DATE:	December 18, 2018
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SUBJECT OF PETITION:	Petition for the Authorization of a Qualified Health Claim for Yogurt and Reduced Risk of Diabetes
SUBMITTED TO:	Office of Nutrition, Labeling and Dietary Supplements (HFS-800) Center for Food Safety and Applied Nutrition Food and Drug Administration 5001 Campus Drive College Park, MD 20740

Petition for the Authorization of a Qualified Health Claim for Yogurt and Reduced Risk of Diabetes

I. INTRODUCTION

The undersigned, Danone North America (Danone), submits this petition for a qualified health claim (QHC) in reference to the ability of yogurt to reduce the risk of type 2 diabetes mellitus (T2DM). In accordance with the guidance documents posted by the Food and Drug Administration (FDA) on July 10, 2003 and in January 2009, this petition addresses all of the elements set forth in 21 C.F.R. § 101.70 for unqualified health claims.

Proposed wording of the claim is, "*Eating yogurt regularly may reduce the risk of type 2 diabetes. FDA has concluded there is limited information supporting this claim." or, "Eating yogurt regularly may reduce the risk of type 2 diabetes according to limited scientific evidence."* The claim would apply exclusively to all types of yogurt that meet FDA's standards of identity (21 C.F.R. §§ 131.200, 131.203 and 131.206). The body of evidence supporting the claim examined the effects of all types of yogurt, including with varying fat and sugar content. This evidence supports the health effects of yogurt as a food rather than related to any single nutrient or compound and thus independent of fat or sugar content. This rationale is further developed in Section III-H-2. Danone also proposes that the phrases "*about three to four servings per week*" and "*at least three servings per week*" be designated as optional components of the claim to be inserted as parenthetical statements after the word "regularly".

A. Justification and public benefits of the proposed claim

Yogurt is a delicious, nutrient dense food that is recommended as a component of all three healthy dietary patterns described in the 2015-2020 *Dietary Guidelines for Americans* (DGAs).

The nutrient profile of yogurt is characterized by high quality protein (complete and highly digestible), along with various micronutrients essential for health including vitamins A, B_2, B_5 and B_{12}, calcium, magnesium, potassium, phosphorus, iodine and zinc, while being relatively low in sodium (Wang et al., 2013). Many yogurts are also fortified with vitamin D and certain probiotics. In addition to the nutrients provided by yogurt itself, consumers of this nutritious food tend to have higher overall diet quality than non-consumers (Webb et al., 2014, Tremblay and Panahi, 2017), yogurt can replace more energy-dense snacks (Keast et al., 2015) and some evidence also suggests yogurt may assist in weight management (Tremblay et al., 2015, Schwingshackl et al., 2016, Sayon-Orea et al., 2017).

Most importantly, the proposed claim is substantiated by the totality of scientific evidence on yogurt as a food. Specifically, 10 of 12 (83 percent) of the analyses from high or medium quality prospective cohort studies (presented in 10 publications) that furnish useful information for evaluation of the proposed claim provided direct or suggestive evidence that yogurt consumption is inversely associated with risk of T2DM in subjects who were free of this disease at baseline. Furthermore, all five meta-analyses and systematic review papers that have been published reported such an inverse association based on the pooled observational data.

This scientific evidence provides compelling justification for the proposed claim which has the potential to help consumers reduce their risk of T2DM through a simple, realistic and achievable dietary modification. The incidence of T2DM has reached epidemic proportions in the U.S., and we respectfully ask FDA to exercise its enforcement discretion so that this practical, actionable information can be provided to U.S. consumers through the highly effective means of a QHC. The FDA recently made public comments highlighting that qualified health claims provide an

important pathway and incentive for food companies to increase the production, distribution, and marketing of healthy foods such as yogurt. While yogurt consumption is slowly increasing in the US, it remains at extremely low levels. Specifically, 24-hour recall data from 33,932 adults (aged 20 years or older) in the National Health and Nutrition Examination Survey (NHANES) showed a change in mean consumption from 0.04 to only 0.07 servings per day between 1999-2000 and 2011-2012, respectively (Rehm et al., 2016). Given this low consumption, such a QHC is important to encourage food companies to increase yogurt in the food supply and inform consumers of current evidence in order to help them make informed choices.

B. Governmental and professional organization recommendations

1. The 2015-2020 *Dietary Guidelines for Americans (DGAs)*

As noted above, yogurt is prominently featured in the 2015-2020 DGAs (U.S. Department of Agriculture and U.S. Department of Health and Human Services, 2015), along with other dairy including milk and cheese and/or fortified soy beverages, specifically listed as components of a healthy eating pattern in the "Key Recommendations" section of the guidelines. Furthermore, yogurt is specifically recommended as a source of dairy in all three of the healthy eating patterns described: The healthy U.S.-Style eating pattern, the healthy Mediterranean-Style eating pattern and the healthy vegetarian-style eating pattern (see Appendices 3, 4 and 5 of the DGAs). Multiple types of yogurt are also identified as nutrient dense sources of potassium (Appendix 10), calcium (Appendix 11) and vitamin D (Appendix 12) featured in these healthy eating patterns. Furthermore, potassium, calcium, and vitamin D are all identified by the DGAs as nutrients of public health concern which are lacking in the American diet.

The DGAs also specifically identified yogurt as a recommended source of dairy,

> Because most cheese contains more sodium and saturated fats, and less potassium, vitamin A, and vitamin D than milk or **yogurt**, increased intake of dairy products would be most beneficial if more fat-free or low-fat milk and **yogurt** were selected rather than cheese. Strategies to increase dairy intake including drinking fat-free or low-fat milk (or a fortified soy beverage) with meals, choosing **yogurt** as a snack, or using **yogurt** as an ingredient in prepared dishes such as salad dressings or spreads. [Emphasis supplied]

The report of the 2015 Dietary Guidelines Advisory Committee (DGAC) (Dietary Guidelines Advisory Committee, 2015) notes that reduced risk of T2DM would be one of the health benefits of increased dairy consumption. Specifically, this report states,

> Dairy foods in the USDA Food Patterns include fluid milk, cheese, **yogurt**, ice cream, milk based replacement meals and milk products, including fortified soymilk, but do not include almond or other plant-based "milk-type" products. Dairy foods are excellent sources of nutrients of public health concern, including vitamin D, calcium, and potassium. Consumption of dairy foods provides numerous health benefits including lower risk of **diabetes**, metabolic syndrome, cardiovascular disease and obesity. [Emphasis supplied]

These statements clearly demonstrate that the 2015-2020 DGAs recognize the positive contributions yogurt can make to the diet, including lowering risk of diabetes.

2. MyPlate

Lowfat and fat-free yogurts are specifically identified as a recommended source of dairy by the U.S. Department of Agriculture (USDA) in MyPlate. MyPlate is the official governmental source of consumer-oriented nutrition education in the U.S. An example of a MyPlate-oriented educational material that recognizes yogurt is shown below in Figure 1.

Figure 1
MyPlate Dairy Checklist from USDA

Source: https://twitter.com/MyPlate?ref_src=twsrc%5Egoogle%7Ctwcamp%5Eserp%7Ctwgr%5Eauthor

3. The American Diabetes Association

The latest edition of "Standards of Medical Care in Diabetes" from the American Diabetes Association (ADA) (2017) noted that yogurt consumption may be associated with reduced risk of T2DM . This document states,

> Whereas overall healthy low-calorie eating patterns should be encouraged, there is also some evidence that particular dietary components impact diabetes risk. Data suggest that whole grains may help to prevent type 2 diabetes. Higher intakes of nuts, berries, **yogurt**, coffee, and tea are associated with reduced diabetes risk. Conversely, red meats and sugar-sweetened beverages are associated with an increased risk of type 2 diabetes[1]. [Emphasis supplied]

[1]http://care.diabetesjournals.org/content/diacare/suppl/2016/12/15/40.Supplement_1.DC1/DC_40_S1_final.pdf

Yogurt is also a food that is often recommended by the ADA for people living with diabetes as part of a diabetes management plan[2].

4. The Joslin Clinical Diabetes Guidelines

Yogurt is a food that is recommended by the Clinical Nutrition Guideline for Overweight and Obese Adults with Type 2 Diabetes, Prediabetes or Those at High Risk for Developing Type 2 Diabetes by the Joslin Diabetes Center and the Joslin Clinic (version 10-19-16). The Joslin Clinical Diabetes Guidelines concludes that,

- "Recent evidence demonstrates saturated fat from dairy foods (milk, **yogurt**, cheese) may be acceptable within the total daily caloric intake [GRADE system 2B] [Emphasis supplied]
- Foods with a lower glycemic index content should be selected [GRADE system 2B] (e.g. whole grains, legumes, fruits, green leafy and non-starchy vegetables, milk and **yogurt**) [Emphasis supplied]
- The following particular foods were shown to be associated with a reduced risk of developing type 2 diabetes in some studies: Oat cereal, **Yogurt,** Dairy products, Tea, coffee and decaffeinated coffee, Green leafy vegetables, Fish and seafood (only in Asia), Red grapes, apples, blueberries, Nuts (especially walnuts) [Emphasis supplied]

In summary, yogurt is recommended as one of the preferred sources of dairy foods for healthy eating according to official U.S. government policy and by select professional organizations. Several of these recommendations specifically mention the association of yogurt with reduced risk of T2DM. This section is not intended to provide a comprehensive list of the many nutrition education materials available to consumers that recommend yogurt as part of a healthy diet;

[2] http://www.diabetes.org/food-and-fitness/food/what-can-i-eat/making-healthy-food-choices/dairy.html

however, it does show that major public health organizations recognize the benefit of encouraging the use of this nutritious food.

II. PRELIMINARY REQUIREMENTS

A. Diabetes is a disease that markedly affects the general U.S. population.

Diabetes covers several categories such as type 1 diabetes, T2DM and gestational diabetes mellitus. As noted in the introduction, the most recent data from the Centers for Disease Control and Prevention (2017) state that 23.1 million adults (7.2% of the population) had been diagnosed with diabetes in 2015 and another 7.2 million individuals were believed to have this disease but had not yet been diagnosed. Approximately 95% of the population with diabetes is estimated to have T2DM. Furthermore, an additional 84.1 million adults (33.9% of the population) in the U.S. were estimated to have pre-diabetes in 2015 and only about 11.6% of them were aware of this condition. T2DM develops over time upon a progression from normal glucose tolerance with insulin resistance to impaired glucose tolerance to the full disease and this occurs due to progressive loss of β-cell insulin secretion and peripheral insulin resistance. Based on trends since 2000, an estimated 40% of US adults age 20 years and older will develop diabetes in their lifetime. Clearly diabetes (especially T2DM) is a disease that markedly affects the general U.S. population.

T2DM is a multifactorial disease. While some genetic influences have been identified, it is strongly influenced by lifestyle factors, in particular diet and weight control; and the risk of developing T2DM increases with age, poor diet, obesity, and physical inactivity. According to the American Diabetes Association, the T2DM diagnosis criteria is fasting plasma glucose concentrations $\geq$7.0 mmol/L or 2-h plasma glucose concentrations $\geq$ 11.1 mmol/L during an

oral glucose tolerance test (OGTT) when using dose of 75 g glucose or HbA1c $\geq$ 6.5% (48 mmol/mol) or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL.

B. Yogurt contributes taste, aroma and nutritive value to the diet

The numerous forms, flavors and varieties of yogurt available in the marketplace is a testament to the fact that yogurt contributes taste and aroma to the diet. Furthermore, as noted above, most yogurts contain high-quality protein and micronutrients including riboflavin, vitamin B12, magnesium, and zinc, as well as nutrients of concern in the American diet such as calcium and vitamin D (Webb et al. 2014). Some yogurts also contain additional probiotic cultures that may provide additional benefits.

C. Yogurt is safe and lawful

Standards of identity have been codified to assure the safety and lawfulness of yogurt (21 C.F.R. 21 §131.200), lowfat yogurt (21 C.F.R. §131.203), and nonfat yogurt (21 C.F.R. §131.206). As noted previously, Danone proposes that foods must comply with any of these standards in order to be eligible for the proposed claim, based on the body of scientific evidence as described below.

III. SUMMARY OF SCIENTIFIC EVIDENCE SUPPORTING THE CLAIM

A. Overview

Scientific evidence provides compelling support for the proposed claim. This contention is based on the large majority of high and moderate quality prospective cohort studies that have reported significant protective associations between yogurt consumption and T2DM in subjects who were free of this disease at baseline. The food frequency questionnaires (FFQs) employed

by these studies included multiple forms of yogurt with varying fat or added sugar content. The scientific evidence shows that consumption of yogurt, as a food category, is inversely associated with the incidence of T2DM (see additional information in Section III. H. 2). This protective association is also supported by all five published meta-analyses which have unanimously reported such protective associations based on pooled data from these studies. In comparison, the identified controlled intervention studies that examined the effect of yogurt on T2DM-related surrogate endpoints were not sufficiently controlled to provide useful information for assessment of a health claim in this area, as described in the agency's guidance documents note above. For example, in these interventions, conventional yogurt was compared to a modified yogurt (e.g., supplemented with brewer's yeast, vitamin D, probiotic bacteria, etc.) but not to a non-yogurt placebo. Therefore, the effect of conventional yogurt on T2DM-related parameters could not be assessed. However, the consistency of the relevant observational data is more than adequate to justify the proposed qualified health claim which would benefit the US population that is at high risk of developing diabetes.

B. Literature Search of Pertinent Evidence

A comprehensive search of the existing, publicly available scientific literature (MEDLINE database via PUBMED) was performed on April 3, 2018 with no date limitations to identify all relevant studies pertaining to yogurt consumption and diabetes incidence, glucose or insulin related variables.

Search terms were as follows (Yogurt OR yoghurt OR yoghourt OR "fermented milk" OR "cultured milk" OR "dairy products" OR "dairy product") AND (diabet$" or "diabet*" or "diabetes OR "glycated hemoglobin" OR "glycated haemoglobin" OR "Hemoglobin A1c" OR "impaired fasting glucose" OR "oral glucose tolerance test" OR "2-h Glucose" OR "fasting

blood glucose " OR "fasting plasma glucose" OR "fasting glucose" OR glycemic OR glycemia OR glycaemia OR "random plasma glucose" OR insulin OR insulinaemia OR insulinemia OR insulinaemic OR "insulin resistance" OR "insulin sensitivity" OR "euglycemic hyperinsulinemic clamp" OR homeostasis model assessment" OR "quantitative insulin sensitivity check index" OR "insulin sensitivity index" OR "Matsuda index" OR FBG OR FPG OR HbA1c OR HOMA-IR OR QUICKI OR QUICK1 OR ISI or "hyperglycemia" OR "hyperglycaemia" OR "prediabetes" OR "glucose tolerance" OR "Metabolic Syndrome" OR "MetS"OR MetX)".
The inclusion and exclusion criteria used to identify studies germane to the proposed claim followed the PICOS (Population, Intervention, Comparison, Outcome) framework.

C. Reviews, systematic review papers and meta-analyses

Various meta-analyses that have examined pooled data from prospective cohort studies on the association between yogurt consumption and the incidence of T2DM (Tong et al., 2011, Aune et al., 2013, Gao et al., 2013, Chen et al., 2014, Gijsbers et al., 2016) have reported significant inverse associations.

The earliest meta-analysis was published by Tong et al. (2011) based on four cohorts from three publications (Choi et al., 2005, Liu et al., 2006, Kirii et al., 2009). The authors found that yogurt consumption was inversely associated with incident T2DM (comparing the highest to the lowest intake category[3], RR (Relative Risk)=0.83; 95% CI (Confidence Interval), 0.74-0.93).

Aune et al. (2013) conducted a systematic review and meta-analysis that employed pooled data from seven prospective cohort studies that examined the association between yogurt

[3] Unless otherwise noted, associations expressed as Relative Risk (RR) or similar terms pertain to the highest vs. lowest consumption category for the parameter being reported.

consumption and T2DM (Choi et al., 2005, Liu et al., 2006, Kirii et al., 2009, Margolis et al., 2011, Sluijs et al., 2012, Grantham et al., 2013, Soedamah-Muthu et al., 2013) and between combined fermented dairy consumption (including yogurt, cheese and thick fermented milk) and T2DM (Sluijs et al., 2012). These studies included 19,082 cases of T2DM among 254,892 total participants. The summary RR using a random effects model for high vs. low yogurt consumption was 0.86 (95% CI, 0.75-0.98) with moderate heterogeneity (I^2 = 58.9%, p for heterogeneity = 0.02). The summary RR for 200 grams yogurt consumption per day was 0.78 (95% CI, 0.60-1.02) with a moderate-high heterogeneity (I^2 = 69.9%, p = 0.003). There was evidence of a non-linear protective association between yogurt and T2DM with reduction in risk until intakes of 120-140 g/d (about four servings/week), and no further lowering in risk thereafter.

Gao et al. (2013) conducted a meta-analysis using the same seven cohort studies as Aune et al. (2013) (Choi et al., 2005, Liu et al., 2006, Kirii et al., 2009, Margolis et al., 2011, Sluijs et al., 2012, Grantham et al., 2013, Soedamah-Muthu et al., 2013) and reported very similar results. The pooled RRs between high and low yogurt consumption and risk of T2DM was 0.85 (95% CI, 0.75-0.97) based on 254,552 subjects and 18,532 cases with moderate heterogeneity (1^2 = 55%, p=0.02). A 50-gram increment of daily yogurt consumption was also inversely associated with T2DM (RR=0.91; 95% CI, 0.82-1.00).

Chen et al. (2014) examined possible associations between yogurt consumption and T2DM from three prominent prospective cohort studies: The Health Professionals Follow-Up Study (1986 to 2010), the Nurses' Health Study (1980 to 2010) and the Nurses' Health Study II (1991 to 2009). As part of this publication, a meta-analysis was conducted on the results from these studies as well as six additional prospective cohort studies that examined the association between yogurt (5

studies) and between combined cheese, yogurt and thick fermented milk consumption (1 study) and incidence of T2DM (Liu et al., 2006, Kirii et al., 2009, Margolis et al., 2011, Sluijs et al., 2012, Grantham et al., 2013, Soedamah-Muthu et al., 2013). There were 35,863 cases of T2DM reported among 459,790 participants. Each daily serving of yogurt was associated with a reduced incidence of T2DM (RR=0.86; 95% CI, 0.78-0.94) with significant heterogeneity (I^2 = 63.2%, p=0.005). In comparison, there was no such association for total dairy consumption (RR=0.98; 95% CI, 0.96-1.01), with significant heterogeneity (I^2 = 58.8%, p=0.003). The RRs for the random-effect model per each daily serving of yogurt was 0.82 (95% CI, 0.70-0.96) while the analogous RR for the fixed-effects model was 0.84 (95% CI, 0.78-0.90). The authors concluded, "We found that higher intake of yogurt is associated with a reduced risk of T2DM, whereas other dairy foods and consumption of total dairy are not appreciably associated with incidence of T2DM. The consistent findings for yogurt suggest that it can be incorporated into a healthy dietary pattern. However, randomized clinical trials are warranted to further examine the causal effects of yogurt consumption as well as probiotics on body weight and insulin resistance."

Gijsbers et al. (2016) conducted a meta-analysis of yogurt consumption and T2DM based on 11 studies [yogurt consumption (9 studies), cheese, yogurt and thick fermented milk consumption (1 study) and fermented milk consumption (1 study)] (Liu et al., 2006, Kirii et al., 2009, Margolis et al., 2011, Sluijs et al., 2012, Grantham et al., 2013, Soedamah-Muthu et al., 2013, Chen et al., 2014, Diaz-Lopez et al., 2015, Ericson et al., 2015) among 438,140 participants. There was a 14 percent reduced risk of T2DM for an 80 g/d intake of yogurt (RR=0.86; 95% CI, 0.83-0.90, p <0.001) with significant heterogeneity (I^2 = 73%, p=0.001). There was no further risk reduction for higher intakes. The RR for a 50-gram incremental increase in yogurt consumption was 0.94

(95% CI, 0.90-0.97) for the entire sample, with a stronger protective association among women (RR=0.89; 95% CI, 0.83-0.95) and among those greater than 60 years of age (RR=0.74; 95% CI, 0.60-0.90). The latter calculation was based on only two studies. The authors concluded, "This dose-response meta-analysis of observational studies suggests a possible role for dairy foods, particularly yogurt, in the prevention of T2DM. Results should be considered in the context of the observed heterogeneity."

The most recent review of observational studies pertaining to yogurt (and other dairy) and T2DM was reported by Salas-Salvado et al. (2017). These authors noted that the most recent meta-analysis (Gijsbers et al., 2016) reported that yogurt consumption of 80-125 g/d resulted in a 14% reduction in the risk of T2DM compared to no consumption. The authors stated, "We conclude that yogurt consumption, in the context of a healthy dietary pattern, may reduce the risk of type 2 diabetes in healthy and older adults at high cardiovascular risk."

Pasin and Comerford (2015) published a systematic review of the clinical evidence in the area of T2DM and dairy products. The paper noted that the majority of clinical trials that examined the effect of dairy protein supplementation in subjects with T2DM have been limited to acute studies designed to measure glycemic indices. However, the authors conclude, "Despite the inconsistencies in study design between the yogurt trials, such as the amount of yogurt consumed, or the addition of vitamins, minerals, or probiotic strains, the results show the promise of beneficial effects from fortified cultured dairy product consumption on glycemic control and related markers (i.e., HbA1c, insulin sensitivity, lipoprotein concentrations, inflammatory molecules, endothelial biomarkers, and antioxidant status). Further studies on popular cultured dairy products such as conventional yogurts, Greek yogurt, and kefir would

provide valuable insights on how various probiotic strains and nutrient fortifications may affect insulin and glucose responses differently than noncultured dairy products."

Two additional publications that systematically reviewed the literature concluded that yogurt consumption is likely to be protective of T2DM. Drouin-Chartier et al. (2016) concluded that there is a "high" quality of evidence for such an association based on the five meta-analyses discussed above along with two prospective cohort studies that were not included in these meta-analyses (O'Connor et al., 2014, Diaz-Lopez et al., 2015). In addition, Micha et al. (2017) categorized the protective association between yogurt intake and incidence of T2DM as "probable or convincing" based on an assessment of the epidemiologic literature using the Bradford Hill criteria. There was "consistent evidence from several well-designed studies with relatively few limitations" for the Hill criteria of temporality, coherence, specificity, and biological gradient while the criteria of strength, consistency, analogy, plausibility and experiment were designated "consistent evidence from several studies but with some important limitations".

The publications discussed in this section show that the totality of the literature supports the proposed claim. In addition, the individual observational studies discussed in the following section provide further relevant and compelling support for the proposed claim.

D. Observational studies

Detailed information extracted from these individual observational studies is presented in Table 1. This information includes the study design, population characteristics, dietary assessment methodology, diabetes assessment methodology, the amount of yogurt consumed in each consumption category, the number of cases of T2DM observed, and detailed results with respect

to the association of yogurt with incidence of T2DM or its surrogate markers and reviewer comments. The studies were classified as low, medium or high quality according to the criteria specified by FDA in the January 2009 Guidance documented cited above. A synopsis of each study and an assessment of their overall support for the proposed claim are provided in the following section.

1. High and moderate quality studies that provide direct, consistent support for the proposed claim

The following observational studies are of high or medium quality and provide clear evidence that yogurt consumption is significantly associated with reduced risk of T2DM in populations that can be extrapolated to healthy U.S. residents. All of the T2DM-related outcome measures reported in these studies showed a statistically significant protective association regardless of the form (e.g., fat level) of yogurt examined.

Liu et al. (2006) reported that multivariate adjusted yogurt consumption was inversely associated with incidence of T2DM (RR=0.82; 95% CI, 0.70-0.97, p for trend[4] = 0.03) among 39,876 women (aged 47-63 years at baseline) after an average follow-up period of 10 years. The women were members of the Women's Health Study residing in the U.S. Potentially confounding variables that were used for multivariate adjustment were total energy intake, randomized-treatment assignment, age, family history of diabetes, smoking status, BMI, hypercholesterolemia, hypertension, hormone usage, physical activity, alcohol consumption, and

[4] Please note that throughout this document, P-values that are noted "for trend" are for the overall linear trend across categories of consumption and do not always refer to significance of the specific Relative Risk value, which may be comparing categories of higher vs. lower consumption. Significance of the RR values is indicated by the lack of unity in the 95% Confidence Interval.

dietary intakes of fibers, total fat, calcium, vitamin D, magnesium and glycemic load. **FDA Quality Score = High**

Margolis et al. (2011) conducted a prospective cohort study among 82,076 members of the Women's Health Initiative during an average follow-up period of 7.9 years. The highest quintile of yogurt consumers (two or more servings per week) experienced a 54% reduction in the risk of T2DM (RR=0.46; 95% CI, 0.31-0.68, p for trend =0.004) after adjustment for age, race/ethnicity, total energy intake, income, education, smoking, alcohol consumption, postmenopausal hormone use, physical activity, family history of diabetes, BMI, blood pressure and dietary factors including glycemic load, total fat, dietary fiber and magnesium intake. The authors concluded, "High yogurt consumption was associated with a significant decrease in diabetes risk." **FDA Quality Score = High**

Chen et al. (2014) conducted an analysis among 67,138 members of the Nurses' Health Study from data collected between 1980 and 2010. Yogurt intake was associated with a significant reduction in risk of T2DM (RR=0.84; 95% CI, 0.78-0.91, P for trend <0.001) for the highest quartile of intake (2.9 servings per week compared to less than one serving/month). The RR for one incremental serving of yogurt per day was also significantly protective (RR=0.75; 95% CI, 0.65-0.86). The data were adjusted for numerous potential confounding variables: age, follow up period, BMI, total energy intake, race, smoking status, physical activity, alcohol consumption, menopausal status, menopausal hormone use, family history of diabetes, diagnosed hypertension or hypercholesterolemia at baseline, glycemic load of the diet as well as intake of *trans*-fats, red and processed meat, nuts, sugar sweetened beverages, coffee and other individual dairy foods. The authors concluded, "Higher intake of yogurt is associated with a reduced risk of T2D [Type

2 Diabetes], whereas other dairy foods and consumption of total dairy are not appreciably associated with incidence of T2D." **FDA Quality Score = High**

A prospective cohort study among 3,434 Spanish participants in the PREDIMED study (Prevención con Dieta Mediterránea) during a mean follow-up period of 4.1 years was reported by Diaz-Lopez et al. (2015). Subjects with the highest total yogurt intake (123-185g/day) exhibited a 40% lower risk of T2DM (RR= 0.60; 95% CI, 0.42-0.86, P for trend =0.002) compared to those with the lowest intake (1.7-29g/day). Notably, when separately evaluated, both low and full fat yogurts exhibited protective associations against T2DM. The RR for the highest tertile of lowfat yogurt intake (96-157g/day) vs. the lowest was 0.68 (95% CI 0.47-0.97), P for trend =0.047; while analogous data for full fat yogurt (29-71g/day) was 0.66 (95% CI 0.47-0.92), P for trend =0.020. The data were adjusted for age, sex, BMI, intervention group, baseline smoking status, physical activity, educational level, hypertension or antihypertensive drug use, fasting glucose, HDL-C, TGs and dietary variables including vegetable, legume, fruit, cereal, meat, fish, olive oil, nut and alcohol consumption. An updated assessment of the association between full fat yogurt and T2DM among 3,349 members from this cohort after 4.3 years confirmed the protective association (RR=0.65, 95% CI, 0.45-0.94, p for trend =0.02) and was subsequently reported by Guasch-Ferré et al. (2017) (see below). The authors concluded, "A healthy dietary pattern incorporating a high consumption of dairy products and particularly yogurt may be protective against T2DM in older adults at high cardiovascular risk." **FDA Quality Score = Moderate**

O'Connor et al. (2014) conducted a nested case-cohort study among 4,127 members of the Epic – Norfolk Cohort in the UK. After exclusion for uncertain T2DM status, incomplete or implausible dietary data and certain chronic diseases, the final sample included 753 cases of

T2DM and 3,374 healthy controls. The highest tertile of yogurt consumption (44-513g/day) was inversely associated with T2DM (RR=0.72; 95% CI, 0.55-0.95, P for trend = 0.017) compared to subjects with no yogurt intake after adjustment for age, sex, BMI, family history of diabetes, smoking, alcohol consumption, physical activity index, social class, education and intakes of energy, fiber, fruit, vegetables, red meat, processed meat and coffee. The mean follow-up period was 11 years. The authors concluded, "Greater low-fat fermented dairy products intake, largely driven by yoghurt intake, was associated with a decreased risk of type 2 diabetes development in prospective analyses. These findings suggest that the consumption of specific dairy types may be beneficial for the prevention of diabetes, highlighting the importance of food group subtypes for public health messages." **FDA Quality Score = Moderate**

Babio et al. (2015) examined individuals from the PREDIMED cohort who were at high risk of cardiovascular disease (CVD). The study examined one of the metabolic syndrome (MS) factors, i.e. high fasting plasma glucose (defined as ≥100 mg/dL). Yogurt consumption was inversely associated with high fasting plasma glucose (FPG) (RR=0.72; 95% CI, 0.61-0.85, p for trend = 0.004) after correction for sex, age, leisure time physical activity, BMI, current smoking, former smoking, use of hypolipidemic, antihypertensive or hypoglycemic agents (including insulin) at baseline plus mean consumption during the follow-up period of vegetables, fruit, legumes, cereals, fish, red meat, cookies, olive oil, nuts and alcohol. Notably, as seen in other studies which separately evaluated types of yogurt, a protective association was observed for lowfat yogurt (RR=0.81; 95% CI, 0.68-0.96. p for trend =0.13) and full fat yogurt (RR=0.79; 95% CI, 0.66-0.94, p for trend =0.005). The authors concluded that yogurt is associated with reduced risk of all MS components (including elevated fasting blood glucose (FBG) concentrations). **FDA Quality Score = Moderate**

The most recent study to provide direct support for the proposed claim was published by Guasch-Ferré et al. (2017) who reported that full fat yogurt consumption was inversely associated with T2DM (RR=0.65; 95% CI, 0.45-0.94, p for trend =0.02) among 3,349 members of the PREDIMED cohort after an average follow-up period of 4.3 years. This outcome was an updated finding from the report by Diaz-Lopez et al. (2015) discussed above. No other outcome measures related to T2DM were reported in this publication. **FDA Quality Score = Moderate**

2. High and moderate quality studies that provide suggestive support for the proposed claim

The following observational studies are of high or moderate quality and provide additional suggestive evidence that yogurt consumption is associated with reduced risk of T2DM, however, one or more of the outcome measures reported in these studies did not show a statistically significant protective association.

Beydoun et al. (2008) assessed ethnic differences in dairy and related nutrient consumption and their association with obesity, central obesity and the MS using 1999-2004 NHANES data. The analysis included 4,519 adults 18+ years of age who provided complete data on diet as well as anthropometric, biochemical and other parameters related to the MS. In multivariate linear regression, yogurt intake (servings) was significantly associated with reduced FBG concentrations in the overall sample ($r= -4.29$, $p<0.05$) and among men ($r= -7.38$, $p<0.05$) but not women ($r= -2.92$, $p>0.05$) after adjustment for age, sex, ethnicity, education, poverty income ratio, energy intake and physical activity. Each yogurt serving was also associated with a 2 to 2.5-fold lower prevalence of obesity, central obesity and MS in the overall sample. The NHANES study uses a cross-sectional design, but employs a large, geographically and demographically balanced sample and represents the best dietary intake data available for the

U.S. population. Therefore, the study was assigned a "moderate" FDA quality score rather than the low score that characterizes most cross-sectional studies. The authors concluded, "Our findings, based on the most recent nationally representative US data, revealed a significant inverse association between consumption of dairy products and their related nutrients, particularly milk, yogurt, calcium, and magnesium, and health outcomes such as obesity, central obesity, and MetS [metabolic syndrome]." **FDA Quality Score = Moderate**

Chen et al. (2014) analyzed data from 85,884 members of the Nurses' Health Study II from 1991 to 2009. Greater yogurt intake was associated with a borderline significant reduction in risk of T2DM for the highest vs. lowest quartile of intake (2.7 servings per week compared to 0 servings/month, RR= 0.90; 95% CI, 0.81-1.00) but with a significant overall trend across quartiles (P for trend =0.02) during a maximum follow-up of 16 years. The data were adjusted for age, follow up period, BMI, total energy intake, race, smoking status, physical activity, alcohol consumption, menopausal status, menopausal hormone use, family history of diabetes, diagnosed hypertension or hypercholesterolemia at baseline, glycemic load of the diet as well as intake of trans-fats, red and processed meat, nuts, sugar sweetened beverages, coffee and other individual dairy foods. The association between one incremental daily serving of yogurt, evaluated linearly, and T2DM did not reach statistical significance (RR=0.94; 95% CI, 0.80-1.10).

As described above, this same analysis also included findings from the separate Nurses' Health Study (RR=0.84; 95% CI, 0.78-0.91, p for trend =0.02) and Health Professionals' Follow-Up Study (RR=0.95; 95% CI, 0.84-1.08, p=0.30) cohorts. The pooled, multivariate-adjusted data from the three studies showed that yogurt was inversely associated with the risk of T2DM (RR=0.88; 95% CI, 0.83-0.93, p for trend <0.001). Therefore, the collective data from these

three large US prospective cohort studies provides strong support for the proposed claim. **FDA Quality Score = High**

Hruby et al. (2017) conducted a prospective study on 2,809 members of the Framingham Heart Study Offspring Cohort over an average follow-up period of 12 years in order to assess the association between yogurt and prediabetes (defined as FBG ≥ 100 and <125 mg/dL or glucose ≥140 to <200 mg/dL after a 2-h OGTT) and T2DM (FBG ≥126 mg/dL). Yogurt consumption was not associated with the development of prediabetes among 1,867 subjects free of this condition at baseline when comparing the upper quartile of consumption (three or more servings per day) with non-consumers (RR=0.95; 95% CI, 0.72-1.26, P for trend =0.33) after adjustment for age, sex, energy intake, parental history of diabetes, smoking status, dyslipidemia or treatment, hypertension or treatment, baseline BMI, weight change since baseline as well as intake of coffee, nuts, fruits, vegetables, meats, alcohol, fish, total glycemic index and other dairy. There was a non-linear association between yogurt intake and the development of prediabetes among these subjects. Yogurt intake in the third quartile (1 to <3 servings per day) was inversely associated (RR=0.76; 95% CI, 0.62-0.92) with development of this condition compared to the first quartile (zero servings per day). Yogurt consumption was not associated with the development of T2DM among the small number (N=925) of subjects with prediabetes at baseline (RR=1.24; 95% CI, 0.67-2.29, P for trend =0.89). **FDA Quality Score = High**

Kim and Kim (2017) reported 10-year follow-up data from 2,651 members of the Korean Genome and Epidemiological Study. Yogurt consumption was inversely associated with hyperglycemia (defined as FBG ≥5.6mmol/l, current use of insulin or oral hypoglycemic medications or a physician's diagnosis of T2DM) (RR=0.73; 95% CI, 0.62-0.85, p for trend <0.0001) for the entire cohort after adjustment for age, sex, BMI, residential location,

educational level, household income, smoking status, alcohol intake, physical activity as well as energy, calcium and fiber intake. Similar results were seen for men (RR=0.66; 95% CI, 0.52-0.82, p for trend <0.0001) while those for women did not reach statistical significance comparing the highest to lowest quartile (RR=0.81; 95% CI, 0.65-1.02) but did reach statistical significance across quartiles (P for trend = 0.0195). This study provides additional evidence that yogurt consumption is associated with reduced risk of T2DM using a surrogate endpoint accepted by FDA for this disease (i.e., FBG), although the relevance of the study to the U.S. population could be limited due to dietary and cultural differences. **FDA Quality Score = Moderate**

3. High and moderate quality studies that do not provide support for the proposed claim

The studies discussed in this section were assigned high or moderate FDA quality ratings but did not report statistically significant inverse associations between yogurt consumption and T2DM. Many of the RRs reported were less than 1.0 (indicating a non-significant protective association). No study reported a statistically significant *increased* risk of T2DM.

Choi et al. (2005) reported that yogurt intake was not significantly associated with T2DM (RR=0.83; 95% CI, 0.66-1.06; p-for trend = 0.11) after an average of 12 years follow-up among 41,254 men in the Health Professionals Follow-up Study. These subjects experienced 1,243 cases of T2DM. The analysis compared the highest quartile (≥2 servings of yogurt per week) vs. lowest (<1 serving per month) and was adjusted for age, total energy intake, biennial follow-up time (6 periods), family history of diabetes, smoking, BMI, hypercholesterolemia, hypertension, physical activity, and intake of alcohol, cereal fiber, *trans* fat, polyunsaturated to saturated fat ratio and glycemic load. Multivariate analysis showed that total low-fat dairy foods, including skim/low-fat milk, sherbet, yogurt, cottage/ricotta cheese, were inversely associated with

incident T2DM (RR=0.74; 95% CI, 0.60-0.91; p for trend <0.001) while high-fat dairy foods were not (RR=0.82; 95% CI, 0.66-1.02, p for trend =0.12). These findings were subsequently updated and reported by Chen et al. (2014) who observed that yogurt consumption was not significantly associated with T2DM (RR=0.85; 95% CI, 0.68-1.06) among 41,436 members of this cohort who experienced 3,364 cases of T2DM after a maximum of 24 years follow up. However, the confidence intervals of these findings included the potential for meaningful benefit and were consistent with prior significant studies. In addition, as previously noted, pooled data from this study as well as the Nurses' Health Study and the Nurses' Health Study II showed an overall inverse association between yogurt consumption and T2DM (RR=0.88; 95% CI, 0.83-0.93, p for trend =0.02). **FDA Quality Score = High**

Kirii et al. (2009) studied the association of yogurt with T2DM among 59,796 members of the Japan Public Health Center prospective cohort study with a mean follow-up of five years. There was no association between the lowest (zero g/d) and highest (≥60g/d) tertiles of yogurt consumption and T2DM among men (RR=1.01; 95% CI, 0.75-1.36, p for trend =0.94) or women (RR= 0.77; 95% CI, 0.58-1.01, p for trend =0.13) based on a total of 1,114 T2DM cases. The data were adjusted for age, area, BMI, family history of diabetes, smoking status, alcohol intake, history of hypertension, exercise frequency, coffee consumption, energy adjusted magnesium intake and total energy intake. The 147-item FFQ used in this study was validated for vitamin D and calcium, but it was not clear whether this instrument was validated for dairy. In addition to these shortcomings, this study has little applicability to the proposed claim because it was conducted in Japan. Numerous differences may make it difficult to extrapolate results obtained in Japanese subjects to the healthy U.S. population. **FDA Quality Score = Moderate**

Grantham et al. (2013) studied 5,582 participants in the Australian Diabetes Obesity and Lifestyle Study (AusDiab) who experienced 209 cases of T2DM during the average five-year follow-up period. Yogurt consumption was not associated with reduced risk of T2DM in men (RR=1.02; 95% CI, 0.56-1.88), women (RR=1.23; 95% CI, 0.74-2.04) or the total population (RR=1.14; 95% CI, 0.78-1.67) when comparing the upper and lower tertiles after adjustment for age, sex, energy intake, family history of diabetes, education level, physical activity, smoking, triglycerides, HDL concentration, systolic blood pressure, waist circumference and hip circumference. The median intake of yogurt in men and women was 20 and 41g/day, respectively. A total of 35.3% of men and 18.4% of women did not consume this food. The amount of yogurt consumed for each tertile was not provided. However, the average daily intake of yogurt among *consumers* of this food suggest an average intake of only about 30.9 g/d for men and 50 g/d for women (in comparison, one serving of yogurt (one cup) = 245 g). Given this relatively modest intake, it is possible that the highest tertile of yogurt intake was insufficient to exert a beneficial effect on glucose homeostasis. The study was also relatively small compared to other prospective cohort studies and observed only 209 T2DM cases. There was only one other prospective cohort study in Table 1 with a smaller number of subjects (3,799) (Hruby et al., 2017) while six cohorts (in four publications) had 50,000 subjects or more (Choi et al., 2005, Margolis et al., 2011, Kirii et al., 2009, Chen et al., 2014). In addition, 50.3% of the original cohort was excluded from the analysis due to incomplete data or failure to return for the five-year follow-up. A separate publication regarding this cohort reported that eligible participants who responded for testing had significantly lower 2-hour plasma glucose and HbA1c concentrations at baseline than those who did not (Magliano et al., 2008). It is therefore likely that the results obtained from study participants do not reflect the general population. In

addition, the paper provided little information on the FFQ used; and it is unclear whether this instrument was validated for yogurt. Hodge et al. (2000) reported that this FFQ has been validated for nutrient intake, but no such validation for dairy or other foods was reported. The limitations of this study with respect to the proposed claim make it difficult to draw meaningful conclusions. **FDA Quality Score = Moderate**

Soedamah-Muthu et al. (2013) reported that yogurt consumption was not associated with risk of T2DM (RR= 1.04; 95 % CI, 0.77-1.42, P for trend =0.77) among 4,186 London-based civil servant workers during a 9.8 year follow-up period. Yogurt intake for the upper vs. lower tertiles were 117 g/d (less than half a serving per day) and zero g/d, respectively, and the data were adjusted for age, ethnicity, employment grade, smoking, alcohol intake, BMI, change in BMI throughout the study, physical activity, family history of coronary heart disease or hypertension and dietary factors including intake of fruit, vegetables, bread, meat, fish, coffee, tea and total energy. As similarly noted for Grantham et al. (2013), this study had relatively low intakes of yogurt and was relatively small compared to other prospective cohort studies as was the number of T2DM cases identified (273). In addition, the FFQ used in this study was not validated for dairy (Brunner et al., 2001) and the assessment of such products had been problematic for the initial (phase 3) follow-up period. Consequently, the investigators used data from the second follow-up period (phase 5) as the baseline for this study. Regardless of prior problems with the dietary assessment of dairy, the fact that the FFQ was not validated is a serious concern that severely limits the conclusions that can be drawn. This study is being given a "moderate" FDA quality score due to its prospective design and other positive attributes; however, the lack of a validated dietary assessment tool for dairy products severely limits it applicability to the proposed claim. **FDA Quality Score = Moderate**

Chen et al. (2014) conducted an analysis of data from 51,529 men (aged 50-75 years) who were members of the Health Professionals Follow-Up Study collected between 1986 and 2010. There was no association between yogurt consumption and T2DM for the highest vs. lowest intake category (RR=0.95; 95% CI, 0.84-1.08) during a maximum follow-up period of 24 years. The data were adjusted for age, follow up period, BMI, total energy intake, race, smoking status, physical activity, alcohol consumption, menopausal status, menopausal hormone use, family history of diabetes, diagnosed hypertension or hypercholesterolemia at baseline, glycemic load of the diet as well as intake of *trans*-fats, red and processed meat, nuts, sugar sweetened beverages, coffee and other individual dairy foods. The association between one incremental serving of yogurt per day and T2DM was also not significant (RR=0.85; 95% CI, 0.68-1.06).

As noted previously, this publication reported that when the results of this cohort were pooled with data from the Nurses' Health Study and the Nurses' Health Study II, yogurt consumption was inversely associated with the risk of T2DM (RR=0.88; 95% CI, 0.83-0.93, p for trend <0.001). Therefore, the collective data from these three large US prospective cohort studies provides strong support for the proposed claim. **FDA Quality Score = High**

Brouwer-Brolsma et al. (2016) reported that yogurt intake was not associated with T2DM among 2,974 Dutch participants in the Rotterdam Study after an average of 9.5 years (RR = 0.85; 95% CI, 0.64-1.14, P for trend =0.53). The data were adjusted for age and sex, lifestyle factors (alcohol consumption, smoking, education, BMI and physical activity), dietary factors (total energy intake, energy adjusted meat intake, energy adjusted fish intake) and potential intermediates (i.e. total cholesterol, HDL-cholesterol, C-reactive protein and hypertension). Mean yogurt consumption in the lowest (zero g/d) and highest (≥109 g/d) quartiles were used for this assessment. There were 7,983 subjects eligible to participate in the study; however reliable

dietary intake data and T2DM incidence were only available for 2,974 (37%). No data were provided on significant differences between individuals who participated in the study and those who did not. The relatively small size of this study, relatively low yogurt intake, and the modest number of T2DM cases (395) may have contributed to the broad 95% CIs observed and lack of statistical significance. More importantly, as with the two previous studies discussed in this section, the FFQ used was validated for dairy-related *nutrients*, but not for yogurt or other dairy *products* (Klipstein-Grobusch et al., 1998). As noted above, this lack of validation is a serious concern that severely limits the conclusions that can be drawn from this study with respect to the proposed claim. **FDA Quality Score = Moderate**

4. Low quality studies

Seventeen low quality studies were identified that examined associations between yogurt consumption and T2DM and/or one or more of its surrogate endpoints. About half of these studies provided some support for the proposed claim, though none of these studies are robust enough to materially influence FDA's assessment. All but three of these studies (Pereira et al., 2002, Sayon-Orea et al., 2015, Panahi et al., 2017a) used a cross-sectional design. The agency's 2009 Guidance document on health claims indicates that such studies can be useful for identifying possible correlates between diet and prevalence of a disease, and for providing baseline information for subsequent prospective studies, but because such studies measure dietary intake and disease status at a single point in time, it is not possible to determine whether dietary intake of the substance is a factor affecting disease risk or a result of having a disease. Detailed information about these studies is presented in Table 1 and the main findings are enumerated below in chronological order. However, a detailed discussion of these studies is not provided due to their limited ability to help assess the validity of the proposed claim.

Pereira et al. (2002) reported that yogurt consumption was not significantly associated with risk of abnormal glucose homeostasis (RR=0.44; 95% CI, 0.12, 1.62) or insulin resistance syndrome (RR=0.58; 95% CI, 0.20-1.66) (defined as high FPG, elevated fasting plasma insulin and/or use of medications to control blood glucose) among 3,157 members of the U.S.-based Coronary Artery Risk Development in Young Adults (CARDIA) study. The mean follow-up period was ten years. This study used a prospective cohort design but was given a low quality score because only data from overweight (BMI $\geq$ 25 kg/m^2) cohort members at baseline were used to assess the association between yogurt consumption and T2DM. This approach was taken because of an interaction between dairy intake and overweight status. Therefore, the results reflect only the overweight and obese members of the cohort and cannot be extrapolated to the entire population. In addition, the study did not assess T2DM *per se* but used "abnormal glucose homeostasis" defined as fasting plasma insulin ≥20 μU/ml, FBG of ≥110 mg/dl, or use of medications to control blood glucose. These parameters are not accepted standards for the incidence of diabetes.

Panagiotakos et al. (2005) reported that yogurt consumption was not associated ($p>0.05$) with FPG (partial correlation coefficient -0.003, adjusted for age and sex), plasma insulin (-0.009), homeostatic model assessment of insulin resistance (-0.011 for HOMA-IR) or homeostatic model assessment of β-cell insulin secretory capacity (-0.011 for HOMA-B) in a cross-sectional analysis of 4,056 Greek adults. The study did not provide data on yogurt consumption and the incidence of T2DM.

Snijder et al. (2007) found that yogurt was not associated with fasting glucose (β ± SE=0.02±0.06 mmol/l, p=0.69), 2-h glucose (0.07±0.12mmol/l, P=0.58) or fasting insulin (-

1.59±2.05 mmol/l, P=0.44) concentration in a cross-sectional analysis of among 1,896 Dutch adults. No data on the incidence of T2DM were provided.

Kim (2013) reported that yogurt consumption 4-6 times per week, compared with none or rarely, was significantly associated with reduced prevalence of hyperglycemia (FPG ≥100 mg/dL) (OR=0.76; 95% CI, 0.63-0.93, P for trend =0.0213) and metabolic syndrome (OR=0.77; 95% CI, 0.62-0.95, P for trend =0.0067). However, higher intakes of yogurt (at least once per day) were not significantly associated with risk (OR=0.89; 95% CI, 0.64-1.25 and OR=0.71; 95% CI, 0.48-1.05; respectively), compared with those who consumed yogurt "none/rarely;" although the trend for each outcome remained significant across categories of yogurt consumption (P for trend =0.0213; and P for trend =0.0067; respectively). This analysis was conducted among 4,862 participants in the Fifth Korean National Health Examination Survey; findings from this population may be difficult to extrapolate to healthy U.S. adults due to extreme dietary and cultural differences.

Wang et al. (2013) reported that cross-sectional multivariate analysis among 6,526 members of the Framingham Heart Study Offspring Cohort (examination seven) and the Generation Three Cohort (examination one) showed that yogurt consumers had a lower FBG (97.5 mg/dL; 95% CI, 96.8-98.2, P=0.02) than non-consumers (98.4 mg/dL; 95% CI, 97.7-99.1) after adjustment for age, sex, physical activity, energy intake, smoking status, DGAI score, use of supplements and BMI. Fasting insulin and HOMA-IR were also lower among yogurt consumers than non-consumers after adjustment for age, sex, physical activity, energy intake and smoking status, but not after correction for additional potentially confounding variables, including DGAI score, use of supplements and BMI. The results were based on only two yogurt intake classifications (i.e., consumers and non-consumers) and the study did not report incidence of clinical T2DM.

Abreu et al. (2014) conducted a cross-sectional analysis pertaining to dairy consumption among 494 Portuguese adolescents (15-18 years of age). There was no significant difference in fasting glucose (P=0.708) or fasting insulin (P=0.724) or HOMA-IR (P=0.815) between yogurt consumers below and above the median (~54 g/d). This study employed only two yogurt intake classifications and did not report incidence of clinical T2DM.

Drehmer et al. (2015) studied 10,010 members of the Brazilian Longitudinal Study of Adult Health. Cross-sectional analysis showed that a 1-serving/d difference in intake of yogurt was associated with significantly lower HbA1c concentrations (-0.04%; 95% CI, -0.06 to -0.01) after multivariate adjustment. There were no such associations for FBG (-0.29 mg/dL; 95% CI, -1.03-0.44) or 2-hr post glucose load (-0.31 mg/dL; 95% CI, -2.20 to -1.58). Data on incident T2DM were not reported.

Moslehi et al. (2015) conducted a nested case-control study among 178 T2DM patients and 520 randomly matched controls from the Tehran Lipid and Glucose study cohort. There was no difference in mean daily yogurt consumption between cases (179.9 g/d; 95% CI, 66.5-241.3) and controls (165.2 mg/d; 95% CI, 90.6-238.4), p=0.691. There was also no association between yogurt consumption and T2DM comparing the top tertile (276 g/d) with the bottom (66g/d) (RR=0.92; 95% CI, 0.59-1.42, p for trend = 0.765) after multivariate adjustment. Approximately 59% of T2DM patients were excluded from the study due to "incomplete data" and no data were provided on possible differences between those who were excluded and those who were not. These results cannot be extrapolated to the healthy, general U.S. population due to dietary and cultural differences.

Sayon-Orea et al. (2015) studied the association of yogurt consumption and incidence of the metabolic syndrome among 8,063 members of the Spanish SUN cohort over a mean follow-up period of six years. No data on T2DM were reported. However, Figure 1 in the paper provided graphic data on yogurt consumption and impaired glucose metabolism (defined as ≥100 mg/dL FBG concentration or drug treatment for elevated blood glucose) for consumption of ≥875 g per week (seven servings or more) compared to ≤250 g per week (two servings or less). Numerical values for such associations (estimated from the figure) were non-significant for total yogurt (RR=0.98; 95% CI, 0.83-1.3), full fat yogurt (RR=1.15; 95% CI, 0.65-1.25) and lowfat yogurt (RR=0.90; 95% CI, 0.65-1.25) after adjustment for age, sex, baseline weight, energy intake, alcohol intake, soft drinks, red meat, French fries, fast food, Mediterranean diet, physical activity, sedentary behavior, hours sitting, smoking, snacking between meals and special diet adherence. This study was assigned a low FDA quality score despite its prospective design because it did not measure the incidence of T2DM or abnormal FBG. Subjects with the latter condition were grouped with those on drug treatment and defined as "impaired glucose metabolism". In addition, 50.6% of eligible participants were excluded for various reasons including missing or implausible data.

Zhu et al. (2015) analyzed NHANES data from 5,124 U.S. children aged 2-18 years, with a final analysis that included 930 individuals for a glucose analysis and 913 individuals for an insulin analysis. Frequent yogurt consumers had lower levels of fasting insulin (52.3±5.6 pmol/L vs. 65.9 ±4.3 pmol/L, P<0.001), lower HOMA-IR (1.94±0.28 vs. 2.55± 0.20, P<0.001) and higher quantitative insulin sensitivity check index (QUICKI) (0.352± 0.005vs. 0.345± 0.004, P=0.03) than infrequent consumers. FBG, however, was not associated with frequency of yogurt consumption after multivariate analysis (5.13± 0.08 mmol/L for infrequent consumers vs. 5.11 ±

0.08 mmol/L for frequent consumers (p=0.64)). This study used only two classifications of yogurt consumption and did not report incidence of T2DM.

Cormier et al. (2016) studied 664 members of the Canadian INFOGENE study using a cross-sectional design and reported no significant difference between consumers and non-consumers of yogurt for FBG (5.76 ± 0.96 mmol/L, vs. 5.74 ± 1.10 mmol/L, respectively, P=0.94), fasting insulin (96.7 ± 83.3 vs. 75.3 ± 52.8 pmol/L, P=0.16) or HOMA-IR (25.0 ± 23.7 vs. 19.9 ± 17.2, P=0.30) after adjustment for age, sex, BMI, physical activity and dietary pattern scores (Prudent & Western). The paper did not report excluding any subjects from the analysis.

Eussen et al. (2016) conducted a cross-sectional analysis of 2,391 subjects in the Maastricht study. The highest tertile of yogurt intake was associated with significantly reduced risk of impaired glucose metabolism (impaired fasting glucose and / or impaired glucose tolerance) (RR= 0.67; 59% CI, 0.50-0.90, p for trend <0.01), but not newly diagnosed T2DM (RR=0.60; 95% CI, 0.35-1.02, p for trend =0.06). It was unclear if the FFQ used for this study was validated for dairy products.

Feeney et al. (2017) reported that there was no significant difference in fasting serum glucose (P=0.454), serum insulin (P=0.577), HOMA-IR (P=0.922) or QUICKI (P=0.176) across tertiles of yogurt intake among a sample of 1,136 participants who donated a blood sample in the Irish National Adult Nutrition Survey after adjustment for age, gender, BMI, healthy eating index score and mean daily energy intake. This study failed to adjust for many other potentially confounding variables such as smoking status, physical activity, alcohol consumption, menopausal status, menopausal hormone use, or dietary factors such as intake of *trans*-fats, red

and processed meat, nuts, sugar sweetened beverages, coffee and other individual dairy foods. The study also did not report incidence of T2DM.

Liang et al. (2017) cross-sectionally studied 4,343 residents from two urban and three rural counties of Qingdao, China. Multivariate analysis revealed that yogurt consumption was significantly associated with reduced risk of T2DM in women (RR=0.56; 95% CI, 0.32-0.98) but not men (RR= 0.98; 95% CI, 0.69-1.38). Quantitative data on yogurt intake were not provided. The results of this study cannot be extrapolated to the healthy U.S. population due to dietary and cultural differences.

Panahi et al. (2017a) conducted a cross-sectional analysis among 952 French Canadian participants in the Quebec Family Study as well as a prospective analysis of a subset of this cohort (n=188) after a mean follow-up period of six years. Subjects were classified as yogurt consumers (≥1 serving/day) or non-consumers (0 serving/day) although no quantitative data on yogurt consumption were provided. The cross-sectional analysis revealed no differences in FBG, fasting insulin concentrations or area under the curve (AUC) for glucose or AUC for insulin among men after adjustment for age, nutrient risk food index, physical activity and percent body fat. Among women, yogurt consumers had significantly lower fasting insulin (P=0.05) and AUC for both glucose (P=0.04) and insulin (P=0.008), but not FBG, after adjustment for the potentially cofounding variables noted above. In the prospective analysis (n=87 men; n=101 women), there was no difference between yogurt consumers and non-consumers in FBG (P=0.26), fasting insulin (P=0.53) or AUC for both glucose (P=0.78) and insulin (P=0.43) in men or women after adjustment for all the above factors. The prospective part of this study included only 26% of the original cohort. Only two categories were used to

classify yogurt consumption, and no quantitative data on consumption of this food were provided.

Hobbs et al. (2018) analyzed cross-sectional data on yogurt consumption from the National Diet and Nutrition Survey (NDNS) in the UK among 1,687 children aged 4-18 years of age. Yogurt consumers were defined as those who consumed at least one serving of yogurt (full fat, lowfat or fat-free) or fromage frais (a type of smooth soft fresh cheese with the consistency of thick yogurt) at least once according to four-day diet records. Yogurt consumption was not associated with FPG or HbA1c concentrations among children 4-10 years of age, however HbA1c concentrations were lower (P=0.01) among the highest tertile of consumers among children 11-18 years of age. There were no such differences for FBG in this age category. The short period of dietary assessment (4 days) and inclusion of fromage frais consumption in the yogurt consumer's category complicates interpretation of this study.

Brouwer-Brolsma et al. (2018) conducted a cross-sectional study among 112,086 healthy, Dutch adults with a mean age of 45 years. Total yogurt consumption was not associated with the incidence of pre-diabetes (OR=0.99; 95% CI, 0.96-1.03; P for trend = 0.76) or T2DM (OR=0.97; 95% CI, 0.84-1.11; P for trend = 0.59) after adjustment for age, sex, alcohol consumption, smoking, education, physical activity, energy intake, energy-adjusted intake of bread, pasta, rice, potato, fruit, vegetables, legumes, meat, fish, coffee, tea, soda/fruit juice, other dairy product groups, BMI and waist circumference. Fully-adjusted intake of full fat yogurt was associated with pre-diabetes (OR=1.07; 95% CI, 1.02-1.12; P for trend = 0.007), however there was no such association for the combination of pre-diabetes and T2DM (OR=1.03; 95% CI, 0.86-1.23, P for trend = 0.40). This study used a 110-item FFQ (the flower FFQ) which had not been validated.

5. Non-applicable observational studies

A variety of observational studies were identified by our literature search that reported associations between T2DM (and/or one or more of its surrogate endpoints) and the combination of yogurt with one or more additional foods (e.g., cheese, thick fermented milk, milk, buttermilk) rather than for yogurt *per se* (Fumeron et al., 2011, Sluijs et al., 2012, Ali et al., 2013, Niu et al., 2013, Shin et al., 2013, Samara et al., 2013, Struijk et al., 2013, Ericson et al., 2015). These studies, therefore, do not provide useful information about the proposed claim; however, they are cited here in the spirit of providing FDA with the totality of scientific information.

Table 1

Data Extraction Table for Observational Studies that Assessed the Association between Yogurt Intake and Diabetes-Related Parameters

Author	Study Design, Population Characteristics and Follow-Up Period	Dietary Assessment and Diabetes Related Endpoints	Summary of Results	Comments
Pereira et al. (2002)	Prospective Cohort design N=5,115 participants, aged 18-30y were recruited to form the Coronary Artery Risk Development in Young Adults (CARDIA) study (USA). Participants were excluded due to missing dietary data (N=1,175), implausible reported dietary intake (<800kcal or >8000kcal/d for men and <600kcal or >6,000kcal/d for women) (N=707), were pregnant at or within 180 days of baseline (N=184) or due to use of medications which may affect blood glucose levels (N=87). Thus, the final analysis included N=3,157 individuals. Median follow up = 10 y.	Dietary information over the last 28 days was ascertained via 700-item validated, semi-quantitative food frequency questionnaire (FFQ). Weekly consumption of each food (times/week) was used to estimate relative intake per week. The substance was yogurt. Total dairy products were considered to be 100% dairy (e.g. milk) or included dairy as one of the main ingredients (e.g. dips made with sour cream). 90% of total dairy products were milk, milk drinks, butter, cream and cheese. Milk was considered reduced fat if it had <2% fat and cheeses/desserts were considered reduced fat if they had <15% fat. Fasting insulin and FBG levels were measured (at least 8-h fast). Abnormal glucose homeostasis was defined as high fasting plasma insulin (approximately the 90th percentile of the fasting insulin distribution measured in μU/mL), raised fasting glucose (at least 110 mg/dl or 6.1mmol/L) or use of medications to control blood glucose.	Median yogurt consumption ranged from 0 for black subjects to 0.3 times/week among white subjects with BMIs >25Kg/m^2. Multivariate analysis included age, sex, race, daily caloric intake, study center, baseline BMI, education level in years, daily alcohol intake, current smoking status, daily physical activity units, use of vitamin supplements, intake of polyunsaturated fat as % total energy, milligrams of caffeine intake, grams of fiber intake per 1,000 calories, intake frequency of whole and refined grains, meat, fruit, vegetables, soda and dietary intake of magnesium, calcium and vitamin D. For After multivariate analysis, the OR (95% CI) for 1 daily eating occasion of yogurt and risk of abnormal glucose homeostasis was 0.44 (0.12-1.62) and 0.58 (0.20-1.66) for insulin resistance syndrome. Multivariate analysis showed there were non-significant inverse associations for a one daily serving increase in yogurt consumption and abnormal glucose homeostasis (OR=0.44; 95% CI, 0.12-1.62) and insulin resistance syndrome (OR=0.58; 95% CI, 0.20-1.66).	FDA Quality Score = Low There was an interaction between dairy intake and overweight status which caused the investigators to limit analysis of dairy intake to those subjects who were overweight or obese at baseline. Yogurt consumption was very low (≤0.5 times per week among the highest demographic group (white, non-overweight/obese) and even lower among obese (0 and ≤0.3 times/wk among white & black subjects)) respectively. Since ORs were reported only for obese individuals, it is very difficult to make conclusions about the general population due to very low consumption and lack of detailed information on yogurt intake. The study was initiated in 1985 before an increase in the popularity of yogurt in the U.S. Impaired fasting glucose cut off was reduced to 100 mg/dl.

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Choi et al. (2005)	Prospective Cohort design N= 51,529 men, aged 40-75 y in 1986 from the Health Professionals Follow-up Study cohort were potentially eligible for inclusion. N=10,275 subjects excluded due to implausibly high (>4,200 kcal/d) or low (<800 kcal/d) energy intake and/or blank responses for >70 of the 131 food items on the diet questionnaire, history of diabetes, CVD, or cancer (except non-melanoma skin cancer). Thus, the final analysis included N=41,254 men. Mean follow-up period = 12 y	Semi-quantitative FFQ of approximately 130 foods & beverages during the previous year validated against two 1-wk diet records in this cohort. Pearson correlation coefficients for intake, adjusted for week-to-week variation in the diet records were 0.62 both for low-fat dairy foods and for high-fat dairy foods. The substance was yogurt. Type of yogurt not explicitly specified, but it was included among "low-fat dairy foods" which suggests high fat yogurts may have been excluded. The average daily intakes of individual dairy items were combined to compute dairy intake: low-fat dairy products, including skim/low fat milk, sherbet, yogurt, and cottage/ricotta cheese; high-fat dairy foods, including whole milk, cream, sour cream, ice cream, cream cheese, and other cheese; and all dairy products, including all of the above. Self-reported diagnosis of T2DM confirmed by at least one of the following: (1) FBG ≥140 mg/dL, random PG ≥200 mg/dL, PG ≥200 mg/dL after ≥2 hr. during oral glucose tolerance test plus one or more symptoms (excessive thirst, polyuria, weight. loss, hunger); (2) ≥2 elevated PG's on different occasions; (3) insulin or oral hypoglycemic medications. The validity of assessment of T2DM was verified with medical records in a sample of 71 participants N=1,243 incident cases of T2DM were documented during follow up.	Yogurt intake was divided into quartiles. These ranged from <1 serving/month for the first, 1-3 servings/month for the second, 1 serving/week for the third and ≥2 servings/week for the fourth. Multivariate analysis included adjustment for age, total energy intake, biennial follow-up time (6 periods), family history of diabetes, smoking, BMI, hypercholesterolemia at baseline hypertension at baseline, physical activity, and intake of alcohol, cereal fiber, *trans* fat, polyunsaturated to saturated fat ratio and glycemic load. Yogurt intake was not associated with incident T2DM (Highest vs. lowest quartile: RR=0.83 (95% CI, 0.66-1.06; P for trend = 0.11, therefore no linear relationship observed)	FDA Quality Score = High Data from this study were subsequently updated and reported by Chen et al. (2014).

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Panagiotakos et al. (2005)	Cross-Sectional design. N=4,056 participants, aged 31-59 y from the Attica region of Greece were invited to participate and N=3,042 agreed. 5% of men and 3% of women were excluded due to history of cardiovascular/atherosclerotic disease or chronic viral infection. Additional exclusion criteria include T2D, cold/flu/acute respiratory infection, dental problems, and any type of recent surgery (previous few weeks). N= 118 men and N=92 women were excluded due to diagnosis of T2D. Thus, the final analysis included N=2,832 (N= 1,393 men and N=1,439 women) individuals without diabetes or cardiovascular disease at baseline Median follow up = 0 y (cross sectional study)	Usual dietary intake over the last year was collected via dietitian-administered, validated, 156-item, semi-quantitative FFQ. Participants were asked to report daily or weekly average intake and the frequency was determined by consumption/month. The substance was yogurt. T2DM was ascertained via fasting blood glucose (FBG) test after a 12-h fast. A diagnosis was confirmed in line with the American Diabetes Association (ADA) diagnostic criteria. A FBG level ≥125 mg/dL was classed as having T2DM and subjects excluded. Impaired fasting glucose (IFG) was defined as a FBG between 100 and 125mg/dL. Fasting insulin was measured in µU/ml. Insulin resistance (IR) was assessed by calculating homeostasis model assessment (HOMA-R). For calculation of insulin secretory capacity, HOMA-B was used.	Correlation coefficients were adjusted for age and sex. Partial correlation coefficient for yogurt consumption was -0.009 for insulin: -0.003 for FBG: -0.011 for HOMA-R and -0.011 for HOMA-B (P>0.05 for all).	FDA Quality Score = Low No data on yogurt consumption. The paper examined markers of T2DM but not incidence of this disease. Greek subjects may not reflect the healthy U.S. population due to different dietary patterns.

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Liu et al. (2006)	Prospective Cohort design. N=39,876 females age 47-63 years as part of the Womens' Health Study in the United States. N=2,693 women were excluded due to missing dietary data or diagnosis of diabetes at baseline. Thus, the final analysis included N=37,183 individuals Mean follow-up =10 y.	Habitual dietary intake over the previous year was ascertained via 131-item validated semi-quantitative FFQ. The substance was yogurt. Total dairy products included low and high fat varieties of milk, sherbet, yogurt, cheese, cream, sour cream, ice cream. Yogurt was listed among "low fat dairy products" including skim or low-fat milk, sherbet and cottage/ricotta cheese. However, the FFQ used for this study does not differentiate yogurt on the basis of fat content. Therefore, it is assumed all forms of yogurt are included in the analysis. Incident T2DM was identified by self-report. In up to 30% of reported cases, these were validated by 1 or more of 3 different methods (ADA criteria). The first was a phone interview completed by a study physician (N=473). The second method was a supplemental questionnaire that was sent to a random sample of 147 women and the third involved reviewing the medical charts of as many of the 147 above women who consented to this. Self-reported diagnoses of diabetes were confirmed in 91% of charts. N=1,603 incident cases of T2DM were documented during follow up.	Yogurt intake was divided in quartiles (<1 servings/month for the first, 1-3 servings/month for the second, 1 serving/week for the third and ≥2 servings/week for the fourth. Multivariate analysis involved adjustment for total energy intake, randomized-treatment assignment, age, family history of diabetes, smoking status, BMI, hypercholesterolemia, hypertension, hormones, physical activity, alcohol consumption, dietary intakes of fibers, total fat glycemic load, dietary calcium, vitamin D and magnesium. After multivariate analysis, the risk of T2DM was inversely associated with yogurt intake RR for highest quintile of intake = 0.82 (95% CI, 0.70-0.97), P for trend=0.03.	FDA Quality Score = High Strong evidence in support of the proposed claim

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Snijder et al. (2007)	Cross-Sectional design. N=2,484 participants, aged 50-75 y were eligible for the Hoorn Study which is a population-based cohort study of glucose tolerance in the Netherlands. Participants were excluded if they had missing data on dietary intake (N=78), BMI (N=7), waist circumference (N=12), systolic/diastolic blood pressure (N=2), HDL cholesterol (N=6), LDL cholesterol (N=11), physical activity (N=295), smoking status (N=21), income level (N=152) or educational level (N=147). Thus, the final analysis included N=1,896 (N=852 men and N=1,044 women) individuals. Mean follow-up = 0 y (cross sectional study)	Dietary data were ascertained via self-administered 92-item semi-quantitative FFQ which used average household portions. The substance was yogurt. Yogurt included all low-fat, skim and whole-yogurts. For all liquid and solid dairy products, one serving was defined as 150 and 20 g, respectively. Total dairy intake included high and low-fat varieties of milk, yogurt, cheese and dairy dessert (yogurt, curds and custard). Low-fat dairy included products that were ≤2% fat and high-fat dairy included products >2% fat. FBG (mmol/L) and insulin (mmol/L) were measured along with a 2-h post-load glucose (mmol/L) after a 75g oral glucose load.	The median consumption of yogurt was 0.5 servings/day. Multivariate analysis included adjustments for intakes of total energy, alcohol and fiber as well as use of antihypertensive medications, smoking, physical activity, income and education. Yogurt intake (serving/day) was not associated with FBG ($\beta \pm SE$=0.02±0.06 mmol/l, P=0.69), 2-h glucose (0.07±0.12 mmol/l P=0.58) or fasting insulin (-1.59±2.05mmol/l, P=0.44).	FDA Quality Score = Low The paper did not specify whether the FFQ was validated for dairy foods. The paper examined markers of T2DM but not incidence of this disease.

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Beydoun et al. (2008)	Cross-Sectional design. N=17,061 adults ≥18 years (N=8,091 men and N=8970 women) were eligible as part of the National Health and Nutrition Examination Survey (NHANES) in the United States. N=2,052 were missing dietary data. A further N=391 were missing anthropometric data. N=10,099 were excluded as they were missing data such that metabolic syndrome could not be assessed. This left N=4,519 participants for analysis. Mean follow-up = 0 yr (cross sectional study)	Dietary data were collected by a trained interviewer every two years via at least one 24-h recall. The substance was yogurt. Total dairy included milk, yogurt, cheese. FBG was measured (mg/dL).	The mean intake of yogurt was 6.2g/day (0.03 servings/day). Multivariate analysis included age, sex, ethnicity, education, poverty income ratio, energy intake and physical activity. After multivariate analysis, yogurt intake was significantly associated with reduced FBG (-4.29mg/dl), $P<0.05$ in the total sample and among men (-7.38, $p<0.05$) but not among women (-2.92, $p>0.05$).	FDA Quality Score = Moderate Yogurt consumption was associated with reduced BMI, waist circumference, systolic blood pressure and reduced number of disturbed MS parameters among both genders, and increased HDL-C among women. The paper examined markers of T2DM but not incidence of this disease. Although NHANES is a cross-sectional dataset, it has a very large N and makes direct contact with the participants; therefore, the study was assigned a moderate quality score.

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Kirii et al. (2009)	Prospective Cohort design. N=140,420 adults, aged 40-69y were eligible for the Japan Public Health Center-based Prospective Study. This consisted of 2 cohorts, commenced 3 years apart. Data were collected at baseline, after 5 years and after 10 years however the FFQ used from year 5 on was deemed more comprehensive so served as the baseline in this analysis. N=23,748 from Tokyo and Osaka were excluded due to differences in recruitment criteria. Of the resulting eligible individuals (N=116,672), N=71,075 responded at year 10. N=10,694 were excluded due to a history of a number of relevant chronic diseases and an additional N=585 were excluded due to reported implausible dietary intake (>3 or <3 standard deviations of energy intake). Thus, the final analysis included N=59,796 (N=25,877 men and N=33,919 women) individuals. Mean follow-up period=5 y	Dietary information was ascertained via a validated 147-item FFQ. There were 9 responses which ranged from "rarely" to "≥7 times/day". Respondents could describe their usual portion as less than half, the same or more than 1.5 times the standard portion. The substance was yogurt. Participants reported if they had ever been diagnosed as having diabetes and if so, when the initial diagnosis was made. No information was collected on T2D. Self-reported diabetes was validated by review of medical records and plasma glucose where available (diagnostic criteria: fasting plasma glucose ≥7.8 mmol/l; and casual plasma glucose ≥11 mmol/l) with a sensitivity and specificity of 82.9 and 99.7% respectively. N=1,114 incident cases of T2DM were documented during follow up.	Yogurt intake 3 groups: 0g/day (N=15, 820 men and N=12,551 women), 0.1 -<60g/day (N=7,528 men and N=14,100 women) and ≥ 60g (N=2,529 men and N=7,268 women) per day. Multivariate analysis included age, area, BMI, family history of diabetes, smoking status, alcohol intake, history of hypertension, exercise frequency, coffee consumption, energy adjusted magnesium intake and total energy intake. There was no association between yogurt consumption and T2DM comparing the highest versus the lowest level of intake. The OR was 1.01 (95% CI, 0.75-1.36), P for trend =0.94 for men and OR=0.77 (95% CI, 0.58-1.01), P for trend=0.13 for women.	FDA Quality Score = Moderate The standard portion of yogurt was not specified. Data from the Japanese population not reflective of the general U.S. population due to dietary and other differences. 57% of sample excluded due to incomplete or implausible data or non-response. The type of yogurt was not specified. Not clear if the FFQ was validated for dietary components other than vitamin D and calcium. No information collected on type of diabetes reported.

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Margolis et al. (2011)	Prospective Cohort design N= 93,676 participants, aged 50-79y, formed the Womens' Health Initiative (WHI) cohort in the United States district of Columbia. Exclusion factors included having diabetes at enrollment (N=4,692), missing data on diet or covariates (N=5,321), reporting implausibly low (≤500kcal/d) total energy intake (N=950) or reporting implausibly high (≥3,500kcal) total energy intake (N=637). Thus, the final analysis included N=82,076 women. Median follow up period = 7.9 y	Habitual dietary intake over the previous 3 months was measured via 2 self-administered 122-item semi quantitative FFQs – one at baseline and one three years later. If individuals developed diabetes between their first and 2nd FFQ, only the first was used to estimate dietary intake. Information on "yogurt" and "non-fat yogurt" was collected. A serving of milk was considered to be 8oz (250g), but the service size of yogurt was not explicitly stated. Incident T2DM was ascertained through yearly mailed self-administered questionnaire. Participants were asked to report if they commenced on insulin or other antidiabetic medications. Additionally, at the year 3 visit, participants were asked to bring all medications with them for a medication inventory. Validation of self-reported T2DM was completed with the medication inventory at year three and an independent study which assessed medical records. A validation study found that 82% of new-onset self-reported diabetes was confirmed by review of medical records obtained from WHI participants (unpublished data). N=3,946 incident cases of T2DM were documented during follow up.	Intake of yogurt was divided into quartiles: <1/month, 1/month-≤3/month; >3/month-<2/week and ≥2/week for the first to the fourth. The median intake of yogurt was ½ serving/week or 125g/week. 38% reported rarely or never consuming yogurt. Multivariate analysis was completed including adjustment for age, race/ethnicity, total energy intake, income, education, smoking, alcohol consumption, postmenopausal hormone use, physical activity, family history of diabetes, BMI, systolic/diastolic blood pressure, interaction term between quintiles of yogurt intake and time dietary factors including glycemic load, total fat, dietary fiber and magnesium intake. Yogurt intake was associated with 54% reduced risk of T2DM (comparing the highest versus the lowest quintile of intake (RR= 0.46; 95% CI, 0.31- 0.68, P for trend =0.004).	FDA Quality Score = High Validation of the WHI FFQ was reported separately (Patterson et al., 1999). This study provides strong support for the proposed claim.

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Grantham et al. (2013)	Prospective Cohort design N=11,005 adults, aged ≥25 from the AusDiab study (a national, population-based survey in Australia) were potentially eligible for inclusion. N=4,710 were lost to follow up. N=85 did not complete a FFQ at baseline, and N=175 were excluded as they were in the top 1% of energy or dairy intake. The final analysis included N=5,582 individuals. Mean follow-up period: 5 y	Habitual dietary intake over the last 12 months was collected via self-administered FFQ. There were ten responses which ranged from "never" to "3 or more times per day". The substance was yogurt. A serving was 200g. Blood samples were collected after an overnight fast ≥9h. Individuals also completed a 75g oral glucose tolerance test. Incident diabetes was defined as fasting blood glucose ≥7mmol/l or a 2-h post-load plasma glucose ≥11.1mmol/l or current treatment with insulin or oral hypoglycemic agents. N=209 incident cases of T2DM were documented during follow up.	The median intake of yogurt in men was 20g and 41 g/day in women. 35.3% men and 18.4% women were non-consumers of yogurt. Multivariate analysis included adjustments for age, sex, energy intake, family history of diabetes, education level, physical activity, smoking, triglycerides, HDL cholesterol, systolic blood pressure, waist circumference and hip circumference. Yogurt was not associated with reduced risk of incident T2MD in men OR=1.02 (95% CI, 0.56-1.88) or women: OR=1.23 (95% CI, 0.74- 2.04) or the total population: OR=1.14 (95% CI, 0.78-1.67).	FDA Quality Score = Moderate 50.3% of the cohort was excluded due to incomplete data or other factors. Small number of incident T2DM cases (N=209). Details about the FFQ (e.g., number of food items) were not provided. This instrument has been validated for nutrient intake in a separate publication (Hodge et al., 2000), but no such validation for dairy or other foods was reported. The type of yogurt included in the analysis was not clearly specified. This food was listed under "low-fat" dairy but not under "full-fat" dairy. It is therefore possible that full-fat yogurt was excluded.

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Kim (2013)	Cross-Sectional design. N=6,740 adults (≥19 y) were selected out of the initial N=8,958 adults from 5th Korean National Health Examination Survey. Only N=5,701 answered a food frequency questionnaire and an additional N=839 were excluded due to missing socioeconomic, anthropometric and biochemical information. Thus, the final analysis included N=4,862 (N=1,993 men and N=2,869 women) individuals. Mean follow-up period= 0 y (cross sectional study)	Habitual dietary intake over the previous year was ascertained via FFQ. There were nine categories of responses classified in 4 groups ranging from "none or rarely" to "one or more times per day". The substance was yogurt. The variable "yogurt" included all low-fat, skim and whole yogurt. After an overnight fast, blood samples were taken to measure FBG. Hyperglycemia was defined as a FBG ≥100mg/dL (5.5mmol/L) or current use of insulin or oral hypoglycemia medication or a physician's diagnosis.	Yogurt intake was divided into 4 categories: none or rarely consumed (N=1,636, N=743 men and N=893 women), ≤2-3/month (N=1,570, N=705 men, N=865 women), ≤4-6 per week (N=1,388, N=544 men, N=844 women) and ≥once/day (N=268, N=93 men and N=175 women). Multivariate analysis included adjustment for age, sex, education, income, smoking, BMI, alcohol intake, physical activity and intakes of energy, fat, calcium and fiber. After multivariate analysis, yogurt intakes ≥once/day versus none/ rarely yogurt intake was not significantly associated with high fasting glucose OR=0.89 (95% CI, 0.64-1.25), P for trend=0.0213.	FDA Quality Score = Low The data from the Korean population cannot be applied to the general U.S. population due to dietary and other differences. The criterion used to define hyperglycemia (≥100 mg/dL) does not represent T2DM (≥126 mg/dL). Very little detail was provided on the FFQ (e.g., number of food items, validation, serving size of yogurt).

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Soedamah-Muthu et al. (2013)	Prospective Cohort design. N=10,308 adults (N=6,895 men and N=3,413 women aged 35-55 y) as part of the Whitehall II Study in the United Kingdom. Due to inconsistent results for milk intake in previous phases of the study, only data from phase 5 was included in this study leading to a cohort of N=5,088 participants. N=463 were excluded due to lack of information on confounders and N=99 were excluded for missing information on dietary intake, leaving a total of N=4,526 in the final analysis (N=3, 252 men and 1, 274 women). A further 133 subjects were excluded due to missing information on diabetes status. Thus, the final analysis included N=4,186 individuals. Mean follow up period = 9.8 y	Self-reported habitual dietary intake over the last year was collected with a 114-item FFQ. Although this tool was validated against a 7-day food record previously, it was not validated for dairy. All types of yogurt were included, and insufficient information was available to facilitate classification of different types of yogurt (e.g. by sugar or fat content). Options for consumption frequency ranged from never or less than once per month to 6 or more portions per day. One standard serving was considered to be 125g. Total dairy included all dairy products except butter and ice cream. Low fat dairy included cottage cheese, semi-skimmed/skimmed milk and milk-based hot drinks. High-fat dairy included full-fat cheese, yogurt, milk puddings and whole/channel island milk. Information on diabetes status was collected via self-report of doctors' diagnosis, initiation of anti-diabetic medication (oral hypoglycemic agents or insulin) and a 2h 75g oral glucose tolerance test at phases 5, 7 and 9 using WHO 1999 classification. Data were collected every 4-6 years. N=273 incident cases of T2DM were documented during follow up.	Yogurt intake was divided into tertiles: 0g/day for the first, 21g/day for the second and 117g/day for the third tertile. The median yogurt consumption was 21g/day. Multivariate analysis included age, ethnicity, employment grade, smoking, alcohol intake, BMI, physical activity, family history of coronary heart disease or hypertension and dietary factors included intake of fruit, vegetables, bread, meat, fish, coffee, tea and total energy. Yogurt intake was not associated with risk of T2D: HR for the highest tertile of intake versus the lowest tertiles was 1.04 (95% CI, 0.77-1.42), P for trend =0.77.	FDA Quality Score = Moderate FFQ not validated for dairy. Small number of incident T2DM cases (273). Associations based on tertiles rather than quartiles or quintiles.

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Wang et al. (2013)	Cross-Sectional design N=7,634 adults (aged 19-89 years) from the Framingham heart study offspring cohort (FHSOC) and examination 1 of the generation three cohort (GTC) in the United States were potentially eligible for inclusion. Participants were excluded from the current analysis if they had missing (N=709) or invalid FFQ data (reported total energy intake of <600kcal/day for all or >4000 kcal/day for women and >4200kcal/day for men or more than 12 blank items) (N=256) or data missing on yogurt consumption (N=143). Thus, the final analysis included N=6,526 individuals. Mean follow-up period= 0 y (cross sectional study)	Habitual intake over the last year was obtained by a self-administered, validated, 126-item, semi-quantitative FFQ. There were 9 categories to choose for frequency of consumption ranging from "never or less than one serving/month" to "more than 6 servings/day". Yogurt was the substance. One serving was 1 cup of yogurt. Yogurt was coded as "yogurt with fruit, low-fat, containing 10g protein per 8oz." For statistical analysis, participants were divided into consumers of yogurt (consumption of greater than 0 servings/week) or non-consumers (consuming 0 servings/week) Blood samples were taken after an 8 hour fast and used to measure serum glucose (mg/dL) and insulin (mU/L). These values were used to calculate the homeostasis model of assessment of insulin resistance (HOMA-IR).	Yogurt consumption was 0.00 ± 0.00 servings/week in non-consumers (n=3,016) and 2.27 ± 2.56 servings/week in consumers (N=3,510). The first model of multivariate analysis included age, sex, smoking, physical activity index and total energy intake. The second model additionally adjusted for dietary guideline adherence index and the final model additionally adjusted for vitamin or mineral supplement use and BMI. With the first model of multivariate analysis, yogurt consumers vs. non-consumers had significantly lower fasting glucose (97.2 mg/dL; 95% CI, 96.5-97.9 vs 98.7 mg/dL; 95% CI, 98.0-99.5), fasting insulin (81.4 pmol/L; 95% CI, 79.9-82.9 vs. 83.8 pmol/L; 95% CI, 82.2-85.4) and HOMA-IR (3.27; 95% CI, 3.20-3.35 vs 3.42 pmol/L; 95% CI, 3.34-3.50) all P <0.001. Adjustment for all variables attenuated this relationship for insulin (P=0.40) and HOMA-IR (P=0.15); however, the inverse association for fasting glucose remained significant (98.4 mg/dL; 95% CI, 97.7-9.99 vs, 97.5 mg/dL; 95% CI, 96.8-98.2, P=0.02).	FDA Quality Score = Low This study did not measure incident T2DM and did not calculate RRs for prediabetes.

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Abreu et al. (2014)	Cross-Sectional design. N=1,515 adolescents aged 15-18 years (208 boys, 286 girls) were recruited as part of the Azorean Physical Activity and Health Study II Cohort which was conducted in 6 of 9 Azorean Islands of Portugal. Blood samples were only taken for N=850. N=356 adolescents were excluded due to refusal to provide blood samples (N=297), lack of information on several variables (N=36) and lack of information on dietary intake (N=23). Included and excluded participants did not differ significantly with respect to age, sex and parental education. Thus, the final analysis included N=494 individuals. Mean follow-up period = 0 (Cross-sectional study)	Self-reported intake over the last year was measured via a 91-item, semi-quantitative FFQ which was previously validated for Portuguese adults. The FFQ was adapted to include foods deemed popular in adolescents. There were 9 response options ranged from "never" to "six or more times per day" and used standard portion sizes. There was also a "free response" section where participants could list additional foods if desired. The substance was yogurt. The yogurt group included all types of yogurt. Participants were divided into 2 categories according to the amount of each food group consumed. Participants were designated as having "low" intake if their intake was below the median amount of the total sample and "appropriate" if their intakes were higher than this amount. Total dairy included milk, yogurt and cheese. Fasting blood glucose (mmol/L) and insulin (µU/mL) were measured from blood taken after a 10 hour fast. IR was assessed by calculating homeostasis model assessment (HOMA). Data for blood glucose are reported as mean± standard deviation. Data for Insulin resistance and HOMA are reported as median (interquartile range).	The median intake of yogurt in the total sample was 53.57g/d. N=307 adolescents had "low" intakes of ≤53.56g/day and N=187 had "appropriate" intake. There were no significant differences in potentially confounding sociodemographic parameters between "low" and "appropriate" intake groups. "Appropriate" consumers of yogurt had higher total energy carbohydrate, fat, fiber, milk and cheese intake. There was no significant difference in fasting glucose (4.81vs 4.83, P=0.708), fasting insulin (7.97 vs 8.20, P=0.724) or HOMA-IR (1.71 vs 1.71, P=0.815) between the "low" and "appropriate" yogurt intake groups.	FDA Quality Score = Low Participants are aged 15-18 years. Adjustments missing Small sample size and high exclusion rate (~42%). No measurement of T2D. Analysis of intake data based on only two classifications.

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Chen et al. (2014)	Prospective Cohort design. N=121,700 women, aged 30-55 y were eligible for inclusion as part of the Nurses' Health Study in the United States were potentially eligible for inclusion. N=54,562 participants were excluded if they had a diagnosis of diabetes mellitus (type 1, type 2 and gestational), cardiovascular disease or cancer (except non-melanoma skin cancer) at baseline (N=1,980); if they left >70 of the 131 FFQ items blank; or reported an unusually low (500/800kcal/day for women/men) or high (>3,500/4,200kcal for women/men) total caloric intake; data was absent for baseline dairy intake or data of diabetes diagnosis. Thus, the final analysis included N=67,138 women. Maximum follow up period = 30 y	131-item validated, FFQs were completed every 4 years. The FFQ included standard portion size with nine possible responses for frequency of consumption ranging from "never or less than once per month" to "6 or more times per day". Yogurt was the substance. From 1994, yogurt was divided into "plain" (plain or with NutraSweet) and "flavored" (without NutraSweet). The correlation coefficients between FFQ and multiple diet records were 0.97 for yogurt. Total dairy products include milk, ice cream, yogurt, cheese and cream. A standard serving of milk was 8oz. Incident T2DM was confirmed with a validated supplementary questionnaire whereby participants reported at least one of the following: 1) one or more classic symptoms (excessive thirst, polyuria, weight loss, hunger) and FBG concentrations ≥7.8 mmol/l or random plasma glucose concentrations ≥11.1 mmol/L; 2) ≥2 elevated plasma glucose concentrations on different occasions (fasting concentrations ≥7.8 mmol/L, random plasma glucose concentrations ≥11.1 mmol/L, and/or concentrations of ≥11.1 mmol/L after ≥2 hours shown by oral-glucose-tolerance testing) in the absence of symptoms; or 3) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). N=7,841 incident cases of T2DM were documented during follow up.	Yogurt intake was divided into 4 categories. Intake was classified as <1 servings/month, 1.8 servings/month, 1.2 serving/week and 2.9 servings/week. Multivariate analysis included adjustments for age, BMI, total energy intake, race, smoking status, physical activity, alcohol consumption, family history of diabetes, diagnosed hypertension or hypercholesterolemia at baseline, glycemic load of the diet as well as intake of trans-fats, red and processed meat, nuts, sugar sweetened beverages, coffee and other individual dairy foods. Yogurt consumption was inversely associated with the incidence of T2D. The RR for the highest versus the lowest category of intake was 0.84 (95% CI, 0.78- 0.91), P for trend <0.001. The HR for one serving /day was also statistically significant (RR= 0.75; 95% CI, 0.65- 0.86).	FDA Quality Score = High There is ambiguity on the serving size used for yogurt. The paper stated it used 244 g as the standard serving size for milk and yogurt in conjunction with a meta-analysis that was included in the paper, but did not clearly specify whether this value was also used for the individual studies as well. It is possible that a value of 227 grams (8 oz.) was used for this purpose as is typically done with the Willett FFQ (Hruby et al., 2017). The T2DM diagnosis criteria from American Diabetes Association evolved over time, currently fasting plasma glucose ≥ 7.0 mmol.

Author	Study Design, Population Characteristics and Follow-Up Period	Dietary Assessment and Diabetes Related Endpoints	Summary of Results	Comments
Chen et al. (2014)	Prospective cohort design. N=116,671 women, aged 25-42 y in the Nurses' Health Study II in the United States (1991-2009) were potentially eligible for inclusion. N=30,787 participants were excluded if they had a diagnosis of diabetes mellitus (type 1, type 2 and gestational), cardiovascular disease or cancer (except non-melanoma skin cancer) at baseline (N=1,991); if they left >70 of the 131 FFQ items blank; or reported an unusually low (500/800kcal/day for women/men) or high (>3,500/4,200kcal for women/men) total caloric intake; data were absent for baseline dairy intake or data of diabetes diagnosis. Thus, the final analysis included N=85,884 women. Maximum follow up period =16 y	131-item validated, FFQs were completed every 4 years. The FFQ included standard portion size with nine possible responses for frequency of consumption ranging from "never or less than once per month" to "6 or more times per day". Yogurt was the substance. From 1994, yogurt was divided into "plain" (plain or with NutraSweet) and "flavored" (without NutraSweet). The correlation coefficients between FFQ and multiple diet records were 0.97 for yogurt. Total dairy products include milk, ice cream, yogurt, cheese and cream. A standard serving of milk was 8oz. Incident T2DM was confirmed with a validated supplementary questionnaire whereby participants reported at least one of the following: 1) one or more classic symptoms (excessive thirst, polyuria, weight loss, hunger) and FBG concentrations ≥7.8 mmol/l or random plasma glucose concentrations ≥11.1 mmol/L; 2) ≥2 elevated plasma glucose concentrations on different occasions (fasting concentrations ≥7.8 mmol/L, random plasma glucose concentrations ≥11.1 mmol/L, and/or concentrations of ≥11.1 mmol/L after ≥2 hours shown by oral-glucose-tolerance testing) in the absence of symptoms; or 3) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). N=3,951 incident cases of T2DM were documented during follow up.	Yogurt intake was divided into 4 categories. Intake was classified as <1 servings/month, 2.1 servings/month, 1.0 serving/week and 2.7 servings/week. Multivariate analysis included adjustments for age, BMI, total energy intake, race, smoking status, physical activity, alcohol consumption, family history of diabetes, diagnosed hypertension or hypercholesterolemia at baseline, glycemic load of the diet as well as intake of trans-fats, red and processed meat, nuts, sugar sweetened beverages, coffee and other individual dairy foods. The RR for T2D for the highest versus the lowest category of intake was of borderline statistical significance (RR=0.90; 95% CI; 0.81-1.00) with a highly significant P for trend (<0.02). HR for one serving /day was 0.94 (95% CI, 0.80-1.10).	FDA Quality Score = High There is ambiguity on the serving size used for yogurt. The paper stated it used 244 g as the standard serving size for milk and yogurt in conjunction with a meta-analysis that was included in the paper, but did not clearly specify whether this value was also used for the individual studies as well. It is possible that a value of 227 grams (8 oz.) was used for this purpose as is typically done with the Willett FFQ (Hruby et al., 2017). The T2DM diagnosis criteria from American Diabetes Association evolved over time, currently fasting plasma glucose ≥ 7.0 mmol.

Author	Study Design, Population Characteristics and Follow-Up Period	Dietary Assessment and Diabetes Related Endpoints	Summary of Results	Comments
Chen et al. (2014)	N=51,529 men (aged 50-75 years of age) in the Health Professionals Follow-Up Study (1986-2010) in the United States were potentially eligible for inclusion. N=10,050 participants were excluded if they had a diagnosis of diabetes mellitus (type 1, type 2 and gestational), cardiovascular disease or cancer at baseline (N=1986); if they left >70 of the 131 FFQ items blank; or reported an unusually low (500/800kcal/day for women/men) or high (>3,500/4,200kcal for women/men) total caloric intake; data was absent for baseline dairy intake or data of diabetes diagnosis. Thus, the final analysis included N=41,479 individuals. Maximum follow up period = 24 y	131-item validated FFQs were completed every 4 years. The FFQ included standard portion size with nine possible responses for frequency of consumption ranging from "never or less than once per month" to "6 or more times per day". The substance was yogurt. From 1994, yogurt was divided into "plain" (plain or with NutraSweet) and "flavored" (without NutraSweet). The correlation coefficients between FFQ and multiple diet records were 0.97 for yogurt. Total dairy products include milk, ice cream, yogurt, cheese and cream. A standard serving of milk was 8oz. Incident T2DM was confirmed with a validated supplementary questionnaire whereby participants reported at least one of the following: 1) one or more classic symptoms (excessive thirst, polyuria, weight loss, hunger) and fasting plasma glucose concentrations ≥7.8 mmol/l or random plasma glucose concentrations ≥11.1 mmol/L; 2) ≥2 elevated plasma glucose concentrations on different occasions (fasting concentrations ≥7.8 mmol/L, random plasma glucose concentrations ≥11.1 mmol/L, and/or concentrations of ≥11.1 mmol/L after ≥2 hours shown by oral-glucose-tolerance testing) in the absence of symptoms; or 3) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). N=3,364 incident cases of T2DM were documented during follow up.	Yogurt intake was divided into 4 categories. Intake was classified as <1 serving/month, 2.1 servings/month, 1 serving/week and 3 servings/week. Results were adjusted for multiple confounding factors including age, BMI, total energy intake, race, smoking status, physical activity, alcohol consumption, family history of diabetes, diagnosed hypertension or hypercholesterolemia at baseline, glycemic load of the diet as well as intake of trans-fats, red and processed meat, nuts, sugar sweetened beverages, coffee and other individual dairy foods. There was no significant association between yogurt consumption and incident T2D. The RR for the highest versus the lowest category of intake was 0.95 (95% CI, 0.84-1.08), P for trend=0.30. The HR for one serving /day was 0.85 (95% CI, 0.68-1.06).	FDA Quality Score = High There is ambiguity on the serving size used for yogurt. The paper stated it used 244 g as the standard serving size for milk and yogurt in conjunction with a meta-analysis that was included in the paper, but did not clearly specify whether this value was also used for the individual studies as well. It is possible that a value of 227 grams (8 oz.) was used for this purpose as is typically done with the Willett FFQ (Hruby et al., 2017). The T2DM diagnosis criteria from American Diabetes Association evolved over time, currently fasting plasma glucose ≥ 7.0 mmol.

Author	Study Design, Population Characteristics and Follow-Up Period	Dietary Assessment and Diabetes Related Endpoints	Summary of Results	Comments
O'Connor et al. (2014)	Nested Case-Control design. N=4,000 random sub-cohort and N=892 cases of incident diabetes were potentially eligible from the United Kingdom EPIC Cohort which consists of N=25,639 men and women aged 40-79 years. Participants were excluded if they had prevalent or uncertain diabetes status (N=83), had missing food dietary data (N=18), missing data for other covariates (n=3) or an implausible ratio of energy intake to basal metabolic rate (top and bottom 1% of distribution) (N=82). N=436 were excluded with prevalent myocardial infarction, stroke and cancer. The final analysis included N=4,127 individuals including N=753 cases (N=128 of whom were in the subcohort) and N=3,374 controls (all of whom were from the subcohort). . Mean follow up=11 years	Dietary intake was measured prospectively via a 7-day food diary; food weights were estimated using photographs which represented portion sizes, household measures and standard units. A trained nurse provided instructions for the first day. The substance was yogurt. Total yogurt included full, low and 0% fat varieties. Yogurt was defined as being "full fat" if the fat percentage was greater than 3.9%. A portion was 125g. Total dairy included high and low-fat varieties of butter, cheese, cream, crème fraiche, dried/powdered milk, evaporated milk, milk, sour-cream, yoghurt and baby milk. Incident and prevalent T2DM was ascertained through self-report of doctor-diagnosed diabetes or diabetes-specific medication use or medication brought to study follow-up health check. This information was then verified through general practitioner or hospital diabetes registers, hospital admission data or data from the office of national statistics mortality.	Yogurt contributed to 7.6% of total dairy intake which was 268g/day. Tertiles (g/day) of dairy intake ranged from 0 (N=2,698), 21.5 (0.1-44g/day, N=723) to 80 (44-513g/day, N=706). Multivariate analysis was completed adjusting for age, sex, BMI, family history of diabetes, smoking, alcohol consumption, physical activity, social class, education and intakes of energy, fiber, fruit, vegetables, red meat, processed meat and coffee. After multivariate analysis, yogurt intake was inversely associated with the hazard of diabetes, HR=0.72 (95% CI, 0.55- 0.95), P for trend= 0.017 Inclusion of N=436 participants with prevalent chronic disease did not attenuate the fully-adjusted inverse association between yogurt and T2DM (OR=0.72; 95 CI, 0.55-0.95).	FDA Quality Score = Moderate Dietary data obtained by food record so that validation of a FFQ does not apply. Exclusion of subjects diagnosed with T2DM during the first two years of follow-up to minimize the possibility of reverse causality did not materially alter the protective association with yogurt consumption.

Author	Study Design, Population Characteristics and Follow-Up Period	Dietary Assessment and Diabetes Related Endpoints	Summary of Results	Comments
Babio et al. (2015)	Prospective Cohort design. N=5,801 prospective participants from the Spanish PREDIMED cohort (N=7,447 adults aged 55-80y) who had information available on biochemical determinations for at least ≥2 y were identified. Individuals were excluded if they had metabolic syndrome at baseline (N=3,707) or if data were missing such that it could not be determined if the participant had a diagnosis of metabolic syndrome (n=226), fasting glucose not measured, incomplete baseline FFQ or extreme intakes of energy (500-3,500kcal/d and 800-4,00l kcal/d). Thus, the final analysis included N=1,844 individuals. Mean follow up period= 3.2 y	At baseline and yearly thereafter, dietary information was collected via a dietitian-administered 137-item, validated, semi-quantitative FFQ. There were nine consumption categories ranging from "never" to ">6 servings/day". The substance is yogurt. Categories of yogurt consumption were total, full-fat and low-fat. Total dairy products included low-fat/skim milk and yogurt, whole milk, condensed milk, whole yogurt, custard, and all types of cheeses (petit Swiss, ricotta, cottage and semi-cured/cured cheese). FBG was measured after an overnight fast. High FBG was defined as ≥100 mg/dL (≥5.5 mmol/L)] or drug treatment for hyperglycemia.	Yogurt intake was divided into tertiles. Total yogurt consumption for the first, second and third tertiles were 7, 70 and 127 g/d, respectively. Analogous data for low-fat yogurt consumption were 1, 46 and 124 g/d, and for whole-fat yogurt were 0, 6 and 46 g/d, respectively. Multivariate analysis included: intervention group; sex; age; leisure time physical activity (metabolic equivalent task/day; BMI; current smoking; former smoking; hypoglycemic, hypolipidemic, antihypertensive, and insulin treatment at baseline and consumption during follow-up of vegetables, fruit, legumes, cereals, fish, red meat, cookies, olive oil, and nuts, as well as alcohol. The consumption of total yogurt (HR =0.72; 95% CI, 0.61- 0.85, P for trend = 0.004), whole-fat yogurt (HR= 0.79; 95% CI, 0.66- 0.94, P for trend =0.005) and low-fat yogurt (HR=0.81; 95% CI, 0.68- 0.96, P for trend =0.13) were inversely associated with the risk of high FBG.	FDA Quality Score = Moderate The PREDIMED study was designed to examine development of MS. Incident T2DM was not reported. Elevated FBG (one of the components of MS) was the only T2DM surrogate endpoint reported.

Author	Study Design, Population Characteristics and Follow-Up Period	Dietary Assessment and Diabetes Related Endpoints	Summary of Results	Comments
Diaz-Lopez et al. (2015)	Prospective Cohort design N=7,447 men aged 60-80 years and women aged 55-80 years participated in the PREDIMED study in Spain. In this analysis, only participants without diagnosed diabetes (N=3,833) were included, Furthermore, N=379 subjects were excluded if they lacked measures of glucose control, did not have a baseline FFQ or had implausible dairy energy intake. Thus, the final analysis included N=3,454 (N=1,313 men and N=2,141 women) individuals Median follow up = 4.1 y (2.5-5.7)	Participants completed at baseline and yearly, a validated 137 semi-quantitative food frequency questionnaire. The intra-class correlation coefficient between dairy product consumption from the FFQ and repeated food records was 0.84. The substance was yogurt which included low and whole fat yogurt. A serving of yogurt was 125g.Total dairy included all types of milk, yogurt, cheese, custard, whipped cream, butter and ice cream. Low-fat dairy included semi-skim/skim milk and skim yogurt. Whole-fat dairy included whole-fat milk and whole-fat yogurt. T2DM was identified via clinical diagnosis or use of antidiabetic medications at baseline. Incident diabetes was ascertained through application of the ADA criteria to blood samples taken yearly. The criteria indicated a diagnosis of T2DM in the case of fasting plasma glucose ≥126mg/dl (7mmol/L) or 2h plasma glucose of ≥200mg/dL (11.1mmol/L) after a 75g oral glucose load. Patient medical records were also reviewed yearly. The diagnosis of diabetes was only taken as confirmed as the endpoint of the study when the diagnosis was confirmed within 3 months of initial diagnosis via a biochemical test using the same criteria. N=270 incident cases of T2DM were documented during follow up.	Yogurt contributed 24% of total intake of which 70% was skimmed. Total yogurt intake (g/day) for the first, second and third tertiles was 13, 71 and 128 g/d. Low fat yogurt intake (g/day) was 3, 44 and 120 g/d for the first to third tertiles. Analogous data for whole fat yogurt intake were 0, 7 and 45 g/d. Multivariate analysis adjusted for age, sex, BMI, intervention group, baseline smoking status, leisure time, physical activity, educational level, hypertension or antihypertensive drug use, fasting glucose, HDL-cholesterol, triglycerides and dietary variables including vegetable, legume, fruit, meat, fish, cereals, olive oil, nut and alcohol consumption. Subjects with the highest total yogurt intake exhibited a 40% lower risk of T2DM compared to the lowest, HR = 0.60 (95%CI, 0.42-0.86), P for trend=0.002. HR for the highest tertile versus lowest tertile of low fat yogurt intake = 0.68 (95% CI, 0.47-0.97), P for trend <0.047. HR for the highest tertile of whole fat yogurt intake versus lowest tertile = 0.66 (95% CI, 0.47-0.92); P for trend <0.020.	FDA Quality Score = Moderate Small number of T2DM cases. Guasch-Ferré et al. (2017) reported an updated calculation of the full-fat yogurt data from this cohort based on 3,349 individuals (RR=0.65; 95 %CI, 0.45-0.94, p for trend=0.02)

Author	Study Design, Population Characteristics and Follow-Up Period	Dietary Assessment and Diabetes Related Endpoints	Summary of Results	Comments
Drehmer et al. (2015)	Cross-Sectional design. The original cohort consisted of N=15,105 adults, aged 35-74 y living in six cities in the northeast, southeast and south regions of Brazil (ELSA cohort). N=5,095 participants with known diabetes or other certain chronic diseases, those who used oral hypoglycemic medications or insulin, women who had previous gestational diabetes and those who had low (≤1,289kcal/day) or high (≥6,372kcal/day) reported energy intake were excluded. Thus, the final analysis included N=10,010 (N=4,575 men and N=5,435 women) individuals. Mean follow-up period= 0y (cross sectional study)	Dietary intake over the last 12 months was measured via a self-administered, validated, 114-item, quantitative FFQ. There were eight possible responses for frequency of consumption ranging from ">3 times/day" to "never/almost never". Yogurt was classified as "regular" or "low-fat". A serving of yogurt was 120g. Total dairy products included milk (skimmed milk, low fat milk, whole milk), yogurt (regular, low-fat), cheese (regular, low-fat), ice cream, desserts made with milk (pudding, mousses) and butter. Servings of total dairy were based on the servings for each individual dairy food including yogurt (120g), milk (240g), cheese (30g), ice cream (80g), dairy desserts (50g) and butter (5g). Blood samples were taken and the following tests were conducted: FBG (mg/dL), fasting insulin (µIU/mL), 2 h 75g oral glucose tolerance test (mg/dL), glycated hemoglobin (%) and post-load insulin. Newly diagnosed T2DM was defined as FBG ≥126mg/dL or 2-h post load glucose of ≥200mg/dL or HbA1c ≥6.5%.	The median intake of yogurt in the group was 60g/d. Multivariate analysis involved adjustment for height, waist circumference, hip circumference, age, sex, race, occupational status, education, family income (continuous variable), and study center, menopausal status, family history of diabetes, smoking status, alcohol intake, physical activity, calorie intake and non-dairy food groups (fruit, tea, sodas, overall and processed red meat, processed white meat, non-dairy desserts, refined grains and sweets). Yogurt was associated with a significant difference in HbA1c. The adjusted difference in HbA1c for yogurt intake of 1 serving/day was -0.04 (95% CI, -0.06 to -0.01). There was no significant difference in fasting glucose -0.29 (95% CI, -1.03 to 0.44) and 2 h post load glucose -0.31 (95% CI, -2.20 to 1.58) associated with a 1-serving/day difference in intakes of yogurt.	FDA Quality Score = Low The association between yogurt and T2DM not measured. Milk fat content of "low fat" milk not specified. Portion size used for total, full-fat and low-fat dairy unclear.

Author	Study Design, Population Characteristics and Follow-Up Period	Dietary Assessment and Diabetes Related Endpoints	Summary of Results	Comments
Moslehi et al. (2015)	Nested Case-Control design. N=15,005 participants, aged ≥3 years eligible for inclusion as part of the Tehran lipid and glucose study in Iran. Cases were participants which were free of T2DM at recruitment for the study but later developed it during follow-up. N=37 were excluded due to use of hypoglycemic agents. There were N=520 cases of new diagnosed T2DM and of them, N=215 were excluded due to missing data. Thus, N=178 cases were eligible for analysis. Three randomly selected controls were chosen for each case leading to N=520 matched controls. Thus, the final analysis included N=698 (319 men and N=379 women) individuals (mean age= 43.6 y). Median follow up period = 9 y	Dietary intake was ascertained via a validated, 168-item, semi-quantitative FFQ with standard serving sizes on a daily, weekly or monthly basis. Participants were followed up every 3 years. The substance was yogurt and all types of were included. Total dairy included all dairy products except for ice cream and butter. Low-fat dairy included low-fat milk and yoghurt (<2% of total fat content), and low-fat cheese (<20% of total fat content); high-fat dairy included high-fat milk, high-fat yoghurt (≥2% of total fat content), high-fat cheese (≥20% of total fat content), and chocolate milk. A diagnosis of diabetes was confirmed when participants had at least one of the ADA Criteria which are FPG ≥126mg/dl (7mmol/l) or 2h plasma glucose of ≥200 mg/dL (11.1mmol/l) after a 75g oral glucose challenge. Glucose was measured after a 12-14 h overnight fast. N=178 incident cases of T2DM were documented during follow up.	Yogurt intake was divided into tertiles. Intake ranged from 66g/day for the first (N=228), 167g/day for the second (N=228) and 276g/day for the third tertile (N=223). The median yogurt intake was 165g (82-239g). In men, intake tertiles (g/day) ranged from 63 for the first, 161 for the second and 297g/day for the third while in women, intake tertiles (g/day) of yogurt intake ranged from 66 for the first, 230 for the second and 263 for the third. Multivariate analysis included age, sex, family history of diabetes, date of blood draw, baseline BMI, waist circumference at baseline, blood pressure, hypercholesterolemia, hypertriglyceridemia and total energy intake. Yogurt intake was not significantly associated with T2D. The OR for T2DM for the highest versus the lowest tertile of yogurt intake was 0.92 (95% CI, 0.59-1.42), P for trend=0.765. For every 100g increase in yogurt consumption, the OR was 0.91 (0.66-1.24), P=0.541. In men, the OR for risk of T2DM in the highest tertile of intake compared to the lowest was 1.26 (95% CI, 0.65-2.43), P for trend=0.453. For every 10g increase in dairy consumption, the OR was 0.99 (95% CI, 0.62-1.57), P=0.453. In women, the OR for risk of T2DM in the highest tertile of intake compared to the lowest was 0.72 (95% CI, 0.39-1.31), P for trend =0.304. For every 10g increase in dairy consumption, the OR was 0.86 (95% CI, 0.56-1.33), P =0.304	FDA Quality Score = Low Iranian subjects do not reflect the general U.S. population. Approximately 59% of T2DM patients were excluded from the analysis due to incomplete data. Relatively limited adjustment for potentially confounding variables.

Author	Study Design, Population Characteristics and Follow-Up Period	Dietary Assessment and Diabetes Related Endpoints	Summary of Results	Comments
Sayon-Orea et al. (2015)	Prospective Cohort design. N=15,909 university graduates (20-90yrs) of the SUN project cohort in Spain were potentially eligible for inclusion. For this analysis, N=4,084 were excluded for meeting at least one of the criteria for the metabolic syndrome (MS) at baseline. N=1,187 were excluded for reporting energy intake values outside of predefined limits (<500kcal or >3,500kcal for women or <800kcal or >4,000kcal for men), N=578 were lost to follow up, N=1,997 did not provide relevant information about diagnostic criteria for the MS at the 6th year follow up. Thus, the final analysis included N=8,063 (N=2,758 men and 5,305 women) individuals. Minimum follow up period =6 y	A validated, semi-quantitative, 136-item FFQ was used to assess habitual dietary intake over the last 12 months. Frequencies of intake were divided into 9 categories ranging from never/almost never to >6 servings/day. The substance was yogurt. Total yogurt was defined as the sum of whole-fat and low-fat yogurt. One serving was 125g. Impaired glucose metabolism was defined as fasting glucose ≥100mg/dL or drug treatment of elevated glucose. The number of cases with impaired glucose metabolism was N=224 and N=149 for the lowest highest tertile of total yogurt intake; N=323 and N=10 for the lowest and highest tertile of whole fat yogurt intake and N=431 and N=48 for the lowest and highest tertile of low fat yogurt intake.	The group was divided into tertiles of total yogurt intake: In the analysis for incident metabolic syndrome, N=2,689 (N=1,051 men; N=1,638 women) consumed 0-250g/week (0-2 servings/day); N=3,089 (N=1,044 men; N=2,045 women) consumed >250 to <875g/week (>2 to <7 servings/week) and N=2,285 (N=663 men; N=1,622 women) consumed ≥875g/week (≥7 servings/week). In this analysis, whole fat yogurt intake tertiles: there were N= 4,160 in the first, N=1,242 in the second tertile and N=1,482 in the third. Low fat yogurt intake tertiles: there were N= 4,160 in the first, N=2,421 in the second tertile and N=831 in the third. Multivariate analysis included age, sex, baseline weight, physical activity, sedentary behavior, hours sitting, smoking status, snacking between meals, following a special diet and intakes of total energy, alcohol, soft drinks, red meat, French fries, fast food, Mediterranean diet The OR for risk of impaired glucose metabolism in the highest tertile of intake compared to the lowest were not provided but inferred from the forest plot: 0.98 (95% CI, 0.83-1.3) for total yogurt; 1.15 (95% CI, 0.88-1.45) for whole-fat yogurt and 0.90 (95% CI, 0.65-1.25) for low-fat yogurt.	FDA Quality Score = Low OR's and CI in the "Summary of Results (Yogurt)" column are estimated from the forest plot. No numerical p-values were provided. This study did not measure incidence T2DM or incidence of impaired fasting glucose. The subjects with impaired fasting glucose were grouped with those on drug treatment and named impaired glucose metabolism. 50.6 percent of potentially eligible subjects were excluded.

Author	Study Design, Population Characteristics and Follow-Up Period	Dietary Assessment and Diabetes Related Endpoints	Summary of Results	Comments
Zhu et al. (2015)	Cross-Sectional design. N=5,124 (N=1,717 boys and N=1,801 girls), out of an initial population of N=5,185 children aged 2-18y were eligible for inclusion as part of the National Health and Nutrition Examination Survey in the United States after excluding pregnant or lactating females (N=56) and breastfed toddlers (N=5). The final analysis included N=930 individuals for the glucose analysis and N=913 individuals for the insulin, HOMA-IR and QUICKI analyses after excluding subjects with missing information on covariates. Mean follow-up period= 0 y (cross sectional study)	Dietary intake over the last 12 months was ascertained through a self-administered food frequency questionnaire and at least one 24-hour recall. The substance was yogurt. The FFQ asked "how often do you eat yogurt?" to which the responses ranged from "never" to "two or more times per day". Frequent consumers were classified as consuming yogurt at least once/week and participants were classified as infrequent consumers if they did not consume yogurt in the past 12 months or less than once/week. FBG (mmol/L) and insulin (pmol/L) were measured in individuals older than 12 years of age and only if individuals had a morning appointment for assessment. IR was assessed by homeostatic model assessment of insulin resistance (HOMA-IR) and insulin sensitivity was calculated by quantitative insulin sensitivity check index (QUICKI).	N=3,518 (1,717 boys and 1,801 girls) were infrequent consumers of yogurt. N=1,606 (33.1% of the group) were frequent yogurt consumers (consumed yogurt at least once/week). The median frequency of yogurt intake was "2 times per week" in consumers and "1-6 times per year" in non-consumers. Multivariate analysis involved adjustment for age, gender, race, income-to-poverty ration, physical activity level, energy intake and diet quality. Frequent yogurt consumers had lower levels of fasting insulin (52.3±5.6 *vs.* 65.9±4.3, P<0.001), HOMA-IR (1.94±0.28 *vs.* 2.55± 0.20, P<0.001) and QUICKI (0.352± 0.005 *vs.* 0.345± 0.004, P=0.03). FBG, however, was not associated with frequency of yogurt consumption (5.11±0.08 for frequent *vs.* 5.13±0.08 for infrequent consumers, P=0.64).	FDA Quality Score = Low Limited detail on the substance. Children 2-18 do not reflect the intended audience for the proposed claim. No assessment of incident T2D.

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Brouwer-Brolsma et al. (2016)	Prospective Cohort design. N=7,983 adults, aged ≥55 y, were eligible for inclusion in the Rotterdam Study in the Netherlands. Exclusion criteria include prevalent diabetes cases at baseline and unreliable data provision on dairy intake or incident diabetes. Thus, the final analysis included N=2,974 (N=1,190 men and N=1,784 women) individuals Mean follow up period = 9.5±4.1 y	Intake over the last 12 months was measured via a validated, semi-quantitative 170-item FFQ. The substance was yogurt (all types of yogurt, including plain yogurt, and flavored/fruit yogurt). Total dairy products included all types of dairy products except butter. Every four years, incident T2DM cases were ascertained through general practitioner records, hospital discharge letters and serum glucose levels. T2DM was registered by a general practitioner and met at least one of the following: FBG concentration ≥7.0 mmol/l; random plasma glucose concentrations ≥11.1 mmol/L; use of anti-diabetes medication and/or following dietary guidelines for T2DM. N=393 incident cases of T2DM were documented during follow-up period.	Yogurt intake (g/day) for the first to fourth quartiles was: ≤1 (N=743), 2-45 (N=744), 46-108 (N=744) and ≥109 (N=743), respectively. Multivariate adjustment for age, sex, alcohol consumption, smoking, education, BMI and physical activity, total energy intake, energy adjusted meat intake, energy adjusted fish intake and potential intermediates (i.e. total cholesterol, HDL-cholesterol, C-reactive protein and hypertension). There was no significant association between yogurt consumption and risk of T2DM: HR for highest vs lowest quartile of intake = 0.85 (95% CI, 0.64-1.14), P for trend=0.53.	FDA Quality Score = Moderate FFQ not specifically validated for dairy Only 37% of eligible participants provided reliable data on dairy intake. Relatively small number of T2DM cases.

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Cormier et al. (2016)	Cross-Sectional design. N=664 subjects, aged 18-55 y from the INFOGENE study database were used. These subjects were recruited from the Quebec City metropolitan area of Canada. Mean follow-up period= 0 y (cross sectional study)	Intake over 12 months was measured via a validated 91-item FFQ which was administered by a registered dietitian. Yogurt is the substance. One serving was 175g. Yogurt included fat-free (0% milk fat), low-fat (<2% milk fat) and high-fat (≥2% milk fat) yogurt. FBG (mmol/L) and insulin (ρmol/L) were measured from blood taken after a 12 hour fast. IR was assessed by calculating homeostatic model assessment of insulin resistance (HOMA-IR).	The mean daily consumption of yogurt was 82.3g/day among N=564 consumers (N=100 were non-consumers). Multivariate adjustment for age, sex, BMI, physical activity and dietary pattern scores (Prudent & Western) There was no significant difference between non-consumers and consumers of yogurt for FBG (5.76 vs 5.74 mmol/L, P=0.94), fasting insulin (96.7 vs 75.3 ρmol/L, P=0.16) and HOMA-IR (25.0 vs 19.9, P=0.30).	FDA Quality Score = Low The paper did not report any exclusions from the study.

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Eussen et al. (2016)	Cross-Sectional design. N=3,451 adults, aged 40-75 y were recruited for the Maastricht study in the Netherlands. Participants were excluded if they had previously been diagnosed with T2DM (N=883). Additionally, N=117 individuals did not return completed food frequency questionnaires and N= 60 individuals reported implausible energy intakes (<500-800kcal/day or 3,500-4,200kcal/day for females-males, respectively) and so were excluded. Thus, the final analysis included N=2,391(N=1,146 men and N=1,245 women) individuals Mean follow-up period= 0 y (cross sectional study)	Dietary intake data over the last 12 months were ascertained via a 253-item, self-administered FFQ. The substance was yogurt: including regular or drink yogurt, natural or fruit yogurt and whole-fat, low-fat and skimmed yogurts, with or without artificial sweeteners. A serving of yogurt was 150g. Total dairy products included milk (including whole-fat, low-fat, skimmed, coffee and chocolate), porridge, cheese and regular or drink yogurt (natural or fruit whole-fat, low-fat and skimmed (with or without artificial sweeteners)). A serving of dairy was 100g. FBG was measured from blood samples taken after an overnight fast. A 2-h oral glucose tolerance test was completed after 75g glucose drink. Diabetes was defined via the World Health Organization 2006 criteria. Those who had impaired FBG or impaired glucose tolerance were defined as having impaired glucose metabolism (IGM). N=125 cases of T2DM identified. N=470 had IGM.	Yogurt was consumed by 80% of the participants. Yogurt intake was divided into tertiles: ≤10.5g/day for the first, 13.5-63/day for the second and ≥63g/day for the third. Multivariate analysis included adjustment for age, sex, education, BMI, physical activity, smoking, intakes of energy, vegetables, fruits, meat and fish. Compared with the lowest tertile multivariate adjusted data showed the highest tertile of yogurt intake was associated with significantly reduced risk of IGM (OR= 0.67; 95% CI, 0.50-0.90, P for trend <0.01). In the continuous model, there was no association with yogurt intake other than p for trend (OR= 0.90; 95%CI, 0.71- 1.15, P for trend <0.01. Compared with the lowest tertile, and the highest tertile, the OR for yogurt and newly diagnosed T2DM was not statistically significant (OR=0.60; 95% CI, 0.35-1.02, P= for trend =0.06) after multivariate adjustment. However, in the fully adjusted continuous model, the OR for one serving of yogurt was significantly associated with reduced risk of T2DM (OR=0.47; 95% CI, 0.24-0.89, P for trend =0.06).	FDA Quality Score = Low It is not clear if FFQ is validated

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Feeney et al. (2017)	Prospective Cohort design. N=1,500 adults aged 18-90y (N=740 Men, N=760 Female) who formed part of the Irish National Adult Nutrition Survey in Ireland and were available for analysis. N=1,136 provided a fasting blood sample and were included in the assessment of T2D-related surrogate endpoints. Mean follow up period = 0 y (cross sectional study)	Dietary intake was ascertained via a 4-day semi-weighed food diary. Participants were provided with scales and requested to record the amounts of all foods and beverages consumed (including leftovers). Where it was not possible to weigh a food, a food portion atlas was used by an interviewer to estimate weight. The substance was yogurt. Total yogurt included drinking yogurts, some of which could be classified as probiotic drinking yogurts. Total dairy included milk, cheese, yogurt, butter and cream. Fasting insulin (uIU/mL) and FBG (mmol/L) were measured. IR was assessed by calculating homeostasis model assessment (HOMA). Quantitative insulin sensitivity check index (QUICKI) was calculated as an indicator of insulin sensitivity.	Participants were classified as yogurt consumers (N=688) or non-consumers (N=809). Within consumers, intake (g/day) of yogurt ranged from 21.7±0.74 for low consumers (N=229), 56.4 ±0.9 for medium consumers (N=231) to 131.2±3.73 for high consumers (N=228). Multivariate analysis included age, gender, body mass index (BMI), healthy eating index score and mean daily energy intake. Smoking habits and social class did not vary across groups and adjusting with these did not affect the outcomes. There was no difference in serum FBG between categories of dairy intake (5.22±0.05, 5.38±0.08, 5.26±0.08 and 5.26±0.09 for non, low, medium and high consumers respectively, P=0.454) There was no difference in serum insulin between categories of dairy intake (9.58±0.32, 8.83±0.58, 9.05±0.55 and 8.9±0.6 for non, low, medium and high consumers respectively, P=0.577) There was no difference in HOMA between categories of dairy intake (2.33±0.11, 2.19±0.19, 2.24±0.18 and 2.27±0.2 for non, low, medium and high consumers respectively, P=0.922) There was no difference in QUICKI between categories of dairy intake (0.35±0, 0.36±0, 0.36±0 and 0.36±0 for non, low, medium and high consumers respectively, P=0.176)	FDA Quality Score = Low Incident T2DM not reported.

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Guasch-Ferré et al. (2017)	Prospective Cohort design. N=7,477 adults, aged 55-80y at high risk of cardiovascular disease were recruited as part of the PREDIMED study in Spain. Exclusion criteria included severe chronic illness, body mass index ≥40kg/m^2 and alcohol or drug misuse. For this analysis, additional exclusions were made: N=3,614 had T2DM at baseline, N=292 lacked measures of blood glucose control, N=94 were not followed up, N=98 had implausible reported daily energy intake (<800 or >4,000kcal/d for men and <500 or >3,500kcal/d for women) or had not completed baseline FFQs. Thus, the final included N=3,349 (N=1,267 men and N=2,082 women) individuals. Median follow up period = 4.3y	Dietary intake was obtained via a dietitian-administered validated, 137-item, semi quantitative FFQ at baseline and yearly. There were nine responses for frequency of consumption ranging from "never or almost never" to" >6 times/day". The substance was whole fat yogurt. One serving was 125g. T2DM was diagnosed according to the ADA criteria: FBG concentrations ≥7.0mmol/l (≥126.1mg/dL) or 2-h plasma glucose concentrations ≥11.1mmol/l (≥200mg/dL) after an oral dose of 75g glucose or the recent use of an oral/insulin medication. A review of medical records was completed yearly by physicians or investigators blinded to the intervention. New diagnoses were identified by medical diagnoses reported in medical charts or on glucose testing (completed≥1/y). A second test required within three months of the first diagnosis to confirm the diagnosis of new case of T2DM. N=266 incident cases of T2DM were documented during follow up.	Data on intake of yogurt not provided. Multivariate analysis included age, sex, intervention group, BMI, smoking status, educational status, leisure time physical activity, baseline hypertension or use of antihypertensive medications, hypercholesterolemia or use of lipid lowering medications, fasting plasma glucose, yearly updated total energy intake, intake of alcohol, vegetables, fruits, legumes, cereals, fish, meat, dairy, olive oil, nuts and biscuits. The HR for T2DM by increasing the consumption of 1 serving of whole fat yogurt was 0.65 (95% CI, 0.45- 0.94), P=0.02	FDA Quality Score = Moderate Same cohort as Diaz-Lopez et al. (2015) and Babio et al. (2015) Only data for whole fat yogurt are reported in this paper. Intake data stratified by dietary saturated fat. Not adjusted for family history of diabetes.

Author	Study Design, Population Characteristics and Follow-Up Period	Dietary Assessment and Diabetes Related Endpoints	Summary of Results	Comments
Hruby et al. (2017)	Prospective Cohort design. N=3,799 participants aged 54±9.7 years were eligible for inclusion at examination 5 of the Framingham heart study in the United States. Individuals were excluded if they had a history of diabetes or were identified as having diabetes at baseline (N=375), were missing blood glucose data (N=101), had invalid dietary data at baseline (N=318), were missing necessary covariates (N=26) or had no follow-up data on diabetes status (n=170). These exclusions left N=2,809 (N=1,292 men and N=1,517 women (54%)) participants for analysis. Risk of prediabetes (PD) was assessed in N=1,867 individuals who were initially healthy at baseline. Risk of T2DM was assessed in N=925 individuals who had prediabetes at baseline. Risk of incident PD of T2DM was assessed in N=1,884. Mean follow up period = 12 years	Dietary information was collected from a 126-item, validated, semi-quantitative FFQ (Harvard) at each examination. Possible intake categories ranged from never or <1 time/month to ≥6 times/day. The substance was yogurt. An average portion of yogurt was defined as 227g. Total dairy (servings/week) was calculated as the sum of foods that meet the USDA MyPlate definition of dairy which is "foods made from milk that retain their calcium content" which included milk, sherbet/ice milk, ice cream, yogurt and cheese. Low-fat dairy included skim milk, sherbet/ice milk and yogurt. High-fat dairy included whole milk, ice cream and cheese. Fasting blood glucose was measured. Participants were defined as having PD at baseline if they had a fasting glucose ≥5.6 to <7mmol/L (≥100 to <126mg/dL) or glucose ≥7.8 to <11.1mmol/L (≥140 to <200mg/dL) after a 2-h oral glucose tolerance test. Incident prediabetes was defined as fasting glucose ≥5.6 to <7mmol/L (≥100 to <126mg/dL). T2DM at baseline was defined as fasting plasma glucose ≥7.0mmol/l (126mg/dL) or glucose ≥11.1mmol/L (≥200mg/dL) after a 2-h oral-glucose tolerance test or use of an oral hypoglycemic drug or insulin. Incident T2DM was defined as reported use of an oral hypoglycemic drug or insulin, or the first incident measurement of FBG ≥7.0mmol/L (≥126 mg/dL). In normoglycemic individuals, N=902 incident cases of PD were documented during follow-up. In those with impaired fasting glucose or impaired glucose tolerance at baseline, N=196 incident cases of T2DM were documented during follow up.	36% of participants reported never consuming yogurt. Yogurt intake was divided into 4 groups: 0, >0 to <1, 1 to <3 or ≥3 svg/wk. The median intake of yogurt in initially healthy individuals was 0, 0.3, 1.7 and 4svg/wk for quartiles 1-4, respectively. Analogous data for those with PD at BL were 0, 0.4, 1.7 and 4.2 svg/wk, respectively Multivariate analysis for risk of PD included age, sex, energy intake, parental history of diabetes, smoking status, dyslipidemia or treatment, hypertension or treatment, means of other dietary characteristics including intake of coffee, nuts, fruits, vegetables, meats, alcohol, fish, the glycemic index, other dietary intake as appropriate (i.e., for associations of low-fat dairy intake, high-fat dairy intake was included), baseline BMI and weight change over follow up. The risk of T2DM in the entire population was additionally adjusted for glycemic status. The HR for risk of PD in normoglycemic individuals for the highest vs. lowest quartile was 0.95 (95% CI, 0.72- 1.26), P for trend =0.33. However, yogurt was non-linearly associated with risk of PD among these subjects: The fully-adjusted RR of the third vs. first quartile was significant (HR= 0.76; 95% CI, 0.62-0.92, P-nonlinear trend = 0.04). The HR for risk of T2DM in those with PD at BL for the highest vs. lowest quartile was 1.24 (95% CI, 0.76- 2.29), P for trend=0.89. The HR for risk of PD or T2DM in normoglycemic individuals for the highest vs. the lowest quartile was 0.95 (95% CI, 0.72-1.25), P for trend =0.31. The HR for risk of T2DM in initially health individuals for the highest vs. the lowest quartile was 1.30 (95% CI, 0.72-1.25), P for trend=0.31.	FDA Quality Score = High A cross sectional study was previously published by Wang et al. (2013) and looked only at examination 7 of this cohort. Yogurt consumption was non-linearly associated with risk of prediabetes among initially healthy subjects. The fully-adjusted HR of the third vs. first quartile was 0.76 (95% CI, 0.62-0.92, p-nonlinear trend = 0.04). Relatively small number of T2DM cases.

Author	Study Design, Population Characteristics and Follow-Up Period	Dietary Assessment and Diabetes Related Endpoints	Summary of Results	Comments
Kim and Kim (2017)	Prospective Cohort design. N=10,030 adults, aged 40-69y were recruited in the Ansan and Ansung regions of Korea (Korean Genome and Epidemiological Study (KoGES)). Exclusion criteria included metabolic syndrome at baseline (N=2,977), declining follow up (N=747), diagnosis of cardiovascular disease or cancer (N=137), lack of baseline or follow-up FFQ data (N=659) or implausible reported energy intake (<500 or >5,000kcal/day) (N=90). Thus, the final analysis included N=5,510 (N=2,859 men and N=2,651 women) individuals Median follow up period= 10y	Dietary information over the last 12 months was collected via a dietitian-administered 103-item, validated, semi-quantitative FFQ. There were nine options for frequency of consumption ranging from "never or almost never" to "3 times/day". There were three options for portion size (1/2 serving, 1 serving or ≥2 servings). The substance was yogurt. A serving of liquid yogurt was 130ml and solid yogurt was 150ml. Total dairy products included milk, yogurt and cheese. FBG (mmol/l) was measured (at least 8h fast). Hyperglycemia was defined as FBG ≥5.6mmol/l, current use of insulin or oral hypoglycemic medications or a physician's diagnosis of T2D.	Yogurt intake was divided into four groups: none (N=1,632 (N=877 men, N=755 women)); <1 serving/week (N=1,949 (N=910 men, N=1,039 women)); ≥1-≤4 servings/week (N=1,813 (N=763 men, N=1,050 women)) and >4 servings/week (N=957 (N=347 men, N=610 women)) for the first-fourth quartile, respectively Multivariate analysis included age, sex, BMI, place of residence, educational level, household income, smoking status, alcohol intake, physical activity, energy, calcium and fiber intake. Yogurt was inversely associated with hyperglycemia among the entire sample. For the highest vs. the lowest quartile, the HR was 0.73 (95% CI, 0.62- 0.85), P for trend <0.0001. In men, the HR was 0.66 (95% CI, 0.52- 0.82), P for trend <0.0001 and in women, the HR was 0.81 (95% CI, 0.65-1.02), P for trend = 0.0195.	FDA Quality Score = Moderate Data from the Korean population do not reflect the healthy general U.S. population.

Author	Study Design, Population Characteristics and Follow-Up Period	Dietary Assessment and Diabetes Related Endpoints	Summary of Results	Comments
Liang et al. (2017)	Cross-Sectional design. N=7,611 adults aged 35-74y were invited to the survey from three urban districts and three rural counties of Qingdao, China. N=2,501 did not attend and N=767 individuals were excluded due to missing information. Thus, the final analysis included N=4,343 (N=1,641 men and N=2,702 women) individuals. Mean follow up period = 0 y (cross sectional study)	Participants were interviewed by trained doctors and nurses. Habitual dietary intake over the last 12 months was ascertained via an interviewer administered, validated, 54-item FFQ. The substance was yogurt. After an overnight fast, FBG and a 75g oral glucose tolerance test was performed on those without diagnosed diabetes. Previously diagnosed T2DM was confirmed by an examiner at the survey site according to reported prior history of diabetes diagnosis or antidiabetic treatment. Newly diagnosed T2DM was defined as fasting plasma glucose ≥7.0mmol/l and/or 2-h plasma glucose ≥11.1mmol/L according to the 2006 WHO/IDF diagnostic criteria. N=692 cases of T2DM were identified.	Data on intake of yogurt not provided. Multivariate analysis included adjustments for age, family history of diabetes, body mass index, systolic blood pressure, physical activity, 24-h energy intake, educational level, smoking habits drinking status and dietary factors such as meats, seafood, soft drink, dairy products, soy products, nutrients and tea intake. Yogurt was significantly associated with reduced risk of T2DM in women (OR=0.56; 95% CI, 0.32-0.98) but not men (OR=0.98; 95% CI, 0.69-1.38).	FDA Quality Score = Low Data on yogurt intake not specified. Small number of foods in the FFQ.

Author	Study Design, Population Characteristics and Follow-Up Period	Dietary Assessment and Diabetes Related Endpoints	Summary of Results	Comments
Panahi et al. (2017a)	Cross-Sectional design with prospective analysis on a subset of the original cohort. N=952 participants, aged 10-73 y were enrolled in the Québec Family Study in Canada. Participants were French Canadian. Exclusion criteria included age <21y or >64y, diabetes or glucose intolerance at baseline and body weight change greater than 2kg during the 6 months prior to baseline testing. Thus, the final cross-sectional analysis included N=839 (N= 375 men and N=464 women) individuals. N=248 had follow up data available. Participants that were consumers (N=37) and non-consumers (N=122) with data both at baseline & follow-up were included in the prospective analysis. Mean follow up period = 6±0.9 y	Self-reported dietary intake was assessed via 3-day dietary records (2 weekdays and 1 weekend day) at baseline and follow-up. Participants were instructed by dietitians. The substance was yogurt. FBG (mmol/L) and insulin (pmol/L) was measured after a 12-h overnight fast. Participants also underwent a 2-h oral glucose tolerance test (mmol/L). T2DM was defined as use of insulin or a hypoglycemic agent, FBG concentrations of ≥126mg/dL (7.0mmol/l) or 2-h post-load plasma glucose concentration of ≥200mg/dL (11.1mmol/l) or glucose intolerance defined as a 2-h post-load plasma glucose concentration of ≥140mg/dL (7.8mmol/l). FBG and insulin area under the curve (AUC) was measured in min mmol/L and min pmol/L respectively.	<u>Cross-sectional analysis:</u> Participants were classified as yogurt consumers (N=295) (N=108 men and N=187 women) if they consumed ≥1 serving per day. N=544 (N=267 men and N=277 women) were non-consumers (0 servings/d). Results were adjusted for age, nutrient risk food index, physical activity and % body fat. In men, there was no difference in FBG (5.5±1 vs 5.7±2, P=0.69), fasting insulin (85±61 vs 64±46, P=0.10) or AUC for glucose (1,295±365 vs 1,306±520, P=0.82) and insulin (82,002±52,401 vs 61,561±36,960, P=0.20) between consumers and non-consumers. In women, there was no difference between non-consumers and consumers in FBG (5.3±1 vs 5.2±1, P=0.99). There was a significant difference in fasting insulin (83±67 vs 70±47, P=0.05) and AUC for both glucose (1253±327 vs 1161±295, P=0.04) and insulin (88,092±54,344vs 539,347±38,785, P=0.008). <u>Prospective analysis:</u> In men: no significant difference (NSD) between non-consumers and consumers in: FBG at baseline (5.7±1 vs 5.0±0, P=0.26) or follow up (5.9±2 vs 5.3±1, P=0.26); fasting insulin at baseline (88±60 vs 39±31, P=0.53) or follow up (89±63 vs 50±33, P=0.53); glucose AUC at baseline (1266±458 vs 1125±352, P=0.78) or follow up (1399±528 vs 1159±214, P=0.78); Insulin AUC at baseline (78,514±42,458 vs 46,916±29,365, P=0.43) or follow up (80,293±42,502 vs 56,084±27,493, P=0.43). In women: NSD between non-consumers and consumers in: FBG at baseline (5.1±1 vs 4.7±0, P=0.21) or follow up (5.5±1 vs 5.0±1, P=0.21), fasting insulin at baseline (66±45 vs 42±26, P=0.83) or follow up (74±41 vs 54±28, P=0.83); glucose AUC at baseline: 1206±249 vs 1036±150, P=0.34) or follow up (1304±391 vs 1089±229, P=0.34) or insulin AUC at baseline (73,474±45,968 vs 55,247±21,289, P=0.50) or follow up (80,004±36,443 vs 65,209±43,142, P=0.50).	FDA Quality Score = Low Small sample size – especially for the follow-up study which included only 26% of the original cohort. Results not given for total population (only for each sex separately). No data on yogurt intake. Categorization of yogurt intake limited to consumers and non-consumers. Among men, the prospective analysis showed that there was a significant difference between consumers and non-consumers of yogurt for fasting glucose (P=0.0004) and glucose AUC (P=0.0008) when adjusted for age, nutrient risk food index and physical activity only. In addition, prospective data for women showed a significant difference between consumers and non-consumers of yogurt for FBG (P<0.0001), fasting insulin (P=0.02) and glucose AUC (P=0.02) when adjusted for age, nutrient risk food index and physical activity only.

Author	Study Design, Population Characteristics and Follow-Up Period	Dietary Assessment and Diabetes Related Endpoints	Summary of Results	Comments
Hobbs et al. (2018)	Cross-sectional design N=1,687 children 4-18 years of age from years one through four of the National Diet and Nutrition Survey (NDNS) in the UK.	Yogurt intakes were calculated based on the average weight of yogurt consumed per day from 4-day diet diaries. All types of yogurt were considered including fat free, low-fat, high-fat and Greek. Fromage frais (a type of smooth soft fresh cheese with the consistency of thick yogurt) was also included. Fasting blood samples were collected in a follow-up household visit by a nurse. Analyses of these samples included glycated hemoglobin (HbA1c) and glucose.	38% of children 4-10 years of age and 69% of those aged 11-18 years did not consume yogurt during the 4-days of diet recording. Mean yogurt consumption (g/d ± SD) among 4-10 year olds: No consumption (N=307), tertile 1= 19.4 g/d ± 7.8 (N=166), tertile 2=43.2±8.3 (N=155) and tertile 3=98.4±35.7 (N=175). Analogous data for ages 11-18 were: No consumption (N=610), tertile 1=19.9±7.8 (N=97), tertile 2=40.9±8.3 (N=89) and tertile3=105.4±37.5 (N=88). There were no associations between fasting plasma HbA1c and yogurt consumption among children 4-10 years of age. The "No Consumption" category and all three tertiles were 5.3% (NS). There were also no associations for FPG: Mean value for the "no consumption" category was 4.8 mmol/L and the remaining three categories were 4.7 mmol/L. Plasma HbA1c concentrations were inversely associated with yogurt consumption among children 11-18 years of age: Mean values for the "No Consumption" category and tertiles 1 to 3 were 5.3±0.3, 5.3±0.3, 5.3±0.3 and 5.1±0.3 (p=0.010 after adjustment for age, sex, BMI, energy intake and Healthy Eating Index (HEI) score). There were no significant associations for FPG among the older children. Mean values for the "No Consumption" category and tertiles 1 to 3 were 4.8±0.4, 4.8±0.3, 4.8±0.3 and 4.7±0.4, respectively (p=0.45 after adjustment for age, sex, BMI, energy intake and Healthy Eating Index (HEI) score).	FDA Quality Score=Low Cross-sectional study among children. Four-day diet diaries do not measure long-term intake patterns and may therefore not characterize typical yogurt consumption. Inclusion of fromage frais in the yogurt consumption category complicates interpretation of the data.

Author	Study Design, Population Characteristics and Follow-Up Period	Dietary Assessment and Diabetes Related Endpoints	Summary of Results	Comments
Brouwer-Brolsma et al. (2018)	Cross-sectional design N=167,729 healthy Dutch individuals agreed to participate in the Lifelines Cohort Study. The initial participants (aged 25-50) were recruited through their general practitioner and asked if they had family members who would also participate. The goal was to obtain a three-generation cohort. N=144,095 completed a FFQ. N=29,413 were excluded due to unreliable dietary data and N=2,596 due to diagnosis of diabetes. Therefore, N=112,086 were included in the final analysis.	Dietary intake was assessed using the "flower FFQ" which has been developed as an alternative to more time-consuming surveys. This survey, which has not yet been validated, included 110 food items from the major food groups. The dairy group included questions for yogurt, skimmed yogurt, full-fat yogurt and flavored yogurt drinks. The substance was yogurt. A serving of yogurt was 150 g. Fasting blood samples were collected at baseline and analyzed for glycated hemoglobin (HbA1c) and glucose. Pre-diabetes was defined as FPG between 5.6 and 6.9 mmol/L (100 – 124 mg/dL) or HbA1c of 5.7-6.4% and T2DM was defined as FPG ≥ 7.0 mmol/L (126 mg/dL) or HbA1c ≥ 6.5%.	Median total intake of yogurt among all participants was 17 g/d. Total yogurt intake (g/d) by tertile was: 0 for T1 (N=34,716), 23 for T2 (N=39,063) and 34 for T3 (N=38,307). No other category of "pure" yogurt was reported. There were no significant associations between total yogurt consumption and pre-diabetes. Fully adjusted OR=0.99 for T1 vs. T3 (95% CI, 0.96-1.03), P for trend = 0.76 after adjustment for age, sex, alcohol consumption, smoking, education, physical activity, energy intake, energy-adjusted intake of bread, pasta, rice, potato, fruit, vegetables, legumes, meat, fish, coffee, tea, soda/fruit juice, other dairy product groups, BMI and waist circumference. An additional 150 g serving of yogurt was also not associated with pre-diabetes after adjustment for these variables (OR=0.98; 95% CI, 0.93-1.03). However, subdivided analysis based on fat content showed a positive association with full-fat yogurt and pre-diabetes (OR=1.07; 95% CI, 1.02-1.12, P for trend=0.007) but not for low-fat yogurt. Full-fat yogurt was not associated with the incidence of pre-diabetes and T2DM combined (OR=1.03; 95% CI, 0.86-1.23, P for trend = 0.08). Total yogurt consumption was also not associated with incidence of T2DM after complete adjustment (OR=0.97, 95% CI, 0.84-1.11; P for trend = 0.59).	FDA Quality Score=Low FFQ not validated.

E. Intervention studies

Twenty non-acute intervention studies (Rajala et al., 1988, Schaafsma et al., 1998, Rizkalla et al., 2000, Nakamura et al., 2002, Nazare et al., 2007, Berthold et al., 2011, Chang et al., 2011, Nikooyeh et al., 2011, Shab-Bidar et al., 2011, Ejtahed et al., 2012, Sialvera et al., 2012, Asemi et al., 2013, Mohamadshahi et al., 2014, Nabavi et al., 2014, Hutt et al., 2015, Esmaillzadeh et al., 2015, Maki et al., 2015, Neyestani et al., 2015, Jafari et al., 2016, Madjd et al., 2016) were identified by literature search that provided yogurt to human subjects and measured one or more of the diabetes-related surrogate endpoints approved by FDA for the substantiation of health claims (i.e., FBG concentration, glucose tolerance and insulin resistance). However, none of these studies were sufficiently controlled to allow the independent effect of conventional yogurt to be compared to an appropriate control. Specifically, in these interventions conventional yogurt was compared to a modified yogurt (e.g., supplemented with brewer's yeast, vitamin D, probiotic bacteria, etc.) but not to a non-yogurt placebo. Therefore, the effect of conventional yogurt on T2DM-related parameters could not be assessed.

FDA's 2009 Guidance document on health claims explains that such studies are not capable of providing information necessary to evaluate health claims. Specifically, this guidance states,

> An appropriate control group represents study subjects who did not receive the substance. If an appropriate control group is not included, then it is not possible to ascertain whether changes in the endpoint of interest were due to the substance or due to unrelated and uncontrolled extraneous factors [citations omitted]. Without an appropriate control group, scientific conclusions cannot be drawn about a substance/disease relationship and, therefore, the agency does not intend to use these studies to evaluate the substance/disease relationship.

Therefore, none of the intervention studies identified by our literature search are applicable to the proposed claim.

In addition to the lack of a control group for conventional yogurt, many of these intervention studies had other characteristics that make them unsuitable for substantiation of health claims (i.e. short duration of the intervention to detect incident of diabetes, unpowered to detect effect on glucose related variables as pre-defined primary outcome). Specifically, eleven of the studies were conducted in populations that have profound dietary and cultural differences compared to those of healthy U.S. consumers (Chang et al., 2011, Nikooyeh et al., 2011, Shab-Bidar et al., 2011, Ejtahed et al., 2012, Asemi et al., 2013, Mohamadshahi et al., 2014, Nabavi et al., 2014, Esmaillzadeh et al., 2015, Neyestani et al., 2015, Jafari et al., 2016, Madjd et al., 2016), seven were conducted in subjects that already had T2DM (Nikooyeh et al., 2011, Shab-Bidar et al., 2011, Ejtahed et al., 2012, Mohamadshahi et al., 2014, Esmaillzadeh et al., 2015, Jafari et al., 2016, Neyestani et al., 2015), one was conducted in pregnant women (Asemi et al., 2013), one was conducted in subjects with non-alcoholic fatty liver disease (Nabavi et al., 2014), one was conducted in hospitalized patients (Rajala et al., 1988) and two used multiple interventions so that the effect of yogurt could not be isolated (Nakamura et al., 2002, Maki et al., 2015).

In addition to the studies cited above, a variety of intervention studies were identified by our literature search that were also incapable of providing useful scientific information about the yogurt/diabetes relationship and were therefore excluded from our assessment of the evidence. The reasons for exclusion of these studies were: a modified yogurt rather than yogurt itself was provided (Nikooyeh et al., 2011, Heravifard et al., 2013, Nikooyeh et al., 2014, Ivey et al., 2014, Hove et al., 2015, Hulston et al., 2015, Burton et al., 2017), endpoints of interest were not reported (White et al., 2009, Ejtahed et al., 2011) and only acute effects (e.g., glycemic index) were reported (Shively et al., 1986, Ostman et al., 2001, Chlup et al., 2006, Dougkas et al., 2012, El Khoury et al., 2014, Vien et al., 2017). Once again, these studies are not useful for evaluation

of the proposed claim, but are cited in an effort to provide FDA with the totality of scientific evidence.

F. Good laboratory practice

In accordance with 21 C.F.R. § 101.70(c) and 21 C.F.R. § 170(d), Danone declares that to the best of its knowledge, all non-clinical studies relied upon in this petition were conducted in compliance with the good laboratory practice regulations set forth in 21 C.F.R. Part 58. Moreover, all clinical or other human investigations relied upon were either conducted in accordance with the requirements for institutional review set forth in 21 C.F.R. Part 56 or were not subject to such requirements in accordance with 21 C.F.R. §§ 56.104 or 56.105, and were conducted in compliance with the requirements for informed consent set forth in 21 C.F.R. Part 50.

G. Summary and conclusions

As noted in the introduction to this section, Danone strongly believes that the totality of the evidence supports the proposed claim based on the large preponderance of evidence from the applicable prospective cohort studies. All of the studies that provide such information employed some of the most widely accepted and important cohorts in the field of epidemiology.

As noted in the introduction and discussed in sections III. D. 2 and 3, 10 of the 12 analyses from high or medium quality prospective cohort studies (in 10 publications) that provided useful information for evaluation of the proposed claim present direct or suggestive support.

Specifically, direct support was provided by Liu et al. (2006) from the Womens' Health Study, Margolis et al. (2011) from the Womens' Health Initiative, Chen et al. (2014) from the Nurses' Health Study, Diaz-Lopez et al. (2015) from the PREDIMED cohort, O'Connor et al. (2014) from the EPIC cohort, Babio et al. (2015) from the PREDIMED cohort, and Guasch-Ferré et al. (2017) also from the PREDIMED cohort. Suggestive evidence was furnished by Beydoun et al. (2008) from the NHANES study, Chen et al. (2014) from the Nurses' Health Study II, and Hruby et al. (2017) from the Framingham Heart study. Kim and Kim (2017) also provided suggestive support for the proposed claim, however the results are not applicable to the U.S. population because the study was conducted in Korea.

Only two high or medium quality studies that provided useful information for evaluation of the claim did not provide supportive evidence: Choi et al. (2005) from the Health Professionals' Follow-up Study and Chen et al. (2014) also from the Health Professionals' Follow-up Study. Four studies that fell into this category also did not support the claim, but they are irrelevant because they do not provide useful scientific evidence for evaluation of the proposed claim. Kirii et al. (2009) was conducted in Japan where dietary and cultural differences preclude extrapolation to the U.S. population and three studies (Grantham et al., 2013, Soedamah-Muthu et al., 2013, Brouwer-Brolsma et al., 2016) used FFQs to collect dietary data that were not validated for dairy. The remaining observational studies discussed in the previous section (and detailed in Table 1) were low quality studies that have little validity for substantiation of the proposed claim.

It is recognized that strong conclusions should not be drawn on the basis of any single research study. The five published meta-analyses that have systematically examined and extracted pooled data on the association between yogurt consumption and T2DM from prospective cohort studies

(Tong et al., 2011, Aune et al., 2013, Gao et al., 2013, Chen et al., 2014, Gijsbers et al., 2016) are a further testament to the consistency of support for the proposed claim. All five of these meta-analyses, including the most recent (Gijsbers et al., 2016), reported statistically significant inverse associations between yogurt consumption and risk of T2DM. In addition, two recently published systematic review papers (Drouin-Chartier et al., 2016, Micha et al., 2017) concluded that there is convincing evidence that yogurt consumption is inversely associated with the risk of T2DM.

As previously discussed, no controlled intervention studies were identified that compared the effects of conventional yogurt to a suitable control on FDA authorized surrogate endpoints for T2DM.

Danone strongly believes that the totality of scientific information supports the proposed wording of the claim, "*Eating yogurt regularly may reduce the risk of type 2 diabetes. FDA has concluded there is limited information supporting this claim." or, "Eating yogurt regularly may reduce the risk of type 2 diabetes according to limited scientific evidence."* This conclusion is based on the consistency of the evidence, as described above, as well as previous QHCs authorized by FDA.

As noted above, 83% of the analyses from high or medium quality studies applicable to the proposed claim provide direct or suggestive support. This consistency of support is much greater than that for the other FDA-authorized diabetes-related QHCs (50% of applicable studies for the high amylose maize resistant starch claim, 42% for the psyllium husk claim and 17% for the whole grains claim). We therefore strongly believe that the proposed qualifying language reflects the high level of consistency of the totality of the scientific evidence.

In conclusion, the proposed claim is supported by a large predominance of the totality of scientific information as illustrated by the individual studies and all published meta-analyses. Danone, therefore, strongly believes that the proposed claim is justified, and we respectfully ask the agency to exercise its enforcement discretion so that this important public health information can be disseminated to the U.S. population.

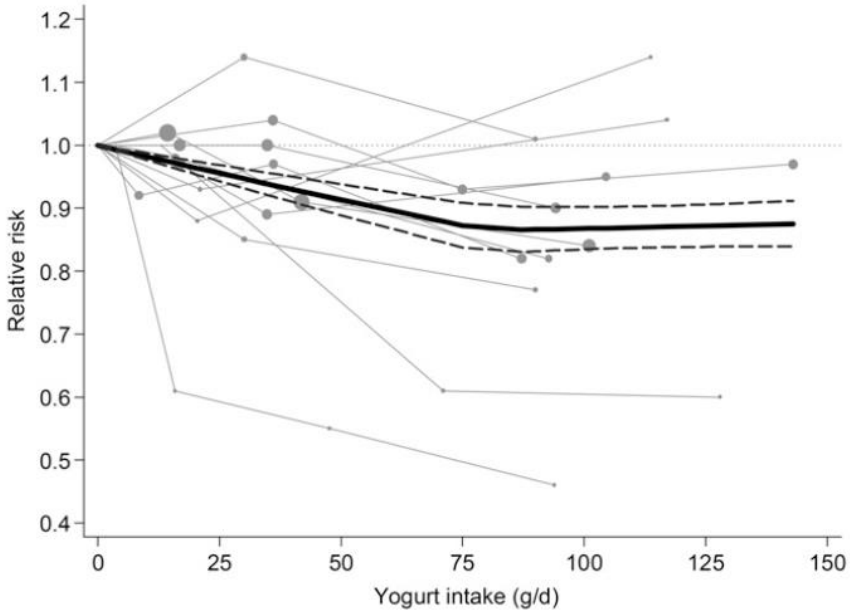
H. Other scientific summary considerations

1. Is there an optimum level of yogurt to be consumed beyond which no benefit would be expected?

The most recent meta-analysis that examined the association between yogurt and the incidence of T2DM (Gijsbers et al., 2016) reported a non-linear protective association. Specifically, there was a 14 percent lower risk for this disease among subjects with an intake of 80 grams yogurt per day compared to zero grams per day (RR=0.86; 95% CI, 0.83-0.90, p <0.001. This finding is illustrated in Figure 2.

Figure 2

Spaghetti plot for Nonlinear Association between Yogurt Intake and Diabetes Risk



RR=0.86 at 80 g yogurt per day compared to zero grams per day (95% CI, 0.83-0.90) including 11 studies (12 study populations (n=438,140 individuals)). Linearity of association was analyzed with the use of spline analysis. The association was further analyzed with the use of random-effects dose-response generalized least-square trend meta-regression analysis. Each solid gray line represents a study population. The circles are placed at the study-specific RRs that are related to the corresponding quantity of intake. The area of the circle is proportional to the study-specific weight. The solid black line represents the pooled RR at each quantity of intake, and the dashed black line is the corresponding 95% CI. The dotted gray line represents the reference line. Source: Gijsbers *et al., Am J Clin Nutr* 2016;103:1111.

There was no further decrease in risk at higher intake amounts. In this analysis, the reported range of median yogurt intake was 17-71g/ day with only two studies reporting yogurt intake above 100 g/day (i.e. 117g/day and 128 g/d (Soedamah-Muthu et al. (2013) and Diaz-Lopez et al. (2015), respectively).

We do not believe this analysis provides unequivocal evidence that there is no further benefit to yogurt consumption beyond 80 grams per day. Numerous factors including the demographic characteristics of the population(s) studied and health status of the individuals examined preclude

such a conclusion. Nevertheless, this meta-analysis includes the data most germane to the proposed claim, and we cannot exclude the possibility of a benefit threshold considering the nonlinearity observed. However, such a threshold would have little practical bearing on the claim because an 80 gram per day plateau equates to 3.3 six-ounce servings per week, which is consistent with the proposed minimum effective "dose" of the proposed claim of "about three to four servings per week" or "at least three servings per week" (see Section IV below), and is easily compatible with the My Plate recommendation on Dairy foods.

2. What other nutritional or health factors are important to consider when consuming yogurt?

a) Nutrient density/diet quality

As noted in the introduction, yogurt is a highly nutritious food that is acclaimed by a variety of governmental and professional organizations and is recommended by the *Dietary Guidelines for Americans.* Numerous review papers have been published that describe the positive nutritional contribution of yogurt as well as the fact that yogurt consumers tend to have healthier overall diets than non-consumers. For example Webb et al. (2014) discussed the nutritional attributes of yogurt and concluded,

> Yogurt naturally contains calcium and potassium, and some products are fortified with vitamin D. All of these nutrients were identified in the DGA as "nutrients of concern," because typical intake falls far short of recommended intakes. Yogurt can also be an excellent source of high-quality protein, which promotes satiety, helps in maintaining a healthy body weight, and aids muscle and bone growth. In addition, yogurt is low in sodium and contributes 1.0% or less of added sugars to the diets of most individuals in the United States; however, 90% of children and adults consume less than 8 ounces (1 cup) of yogurt per week. Thus, consuming 1 serving of yogurt per day would help to meet the DGA-recommended dairy servings and would provide nutrients of concern.

Yogurt consumption is also associated with a better overall dietary pattern. The most recent review paper on this topic (Panahi et al., 2017b) concluded,

> Yogurt consumption has been associated with healthy dietary patterns and lifestyles, better diet quality and healthier metabolic profiles. Studies have shown that frequent yogurt consumers do not only have higher nutrient intakes, but also an improved diet quality, which includes higher consumption of fruits and vegetables, whole grains, and dairy compared with low or non-consumers indicating better compliance with dietary guidelines. "

Other review papers that have made similar conclusions include Sigman-Grant et al. (2003), Ranganathan et al. (2005), Marette and Picard-Deland (2014),Weaver (2014), Webb et al. (2014) and Tremblay and Panahi (2017).

Several of the studies that examined the association between yogurt consumption and incidence of T2DM summarized in Table 1 also provided information on the correlation between yogurt intake and diet quality. Specifically, Wang et al. (2013) reported that consumers of yogurt were less likely than non-consumers to have inadequate intakes (based on the National Academy of Medicine's Estimated Average Requirements (EARs)) of vitamins B_1, B_2, B_6, B_{12}, A, C, D and E as well as folate, calcium, magnesium and zinc. Subjects in this study were members of the Framingham Heart Study Offspring (1998-2001) and Third Generation (2002-2005) cohorts.

Abreu et al. (2014) reported that low consumers of yogurt among 494 adolescents from Portugal had lower dietary fiber intake compared to more frequent yogurt consumers (9.2 vs. 10.1 g/1,000 kcal. P=0.003).

Sayon-Orea et al. (2017) found that protein intake was higher (18.3 vs. 17.5 %, $p<0.001$) and saturated fat intake was lower (12.0 vs. 12.8 %en, $p<0.001$) among Spanish adults who consumed seven servings of yogurt per week vs. those who consumed 0-2 servings or more per week.

Zhu et al. (2015) reported that children 2-18 years of age who consumed yogurt at least once per week had a higher Healthy Eating Index (HEI) score than those with less frequent consumption (48.52 vs., 50.56, p=0.04) based on data from the 2003-2006 NHANES. Higher consumption of yogurt was also associated with greater consumption of total fruit (p=0.03), whole fruit (p=0.03), whole grains (p=0.005), milk (p=0.002) and oils (p=0.003), but not total vegetables, dark green/orange vegetables/legumes, total grains or meat and beans.

Panahi et al. (2017a) observed that the Nutrient-Rich Foods Index (NRF) was higher among participants in the Quebec Family Study who consumed at least one serving of yogurt per day compared to those who consumed less (43 vs. 38, p<0.001).

The only study summarized in Table 1 that examined the association between yogurt consumption and diet quality that did not report at least one positive finding was Cormier et al. (2016). There was no significant difference between yogurt consumers and non-consumers for intake of proteins, cholesterol, SFA, MUFA or PUFA in this study of 664 residents of Quebec City. The only dietary parameter that exhibited such a difference was total carbohydrate which was slightly higher among yogurt consumers (291.6 vs. 300.2 g/d, p=0.045). However, the conclusions that can be drawn from this study are limited because it employed a marginal dietary assessment tool (a single 91-item FFQ) and studied a homogeneous French Canadian population whose dietary practices are unlikely to reflect their U.S. counterparts.

A recent study not summarized in Table 1 compared yogurt consumers and non-consumers in the 2005-2006 Italian Food Consumption Survey (Mistura et al., 2016). Yogurt consumers had higher scores on the Probability of Adequate Nutrient Intake (PANDiet) Index compared to non-consumers (60.58 vs., 58.58, p<0.001). Yogurt consumers also had significantly (p<0.001)

higher individual PANDiet adequacy scores (based on the EAR) for dietary fiber, vitamin A, thiamin, riboflavin, vitamin B_6, folate, vitamin B_{12}, vitamin C, vitamin E, calcium, magnesium, zinc, phosphorous and potassium. The score for iron was also significantly ($p<0.01$) better for yogurt consumers. There were no significant differences between consumers and non-consumers for protein, total carbohydrate, total fat, niacin or vitamin D. The authors concluded, "Yogurt consumers were more likely to have adequate intakes of vitamins and minerals, and a higher quality score of the diet."

b) Added sugars

As noted previously, yogurt is a nutrient dense food. Some flavored forms of yogurt (especially fruit-containing varieties) contain added sugars. Several major organizations including the AHA, IOM, and DGAs have recognized that use of such ingredients can be justified in order to increase the palatability and overall consumption of nutrient dense products. Specifically, a scientific statement from the AHA on dietary sugars and cardiovascular health (Johnson et al., 2009) concluded that, "The form in which added sugars are consumed appears to be an important modifier of the impact of dilution (Gibson, 2007). Soft drinks, sugar, and sweets are more likely to have a negative impact on diet quality, whereas dairy foods, milk drinks, and presweetened cereals may have a positive impact (Frary et al., 2004)." Furthermore, a report from the IOM entitled, "School Meals: Building Blocks for Healthy Children," (IOM, 2010) concluded,

> With careful menu planning, enough discretionary calories should be available to cover flavored fat-free milk in place of plain fat-free milk as a daily option, some flavored low-fat yogurt, and some sweetened ready-to-eat cereals. These are highly nutritious foods that are very popular with many schoolchildren and that are identified in the AHA statement as potentially having a positive impact on diet quality. Fruits in light syrup contain about 10 grams of added sugars per half cup serving. The omission of those sweetened foods might result in decreased student participation as well as in reduced nutrient intakes.

The 2015-2020 DGAs concluded that limited amounts of added sugars are appropriate to improve the palatability of nutrient dense foods such as yogurt. Specifically, the DGAs state,

> There is room for Americans to include limited amounts of added sugars in their eating patterns, including to improve the palatability of some nutrient-dense foods, such as fruits and vegetables that are naturally tart (e.g., cranberries and rhubarb). Healthy eating patterns can accommodate other nutrient dense foods with small amounts of added sugars, such as whole-grain breakfast cereals or fat-free yogurt, as long as calories from added sugars do not exceed 10 percent per day, total carbohydrate intake remains within the AMDR, and total calorie intake remains within limits.

These dietary recommendations indicate that the use of modest amounts of added sugars is appropriate for nutrient dense foods.

Importantly, all forms of yogurt, regardless of sugar content, were included in the FFQs employed by the observational studies summarized in Table 1. Therefore, the totality of scientific evidence supports the protective association of yogurt as a category with risk of T2DM. It is also noted, that the amount of added sugars on products bearing the proposed claim will be clearly labeled as a component of the newly revised nutrition facts panel, providing this information to consumers.

c) Fat content

The fat content of yogurts consumed in the U.S. and elsewhere range from fat free varieties to those made from whole milk which contain approximately 5.5 grams per 170 g RACC according to the USDA National Nutrient Database for Standard Reference.

As noted previously, all forms of yogurt, regardless of fat content, were included in the FFQs employed by the observational studies summarized in Table 1. In addition, three of the medium or high quality studies in this table also reported associations specifically for full-fat yogurts.

Babio et al. (2015) reported that both full-fat yogurt (RR=0.79; 95% CI, 0.66-0.94, P for trend=0.005) and lowfat yogurt (RR=0.81; 95% CI, 0.68-0.98, P for trend =0.13) were inversely associated with high fasting plasma glucose among elderly men and women from the PREDIMED cohort. Diaz-Lopez et al. (2015) observed that both full-fat (RR=0.66; 95% CI, 0.47-0.92; P for trend = 0.20) and lowfat yogurt (RR=0.68; 95% CI, 0.47-0.97, P for trend = 0.047) were inversely associated with incidence of T2DM after multivariate adjustment among the same cohort. Finally, the most recent data from this cohort (Guasch-Ferré et al., 2017) showed that full-fat yogurt was inversely associated with incident T2DM after multivariate adjustment (RR=0.65; 95% CI, 0.45-0.94, P for trend = 0.02) among 3,349 adults 55 to 80 years of age followed for a mean of 4.3 years.

We are aware of no evidence that indicates fat content is an important differentiator with respect to use of the claim, as the scientific evidence supports the protective association of yogurt with risk of T2DM. It is noted that Danone is proposing that all of the provisions of 21 C.F.R. §101.14(a)(4) be applied, which will ensure that products with excessive amounts of total or saturated fat will be automatically excluded from bearing the claim.

d) Weight management

Yogurt is unlikely to increase overweight or obesity. Indeed, consistent with its protective association with T2DM, higher yogurt consumption is frequently associated with long-term relative weight management. Based on prospective investigations from Nurses' Health Study, Nurses Health Study II, as well as the Health Professionals Follow-up Study cohorts (Mozaffarian et al., 2011), each cohort individually showed that increases in yogurt consumption were significantly associated with less weight gain over time (P<0.01 each), after adjustment for

age, baseline body-mass index, sleep duration, physical activity, alcohol use, television watching, smoking, and multiple other dietary factors simultaneously including fruits, vegetables, nuts, whole grains, refined grains, processed meats, butter, cheese, milk, and others. Pooling all three studies, each additional serving of yogurt per day was associated with a −0.82 lb lower weight gain over 4 years (95% CI, -0.99, -0.67; p for trend <0.0001). No such association was found with nonfat or lowfat milk, whole milk, or cheese consumption.

A more recent systematic review by Sayon-Orea et al. (2017) identified three cohort studies that examined the relation between yogurt consumption and the risk of overweight or obesity (Pereira et al., 2002, Martinez-Gonzalez et al., 2014, Rautiainen et al., 2016) and eight studies (in six publications) that studied the risk of overweight/obesity and/or changes in body weight or waist circumference (Vergnaud et al., 2008, Mozaffarian et al., 2011, Romaguera et al., 2011, Wang et al., 2014, Martinez-Gonzalez et al., 2014, Santiago et al., 2016). The majority of these studies reported statistically significant inverse associations between yogurt consumption and at least one obesity-related outcome measure. The exceptions were Pereira et al. (2002) who found a non-statistically significant association between yogurt consumption and obesity (RR=0.47; 95% CI, 0.16-1.43) in the CARDIA study and Rautiainen et al. (2016) who observed a direct association between yogurt and obesity (RR=1.16; 95% CI, 1.02-1.31) among subjects in the Womans' Health Initiative. The systematic review paper authors concluded,

> Although an inverse association between yogurt consumption and the risk of developing overweight or obesity was not fully consistent or always statistically significant, all studies but one showed in their point estimates inverse associations between yogurt consumption and changes in waist circumference, changes in weight, risk of overweight or obesity and of metabolic syndrome during follow-up, although not all estimates were statistically significant (2 studies). Prospective cohort studies consistently suggested that yogurt consumption may contribute to a reduction in adiposity indexes and the risk of metabolic syndrome.

Several studies were identified that examined the association between specific types of yogurt and obesity-related parameters. Crichton and Alkerwi (2014) reported that full fat yogurt (RR=0.57; 95% CI, 0.39-0.85) but not lowfat yogurt (RR=1.54; 95% CI, 1.07-2.23) was inversely associated with global obesity (BMI ≥30 kg/m^2) among 1,352 participants in the "Observation of Cardiovascular Risk Factors in Luxembourg" study. Full fat yogurt was also inversely associated (RR=0.58; 95% CI, 0.41-0.83) with abdominal obesity (waist circumference ≥102 cm) but lowfat yogurt was not (RR=1.45; 95% CI, 1.04-2.01). Consistent findings were reported from the PREDIMED cohort by Santiago et al. (2016). Multivariate analysis showed that consumption of full fat yogurt was significantly associated (RR=1.43; 95% CI, 1.06-1.93) with reversion of abdominal adiposity among 4,545 members of this cohort while there was no such association for lowfat yogurt (RR=1.02; 95% CI, 0.73-1.44).

Smith et al. (2015) evaluated how changes in the consumption of sweetened flavored yogurt and artificially sweetened or plain yogurt related to four-year weight change using pooled data from the Health Professionals Follow-Up Study, the Nurses' Health Study, and the Nurses' Health Study II. Multivariate analysis showed that each daily serving increase in both artificially sweetened or plain yogurt (-0.71 kg; 95% CI, -0.92 to -0.52) and sweetened flavored yogurt (-0.23 kg; 95% CI, -0.41 to -0.05) were associated with relative weight loss.

While no appropriately placebo-controlled intervention studies have evaluated yogurt consumption and weight control, numerous RCTs have tested the effects of overall dairy consumption on weight loss. Meta-analysis of 30 of these trials (Chen et al., 2012) found no effect of dairy products on total body weight change (-0.14 kg, 95% CI, -0.66 to 0.38). However, increased intake of dairy products resulted in greater weight loss among 15 of these

studies that included energy restriction (-0.94 kg; 95% CI, -1.53 to -0.34). These data suggest that dairy products do not contribute to weight gain and may be beneficial as part of an energy-restricted weight loss diet. No data for yogurt separately were provided in this meta-analysis. In summary, there is overwhelming evidence that yogurt, including multiple varieties, is a nutrient dense food that contributes not only a variety of nutrients to the diet, but is also associated with an overall healthier dietary pattern and is likely to be beneficial for weight management.

3. Is there any level at which an adverse effect from yogurt occurs for any segment of the population?

Danone is aware of no potential adverse effects of yogurt consumed as part of a balanced diet and healthy lifestyle. As noted previously, yogurt is a nutrient dense food that is recommended by the 2015-2020 *Dietary Guidelines for Americans* as part of a healthy eating pattern. This pattern includes three cup-equivalents per day of dairy products. Low or non-fat yogurt is recommended as a preferred form of dairy to meet this recommendation because these foods have less saturated fat and sodium and more potassium, vitamin D and vitamin A than most cheeses.

4. Are there certain populations that must receive special considerations?

Consumers with severe intolerance to lactose and/or allergy to milk proteins could be affected by consumption of yogurt. However, lactose is partially consumed during the yogurt fermentation process, and for most consumers who suffer from lactose intolerance, yogurt offers a nutrient-dense, more easily digestible alternative to milk and other milk products.

Regarding allergy to milk, this is an inflammatory response to milk proteins which is distinct from lactose intolerance. Yogurt should not be consumed by individuals with this milk allergy. FDA has concluded that the presence of an allergenic ingredient does not disqualify a food product from making a health claim because the declaration of such an ingredient on the label is sufficient to alert consumers who could be adversely affected (64 *Federal Register* 57700, 57707, October 26, 1999). The fact that yogurt is clearly recognized as a dairy product further minimizes the possibility of unintentional consumption of lactose or milk protein.

5. Prevalence of diabetes in the U.S. population and relevance of the claim in the context of the total daily diet.

The most recent data from the Centers for Disease Control and Prevention (2017) state that 23.1 million adults (7.2% of the population) had been diagnosed with diabetes in 2015 and another 7.2 million individuals were believed to have this disease but had not yet been diagnosed. Approximately 95% of the population with diabetes is estimated to have T2DM. Furthermore, an additional 84.1 million people in the U.S. were estimated to have pre-diabetes in 2015 and only about 11.6% of them were aware of this condition. Based on 2000–2011 data, Gregg et al. (2014) reported that lifetime risk of diagnosed diabetes from age 20 years onwards was 40.2% for men and 39.6% for women. Clearly diabetes (especially T2DM) is an enormous public health concern in the U.S.

As mentioned previously, dairy (including yogurt) is a nutrient dense food that is recommended by the 2015-2020 *Dietary Guidelines for Americans* for frequent consumption. Specifically, the recommended daily intake of dairy in the healthy U.S.-Style Eating Pattern ranges from two cup-equivalents for persons who require 1,000 kcal per day to three cup-equivalents for those who

require 1,600 kcal per day or more. Clearly dairy is an integral part of the dietary pattern and yogurt is specifically recommended as a form of this food group that is lower in saturated fat and sodium than other forms (e.g. cheese). Danone believes that availability of the proposed claim will encourage consumers to choose this nutrient dense food as part of a healthy eating pattern.

IV. MINIMUM EFFECTIVE DOSE

Intervention studies that provided specified amounts of yogurt and measured diabetes-related endpoints are not available to determine a precise minimum effective "dose" as has been the case with most of the health claims previously authorized by FDA. However, the prospective cohort studies that demonstrated significant protective associations between yogurt consumption and incident T2DM can be used to estimate such amounts. Table 2 lists the amount of yogurt eaten by consumers in the upper intake category (i.e., tertile, quintile) of such high or moderate quality studies that are germane to the proposed claim and reported significant protective associations between yogurt and T2DM. Several studies reported such associations, but did not provide quantitative data for the upper consumption category (Babio et al., 2015, Guasch-Ferré et al., 2017) or were not germane to the claim (Kim and Kim, 2017).

The data presented in Table 2 show that the number of eight-ounce servings (the 1993 RACC) of yogurt consumed per week among subjects in the upper intake level of studies that reported significant protective associations between yogurt and T2DM range from two or more, to four. Analogous results for a six-ounce serving (the 2016 RACC) were 2.6 or more, to 5.3 servings per week. The studies reported by O'Connor et al. (2014) and Diaz-Lopez et al. (2015) are less reliable for estimation of the minimum effective "dose" because they employed only three consumption categories which resulted in very broad tertiles. This situation allows less precision in the estimation of a minimum effective "dose" than studies with greater number of intake

Table 2
Servings of Yogurt per Week in the Upper Intake Category of Prospective Cohort Studies that Reported Significant Protective Association and were Germane to the Proposed Claim

Reference	**Cohort**	**Grams per day reported**	**Intake categories**	**Servings per week**	
				8 oz serving (225g)	**6 oz serving (170 g)**
Liu et al. (2006)	Womens' Health Study	-	Quartiles	≥2	≥2.6
Margolis et al. (2011)	Womens' Health Initiative	-	Quartiles	≥2	≥2.6
Chen et al. (2014)	Health Professionals Follow-up Study	-	Quintiles	3.0*	4.0*
Chen et al. (2014)	Nurses' Health Study (I)	-	Quintiles	2.9**	3.8**
O'Connor et al. (2014)	EPIC cohort	80	Tertiles	2.5***	3.3***
Diaz-Lopez et al. (2015)	PREDIMED	128	Tertiles	4.0***	5.3***

*It is possible that a 244g serving size was used by these authors. Use of this value would result in 3.2 servings/wk for an 8 oz serving and 4.3 for a 6 oz serving.
** It is possible that a 244g serving size was used by these authors. Use of this value would result in 3.1 servings/wk for an 8 oz serving and 4.2 for a 6 oz serving.
*** Calculated from grams per day reported in the paper

categories. The number of servings of yogurt per week consumed by the upper intake categories for the remaining (most persuasive) four studies ranges from two or more, to 3.0 for an eight-ounce serving and from 2.6 or more, to 4.0 for a six-ounce serving. Danone believes the latter values are more appropriate for use with the proposed claim because they are based on the newly revised RACC and (more importantly) more closely reflect common practice among U.S. consumers. We therefore propose that the phrases, "about 3 to four servings per week" and "at least 3 servings per week" be designated as optional components of the claim.

V. NATURE OF THE FOOD ELIGIBLE TO BEAR THE CLAIM

As noted previously, Danone proposes that foods that comply with the standards of identity for yogurt (21 C.F.R. 21 §131.200, 131.203 and 131.206) be eligible for the proposed claim. All of the general requirements of health claims specified in 21 C.F.R. §101.14 would also apply.

VI. DETERMINATION OF COMPLIANCE

Compliance with the proposed claim will be obvious because such products will be labeled according to one of the aforementioned standards of identity.

VII. ENVIRONMENTAL IMPACT ASSESSMENT

Danone chooses to avail itself of the categorical exclusion with respect to an environmental impact assessment provided by 21 CFR § 25.32(p). Accordingly, an environmental impact assessment is not required for this submission.

VIII. CONCLUSIONS AND CERTIFICATION

Yogurt is a nutritious food that is recommended as a preferred form of dairy for healthy eating patterns by the 2015-2020 DGAs and other authoritative sources. Data from a large preponderance of observational studies that meet FDAs criteria for the substantiation of health claims demonstrate that this food is inversely associated with the risk of T2DM in individuals who were initially free of this disease. This fact is also supported by pooled data from all of the meta-analyses that have been published in the area. Yogurt is also a nutrient-dense food that provides significant concentrations of major nutrients in comparison with its energy amounts,

high quality protein, as well as a wide array of other micronutrients; and individuals who consume yogurt tend to have a better overall diet quality than non-consumers. As a result, increased consumption of yogurt prompted by the new claim has the dual benefit of reducing the risk of T2DM while improving quality of the overall diet. The proposed claim is important to encourage food manufacturers to increase yogurt in the food supply and to inform consumers of current evidence in order to help them make informed choices. Danone, therefore, respectfully asks that FDA consider the consolidated scientific evidence present in this petition and exercise its enforcement discretion to permit use of the proposed claim.

I hereby certify that, to the best of my knowledge, this petition is a representative and balanced submission that includes unfavorable information as well as favorable information known to me to be pertinent to the evaluation of the proposed qualified health claim.

Respectfully submitted,

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