The Effect of Diets Rich in Low-Fat or Full-Fat Dairy Foods on Insulin Sensitivity: The Influence of Other Dietary Factors

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Abstract

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Background: Type 2 diabetes mellitus (T2DM) is a public health threat that jeopardizes the health of current and future generations in the United States. Reduced insulin sensitivity, also called insulin resistance, is a major contributing factor in the development of glucose intolerance and T2DM. Insulin sensitivity is impacted by numerous dietary and non-dietary factors. In dietary intervention studies, emerging research has found that individuals do not respond the same way to standardized dietary interventions, suggesting that factors other than the primary dietary exposure of interest influence an individual's response.

Aims: We conducted a secondary data analysis using primary data from the DAIRY randomized dietary intervention trial (Schmidt et al., Submitted for publication) to assess the extent to which alternative dietary factors that were not controlled for (i.e. healthy eating index independent of dairy (HEI-ID), fiber intake and added sugar intake) might at least partly explain group or interindividual differences in the impact of a dairy intervention on insulin sensitivity in individuals with the metabolic syndrome. Aim 1: Assess the impact of adjusting for (a) baseline or (b) changes in HEI-ID, fiber intake, and added sugar intake on the differential effect of the dietary interventions on the Matsuda-DeFronzo insulin sensitivity

index (ISI, primary) and homeostatic model assessment of insulin resistance (HOMA-IR, secondary). Aim 2: Investigate whether interindividual differences in the Matsuda ISI (primary) and HOMA-IR (secondary) are explained by (a) baseline or (b) changes in HEI-ID, fiber intake, and added sugar intake.

Methods: We created a database of participant-level dietary intake data from 24-hour dietary recalls, using reports generated from the Nutrition Data System for Research (NDSR) software and database. Participant-level data was broken out as “baseline” (average of 2 recalls) and “intervention” (average of 3 recalls) for all variables. To address Aim 1, we conducted both *per protocol* and *intent-to-treat* repeated measures analysis of variance (RM-ANOVA) for Matsuda ISI (primary) and HOMA-IR (secondary), adjusting for (a) baseline or (b) changes in HEI-ID, fiber intake, and added sugar intake. To address Aim 2, we conducted both *per protocol* and *intent-to-treat* multiple linear regression analyses for Matsuda ISI (primary) and HOMA-IR (secondary), including dietary intervention group, as well as (a) baseline or (b) changes in HEI-ID, fiber intake, and added sugar intake, as additional independent variables.

Results: Adjusting both *per protocol* and *intent-to-treat analyses* for baseline and changes in HEI-ID, fiber intake or added sugar intake between wash-in and intervention diet periods did not impact the significant decreases in the Matsuda ISI and increases in HOMA-IR observed in the low-fat and full-fat dairy intervention groups in the main study. With the exception of one weakly significant association between change in HEI-ID and change in HOMA-IR , neither baseline, nor changes in HEI-ID, fiber intake or added sugar intake between wash-in and intervention diet periods, predicted interindividual differences in the Matsuda ISI or HOMA-IR that resulted from the dairy dietary intervention.

Conclusions: These results demonstrate that the impact of low-fat and full-fat dairy on insulin sensitivity in individuals with the metabolic syndrome, as observed in the primary study analysis, was independent from dietary changes in fiber, added sugar, or the HEI-ID that resulted from the incorporation of dairy into study participants’ diets. These effects occurred independent of changes in fat mass. Aside from the one weakly significant association noted above, these results also reveal that HEI-ID, fiber intake and added sugar intake did not predict changes in insulin sensitivity in the context of this intervention study.

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II. Introduction

II.a. Problem and Significance

As public health threats, the burdens of metabolic syndrome, type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) incur tremendous costs in terms of both healthcare expenditures and lives impacted. Specifically, according to the National Health and Nutrition Examination Survey (NHANES), the prevalence of metabolic syndrome in the United States (US) increased by 35% from 1988-1994 to 2007-2012 (Moore, Chaudhary, & Akinyemiju, 2017) This increase reflects an overall prevalence of 34.2% of adults 18 years and older (Moore et al., 2017). Additionally, the Centers for Disease Control and Prevention (CDC) estimates that 12.2% of US adults (30.2 million) have either diagnosed or undiagnosed diabetes; further, based on NHANES 2013-2016 data, the American Heart Association (AHA) reports that 48.0% of US adults over the age of 20 years (121.5 million) have CVD, including hypertension (Benjamin, Muntner, & Bittencourt, 2019; CDC, 2018). Beyond the suffering associated with these diseases, T2DM and CVD are also significant financial burdens to the US healthcare system, costing $327 billion and $199 billion per year, respectively (NCCDPHP, 2019). In addition to these economic costs, the cost of lives lost is also material. Specifically, heart disease was the leading cause of death in the US in 2017 (165 deaths per 100,000 people), while diabetes also ranked within the top ten causes of death (21.5 deaths per 100,000 people), based on data from the National Vital Statistics System (NCHS, 2018). Accordingly, these conditions incur significant societal costs that threaten the health of current and future generations in the US.

The presence of the constellation of factors defining metabolic syndrome (e.g. high triglycerides, low HDL, hypertension, abdominal obesity, dysglycemia) increases an individual's risk of T2DM, a disease characterized by hyperglycemia due to glucose intolerance (NIH NIDDK, 2016b). Glucose intolerance is the result of insulin resistance characterized by defective insulin signaling that is not fully compensated for by increased insulin secretion (Lann & LeRoith, 2007). While the adipose tissue inflammation and lipotoxicity associated with obesity may contribute to the development and progression of insulin resistance, insulin resistance itself may compound the progression of metabolic syndrome to chronic

disease, including both T2DM and CVD (Guo, 2014; Meigs et al., 2007; Zafar, Khaliq, Ahmad, Manzoor, & Lone, 2018). Moreover, as an underlying factor of metabolic syndrome and a contributor to the progression of T2DM and CVD, insulin sensitivity is an important indicator of metabolic health.

First-line treatment for diagnosed T2DM and CVD includes lifestyle modifications to diet and physical activity, often resulting in weight loss (Guess, 2018; NIH NIDDK, 2016a; NIH NLM, 2018). Among overweight individuals, evidence suggests that weight loss itself is predominantly responsible for reduction in risk of T2DM specifically (Guess, 2018). This may occur via improved insulin sensitivity, improved beta-cell function, or a combination of both (Guess, 2018). Accordingly, in terms of the former, identifying interventions that enhance insulin sensitivity is a critical component of preventing the onset of and progression to cardiometabolic disease. Existing observational and experimental evidence supports the favorable effects of the following dietary interventions on insulin sensitivity and/or the risk of metabolic syndrome and T2DM: the Mediterranean dietary pattern, an overall “healthy” dietary pattern (as measured by indices such as HEI), whole grains, fiber, fruits and vegetables, and dairy (Anania, Perla, Olivero, Pacifico, & Chiesa, 2018; G. C. Chen et al., 2015; J. P. Chen, Chen, Wang, Qin, & Bai, 2017; Drouin-Chartier et al., 2016; Kim & Je, 2016; Neale, Batterham, & Tapsell, 2016; Schwingshackl, Hoffmann et al., 2017; Schwingshackl, Bogensberger, & Hoffmann, 2018). That said, observational and experimental evidence do not always align, and epidemiological studies are fraught with limitations, such as bias and confounding (Ioannidis, 2018). For instance, a recent systematic review by Drouin-Chartier et al. (2016) identified both positive and neutral effects of dairy consumption on CVD-related clinical outcomes, including metabolic syndrome and T2DM risk.

While the totality of evidence may point to a possible impact of dietary patterns and whole foods on insulin sensitivity, the field is increasingly becoming aware of interindividual differences in response to foods or diets (Ioannidis, 2018; Raubenheimer & Simpson, 2016). For example, Zeevi et al. (2015) found that individuals vary dramatically in their glycemic response to the same test meal. These disparate effects of dietary interventions on markers of glucose homeostasis may be influenced by myriad dietary and non-dietary factors (e.g. genetics, gut microbiome), and researchers are increasingly seeking to

understand the pathways whereby this occurs (Healey, Murphy, Brough, Butts, & Coad, 2017; Milenkovic et al., 2017; Rideout, 2011).

The following literature review will highlight 1) recent epidemiological and experimental evidence characterizing the associations between different dietary factors and incident T2DM or glucose tolerance, 2) the impact of dairy consumption on incident T2DM or glucose homeostasis, and 3) the influence of inter- and intraindividual differences on responses to dietary interventions.

II.b. Literature Review

Diet and T2DM: Observational Evidence

Epidemiological studies have extensively evaluated the association between the risk of T2DM and various dietary patterns, foods, and nutrients. Studied nutritional patterns range from the broadly defined "healthy" to the more prescriptive Mediterranean diet, DASH diet, and vegetarianism. Constituents of these dietary patterns (e.g. fruits and vegetables, nuts, legumes and whole grains) have also been analyzed in addition to their micronutrient and phytochemical components (e.g. magnesium, polyphenols). Although identifying preventive nutritional interventions for T2DM is a primary goal, other studies have assessed the extent to which specific food items (such as added sugar or meat) may promote the development of T2DM.

Overall Dietary Pattern

An overall healthy dietary pattern may reduce the risk of the development of T2DM. Alhazmi et al. (2014) analyzed the association between dietary pattern and risk of T2DM in a systematic review and meta-analysis of 15 cohort studies. These studies took place in the United States, Europe, Asia and Australia. Data from 378,525 healthy adult participants with no history of T2DM were analyzed, and follow up spanned 4 to 23 years. Of the 15 included studies, 14 adjusted for potential confounders, including measures of adiposity such as BMI or waist circumference, even though Alhazmi et al. (2014) did not mention which specific adjustments were made in which study. The definition of "healthy diet" across the included studies varied. Overall, in comparing the highest adherence to the lowest adherence of a healthy

dietary pattern, the authors determined there was a 21% reduced risk of T2DM among those participants with the highest adherence to a healthy dietary pattern (RR = 0.79, 95% CI = 0.74-0.86, $p < 0.005$, I^2 = 9.3%) (Alhazmi et al., 2014). The authors did not detail how they delineated measures of dietary adherence in their meta-analysis, i.e. whether the exposure was categorized into quintiles, quartiles, tertiles, or some other way. On the other hand, in comparing the highest adherence to the lowest adherence of an overall unhealthy dietary pattern, Alhazmi et al. (2014) found a 44% increased risk of T2DM among those participants with the highest adherence to an unhealthy dietary pattern (RR = 1.44, 95% CI = 1.33-1.57, $p <0.005$, I^2 = 3.0%). Accordingly, while the meta-analysis included a diversity of dietary patterns and populations, the authors concluded that the risk of T2DM decreases as the relative healthfulness of a diet increases. They also noted the potential for residual confounding, implying factors other than dietary pattern that were not adjusted for may have influenced the risk of T2DM.

Maghsoudi, Ghiasvand and Salehi-Abaegouei (2016) conducted a similar systematic review and meta-analysis of 10 prospective cohort studies. In their analysis, the authors evaluated the association between dietary pattern and incident T2DM among adults, as well as the sources of difference among study outcomes (Maghsoudi et al., 2016). Of the 10 included studies from the United States, Europe, Australia and Asia, 7 adjusted for measures of adiposity, including BMI; no further adjustments were noted in the meta-analysis. Maghsoudi et al. (2016) corroborated Alhazmi et al.'s findings and determined there was a 14% reduction in risk of incident T2DM when comparing the highest to the lowest adherence to a "healthy" dietary pattern (RR = 0.86, 95% CI = 0.82-0.90, p value not reported, I^2 = 2.3%). The authors did not detail how they delineated measures of dietary adherence in meta-analysis (e.g. quintiles, tertiles, etc.). Conversely, there was a 30% increased risk of incident T2DM when comparing the highest versus lowest adherence to an "unhealthy" dietary pattern, though this association was marked by high heterogeneity (RR = 1.30, 95% CI = 1.18-1.43, p value not reported, I^2 = 64.1%). The authors noted that "healthy" dietary patterns were comprised of foods like fruits, vegetables, and whole grains, while "unhealthy" dietary patterns included more red meat, processed foods and full-fat dairy (Maghsoudi et al., 2016). Similar to Alhazmi et al. (2014), residual confounding may have influenced the results reported by Maghsoudi et al. (2016), given the variation of adjustment for confounders in the primary studies.

While the relative healthfulness of an overall diet may influence the risk of developing T2DM, current evidence is less conclusive when considering macronutrient distribution. In another systematic review and meta-analysis by Alhazmi et al. (2012), the researchers derived pooled-effect estimates from 22 cohort studies of healthy participants with no prior history of T2DM, describing the association between the risk of T2DM and carbohydrate, fat and protein intake, respectively. All but one study included adjustment for a measure of adiposity, such as BMI. While the authors found a significant 11% increase in risk of T2DM for the highest compared with the lowest quintile of carbohydrate intake (RR = 1.11, 95% CI = 1.01-1.22, $p = 0.04$, $I^2 = 35.4\%$), the significance was attenuated in subgroup analysis for females (RR = 1.09, 95% CI = 0.97-1.24, $p = 0.13$, I^2 not reported) (Alhazmi et al., 2012). Further, these results were no longer significant with the removal of potentially duplicative data from the Nurses' Health Study. Though the authors identified a 21% lower risk of T2DM for the highest compared with the lowest quintile of vegetable fat intake (RR = 0.79, 95% CI = 0.71-0.86, $p < 0.01$, I^2 not reported), they did not identify a significant association between total fat intake and T2DM risk. Lastly, the researchers also found no association between T2DM risk and the highest compared with the lowest quintile of total protein intake (RR = 1.02, 95% CI = 0.91-1.15, $p = 0.67$, $I^2 = 0.0\%$). Although the lack of irrefutably significant findings in this study may point towards a more limited role of macronutrient composition in T2DM risk, the authors also limited their analysis to a linear random effects model, which made it difficult to detect other relationships between dietary macronutrient intakes and incident T2DM, such as reversed U-shaped.

While macronutrient distribution may not heavily influence the risk of developing T2DM, specific health-promoting dietary patterns may be influential. Jannasch, Kroger and Schulze (2017) conducted a systematic literature review and meta-analysis of 48 studies from the United States, Europe, Asia and Australia in order to assess the association between dietary patterns and T2DM. The 48 studies included 27 studies that utilized *a priori* approaches to derive dietary patterns (e.g. dietary pattern indices) and 21 studies that employed *a posteriori* approaches (e.g. principal component analyses, factor analyses or cluster analyses). Of the studies taking *a priori* approaches, only 3 did not adjust for measures of adiposity, such as BMI, waist circumference and/or waist to hip ratio. Of the studies with *a posteriori*

approaches, only 2 did not adjust for adiposity. The included studies covered 16 cohorts and were comprised of 1.5 million participants. Studies exclusively enrolling participants with T2DM, impaired glucose tolerance or insulin resistance were excluded. The authors completed three meta-analyses based on 1) *a priori* dietary pattern, 2) principle component or factor analyses, and 3) reduced rank regression (RRR). Aside from the adjustments made for adiposity in the original studies, the authors did not mention any further adjustments for adiposity in meta-analyses.

First, in comparing the highest to the lowest quantiles of intake of a Mediterranean dietary pattern, Dietary Approaches to Stop Hypertension (DASH) diet, or alternative Healthy Eating Index (AHEI), Jannasch, et al. (2017) found a reduced risk of T2DM across all three dietary patterns (Mediterranean: RR = 0.87, 95% CI = 0.82-0.93, p <0.0001, I^2 = 26%; DASH: RR = 0.82, 95% CI = 0.74-0.92, p = 0.0005, I^2 = 62%; AHEI: RR = 0.79, 95% CI = 0.70-0.89, p = 0.0001, I^2 = 88%; respectively). In other words, those in the highest quantiles for scores of the Mediterranean diet, DASH diet, or AHEI had a decreased risk of T2DM by 13%, 18% and 21% compared to those in the lowest quantile.

Second, in comparing the highest to the lowest quantiles of intake of a “mainly healthy” or “mainly unhealthy” diet as derived by principal component analysis, the authors concluded that the relative healthfulness of a diet was inversely associated with the risk of T2DM (Jannasch et al., 2017). Specifically, consuming the highest quantile of a “mainly healthy” dietary pattern reduced the risk of T2DM by 16% (RR: 0.84, 95% CI = 0.77-0.91, p <0.0001, I^2 = 6%), and consuming the highest quantile of a “mainly unhealthy” dietary pattern increased the risk of T2DM by 44% (RR: 1.44, 95% CI = 1.27-1.62, p <0.00001, I^2 = 0%).

Lastly, in a third set of meta-analyses, the authors applied three existing RRR patterns to external study populations in order to assess the predicted impact on T2DM risk. When comparing extreme quantiles, these meta-analyses mirrored the original risk assessments with one identifying a reduced risk of T2DM by 49% (RR = 0.51, 95% CI = 0.27-0.98, p = 0.04, I^2 = 86%) and the other two exhibiting an increased risk of T2DM by about 40% and 150%, respectively (RR = 1.39, 95% CI = 1.25-1.54, p < 0.00001, I^2 =

0%; RR = 2.53, 95% CI = 1.56-4.10, p = 0.0002, I^2 = 94%; respectively). From these RRR pattern meta-analyses, Jannasch et al. (2017) concluded that food items characteristic of increased risk included refined grains, sugar-sweetened beverages, and processed meat. Considering all meta-analyses in totality, the authors identified several common dietary patterns associated with T2DM risk and cited advantages of utilizing a RRR approach over *a priori* methods to derive dietary patterns that would reduce the risk of T2DM across diverse populations (Jannasch et al., 2017).

Mediterranean Dietary Pattern

Of the dietary patterns associated with a reduced risk of T2DM, the Mediterranean diet is one of the most frequently studied. In a meta-analysis of 17 predominantly observational studies with a total sample size of 159,187 adult participants from the US, Spain, Greece, Italy, UK, and Cyprus, Koloverou et al. (2014a) assessed the impact of a Mediterranean dietary pattern on the risk of T2DM. The authors noted that most of the included studies adjusted for potential confounders, including BMI. Among the prospective studies, Koloverou et al. (2014a) concluded there was a significant 23% reduced risk of developing T2DM among the highest compared to the lowest centile of adherence to the Mediterranean diet (RR = 0.77, 95% CI = 0.66-0.89, p value not reported, I^2 = 58%) (Koloverou et al., 2014a). In cross-sectional studies, the authors reported a significant 9% reduced odds of developing T2DM for the highest compared to the lowest centile of dietary adherence (OR: 0.91, 95% CI: 0.88-0.95, p value not reported, I^2 = 22%).

Additionally, in subgroup analysis, while seemingly healthy participants with the highest centile of adherence to a Mediterranean dietary pattern experienced a 17% reduced risk of T2DM compared to the lowest centile (RR: 0.83, 95% CI = 0.70-0.96, p value not reported, I^2 = 74.7%), less healthy individuals at a higher risk for CVD and diabetes who followed a comparably adherent dietary pattern presented with a 35% reduced risk of T2DM (RR: 0.65, 95% CI = 0.51-0.78, p value not reported, I^2 = 0.80%) (Koloverou et al., 2014a). The difference in effect size between these two populations was significant (p = 0.014), suggesting the Mediterranean dietary pattern could be especially impactful in T2DM prevention (Koloverou et al., 2014a). While the researchers espoused the protective associations of the Mediterranean dietary pattern on the risk of T2DM, evaluating which components of the overall pattern

contributed most to this advantageous association fell outside of the scope of their study. Further, they also cited the potential for significant publication bias, which impacts the weight of their findings (Koloverou et al., 2014a).

Fruits and Vegetables

There are several elements of the Mediterranean dietary pattern which may favorably influence T2DM risk, including a nutritional profile that is rich in antioxidants, magnesium and fiber (Koloverou et al., 2014a). In terms of the former, fruits and vegetables are important dietary sources of antioxidants (Kaur & Kapoor, 2001). In a systematic review and meta-analysis of 10 prospective cohort studies including 434,342 participants from North America, Asia and Europe who did not have T2DM at baseline, Li et al. (2014) evaluated the association and dose-response between fruit and vegetable intake and T2DM risk. All included studies adjusted for adiposity via BMI. Li et al. (2014) noted that most studies quantified the degrees of intake by dividing fruit and vegetable consumption into fifths; others used tertiles or quartiles. In their analyses, the authors utilized study-specific categories for the highest and the lowest degrees of fruit and vegetable intakes (Li et al., 2014).

In their random effects model, Li et al. (2014) concluded that having the highest compared to the lowest quantile of intake for fruit and green leafy vegetables reduced the risk of T2DM by 7% and 13%, respectively (fruit: RR: 0.93, 95% CI = 0.88-0.99, p = 0.015, I^2 = 0%; green leafy vegetables: RR: 0.87 95% CI = 0.81-0.93, p =0.000, I^2 = 0%) (Li et al., 2014). In their dose-response analyses, they found that an increase in fruit consumption of 1 serving per day led to a 6% reduced risk of T2DM (RR: 0.94, 95% CI = 0.89-1.00, I^2 = 0%), and there was a mild curvilinear association between fruit intake and T2DM risk (p = 0.059) (Li et al., 2014). For green leafy vegetables, an increase in intake by 0.2 servings per day led to a 13% reduction in risk (RR: 0.87, 95% CI = 0.76-0.99, I^2 = 20.9%), and there was a significant curvilinear association between intake and T2DM risk (p = 0.036) (Li et al., 2014). Though green leafy vegetable intake was inversely associated with T2DM risk, Li et al. (2014) identified no significant associations with total vegetable intake or combined fruit and total vegetable intake (p = 0.068 and p = 0.202, respectively). The authors did not address the mechanisms behind this nuance in their findings, though study

heterogeneity for total vegetable and combined fruit and vegetable intakes may be a contributing factor (Li et al., 2014).

Food Groups

Similarly, Schwingshackl et al. (2017) identified a lack of association between vegetable consumption and risk of T2DM (RR = 0.95, 95% CI = 0.89-1.01, p = 0.08, I^2 =59%). In a systematic review and series of meta-analyses, the authors evaluated 10-21 prospective studies for each of 12 *a priori* defined food groups (whole grains, refined grains, vegetables, fruits, nuts, legumes, eggs, dairy, fish, red meat, processed meat, and sugar-sweetened beverages) to determine their respective associations with T2DM risk (Schwingshackl et al., 2017). Of the 88 total studies evaluated across all predefined food groups, only 7 studies did not adjust for measures of adiposity, such as BMI, waist to hip ratio, waist circumference, or a combination. Participants of the included studies were adults who were free of T2DM at baseline.

Schwingshackl et al. (2017) found an inverse association between T2DM risk and the highest compared to lowest categories for intakes of dairy products, fruit, and whole grains (Schwingshackl et al., 2017). Specifically, consuming the highest versus the lowest category intake of dairy reduced the risk of T2DM by 9%; of fruit, 4%; and of whole grains, 23% (dairy: RR = 0.91, 95% CI = 0.855-0.97, p = 0.004, I^2 = 63%; fruit: RR = 0.96, 95% CI = 0.93-1.00, p = 0.05, I^2 = 29%; whole grains: RR = 0.77, 95% CI = 0.71-0.84, p < 0.00001, I^2 = 86%) (Schwingshackl et al., 2017). In subgroup analysis, risk reduction was observed for low fat dairy but not full fat dairy (low fat: RR: 0.97, 95% CI: 0.94-1.00, p value not reported, I^2 = 71%; full fat: RR: 1.00, 95% CI: 0.96-1.04, p value not reported, I^2 = 69%). For fruit and whole grains, but not dairy, Schwingshackl et al. (2017) also observed non-linear dose-response associations between consumption and T2DM risk. Fruit intakes up to 200-300 g/day led to a 10% reduction in risk of T2DM, while whole grain intakes up to 50 g/day led to a 25% reduction in risk (both $p_{non\text{-}linearity} < 0.001$) (Schwingshackl et al., 2017). For dairy, every 200 g/day increase in consumption led to a 3% reduction in risk (RR: 0.97, 95% CI: 0.94-0.99, p value not reported, I^2 = 74%) (Schwingshackl et al., 2017).

In contrast to these inverse associations, Schwingshackl et al. (2017) identified a direct association between T2DM risk and the highest compared to the lowest category intake of red meat, processed meat, and sugar-sweetened beverages. Specifically, consuming the highest versus lowest category intake of red meat increased the risk of T2DM by 21%; of processed meat, 27%; and of sugar-sweetened beverages, 30% (red meat: RR = 1.21, 95% CI = 1.13-1.30, $p < 0.00001$, $I^2 = 65\%$; processed meat: RR = 1.27, 95% CI = 1.20-1.53, $p < 0.00001$, $I^2 = 55\%$; sugar-sweetened beverages: RR = 1.30, 95% CI = 1.20-1.40, $P < 0.00001$, $I^2 = 34\%$). For processed meat and sugar-sweetened beverages, but not red meat, the authors reported evidence for non-linear dose-response associations between intake and T2DM risk (Schwingshackl et al., 2017). Processed meat intakes up to 50 g/day led to a non-linear increase in risk by 30%, while sugar-sweetened beverage intakes exhibited a non-linear increase in risk along the continuum of increasing consumption ($p_{non\text{-}linearity} < 0.001$ and $p_{non\text{-}linearity} = 0.007$, respectively) (Schwingshackl et al., 2017). For red meat, every 100 g/day increase in consumption led to a 17% increase in risk (RR: 1.17, 95% CI: 1.08-1.26, p value not reported, $I^2 = 83\%$) (Schwingshackl et al., 2017).

In addition to identifying no association between vegetable intake and T2DM, Schwingshackl et al. (2017) observed a lack of association with other food groups, including eggs, fish, nuts, legumes, and refined grains. While the authors discussed how their results corroborate other observational studies within the broader body of literature, they also admit their findings are limited based on the degree of heterogeneity exhibited across most of their meta-analysis results (Schwingshackl et al., 2017).

Vegetarianism

Beyond the Mediterranean dietary pattern, vegetarianism has been studied in order to assess its impact on T2DM risk. Specifically, Lee and Park (2017) evaluated the association between T2DM risk and a vegetarian dietary pattern in a systematic review and meta-analysis of 14 cohort or cross-sectional studies from North America, Europe, Southeast Asia and Western Pacific. Five of 14 studies did not explicitly note adjustments for adiposity (mostly BMI, also waist circumference or waist-to-hip ratio). Participants of the included studies were adults; baseline glucose homeostasis and/or insulin sensitivity

was not noted. Compared to omnivores, the odds of developing T2DM was reduced by 27% in vegetarians (OR: 0.73, 95% CI = 0.61-0.87, p value not reported, I^2 = 82.8%) (Lee & Park, 2017). Accordingly, plant-based foods may be beneficial in reducing the risk of T2DM. This was also supported by Qian et al.'s (2019) findings in a more recent systematic review and meta-analysis. In a random-effects meta-analysis of 9 cohort studies with 307,099 participants including adults with T2DM, Qian et al. (2019) quantified a 23% reduction in risk of T2DM as a result of adherence to a plant-based dietary pattern (RR: 0.77, 95% CI = 0.71-0.84, p value not reported, I^2 = 44.5%). All 9 cohorts adjusted for potential confounders including BMI or waist circumference, and the authors also conducted exploratory random-effects meta-analyses on 6 of 9 studies both with and without adjustment for BMI. In these exploratory analyses, Qian et al. (2019) identified a 47% reduction in risk of T2DM without adjustment for BMI and a 21% reduction with adjustment for BMI, suggesting some of the influence of plant-based diets on T2DM risk may be indirect via its effects on body weight (without adjustment: RR: 0.53, 95% CI: 0.49-0.58, p value not reported, I^2 = 28.6%; with adjustment: RR: 0.79, 95% CI: 0.74-0.85, p value not reported, I^2 = 0.0%). The authors did not limit studies to vegetarianism or veganism, which suggests a protective association of plant-based foods on T2DM risk even in the context of a less restrictive diet plan.

Nuts and Legumes

Aside from fruits and vegetables, other plant-based foods are also associated with a lower incidence of diabetes. For instance, Afshin et al. (2014) conducted a systematic review and meta-analysis of 25 observational studies and 2 RCTs with a total sample size of 501,791 generally healthy participants. They assessed the association between nut and legume consumption with incidence of cardiometabolic outcomes, including ischemic heart disease, stroke and diabetes (Afshin et al., 2014). While the included studies adjusted for possible confounders, including sociodemographics and other risk factors and/or dietary variables, the authors did not specifically note adjustments for measures of adiposity (Afshin et al., 2014). In terms of diabetes specifically, the authors identified an inverse association between nut consumption and incident diabetes – in random effects analysis, there was a 13% reduced risk of diabetes per four servings (28.4 g) of nuts per week (RR = 0.87, 95% CI = 0.81-0.94; p value not reported; I^2 = 21.9%) (Afshin et al., 2014). Afshin et al. (2014) attributed the protective associations of

nuts to their nutritional profile of unsaturated fatty acids, plant-based protein, fiber, and assorted micronutrients. The authors did not identify an association between legume consumption and incident diabetes in pooled analysis (RR = 0.79, 95% CI = 0.50-1.24; p value not reported; I^2 not reported), though there was a 21% reduction in risk of diabetes for every four weekly servings (100 g) of legumes with fixed-effects inverse variances weighting (95% CI: 0.71-0.87, p value not reported; I^2 not reported) (Afshin et al., 2014).

Whole Grains

Another nutrient-rich plant food found in dietary patterns such as the Mediterranean diet or vegetarianism are whole grains. In a systematic review and meta-analysis of 16 cohort studies from the United States, Europe, Asia and Australia, Aune et al. (2013b) evaluated the risk of T2DM based on intake of whole and refined grains. All but one study adjusted for measures of adiposity, including BMI and/or waist-to-hip ratio or waist circumference. The authors identified a 32% reduced risk for every 3 servings per day of whole grains (95% CI = 0.58-0.81, p value not reported; I^2 = 82%) and a 26% reduction in risk for the highest compared to the lowest categories of whole grain intake across studies (95% CI: 0.71-0.78, p value not reported, I^2 = 0%) (Aune et al., 2013b). Moreover, Aune et al. (2013b) noted a nonlinear association for whole grain consumption and T2DM risk, reflecting the greatest benefit for intakes up to two daily servings. In a stratified analysis among those studies which included analyses both with and without adjustment for BMI, they noted an attenuation in the risk reduction per 3 daily servings by 16% points, suggesting changes in adiposity mediate the reduction in risk (with BMI adjustment: RR: 0.69, 95% CI: 0.60-0.80, p value not reported, I^2 = 58%; without BMI adjustment: RR: 0.53, 95% CI: 0.41-0.69, p value not reported, I^2 = 88%) (Aune et al., 2013b). Lastly, the authors found no association between refined grain intake and incidence of T2DM, indicating that while whole grains may be protective, refined grains may not be inherently damaging in isolation (Aune et al., 2013b).

Added Sugar

Lastly, while many studies strive to identify dietary patterns, food items and/or nutrients that can help reduce the risk of T2DM, others seek to quantify the burden of foods, such as added sugar, on risk. In

terms of the latter, Imamura et al. (2015) sought to evaluate the association between the incidence of T2DM and intake of sugar sweetened beverages, artificially sweetened beverages, or fruit juice. They conducted a systematic review and meta-analysis of 17 cohort studies and 10,126,754 person years from the United States, Japan and Finland (Imamura et al., 2015). Participants of the included studies were adults without diagnosed T2DM. Overall, the authors found that there was an 18% increase in the incidence of T2DM per serving per day of sugar sweetened beverages (95% CI = 1.088-1.28, $p < 0.05$, $I^2 = 89\%$); this increase was attenuated to 13% per serving per day when the analysis was adjusted for BMI (95% CI = 1.06-1.21, $p < 0.05$, $I^2 = 79\%$) (Imamura et al., 2015). The BMI-adjusted increase in incidence of T2DM for artificially sweetened beverages and fruit juice was 8% (95% CI = 1.02-1.15, $p < 0.05$, $I^2 = 64\%$) and 7% (95% CI = 1.01-1.14, $p < 0.05$, $I^2 = 51\%$) per serving per day, respectively (Imamura et al., 2015). Accordingly, Imamura et al. (2015) concluded that sugar sweetened beverages increased the risk of T2DM independent of BMI, and neither artificially sweetened beverages, nor fruit juice were viable replacements. That said, in a separate meta-analysis, Xi et al. (2014) observed a significant 28% increase in risk of T2DM among those with the highest compared with the lowest category of sugar-sweetened fruit juice consumption (95% CI = 1.04-1.59, $p = 0.02$, $I^2 = 43.3\%$), while consumption of 100% fruit juice did not exhibit an increased risk of T2DM (with adjustment for BMI: RR: 0.98, 95% CI: 0.84-1.15; without adjustment for BMI: RR: 1.11, 95% CI: 0.92-1.34). Thus, the current evidence is inconclusive concerning the extent to which fruit juice influences T2DM risk.

Diet and Glucose Homeostasis: Experimental Evidence

While population-level observational studies suggest seemingly straight-forward dietary variables associated with a reduced risk of T2DM, experimental studies assessing the influence of these variables on measures of glucose homeostasis are less conclusive. Systematic reviews and meta-analyses analyzing existing dietary intervention trials are fraught with challenges, including but not limited to heterogeneity, risk of bias, small sample sizes, and variable duration and dosages of interventions. Further, much of the literature scrutinizes individual nutrients (e.g. folate, vitamin D, vitamin E) without contextualizing the participants' overall dietary behavior. Accordingly, while meta-analyses of intervention

trials provide some degree of evidence, there is also a preponderance of contradiction in terms of the associations between dietary patterns and glucose homeostasis or insulin sensitivity.

Overall Dietary Pattern

In accordance with findings from observational studies, experimental evidence suggests that many different dietary approaches may improve glycemic control (Ajala, English, & Pinkney, 2013). In a systematic review and meta-analysis among individuals with T2DM, Ajala et al. (2013) used a fixed-effect inverse-variance model to determine the weighted mean difference (WMD) of diet on glycemic control and other cardiometabolic endpoints across 16 randomized controlled trials (RCTs) including 3,073 participants. The majority of studies enrolled participants who were overweight or obese. Dietary interventions ranged from 6 months to 4 years and included low-carbohydrate, vegetarian, vegan, low-glycemic index, high-fiber, Mediterranean, high-protein and control diets (Ajala et al., 2013). Five of the 16 studies individually reported intervention effects on weight loss and BMI, though no study reported baseline differences in participant characteristics. Of the dietary approaches, the authors identified the low-carbohydrate, low-GI, Mediterranean and high-protein diets as being most effective in improving glycemic control based on HbA1C compared to control diets (low-carbohydrate: WMD = -0.12%, 95% CI: -0.24% to -0.00%, p = 0.04, I^2 = 75%; low-GI: WMD = -0.14%, 95% CI: -0.23% to -0.03%, p = 0.008, I^2 = 80%; Mediterranean: WMD = -0.47%, 95% CI: -0.64% to -0.30%, p < 0.00001, I^2 = 82%; high-protein: WMD = -0.28%, 95% CI: -0.38% to -0.18%, p < 0.00001, I^2 = 60%) (Ajala et al., 2013). In other words, the low-carbohydrate, low-GI, Mediterranean, and high-protein diets drove the following significant decreases in HbA1C compared to control diets: -0.12%, -0.14%, -0.47%, and -0.28%, respectively (Ajala et al., 2013). In meta-analysis, only the Mediterranean diet significantly impacted weight loss compared to the control diets, which could have contributed to its relatively greater influence on glycemic control (WMD = -1.84 kg, 95% CI: 2.54 to -1.15, p <0.00001) (Ajala et al., 2013).

Also among individuals with T2DM, a more recent review of systematic reviews and meta-analyses conducted by Kahleova et al. (2019) similarly identified favorable effects of the Mediterranean diet and vegetarian dietary pattern on fasting plasma glucose outcomes (Mediterranean: MD: -0.50 mmol/L, 95%

CI: -0.81 to -0.20, p value not reported, I^2 = 96.7; vegetarian: MD: -0.56 mmol/L, 95% CI: -0.99 to -0.13, p = 0.01, I^2 = 0%; respectively). In other words, in meta-analysis, adoption of a Mediterranean diet resulted in a 0.50 mmol/L (9 mg/dL) decrease in fasting plasma glucose compared to the control, while vegetarian diets drove a significant 0.56 mmol/L decrease in the same measure. This interpretation should be read with caution, given both diets also led to a reduction in both waist circumference and body weight, and meta-analyses were not adjusted for changes in these measures of adiposity. Additionally, the DASH diet significantly reduced both fasting plasma insulin and HbA1C by -0.15 uU/mL and -0.53%, respectively, compared to the control (fasting insulin: 95% CI: -0.22 to -0.08, p <0.001, I^2 = 0%; HbA1C: 95% CI: -0.62 to -0.43, p <0.001, I^2 = 99%) (Kahleova et al., 2019). As before, this interpretation should be used cautiously because the DASH diet also exerted a favorable effect on body weight, driving a mean reduction of -1.42 kg compared to the control (95% CI: -2.03 to -0.82, p < 0.0001, I^2 = 71%) (Kahleova et al., 2019). This meta-analysis was also not adjusted for changes in body weight, suggesting changes in this measure of adiposity could obscure the true impact of the DASH diet on fasting insulin levels compared to the control.

Mediterranean Dietary Pattern

In addition to the protective effects in individuals with diagnosed T2DM, the Mediterranean dietary pattern may also be beneficial in promoting glycemic control in individuals at risk for T2DM (Esposito et al., 2015). In a systematic review and meta-analysis of 8 meta-analyses and 5 RCTs, Esposito et al. (2015) implemented random-effects models and convergence analyses to evaluate the impact of the Mediterranean diet on glycemic control, cardiometabolic risk and metabolic syndrome remission in individuals with or at risk for T2DM. In individuals with T2DM, the researchers estimated an overall 0.47% reduction in HbA1C driven by the Mediterranean diet compared with control diets (95% CI = -0.56% to -0.38%, p = 0.0001, I^2 = 3.5%) (Esposito et al., 2015). Moreover, they identified a 49% increased chance of achieving metabolic syndrome remission within 2-5 years among adults randomized to the Mediterranean diet compared with controls (95% CI: 14%-96%, p = 0.004, I^2 = 71%), though they did not identify which metabolic syndrome criteria were impacted the most to influence remission (Esposito et al., 2015). A major limitation of Esposito et al.'s (2015) findings is that the authors did not address how the

included studies originally adjusted for possible covariates, nor did they subsequently adjust for covariates in meta-analysis.

In terms of individuals without T2DM, Esposito et al. (2015) noted two meta-analyses of predominantly cohort studies, which attributed a significant 19-23% reduction in risk of T2DM to the Mediterranean diet in individuals without T2DM at baseline (95% CI: 0.73-0.90, 0.66-0.89, respectively, p values not reported) (Koloverou, Esposito, Giugliano, & Panagiotakos, 2014b; Schwingshackl, Missbach, König, & Hoffmann, 2015). Accordingly, it is plausible that the Mediterranean dietary pattern may favorably influence glycemic control and therefore, T2DM outcomes, among those with, as well as those at risk for, the disease. Esposito et al. (2015) attributed these favorable effects to the anti-inflammatory and antioxidant properties of the Mediterranean dietary pattern.

Unsaturated Fatty Acids

One purported benefit of the Mediterranean diet is its inclusion of unsaturated fatty acids (e.g. MUFAs via olive oil and PUFAs via fish), which may have favorable physiological effects on inflammation and endothelial function (Schwingshackl et al., 2015). To evaluate the differential impact of saturated and unsaturated fatty acids on glucose and insulin homeostasis in adults, Imamura et al. (2016) conducted a systematic review and dose-response meta-regression analysis of 102 trials with 4,220 adult participants from the United States, Canada, Europe, Australia, and Asia. Of the 102 included trials, about one-third were restricted to participants with diabetes and about three-quarters included participants with average BMIs within the overweight to obese range. The researchers assessed the impact of isocaloric substitutions of saturated fatty acids, unsaturated fatty acids and carbohydrates on fasting glucose, HbA1C, 2-hour glucose tolerance, fasting insulin, insulin sensitivity and insulin secretion (Imamura et al., 2016). *A priori* defined potential sources of heterogeneity included measures of adiposity, such as BMI and mean weight change, among other non-adiposity variables.

Among their findings, Imamura et al. (2016) identified that a 5% isocaloric substitution of PUFA for SFA resulted in a 0.04 mmol/L significant decrease in fasting glucose concentrations (95% CI: -0.07 to -0.01, p

= 0.028), while no other substitution led to significant changes in this measure. The clinical significance of this minor decrease is questionable. Additionally, a 5% replacement of carbohydrates or SFA with isocaloric MUFA or PUFA reduced HbA1C from -0.09% to -0.12%, and -0.11% to -0.15%, respectively (CHO → MUFA: 95% CI: -0.19% to -0.05%; SFA → MUFA: 95% CI: -0.23% to -0.05%; CHO → PUFA: 95% CI: -0.17% to -0.05%; SFA → PUFA: 95% CI: -0.23% to -0.06%; all p <0.001) (Imamura et al., 2016). Changes in HOMA-IR followed the same pattern as HbA1C, where a 5% isocaloric replacement of carbohydrates or SFA with isocaloric MUFA or PUFA reduced HOMA-IR from -2.4% to -3.1%, and -3.4% to -4.1%, respectively (CHO → MUFA: 95% CI: -5.8% to -0.3%; SFA → MUFA: 95% CI: -6.4% to -0.8%; CHO → PUFA: 95% CI: -5.9% to -0.8%; SFA → PUFA: 95% CI: -6.4% to -1.6%; all p <0.05) (Imamura et al., 2016). Further, a 5% isocaloric replacement of carbohydrate with SFA or PUFA led to significant reductions in fasting insulin concentrations of 1.1 pmol/L and 1.6 pmol/L, respectively (CHO → SFA: 95% CI: 0.6-1.6, p = 0.001; CHO → PUFA: 95% CI: 0.4-2.8, p = 0.015) (Imamura et al., 2016). Imamura et al. (2016) also reported an average 0.51 pmol/L/min significant increase in acute insulin response as a result of 5% isocaloric substitutions of carbohydrates, SFA and MUFA with PUFA (CHO → PUFA: mean: 0.49 pmol/L/min, 95% CI: 0.17-0.80; SFA → PUFA: mean: 0.51 pmol/L/min, 95% CI: 0.20-0.82; MUFA → PUFA: mean: 0.52 pmol/L/min, 95% CI: 0.21-0.82; all p <0.01).

In assessing sources of heterogeneity, Imamura et al. (2016) noted that stratifying by BMI influenced the effects of MUFA on fasting glucose, though no measure of adiposity explained any heterogeneity for fasting insulin, HbA1C or HOMA-IR. While the authors further assessed the impact of weight change in concert with dietary variables in sensitivity analyses, they did not isolate the effects of changes in adiposity on their studied outcomes, which leaves room for questioning the extent to which this may have influenced their reported results. Keeping in mind these possible limitations, these findings from Imamura et al. (2016) indicate that both MUFAs and PUFAs may support glucose homeostasis based on their respective effects on fasting glucose, HbA1C, HOMA-IR, and/or insulin response compared to SFA or carbohydrates.

Despite these potentially favorable glycemic outcomes, the totality of evidence regarding unsaturated fatty acids is not conclusive. For example, in a much larger systematic review and random-effects meta-analysis of 83 RCTs including 121,070 participants from Europe, North America, South America, Asia and Australia, Brown et al. (2019) evaluated the impact of total PUFA, omega-6, long chain omega-3 (EPA/DHA), and omega-3 on new diagnoses of diabetes or prediabetes, glycemic control, serum insulin and insulin resistance. Participants were non-pregnant adults at risk for diabetes. In their meta-analysis of incident diabetes and prediabetes, Brown et al. (2019) reported a modicum of evidence. Of their included RCTs, none assessed the incidence of impaired glucose tolerance when comparing the highest to the lowest categories of intake of long-chain omega-3s, ALA, omega-6, or total PUFAs. Due to very low quality of evidence, the authors reported unclear influences on T2DM diagnosis of the highest compared to the lowest categories of intake of ALA, omega-6, and total PUFAs (Brown et al., 2019). They reported moderate quality evidence that long-chain omega-3s have limited or no effect on T2DM diagnosis when comparing the highest to the lowest categories of intake (RR: 1.00, 95% CI: 0.85-1.17, p value not reported, I^2 = 45%).

In their meta-analysis of measures of glucose homeostasis and control, the researchers determined that comparing the highest to the lowest categories of both total PUFA and ALA intakes respectively did not have a significant effect on fasting glucose, fasting insulin, HbA1C, or HOMA-IR (Brown et al., 2019). Additionally, they noted that the influence of omega-6 fatty acids on these same measures was unclear due to very low to low quality of evidence (Brown et al., 2019). Moreover, the authors found that long-chain omega-3s did not significantly change fasting serum insulin, HbA1C, or HOMA-IR, though they did significantly increase fasting glucose by 0.04 mmol/L when comparing the highest to the lowest categories of intake (95% CI: 0.02-0.07, p <0.001, I^2 = 0%) (Brown et al., 2019). The authors concluded that long-chain omega-3s, ALA, omega-6s and total PUFAs have little to no influence on incident T2DM or glucose metabolism (Brown et al., 2019). While the authors also conducted meta-analyses on secondary outcomes related to adiposity (i.e. weight, BMI, % body fat, waist circumference, waist-to-hip ratio and total body fat) for highest compared with lowest category intakes of long-chain omega-3s, ALA, omega-6, or total PUFAs, they included this data in supplementary figures only, did not report p values,

and nearly all confidence intervals crossed 0.00, suggesting no effect (Brown et al., 2019). The authors did not adjust any of their meta-analyses for adiposity. Moreover, they also pointed to sister publications reporting little to no effects of higher intakes of long-chain omega-3s, ALA, omega-6, or total PUFAs on measures of adiposity including body weight and BMI (Abdelhamid et al., 2018; Abdelhamid et al., 2020; Hooper et al., 2018). Accordingly, the conclusions reported by Brown et al. and Imamura et al. are seemingly contradictory, though their inclusion criteria differed in terms of the dietary interventions evaluated (i.e. substitution versus predominantly supplementation).

While the evidence for the impact of PUFAs on glucose homeostasis and insulin response may not be clear cut, the evidence for the influence of MUFAs may be more consistent. In a systematic review and meta-analysis of 4 cohort studies and 29 intervention trials, Schwingshackl et al. (2017) assessed the impact of olive oil consumption on risk and management of T2DM. Studies included a total of 187,068 adult participants (98% cohort, 2% RCT) from Europe, North America, Australia/New Zealand, and Asia (Schwingshackl et al., 2017). In their random-effects meta-analyses of cohort studies with participants free of T2DM at baseline, the authors observed a 16% reduced risk of T2DM among the highest compared to the lowest categories of olive oil intake (RR: 0.84, 95% CI: 0.77-0.92, $p < 0.01$, $I^2 = 22\%$) and a 9% reduction in risk per 10 g/day of olive oil (RR: 0.91, 95% CI: 0.87-0.95, $p < 0.01$, $I^2 = 0\%$) (Schwingshackl et al., 2017). They characterized this relationship as being nonlinear, reflecting a 13% decreased risk of T2DM up to 15-20 g/day of olive oil ($p < 0.01$) (Schwingshackl et al., 2017). Of the included cohort studies, all but one adjusted for BMI; Schwingshackl et al. (2017) did not discuss any further adjustments for measures of adiposity in their meta-analyses.

In their random effects meta-analyses of experimental trials with participants with T2DM at baseline, Schwingshackl et al. (2017) reported a significant 0.27% decrease in HbA1C (MD: -0.27%, 95% CI: -0.37% to -0.17%, $p < 0.01$, $I^2 = 0\%$) and 0.44 mmol/L decrease in fasting plasma glucose (MD: -0.44, 95% CI: -0.66 to -0.22, $p<0.01$) among the olive oil intervention groups compared to the controls (Schwingshackl et al., 2017). While the authors reported mean baseline BMI for all included experimental studies, and they mention extracting multivariate adjusted data, they do not indicate the extent to which

these studies initially adjusted for measures of adiposity specifically, nor do they note subsequent adjustment in meta-analysis – this may be a limitation (Schwingshackl et al., 2017). Based on these meta-analysis findings from both cohort and experimental studies, Schwingshackl et a. (2017) suggested a protective effect of olive oil on T2DM risk and glycemic control. On the other hand, they admitted several limitations which weaken the interpretation of these protective findings, such as the extent to which phytochemical properties of olive (e.g. carotenoids, tocopherols, polyphenols, and oleic acid), and not the olive oil triglycerdides themself, may be influencing these outcomes. Accordingly, the role of both PUFAs and MUFAs in supporting glucose homeostasis may be questionable.

DASH Dietary Pattern

Another dietary pattern that is rich in unsaturated fatty acids is the Dietary Approaches to Stop Hypertension (DASH) diet (Shirani, Salehi-Abargouei, & Azadbakht, 2013). In order to evaluate the effect of the DASH diet on fasting blood glucose, serum fasting insulin, and HOMA-IR, Shirani et al. (2013) conducted a systematic review and meta-analysis of 9 RCTs, inclusive of 1,239 participants from the United States, United Kingdom and Iran. Study participants ranged from healthy adults to adults with overweight, obesity, T2DM and/or metabolic syndrome; the authors did not note what, if any, covariates were adjusted for in the original analyses (Shirani et al., 2013). In meta-analysis, adherence to the DASH diet was not associated with significant changes in either fasting blood glucose (MD: -0.26, 95% CI: -0.56-0.05, $p = 0.1$, $I^2 = 4.8\%$) or HOMA-IR (MD: -0.26, 95% CI: -0.56 to 0.05, $p = 0.1$, $I^2 = 4.8\%$), however the DASH diet was associated with significant 0.15 pmol/L reduction in fasting insulin compared to the controls (MD: -0.15, 95% CI: -0.22 to -0.08, $p < 0.001$, $I^2 = 0.0\%$) (Shirani et al., 2013). In subgroup analysis, this was especially apparent for studies lasting longer than 16 weeks (MD: -0.16, 95% CI: -0.23 to -0.08, $p < 0.001$) and for participants with the metabolic syndrome or hyperlipidemia (MD: -0.16, 95% CI: -0.26 to -0.05, $p < 0.001$) (Shirani et al., 2013). The significance of the impact of the DASH diet on fasting insulin but not on fasting glucose or HOMA-IR was explained in the authors' sensitivity analysis, where they identified one heavily influential study whose exclusion attenuated the significance of the findings (Shirani et al., 2013). Accordingly, though the authors continued to espouse a positive effect of the DASH diet on fasting insulin, their statistical analysis seems to suggest more ambiguity than they

admit regarding the efficacy of the diet on measures of glucose homeostasis (Shirani et al., 2013). Moreover, they did not discuss how studies took into account changes in measures of adiposity, which casts more uncertainty around their results.

Food Groups

While holistically the DASH diet may not have a material effect on glucose homeostasis, experimental evidence suggests that components of the DASH diet might be more influential (Schwingshackl, Hoffmann, Iqbal, Schwedhelm, & Boeing, 2018). In a systematic review and network meta-analysis of 66 RCTs including 3,595 adults participants (8% with T2DM), Schwingshackl et al. (2018) evaluated the impact of the major food groups on intermediate-disease markers, such as LDL cholesterol, plasma triglycerides, fasting glucose, HbA1C and HOMA-IR. In random effects network meta-analysis, the authors determined that the consumption of nuts, whole grain and refined grains (dose and duration unspecified) reduced fasting glucose anywhere from 0.35 to 0.49 mmol/L in comparison to fruit, vegetables and red meat (p values not reported) (Schwingshackl et al., 2018). Further, the consumption of whole grains (dose and duration unspecified) reduced HOMA-IR by 0.22 compared to the consumption of refined grains (MD: -0.22, 95% CI: -0.40 to -0.05, p value not reported) (Schwingshackl et al., 2018). Although the authors did extract mean baseline BMI from the included studies, they did not specify the extent to which extracted data was adjusted for possible covariates, nor did they mention making adjustments in meta-analysis to account for possible cofounders, such as adiposity. To that end, while nuts and whole grains *may* be vital components of a dietary pattern that aids in glucose homeostasis, Schwingshackl et al. (2018) did not rule out that these findings may be artifacts driven by confounding.

Nuts and Legumes

The evidence for the influence of nuts on glucose homeostasis is inconsistent. While Schingshackl et al. (2018) reported *possible* benefits of nuts in reducing fasting glucose, Tindall et al. (2019) found evidence to the contrary. In a systematic review and meta-analysis of 40 RCTs including 2,832 adult participants over a period of 1-12 months, Tindall et al. (2019) evaluated how tree nuts and peanuts influence glucose homeostasis endpoints, including fasting glucose, fasting insulin, HbA1C and HOMA-IR. Study

participants represented a range of metabolic health, including individuals classified as healthy, as well as those with T2DM, overweight or obesity, metabolic syndrome, hyperlipidemia, and hypercholesterolemia. In their random effects meta-analyses, while the authors reported no overall effect of nut consumption on fasting glucose or HbA1C, they did identify a significant 0.23 decrease in HOMA-IR (WMD: -0.23, 95% CI: -0.40 to -0.06, $p < 0.05$, $I^2 = 51.7\%$) and 0.40 μIU/mol decrease in fasting insulin (WMD: -0.40 microUL/mL; 95% CI: -0.73 to -0.07, $p < 0.05$, $I^2 = 49.4\%$) as a result of increased nut consumption (Tindall et al., 2019). The researchers conducted numerous subgroup analyses, and among their findings, they concluded that the weight status of participants had no bearing on the reported effect sizes; they did not specify if "weight status" considered only baseline BMI or reflected any changes in adiposity resulting from the interventions (Tindall et al., 2019). Additionally, Tindal et al. (2019) did not find a dose-response relationship between nut consumption and any of these measures of glucose homeostasis. Based on their totality of results, the authors concluded that nuts exerted their influence on glucose homeostasis by improving insulin sensitivity (Tindall et al., 2019).

Whole Grains

Comparable to the variable evidence supporting the impact of nut intake on glucose homeostasis, the evidence for whole grains may be equally questionable. Similar to Schwingshackl et al.'s (2018) findings that whole grains favorably influenced fasting glucose and HOMA-IR, another recent systematic review and meta-analysis of RCTs reported similar conclusions. Specifically, Marventano et al. (2017) evaluated 41 studies including 1,033 participants from Sweden, Finland, Canada, United Kingdom, United States, Australia, Denmark, Italy, Germany, Japan, Kuwait, Singapore, Spain, and Switzerland. Study participants were healthy and included a spectrum of BMI classifications, ranging from healthy to obese (Marventano et al., 2017). The number of participants per study ranged from 10 to over 200 (Marventano et al., 2017). In inverse-variance random effects meta-analyses, the authors assessed the acute, medium- and long-term impact of whole grain meals on glycemic control and insulin sensitivity compared with controls (Marventano et al., 2017). Based on the study's inclusion criteria, controls consisted of foods with lower levels or no whole grains compared to the intervention meals (Marventano et al., 2017).

In terms of the acute effects, Marventano et al. (2017) determined that glucose iAUC was reduced by 29.7 mmol x min/L for the time period of 0-120 minutes following the consumption of a whole grain meal compared with a control meal (95% CI: -43.57 to -15.85, p value not reported, I^2 =80%); this decrease was attenuated to an insignificant 15.40 mmol min/L for the time period of 0-180 minutes (95% CI: -31.52 to 0.73, p value not reported, I^2 =0%). Insulin iAUC significantly decreased by 2.01 nmol min/L for the time period of 0-120 minutes and by 3.64 nmol min/L for the time period of 0-180 minutes as a result of the consumption of a whole grain meal compared to a control (0-120: MD: -2.01 nmol min/L, 95% CI: -2.88 to -1.14, p value not reported, I^2 = 0%; 0-180: MD: -3.64 nmol min/L, 95% CI: -5.00 to -2.28, p value not reported, I^2 = 0%) (Marventano et al., 2017).

In terms of the medium- and long-term effects resulting from whole grain meal consumption compared with a control meal, Marventano et al. (2017) noted a modestly significant 0.08 mmol/L decrease in fasting glucose (95% CI: -0.16 to -0.01, p value not reported, I^2 = 0%) and 0.39 decrease in HOMA-IR (95% CI: -0.69 to -0.08, p value not reported, I^2 = 0%) following sensitivity analyses; yet they also identified no difference between intervention and control meals for fasting insulin (MD: -2.26 pmol/L, 95% CI: -6.58-2.06, p value not reported, I^2 = 17%). While the authors stratified the medium- and long-term studies based on baseline BMI in subgroup analyses and reported no significant differential findings, they seemingly did not adjust their meta-analyses for changes in pertinent covariates, such as adiposity (e.g. BMI or % fat mass) (Marventano et al., 2017). Based on their results, the authors concluded that whole grain foods were more effective than controls in moderating acute postprandial glucose and insulin response, whereas there was less of an impact in the long-term maintenance of glucose homoeostasis (Marventano et al., 2017).

Vegetarianism

One dietary pattern comprised mostly of nuts, whole grains, fruit and vegetables, and other plant-based food items is vegetarianism. In a systematic review and meta-analysis of 9 trials with 664 participants with T2DM from the United States, Greece, Brazil, Czech Republic and Korea, Viguiliouk et al. (2019) evaluated the impact of vegetarianism on glycemic control and cardiometabolic risk factors. In a random

effects model, the authors concluded that a vegetarian dietary pattern significantly decreased HbA1C by 0.29% (95% CI: -0.45 to -0.12%, p = 0.0006, I^2 = 14%) and fasting glucose by 0.56 mmol/L (95% CI: -0.99 to -0.13 mmol/L, p = 0.01, I^2 = 0%) compared to the control (Viguiliouk et al., 2019). Additionally, Viguiliouk et al. (2019) identified a significant 2.15 kg decrease in body weight, 0.74 decrease in BMI and 2.86 cm decrease in waist circumference as a result of the vegetarian dietary pattern compared to the control, which could have mediated the impact of the intervention on both HbA1C and fasting glucose (BW: 95% CI: -2.95 to -1.34, p < 0.00001, I^2 = 21%; BMI: 95% CI: -1.09 to -0.39, p < 0.0001, I^2 = 60%; WC: 95% CI: -3.76 to -1.96, p < 0.00001, I^2 = 48%). The authors failed to adjust their meta-analyses to account for these changes in body weight, and they also did not conduct subgroup analyses due to the limited number of trials included in each analysis (Viguiliouk et al., 2019). With a confidence of moderate to low, Viguiliouk et al. (2019) concluded that vegetarian dietary patterns may be beneficial for individuals with T2DM.

Low GI Dietary Patterns

Aside from the potentially favorable effects of nuts, whole grains and plant-based diets, other experimental studies suggest that low glycemic index (GI) dietary patterns are advantageous in maintaining glycemic control (Ojo, Ojo, Adebowale, & Wang, 2018). In a systematic review and meta-analysis of 6 dietary intervention studies ranging from 2 to 22 months and including 705 adult participants with T2DM, Ojo et al. (2018) explored the impact of low-GI diets compared with high-GI or control diets on HbA1C and fasting blood glucose. In discussing their methods, the authors provided little detail on their data extraction and did not indicate any consideration given to adjustments made for covariates in the included studies. Compared to the control diets, the authors determined that a low-GI diet reduced HbA1C by 0.22 percentage points (95% CI: -0.31 to -0.13, p <0.00001, I^2 = 13%) and fasting blood glucose by 6.59 mg/dL (95% CI: -12.12 to -1.05, p = 0.02, I^2 = 2%) over the measured time period (Ojo et al., 2018). However, in sensitivity analysis, only the results for HbA1C remained significant (p = 0.0003), suggesting a lack of reliability for the effects on more acute fasting blood glucose (Ojo et al., 2018). The authors also did not discuss any changes in measures of adiposity that might have been associated with

the dietary interventions. Accordingly, while it is plausible a low-GI diet may benefit markers of longer-term glycemic control, the evidence has some limitations.

Dietary Fiber

One popular dietary constituent with purported benefits to glycemic control is fiber (Silva et al., 2013). In order to evaluate the impact of dietary fiber on HbA1C and fasting plasma glucose in individuals with T2DM, Silva et al. (2013) conducted a systematic review and meta-analysis of 11 randomized controlled trials including 605 adult participants. Of the included studies, only six reported baseline body weight and eight provided weight change at intervention follow up (6 = no change, 2 = decrease, 3 = unknown) (Silva et al., 2013). The included studies had a duration of at least 8 weeks and compared either diets with high fiber content to diets with low fiber content, or usual diets with fiber supplementation to usual diets with or without placebo (Silva et al., 2013). Using a random effects model, Silva et al. (2013) determined that added dietary fiber reduced absolute HbA1C values by 0.55 percentage points (95% CI: -0.96 to -0.13, I^2 = 94.1%, $p < 0.001$) and decreased fasting plasma glucose by an average of 9.97 mg/dL (95% CI: -18.16 to -1.78, I^2 = 95.5%, $p < 0.001$). Both of these findings exhibited a high degree of heterogeneity however. The authors identified study follow-up and participant age as the explanatory variables for the significant heterogeneity in these measures (Silva et al., 2013). Additionally, while the authors considered the effects of possible covariates, they only included study design, study follow-up duration, participant age, type of intervention and fiber difference between groups in their adjusted analyses (Silva et al., 2013). To that end, they failed to adjust for other possible covariates, such as change in adiposity, which may have influenced their reported findings that diets high in fiber are beneficial to measures of glycemic control.

Low Carbohydrate Dietary Patterns

Beyond diets characterized by low GI and/or high dietary fiber, additional studies suggest that low-carbohydrate diets may be effective in reducing HbA1C (Huntriss, Campbell, & Bedwell, 2018). In a systematic review and meta-analysis of 7 RCTs ranging in duration from 3 months to 4 years, Huntriss et al. (2018) evaluated the impact of low-carbohydrate diets compared to control diets on measures of

cardiometabolic health, including HbA1C, in adults with T2DM (n = 2204). In terms of HbA1C specifically, the authors identified a significant 0.28% absolute decrease in HbA1C at one year for individuals randomized to low-carbohydrate diets compared to controls (95% CI: -0.53 to -0.02, p = 0.03, I^2 = 54%) (Huntriss et al., 2018). Huntriss et al. (2018) did not find significant changes in weight between the intervention groups at one year, suggesting improvements in HbA1C were independent of longer-term weight loss.

Lastly, as in the observational studies previously discussed, while many experimental studies intend to identify dietary patterns or constituents with protective effects, other trials strive to understand the adverse impact of certain food agents on measures of glucose homeostasis. One such agent is fructose, the consumption of which is fueled by pervasive carriers in the Western diet, such as sucrose and high-fructose corn syrup (ter Horst, Schene, Holman, Romijn, & Serlie, 2016).

Fructose

In a systematic review and meta-analysis, ter Horst et al. (2016) assessed 29 dietary intervention trials inclusive of 1,005 participants from Mexico, Western Europe and the United States. Study participants included adults without T2DM and with BMI classifications ranging from healthy to obese (ter Horst et al., 2016). The authors sought to delineate the effects of isocaloric and hypercaloric fructose substitutions on insulin sensitivity (ter Horst et al., 2016). In the isocaloric comparisons, the authors determined that fructose administration reduced hepatic insulin sensitivity by 0.47 (95% CI: 0.03-0.91, p = 0.04, I^2 = 17%) but exerted no significant effects on fasting insulin, HOMA-IR, or insulin-stimulated glucose disposal rates measured under euglycemic hyperinsulinemic clamp conditions (ter Horst et al., 2016). That said, among participants classified as overweight or obese based on BMI, isocaloric substitutions with fructose did result in a significant 0.38 increase in insulin resistance as measured by HOMA-IR (95% CI: 0.00-0.77, p = 0.05, I^2 = 55%) and 7.10 pmol/L increase in fasting plasma insulin (95% CI: -0.07-14.27, p = 0.05, I^2 = 9%), indicating fructose may differentially effect individuals based on adiposity (ter Horst et al., 2016).

In the hypercaloric comparisons, ter Horst et al. (2016) determined that fructose administration decreased hepatic insulin sensitivity by 0.77 (95% CI: 0.28-1.26, $p = 0.002$, $I^2 = 68\%$) and increased fasting insulin by 3.38 pmol/L (95% CI: 0.03-6.73, $p < 0.05$, $I^2 = 43\%$); however, as before, there were no significant effects on HOMA-IR or insulin-stimulated glucose disposal rates. To note, for both the isocaloric and hypercaloric comparisons, the majority of studies included in random effects models for hepatic insulin sensitivity included participants with BMIs in the normal range, suggesting results may not be generalizable to all BMI classifications. Additionally, the authors did not extract multivariate adjusted data for the included studies, nor did they adjust their meta-analyses for pertinent covariates, such as changes in body weight. To that end, while ter Horst et al.'s (2016) suggested that fructose administered isocalorically or hypercalorically contributes to T2DM incidence through its role in increasing hepatic insulin resistance, their results should be interpreted with caution.

Dairy Consumption and T2DM: Observational Evidence

Dairy is a major food group recommended for Americans by the US Department of Health and Human Services and USDA (2015) due to its micronutrient profile and beneficial effects on bone health (USDA, 2011). Its properties, physiological associations and effects have been extensively studied in the literature, both observationally and experimentally. In terms of incident T2DM, while epidemiological evidence suggests an inverse relationship, the evidence is not without contradiction. Though the following meta-analyses are limited due to potential publication biases, measurement errors, lack of generalizability, questionable power, and heterogeneity, their value lies in their robust sample sizes and duration of follow-up.

Inverse Associations between Total Dairy Consumption and T2DM risk

Both Tong et al. (2011) and Schwingshackl et al. (2017) identified inverse relationships between dairy intake and incident T2DM. In order to evaluate the association between dairy intake and incidence of T2DM, Tong et al. (2011) conducted a meta-analysis of 7 cohort studies from the United States, United Kingdom, Japan and China. Studies included 328,029 adult participants free of T2DM at baseline, and all made statistical adjustments for measures of adiposity, specifically BMI (Tong et al., 2011). Follow-up

ranged from 5 to 25 years (Tong et al., 2011). The authors derived combined relative risks (RR) describing the association between the highest versus lowest categories of dairy consumption and T2DM (Tong et al., 2011). In doing so, they identified a 14% reduced risk of T2DM for the highest compared with the lowest categories of dairy intake (RR: 0.86, 95% CI: 0.79-0.92, p value not reported, I^2 = 29.7%) (Tong et al., 2011). This overall association may have been influenced by the impact of low-fat dairy products, as higher intakes of low-fat dairy resulted in an 18% reduced risk of T2DM (RR: 0.82, 95% CI: 0.74-0.90, p value not reported), while higher intakes of high-fat dairy did not affect the risk of T2DM (RR: 1.00, 95% CI: 0.89-1.10, p value not reported) (Tong et al., 2011). Similarly, in their dose-response analysis, the authors described a 5% reduction, 10% reduction and 2% reduction per serving of total dairy, low-fat dairy, and full-fat dairy, respectively (total: RR: 0.95, 95% CI: 0.92-0.97, p value not reported; low-fat: RR: 0.90, 95% CI: 0.85-0.95, p value not reported; full-fat: RR: 0.98, 95% CI: 0.92-1.05, p value not reported) (Tong et al., 2011). At the product level, both whole milk and yogurt exhibited possible protective associations, reducing the risk of T2DM by 5% (RR: 0.95, 95% CI: 0.86-1.05, p value not reported) and 17% (RR: 0.83, 95% CI: 0.74-0.93, p value not reported), respectively (Tong et al., 2011). Based on their overall findings, Tong et al. (2011) reported an inverse association between dairy intake and T2DM risk, though this association was more pronounced for low-fat dairy foods and yogurt.

An inverse association between dairy intake and T2DM risk was also reported by Schwingshackl et al. (2017) in a meta-analysis of 88 total prospective studies. Participants were adults without diabetes at baseline (Schwingshackl et al., 2017). For their dairy analyses, the authors included 21 studies, all of which adjusted for either BMI, waist circumference or waist-to-hip ratio, among other covariates (Schwingshackl et al., 2017). When comparing the highest versus lowest categories of total dairy food intake, the authors reported a 9% reduction in T2DM risk (RR: 0.91, 95% CI: 0.85-0.97, p value not reported, I^2 = 63%), or a 3% reduction in risk for each incremental 200g of dairy foods consumed per day (RR: 0.97, 95% CI: 0.94-0.99, p value not reported, I^2 = 74%). Schwingshackl et al. (2017) did not uncover evidence supporting a non-linear dose-response relationship. The authors also presented findings similar to those of Tong et al. (2011) concerning dairy fat. When stratifying their risk calculations by low fat and high fat dairy products, Schwingshackl et al. (2017) observed a 3% decrease in T2DM risk

for low-fat dairy products but no change in risk associated with high-fat dairy products (low-fat: RR: 0.97, 95% CI: 0.94-1.00, p value not reported, I^2 = 71%; high-fat: RR: 1.00, 95% CI: 0.96-1.04, p value not reported, I^2 = 69%).

Associations between Consumption of Dairy Sub-Types and T2DM risk

In contrast to Tong et al. (2011) and Schwingshackl et al. (2017), Chen et al. (2014) identified more nebulous results when analyzing the response to dairy fat content. Specifically, Chen et al. (2014) conducted a meta-analysis to explore the associations between consumption of individual types of dairy foods and incident T2DM among US adults. Using data from the Health Professionals Follow-up Study, Nurses' Health Study and Nurses' Health Study II reflecting 3,984,203 person-years of follow-up, the authors used Cox proportional hazard regression and fixed-effects models to derive pooled hazard ratios (HR) (Chen et al., 2014). To account for potential covariates, they developed three models, all of which controlled for BMI (Chen et al., 2014). While the authors determined that a daily increase in the consumption of dairy foods by one serving per day led to a 4% reduced risk of T2DM when adjusting for age, BMI and energy intake (HR: 0.96, 95% CI: 0.94-0.98, p <0.001), this reduction was attenuated by further adjustment for other dietary and non-dietary factors (Chen et al., 2014). Further, in contrast to Tong et al., Chen et al. (2014) identified no differential associations by dairy fat content and the risk of T2DM, as neither low-fat nor high-fat dairy were significantly associated with a change in risk of T2DM (HR: 1.00, 95% CI: 0.98-1.02, p = 0.72; HR: 1.01, 95% CI: 0.98-1.03, p = 0.30; respectively). In fact, when looking at milk specifically, the authors identified significant increases in the risk of T2DM by 2% and 10% for one daily serving of skim/low-fat milk and whole milk, respectively (skim: HR: 1.02, 95% CI: 0.99-1.04, p = 0.006; whole: HR: 1.10, 95% CI: 1.04-1.16, p = 0.02). They also noted a possible adverse role of cheese, each daily serving of which was associated with a 7% increase in the risk of T2DM (HR: 1.07, 95% CI: 1.03-1.11, p = 0.004) (Chen et al., 2014). Conversely, the authors identified protective associations of one daily serving of yogurt and ice cream, which significantly reduced the risk of T2DM by 17% and 22%, respectively (yogurt: HR: 0.83, 95% CI: 0.75-0.92, p <0.001; ice cream: HR: 0.78, 95% CI: 0.71-0.86, p <0.001) (Chen et al., 2014).

Despite utilizing data from the same three health professionals and nurse cohort studies, a subsequent meta-analysis by Drouin-Chartier et al. (2019) described inconsistent results. Drouin-Chartier et al. (2019) excluded participants with diabetes in their analysis, resulting in a total of 2,783,210 person-years. The authors ran two models for each analysis, the second of which adjusted for numerous covariates, including initial BMI; they also conducted exploratory analyses, which further adjusted their results based on 4-year changes in body weight (Drouin-Chartier et al., 2019). In contrast to Chen et al. (2014), Drouin-Chartier et al. (2019) identified that 4-year increases in total dairy and low-fat dairy intakes by >1 serving/day and >0.5 servings/day, respectively, decreased the risk of T2DM in the subsequent four years by 1-2% (total: HR: 0.98, 95% CI: 0.92-1.05, p = 0.008; low-fat: HR: 0.99, 95% CI: 0.93-1.06, p = 0.006). With adjustments for concurrent changes in body weight, these risk reductions were attenuated, though the authors still reported a 1% decrease in risk for total dairy (HR: 0.99, 95% CI: 0.93-1.06, p = 0.02) (Drouin-Chartier et al., 2019). Changes in high-fat dairy intake were not associated with significant differences in risk (p = 0.09) (Drouin-Chartier et al., 2019).

Like Chen et al. (2014), Drouin-Chartier et al. (2019) reported a 9% increase in the 4-year risk of T2DM associated with an increase of >0.5 servings/day of cheese during the four years prior, as well as an 11% decrease in the same measure of risk associated with an increase of >0.5 servings/day of yogurt (cheese: HR: 1.09, 95% CI: 1.02-1.16, p = 0.002; yogurt: HR: 0.89, 95% CI: 0.82-0.96, p < 0.0001). With adjustments for concurrent 4-year changes in body weight, these same increases in consumption of cheese and yogurt were still associated with significant 10% increases and 10% decreases in subsequent 4-year risk of T2DM, respectively (p = 0.002 and p = 0.0003, respectively) (Drouin-Chartier et al., 2019).

The authors reported opposing results for 4-year decreases in intake of total dairy, low-fat dairy, cheese and yogurt. Decreases of >1 serving/day of total dairy were associated with a 4-year T2DM risk increase of 11% (HR: 1.11, 95% CI: 1.03-1.19, p = 0.008), while decreases of >0.5 servings/day of low-fat dairy, cheese and yogurt were associated with +8%, -3% and +9% changes in risk, respectively (low-fat dairy: HR: 1.08, 95% CI: 1.00-1.15, p = 0.006; cheese: HR: 0.97, 95% CI: 0.89-1.05, p = 0.002; yogurt: HR: 1.09, 95% CI: 0.98-1.21, p <0.0001) (Drouin-Chartier et al., 2019). With adjustments for concurrent 4-year

weight changes, these risk changes became +10%, +7%, -3% and +7% for total dairy, low-fat dairy, cheese and yogurt, respectively (p = 0.02, p = 0.04, p = 0.002, p = 0.0003) (Drouin-Chartier et al., 2019). Considering the results from Chen et al. (2014) and Drouin-Chartier et al. (2019) in concert, increases in total dairy and yogurt intake and decreases in cheese intake may be associated with a reduced risk of T2DM, while the T2DM risk may increase with the opposing changes in consumption of each food type.

In contrast to these results, a more generalizable random-effects meta-analysis conducted by Gijsbers et al. (2016) assessed the association between T2DM risk and varying degrees of dairy consumption among 23 study populations inclusive of 579,832 healthy adult participants from the United States, Europe and Australia. Of the included studies, all but two adjusted for measures of adiposity, including BMI, waist circumference and/or waist-to-hip ratio (Gijsbers et al., 2016). Similar to the previous studies, the authors concluded that for every 200 g/day of total dairy intake, the risk of T2DM decreased linearly by 3% (RR: 0.97, 95% CI: 0.95-1.00, p = 0.04, I^2 = 66%) (Gijsbers et al., 2016). Among studies that adjusted for major risk factors, including BMI, the decrease in risk increased to 12% for every 200 g/day of all dairy foods (RR: 0.88, 95% CI: 0.76-1.03, p value not reported) (Gijsbers et al., 2016). Moreover, Gijsbers et al. (2016) also identified inverse associations for yogurt and ice cream – specifically, the risk of T2DM decreased by 14% for an intake of 80 g/day of yogurt (non-linear) and by 19% for an intake of 10 g/day of ice cream (yogurt: RR: 0.86, 95% CI: 0.83-0.90, p <0.001, I^2 = 73%; ice cream: RR: 0.81, 95% CI: 0.78-0.85, p <0.001, I^2 = 86%).

Soedamah-Muthu and de Goede (2018) subsequently updated the meta-analysis from Gijsbers et al. (2016). With the inclusion of additional studies, the authors reported an attenuated (“borderline significant”) 3% reduction in T2DM risk per 200 g/day of total dairy and 6% reduction in risk (non-linear) for an intake of 100 g/day of yogurt (total dairy: RR: 0.97, 95% CI: 0.95-1.00, p value not reported, I^2 = 62.8%; yogurt: RR: 0.94, 95% CI: 0.91-0.97, p < 0.001, I^2 = 68.6%) (Soedamah-Muthu & De Goede, 2018). They also identified “borderline significant” 4% decreases in T2DM risk per 200 g/day of low-fat dairy (RR: 0.96, 95% CI: 0.92-1.00, p value not reported, I^2 = 60.3%) (Soedamah-Muthu & De Goede,

2018). The extent to which Soedamah-Muthu and de Goede's (2018) meta-analyses adjusted for covariates, such as measures of adiposity, is unclear.

As previously discussed, Chen et al. (2014) identified no significant associations between dairy fat and T2DM risk, though they reported adverse outcomes associated with several types of dairy (skim/low-fat milk, cheese, and whole milk). In contrast, Gao et al. (2013) arrived at differing conclusions. Using random-effects models, the authors sought to enumerate the relationship between dairy consumption and risk of T2DM (Gao et al., 2013). Their analysis included 15 prospective cohort studies and 1 case-cohort study from the United States, Asia and Australia with a total of 526,998 participants. Based on their limited inclusion and exclusion criteria, Gao et al. (2013) did not explicitly select studies based on participant age or health status, though most participants were middle-aged or older. All but one study adjusted for possible confounders, including adiposity (e.g. BMI, waist circumference, waist-to-hip ratio) (Gao et al., 2013).

In comparing the highest and lowest categories of dairy intake, Gao et al. (2013) reported an 11% reduced risk of T2DM for total dairy consumption (RR: 0.89, 95% CI: 0.81-0.98, p value not reported, I^2 = 65%). This aligns with the results reported by Tong et al. (2011) and Schwingshackl et al. (2017) and equated to a non-linear dose response of a 6% reduction in risk with an increase of 200 g/d of total dairy (RR: 0.94, 95% CI: 0.91-0.97, p value not reported, I^2 = 51.6%). These reductions in risk may have be driven by low-fat dairy product consumption, as the authors identified a 19% reduced risk of T2DM associated with the highest category of low-fat dairy intake compared with the lowest (RR: 0.81, 95% 0.74-0.89, p value not reported, I^2 = 2%) or a 12% decrease in risk for a 200 g/d increase in low-fat dairy (RR: 0.88, 95% CI: 0.84-0.93, p value not reported, I^2 = 16.3%), yet no significant change in risk was associated with full-fat dairy consumption (Gao et al., 2013). Further, when evaluating milk exclusively, they noted an 18% reduction and 12% increase in risk of T2DM associated with the highest compared with the lowest intakes of low-fat milk and full-fat milk, respectively (low-fat milk: RR: 0.82, 95% CI: 0.69-0.97, p value not reported, I^2 = 40%; full-fat milk: RR: 1.12, 95% CI: 0.99-1.27, p value not reported, I^2 = 0%) (Gao et al., 2013). For every 200 g/d increase, this led to an 17% decrease and 27% increase in the

risk of T2DM attributable to low-fat and full-fat milk, respectively (low-fat milk: RR: 0.83, 95% CI: 0.70-1.00, p value not reported, I^2 = 14%; full-fat milk: RR: 1.27, 95% CI: 0.97-1.67, p value not reported, I^2 = 0%) (Gao et al., 2013).

Gao et al. (2013) also corroborated the previously reported benefits of yogurt, quantifying a 15% reduction in risk when comparing the highest and lowest categories of yogurt intake (RR: 0.85, 95% 0.75-0.97, p value not reported, I^2 = 55%); in contrast to other studies, they also cited a protective association with cheese, specifying an 18% reduction in risk when comparing the highest and lowest categories of cheese intake (RR: 0.82, 95% 0.77-0.87, p value not reported, I^2 = 0%). For every 50 g/d of yogurt, the authors reported a 9% reduction in risk of T2DM (RR: 0.91, 95% CI: 0.82-1.00, p value not reported, I^2 = 74%), and for every 30 g/d of cheese, a 20% reduction in risk (RR: 0.80, 95% CI: 0.69-0.93, p value not reported, I^2 = 59%) (Gao et al., 2013). While the authors conducted subgroup analyses inclusive of baseline BMI to assess sources of heterogeneity, Gao et al. (2013) did not mention conducting adjustments in meta-analysis for changes in measures of adiposity.

In contrast to the aforementioned studies, a meta-analysis by Aune et al. (2013a) identified possible protective associations of dairy across all dairy types and fat content. Using random-effects models, the authors evaluated 17 cohort studies with 426,055 adult participants from the United States, Europe, Asia and Australia (Aune et al., 2013a). All but 3 of the included studies adjusted for measures of adiposity, including BMI, waist circumference and/or hip circumference (Aune et al., 2013a). Study follow-up ranged from 5 to 23 years (Aune et al., 2013a). In their analysis, the authors identified significant reductions in T2DM risk associated with highest compared to lowest intakes of total dairy, low-fat dairy, low-fat/skim milk, cheese and yogurt (Aune et al., 2013a). Specifically, the highest intakes of total dairy were associated with a reduced risk of T2DM by 11% (RR: 0.89, 95% CI: 0.82-0.96, p value not reported, I^2 = 42%), while the incremental decrease in risk per 400 g/d was 7% (RR: 0.93, 95% CI: 0.87-0.99, p value not reported, I^2 = 33%, nonlinear) (Aune et al., 2013a). The highest intakes of low-fat dairy were associated with a reduced the risk of T2DM by 17% (RR: 0.83, 95% CI: 0.76-0.90, p value not reported, I^2 = 0%), and the incremental decrease per 200 g/d was 9% (RR: 0.91, 95% CI: 0.86-0.96, p value not

reported, I^2 = 40%, nonlinear) (Aune et al., 2013a). Similarly, the highest intakes of low-fat/skim milk were associated with reductions in risk of T2DM by 18% (RR: 0.82, 95% CI: 0.69-0.97, p value not reported, I^2 = 40%), and incremental decreases of 11% per 200 g/d (RR: 0.89, 95% CI: 0.84-0.95, p value not reported, I^2 = 0%, linear) (Aune et al., 2013a). Also, the highest intakes of cheese were associated with a 9% decrease in T2DM risk (RR: 0.91, 95% CI: 0.84-0.98, p value not reported, I^2 = 0%), and an incremental decrease of 8% per 50 g/d (RR: 0.92, 95% CI: 0.86-0.99, p value not reported, I^2 = 0%, nonlinear). Lastly, the highest intakes of yogurt resulted in a 14% reduction in T2DM risk (RR: 0.86, 95% CI: 0.75-0.98, p value not reported, I^2 = 59%) with an incremental decrease of 22% per 200 g/d (RR: 0.22, 95% CI: 0.60-1.02, p value not reported, I^2 = 70%, nonlinear) (Aune et al., 2013a). Aune et al. (2013a) did not find significant associations in the highest compared to the lowest intakes of high-fat dairy or total milk with T2DM risk, though there was evidence of 13% reduction in risk per 200 g/d of total milk (RR: 0.87, 95% CI: 0.72-1.04, p value not reported, I^2 = 94%, nonlinear inverse). Based on subgroup analyses, there were no significant differences in risk of T2DM associated with any dairy food intakes between studies that did and did not adjust for BMI (waist circumference, though it is unclear whether these adjustments were based on baseline measurements or changes over time (Aune et al., 2013a).

Dairy Consumption and Glucose Homeostasis: Experimental Evidence

While not without inconsistencies and limitations, epidemiological evidence largely suggests an inverse relationship between dairy intake and incident T2DM. This would imply protective effects of dairy on markers of glucose homeostasis. That said, experimental studies assessing the relationship between dairy food consumption and glucose tolerance and/or insulin resistance report varied results. Experimental studies disagree on the acute insulinotropic effect of dairy foods. Further, both meta-analyses and individual experimental studies are discordant concerning the impact of high compared with low intakes of dairy foods on measures of glucose homeostasis, including fasting glucose, fasting insulin, AUC glucose, AUC insulin, HOMA-IR and Matsuda-ISI.

Studies Evaluating the Acute Insulinotropic Effects

In terms of the acute biochemical impacts of dairy on plasma glucose and insulin response, both Ostman et al. (2001) and Nilsson et al. (2004) identified an insulinotropic effect, while Turner et al. (2015a) did not. That said, study populations differed among the studies, with Turner et al. (2015a) enrolling participants with overweight or obesity and the former two studies enrolling healthy participants with normal BMIs. Ostman et al. (2001) speculated that the acute effect of dairy consumption on these biochemical responses may be influenced by the baseline metabolic status of the population rather than consistently producing the same generalizable effect across all individuals. Accordingly, the insulinotropic effects of dairy may differ in healthy participants compared to those with overweight or obesity based on BMI.

More specifically, Ostman et al. (2001) randomized ten healthy adult participants in Sweden to treatment orders within two related studies in order to evaluate the glycemic and insulinemic responses to 1) regular milk, two fermented milk products, and a lactose solution in comparison to white-wheat bread control and 2) white-wheat bread with either added unfermented milk and cucumber or fermented yogurt and pickled cucumber in comparison to a white-wheat bread control. Other than specifying the following inclusion criteria, the authors did not provide baseline participant characteristics for any other measures: “healthy,” non-smokers, BMI within normal range, and not taking any drug therapies (Östman et al., 2001). In the first study, the researchers randomized participants to treatment order on 5 different occasions over a period of 3 months (Östman et al., 2001). They found that while the glycemic indices were significantly lower among both types of milk products (regular milk, mean +/- SEM: 30 +/- 4, fermented milk: 15 +/- 3) in comparison to the lactose solution (68 +/- 8) and white-wheat bread (100), the postprandial insulinemic index for the milk products (regular milk: 90 +/- 8, fermented milk: 98 +/- 11, 97 +/- 13) was commensurate to the index for white-wheat bread (100) and significantly higher than the index for the lactose solution (50 +/-6) (all $p < 0.05$) (Östman et al., 2001). In other words, the regular and fermented milk products exhibited both low glycemic and high insulinemic indices, running counter to the positive linear associations most often seen with other low glycemic index foods (Östman et al., 2001). Between the regular and fermented milk products, there were no significant differences in either the glycemic or insulinemic indices (Östman et al., 2001). Further, the insulin response following the consumption of

fermented milk surpassed that of pure lactose, which Ostman et al. (2001) attributed to some other factor found within the dairy matrix. While lactic acid has reduced both the glycemic and insulinemic indices in other foods, these results comparing postprandial outcomes for regular and fermented milk did not reflect this expected attenuation, and other factors must have contributed to these responses (Östman et al., 2001.

In the second study, Ostman et al. (2001) randomized participants to treatment order on 3 different occasions over a period of 3 months. In contrast to the findings from the first study, the authors noted a significantly lower glycemic index following the acidic meal (mean +/- SEM: 55 +/- 7) compared with the control and non-acidic meals (control: 100, non-acidic: 79 +/- 10, all $p < 0.05$), as well as a significantly lower insulinemic index compared with both meals as well (acidic: 79 +/- 11, control: 100, non-acidic: 117 +/- 12, all $p < 0.05$) (Östman et al., 2001). Based on the differences in insulinemic indices following consumption of fermented milk products in study 1 (lactose) and both fermented milk and pickled cucumber in study 2 (lactose + acetic acid), the researchers hypothesized that the acetic acid in pickled cucumber was responsible for the variable insulin response due to its propensity to slow gastric emptying (Östman et al., 2001). In totality, these results support an insulinotropic effect of dairy products and a beneficial effect of acetic, but not lactic, acid on postprandial changes in plasma glucose and insulin.

Also among healthy participants, Nilsson et al. (2004) conducted a feeding experiment in order to assess the acute postprandial responses to different sources of protein. Twelve participants consumed 7 test meals in random order with at least one week separating the provision of each meal (Nilsson et al., 2004). Individuals participating in the study were healthy, non-smokers with BMIs in the normal range, who had normal fasting blood glucose at baseline, no evidence of lactose malabsorption and were not taking any prescription drugs (Nilsson et al., 2004). The test meals included reconstituted milk, cheese, whey, cod, and gluten with constant amounts of lactose and were consumed steadily over a duration of 12 minutes (Nilsson et al., 2004). After measuring postprandial plasma glucose and insulin areas under the curve (AUCs), the researchers identified that milk and whey protein meals drove the greatest reductions in plasma glucose AUC over 90 minutes as compared to the reference meal (milk: -62%, whey: -57%, p <

0.05) (Nilsson et al., 2004). Only the whey protein meal exhibited a significant increase in insulin AUC over 90 minutes as compared to the reference meal (whey: +90%, $p < 0.05$), although milk and cheese both exhibited non-significant increases compared to the reference (milk: +24%, cheese: +25%) (Nilsson et al., 2004). These findings resulted in milk and whey having significantly higher insulinogenic indices compared to the reference and all other protein meals (milk: 0.55 +/- 0.08, whey: 0.72 +/- 0.2, $p < 0.05$) (Nilsson et al., 2004). Accordingly, Nilsson et al.'s (2004) findings are consistent with those of Ostman et al. (2001) in corroborating an insulinotropic effect of dairy foods. Given the differences in insulin response between the milk and whey meals, Nilsson et al. (2004) went further to suggest that soluble milk proteins, such as whey, may be important components contributing to the insulinotropic effects of dairy foods.

In contrast, Turner et al. (2015a) enrolled 43 adults with overweight or obesity based on BMI in a study designed to evaluate acute postprandial insulin response following two isoenergetic test meals and did not identify an insulinotropic effect of dairy. Participants were randomized to test meal order inclusive of a low-fat dairy meal and an isoenergetic lean red meat meal, both with comparable macronutrient compositions (Turner et al., 2015a). Meals were consumed in the morning one week apart with comparable foods being consumed over the 24-hour lead-in periods (Turner et al., 2015a). The dairy meal included low fat milk, yogurt, and cheese (plus whole grain bread and margarine), while the red meat meal included various forms of beef fillet (plus whole grain bread, salted butter and orange juice) (Turner et al., 2015a). In their analysis, the researchers found that postprandial glucose AUC did not differ between test meals; nor did postprandial insulin AUC. However, the dairy meal produced a 1.35 mmol/L*3h higher average postprandial glucose iAUC (dairy mean +/- SEM: 2.23 +/- 0.49 mmol/L*3h, red meat: 0.88 +/- 0.57, $p = 0.004$), while simultaneously driving a comparable postprandial insulin iAUC to the red meat meal (dairy mean +/- SEM: 167.5 +/- 24.1 mU/L*3h, red meat: 159.6 +/- 20.0, p = not significant) (Turner et al., 2015a). These results remained significant after adjustments for sex, BMI, and glucose tolerance (normal versus impaired) (Turner et al., 2015a). Therefore, while Ostman et al. (2001) and Nilsson et al. (2004) noted an insulinotropic effect of dairy among healthy participants, Turner et al. (2015a) did not uncover a similar pattern when comparing dairy with lean red meat among overweight or obese participants. Accordingly, though dairy consumption may induce disproportionate increases in

insulin secretion in some individuals, this may not happen uniformly across all populations and may be influenced by other factors, such as overall metabolic status or other dietary constituents.

Studies Evaluating Measures of Glucose Homeostasis

Beyond evaluating the insulinotropic effect of dairy foods, other experimental studies have evaluated the influence of dairy consumption on other markers of glucose homeostasis, including insulin sensitivity and insulin resistance. Meta-analyses and individual trials vary in their conclusions on the effect of high versus low dairy consumption on these measures. As exemplified in the disparate meta-analysis findings from Benatar et al. (2013) and O'Connor et al. (2019), the duration of dairy interventions may play a role in determining the relative protective effects of dairy on insulin sensitivity. Individual studies exhibit a range of alignment with these aggregated conclusions, lending a degree of uncertainty to the results.

In order to assess the impact of dairy consumption on cardiometabolic risk factors, Benatar et al. (2013) conducted a meta-analysis of 20 randomized controlled trials inclusive of 1,677 healthy adult participants without diabetes at baseline from Spain, North America, New Zealand, Malaysia, Australia, China, Greece and Puerto Rico. When comparing higher dairy intakes relative to a usual diet in random effects modeling, the authors identified a nonsignificant mean difference of 1.32 mg/dL in fasting glucose (MD: 1.32, 95% CI: 0.19-2.45, $p = 0.02$, $I^2 = 25\%$) (Benatar et al., 2013). When stratified based on baseline BMI classification, the resulting changes in fasting glucose were comparable (normal BMI MD: 0.36, 95% CI: -2.70 to 3.42; overweight/obese BMI MD: 0.36, 95% CI: -1.08 to 1.80) (Benatar et al., 2013). Additionally, though the authors also reported a nonsignificant 0.94 unit reduction in HOMA-IR with higher levels of dairy consumption, these results exhibited material heterogeneity due to the outcomes of two small studies (MD: -0.94, 95% CI: -1.93 to 0.04, $p = 0.06$, $I^2 = 92\%$) (Benatar et al., 2013). Similarly, when stratified based on BMI classification, the resulting changes in HOMA-IR for each strata were not significantly different (normal BMI MD: -0.16, 95% CI: -0.56 to 0.24; overweight/obese BMI MD: -0.79, 95% CI: -1.94 to 0.37) (Benatar et al., 2013). Despite this lack of significant effect of increased dairy intakes and fasting glucose or HOMA-IR, Benatar et al. (2013) noted a mean increase in body weight of 0.60 kg (95% CI: 0.30-0.90, $p < 0.0001$) and no changes in waist circumference when comparing baseline

to follow-up measures; the increases in body weight were observed independent of intervention dairy fat content and participant baseline BMI. Accordingly, while Benatar et al. (2013) found minimal effects of increased dairy intake on indicators of glucose homeostasis, it is possible their results were influenced by differential changes in body weight and/or waist circumference from baseline to follow-up between participants categorized as having either normal or overweight/obese body types based on BMI at baseline.

Experimental studies both preceding and following Benatar et al.'s (2013) meta-analysis fully support, partially support or contradict the authors' findings, though the bulk of research is either in full or partial agreement. Individual experimental studies aligned with Benatar et al.'s findings include Tanaka et al. (2014), Thompson et al. (2005), Raziani et al. (2016), Dugan et al. (2014), van Meijl and Mensink (2011), Wennersberg et al. (2009), van Loan et al. (2011), Crichton et al. (2012), O'Connor et al. (2019), Gardner et al. (2007), and Engel et al. (2018). These studies enrolled participants with overweight, obesity or metabolic syndrome risk factors and identified no significant effects of dairy interventions on measures of glucose homeostasis. A summary of their main findings follows.

Tanaka et al. (2014) sought to evaluate the impact of dairy (milk, milk + yogurt – fat content unspecified) consumption on metabolic syndrome diagnostic criteria, including waist circumference, serum lipids, blood pressure and fasting blood glucose. The researchers enrolled 200 Japanese men with two or more risk factors for metabolic syndrome and without diabetes in a multicenter, parallel randomized intervention trial for a duration of 24 weeks (Tanaka et al., 2014). 75% of the participants (n = 149) were classified as overweight or obese based on baseline BMI (Tanaka et al., 2014). The authors stratified participants by age and BMI and randomized them to either an intervention group (dairy products + nutritional counseling) or control group (counseling only) (Tanaka et al., 2014). Participants randomized to the dairy intervention group could choose between 400 g/d of milk or a combination of milk and yogurt, all of which was provided by the study (Tanaka et al., 2014). In their analyses, the researchers employed linear models to examine effect modification by variables including BMI, among others (Tanaka et al., 2014).

After 24 weeks, both groups experienced significant changes (improvements) in all primary and secondary end points, except fasting triglycerides (Tanaka et al., 2014). However, in comparing mean changes, Tanaka et al. (2014) observed significantly less pronounced improvements in the dairy group compared to the intervention group: +1.7 cm for waist circumference (dairy: mean: -1.5 cm, SD: 4.1, $p < 0.01$; control: mean: -3.2, SD: 4.1, $p < 0.01$; overall $p < 0.01$), +1.5 kg for body weight (dairy: mean: -1.1 kg, SD: 3.3, $p < 0.01$; control: mean: -2.6, SD: 3.8, $p < 0.01$; overall $p < 0.01$), +0.9% points for percent body fat (dairy: mean: -1.4%, SD: 1.9, $p < 0.01$; control: mean: -2.3, SD: 2.3, $p < 0.01$; overall $p < 0.01$), and +7.7 mg/dL for LDL cholesterol (dairy: mean: -4.6 mg/dL, SD: 19.5, $p = 0.02$; control: mean: -12.3, SD: 20.4, $p < 0.01$; overall $p < 0.01$). Tanaka et al. (2014) also noted nonsignificant intergroup differences of differences in other markers of the metabolic syndrome, including fasting blood glucose (dairy: mean: -2.2 mg/dL, SD: 6.8, $p < 0.01$; control: mean: -3.1, SD: 5.3, $p < 0.01$; overall $p = 0.31$) and HbA1C (dairy: mean: -0.1%, SD: 0.2, $p < 0.01$; control: mean: -0.2, SD: 0.2, $p < 0.01$; overall $p = 0.03$).

However, for both waist circumference and fasting blood glucose, the authors found significant differences based on BMI classification. Across all participants in both groups, those classified as having normal BMIs experienced a mean decrease in waist circumference by -0.8 cm (95% CI: -3.1 to 1.6) and decrease in fasting blood glucose by 2.2 mg/dL (95% CI: -5.6 to 1.2), while those classified as having an overweight/obese BMI experienced increases in both measures that were significantly different than those experienced by those with normal BMIs (WC MD: 2.7 cm, 95% CI: 1.3-4.0; FBG mean: 2.0, 95% CI: 0.0-4.0; $p = 0.01$ and $p = 0.04$, respectively) (Tanaka et al., 2014). Accordingly, in terms of the endpoints related to glucose homeostasis, the authors did not identify a significantly greater improvement in fasting blood glucose or HbA1C among the dairy intervention group compared to the control, and they found significantly reduced improvements among the dairy intervention group in terms of measures of adiposity, such as waist circumference, body weight and % body fat (Tanaka et al., 2014).

Separately, Thompson et al. (2005) assessed the extent to which a high dairy or high dairy + fiber dietary intervention (dairy fat content unspecified) impacted weight loss and secondary endpoints, including fasting glucose, fasting insulin, 2-hour glucose and 2-hour insulin. For a study period of 48 weeks, the

researchers enrolled 90 adult participants (BMI 30-40 kg/m^2) who were stratified by sex and randomized to either 1) one of the two dairy dietary interventions or 2) an isocaloric control diet; 72 participants completed the study (Thompson et al., 2005). All three diets provided a calorie deficit based on estimated individual energy expenditure using the Harris-Benedict equation (Thompson et al., 2005). There were no significant differences in participant characteristics at baseline for variables including body weight, BMI, waist circumference, waist to hip ratio, fasting glucose and fasting insulin (Thompson et al., 2005).

In comparing the three groups, the authors reported no significant differences in fasting glucose or fasting insulin between groups ($p = 0.27$ and $p = 0.67$, respectively) (Thompson et al., 2005). The measures of 2-hour glucose and 2-hour insulin were also not different between groups ($p = 0.42$ and $p = 0.55$, respectively) (Thompson et al., 2005). Further, while all three groups exhibited weight loss, fat loss and reductions in waist circumference, the differences between groups were not significant (Thompson et al., 2005). Accordingly, although neither Tanaka et al. (2014) nor Thompson et al. (2005) specified the dairy fat content of study foods, both identified no significant independent impact of dairy on markers of glycemic tolerance or insulin sensitivity.

In a parallel controlled trial in Denmark, Raziani et al. (2016) randomized 164 adult participants with more than two risk factors for the metabolic syndrome, including elevated waist circumference, to dietary interventions including regular fat cheese, reduced-fat cheese or a carbohydrate control for a 12-week period. The researchers sought to compare the effects of these dietary interventions on LDL cholesterol and metabolic syndrome risk factors, including markers of glucose homeostasis (plasma glucose, insulin and HOMA-IR) (Raziani et al., 2016). Study foods were provided to participants, and non-study foods comprising the rest of their habitual diets were uncontrolled (Raziani et al., 2016). All statistical models adjusted for BMI and changes in body fat (Raziani et al., 2016). In comparing the effects of the regular cheese intervention to the effects of the reduced-fat cheese intervention and control group over the 12-week period, Raziani et al. (2016) identified no significant differences in measures of changes in glucose homeostasis, including fasting glucose, fasting insulin or HOMA-IR (all $p > 0.39$). Unlike Thompson et al. (2005), Raziani et al. (2016) also reported no significant differential changes across groups in measures

of adiposity, including body weight, waist circumference, BMI, fat mass, % fat and lean body mass (all p > 0.16) (Raziani et al., 2016).

Similarly, Dugan et al. (2014) evaluated the effect of a low-fat dairy intervention, inclusive of milk, yogurt and cheese, compared to an isocaloric carbohydrate intervention (granola bar, juice) on markers of metabolic syndrome in a 16-week randomized controlled crossover trial among 37 adult participants with the metabolic syndrome who were low dairy consumers and weight-stable. Overall, the authors identified no significant differences between interventions on measures of fasting glucose, insulin or HOMA-IR (p values not reported) (Dugan et al., 2014). However, the low-fat dairy intervention resulted in significant decreases in both waist circumference and BMI compared to the control diet (WC: low-fat dairy: 107.0 +/- 11.8 versus control: 108.3 +/- 13.0, p = 0.006; BMI: low-fat dairy: 32.7 +/- 20.0 versus control: 33.0 +/- 20.2, p = 0.002) (Dugan et al., 2014). These decreases in waist circumference and BMI were not adjusted for in statistical analysis and therefore, may have influenced the reported measures of glucose homeostasis.

Additionally, van Meijl and Mensink (2011) sought to assess the impact of low-fat dairy intake on metabolic risk factors. In an 18-week randomized crossover trial, the researchers enrolled 40 overweight or obese adult participants who consumed in random order isocaloric low-fat dairy products (milk + yogurt) during the intervention period and fruit juice plus fruit biscuits during the control period (van Meijl & Mensink, 2011). In alignment with the above, van Meijl and Mensink (2011) also noted no significant differences between the two periods for plasma glucose, plasma insulin and HOMA-IR (p = 0.851, p = 0.371, p = 0.433, respectively).

In a multicenter, randomized, parallel intervention study, Wennersberg et al. (2009) explored the effect of increased dairy consumption on body composition and characteristics of the metabolic syndrome over a 6-month study period. Enrolling 121 adults meeting 2+ metabolic syndrome criteria who were low dairy users from Finland, Norway and Sweden, the authors randomized participants to intervention or control groups, allowing the intervention group to consume 3-5 daily servings of a variety of dairy foods of each

individual's choosing and the control group to continue their habitual diet (Wennersberg et al., 2009). After 6 months, there were no significant differences between groups in changes in fasting glucose or HbA1C ($p = 0.399$ and $p = 0.276$, respectively), although there was a significant decrease in HOMA-IR in the dairy intervention group compared to the control group (dairy: -0.6 +/- 6.2 versus control: 3.1 +/- 12.2, $p = 0.037$) (Wennersberg et al., 2009). The authors suggested these findings resulted from an impairment in insulin sensitivity among the control group, rather than an improvement in insulin sensitivity among the dairy group, as there was a significant increase in fasting insulin in the control group compared to the dairy intervention group when including country as a covariate (control: 7.8 pmol/L +/- 22.0 versus dairy: -1.6 +/- 20.7, $p = 0.033$) (Wennersberg et al., 2009). These changes in fasting insulin and HOMA-IR occurred independent of changes in adiposity, as both groups experienced similar, slight decreases in body weight, BMI, waist circumference and percent body fat ($p > 0.632$) (Wennersberg et al., 2009). Differences in adiposity occurred in tandem with differential, though nonsignificant changes in energy intake according to 3-day food records at the end of the 6-month intervention period (control: -150 kJ +/- 220 versus dairy: 684 +/- 2487, $p = 0.07$). Accordingly, with the exception of the aforementioned changes in HOMA-IR attributable to the control group, Wennersberg et al. (2009) identified no significant impact of the dairy intervention on measures of glucose homeostasis.

In a similar, parallel controlled feeding study primarily evaluating the impact of dairy on body composition and weight loss in the United States, van Loan et al. (2011) randomized 78 overweight or obese adults with habitually low dairy intake to adequate (3-4 servings) or low dairy (</= 1 serving) dietary intervention groups with overall energy restriction (-500 kcal/d) for 12 weeks. Participants were pair-matched according to percent body fat at baseline prior to randomization (Van Loan et al., 2011). All foods were supplied to participants, and study dairy products included milk, yogurt and cheese (Van Loan et al., 2011). Between the two groups, the researchers identified comparable mean changes in fasting glucose (adequate: +0.2 mmol/L, low: +0.1 mmol/L) and HOMA (adequate: -0.4, low: -0.2) at week 12 compared to baseline (p values not reported) (Van Loan et al., 2011). However, though not noted as significant, the overall mean decrease in fasting insulin among the adequate dairy group (-41.5 pmol/L) was double that of the low dairy group (-20 pmol/L, p value not reported). Moreover, both groups experienced comparably

significant decreases in body weight (adequate: -6.3 kg +/- 2.9, low: -6.0 +/- 3.1, both p = 0.01;), body fat (adequate: -5.2 kg +/- 2.8, low: -5.1 +/- 3.0, both p = 0.01) and intra-abdominal adipose tissue (adequate: -8.5 cc +/- 6.6, low: -8.9 +/- 8.5, both p = 0.01), suggesting a greater influence of time on these outcomes than the respective interventions (Van Loan et al., 2011). While van Loan et al. (2011) did not specifically address the intergroup difference in change in fasting insulin, it is plausible that the additional 5% decrease in body weight experienced by the adequate dairy group may have resulted in a disproportionally large decrease in fasting insulin..

In an additional trial among overweight and obese, low consumers of dairy in Australia, Crichton et al. (2012) assessed the impact of a reduced fat dairy, non-restrictive diet on cardiometabolic health over a 12-month period. Employing a randomized cross-over study design, the researchers stratified 71 participants by age and sex and then randomized them to one of two groups, which determined the sequence of which the participants would consume either a high dairy or low dairy diet for a duration of 6 months each (Crichton et al., 2012). The high dairy intervention required participants to consume 4 servings/d of reduced fat dairy, while the low dairy intervention (control) limited participants to consuming </= 1 serving/d of dairy (Crichton et al., 2012). The reduced fat dairy products were provided and included milk, flavored milk, yogurt, and custard (Crichton et al., 2012). At the end of each intervention period, body weight, BMI, waist circumference, percent body fat and fasting glucose were comparable between the two interventions (p = 0.18-0.67) (Crichton et al., 2012). However, when evaluating the mean change in these variables during each of the periods, there were significant differences between the interventions in terms of body weight (HD mean change: 1.8 kg +/- 0.4 versus LD: 0.2 +/- 0.5, p = 0.01), BMI (HD mean change: 0.6 kg/m^2 +/- 0.1 versus LD: 0.0003 +/- 0.2, p = 0.01), and hip circumference (HD mean change: 1.5 cm +/- 0.4 versus LD: 0.005 +/- 0.4, p = 0.03); conversely, mean changes in waist circumference (p = 0.14), percent body fat (p = 0.28) and plasma glucose (p = 0.87) remained nonsignificant (Crichton et al., 2012). Additionally, based on self-reported 3-day weighed food records, Crichton et al. (2012) noted significant differences in energy intake between the two periods with records from the high dairy intervention surpassing those from the low dairy intervention by 1120 kJ/d +/- 360 (p < 0.01). The authors noted the expected average weight gain associated with this increase in daily energy during the high

dairy period was 6 kg over six months, which was not realized (actual mean +/- SEM: 1.8 kg +/- 0.4) and which they attributed to decreased fat absorption related to the increased formation of calcium soaps in the intestines (unconfirmed) (Crichton et al., 2012). Accordingly, the inclusion of higher amounts of dairy in an individual's diet over a duration of 6 months increased energy intake and some measures of adiposity (i.e. body weight, BMI), however did not significantly influence fasting blood glucose levels, waist circumference or percent body fat (Crichton et al., 2012).

A similar randomized controlled cross-over trial from O'Connor et al. (2019) enrolled 27 hyperinsulinemic and/or prediabetic Canadian adults with overweight or obesity based on BMI. Participants were randomized to high dairy and adequate dairy interventions for 6 weeks each, plus an intermediary 6-week wash-out period, in order to assess the relative impacts on risk factors for T2DM, including insulin sensitivity, insulin secretion and beta-cell function (O'Connor et al., 2019). The high dairy diet included 4-5 servings/d of dairy products (no fat restrictions), while the adequate dairy diet (and wash-out period) included </= 2 servings/d of dairy products of each participant's choosing, implying that researchers exerted limited control over the dietary intervention (O'Connor et al., 2019). In alignment with the findings from van Loan et al. and Crichton et al., O'Connor et al. (2019) also identified no differences in the changes in fasting glucose, fasting insulin, HOMA-IR, Matsuda insulin sensitivity index (ISI), insulinogenic index and disposition index between the high dairy and adequate dairy interventions after 6 weeks (p values from 0.46-0.96). However, there were substantial interindividual differences in changes in insulin sensitivity and resistance, ranging from -12 to +2 for high dairy Matsuda ISI, -4 to +6 for adequate dairy Matsuda ISI, -2 to +7 for high dairy HOMA-IR, and -4 to +9 for adequate dairy HOMA-IR (O'Connor et al., 2019). This interindividual variability could have been driven by many factors, such as dairy product selection, other components of the diet, genetics, etc. (O'Connor et al., 2019). At the same time, the authors noted no differences between groups in terms of the changes in body weight, BMI, waist circumference and percent body fat over the 6-week intervention period (p values from 0.66-0.95). Accordingly, while O'Connor et al. (2019) did not identify a significant advantage or disadvantage attributable to consuming a higher amount of dairy on measures of glucose homeostasis, this lack of

effect occurred independently of changes in measures of adiposity and may be influenced by an underlying pattern of heterogeneous responses across participants.

In addition to evaluating the impact of high versus low intakes of dairy on glucose control, other experimental studies have assessed dairy interventions compared to other products, such as soy milk and sugar-sweetened beverages. In terms of the former, Gardner et al. (2007) conducted a randomized, three-arm cross-over trial to explore the impact of two soy milk beverages (whole soy bean, soy protein isolate) and low-fat dairy milk on plasma lipids, insulin and glucose in the United States. The researchers randomized 31 hypercholesterolemic adults without diagnosed T2DM to one of three treatment orders, starting with either whole bean soy milk, soy protein isolate milk or dairy milk (Gardner et al., 2007). Each intervention lasted for four weeks and was separated by a 4-week wash-out period (Gardner et al., 2007). The interventions were designed to deliver the same amount of protein per day (25 g), though varied in terms of total energy, fat, cholesterol, fiber and total ounces per day (Gardner et al., 2007). Among the 28 participants who completed the study, Gardner et al. (2007) identified no differences in insulin AUC or glucose (at time 0, 1 or 2 hours) among the interventions, as well as in comparison to the baseline measurements ($p = 0.9$, 0.4, 0.8 and 0.9, respectively). Moreover, all baseline values for fasting insulin and glucose were within the normal range (Insulin AUC: 44 +/- 21, Glucose-Fasting: 90 +/- 7 mg/dL, Glucose-1 hour: 138 +/- 53 mg/dL, Glucose-2 hour: 112 +/- 45 mg/dL) (Gardner et al., 2007). While the authors did not mention changes in BMI or body composition across the interventions, they did identify significant increases in daily energy intake among the milk interventions compared to baseline values (baseline mean +/- SEM: 1870 kcal +/- 523, whole bean: 2068 +/- 515, protein isolate: 1972 +/- 545, dairy milk: 2046 +/- 541, $p = 0.02$), which arguably could have influenced anthropometrics (Gardner et al., 2007). However, an increase in adiposity related to excess caloric intake would purportedly increase both insulin AUC and fasting glucose measures, which was not the case in this study. Accordingly, the authors derived no significant impact of soy or dairy milk on fasting insulin or glucose among the studied population, despite an overall increase in caloric intake.

In order to assess the relative impact of milk on insulin sensitivity, Engel et al. (2018) conducted a secondary data analysis of a 6-month randomized control trial with 60 healthy adult participants with overweight or obesity based on BMI in Denmark. Researchers randomized participants to consume 1 L/d of either 1.5% dairy milk, sucrose-sweetened cola, aspartame-sweetened cola or still mineral water (Engel et al., 2018). Participants consumed their assigned test beverage along with their habitual diet and were allowed to also consume additional water, coffee, tea and alcohol (Engel et al., 2018). In their analyses, the authors adjusted for covariates, including both baseline BMI and change in fat mass (Engel et al., 2018).

Across the interventions, Engel et al. (2018) identified no time x treatment effect or overall treatment effect for glucose or insulin (glucose: $p = 0.601$ and 0.835; insulin: $p = 0.349$ and 0.552; respectively). Concurrently, body weight, BMI and fat mass (significance unknown) were not differentially changed between groups (Engel et al., 2018). Similarly, based on 7-day weighed dietary records, there were significant differences among groups for fat, carbohydrates and protein (all % energy; $p < 0.01$, $p < 0.001$, $p < 0.001$, respectively), though not for other measured pre/post dietary factors (Engel et al., 2018). The authors concluded that there was no differential impact of dairy compared to the other test beverages on glucose homeostasis among healthy adults with overweight or obesity based on BMI (Engel et al., 2018).

In contrast to the above, other experimental studies are only partially in agreement with Benatar et al.'s results, including those from St-Onge et al. (2009), Stancliffe et al. (2011), and Turner et al. (2015b). These authors also enrolled individuals with overweight or obesity and similarly found no changes in fasting glucose. However, they did identify significant differences in fasting insulin and therefore, insulin sensitivity and insulin resistance in response to dairy interventions. The former two studies noted improvements in insulin sensitivity, while the latter noted decreases in insulin senstivity.

In a randomized parallel intervention trial among children aged 8-10 years with BMI and waist circumference above the 95th percentile for age in the United States, St-Onge et al. (2009) evaluated the effect of high versus low dairy intake on weight loss and metabolic risk factors over a 16-week period.

Children randomized to the high dairy group consumed an average of 3 servings of skim milk per day and 1 serving of low fat chocolate milk per day, while children randomized to the low dairy group consumed an average of 3 servings of sugar-sweetened beverages per day, and 0.6 servings of skim milk and 0.7 servings of low fat chocolate milk per week (St-Onge et al., 2009).

Among the 45 children who completed the study, there were no significant effects of the interventions on fasting measures of plasma glucose or insulin (St-Onge et al., 2009). However, the high dairy diet did result in a significant decrease in insulin AUC as measured via OGTT compared to the low dairy diet ($p = 0.044$), indicating a significant decrease in insulin output in reaction to a glucose challenge (St-Onge et al., 2009). This occurred independent of changes in waist circumference, percent body fat and BMI (St-Onge et al., 2009). Therefore, St-Onge et al. (2009) concluded that increased consumption of dairy over a period of 16 weeks led to an improvement in insulin sensitivity among this population, despite its relative lack of effect on fasting glucose, fasting insulin, body weight and body composition.

Similarly, in a randomized parallel intervention trial in the United States, Stancliffe et al. (2011) sought to assess the immediate (1 week) and longer term (4-12 weeks) effects of adequate and low dairy consumption on oxidative stress and inflammation; the authors also measured plasma glucose, insulin and fasting lipid concentrations. Stancliffe et al. (2011) enrolled 40 overweight or obese, low dairy consuming adult participants with the metabolic syndrome, who were randomized to consume either >3.5 or <0.5 servings of dairy per day in conjunction with a weight-maintenance diet over a 12 week period. Participants randomized to the adequate dairy group were supplied with 3 servings of dairy per day (inclusive of milk and/or yogurt), while participants in the low dairy group were supplied with 3 daily servings of other prepackaged foods (e.g. lunch meat, fruit cups, granola bars, etc.) (Stancliffe et al., 2011). Based on each participant's selection of study foods, adjustments were made to the remainder of their diet to maintain a macronutrient composition that was comparable to the average American diet compared to a diet low in dairy (Stancliffe et al., 2011).

At the end of the 12 week intervention period, the researchers identified that while neither intervention significantly impacted plasma glucose, the adequate dairy diet was associated with significant decreases in both plasma insulin and HOMA-IR beginning at 1 week and persisting through the end of 12 weeks (Day 7 insulin: -3.51 +/- 1.18 μU/mL; Day 7 HOMA-IR: -0.71 +/- 0.35; both $p < 0.05$) (Stancliffe et al., 2011). The adequate dairy diet also resulted in a significant 1.3 kg decrease in fat mass, driven by decreases in trunk fat mass, and 2.8 cm decrease in waist circumference at the end of 12 weeks (fat mass: SD: +/- 0.9; $p < 0.05$; WC: SD: +/- 0.8, $p < 0.03$); these were the only significant anthropometric differences attributable to diet (Stancliffe et al., 2011). Nevertheless, the participants' obesity status based on BMI did not influence the significance of the changes in plasma insulin and HOMA-IR previously stated (Stancliffe et al., 2011). Therefore, these results suggested that consuming adequate dairy contributed to increases in insulin sensitivity among the study population (Stancliffe et al., 2011).

Conversely, in a randomized cross-over trial in Australia, Turner et al. (2015b) evaluated the impact of diets high in lean red meat (>/=200 g/d), high in low-fat dairy (4-6 servings milk, cheese, yogurt, and/or custard) and high in neither lean red meat (0 g/d), nor low-fat dairy (<1 serving/d) on measures of insulin sensitivity. The researchers enrolled 73 adults with overweight or obesity based on BMI who were grouped based on glucose tolerance (normal versus impaired) and randomized to three-arm treatment orders comprised of two, 4-week intervention periods and one, 4-week control period, separated by 2-week washout periods (Turner et al., 2015b). Among the 47 participants who completed the study, Turner et al. (2015b) identified no significant changes in fasting glucose among the interventions, however fasting insulin was significantly higher in the high dairy diet compared with the high red meat diet and the control diet (6.6 mU/L +/- 4.1 versus 5.5 +/- 2.4 versus 5.78 +/- 2.9, $p < 0.01$). There were no differences in fasting insulin between the high red met diet and the control, and adjustments for BMI and change in fat mass did not impact these endpoints (Turner et al., 2015b). In accordance with this significantly higher fasting insulin in the high dairy group, insulin resistance, as measured by HOMA-IR, also increased by 16% compared to the red meat and control groups (1.55 +/- 1.0 versus 1.30 +/- 0.7 versus 1.34 +/- 0.7, $p < 0.05$), while insulin sensitivity, as measured by Matsuda ISI, was reduced (7.28 +/- 3.89 versus 7.89 +/- 4.1 versus 7.95 +/- 5.64, $p < 0.05$) (Turner et al., 2015b). Accordingly, in contrast to St-Onge et al. (2009)

and Stancliffe et al. (2011), Turner et al. (2015b) concluded that a diet rich in dairy decreases insulin sensitivity compared to diets rich in lean meat or low in both meat and dairy. This finding was not influenced by changes in adiposity.

Despite the aforementioned studies in full or partial agreement with the meta-analysis from Benatar et al. (2013), at least one study reported dissimilar findings, though it may have been influenced by the selection of study control. Specifically, Maki et al. (2015) identified a favorable effect of dairy on measures of glucose homeostasis, specifically insulin resistance and glucose disposal.

In a 14-week randomized controlled cross-over study that expanded dietary interventions beyond fluids, Maki et al. (2015) explored the effects of dairy and sugar-sweetened products on insulin sensitivity and beta-cell function in adults with high, baseline sugar-sweetened beverage consumption and risk factors for the development of T2DM (i.e. impaired fasting glucose, elevated HbA1C, or at risk for developing T2DM based on the San Antonio Heart Study prediction equation) in the United States. The researchers randomized 43 participants to one of two treatment orders, with each treatment being comprised of either dairy or sugar-sweetened products (Maki et al., 2015). Participants consumed study foods in conjunction with their habitual diet (Maki et al., 2015). Study dairy products included 2% milk and low-fat yogurt without added sugar, while study sugar-sweetened products included non-diet soda and non-diet pudding (Maki et al., 2015). The authors assessed fasting glucose and insulin responses via liquid meal tolerance tests at baseline and the end of each 6-week intervention period (Maki et al., 2015).

In comparing dairy product consumption to that of sugar-sweetened products, Maki et al. (2015) identified significant differential changes between treatment arms in fasting insulin ($p = 0.036$), disposition index ($p = 0.011$) and HOMA2-%S (insulin sensitivity; $p = 0.009$). Between the two interventions, there were no significant differential changes in fasting glucose, 2-hour glucose, glucose AUC, 2-hour insulin, insulin AUC, Matsuda ISI, 30-min change in insulin/change in glucose, insulin secretion index and HOMA2-%B (beta cell function) (Maki et al., 2015). Additionally, there were no significant differential changes in body weight or waist circumference between the two interventions. There were, however, differences between

groups in other dietary factors, with the dairy product intervention leading to significant decreases in carbohydrate ($p < 0.05$), sugar ($p < 0.01$), and fiber ($p < 0.05$) intakes and significant increases in protein ($p < 0.05$) and calcium ($p < 0.05$) (Maki et al., 2015). These differences in diet during each intervention, which were not adjusted for, may have influenced the author's results. In sum, these significant differences in fasting insulin and insulin sensitivity favored the dairy intervention over the sugar-sweetened product; however, these results appeared to be more highly driven by the adverse effects of the sugar-sweetened product intervention rather than overt beneficial effects of dairy products (Maki et al., 2015). Moreover, the authors did not adjust for baseline glucose tolerance, which may have also skewed their results.

Studies Comparing Short-term and Long-term Effects on Glucose Homeostasis

As noted previously, meta-analyses from Benatar et al. (2013) and O'Connor et al. (2019) differed in their conclusions on the effects of dairy intake on glucose homeostasis, suggesting the duration of dairy interventions may play a role in evaluating the relative protective effects. Similar to the previously described individual studies that exhibited a range of evidence largely supporting Benatar et al.'s (2013) findings, other individual studies also stand in support of the conclusions made by O'Connor et al. (2019).

Compared to Benatar et al. (2013), the meta-analysis by O'Connor et al. (2019) is a more recent evaluation of experimental studies evaluating the impact of high versus low categories of dairy intake on risk factors of T2DM. The authors included 38 studies reflecting 3,016 mostly adult participants without diabetes from North America, Europe, Oceania, South America, and Asia (O'Connor et al., 2019). Intervention periods ranged from one week to 48 weeks (O'Connor et al., 2019). The extent to which included studies adjusted their analyses for covariates, such as measures of adiposity, was not noted and therefore, unclear, although Benatar et al. (2013) extracted baseline BMIs which they included in subgroup analyses.

In contrast to the meta-analysis from Benatar et al., O'Connor et al. (2019) identified a positive effect of dairy consumption on fasting glucose levels, reflecting a significant 0.07 mmol/L increase with high

compared to low dairy diets (95% CI: 0.01-0.12, p = 0.01, I^2 = 23%). They also reported an inverse association between dairy intake and HbA1C, reflecting a significant 0.09% decrease among high compared with low dairy diets and suggesting a longer-term benefit to glycemic control (95% CI: -0.16% to -0.03%, p = 0.005, I^2 = 0%) (O'Connor et al., 2019). This was especially pronounced among individuals with a BMI < 30 kg/m^2 (Mean Difference (MD): -0.10, 95% CI: -0.17 to -0.03, p = 0.005, I^2 = 0%) (O'Connor et al., 2019). On the other hand, the authors did not observe significant impacts of high compared with low categories of dairy intake on fasting blood insulin or HOMA-IR (fasting insulin: MD: -2.97 pmol/L, 95% CI: -7.05 to 1.10, p = 0.15, I^2 = 21%; HOMA-IR: Standardized MD (SMD): -0.07, 95% CI: -0.26 to 0.12, p = 0.49, I^2 = 38%; respectively) (O'Connor et al., 2019). A limitation is that the quality of evidence for these endpoints was very low to low according to the GRADE approach (O'Connor et al., 2019). The authors found no evidence of dose-response relationships for these endpoints.

In subgroup analyses however, O'Connor et al. (2019) explored the individual effect estimates for longer-term (>24 weeks) and shorter-term (<24 weeks) studies and found that longer-term studies produced a significant 5.4 pmol/L decrease in fasting insulin levels with high-dairy vs. control diets (95% CI: -10.31 to -0.49, p = 0.03, I^2 = 0%), while HbA1C remained significantly reduced by 0.10% (95% CI: -0.18% to -0.02%, p = 0.02, I^2 = 0%). The differential changes in shorter-term studies became non-significant (p = 0.87, p = 0.16, respectively) (O'Connor et al., 2019). For longer-term studies, the increase in fasting glucose became non-significant (MD: 0.04 mmol/L, 95% CI: -0.6 to 0.14, p = 0.41, I^2 = 29%), signifying a favorable influence of dairy intake on glycemia and insulinemia (O'Connor et al., 2019). Changes in HOMA-IR were similarly non-significant in the longer-term (MD: -0.02, 95% CI: -0.23, 0.20, p = 0.88, I^2 = 39) (O'Connor et al., 2019). Conversely, shorter-term studies reflected a significant 0.08 mmol/L increase in fasting glucose (95% CI: 0.01-0.14, p = 0.02, I^2 = 14%) and 0.33 decrease in HOMA-IR (95% CI: -0.66 to 0.00, p = 0.05, I^2 = 0%) (O'Connor et al., 2019). While these results indicated mixed messages concerning the effects of increased dairy consumption in the short- and long-term, the authors cautioned that other factors may have helped modulate the observed differential changes in glycemic response, such as genetics, baseline glucose tolerance, changes in weight, physical activity or non-dairy dietary factors (O'Connor et al., 2019).

A few individual experimental studies report results that are inconsistent with O'Connor et al.'s (2019) meta-analysis findings. These studies include Hoppe et al. (2004) and Eelderink et al. (2019). Both short-term studies produced results that contradict the premise that increased dairy consumption yields protective effects on glucose homeostasis. The latter enrolled participants with overweight or obesity, which stands in contrast to the inclusion criteria for both of the aforementioned meta-analyses.

In a parallel, non-randomized, non-controlled intervention study in Denmark, Hoppe et al. (2004) assessed the extent to which animal protein in the form of milk or meat influenced fasting blood plasma levels of insulin and insulin-like growth factor I over a 1-week period. The authors enrolled 24 healthy 8-year-old males with regular milk intake <500 mL/d and assigned half of them to consume 1.5 L of skim milk per day and the other half to consume 250 g low-fat meat in conjunction with an *ad libitum* diet (Hoppe et al., 2004).

There were no differences between groups in terms of change in body weight or BMI (Hoppe et al., 2004). However, there were significant differences between groups in terms of baseline and endpoint energy, carbohydrate and fat intake, as well as protein intake at the end of 7 days, and these were not adjusted for in the authors' analysis (Hoppe et al., 2004). In contrast to O'Connor et al.'s (2019) conclusions, Hoppe et al.'s (2004) results suggest that high intakes of dairy, specifically skim milk, may incite a hyperinsulinemic response and impair insulin sensitivity after a 7-day intervention period in this population of prepubescent males. The authors qualified their findings with a suggestion these metabolic changes may play a protective role in this younger population (Hoppe et al., 2004).

Lastly, in a 16-week randomized cross-over trial in the Netherlands, Eelderink et al. (2019) explored the impact of high and low dairy consumption on postprandial glycemic control and metabolic flexibility. The authors enrolled and randomized 52 middle-aged participants who were classified as overweight according to BMI to treatment order using software that minimized intergroup differences in age, gender and BMI (Eelderink et al., 2019). Participants followed a high dairy diet (5-6 portions dairy/d, including

skim milk, low-fat yogurt and reduced fat cheese) for 6 weeks and a low dairy diet (<1 portion dairy/d) for 6 weeks, with an intermediary 4-week wash-out period (Eelderink et al., 2019). Dairy products were consumed by substitution within the context of each participant's habitual diet (Eelderink et al., 2019). The authors conducted secondary analyses adjusting their primary endpoint (metabolic flexibility) for several covariates, including body weight, energy intake and fiber intake; and their secondary endpoints (including measures of glycemic control) for body weight, dietary fiber and beverage consumption (Eelderink et al., 2019). Additionally, the authors performed subgroup analyses based on baseline insulin resistance, BMI and fasting glucose (Eelderink et al., 2019).

At the end of the trial, neither diet resulted in significant changes to fasting glucose (low dairy mean +/- SD: 5.5 mmol/L +/- 0.3, high dairy: 5.5 mmol/L +/- 0.3) or glucose iAUC (0-8 hours: low dairy: 496.3 mmol/L +/- 177.4, high dairy: 502.7 +/- 184.8), although the low dairy diet garnered 0.8 µU/mL lower fasting insulin concentrations compared to the high dairy group (low dairy: 8.1 +/- 2.8, high dairy: 8.9 +/- 3.3, p = 0.024) (Eelderink et al., 2019). Insulin iAUC (0-8 hours) was not significantly different between the interventions (low dairy: 10,653 µU/mL +/- 5797, high dairy: 11135 +/- 6304) (Eelderink et al., 2019). Adjusting these results for body weight, fiber and beverage consumption did not influence their significance (Eelderink et al., 2019). However, in subgroup analysis, the researchers identified a significant difference in glucose iAUC (0-4 hours, p = 0.050) between the group with normal baseline fasting glucose (NFG) and the group with impaired baseline fasting glucose (IFG) in the high dairy diet (though not in the low dairy diet), suggesting a differential intervention effect based on baseline glucose tolerance (NFG/high dairy: 441.0 +/- 160.6 versus IFG/high dairy: 530.9 +/- 190.0; and NFG/low dairy: 490.0 +/- 168.6 versus IFG/low dairy: 490.3 +/- 189.3) (Eelderink et al., 2019).

The high dairy diet group exhibited a greater increase in insulin resistance, as measured by HOMA-IR than the low-dairy control group (low dairy: 1.99 +/- 0.72, high dairy: 2.21 +/- 0.91, p = 0.027). However, the Matsuda Index did not significantly differ between diet groups (low dairy: 4.12 +/- 1.75, high dairy: 3.84 +/- 1.47, p = 0.077) (Eelderink et al., 2019). Adjusting these results for body weight, fiber and beverage consumption did not influence the outcome (Eelderink et al., 2019). Between the two

interventions, there were significant differences in total energy (low dairy: 2151.7 kcal/d +/- 450.7, high dairy: 2264.2 +/- 470.9, p = 0.015), protein (low dairy: 78.8 g/d +/- 16.7, high dairy: 105.9 +/- 19.2, p < 0.001) and saturated fat (low dairy: 25.3 g/d +/- 7.0, high dairy: 32.3 +/- 6.8, p < 0.001), which were not adjusted for in the authors' statistical analyses for markers of glucose homeostasis (Eelderink et al., 2019). Despite this potential limitation, Eelderink et al. (2019) did not observe a beneficial effect of high dairy versus low dairy diets on measures of postprandial glycemic control, similar to the results from Bowen et al. (2005).

Inter-individual Difference in Response to Dietary Interventions: Experimental Evidence

As illustrated in the previously described meta-analyses and experimental studies, the literature describes an array of effects of various dietary patterns and constituents on glucose homeostasis and insulin sensitivity. Also as noted, several authors highlighted other modifiable and non-modifiable factors that theoretically could influence or confound the impact of the studied dietary interventions on these measures. In agreement with these predictions, experimental studies dating to at least the early 2000s have identified substantial inter- and intraindividual variation in postprandial glycemic response following the consumption of the same meal. While the exact degree of variation differs across studies, variation both between and within individuals is common.

For instance, in a study where 25 healthy adults completed sets of meal tolerance tests after consuming 50 g of carbohydrate via white bread or glucose in random order, Vega-Lopez et al. (2007) evaluated participants' mean AUC for serum glucose and insulin in response to the white bread challenge. The authors identified lower AUC values for both glucose (white bread: 2135 +/- 1175, CV = 55%; glucose: 3556 +/- 1686, CV = 47%) and insulin (white bread: 2532 +/- 1591, CV = 63%; glucose: 2945 +/- 1553, CV = 53%) in comparison to the glucose challenge (Vega-López et al., 2007). Although the overall mean glycemic index for white bread was comparable to values published elsewhere (71 +/- 6, CV = 30%), there was a wide range of individual values, spanning 44 +/- 11 (CV = 41%) on the low end and 132 +/- 38 (CV = 51%) on the high end (Vega-López et al., 2007). Further, Vega-Lopez et al. (2007) employed an ANOVA approach to derive coefficients of variance and identified an interindividual coefficient of variance

of 17.8% and an intraindividual coefficient of variance of 42.7%. The authors concluded that the within individual differences had a greater influence on the overall reaction to a carbohydrate test meal than did the between subject differences (Vega-López et al., 2007).

Similarly, in a randomized, controlled dietary intervention study evaluating the glycemic response of 42 healthy adults with normal BMIs to the consumption of bread, cake, cookie and fruit drink test meals, Vrolix and Mensink (2010) identified iAUC glucose inter- and intraindividual coefficients of variance of 13-38% and 33-80%, respectively. These CVs corresponded to iAUC glucose ranges between participants of 18-182 mmol*min/L for bread, 15-136 for the fruit drink, 23-171 for cake, and 12-191 for cookies (Vrolix & Mensink, 2010). Despite these inter- and intraindividual difference, baseline characteristics of the participants did not vary significantly for measures including body weight, BMI and fasting glucose (Vrolix & Mensink, 2010). As suggested by Vega-Lopez et al. (2007), these findings indicate a relatively greater contribution of intraindividual versus interindividual difference to the overall variation in glycemic response among a population of healthy adults (Vrolix & Mensink, 2010). Further, the authors highlighted the limitations of utilizing the GI in the context of individual dietary counseling given the substantial differences in glycemic response experienced between and among individuals to the same foods (Vrolix & Mensink, 2010).

In agreement with Vega-Lopez et al. (2007) and Vrolix and Mensink (2010), Williams et al. (2008) identified a similar pattern of relatively higher intraindividual variation and lower interindividual variation within the context of a randomized dietary intervention trial, evaluating variations in glycemic response following the consumption of white bread, potato, chickpeas and a glucose beverage. For example, in their study among 20 adult participants exhibiting normal responses to 2-hour OGTTs, Williams et al. (2008) noted a wide confidence interval for the potato glycemic index specifically (mean: 87, 95% CI: 76-101) and an associated intra-class coefficient of 0.02; this reflected a low reliability and a strong influence of within-person variability on the overall differential response. Accordingly, based on results from the three aforementioned studies, evidence suggests both inter- and intraindividual differences are exhibited

in response to the same dietary intervention, and intraindividual differences may bear more weight in driving the totality of difference.

More recently, several researchers have focused on what drives interindividual differences in postprandial glycemic response. As previously described, Zeevi et al. (2015) conducted a relatively robust dietary intervention study among 800 non-diabetic adults in Israel. Over a 7 day period, participants consumed one standardized meal per day comprised of 50 g of available carbohydrate; there were three test meals (bread, bread plus butter, and fructose) and one glucose reference meal (Zeevi et al., 2015). The researchers utilized continuous glucose monitoring to measure postprandial glycemic response (Zeevi et al., 2015).

Among their findings, Zeevi et al. (2015) identified that there was high interindividual variability in postprandial glycemic response to the same meal. For instance, they reported the top and bottom 10% of the postprandial glycemic responses to bread to be <15 mg/dL*h and >79 mg/dL*h, respectively (Zeevi et al., 2015). Moreover, there was also variability between individuals in terms of which meal drove the highest postprandial glycemic response (Zeevi et al., 2015). In explaining this postprandial variability, the authors identified associations between postprandial glycemic response and individual participants' HbA1c, BMI, systolic blood pressure, ALT activity, CRP and constituents within the gut microbiome (Zeevi et al., 2015). The authors also commented that genetics and lifestyle could play a role in determining postprandial glycemic response (Zeevi et al., 2015). Accordingly, many intraindividual variables may influence the differential interindividual responses to singular dietary interventions.

A more recent study conducted in the United States employing similar methodologies also identified material differences among participants in glycemic excursion in response to consuming a standardized bagel and cream cheese test meal (Mendes-Soares et al., 2019). The authors enrolled 327 healthy adult participants without diabetes into the study (Mendes-Soares et al., 2019). Following the consumption of the bagel and cream cheese meal, the glycemic excursions among participants ranged from 6-94 mg/dL (mean: 30.7 mg/dL), despite there being significant intraindividual reproducibility (Pearson product

moment correlation R = 0.66) (Mendes-Soares et al., 2019). Like Zeevi et al. (2015), these results from Mendes-Soares et al. (2019) suggest that there is high interindividual variability in postprandial glycemic response to the same meal.

Lastly, Matthan et al. (2016) implemented a randomized, parallel intervention study among 63 healthy adult participants with BMI 20-35 kg/m^2 in the United States. In order to evaluate inter- and intraindividual variations in postprandial glycemic response to glucose (reference) and white bread (test), participants completed 3 sets of food challenges in random order (Matthan et al., 2016). After three repeats of the meal tolerance tests, the authors identified intra- and interindividual coefficients of variance of 20% and 25%, respectively, reflecting a slightly larger contribution by interindividual difference to the overall differential GI value for white bread (Matthan et al., 2016). Further, employing a random-intercept mixed-model to assess the extent to which biological factors influenced interindividual difference, Matthan et al. (2016) attributed the following percentages of variability to these factors: HbA1C (16%), Insulin Index (15%), CRP (11%), Age (10%), and BMI (6%). Matthan et al. (2016) also noted other variables that may influence an individual's postprandial glycemic response, such as physical food structure, food processing or preparation, and overall dietary patterns.

The aforementioned studies affirm that there are intra- and interindividual differences in postprandial glycemic response, which may vary based on myriad modifiable and non-modifiable factors. This variability in glycemic response adds nuance to discussions concerning the relative benefits or harms of individual foods and overall dietary patterns on metabolic function and health in general.

II.c. Conceptual Model

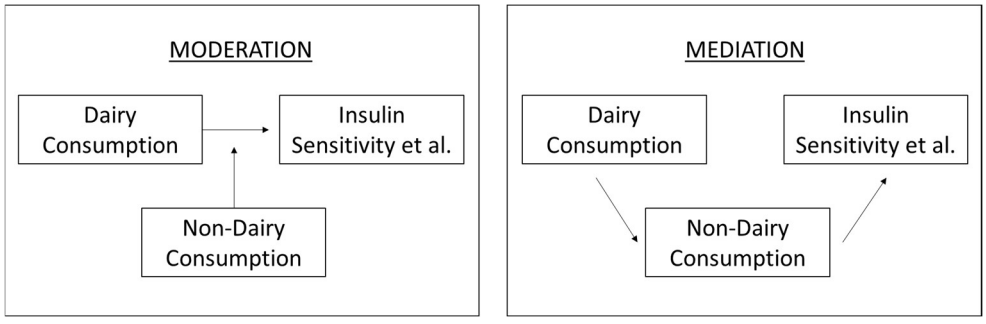
While dietary factors ranging from the overall dietary pattern to specific foods and/or nutrients may exert an influence on an individual's insulin sensitivity and glycemic control, dietary intake always occurs in a setting of other influential factors, such as genetics and the gut microbiome (Healey et al., 2017; Milenkovic et al., 2017; Rideout, 2011). Accordingly, it is not surprising that individuals differ in their response to the same dietary interventions (Zeevi et al., 2015).

In the case of dairy, the *2015-2020 Dietary Guidelines for Americans* recommend a daily consumption of 3 cup equivalents of fat-free or low-fat dairy for adults due to its nutrient density and provision of important micronutrients, such as calcium, phosphorous and vitamin A (US Department of Health and Human Services, 2015). From the previous literature review, it is clear that while epidemiological evidence may associate increased dairy consumption with a reduced incidence of T2DM, dairy intake exerts variable effects within and among individuals in terms of insulin sensitivity and glycemic control.

Of particular interest is how dairy interacts with other components of the diet to exert these effects, given dairy is typically not consumed in isolation among adults. Within a setting of variations in genetics and gut microbiome composition, it is plausible that other constituents of the diet may either moderate or mediate the effect of dairy on markers of glucose homeostasis. As seen in **Figure 1** below, moderation entails modification of the effects of dairy consumption on insulin sensitivity by other constituents of the diet, while mediation necessitates an indirect effect of dairy on insulin sensitivity. Specifically, the consumption of dairy has a direct effect on the consumption of other foods in the diet, for example through substitution, which may then differentially influence an individual's overall insulin sensitivity.

Figure 1.

Conceptual Model: Moderation and Mediation by Non-Dairy Foods



The present analysis strives to assess the extent to which these non-dairy foods influence the effect of dairy on insulin sensitivity, as well as the extent to which variations in insulin sensitivity are explained by differences in the intake of these non-dairy foods.

II.d. Research Aims and Hypothesis

While observational evidence largely suggests a direct statistical relationship between dairy consumption and insulin sensitivity, experimental evidence is contradictory. Two recent studies illuminate the possible adverse effects of dairy intake on insulin sensitivity. In the first, our recent DAIRY study (Schmidt et al., submitted for publication) determined that in individuals with the metabolic syndrome, the consumption of either low-fat or full-fat dairy resulted in a decrease in insulin sensitivity compared to the consumption of a limited dairy diet. In the second study (previously described), a randomized crossover trial by Eelderink et al. (2019) found that overweight individuals experienced an increase in HOMA-IR following a high-dairy compared to a low-dairy diet.

For the DAIRY study specifically, these decreases in insulin sensitivity were not attributable to changes in inflammation, liver fat content or fat mass (Schmidt et al., submitted for publication). Despite producing overall statistically significant decreases in the Matsuda-DeFronzo insulin sensitivity index (Matsuda ISI) and increases in insulin resistance (as measured by HOMA-IR) in both dairy intervention groups, changes in insulin sensitivity may at least partly be due to changes in uncontrolled dietary components separate from the addition of dairy foods, such as reductions in the consumption of fiber-rich foods. Changes in insulin sensitivity were also subject to substantial interindividual variation, suggesting that other factors (e.g. genetics, non-dairy dietary components, etc.) may be influencing the overall response to dairy consumption (Schmidt et al., submitted for publication).

In the present secondary analysis, we will assess the extent to which alternative dietary factors that were not controlled for may at least partly explain the impact of a dairy dietary intervention on insulin sensitivity in individuals with the metabolic syndrome. These dietary factors include the healthy eating index independent of dairy (HEI-ID), fiber intake and added sugar intake. Data from the DAIRY study will be utilized to address the following specific aims:

Primary Aim 1. Assess the impact of adjusting for (a) baseline or (b) changes in HEI-ID, fiber intake, and added sugar intake on the differential effect of the dietary interventions on the Matsuda ISI (primary) and HOMA-IR (secondary).

Hypothesis: Adjusting for changes in dietary HEI, fiber intake, or added sugar intake will attenuate the differential effects of the two dairy diets on Matsuda ISI and HOMA-IR, suggesting that changes in other dietary factors rather than the consumption of dairy foods themselves partly explain the decrease in insulin sensitivity and increase in insulin resistance in the two dairy groups.

Primary Aim 2. Investigate whether interindividual differences in the Matsuda ISI (primary) and HOMA-IR (secondary) are explained by (a) baseline or (b) changes in HEI-ID, fiber intake, and added sugar intake.

Hypothesis: Baseline and changes in HEI-ID, fiber intake and added sugar intake will explain interindividual differences in the Matsuda ISI and HOMA-IR, suggesting that the consumption of dairy foods was not solely responsible for these differences in insulin sensitivity and insulin resistance.

III. Methods

III.a. Study Setting

Our study took place in the greater Seattle area in Seattle, Washington. Study participants were free-living and came to the Fred Hutchinson Cancer Research Center (FHCRC), UW Translational Research Unit (TRU), and the UW Bio-Molecular Imaging Center (BMIC) for screening and clinic visits (Schmidt et al., submitted for publication).

III.b. Subjects

From January 2016 to June 2018, we recruited and enrolled 18- to 75-year-old men and women with the metabolic syndrome (Schmidt et al., submitted for publication). See **Supplementary Table 1** (Appendix) for a complete list of inclusion and exclusion criteria. We recruited participants via letters sent to potentially eligible subjects identified through automated screens of the UW electronic medical record (EMR) system. Following the completion of telephone screening interviews, we invited potential participants to attend in-person screening visits at the FHCRC. During this screening visit, anthropometric measurements and vital signs were taken, fasting blood was collected, and individuals were asked to complete medical, nutritional and medication history questionnaires. Eligible participants then returned for a study initiation visit, where they provided consent for the intervention, were weighed, and completed a modified Blair Physical Activity Questionnaire (PAQ), which assessed habitual physical activity. We enrolled 76 participants in total, of which four were excluded or withdrew during the wash-in phase prior to randomization. Of the remaining 72 participants, three did not complete all clinic visits, and two failed to exhibit adequate dietary compliance. Accordingly, the per protocol analysis for glucose homeostasis-related endpoints included 67 participants, while the intent to treat analysis included 72 participants.

III.c. Study Design and Dietary Interventions

Subsequent to the study initiation visit, participants completed a wash-in diet for 4 weeks ± 1 week (Schmidt et al., submitted for publication). The wash-in diet permitted the weekly consumption of up to 3 servings of nonfat milk and no other dairy products (“limited dairy diet”). Participants could otherwise consume their habitual diet *ad libitum*. Dietary compliance was assessed at a check–in visit during the

wash-in diet period when participants came to FHCRC to pick up their dairy products. Participants were excluded from the trial for noncompliance if they consumed more than three servings of non-study dairy products, failed to complete one or more dairy logs, or did not complete at least one 24-hour dietary recall during this period. Individuals who were excluded due to noncompliance or who dropped out during the wash-in period were not randomized, did not complete any clinic visits, did not count towards the recruitment goal, and were not included in any statistical analyses.

In the last week of the wash-in dietary period, participants underwent baseline assessments and procedures during clinic visit #1 at the UW TRU and the UW BMIC (see “Clinic Visits” and “Lab Procedures” below). Overall, participants were on the wash-in diet for 21 to 28 days prior to completing clinic visit #1. Following the wash-in dietary phase and clinic visit #1, participants were randomized to one of three intervention arms. We utilized a block randomization procedure stratified by gender and HOMA-IR (<5.0 vs. ≥ 5.0 or diagnosis of diabetes). Subjects either continued to consume a diet with little dairy (“limited dairy diet”, control), or switched to a diet including an average of 3.3 servings/day of either nonfat/low-fat dairy products (“low-fat dairy diet”) or full-fat dairy products (“full fat dairy diet”). Subjects were provided with all of their dairy products by the FHCRC Human Nutrition Laboratory (HNL).

As described by Schmidt et al. (submitted for publication), the limited dairy diet included 3 servings/week of nonfat (skim) milk. The low-fat and full fat dairy diets included 23.1 servings/week of dairy products, for an average of 3.3 servings per day. One serving of milk was 240mL; one serving of yogurt, 170g; and one serving of cheese, 42.5g. The low-fat dairy diet consisted of 8 servings of nonfat milk, 7.1 servings of nonfat yogurt, and 8 servings of low-fat cheese (12-18% fat). The full fat dairy diet consisted of 8 servings of whole milk (3.3-3.5% milk fat), 7.1 servings of plain full-fat yogurt (3.3-3.5% milk fat), and 8 servings of full-fat cheese (21-33% fat). Participants randomized to the low-fat and full-fat dairy diets were asked to consume all of the dairy products provided to them each week, while consumption of the nonfat milk was optional in the limited dairy diet. All participants were asked not to consume any other dairy products, and to keep a dairy log of their entire dairy intake.

To assess dietary compliance, we asked participants to also record any non-study dairy food items eaten (Schmidt et al., submitted for publication). On this dairy log, participants also noted any change in medication or supplement intake as well as any illness. Every one to two weeks, participants visited the FHCRC HNL to meet with a kitchen staff member, return any unconsumed dairy foods, and receive a 7-14-day supply of dairy products. Staff weighed all returned dairy products to assess the amount of dairy consumed. Additionally, the returned dairy logs were compared against the returned dairy foods and checked for compliance. We contacted participants by phone if compliance was below the desired level (i.e. <90% of the study dairy foods were consumed, and/or non-study dairy foods were consumed regularly).

Participants completed clinic visit #2 at UW TRU and UW BMIC 12 weeks ± 1 week after starting the intervention diet (Schmidt et al., submitted for publication). Participants who consumed more than 10 servings of non-study dairy were not included in the primary per protocol statistical analyses. Similarly, participants who consumed less than 90% of the dairy products provided were not included in the primary per protocol analysis. We did not officially exclude such participants from the study or penalize them in any other way.

Habitual food intake during the study was assessed via unannounced 24-hour recalls with the assistance of the Nutritional Assessment Shared Resource (NASR) of FHCRC (Schmidt et al., submitted for publication). Participants received serving size booklets developed by NASR that helped them estimate the portion sizes of common food items during the 24-hour recall interviews. Trained and certified NASR staff completed two 24-hour recalls with each participant during the wash-in phase, and another three 24-hour recalls during the intervention study phase. These recall interviews were conducted in an unannounced manner, and employed a multiple-pass method to prompt the collection of detailed dietary intake data using neutral, non-leading questions. Nutrient calculations were performed using the Nutrition Data System for Research (NDSR) software version 2017 developed by the Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN, Food and Nutrient Database 2017.

III.d. Data Collection and Aggregation

Clinic Visits

During clinic visits #1 and #2, participants underwent weight, height, waist and hip circumference measurements; body composition assessment via a dual x-ray absorptiometry (DEXA)-scan; fasting blood draw (40 mL); and 3-hour frequently sampled oral glucose tolerance test (FS-OGTT), among other assessments unrelated to the present analysis (Schmidt et al., submitted for publication).

Lab Procedures

Fasting blood glucose and insulin were analyzed at Northwest Lipid Research Laboratories (Seattle, WA). Glucose was measured by Hitachi 917 autoanalyzer (Roche, Mannheim, Germany), and insulin was measured via AIA 600 II autoanalyzer (Tosoh Bioscience, San Francisco, CA).

Based on fasting blood and FS-OGTT data, we calculated the Matsuda ISI and HOMA-IR. While the former assesses both hepatic and peripheral sensitivity, the latter measures mostly hepatic insulin resistance (Gutch, Kumar, Razi, Gupta, & Gupta, 2015). We derived these measures as follows:

Matsuda-DeFronzo insulin sensitivity index =

10,000/√[(fasting glucose x fasting insulin) x (mean OGTT glucose x mean OGTT insulin)] (Gutch et al., 2015).

HOMA-IR =

fasting insulin (microU/L) x fasting glucose (nmol/L)/22.5 (Gutch et al., 2015).

Dietary Database

We built a database of participant-level dietary intake data from the 24-hour recalls in Microsoft Excel (Microsoft Office 365, Version 2016), using reports generated from the NDSR software and database. Variables included in the database are energy (kilocalories), macronutrients (carbohydrates, protein, and fat, in grams), major lipid subtypes (saturated, monounsaturated, polyunsaturated fatty acids, in grams),

fiber (grams), total sugar (grams), added sugar (grams), alcohol (grams), sodium (grams), calcium (milligrams), Healthy Eating Index (HEI)-2015, and HEI independent of dairy (HEI-ID). The HEI-2015 measures dietary quality and compliance against the 2015-2020 Dietary Guidelines for Americans (Center for Nutrition Policy and Promotion, 2019) (Center for Nutrition Policy and Promotion, 2019). In order to calculate the HEI-2015, individual HEI components[1] were derived by summing their respective constituents, normalizing their values to reflect total reported energy intake (e.g. "per 1,000 kcal" or "% of energy"), and scoring their values according to NIH National Cancer Institute scoring standards (NIH, 2018). To remove the influence of dairy foods, HEI-ID was calculated by excluding the following components from the HEI score: dairy, fatty acid ratio, and saturated fats. Participant-level data was broken out as "baseline" and "intervention" for all variables from each dietary assessment tool. Baseline data reflects the average of 24-hour recalls #1 and #2. Intervention data reflects the average of 24-hour recalls #3-5. Missing data was filled by carrying forward the last values measured.

III.e. Statistical Analyses

Statistical analyses were performed using SPSS for Windows (Version 26; IBM). We conducted both *intent to treat* (ITT) and *per protocol* (PP) analyses. The *per protocol* analysis included participants who completed the dietary intervention and were compliant, attended all clinic visits, had no change in medication or supplementation likely to affect the respective endpoint, and were not impacted by illness that would adversely affect DAIRY study endpoints (Schmidt et al., submitted for publication). All participants were included in a separate *intent to treat* analysis, as long as they completed the first clinic visit and began the assigned intervention diet. In alignment with the original DAIRY study, 67 participants were included in the *per protocol* analysis, while 72 were included in the *intent to treat* analysis. Any differences between the two analyses are noted for consideration in interpreting the results.

In the original DAIRY study, power calculations determined that enrolling sufficient participants to ensure that 60 could be included in the primary per protocol analysis would provide 80% power to detect a 10%

[1] Whole fruits, total fruits, greens and beans, total vegetables, whole grains, refined grains, dairy, seafood and plant proteins, total protein foods, added sugars, fatty acid ratio, saturated fats, and sodium

change in AUC glucose and an adjusted alpha error of 1.67% (Schmidt et al., submitted for publication). A separate power calculation was not conducted for the present secondary analysis.

Primary Aim 1: We assessed the impact of adjusting for baseline, as well as changes in HEI-ID, fiber intake, and added sugar intake on the observed statistically significant decrease in the Matsuda ISI in the two dairy arms in the main study. To do so, we conducted a repeated measures analysis of variance (RM-ANOVA) including the Matsuda ISI as the dependent variable, with time as the within-subject variable (clinic visit #1 vs. #2) and diet (limited dairy vs. low-fat dairy vs. full-fat dairy) as the between subjects variable, adjusted for key variables of glucose homeostasis that were not equally distributed across diet groups at baseline (i.e. glycosylated hemoglobin, area under the curve glucose, and fasting glucose), as well as baseline or changes in HEI-ID, fiber intake, or added sugar intake (each individually). As in the primary analyses, logarithmic transformation was utilized for any data that failed tests for normality, or if the RM-ANOVA residuals were not normally distributed. Means, standard deviations and p-values are reported for normally distributed data; medians, 25th and 75th percentiles, and p-values are reported for non-normally distributed data. We repeated the above in an additional exploratory analysis with HOMA-IR as the dependent variable. We conducted both *intent to treat* and *per protocol* analyses for both endpoints.

Primary Aim 2: The second assessment analyzed the extent to which baseline or changes in HEI-ID, fiber intake and added sugar intake explained inter-individual differences in the Matsuda ISI. Accordingly, we conducted exploratory multiple linear regression analyses across all participants (ITT n = 72, PP n = 67) to evaluate whether individual changes in the Matsuda ISI are associated with the aforementioned dietary variables of interest. Logarithmic transformation was utilized for any variables that failed tests for normality. For both the *per protocol* and *intent to treat* analyses, we ran three models reflecting 1) an unadjusted linear regression with change in Matsuda ISI as the dependent variable and the individual baseline (or change in) dietary variables of interest as the independent variable; 2) multiple linear regression reflecting model #1 with the addition of adjustment for baseline Matsuda ISI as well as variables that significantly differed at baseline ($p<0.10$) – i.e. glycosylated hemoglobin, area under the

curve glucose, and fasting glucose; and 3) multiple linear regression reflecting model #2 with the addition of adjustment for dietary randomization group and changes in potentially confounding, non-dietary variables – i.e. change in fat mass and change in physical activity. Any baseline values of the dietary variables of interest that were significantly associated with changes in Matsuda ISI were adjusted for in subsequent models. The alpha-error level was set to 5% for all analyses. β-coefficients, confidence intervals and p-values were reported for each model. The above models were repeated in an additional exploratory analysis with HOMA-IR in place of Matsuda ISI.

IV. RESULTS

IV.a. Baseline Characteristics

A total of 72 participants completed the wash-in period and were randomized in equal number to each of the dietary intervention groups: limited dairy, low-fat dairy or full-fat dairy (Schmidt et al., submitted for publication). Of the 72 participants, five were excluded due to drop-out or non-compliance, leaving 67 participants for inclusion in the *per protocol* analysis for glucose homeostasis-related endpoints. At baseline, median age ranged from 56 to 65 years across groups with no significant differences among groups (**Table 1**). Likewise, there were no significant differences in sex or race among groups, which ranged from 54.5% to 58.3% male and 71.4% to 79.2% Caucasian, respectively (**Table 1**). There were also no significant differences among groups in anthropometric characteristics, such as BMI and visceral adiposity. Of all measured non-dietary characteristics at baseline, only HbA1C significantly differed among the intervention groups, with the HbA1C of the low-fat and full-fat dairy groups surpassing that of the limited dairy group ($p<0.001$). We also observed borderline significant differences ($0.05 < p < 0.1$) for baseline fasting glucose and baseline area-under-the-curve (AUC) glucose.

While there were no baseline differences in lifestyle variables, such as HEI-2015 and physical activity, or in indices of insulin sensitivity/resistance, there were differences in dietary intake over the course of the study (**Table 1**). In evaluating the inter-group dietary changes during the intervention period compared with baseline, there were significant differences in the changes in daily energy intake ($p = 0.003$), fiber intake ($p = 0.011$), SFA ($p < 0.001$), MUFA ($p = 0.014$), HEI-2015 ($p = 0.008$) and calcium ($p < 0.001$) (**Table 2**), among others. Of course, some of these changes were to be expected based on the nature of the low-fat and full-fat dietary interventions themselves.

IV.b. Adjusting Insulin Sensitivity/Resistance for Specified Dietary Variables (Aim 1)

As reported in the primary study, insulin sensitivity, as measured by Matsuda ISI, was significantly reduced in the low-fat and full-fat dairy groups compared to the limited dairy group in the *per protocol* RM-ANOVA after adjustment for Bonferroni ($p = 0.012$ for overall time * diet interaction) (Schmidt et al., submitted for publication; **Table 3**). Specifically, compared to the limited dairy group which experienced

minimal change in insulin sensitivity relative to baseline (0.00 ± 0.92), the low-fat and full-fat dairy groups experienced significant decreases in insulin sensitivity, amounting to -0.47 ± 1.07 and -0.25 ± 0.91, respectively. These findings remained significant when adjusting the RM-ANOVA for 1) baseline and 2) change in HEI-ID, fiber intake or added sugar intake (p = 0.014-0.021; see **Table 3**). These results did not significantly differ in the *intent to treat* analysis.

Similarly, in the primary study, insulin resistance, as measured by HOMA-IR, was significantly increased in the low-fat and full-fat dairy groups compared to the limited dairy group in the *per protocol* analysis (p = 0.005 for overall time * diet interaction) (Schmidt et al., submitted for publication; **Table 3**). Compared to the limited dairy group which experienced a slight decrease in insulin resistance relative to baseline (-0.44 (-0.86; 0.41)), the low-fat and full-fat dairy groups experienced significant increases in insulin resistance, amounting to +0.75 (-0.32; 1.33) and +0.82 (0.07; 1.84), respectively These findings remained significant when adjusting the RM-ANOVA for 1) baseline and 2) change in HEI-ID, fiber intake or added sugar intake (p = 0.004-0.007; see **Table 3**). These results also did not significantly differ in the *intent to treat* analysis.

IV.c. Association between Insulin Sensitivity/Resistance and Specified Dietary Variables (Aim 2)

Based on our *per protocol* multiple linear regression analyses showing non-significant p values, neither baseline, nor changes in added sugar, dietary fiber, or HEI-ID predicted interindividual differences in Matsuda ISI (**Table 4**). Additionally, with the exception of change in HEI-ID, neither baseline, nor changes in added sugar, dietary fiber, or HEI-ID predicted interindividual differences in HOMA-IR (**Table 5**). For HOMA-IR, change in HEI-ID did not predict interindividual differences in insulin resistance in the first two statistical models; the analysis resulted in a significant p value only with the addition of adjustment for diet randomization group, change in fat mass and change in physical activity. These results did not significantly differ in the corresponding *intent to treat* analyses (see **Supplementary Tables 2-3** in the Appendix).

Table 1. Baseline characteristics of participants included in the primary *per protocol* analysis (n=67).

Variable	Limited dairy (n= 22)	Low-fat dairy (n=24)	Full-fat dairy (n=21)	P value
Age (years)	56 (46; 68)	64 (58; 71)	65 (58; 68)	0.18
Sex (% male)	54.5	58.3	57.1	0.97
Race (% Caucasian)	72.7	79.2	71.4	0.87
Body mass index (kg/m^2)	33.6 ± 5.9	32.6 ± 7.3	32.8 ± 6.4	0.85
Visceral adiposity ($inch^3$)*	148 (97; 202)	104 (71; 202)	124 (78; 177)	0.35
Glycosylated hemoglobin (%)	5.4 (5.0; 5.5)	5.8 (5.5; 6.2)	5.7 (5.4; 5.9)	<0.001
Physical activity (MET-h/week)	37.2 (23.4; 49.6)	41.0 (25.7; 89.7)	37.8 (19.6; 47.9)	0.29
HEI-2015	71.9 ± 9.2	72.8 ± 9.7	72.2 ± 8.5	0.95
Matsuda ISI	2.7 (2.0; 3.8)	2.4 (1.8; 3.8)	2.3 (1.9; 3.4)	0.88
HOMA-IR	2.5 (1.9; 3.5)	3.3 (1.6; 4.4)	3.0 (1.7; 4.4)	0.98
Fasting glucose (mg/dL)	101 (93; 109)	110 (101; 119)	107 (102; 116)	0.09
AUC glucose (mg/dL x min)	25,195 (23,445; 30,708)	29,895 (26,495; 32,849)	27,888 (24,831; 29,881)	0.07

Data are means ± standard deviations, or medians (25th; 75th percentile, for non-normally distributed variables), or percentages (for categorical variables).

Abbreviations: MET-h/week: metabolic equivalent hours per week, HEI-2015: 2015 Healthy Eating Index, Matsuda ISI: Matsuda-DeFronzo insulin sensitivity index, HOMA-IR: homeostasis model assessment index of insulin resistance, AUC glucose: area under the curve glucose (glucose tolerance).

* Sample size for visceral adiposity: limited: n= 21, low-fat: n= 22, full-fat: n= 20

(Schmidt et al., submitted for publication)

Table 2. Changes in dietary intakes during wash-in and intervention phases, based on unannounced 24-hour dietary recalls, for participants included in the *per protocol* analysis (n=67).

Variable	**Limited dairy group (n=22)**		**Low-fat dairy diet (n=24)**		**Full-fat dairy diet (n=21)**		***RM-ANOVA**
	Wash-in Phase	Δ (Intervention – Wash-in)	Wash-in Phase	Δ (Intervention – Wash-in)	Wash-in Phase	Δ (Intervention – Wash-in)	Time x diet
Energy intake (kcal/day)	1,998 (1624; 2307)	80 ± 544[a]	2,041 (1526; 2625)	224 ± 375[a]	1,712 (1364; 2098)	554 ± 467[b]	0.003
Carbohydrates (%E)	46.1 ± 11.4	-0.7 (-3.3; 0.9)[a]	47.7 ± 8.6	1.6 (-4.3; 6.2)[a,b]	46.3 ± 7.1	-4.1 (-7.6; -0.8)[b]	0.020
Added sugars (%E)	9.3 ± 4.5	-0.5 ± 3.3	8.5 ± 4.1	0.7 ± 4.3	9.1 ± 6.1	-0.9 ± 4.1	0.349
Fiber (g/1,000 kcal)	12.3 ± 5.0	0.3 ± 3.8[a]	12.6 ± 3.4	-1.4 ± 2.5[a,b]	12.2 ± 4.4	-2.8 ± 3.3[b]	0.011
Fat (%E)	34.0 ± 8.1	1.3 (-2.7; 5.7)[a]	34.2 ± 7.7	-2.5 (-8.2; -0.4)[b]	35.0 ± 9.0	4.4 (0.6; 7.3)[a]	<0.001
SFA (%E)	8.0 ± 2.0	0.7 (-0.3; 3.8)[a]	8.2 ± 2.1	0.6 (-1.5; 2.1)[a]	8.7 ± 2.6	5.2 (3.4;6.9)[b]	<0.001
MUFA (E%)	14.1 ± 4.3	-0.3 ± 3.8[a]	14.0 ± 3.9	-3.1 ± 2.5[b]	13.7 ± 4.1	-0.2 ± 4.6[a]	0.014
PUFA (%E)	9.2 ± 2.8	0.3 ± 2.3	9.3 ± 3.1	-1.8 ± 3.0	9.7 ± 3.5	-1.1 ± 3.4	0.058
Protein (%E)	15.4 (12.5; 18.1)	0.0 ± 0.1	16.2 (13.7;17.7)	0.1 ± 0.1	15.3 (14.1; 18.6)	0.0 ± 0.1	0.024
HEI-2015	71.9 ± 9.2	-2.5 ± 10.0[a,b]	72.8 ± 9.7	2.9 ± 8.7[b]	72.2 ± 8.5	-5.6 ± 7.6[a]	0.008
Calcium (mg/1,000 kcal)	307 (222; 440)	-9 ± 149.5[a]	298 (252; 358)	401 ± 167[b]	338 (276; 426)	277 ± 194[b]	<0.001

Values are means ± standard deviations or medians (25th; 75th percentiles).

Abbreviations: %E: percent of total energy intake, SFA: saturated fatty acids, MUFA: monounsaturated fatty acids, PUFA: polyunsaturated fatty acids, HEI-2015: 2015 Healthy Eating Index

*Reflects an overall comparison of the three dietary phases by RM-ANOVA. Data with different superscript letters are statistically significantly different in Bonferroni-adjusted post hoc testing ($p<0.017$).

(Schmidt et al., submitted for publication)

Table 3. The effect of consuming a control diet limited in dairy vs. diets rich in either low-fat or full-fat dairy foods on insulin sensitivity and insulin resistance, *per protocol* analysis (n=67).

				[*]RM-ANOVA (Time x diet interaction)						
Group	[+]**Baseline**	[+]**Follow-up**	**Delta**	[^]Adj. AUC, fasting glucose, HbA1C	+Baseline Added Sugar (%E)	+Δ Added Sugar (%E)	+Baseline Fiber (%E)	+Δ Fiber (%E)	+Baseline HEI-ID	+Δ HEI-ID
Matsuda Insulin Sensitivity Index				**0.012**	**0.014**	**0.014**	**0.017**	**0.016**	**0.021**	**0.015**
Limited Dairy	2.7 (2.0; 3.8)	2.8 (2.0; 4.3)	0.00 ± 0.92[a]							
Low-fat Dairy	2.4 (1.8; 3.8)	2.3 (1.5; 3.5)	-0.47 ± 1.07[b]							
Full-fat Dairy	2.3 (1.9; 3.4)	1.9 (1.5; 2.8)	-0.25 ± 0.91[b]							
HOMA-IR				**0.005**	**0.004**	**0.005**	**0.006**	**0.007**	**0.006**	**0.004**
Limited Dairy	2.5 (1.9; 3.5)	2.5 (1.6; 3.9)	-0.44 (-0.86; 0.41)[a]							
Low-fat Dairy	3.3 (1.6; 4.4)	3.1 (2.3; 6.1)	+0.75 (-0.32; 1.33)[b]							
Full-fat Dairy	3.0 (1.7; 4.4)	3.9 (2.4; 5.6)	+0.82 (0.07; 1.84)[b]							

[+]Values are means ± standard deviations or median (25th; 75th percentile) for non-normally distributed data.

[*]Reflects an overall comparison of the three dietary phases by RM-ANOVA. Data with different superscript letters are statistically significantly different in Bonferroni-adjusted post hoc testing ($p<0.017$).

[^]Adjusted for those variables that tended to differ at baseline ($P<0.10$): area under the curve glucose, fasting glucose, and glycosylated hemoglobin at baseline.

Table 4. Multiple linear regression analysis on the change in the Matsuda-DeFronzo insulin sensitivity index, *per protocol* analysis (n=67)

	Model 1	**Model 2**	**Model 3**
Baseline HEI-ID	0.007 (-0.024, 0.038), p=0.645	0.002 (-0.031, 0.034), p=0.924	0.001 (-0.032, 0.035), p=0.928
Baseline fiber intake (g/1,000 kcal)	0.010 (-0.047, 0.068), p=0.719	0.015 (-0.039, 0.069), p=0.588	0.008 (-0.048, 0.064), p=0.776
Baseline added sugar intake (%E)	-0.013 (-0.063, 0.037), p=0.602	-0.009 (-0.055, 0.037), p=0.699	-0.011 (-0.057, 0.036), p=0.645
Change in HEI-ID	-0.007 (-0.037, 0.022), p=0.614	-0.002 (-0.030, 0.026), p=0.887	-0.003 (-0.031, 0.026), p=0.858
Change in fiber intake (g/1,000 kcal)	0.002 (-0.069, 0.073), p=0.955	0.002 (-0.064, 0.069), p=0.944	-0.015 (-0.086, 0.056), p=0.672
Change in added sugar intake (%E)	0.011 (-0.050, 0.073), p=0.710	-0.004 (-0.062, 0.054), p=0.896	0.004 (-0.055, 0.064), p=0.889

Data are unadjusted beta coefficients (95% CIs).

Model 1: unadjusted; change in Matsuda ISI is the dependent variable and the specified dietary factor is the independent variable.

Model 2: adjusted for baseline HbA1c, baseline area-under-the-curve glucose, baseline fasting glucose, and baseline Matsuda (may also include the baseline of any change variable, if baseline is significantly associated with delta Matsuda).

Model 3: as model 2, plus change in total fat mass, change in physical activity, and intervention group.

Table 5. Multiple linear regression analysis on the change in the homeostasis model assessment insulin resistance (HOMA-IR) index, *per protocol* analysis (n=67)

	Model 1	**Model 2**	**Model 3**
Baseline HEI-ID	-0.001 (-0.006, 0.005), p=0.756	-0.002 (-0.008, 0.005), p=0.608	-0.001 (-0.007, 0.005), p=0.690
Baseline fiber intake (g/1,000 kcal)	-0.005 (-0.015, 0.005), p=0.312	-0.007 (-0.017, 0.004), p=0.207	-0.004 (-0.014, 0.006), p=0.380
Baseline added sugar intake (%E)	0.002 (-0.007, 0.011), p=0.671	0.002 (-0.007, 0.011), p=0.670	0.003 (-0.006, 0.012), p=0.555
Change in HEI-ID	-0.003 (-0.008, 0.002), p=0.222	-0.004 (-0.009, 0.001), p=0.137	-0.006 (-0.011, 0.000), p=0.034
Change in fiber intake (g/1,000 kcal)	-0.008 (-0.020, 0.003), p=0.151	-0.008 (-0.020, 0.005), p=0.222	-0.003 (-0.016, 0.010), p=0.687
Change in added sugar intake (%E)	0.007 (-0.004, 0.017), p=0.213	0.008 (-0.003, 0.019), p=0.150	0.008 (-0.003, 0.020), p=0.135

Data are unadjusted beta coefficients (95% CIs).

Model 1: unadjusted; change in HOMA-IR is the dependent variable and the specified dietary factor is the independent variable.

Model 2: adjusted for baseline HbA1c, baseline area-under-the-curve glucose, baseline fasting glucose, and baseline HOMA-IR (may also include the baseline of any change variable, if baseline is significantly associated with delta HOMA-IR).

Model 3: as model 2, plus change in total fat mass, change in physical activity, and intervention group.

V. DISCUSSION

Many dietary patterns and constituents have purported protective effects on an individual's risk of T2DM and markers of glucose homeostasis. In the context of the DAIRY study, baseline and changes in HEI-ID, fiber intake and added sugar intake, neither attenuated, nor explained individual or intervention group responses to the dairy intervention. We found that consumption of diets rich in low-fat or full-fat dairy significantly reduced insulin sensitivity independent of these other dietary changes. These findings support the conclusion that the low-fat and full-fat dairy interventions were primarily responsible for the reductions in insulin sensitivity. Further, in our exploratory, multiple linear regression analyses, we identified that interindividual differences in response to the limited, low-fat and full-fat dairy interventions could not be explained by differences in either baseline or change in these non-dairy dietary factors. In isolation, as well as in concert with other possible covariates, these dietary factors could not explain changes in insulin sensitivity. The one exception was the significant association between change in HEI-ID and change in HOMA-IR after adjustments for baseline AUC glucose, baseline fasting glucose, baseline HbA1C, baseline HOMA-IR, dietary intervention group, change in fat mass and change in physical activity. While statistically significant, it is worth noting that the association was weak and became apparent only in one multi-variable adjusted model. It is also possible that this one isolated significant association was false positive as a result of multiple testing, for which we did not adjust. As the body of evidence linking diet to glucose homeostasis and incident T2DM is inconsistent, so too are our results in the context of the broader body of literature.

From our review of the literature, it was clear that researchers conducting dietary controlled trials among free-living populations do not always adjust their analyses for dietary variables that differ among intervention groups. When these covariates are accounted for, their effects on the significance of the researchers' findings are varied. In the context of the DAIRY study, adjusting the time * diet interaction amongst intervention groups for baseline or changes in HEI-ID, fiber intake and added sugar intake did not influence the significance of the reductions in insulin sensitivity experienced by participants consuming dairy-rich diets. Similarly, Eelderink et al. (2019) adjusted their analyses on the effect of high and low dairy consumption on postprandial glycemic control and metabolic flexibility for fiber intake and

the intake of various beverages. These adjustments did not materially affect their results. Additionally, non-dairy studies have derived similar conclusions. For instance, in a systematic review and meta-analysis evaluating the effects of saturated and unsaturated fats on glucose homeostasis, Imamura et al. (2016) identified that replacing saturated fats with MUFAs or PUFAs improved measures of fasting glucose, insulin response, HbA1C and HOMA-IR. When covariates, such as the intakes of fiber, protein, total energy and trans fats were statistically accounted for, the significance of these findings remained unchanged.

On the other hand, observational studies often consider dietary factors as potential confounders. In this context, many researchers have determined that adjusting for dietary covariates does materially influence the significance of their results. For example, in a systematic review and meta-analysis by Chen et al. (2014), the authors identified a 4% reduction in risk of T2DM associated with an increase in dairy consumption by one serving per day. This finding became insignificant when they adjusted for other dietary factors, such as intakes of trans fat, red and processed meat, nuts, sugar-sweetened beverages and coffee ($p = 0.99$). Accordingly, the propensity to make statistical adjustments for non-study dietary factors and the impact of doing so differs between controlled trials and observational studies.

Due to the significant, interindividual differences observed in changes in insulin sensitivity in the DAIRY study, we sought to evaluate the extent to which other, uncontrolled dietary factors explained these differences. From our literature review, we identified several dietary patterns and factors with possible protective effects on insulin sensitivity. However, even when looking at the discrete effects of singular dietary interventions, this evidence is also inconsistent. For instance, Wang et al. (2017), Fechner et al. (2019), and Gesteiro et al. (2012) reported protective effects of various “healthy” dietary patterns on insulin sensitivity and resistance, while Chiavaroli et al. (2019) did not identify these effects. Similarly, both Briganti et al. (2015) and Reynolds et al. (2020) noted a beneficial influence of fiber intake on insulin resistance; however, Schioldan et al. (2018) reported no such benefits on either insulin sensitivity or insulin resistance. Lastly, though Lowndes et al. (2015) did not observe a detrimental influence of added sugar intake on insulin sensitivity, both Wang et al. (2014) and Ter Horst et al. (2016) cited adverse

effects on insulin resistance. While these studies seek to illuminate how singular dietary factors influence insulin sensitivity and resistance, they fail to address how individual dietary constituents may react with other factors in the dietary milieu. To our knowledge, little research has been conducted in this area.

As previously discussed, researchers have more recently begun to explore other drivers of inter- and intraindividual difference in response to the same dietary interventions. The bulk of the research in this area has explored the wide variations observed in the glycemic index of disparate foods in clinical studies and the corresponding limitations when utilizing the GI as a nutritional tool (Matthan et al., 2016; Vega-López et al., 2007; Vrolix & Mensink, 2010; Williams et al., 2008). Researchers have identified numerous factors that contribute to inter- and intraindividual differences in glycemic response, including variables such as HbA1C, BMI and Insulin Index (Matthan et al., 2016). Further, while factors such as genetics, diet and the gut microbiome may influence an individual's degree of insulin sensitivity, the extent to which each factor contributes to the whole is unclear (Fujisaka et al., 2018; Zeevi et al., 2015). Looking at diet specifically, research from Mozaffarian & Wu (2018) and Thorning et al. (2017) suggests that the physical structure of dairy foods, as well as the methods of processing employed, may influence how discrete dairy nutrients interact with physiological pathways to influence metabolic responses, such as insulin response. However, it is unclear how these characteristics of dairy foods interact with other dietary matrices and nutrients to orchestrate the holistic metabolic response individuals experience when consuming mixed meals. More research is needed in this area in order to truly illuminate how dietary interventions can improve insulin sensitivity and thereby lower the risk of T2DM at the population level.

Our secondary analysis has many strengths. First, the data was collected in the context of a rigorous, well-designed randomized, dietary intervention trial, inclusive of design elements such as participant stratification prior to randomization, a 4-week wash-in period, a 12-week intervention period sufficient to detect changes in study endpoints, the use of validated clinical and lab techniques to assess anthropometrics and blood chemistries, the use of validated equations for insulin sensitivity/resistance, the provision of standardized study dairy products to participants, and the monitoring of dietary compliance. Second, the collection and analysis of dietary data was also methodologically sound. Not

only was dietary intake evaluated via multiple, multi-pass 24-hour recall interviews during both the wash-in and intervention periods, but the nutrient assessment was conducted using NDSR, and the compiled dietary database was checked for accuracy by two individuals. Lastly, we conducted both *intent to treat* and *per protocol* analyses in order to evaluate the influence of participant drop-out on the overall results.

Yet, our analysis also has limitations. Based on the design of the DAIRY study, only individuals with the metabolic syndrome were enrolled; therefore, the results are not generalizable to the general population. The DAIRY study also evaluated the effects of milk, yogurt and cheese in combination, so potential differential effects of each dairy product cannot be delineated. Moreover, sample size calculations were based on the primary endpoint for the DAIRY study, so our secondary analysis of this data may be under-powered to detect significance. It is also plausible that bias could have been introduced since participants were unblinded and dietary intake was based on self-report. Residual confounding may have also been unavoidable, and covariates such as other dietary factors, genetics and the gut microbiome may have influenced our findings. Additionally, we derived an un-validated index (HEI-ID) from a validated one (HEI); it is unclear whether HEI-ID accurately reflects the totality of an individual's diet excluding the impact of dairy.

To conclude, these results demonstrate that the impact of low-fat and full-fat dairy on insulin sensitivity in individuals with the metabolic syndrome, as observed in the primary study analysis, was independent from dietary changes in fiber, added sugar, or the HEI-ID that resulted from the incorporation of dairy into study participants' diets. These effects occurred independent of changes in fat mass. Aside from one significant association between change in HEI-ID and HOMA-IR which may have been influenced by multiple testing, we also identified that HEI-ID, fiber intake and added sugar intake did not predict changes in insulin sensitivity in the context of this intervention study. Notwithstanding, T2DM and prediabetes continue to plague the US population, and lifestyle interventions are urgently needed to both prevent and treat the disease. High quality studies are needed in order to discern how the interactions between different food matrices and nutrients differentially influence the metabolic pathways that determine an individual's overall insulin response.

VI. Appendix

Supplementary Table 1. Participant Selection Criteria (Schmidt et al., submitted for publication)

Inclusion Criteria	Exclusion Criteria
▪ Age 18-75 years ▪ Presence of Metabolic Syndrome (three of five diagnostic criteria, including waist circumference, fasting plasma triglycerides, HDL-cholesterol, blood pressure, and fasting plasma glucose)) ▪ Weight stable (within 10% of current weight over the last six months) ▪ Able to attend scheduled study visits, including picking up study foods/materials at FHCRC ▪ Able to attend study initiation meeting (1.5 hours), two clinic visits (5 hours each) and two additional clinic visits (2 hours) ▪ Willing to follow assigned dietary intervention ▪ Able to provide informed consent	▪ Antidiabetic medications or insulin within the last 6 months ▪ Uncontrolled diabetes ▪ Allergic to milk protein ▪ Presence of major chronic inflammatory or autoimmune disease, or malabsorption syndromes ▪ Presence or history of liver disease or end-stage renal disease requiring dialysis ▪ Uncontrolled thyroid disease ▪ Inability or unwillingness to eat the provided foods ▪ Any contraindications for MRI scan other than body size ▪ Intake of drugs likely to interfere with study endpoints, such as corticosteroids, anabolic steroids, anti-psychotic medications, antiretroviral drugs, and immunosuppressive drugs (within three months of starting the study) ▪ Regular high-dose use of non-steroidal anti-inflammatory drugs (more than three times per week and more than 600 mg per day, within three months of starting the study) ▪ Presence or history of anemia (within three months of starting the study) ▪ History of bariatric surgery ▪ Participation in an intervention study or weight-loss program (within three months of starting the study) ▪ Alcohol intake >2 drinks per day (within 12 months of starting the study) ▪ Use of tobacco products, e-cigarettes, or recreational drugs on more than two days per month (within 12 months of starting the study) ▪ Current or recent pregnancy or breastfeeding (within 12 months of starting the study), or intention of becoming pregnant in the next six months ▪ Fasting triglycerides >1,000 mg/dL ▪ Any cancer other than non-melanoma skin cancer in the last three years ▪ Other significant health condition, as determined by researcher and Physician of Record, that makes the individual unfit to participate

Supplementary Table 2. Multiple linear regression analysis on the change in the Matsuda-DeFronzo insulin sensitivity index, *intent to treat* analysis (n=72)

	Model 1	**Model 2**	**Model 3**
Baseline HEI-ID	0.002 (-0.026, 0.031), p=0.862	-0.001 (-0.029, 0.027), p=0.941	-0.005 (-0.033, 0.024), p=0.733
Baseline fiber intake (g/1,000 kcal)	0.002 (-0.052, 0.055), p=0.952	0.007 (-0.042, 0.056), p=0.778	0.004 (-0.048, 0.055), p=0.881
Baseline added sugar intake (%E)	-0.005 (-0.051, 0.042), p=0.841	-0.003 (-0.047, 0.040), p=0.880	-0.006 (-0.051, 0.038), p=0.781
Change in HEI-ID	-0.001 (-0.028, 0.026), p=0.960	0.002 (-0.023, 0.027), p=0.865	0.005 (-0.021, 0.031), p=0.718
Change in fiber intake (g/1,000 kcal)	0.011 (-0.051, 0.073), p=0.722	0.009 (-0.049, 0.068), p=0.752	-0.005 (-0.068, 0.058), p=0.875
Change in added sugar intake (%E)	-0.001 (-0.058, 0.056), p=0.963	-0.009 (-0.061, 0.044), p=0.744	-0.006 (-0.060, 0.048), p=0.820

Data are unadjusted beta coefficients (95% CIs).

Model 1: unadjusted; change in Matsuda ISI is the dependent variable and the specified dietary factor is the independent variable.

Model 2: adjusted for baseline HbA1c, baseline area-under-the-curve glucose, baseline fasting glucose, and baseline Matsuda (may also include the baseline of any change variable, if baseline is significantly associated with delta Matsuda).

Model 3: as model 2, plus change in total fat mass, change in physical activity, and intervention group.

Supplementary Table 3. Multiple linear regression analysis on the change in the homeostasis model assessment insulin resistance (HOMA-IR) index*, intent to treat* analysis (n=72)

	Model 1	**Model 2**	**Model 3**
Baseline HEI-ID	0.001 (-0.005, 0.006), p=0.780	0.001 (-0.005, 0.007), p=0.760	0.002 (-0.003, 0.008), p=0.401
Baseline fiber intake (g/1,000 kcal)	-0.001 (-0.012, 0.009), p=0.783	-0.003 (-0.013, 0.008), p=0.628	-0.002 (-0.012, 0.009), p=0.733
Baseline added sugar intake (%E)	0.002 (-0.007, 0.011), p=0.671	0.002 (-0.007, 0.011), p=0.670	0.003 (-0.006, 0.012), p=0.555
Change in HEI-ID	-0.003 (-0.008, 0.002), p=0.222	-0.004 (-0.009, 0.001), p=0.137	-0.006 (-0.011, 0.000), p=0.034
Change in fiber intake (g/1,000 kcal)	-0.008 (-0.020, 0.003), p=0.151	-0.008 (-0.020, 0.005), p=0.222	-0.003 (-0.016, 0.010), p=0.687
Change in added sugar intake (%E)	0.007 (-0.004, 0.017), p=0.213	0.008 (-0.003, 0.019), p=0.150	0.008 (-0.003, 0.020), p=0.135

Data are unadjusted beta coefficients (95% CIs).

Model 1: unadjusted; change in HOMA-IR is the dependent variable and the specified dietary factor is the independent variable.

Model 2: adjusted for baseline HbA1c, baseline area-under-the-curve glucose, baseline fasting glucose, and baseline HOMA-IR (may also include the baseline of any change variable, if baseline is significantly associated with delta HOMA-IR).

Model 3: as model 2, plus change in total fat mass, change in physical activity, and intervention group.

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