition of prediabetes. For example, prediabetes was defined as “the first occurrence of fasting plasma glucose ≥ 5.6 to < 7.0 mmol/L” and “fasting plasma glucose between 5.6 and 6.9 mmol/L or HbA1c% [glycated hemoglobin percentage] of 5.7–6.4%” in the studies of Hruby et al. (38) and Brouwer-Brolsma et al. (40), respectively.

Evidence from RCTs on Dairy Products and T2D Risk

There are only 2 reviews (23, 54) and 2 meta-analyses (55, 56) that have been published on RCT-based evidence concerning effects of dairy consumption on T2D risk. An earlier review (57) highlighted that investigating the effect of dairy consumption on health is highly challenging, because only evidence of dairy consumption and biomarkers of T2D is available, with no data on hard endpoints of incident T2D. It is difficult to determine the effect of dairy consumption on T2D risk from the available RCT-based evidence owing to variations in study design, sample size, and types of dairy consumption. In their meta-analysis of RCTs, Benatar et al. (55) investigated the effects of increased dairy food consumption on cardiometabolic risk factors by including data from 20 studies. This meta-analysis showed a high-dairy diet may lead to a moderately improved HOMA-IR (mean -0.94 ; range -1.93 to 0.04 units; $P = 0.06$), albeit with significant heterogeneity existing between studies ($I^2 = 92\%$). Furthermore, a recent meta-analysis of O'Connor et al. (56) with 38 studies showed a higher dairy intake was positively associated with fasting glucose (mean 0.07 mmol/L; 95% CI: 0.01, 0.12 mmol/L; $I^2 = 23\%$; $P = 0.01$) and negatively associated with HbA1c (mean -0.09% ; 95% CI: -0.09% , -0.03% ; $I^2 = 0\%$; $P = 0.005$), whereas the higher dairy consumption was not associated with fasting insulin or HOMA-IR. Both meta-analyses of Benatar et al. (55) and O'Connor et al. (56) reported that most RCTs were small and the quality of evidence was low.

In addition, the systematic review of Turner et al. (54) investigated 10 weight-stable interventions that examined the effect of an increased intake of dairy products or dairy-derived supplements on glucose metabolism and insulin sensitivity, and found the impact to be dependent on the duration of the interventions. Specifically, studies of < 8 wk showed no significant changes in insulin sensitivity, whereas studies between 12 and 24 wk resulted in a favorable effect of higher dairy intake on insulin sensitivity. Results for studies with a longer intervention time of 6 mo were mixed. Of particular importance, few studies reported effects of dairy on a dynamic measure of glucose tolerance, such as

those based on an oral-glucose-tolerance test (OGTT) or intravenous-glucose-tolerance test, and those that did tend to report null effects. Thus, conclusions on the effect of dairy consumption on glucose metabolism and insulin sensitivity need confirmation in large RCTs with more subjects and longer intervention times.

Low-fat dairy has been recommended in several dietary guidelines (19, 58). However, a comprehensive review of Drouin-Chartier et al. (59) assessed evidence from RCTs and reported no harmful effect of dairy consumption, irrespective of fat content, on different aspects of cardiometabolic risk. More recently, Engel et al. (60) conducted a 3-wk crossover dietary intervention in 18 healthy adults to compare the effect of whole milk with skimmed milk consumption. The results showed that ingestion of 0.5 L/d whole milk did not adversely affect fasting glucose or insulin compared with skimmed milk. Thus, the authors concluded that whole milk might be considered part of a healthy diet for the general healthy population. Furthermore, only 1 RCT (61) has compared the effects of regular-fat cheese (25% fat of Riberhus and 32% fat of Sharp Cheddar) with an equal amount of reduced-fat cheese (13% fat of Riberhus and 16% fat of Sharp Cheddar) and it found no differential impact on fasting glucose, fasting insulin, and HOMA-IR.

A major limitation of the literature in this field is that most studies were not designed to test the impact of dairy products on glucose homeostasis, which is reflected in the fact that comprehensive measures of glucose homeostasis were commonly not obtained. Also, the nature of the control treatment chosen in RCTs appears critical, because it likely influences the effects found. If one were to, for example, compare milk with a sugary drink, it would result in different findings than if one were to compare milk with tea or water. Another limitation is that most studies only used fluid milk, most commonly skimmed or low-fat milk, in their dairy diets, i.e., high-fat and/or fermented dairy foods were not commonly tested, or accounted for only a small portion of the administered dairy products. A recent meta-analysis of Barengolts et al. (62) including 9 RCTs and only 472 participants showed no beneficial effects of consuming probiotic yogurt compared with conventional yogurt for improving glucose control in patients with T2D or obesity. This study (62) highlighted the limitation of small RCTs and short-term studies. Furthermore, almost no RCTs specifically tested the impact of cheese or yogurt on glucose homeostasis for general healthy populations. Although yogurt and/or cheese were included as part of the overall dairy intervention in some studies (63–69), the amount of dairy consumed as cheese or yogurt was usually small or not specified, which precludes conclusions about the specific impacts of yogurt or cheese on glucose homeostasis from these studies.

Summary of Evidence from Prospective Cohort Studies and RCTs

Evidence from prospective cohort studies and RCTs suggests that dairy consumption has a neutral or moderately beneficial effect on glucose homeostasis and T2D risk.

One advantage of the prospective cohort studies is that they can show the long-term association between dairy consumption and a disease outcome, such as incident T2D (70). However, analyses of prospective cohort studies have important limitations. For example, residual confounding can never be ruled out from prospective cohort studies, which may have led to the inconsistent findings in studies on dairy consumption and T2D. Furthermore, the definitions of the dairy foods consumed vary substantially across different cohort studies. For example, high-fat dairy in a study by Montonen et al. (50) included cheese, cream, ice cream, and yogurt, whereas high-fat dairy in a study by Soedamah-Muthu et al. (71) was defined as full-fat cheese, yogurt, milk puddings, whole milk, and Channel Island milk. Therefore, additional epidemiological studies should assess the associations between different well-defined types of dairy consumption and T2D risk. In addition, in most longitudinal cohort studies, dairy consumption was only reported at baseline but not during the follow-up period. Thus, it is unknown whether or not the conclusions are affected by dietary changes with time.

Evidence from RCTs on the impact of dairy products on T2D risk largely suggests a null effect or a relatively small inverse effect. Although RCTs could provide strong evidence on a direct clinically relevant measure, i.e., glucose tolerance, few RCTs included such measures. The few RCTs (66, 72–76) that included a mixed-meal test or OGTT suggest no effect of dairy on glucose tolerance. The available studies differed substantially in terms of types of dairy foods studied, the duration of the intervention period, control diet, and subject characteristics. Most studies have been conducted in overweight or obese subjects, with few studies in subjects with normal weight. In addition, few intervention studies have been designed to evaluate the effect of different types of dairy foods or fat content of dairy foods on T2D risk, and there was only 1 RCT (61) which compared the effects on T2D risk of low-fat and full-fat cheese consumption. In terms of investigating causal effects, evidence from suitably designed RCTs could provide more evidence on the mechanisms involved in the associations between dairy consumption and T2D development. However, evidence from long-term RCTs investigating the effect of dairy consumption on T2D risk is very limited. Furthermore, most RCTs have been designed to test the effect of dairy consumption on weight reduction for overweight or obese subjects, but few studies have been designed to specifically test the impact of dairy foods on glucose homeostasis. Therefore, larger and more long-term RCTs are needed to verify the effect of different types of dairy consumption on T2D risk.

Lastly, the evidence from prospective cohort studies, which showed higher intake of subtypes of dairy (e.g., yogurt, low-fat dairy) to be associated with lower T2D risk, needs to be combined with evidence from RCTs wherein the types and doses of dairy products can be regulated and also mechanisms can be investigated. For example, it is suggested that probiotic yogurt consumption may improve glycemic control in T2D subjects (77–80), which

may indicate that yogurt containing certain bacterial species may have a beneficial effect on glucose homeostasis and T2D risk. Therefore, the effect of yogurt and any differential effects of yogurts with different fat, sugar, or protein contents or different bacteria species on T2D risk should be investigated by both prospective cohort studies and RCTs.

Dairy and T2D: Potential Mechanisms

The development of T2D is heavily influenced by obesity and lifestyle. Specifically, abdominal fat deposition and low lean body mass contribute to insulin resistance and increase T2D risk, whereas fat stored in the lower part of the body (gynoid and leg fat) seems protective against the development of cardiometabolic diseases when total adipose tissue mass is the same (13–15). This may reflect a high propensity to accumulate fat in all subcutaneous adipose where it may have a less detrimental effect on insulin sensitivity than visceral fat accumulation (13). A recent meta-analysis of 24 RCTs (18) reported that increased dairy food intake as part of energy-restricted diets gave rise to greater loss in body weight and fat mass, while moderating lean mass loss in 18- to 50-y-old adults. Therefore, dairy consumption may play a beneficial role in managing body composition, which may have a favorable effect on reducing T2D risk. The potential mechanisms of the beneficial effects of dairy consumption on body composition may be due to milk consumption assisting appetite control in the context of energy-restricted diets (81). In addition, the dairy protein-derived BCAAs have been suggested to enhance muscle protein synthesis, lean body mass, and skeletal muscle metabolic function (82).

SFAs have been considered a risk factor for T2D and insulin resistance (83); however, the findings on the association between SFAs and T2D or insulin resistance are mixed (24). Previous studies (28, 84) demonstrated that individual SFAs have differential effects on T2D risk, and suggested that the whole foods (i.e., food matrix) in which SFAs exist can be a stronger determinant of health effects than the total SFA content itself (28, 29). Several plasma phospholipid even-chain SFAs [myristic acid (14:0), palmitic acid (16:0), and stearic acid (18:0)] were reported to be associated with higher T2D risk (85). In contrast, the odd-chain SFAs pentadecanoic acid (15:0) and heptadecanoic acid (17:0) are markers for intake of dairy fat (86). For these, it has been shown that their proportions in erythrocyte membranes are inversely associated with T2D risk (87). An inverse association has also been reported for the proportions of pentadecanoic and heptadecanoic acids in plasma phospholipids with fasting insulin and glucose (88, 89). Furthermore, 2 studies by Mozaffarian et al. (90, 91) have shown an inverse association between the concentration of *trans*-palmitoleic acid in plasma phospholipids and risk of T2D, with the suggestion that *trans*-palmitoleic acid was of dietary origin, mainly from dairy foods. However, the concentration of *trans*-palmitoleic acid in dairy fat is low (92) and it remains a key question as to whether this fatty acid has a functional role in reducing T2D risk or whether it is merely a marker of dairy consumption. In addition,

a cross-sectional investigation in 17 men and women with nonalcoholic fatty liver disease and 15 controls matched for age and BMI indicated dairy fat improves glucose tolerance, possibly via a mechanism involving improved hepatic and systemic insulin sensitivity and reduced liver fat (93).

Other components of dairy foods may also have a part to play, such as calcium, which has been recognized to have an antiobesity bioactivity, and there is also good evidence of a postprandial insulinotropic effect of milk proteins, in particular whey proteins (94). Evidence from RCTs suggests dairy proteins have more potent effects on insulin and incretin secretion than do other animal proteins (95). Although Rideout et al. (69) showed improved insulin sensitivity in high compared with low dairy consumers over a 12-mo RCT period, there is an urgent need for more long-term studies on the effects of dairy on insulin sensitivity.

Systematic reviews indicate that yogurt has a greater impact on metabolic health than nonfermented dairy but the underlying mechanisms remain unknown (96). Yogurt is a nutrient-dense dairy food that may help to reduce weight gain and prevent T2D by contributing to intakes of protein, calcium, bioactive lipids, and several other micronutrients. It has also been suggested that fermentation with bacterial strains produces bioactive peptides that may contribute to the beneficial effect of yogurt on metabolic health (96). Furthermore, fermented dairy may promote gut microbial population shifts (21). It is of interest that Veiga et al. (97) showed that consumption of a fermented milk product (containing *Bifidobacterium animalis* subsp. *lactis*) stimulated colonic production of acetate, butyrate, and total SCFAs. Robertson et al. (98) showed that increased production of SCFAs arising from dietary resistant starch was associated with improved insulin sensitivity, and based on a population study, Layden et al. (99) reported that the concentration of serum acetate, but not propionate or butyrate, was negatively associated with fasting serum insulin and 2-h insulin concentrations after an OGTT. Serum acetate was also inversely associated with visceral adipose tissue. Recent reviews on the links between intestinal SCFAs and diet and health (100–102) concluded that although many biological effects seem to be mediated by SCFAs, more conclusive proof is needed, particularly involving human trials.

Current Status of Research in Relation to Prevention, Prediabetes, and T2D

Several large prospective cohort studies have shown a modest inverse relation between dairy consumption and T2D risk, especially for yogurt. Many different types of dairy foods and subtypes of dairy have been included in cohort studies. There was considerable between-study heterogeneity, which may be due to differences in country, study populations, types of products, and definitions of dairy, and variations in intake, which makes drawing firm conclusions difficult. Evidence from RCTs on each different type of dairy products and effects on T2D outcomes is lacking. The most available acute and long-term RCTs have focused on overweight

or obese populations, whereas studies on subjects with prediabetes would be beneficial to assess the potential of dairy foods to prevent or delay the manifestation of T2D. Furthermore, T2D has a complex pathophysiology and multiple treatments, being responsive to lifestyle changes. The metabolic response to certain dietary interventions such as dairy may vary between individuals, for example, the glycemic response to a dietary intervention seems to be at least partly determined by the specific metabolic status (insulin resistance in particular) of an individual (103–105). Importantly, most human exercise and dietary intervention studies often lack a detailed phenotyping of study participants, or are too small to conduct subgroup analyses that would provide insight into interindividual variability in response. Therefore, deep clinical/metabolic phenotyping, including tissue-specific profiling, may be an important future area to identify individuals or subgroups that benefit or do not benefit from increased dairy consumption (11).

The evidence from available prospective cohort studies and RCTs has both strengths and also weaknesses (106). Most prospective cohort studies have investigated risk factors in large populations with long follow-up periods, but one can never exclude residual confounding in cohort studies. The approach of Mendelian Randomization is recognized as a useful approach in epidemiological studies to demonstrate strong evidence of causality between diet and disease outcomes. To our knowledge, very few Mendelian Randomization studies have been done to investigate the association between dairy consumption and T2D risk, and the genes used are milk related and not yogurt or cheese related. For example, lactase gene (*LCT-139010 C/T*) was used by the study of Bergholdt et al. (43) to investigate dairy consumption and T2D risk; however, fermented dairy products (e.g., cheese and yogurt) have a lower content of lactose than milk, thus, using a lactase gene to examine the association between fermented dairy products and T2D risk may result in underestimated results. In addition, because the effect of confounding factors is always an issue of concern in nutritional epidemiology, comparisons of dairy products with other foods should be investigated in replacement models to take into account the background diet; however, this type of research is still very limited (21, 97, 98).

Although RCTs have the advantage of ruling out residual confounding factors to provide robust evidence for causality between diet and risk factors compared with prospective cohort studies, the available RCTs are generally limited to short intervention times which may not be sufficient to assess the full effect of dairy foods on glucose homeostasis. Also, it is unlikely to have RCTs with hard endpoints of incident T2D (57), thus, further mechanistic studies combined with large prospective studies with replacement models, and large RCTs in adequate populations (metabolically unhealthy/healthy) of sufficient dose and duration are needed to get a complete picture of dairy consumption and T2D risk.

Overall Conclusions/Public Health Relevance and Possible Impact for Public Health Recommendations

Based on the reviewed evidence, epidemiological data and RCTs suggest that there is a neutral or moderate inverse association between dairy consumption and T2D risk. Yogurt was especially associated with a lower T2D risk. Therefore, more and better data from epidemiological studies and RCTs are needed on the impact of dairy consumption on glucose homeostasis. Specifically, there are several key research questions that need to be answered to optimize the benefits of dairy consumption and to close the gaps in the existing knowledge:

- 1) How does an individual's phenotypic status, such as age, sex, weight, disease status, metabolic status, and gut microbiota composition, affect their glucoregulatory responses to different types of dairy consumption?
- 2) How does high-/low-fat, high-/low-sugar, high-/low-protein dairy affect T2D risk?
- 3) What are the underlying mechanisms that explain the inverse association between yogurt and T2D risk?

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