U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR FOOD SAFETY & APPLIED NUTRITION

March 1, 2024

Guy H. Johnson, Ph.D.
Johnson Nutrition Solutions LLC
3801 W. 28th Street
Minneapolis, Minnesota 55416

RE: Petition for a Qualified Health Claim for Yogurt and Reduced Risk of Type 2 Diabetes Mellitus (Docket No. FDA-2019-P-1594)

Dear Dr. Johnson:

This letter responds to the qualified health claim petition you submitted to the Food and Drug Administration (FDA, we, or the agency). The petition was submitted on behalf of Danone North America in accordance with FDA's guidance on the procedures for the submission of qualified health claim petitions and on the evidence-based review system for the scientific evaluation of health claims.[1] The petition requested that the agency review the use of a qualified health claim regarding the relationship between consumption of yogurt and reduced risk of type 2 diabetes mellitus (type 2 diabetes). The petition also noted that the "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."

The petition proposed the following language for a qualified health claim to be used on the labels or in the labeling of yogurt products that meet FDA's standards of identity:

> "Eating yogurt regularly may reduce the risk of type 2 diabetes. FDA has concluded there is limited information supporting this claim."
>
> "Eating yogurt regularly may reduce the risk of type 2 diabetes according to limited scientific evidence."

[1] See FDA, "Guidance for Industry: Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements. July 10, 2003. [https://www.fda.gov/food/food-labeling-nutrition/consumer-health-information-better-nutrition-initiative-task-force-final-report]; see also FDA, "Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims—Final, January 2009 [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-evidence-based-review-system-scientific-evaluation-health-claims].

U.S. Food and Drug Administration
Center for Food Safety & Applied Nutrition
5001 Campus Drive
College Park, MD 20740
www.fda.gov

> The petition also proposed 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."

The petition requested that the "claim…apply exclusively to all types of yogurts that meet FDA's standards of identity (21 CFR §§ 131.200, 21 CFR 131.203, and 21 CFR 131.206)." We note that on July 11, 2021, FDA issued a final rule to amend and modernize the standard of identity for yogurt by allowing greater flexibilities and technical advances in yogurt production. Manufacturers must begin complying with the rule for products labeled on or after January 1, 2024. As part of the final rule, FDA revoked the standards for low-fat yogurt and non-fat yogurt (previously at 21 CFR 131.203 and 21 CFR 131.206, respectively).[2] As a result, low-fat and nonfat yogurt are now covered by our regulations at 21 CFR 130.10. 21 CFR 130.10 sets out requirements for foods that deviate from the standard of identity due to compliance with a nutrient content claim.

As described above, the petition requests the review of a qualified health claim to be used on the labels or in the labeling of all types of yogurts that meet FDA's standards of identity. Because low-fat and non-fat yogurt must now comply with the regulations at 21 CFR 131.10, we interpret your petition to request the review of a qualified health claim to be used on the labels or in the labeling of all products that meet the yogurt standard of identity at 21 CFR 131.200 and products that deviate from the yogurt standard of identity in accordance with 21 CFR 130.10. This change has no other bearing on the contents of your petition.

FDA filed the petition for comprehensive review on April 12, 2019 (Docket number FDA-2019 P-1594) and posted it on the Regulations.gov website with a 60-day comment period, consistent with FDA's guidance for procedures on qualified health claims. The agency received seven comments regarding the petition. Four comments generally supported the claim and noted that the proposed qualified health claim is supported by high and moderate quality prospective cohort studies that have reported significant protective associations between yogurt consumption and type 2 diabetes. Other comments noted that yogurt is a nutrient-dense food that is a natural source of high-quality protein, calcium, potassium, riboflavin, vitamin B12 and phosphorus, and was recommended as a dairy source in the 2015-2020 Dietary Guidelines for Americans.

The three comments that opposed the claim had various reasons for not supporting the claim. Of the opposing comments, one noted that the petition only cited prospective cohort studies and did not submit any supportive evidence from randomized control trials, despite the feasibility of conducting such trials with surrogate markers for type 2 diabetes risk (*i.e.*, fasting blood glucose, glucose tolerance, and insulin resistance). The second opposing comment noted that it is total intake (dietary patterns) that contribute to risk reduction and not a single food or nutrient. The last opposing comment noted that if FDA considers the exercise of enforcement discretion for the use of the proposed claim, such a statement could increase the prevalence of type 2 diabetes, as it would encourage consumers to increase consumption of yogurts, including those that are

[2] We note that we received objections to this final rule and on December 15, 2022, we issued a final rule responding to all but one of the objections. We issued a final order on April 14, 2023, responding to the remaining objection.

high in added sugars. This comment further noted that one out of three U.S. adults today has prediabetes, and any step that may encourage consumption of foods high in added sugars must be weighed against the considerable risk that it will increase the risk of type 2 diabetes.

This letter sets forth the results of FDA's scientific review of the evidence for the requested qualified health claims, as well as the basis of FDA's determination that the current scientific evidence regarding the relationship between yogurt and type 2 diabetes is appropriate for consideration of a qualified health claim on conventional foods. This letter also discusses the factors that FDA intends to consider in the exercise of its enforcement discretion for qualified health claims with respect to the consumption of yogurt and reduced risk of type 2 diabetes.

I. Overview of Data and Eligibility for a Qualified Health Claim

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). The substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup, is at risk (21 CFR 101.14(b)(1)). Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease or health-related condition.[3] In a review of a qualified health claim, the agency first identifies the substance and disease or health-related condition that are the subject of the proposed claim and the population to which the claim is targeted.[4]

FDA considers the data and information provided in the petition, in addition to other written data and information available to the agency, to determine whether the data and information could support a relationship between the substance and the disease or health-related condition.[5] The agency then separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.[6]

In addition to individual reports of human studies, the agency also considers other types of data and information in its review, such as meta-analyses,[7] review articles,[8] and animal and *in vitro* studies. These other types of data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease, or both, but cannot by themselves support a health claim relationship. Reports that discuss a number of different

---

[3] See Whitaker v. Thompson, 353 F.3d 947, 950-51 (D.C. Cir.) (upholding FDA's interpretation of what constitutes a health claim), cert. denied, 125 S. Ct. 310 (2004).

[4] FDA, "Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims—Final, January 2009 [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-evidence-based-review-system-scientific-evaluation-health-claims].

[5] For brevity, "disease" will be used as shorthand for "disease or health-related condition" in the rest of this letter except when quoting or paraphrasing a regulation that uses the longer term.

[6] In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (*i.e.*, disease). Intervention studies provide the strongest evidence for an effect. See *supra,* note 4.

[7] A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

[8] Review articles summarize the findings of individual studies.

studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements, such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-analyses, review articles, and similar publications[9] to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship.[10] If additional studies are identified, the agency evaluates them individually. FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes, such as digestion, absorption, distribution, and metabolism, which affect how humans respond to the consumption of foods and dietary supplements (Institute of Medicine, 2005). Animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors, such as a control group or a statistical analysis, means that scientific conclusions cannot be drawn from the study (Spilker, 1991; National Research Council, 2011). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these are eliminated from further review.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance-disease relationship.

Next, FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (*e.g.*, use of a placebo control versus a non-placebo controlled group), data collection (*e.g.*, type of dietary

[9] Other examples include book chapters, abstracts, letters to the editor, and committee reports.

[10] Although FDA does not generally use meta-analyses in its health claim evaluations for the reasons discussed in the text, the agency will include a meta-analysis in its scientific evaluation if the meta-analysis was conducted with pooled data from all the publicly available studies from which scientific conclusions can be drawn (based on the criteria in FDA's guidance on scientific evaluation of health claims) and the statistical analyses were properly conducted. See *supra*, note 4.

assessment method), the quality of the statistical analysis, the type of outcome measured (*e.g.*, disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (*e.g.*, selection bias and whether important information about the study subjects – *e.g.*, age, smoker vs. non-smoker – was gathered and reported). For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Moderate or low-quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria. Studies from which FDA cannot draw scientific conclusions cannot be used to support the health claim relationship, and therefore are eliminated from further review.

Finally, FDA evaluates the results of the remaining studies. The agency then rates the strength of the total body of publicly available evidence.[11] The agency conducts this rating evaluation by considering the study type (*e.g.*, intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of studies of each type and study sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,[12] and the overall consistency[13] of the total body of evidence.[14] Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance-disease relationship, and, if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship or to prevent the claim from being misleading in other ways.

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of a food, regardless of whether the food is in conventional form or a dietary supplement (21 CFR 101.14(a)(2)). The petition identified all types of yogurts, including with varying fat and sugar content, that meet FDA's standard of identity for yogurt as the substance of the claim. The yogurt standard of identity is set forth in 21 CFR 131.200. Further, as noted on pages one and two of this letter, FDA has revoked the standards for low-fat and non-fat yogurt. As a result, low-fat yogurt and non-fat yogurt are now covered under the general definition and standard of identity in 21 CFR 130.10

Yogurt is an article used for food and, therefore, it is a "food" within the meaning of section 201(f) of the Federal Food, Drug, and Cosmetic Act (the Act). As discussed in the previous paragraph, yogurt must comply with the standard of identity set forth in 131.200, except that

---

[11] See *supra,* note 4.
[12] Replication of scientific findings is important for evaluating the strength of scientific evidence (Wilson, 1990).
[13] Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill AB. 1965); see also Agency for Healthcare Research and Quality, "Systems to rate the scientific evidence" (March 2002) http://archive.ahrq.gov/clinic/epcsums/strengthsum.pdf (accessed September 24, 2022)], defining "consistency" as "the extent to which similar findings are reported using similar and different study designs."
[14] See *supra*, note 4.

certain products may deviate from the standard of identity as set forth in 130.10. The petition noted that 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, B2, B5 and B12, calcium, magnesium, potassium, phosphorus, iodine and zinc, while being relatively low in sodium, and that many yogurts are fortified with vitamin D and certain probiotics. Finally, yogurt as a conventional food, has a long history of being consumed in the United States.

Therefore, FDA concludes that yogurt, the substance identified in the petition, is a food and meets the definition of a substance in the health claim regulation (21 CFR 101.14(a)(2)).

B. Disease or Health-Related Condition

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly, or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition has identified type 2 diabetes as the disease that is the subject of the proposed claims. Diabetes is a disease that occurs when blood glucose (*i.e.*, blood sugar) is too high, resulting in a disorder of metabolism from the body's impaired ability to use blood glucose (sugar) for energy. Over time, having too much glucose in the blood can cause health problems, such as heart disease, nerve damage, eye problems, and kidney disease.[15] In type 2 diabetes, either the pancreas does not make enough insulin, or the body is unable to use insulin effectively, and therefore blood glucose cannot enter the cells to be used for energy. The agency concludes that type 2 diabetes meets the definition of a disease under 21 CFR 101.14(a)(5) because, in persons with this condition, the glucose metabolism systems of the body have been damaged such that the body is not functioning properly.

C. Safety Review

Under 21 CFR 101.14(b)(3)(i), if the substance that is the subject of the health claim is to be consumed at other than decreased dietary levels, the substance must, regardless of whether the food is a conventional food or a dietary supplement, contribute taste, aroma, or nutritive value, or any other technical effect listed in 21 CFR 170.3(o) to the food and must retain that attribute when consumed at levels that are necessary to justify a claim. The substance must be a food or a food ingredient or a component of a food ingredient whose use at the levels necessary to justify the claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Act (21 CFR 101.14(b)(3)(ii)).

FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the Act. For conventional foods, this evaluation involves considering whether the substance, which is either a food or an ingredient that is the source of the substance is generally recognized as safe (GRAS), approved as a food additive, or authorized by a prior sanction issued by FDA (see 101.70(f)).

[15] National Institutes of Health (NIH), "Diabetes" [https://www.niddk.nih.gov/health-information/diabetes] (accessed September 24, 2022)].

Yogurt has a long history of human use and is a fermented milk product. The first mention of yogurt dates to about 5000 BC and the process was discovered in the Middle East, where nomadic tribes stored milk in homemade animal skins made from the intestinal gut of animals (Fisberg, et al., 2015). When exposed to the gastrointestinal bacteria present in the animals, the milk would ferment. Common bacteria found in the intestinal gut of the animals are *Lactobacillus bulgaricus* and *Streptococcus thermophilus*, which are also present in the starter cultures used during the yogurt manufacturing process (Chandan, et.al., 2017). Yogurt is commonly consumed in the United States and all over the world and can be fortified with additional nutrients such as calcium, vitamins, fatty acids, and proteins. Yogurt can also be made from non-dairy alternatives.

Additionally, the petition noted that yogurt is safe and lawful since standards of identity have been codified to assure the safety and lawfulness of yogurt (21 CFR 131.200), low-fat yogurt (21 CFR 131.203) and non-fat yogurt (21 CFR 131.206). Please note that, as discussed on pages one and two of this letter, FDA has revoked the standards of identity for low-fat yogurt and non-fat yogurt. Consequently, yogurt must comply with the standard of identity set forth in 21 CFR 131.200, except that certain products may deviate from the standard of identity as set forth in 21 CFR 130.10. (See explanation on pages one and two of this letter). The petition also noted that yogurt contributes taste, aroma, and nutritive value to the diet, and the many flavors and varieties of yogurt commercially available shows that yogurt provides taste and aroma in the diet.

FDA agrees that the petition demonstrated to FDA's satisfaction that yogurt is safe and lawful. Therefore, FDA concludes, under the preliminary requirements of 21 CFR 101.14(b)(3)(ii), the use of yogurt at the levels necessary to justify the claim is safe and lawful.

II. Agency's Consideration of a Qualified Health Claim

FDA identified incidence of type 2 diabetes[16] and the following surrogate endpoints as appropriate to use in identifying type 2 diabetes risk reduction for purposes of a health claim evaluation: impaired fasting glucose, defined as fasting plasma glucose of 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L); or impaired glucose tolerance, defined as 2-hr plasma glucose (PG) during 75-gram oral glucose tolerance test of 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L); or HbA1c 5.7 to 6.4 % (39-47 mmol/mol).[17] These disease incidence and surrogate endpoints were used to evaluate the potential effects of yogurt on type 2 diabetes risk.

[16] A diagnosis of type 2 diabetes can be made after positive results on any one of three tests, with confirmation from a second positive test on a different day: 1) fasting is defined as no caloric intake for at least 8 hours with a fasting plasma glucose of (FPG) ≥ 126 mg/dL (7.0 mmol/L); or 2) 2-hour plasma glucose (2-hr PG) ≥ 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test (OGTT); or 3) HbA1c ≥ 6.5% (48 mmol/mol). In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) are considered risk factors for type 2 diabetes (U.S. FDA Memorandum to the File (Docket No. FDA-2020-Q-0051), 2020 and U.S. FDA Memorandum to the File, 2024).

[17] Evidence of insulin resistance when combined with any of the parameters described (*i.e.*, impaired fasting glucose, impaired glucose tolerance, or HbA1c) would strengthen risk for type 2 diabetes. (U.S. FDA Memorandum to the File (Docket No. FDA-2020-Q-0051), 2020 and U.S. FDA Memorandum to the File, 2024).

The petition cited 117 publications[18] as evidence to substantiate the relationship for the proposed claims (see Docket Number FDA-2019-P-1594), including 50 observational studies (32 studies evaluating the substance-disease relationship);[19] 33 human intervention studies[20] (20 evaluating the substance-disease relationship[21]); 11 reviews;[22] eight meta-analyses;[23] nine publications related to nutrition, dietary intake and validation of dietary assessment tools;[24] three reports (Institute of Medicine, 2010; Dietary Guidelines Advisory Committee, 2015-2020; CDC National Diabetes Statistics Report, 2017); two position statements (American Diabetes Association, 2017; Johnson et al., 2009); and one methodological study (Chlup et al., 2006). FDA identified through a literature search[25] the following scientific articles on the relationship

[18] The Chen et al. 2014 publication reported on individual observational studies and meta-analysis, therefore, this publication is counted twice under these two categories.

[19] Panahi et al., 2018; Abreu et al., 2014; Hobbs et al., 2018; Wang et al., 2013; Kim 2013; Beydoun et al., 2008; Snijder et al., 2007; Crichton and Alkerwi 2014; Sigman-Grant et al., 2003; Zhu et al., 2015; Panagiotakos et al., 2005; Brouwer-Brolsma et al., 2018; Eussen et al., 2016; Drehmer et al., 2015; Cormier et al., 2016; Liang et al., 2017; Niu et al., 2013; Moslehi et al., 2015; Vergnaud et al., 2008; Grantham et al., 2013; Chen et al., 2014; Shin et al., 2013; Samara et al., 2013; Kim and Kim 2017; Sayon-Orea et al., 2015; Sluijs et al., 2012; Feeney et al., 2017; Struijk et al., 2013; Smith et al., 2015; Wang et al., 2014; Martinez-Gonzalez et al., 2014; Rautiainen et al., 2016; Romaguera et al., 2011; Ericson et al., 2015; Magliano et al., 2008; Fumeron et al., 2011; Pereira et al., 2002; Brouwer-Brolsma et al., 2016; Choi et al., 2005; Diaz-Lopez et al., 2016; Guasch-Ferre et al., 2017; Hruby et al., 2017; Kirii et al., 2009; Liu et al., 2006; Margolis et al., 2011; Soedamah-Muthu et al., 2013; Mozaffarian et al., 2011; Santiago et al., 2016; Babio et al., 2015; O'Connor et al., 2014.

[19] Panahi et al., 2018; Abreu et al., 2014; Hobbs et al., 2018; Wang et al., 2013; Kim 2013; Beydoun et al., 2008; Snijder et al., 2007; Crichton and Alkerwi 2014; Sigman-Grant et al., 2003; Zhu et al., 2015; Panagiotakos et al., 2005; Brouwer-Brolsma et al., 2018; Eussen et al., 2016; Drehmer et al., 2015; Cormier et al., 2016; Liang et al., 2017; Niu et al., 2013; Moslehi et al., 2015; Vergnaud et al., 2008; Grantham et al., 2013; Chen et al., 2014; Shin et al., 2013; Samara et al., 2013; Kim and Kim 2017; Sayon-Orea et al., 2015; Sluijs et al., 2012; Feeney et al., 2017; Struijk et al., 2013; Smith et al., 2015; Wang et al., 2014; Martinez-Gonzalez et al., 2014; Rautiainen et al., 2016; Romaguera et al., 2011; Ericson et al., 2015; Magliano et al., 2008; Fumeron et al., 2011; Pereira et al., 2002; Brouwer-Brolsma et al., 2016; Choi et al., 2005; Diaz-Lopez et al., 2016; Guasch-Ferre et al., 2017; Hruby et al., 2017; Kirii et al., 2009; Liu et al., 2006; Margolis et al., 2011; Soedamah-Muthu et al., 2013; Mozaffarian et al., 2011; Santiago et al., 2016; Babio et al., 2015; O'Connor et al., 2014.

[20] Asemi et al., 2013; Chang et al., 2011; Ejtahed et al., 2012; Ejtahed et al., 2011; El Khoury et al., 2014; Esmaillzadeh et al., 2015; Heravifard et al., 2013; Hove et al., 2015; Hulston et al., 2015; Hutt et al., 2015; Ivey et al., 2014; Jafari et al., 2016; Madjd et al., 2016; Maki et al., 2015; Mohamadshahi et al., 2014; Nabavi et al., 2014; Nakamura et al., 2002; Nazare et al., 2007; Neyestani et al., 2015; Nikooyeh et al., 2011; Nikooyeh et al., 2014; Ostman et al., 2001; Rizkalla et al., 2000; Schaafsma et al., 1998; Shab-Bidar et al., 2011; Shively et al., 1986; Vien et al., 2017; Burton et al., 2017; Dougkas et al., 2012; Sialvera et al., 2012; Rajala et al., 1988; White et al., 2009; Berthold et al., 2011.

[21] Asemi et al., 2013; Chang et al., 2011; Ejtahed et al., 2012; Esmaillzadeh et al., 2015; Hutt et al., 2015; Jafari et al., 2016; Madjd et al., 2016; Maki et al., 2015; Mohamadshahi et al., 2014; Nabavi et al., 2014; Nakamura et al., 2002; Nazare et al., 2007; Neyestani et al., 2015; Nikooyeh et al., 2011; Rizkalla et al., 2000; Schaafsma et al., 1998; Shab-Bidar et al., 2011; Sialvera et al., 2012; Rajala et al., 1988; Berthold et al., 2011.

[22] Drouin-Chartier et al., 2016; Gibson 2007; Marette and Picard-Deland 2014; Panahi et al., 2017; Pasin and Comerford 2015; Salas-Salvado et al., 2017; Sayon-Orea et al., 2017; Tremblay et al., 2015; Tremblay and Panahi 2017; Weaver 2014; Webb et al., 2014.

[23] Gao et al., 2013; Gijsbers et al., 2016; Micha et al., 2017; Chen et al., 2012; Schwingshackl et al., 2016; Aune et al., 2013; Tong et al., 2001; Chen et al., 2014.

[24] Brunner et al., 2001; Ranganathan et al., 2005; Rehm et al., 2016; Frary et al., 2004; Mistura et al., 2016; Ali et al., 2013; Hodge et al., 2000; Klipstein-Grobusch et al., 1998; Patterson et al., 1999.

[25] Most of the scientific articles identified by FDA were published after the petition was submitted to the Agency.

between yogurt consumption and reduced risk of type 2 diabetes: 14 observational studies;[26] five meta-analyses;[27] two reviews (Awwad et al., 2022; Mitri et al., 2019) and one human intervention study (Watanabe et al., 2018). The meta-analyses, reviews, and the human intervention study identified by FDA were not included in the current health claim evaluation for the reasons described in this section (Section II. A).

A. Assessment of Review Articles, Meta-analysis, and Other Background Materials

"Background materials" here refers to review articles, meta-analyses, reports from federal agencies, and other articles that provide background information on yogurt and type 2 diabetes. Although useful for background information and identifying additional studies, these materials do not contain sufficient information on the individual studies reviewed and, therefore, FDA could not draw any scientific conclusions regarding the substance-disease relationship from these sources. FDA could not determine factors such as the study population characteristics (*e.g.*, studies should not include subjects who had already been diagnosed with type 2 diabetes) or the nutrient composition of the products used (*e.g.*, all types of yogurts, whole-fat, low-fat yogurt, or non-fat yogurt). Similarly, the lack of detailed information on studies summarized in review articles, meta-analyses, and reports prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies (*e.g.*, whether the dietary assessment tool was validated adequately to measure yogurt intake), and data analysis (*e.g.*, whether the statistical analysis was adjusted for possible confounders). FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. As a result, the background materials supplied by the petitioner and in comments submitted regarding this petition did not provide information from which scientific conclusions can be drawn regarding the substance-disease relationship claimed by the petitioner.

B. Assessment of Intervention Studies

The petition identified 20 controlled intervention studies[28] that examined the effect of yogurt on type 2 diabetes-related surrogate endpoints and determined that these studies were not sufficiently controlled to provide useful information for assessment of a health claim. 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 petition concludes, and FDA agrees, that the effect of conventional yogurt on type 2 diabetes-related parameters could not be assessed from these studies. For this reason, among others, scientific conclusions could not be drawn from any of these 20 studies.

---

[26] Buziau et al., 2019; Drouin-Chartier et al., 2019; Ibsen et al., 2017; Ibsen et al., 2021; Jeon et al., 2018; Mena-Sanchez et al., 2018; Rosenberg et al., 2020; Slurink et al., 2023; Slurink et al., 2022a; Slurink et al., 2022b; Stuber et al., 2021; Trichia, et al., 2020; Yuzbashian et al., 2021; Zhang et al., 2022.

[27] Alvarez-Bueno et al., 2019; Feng et al., 2022; Neuenschwander et al., 2019; Soedamah-Muthu & de Goede, 2018; Zhang et al., 2022.

[28] See *supra*, note 21.

C. Assessment of Observational Studies

FDA reviewed 46 observational studies designed to evaluate the relationship between yogurt intake and reduced risk of type 2 diabetes. Of 46 observational studies, scientific conclusions could not be drawn from 18 of them.[29]

Eight observational studies[30] did not exclude subjects with type 2 diabetes at baseline. Health claims involve reducing the risk of a disease in people who do not have the disease that is the subject of the claim. FDA considers evidence from studies with subjects who have the disease that is the subject of the claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease.[31] Because there is no clear mechanism(s) by which yogurt may affect glucose and/or insulin metabolism, it is unknown whether results from studies on the treatment of diabetes with yogurt (*i.e.*, consumption of yogurt by people with type 2 diabetes) can be extrapolated to risk reduction of type 2 diabetes in individuals without diabetes. Therefore, the agency could not draw any scientific conclusions from these studies for this claim.

Another four observational studies[32] did not adjust the analysis for relevant confounders (*e.g.*, physical activity). One study[33] was excluded because soft drinks, which are considered sugar-sweetened beverages, were not listed in the food frequency questionnaire (FFQ), and therefore, intake of soft drinks by study participants was not captured. Sugar-sweetened beverages contribute to total energy intake, which is a confounder that needs to be accounted for when evaluating an association between consumption of a food or food component and type 2 diabetes. Because in observational studies the subjects are not randomized based on various disease risk factors at the beginning of the study, known confounders of disease risk need to be collected and adjusted for to minimize bias. Additionally, two observational studies[34] included mixed substances and therefore failed to evaluate the independent effect of yogurt. Three observational studies[35] evaluated the effect of substitution among dairy products (*e.g.*, whole-fat yogurt instead of whole-fat milk) and reduced risk of type 2 diabetes, and therefore, these studies do not evaluate the independent effect of yogurt, but compare the effect of one dairy product when substituted by another dairy product on type 2 diabetes, which is outside of the scope of this health claim evaluation. For the reasons cited above, scientific conclusions could not be drawn from these studies.

Therefore, there were 28 observational studies that reported on the relationship between yogurt consumption and risk of type 2 diabetes from which scientific conclusions could be drawn. Among these 28 observational studies, the association between yogurt intake and incidence of

---

[29] This section contains a general discussion of major flaws in the reports of observational studies from which scientific conclusions could not be drawn. Such studies may have other flaws in addition to those specifically mentioned.
[30] Beydon et al., 2008; Cormier et al., 2016; Kim et al. 2013; Kim and Kim 2017; Mena-Sanchez et al., 2018; Snijder et al. 2007; Wang et al., 2013; Zhu et al., 2015.
[31] See *supra*, note 4.
[32] Abreu et al., 2014; Feeney et al., 2017; Panahi et al., 2017; Panagiotakos et al., 2005.
[33] Grantham et al. 2012.
[34] Hobbs et al., 2018; Rosenberg et al., 2020.
[35] Ibsen et al., 2017, Ibsen et al., 2021, and Stuber et al., 2021.

type 2 diabetes was investigated in 15 prospective cohort studies[36] and two nested case-control studies.[37] The association between yogurt intake and validated surrogate endpoints of type 2 diabetes (*e.g.*, fasting blood glucose alone or as an individual component of metabolic syndrome,[38] impaired glucose metabolism, HbA1c, and prediabetes alone or in combination with insulin resistance) was investigated in eight prospective cohort studies.[39] One study reported on the incidence of type 2 diabetes and a validated surrogate endpoint for type 2 diabetes (Hruby et al., 2017). There were another four cross-sectional studies[40] that evaluated the validated surrogate endpoints of type 2 diabetes, with two studies also including analyses on the incidence of newly diagnosed type 2 diabetes. A brief description of these studies is provided below.

Except for one study (O'Connor et al., 2014) that used a 7-day food diary to collected data on yogurt intake, the other observational studies estimated yogurt intake by using FFQs, where study participants answered questions on their frequency of yogurt consumption over a period of time from a list of foods pre-established in the questionnaire. Some FFQs listed only "yogurt," whereas others listed a variety of yogurt types, *e.g.*, in terms of fat content (low, high, whole, full, non) or flavors (plain versus flavored), but did not distinguish types of yogurts in other ways, *e.g.*, based on levels of added sugars. For this health claim evaluation, the individual types of yogurts are described the same way they are reported in the articles. If no specific type of yogurt was reported, it is described only as "yogurt." When more than one type of yogurt was reported, the combined analysis of all types of yogurts is referred to in this evaluation as "total yogurt." We also assume the yogurt consumed in these studies was commercially available and met the SOI for yogurt.

Yogurt Intake and Incidence of Type 2 Diabetes

Prospective Cohort and Nested Case-Control Studies

Choi et al. (2005) analyzed data from the Health Professionals Follow-up Study (HPFS)[41] to

---

[36] Buziau et al., 2019; Chen et al., 2014; Brouwer-Brolsma et al., 2016; Choi et al., 2005; Diaz-Lopez et al., 2016; Drouin-Chartier et al., 2019; Guasch-Ferre et al., 2017; Hruby et al., 2017; Jeon et al., 2019; Kirii et al., 2009; Liu et al., 2006; Margolis et al., 2011; Soedamah-Muthu et al., 2013; Yuzbashian et al., 2021; Zhang et al. 2022.
[37] Moslehi et al., 2015; O'Connor et al. 2014.
[38] Metabolic syndrome is defined in accordance with the updated harmonized criteria of the International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute (Alberti et al., 2009). Individuals are diagnosed with metabolic syndrome if they have three or more of the following components: hypertriglyceridemia [≥ 150 mg/dL (≥ 1.7 mmol/L)] or drug treatment for elevated triglycerides; low concentrations of HDL cholesterol [< 50 mg/dL (< 1.3 mmol/L) and < 40mg/dL (< 1.03 mmol/L) in women and men, respectively] or drug treatment for low HDL cholesterol; elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥85 mmHg) or being treated for hypertension; high fasting plasma glucose [≥ 100 mg/dL (≥ 5.5 mmol/L)] or drug treatment for hyperglycemia; and elevated waist circumference for European individuals (≥ 88 cm in women and ≥ 102 cm in men).
[39] Sayon-Orea et al., 2015; Pereira et al., 2002; Hruby et al., 2017; Babio et al., 2015; Trichia et al., 2020: Slurink et al., 2023; Slurink et al., 2022a; Slurink et al., 2022b.
[40] Brouwer-Brolsma et al., 2018; Drehmer et al., 2015; Eussen et al., 2016; Liang et al., 2017.
[41] The Health Professionals Follow-Up Study (HPFS) began in 1986 enlisting 51,529 U.S. male health professionals aged 40 to 75 years old. The purpose of the study is to evaluate a series of hypotheses about men's health relating nutritional factors to the incidence of serious illnesses, such as cancer, heart disease, and other vascular diseases. Available at https://sites.sph.harvard.edu/hpfs/ (Accessed on August 1, 2022).

evaluate the association between yogurt[42] consumption and incidence of type 2 diabetes. 41,254 men (40-75 y) without a history of diabetes, cardiovascular disease, and/or cancer at baseline participated in this high methodological quality study with a 12-year follow-up. During this period, 1,243 incident cases of type 2 diabetes were reported. Examining the independent effect of individual dairy foods in a multivariate analysis adjusted for confounders,[43] consumption of yogurt was not statistically significantly associated with a reduced risk of type 2 diabetes when comparing those in the highest quartile (³ 2 servings per week) with those in the lowest quartile (< 1 serving per month) of intake (relative risk (RR)[44] = 0.83; 95% confidence interval (95 % CI)[45]: 0.66, 1.06)[46].

Liu et al. (2006) analyzed data from the Women's Health Study (WHS)[47] to evaluate the association between yogurt[48] consumption and incidence of type 2 diabetes. 37,183 women (45 y and older) without a history of diabetes, cardiovascular disease, and/or cancer at baseline participated in this high methodological quality study. During a 10-year follow-up, 1,603 incident cases of type 2 diabetes were reported. In a multivariate analysis adjusted for confounders,[49] consumption of yogurt was statistically significantly associated with a reduced risk of type 2 diabetes for women who consumed ³ 2 servings per week of yogurt compared with those who consumed < 1 serving per month (RR = 0.82; 95% CI: 0.70, 0.97). The inverse association with type 2 diabetes was mainly associated with low-fat dairy intake, in which yogurt was included (RR = 0.69; 95% CI: 0.52, 0.91), but not with high-fat dairy intake (RR = 0.99; 95% CI: 0.82, 1.20).

---

[42] Yogurt was described in the FFQ as "yogurt," but it was included in the analysis for low-fat dairy foods, which included skim/low-fat milk, sherbet and ice milk, and yogurt.

[43] The multivariate analysis was adjusted for age, BMI, total energy intake, biennial follow-up time (6 months), family history of diabetes, smoking status, hypercholesterolemia, hypertension, physical activity, alcohol intake, cereal fiber intake, trans-fat intake, ratio of polyunsaturated to saturated fat, and glycemic load.

[44] The relative risk (RR) of developing a disease (*e.g.*, type 2 diabetes) is expressed as the ratio of the risk (incidence) in exposed individuals (*e.g.*, individuals who consume yogurt) to that in unexposed (*e.g.*, individuals who do not consume yogurt). (Epidemiology Beyond Basics, Jones & Bartlett Learning, LLC, an Ascend Learning Company, page 89, 2018).

[44] The relative risk (RR) of developing a disease (*e.g.*, type 2 diabetes) is expressed as the ratio of the risk (incidence) in exposed individuals (*e.g.*, individuals who consume yogurt) to that in unexposed (*e.g.*, individuals who do not consume yogurt). (Epidemiology Beyond Basics, Jones & Bartlett Learning, LLC, an Ascend Learning Company, page 89, 2018).

[45] The 95% confidence interval (95% CI) estimates precision of a point estimate or of an association measure (e.g., relative risk) (Epidemiology Beyond Basics, Jones & Bartlett Learning, LLC, an Ascend Learning Company, page 418, 2018).

[46] For observational studies, confidence intervals for risk are significant when the value is less than or greater than "1". Many studies analyze for the statistical significance of the linear relationship (P for trend) between the substance and the disease. While this trend may be significant (P < 0.05), the difference in risk between subjects at the various levels of intake (*e.g.*, tertiles, quartiles or quintiles of intake) may not be significant (See *supra,* note 4 [Section III.F]).

[47] The Women's Health Study was designed as a randomized trial of low-dose aspirin and vitamin E supplementation for the primary prevention of cardiovascular disease and cancer in initially healthy women. The initial trial included 39,876 female health professionals aged 45 years and older who were followed for an average of 10 years. Available at https://whs.bwh.harvard.edu/methods.html (Accessed on August 1, 2022).

[48] See *supra*, note 42.

[49] Multivariate model adjusted 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 fiber, total fat, dietary glycemic load, dietary calcium, vitamin D, and magnesium.

Kirii et al. (2009) analyzed data from the Japan Public Health Center-based Prospective Study (JPHC—cohorts I and II)[50] to investigate the association between consumption of yogurt and incidence of type 2 diabetes among men and women who had no history of diabetes, cardiovascular disease, cancer, and chronic liver and kidney diseases at baseline. Data from 59,796 middle-aged men and women (cohort I: 40-59 y, and cohort II: 40-69 y) were evaluated in this moderate-quality methodological study with a 5-year follow-up. During this period, 1,114 incident cases of type 2 diabetes were reported. In a multivariate analysis adjusted for confounders,[51] consumption of yogurt was not statistically significantly associated with a reduced risk of type 2 diabetes among men and women who consumed ³ 60 grams per day compared with those who consumed 0 grams per day (OR = 1.01; 95% CI: 0.75, 1.36, and OR = 0.77; 95% CI: 0.58, 1.01, respectively).

Margolis et al. (2011) analyzed data from the Women's Health Initiative Observational Study (WHI-OS)[52] to investigate the association between consumption of yogurt and incidence of type 2 diabetes among postmenopausal women. After excluding those who reported diabetes at baseline, data from 82,076 postmenopausal women aged 50-79 y were evaluated in this moderate-quality methodological study with a 7.9-year follow-up. During this period, 3,946 incident cases of type 2 diabetes were reported. In a multivariate analysis adjusted for confounders,[53] consumption of yogurt was statistically significantly associated with a reduced risk of type 2 diabetes among women who consumed ³ 2 servings per week compared with those who consumed < 1 serving per month (RR = 0.46; 95% CI: 0.31, 0.68).

Soedamah-Muthu et al. (2013) investigated the association between consumption of yogurt[54] and incidence of type 2 diabetes in the Whitehall II prospective cohort study.[55] 4,186 men and women (35-55 y) without incident diabetes at baseline participated in this moderate methodological quality study. During 9.8 ± 1.9 follow up years, 273 incident cases of type 2

---

[50] The participants of cohort I included residents, aged 40 to 59 years, in five Japanese Public Health Center areas (Iwate, Akita, Nagano, Okinawa and Tokyo); the participants of cohort II included residents, aged 40 to 69 years, in six Public Health Center areas (Ibaraki, Niigata, Kouchi, Nagasaki, Okinawa and Osaka).

[51] Adjusted for age, area (nine Public Health Center areas), BMI, family history of diabetes, smoking status, alcohol intake, history of hypertension, exercise frequency, consumption of coffee, energy-adjusted magnesium and total energy.

[52] The Women's Health Initiative Observational Study was established to explore the predictors and natural history of morbidity and mortality causes in postmenopausal women. 93,676 women aged 50–79 y were enrolled at 40 centers throughout the United States between October 1,1993 and December 31, 1998. Subjects were excluded if they did not plan to reside in the area for at least 3 years, had medical conditions predictive of survival less than 3 years, or had complicating conditions such as alcoholism, drug dependency or dementia (Langer et al., 2003).

[53] Adjusted for age, race/ethnicity, total energy intake, income, education, smoking, alcohol consumption, use of postmenopausal hormone therapy, physical activity, family history of diabetes, BMI, and blood pressure, glycemic load, total fat, dietary fiber, and magnesium.

[54] Authors reported being unable to distinguish types of yogurts as no information was available on sugar or fat content.

[55] The Whitehall II cohort consists of London-based office staff working in twenty Civil Service departments during recruitment in 1985–1988. The initial cohort consisted of 10,308 civil servants aged 35–55 years. During the follow-up, FFQs were completed at phase 3 (1991–1993), phase 5 (1997–1999), phase 7 (2003–2004) and phase 9 (2007–2009). The phase 5 FFQ was selected as baseline for the study due to inconsistency related to milk intake in the FFQ administered in phase 3.

diabetes occurred. In a multivariate analysis adjusted for confounders,[56] those in the highest tertile of intake (117 grams per day, median yogurt intake) were not statistically significantly associated with a reduced risk of type 2 diabetes as compared with those in the lowest tertile of intake (0 gram per day, median yogurt intake) (hazard ratio (HR)[57] = 1.04; 95% CI: 0.77, 1.42). Additional adjustments for changes in BMI during the follow-up did not alter the results for diabetes.[58]

O'Connor et al. (2014) investigated the association between consumption of yogurt[59] and incidence of type 2 diabetes among men and women (40-79 y) in a nested case-cohort within the European Prospective Investigation into Cancer (EPIC)-Norfolk Study.[60] Data from 4,127 subjects (753 cases and 3,502 sub-cohort, including 128 sub-cohort cases) were examined in this moderate methodological quality study.[61] In a multivariate analysis adjusted for confounders,[62] men and women who consumed a median intake of 80 gram per day of all types of yogurts (full-, low-, reduced-, non-fat) were statistically significantly associated with a reduced risk of type 2 diabetes as compared with those who did not consume yogurt (HR = 0.72; 95% CI: 0.55, 0.95). Inclusion of saturated fat in the most adjusted model marginally attenuated the hazard of type 2 diabetes (HR = 0.73; 95% CI: 0.56, 0.95).

---

[56] Adjusted for age, ethnicity, employment grade, smoking, alcohol intake, BMI, physical activity and family history of CHD/hypertension, fruit and vegetables, bread, meat, fish, coffee, tea and total energy intake.

[57] Hazard ratio analysis is based on time-to-event (or survival) data. The assumption underlying this approach is that exposure to a certain risk factor (or the presence of a certain characteristic) is associated with a fixed relative increase in the instantaneous risk of the outcome of interest compared with a baseline or reference hazard (*e.g.*, the hazard in the unexposed) (Epidemiology Beyond Basics, Jones & Bartlett Learning, LLC, an Ascend Learning Company, page 299, 2018).

[58] Data was not shown in the article.

[59] Yogurt including full-, low-, reduced-, and 0% fat.

[60] The EPIC (European Prospective Investigation into Cancer) Norfolk study is a population-based prospective cohort study. Over 30,000 men and women who were aged 39-49 y and living in Norwich and surrounding towns and rural areas were recruited into the EPIC-Norfolk study between 1993 and 1997. The participants have continued to contribute information about their diet, lifestyle and health through questionnaires and health checks for over 25 years. Available at https://www.epic-norfolk.org.uk (Accessed on August 8, 2022).

[61] The nested case-cohort included 4,000 sub-cohort participants selected at random from the entire cohort, and 892 incident diabetes cases were ascertained. Due to the randomly selected nature of the sub-cohort, 143 of these cases were included within the sub-cohort, which the case-cohort design allows and accounts for in the analysis. Subjects were excluded if they had prevalent and uncertain diabetes status (n=83), those with missing food diary data (n=18) and other covariates (n=3), and those with an implausible ratio of energy intake to basal metabolic rate (n=82; top and bottom 1% of the distribution). Individuals with prevalent myocardial infarction, stroke and cancer were also excluded (n=436) to account for possible post-diagnosis changes in diet.

[62] Multivariate model was adjusted for age, sex, BMI, family history of diabetes, smoking status, usual alcohol consumption, physical activity, social class, education, and dietary covariates, including energy intake, intake of fiber, fruit, vegetables, red meat, processed meat and coffee.

Chen et al. (2014) analyzed data from three large prospective cohort studies in the U.S., Nurse's Health Study (NHS) and Nurse's Health Study II (NHS II)[63] and HPFS,[64] to evaluate the association between yogurt[65] consumption and incidence of type 2 diabetes. All three studies were of high methodological quality. After applying the exclusion criteria,[66] data from 41,479 men (40-75 y) in the HPFS, 67,138 women (30-55 y) in the NHS, and 85,884 women (25-42 y) in the NHS II were included in the analysis. A total of 15,156 cases of incidence of type 2 diabetes were reported, 3,364 cases during a maximum of 24 years of follow-up in the HPFS, 7,841 cases during a maximum of 30 years in the NHS, and 3,951 cases during a maximum of 16 years in the NHS II. All three studies compared the outcome of those in the lowest quintile (< 1 serving per month) with those in the highest quintile (³ 2 servings per week) of yogurt intake. In a multivariate analysis adjusted for confounders,[67] consumption of yogurt was statistically significantly associated with a reduced risk of type 2 diabetes in the NHS cohort (HR = 0.84; 95% CI: 0.78, 0.91), but not in the HPFS cohort (HR = 0.95; 95% CI: 0.84, 1.08) or the NHS II cohort (HR = 0.90; 95% CI: 0.81, 1.00). The result was similar when comparing increments of one serving of yogurt per day, in which a statistically significant association with reducing the risk of type 2 diabetes was observed in the NHS cohort (HR = 0.75; 95% CI: 0.65, 0.86), but not in the HPFS cohort (HR = 0.85; 95% CI: 0.68, 1.06) or the NHS II cohort (HR = 0.94; 95% CI: 0.80,1.10). In a further analysis of pooled data from these three cohorts, yogurt consumption was statistically significantly associated with a reduced risk of type 2 diabetes (HR = 0.83; 95% CI: 0.75, 0.92).[68] The authors also conducted a sensitivity analysis by not updating dietary information after self-reported diagnosis of hypertension or hypercholesterolemia during the follow-up and the inverse association between yogurt consumption and risk of type 2 diabetes remained statistically significant (HR = 0.83; 95% CI: 0.72, 0.95 and HR = 0.86; 95% CI: 0.78,

---

[63] The Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II) are among the largest prospective investigations into the risk factors for major chronic diseases in women. The NHS was established in 1976, when 121,700 nurses aged 30 to 55 years old returned a completed baseline questionnaire about lifestyle and medical history. An FFQ for collecting dietary information was added in 1980 and continued to be mailed at four-year intervals. The NHS II was established in 1989, when 116,430 nurses aged 25 to 42 years old completed the baseline questionnaire. In 1991, the first FFQ was collected, and continued to be administered at four-year intervals. Available at https://nurseshealthstudy.org/about-nhs/history (Accessed on September 24, 2022).

[64] See *supra*, note 41.

[65] Yogurt was described in the FFQ as "yogurt." From 1994 in NHS and HPFS and 1995 in NHS II, yogurt consumption was separated into two items, "plain yogurt" (plain or with NutraSweet) and "flavored yogurt" (without NutraSweet). When described as "plain yogurt" or "flavored yogurt" the analysis was performed by type of yogurt, otherwise, the term "yogurt" encompasses both types of yogurts.

[66] Men and women were excluded if they had diagnoses of diabetes (including type 1 and type 2 diabetes and gestational diabetes only), cardiovascular disease, or cancer at baseline (1986 for HPFS, 1980 for NHS, and 1991 for NHS II, when we first assessed diet in these cohorts). In addition, participants who left >70 of the 131 food items blank on the baseline FFQ or who reported unusual total energy intakes (that is, daily energy intake < 800 or > 4,200 kcal/day for men and < 500 or > 3,500 kcal/day for women) were excluded. Participants without baseline information on dairy consumption or follow-up information on diabetes diagnosis date were also excluded.

[67] The analysis was simultaneously controlled for age, calendar time with updated information at each two-year questionnaire cycle, BMI, and total energy intake, and further adjusted for race, smoking, physical activity, alcohol consumption, menopausal status and menopausal hormone use (NHS and NHS II participants only), oral contraceptive use (NHS II participants only), family history of diabetes and diagnosed hypertension or hypercholesterolemia at baseline, trans-fat intake, glycemic load, and intakes of red and processed meat, nuts, sugar-sweetened beverages and coffee. When analyzing for yogurt intake, an additional adjustment for other types of dairy products was performed.

[68] No significant interaction was observed between yogurt consumption and BMI at baseline.

0.94), respectively, for one serving per day increment. When evaluating the consumption of yogurt by type, neither plain yogurt (HR = 0.96; 95% CI: 0.88, 1.06) nor flavored yogurt (HR = 0.88; 95% CI: 0.77, 1.01) was statistically significantly associated with a reduced risk of type 2 diabetes.[69]

Moslehi et al. (2015) investigated the association between yogurt[70] consumption and incidence of type 2 diabetes among men and women in a nested case-cohort study within the Tehran Lipid and Glucose Study (TLGS).[71] Data from 698 subjects (178 cases and 520 controls) with a mean age of 43.6 ± 12 y at baseline, were examined in this moderate methodological quality study. Assessment of dietary data began in 2005, therefore, dietary data during the third (2005–2008) or the fourth (2008–2011) cycles were used in the analysis. After a 9-year follow-up, in a multivariate analysis adjusted for confounders,[72] men and women in the highest tertile of yogurt intake (276 grams per day) did not show a statistically significantly association with a reduced risk of type 2 diabetes as compared to those in the lowest tertile of yogurt intake (66 grams per day) (odds ratio (OR)[73] = 0.92; 95% CI: 0.59, 1.42).

Brouwer-Brolsma et al. (2016) analyzed data from the Rotterdam Study[74] to investigate the association between consumption of yogurt[75] and incidence of type 2 diabetes among Dutch people aged 55 y and older. Analyses were conducted using data of 2,974 participants for this moderate methodological quality study. During 9.5 ± 4.1 years of follow-up, 393 incident cases of type 2 diabetes were reported. In a multivariate analysis adjusted for confounders,[76] consumption of yogurt was not statistically significantly associated with a reduced risk of type 2 diabetes among those who were in the lowest quartile (£ 1 gram per day) compared to those in the highest quartile (³109 grams per day) of yogurt intake (HR = 0.85; 95% CI: 0.64, 1.14).

---

[69] P-value > 0.05, but specific p-value was not reported.

[70] Yogurt includes all types of yogurts (*e.g.*, low-fat and high-fat yogurt).

[71] The Tehran lipid and glucose study (TLGS) is a large-scale community based prospective study performed on a representative sample of residents (between 3 and 69 years old) of district-13 of Tehran, capital of Iran. The TLGS was first designed in 1997 and implemented in 1999 with the aim of studying epidemiology of non-communicable disease risk factors and outcomes (Azizi et al., 2018).

[72] Multivariate model was adjusted for age, sex, date of blood drawn, family history of diabetes, total physical activity, BMI and waist circumference adjusted for BMI at baseline, total energy intake, and additionally adjusted for high blood pressure, high triglycerides, and high cholesterol, at baseline and change in BMI.

[73] An odds ratio is the odds of developing the disease in exposed compared to unexposed individuals. It is calculated in case control studies by measuring disease development in subjects based on exposure to the substance. An adjusted odds ratio controls for potential confounders.

[74] The Rotterdam Study is an ongoing prospective cohort study that started in 1990 in the city of Rotterdam, the Netherlands. The study aims to unravel etiology, preclinical course, natural history and potential targets for intervention for chronic diseases in mid-life and late life. The study focuses on cardiovascular, endocrine, hepatic, neurological, ophthalmic, psychiatric, dermatological, otolaryngological, locomotor, and respiratory diseases. As of 2008, 14,926 subjects aged 45 years or over comprise the Rotterdam Study cohort. Since 2016, the cohort is being expanded by persons aged 40 years and over (Ikram et al. 2020).

[75] Yogurt was described as all types of yogurts, including plain yogurt, and flavored/fruit types.

[76] Multivariate model adjusted for age, sex, alcohol, smoking, education, physical activity, BMI, 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).

Diáz-López et al. (2016) investigated the association between consumption of low-fat yogurt, whole-fat yogurt, and total intake of yogurt and type 2 diabetes in non-diabetic elderly men (55-80 y) and women (60-80 y) at high cardiovascular risk from the PREDIMED (Prevención con Dieta Mediterránea) study in Spain.[77] In this high-quality methodological study, a total of 3,454 subjects were prospectively followed up for 4.1 (2.5-5.7) years. During this period, 270 incidences of type 2 diabetes were reported. In a multivariate analysis adjusted for confounders,[78] men and women in the highest tertile of total yogurt intake (128 grams per day) were statistically significantly associated with a 40% reduced risk of type 2 diabetes as compared with those in the lowest tertile of intake (13 grams per day) (HR = 0.60; 95% CI: 0.42, 0.86). In a further analysis, those in the highest tertile of intake of low-fat (120 grams per day) and whole-fat (45 grams per day) yogurt were also statistically significantly associated with risk reduction of type 2 diabetes, demonstrating a 32% (HR = 0.68; 95% CI: 0.47, 0.97) and 34% (HR = 0.66; 95% CI: 0.47, 0.92) reduction compared to those in the lowest tertile of intake (3 and 0 grams per day), respectively.

Another scientific article was published also analyzing data from the PREDIMED prospective cohort study[79] but with a slightly longer median follow-up period of 4.3 y (Guash-Ferré et al. 2017). The main objective of this high-quality methodological study was to evaluate the association between intake of saturated fatty acids and risk of type 2 diabetes with a specific goal of evaluating the association between the consumption of one serving of whole-fat yogurt, as one of the animal foods sources rich in saturated fatty acids, and risk of type 2 diabetes. During the 4.3-year follow-up period, 266 incidences of type 2 diabetes were reported among the 3,349 non-diabetic elderly men (55-80 y) and women (60-80 y) who were at high cardiovascular risk at baseline.[80] The results demonstrated that intake of whole-fat yogurt (125 grams) was statistically significantly associated with a lower risk of type 2 diabetes (HR = 0.65; 95% CI: 0.45, 0.94).

---

[77] The PREDIMED (Prevención con Dieta Mediterránea) study is a large, parallel group, randomized, multicenter, and controlled trial designed to assess the effect of the Mediterranean diet on the primary prevention of cardiovascular disease. Recruitment of non-diabetic elderly men (55-80 y) and women (60-80 y) at high cardiovascular risk took place between October 2003 and January 2009, where 7,447 participants were randomly assigned to three intervention groups: two Mediterranean diet groups (supplemented with either virgin olive oil or nuts) and a control low-fat diet group. Available at http://www.predimed.es (Accessed on August 4, 2022).

[78] Adjusted for age, sex, and BMI, dietary intervention group (MedDiet supplemented with virgin olive oil, and/or nuts, or control group), leisure time physical activity, educational level, smoking, hypertension, or antihypertensive use, and fasting glucose, HDL-cholesterol, and triglyceride concentrations, cumulative average consumption of dietary variables in energy-adjusted quintiles (vegetables, legumes, fruits, cereals, meat, fish, olive oil, and nuts), alcohol and alcohol squared in g/day, stratified by recruitment center.

[79] See *supra*, note 77.

[80] We noted a slight discrepancy in the number of incidences of type 2 diabetes reported in the Guash-Ferré et al. 2017 (266 incidences during a period of follow-up of 4.3 years) compared to those reported in a year earlier by Diaz-Lopez et al. 2016 (270 incidences during a period of 4.1 years of follow-up).

Hruby et al. (2017) analyzed data from the Framingham Heart Study Offspring Cohort[81] for the relationship between yogurt[82] intake and incidence of type 2 diabetes among 925 individuals (mean age of 54 ± 9.7 y) including those with impaired fasting glucose or impaired glucose tolerance at baseline (31.8% of the total sample). This study was of a moderate methodological quality. During the 11.5 ± 3.5 year follow up, 196 participants developed incident type 2 diabetes. In a multivariate analysis adjusted for confounders,[83] yogurt consumption in the highest quartile (³ 3 servings per week[84]) was not statistically significantly associated with reduced risk of type 2 diabetes as compared with those in the lowest quartile (0 gram per week) of yogurt intake (HR = 1.24; 95% CI: 0.67, 2.29). In a secondary analysis, the 196 cases of type 2 diabetes from those with impaired fasting glucose or impaired glucose tolerance at baseline were combined with 40 cases from initially healthy individuals who developed type 2 diabetes after a prediabetic stage and 17 cases from those who were healthy at baseline and developed type 2 diabetes without a prediabetic stage. Therefore, out of 2,809 individuals initially free of type 2 diabetes, 253 cases of type 2 diabetes were included in this secondary analysis. Still, a statistically significant association with reduced risk of type 2 diabetes was not observed among those in the highest quartile (³ 3 servings per week) compared with those in the lowest quartile (0 gram per week) of yogurt intake (HR = 1.30; 95% CI: 0.76, 2.24).

Buziau et al. (2019) analyzed data from the Australian Longitudinal Study on Women's Health (ALSWH)[85] on consumption of yogurt[86] and incidence of type 2 diabetes among middle-aged women (mean age of 52.5 ± 1.5 y, mean BMI: 26.8 ± 5.4) in this moderate-quality methodological study. Data from 7,633 women were included in the analysis, after excluding women who had diabetes and impaired glucose tolerance at baseline or had missing data on type 2 diabetes at baseline and follow-up. 701 incidence cases of type 2 diabetes were reported during a maximum of 15-year follow-up. After adjusting for several confounders,[87] consumption of yogurt was statistically significantly associated with a reduced risk of type 2 diabetes when comparing women in the highest tertile (114 grams per day) with those in the lowest tertile (0

---

[81] The National Heart, Lung, and Blood Institute's Framingham Heart Study Offspring Cohort is a community-based longitudinal study of cardiovascular disease that began in 1971. 5,124 men and women, ages 5-70 years at entry consisting of offspring of the original Framingham cohort (and spouses of the offspring) participated in the study. In the fifth examination cycle (1991–1995) of the Offspring Cohort, 3799 participants underwent a standard medical examination consisting of laboratory and anthropometric as well as dietary intake assessments. For this study, participants were followed from the fifth exam (baseline) through the eighth exam (2005–2008). Available at https://biolincc.nhlbi.nih.gov/studies/framoffspring/

[82] See *supra*, note 42.

[83] The multivariate model was adjusted for age, sex, and energy intake, parental history of diabetes, baseline smoking status, dyslipidemia or treatment, and hypertension or treatment, means of other dietary characteristics, including intake of coffee, nuts, fruits, vegetables, meats, alcohol, fish; the glycemic index (used as a measure of carbohydrate quality); and other dairy intake, as appropriate (for example, for associations of low-fat dairy intake, high-fat dairy intake was included in the model), baseline BMI and weight change over follow-up.

[84] One serving of yogurt = 227 g.

[85] The Australian Longitudinal Study on Women's Health (ALSWH) involves three age cohorts of Australian women (> 58,000) who were younger (aged 18–23y), middle-age (aged 45–50 y) and older (aged 70–75 y) in 1996 (baseline), and who were selected from the national Medicare health insurance database (Lee et al., 2005). Buziau et al. (2019) included data from the cohort aged 45–50 y in 1996, they were surveyed every 2–3 y. Dietary intake was first collected at survey 3 in 2001 (baseline) and at surveys 5–7. However, at surveys 5 and 6, dietary intake was assessed as frequencies and was not expressed as grams per day.

[86] The substance was described as "yogurt." Fat content was not available for yogurt products.

[87] Adjusted for age, BMI, smoking status, alcohol consumption, physical activity, and educational level.

gram per day) of yogurt intake (OR: 0.81; 95% CI: 0.67, 0.99).[88] However, when further adjusted for total energy and other dietary intake,[89] yogurt intake was no longer statistically significantly associated with reduced risk of type 2 diabetes (OR: 0.88; 95% CI: 0.71, 1.08).

The association between yogurt intake and incidence of type 2 diabetes was recently evaluated in two large population-based studies in Korea, the Ansan and Asung study (Jeon et al. 2019) and the Health Examinees (HEXA) study (Zhang et al. 2022), which are both part of the Korean Genome and Epidemiology study (KoGES). [90]

In Jeon et al. (2019), 8,574 men and women aged 40-69 y, without history of type 2 diabetes, cardiovascular disease, and cancer at baseline participated in this moderate methodological quality study. 1,173 incidence cases of type 2 diabetes were reported during an average follow-up of 7.3 y. In a multivariate analysis adjusted for confounders,[91] consumption of yogurt was statistically significantly associated with a reduced risk of type 2 diabetes among middle-aged men and women who consumed a median intake of 5 servings per week (highest quartile) as compared to those consuming 0 (zero) servings per week (lowest quartile) (HR = 0.73; 95% CI: 0.61, 0.88).

In Zhang et al. (2022), 36,393 women and 16,895 men aged 40-69 y and without history of type 2 diabetes at baseline participated in this moderate methodological quality study. Incidence cases of type 2 diabetes occurred among 1,335 women and 1,045 men.[92] In a multivariate analysis adjusted for confounders,[93] consumption of yogurt was statistically significantly associated with a reduced risk of type 2 diabetes among men who consumed ³ 1 serving (120 mL) per day as compared to men who did not consume yogurt (HR = 0.75; 95% CI: 0.60, 0.93). However, yogurt intake was not statistically significantly associated with reduced risk of type 2 diabetes among women (HR = 0.87; 95% CI: 0.73, 1.04). The authors did further analyses by calculating the hazard ratio for each additional serving of yogurt per day among men and women. For women, increasing the consumption of yogurt by one serving per day was statistically significantly associated with a reduced risk of type 2 diabetes (HR = 0.89; 95% CI: 0.79, 0.99),

[88] Median intake (range): 0 (0-3) gram per day (lowest tertile) and 114 (73-140) gram per day (highest tertile).
[89] Dietary intake of fruits, vegetables, whole-grain bread, red meat, processed meat, sugar-sweetened beverages, coffee, and tea.
[90] The Korean genome and epidemiology study (KoGES) is a large prospective cohort study initiated by the Korean National Research Institute of Health and Centers for Disease Control and Prevention and the Ministry of Health and Welfare. The population-based cohorts consist of community-dwellers and participants recruited from the national health examinee registry, men and women, aged 40 years and older at baseline. In the KoGES-Ansan and Ansung study, 10,030 participants were enrolled between 2001-2002, and for the KoGES-health examinee (HEXA) study, 173,357 participants were enrolled between 2004-2013 (Kim et al., 2017).
[91] Multivariate model adjusted for age, sex, BMI, residential area, education level, household income, physical activity, alcohol consumption, and smoking status, history of hypertension, family history of type 2 diabetes, use of antihypertensive medication, use of dietary supplements, and intakes of vegetables, fruits, red meat, processed meat, soft drinks, coffee, and tea.
[92] The baseline survey was performed using a two-stage approach: phase I occurred between 2004 and 2008, and phase II between 2009 and 2013. Participants completed the baseline and follow-up surveys between 2012 and 2016 (Health Examinees Study Group, 2015).
[93] Multivariate model adjusted for age, BMI, education level, smoking status, alcohol consumption, physical activity, and total energy intake.

but not for men (HR = 0.86; 95% CI: 0.74, 1.01). All the analyses investigating the association between the consumption of yogurt and risk of type 2 diabetes were separated by sex, with no results reported for the entire study population.

Cross-Sectional Studies

Eussen et al. (2016) evaluated cross-sectionally data from the Maastricht Study[94] on the association between consumption of yogurt and newly diagnosed type 2 diabetes and impaired glucose metabolism among 2,391 participants (age range: 40-75 y). In a multi-variety analysis, after adjusting for confounders,[95] the total intake of yogurt[96] was not statistically significantly associated with a reduced risk of newly diagnosed type 2 diabetes when comparing those in the highest tertile of intake (³ 63 grams per day) with those in the lowest tertile of intake (£10.5 grams per day) (OR = 0.60; 95% CI: 0.35, 1.02). However, in the continuous model, one serving (150 grams) of total yogurt consumption was statistically significantly associated with a reduced risk of newly diagnosed type 2 diabetes (OR = 0.47; 95% CI: 0.24, 0.89). On the contrary, intake of yogurt was statistically significantly associated with a reduced risk of impaired glucose metabolism when comparing those in the highest tertile of intake (³ 63 grams per day) with those in the lowest tertile of intake (£10.5 grams per day) OR = 0.67; 95% CI: 0.50, 0.90, but not in the continuous model of one serving (150 grams) of yogurt (OR = 0.90; 95% CI: 0.71, 1.15). This study was of a moderate methodological quality.

Liang et al. (2017) evaluated data from a cross-sectional survey in China[97] on the association between consumption of yogurt and risk reduction of type 2 diabetes among 4,343 men and women (age range: 35-74 y; BMI: 24-27 kg/m^2). In a multi-variety analysis, after adjusting for confounders,[98] the intake of yogurt was statistically significantly associated with a reduced risk of type 2 diabetes among women (OR = 0.56; 95% CI: 0.32, 0.98), but not among men (OR = 0.98; 95% CI: 0.69, 1.38). The amount of yogurt consumed was not reported in this study. This study was of a moderate methodological quality.

---

[94] The Maastricht Study is an extensive phenotyping study that focuses on the etiology of type 2 diabetes, its classic complications, and its emerging comorbidities. The study uses state-of-the-art imaging techniques and extensive biobanking to determine health status in a population-based cohort of 10,000 individuals that is enriched with type 2 diabetes individuals. The Maastricht study will specifically focus on possible mechanisms that may explain why type 2 diabetes accelerates the development and progression of classic complications, such as cardiovascular disease, retinopathy, neuropathy and nephropathy and of emerging comorbidities, such as cognitive decline, depression, and gastrointestinal, musculoskeletal and respiratory diseases. Enrollment started in November 2010 (Schram et al. 2014).

[95] The analysis was adjusted for age, sex, education, BMI, physical activity, smoking and intakes of energy, alcohol, vegetables, fruits, meat and fish.

[96] Total yogurt intake included seven items: natural yogurt (whole-fat, low-fat, and skimmed) and fruit yogurt (whole-fat, low-fat, skimmed, and skimmed with artificial sweetener). A validation study of the FFQ was later published in van Dongen et al. 2019.

[97] The cross-sectional survey was conducted in three urban districts (Shinan, Shibei, and Sifang) and three rural counties (Jiaonan, Huangdao, and Jimo) in Qingdao, China.

[98] Adjusted for age, family history of diabetes, BMI, systolic blood pressure, physical activity, educational level, and smoking habits as well as alcohol, fruit and vegetable, red meat, seafood, soft drink, dairy product, soy product, nutrient, tea, and total energy intake.

Brouwer-Brolsma et al. (2018) evaluated cross-sectionally data from the Lifelines Cohort Study[99] on the relationship between consumption of yogurt, skimmed yogurt, and full-fat yogurt and incidence of type 2 diabetes and prediabetes among 112,086 Dutch people with a mean age of 45 ± 13 y. After adjusting for confounders,[100] no statistically significant association was observed between total consumption of yogurt[101] and incidence of newly diagnosed type 2 diabetes and prediabetes at a 150 gram-serving (OR = 1.02; 95% CI: 0.84, 1.23; OR = 0.98; 95% CI: 0.93, 1.03, respectively) or when comparing the highest tertile (69 grams per day, median intake) to the lowest tertile (0 gram per day) of intake (OR = 0.97; 95% CI: 0.84, 1.11; OR = 0.99; 95% CI: 0.96, 1.03, respectively). Similarly, no statistically significant association was observed between intake of skimmed yogurt and incidence of newly diagnosed type 2 diabetes and prediabetes at a 150 gram-serving (OR = 1.06; 95% CI: 0.86, 1.30; OR = 0.95; 95% CI: 0.90, 1.00, respectively) or when comparing the highest tertile (54 grams per day, median intake) to the lowest tertile (0 gram per day) of intake (OR = 0.99; 95% CI: 0.86, 1.23; OR = 0.97; 95% CI: 0.93, 1.01, respectively). However, intake of full-fat yogurt was statistically significantly positively associated with prediabetes when comparing the highest tertile (14 grams per day, median intake) to the lowest tertile (0 gram per day) of intake (OR = 1.07; 95% CI: 1.02, 1.12) but not at 150 gram-serving (OR = 1.09; 95% CI: 0.99, 1.19). No statistically significant association was observed between full-fat yogurt intake and newly diagnosed type 2 diabetes when comparing the highest (14 grams per day, median intake) to the lowest (0 gram per day) tertile of intake (OR = 1.03; 95% CI: 0.86, 1.23), or at 150 gram-serving (OR = 0.89; 95% CI: 0.61, 1.30). This study was of a moderate methodological quality.

Change in Yogurt Intake and Incidence of Type 2 Diabetes

Prospective Cohort Studies

Drouin-Chartier et al. (2019) analyzed data from the prospective cohorts HPFS,[102] NHS and NHS II,[103] to evaluate the association between changes in yogurt[104] consumption and incidence of type 2 diabetes. All three studies were of high methodological quality. After applying the exclusion criteria,[105] data from 34,224 men (40-75 y) in the HPFS, 76,531 women (30-55 y) in

[99] The Lifelines Cohort Study is a large population-based cohort study and biobank that was established as a resource for research on complex interactions between environmental, phenotypic and genomic factors in the development of chronic diseases and healthy ageing. Between 2006 and 2013, inhabitants of the northern part of The Netherlands and their families were invited to participate, thereby contributing to a three-generation design. Baseline data were collected for 167 729 participants, aged from 6 months to 93 years (Scholtens et al. 2015).

[100] The analysis was adjusted for age, sex, alcohol, smoking, education, physical activity, total energy intake, the intake of energy-adjusted bread, pasta, rice, potato, fruit, vegetables, legumes, meat, fish, coffee, tea, soda/fruit juice, other dairy product groups, BMI and waist circumference.

[101] Yogurt included all types of yogurt; skimmed yogurt included all types of skimmed yogurt (0.2 g fat); and full-fat yogurt included all types of full-fat yogurt (2.9 g fat). A validation study of the FFQ was recently published in Brouwer-Brolsma et al. 2022.

[102] See *supra*, note 41.

[103] See *supra*, note 63.

[104] See *supra*, note 65.

[105] Subjects were excluded if they had diabetes (type 1, type 2, and gestational diabetes), cancer, cardiovascular disease, or who died before baseline. Those whose last returned questionnaire was at baseline were excluded. Also excluded were participants who did not complete two consecutive FFQs during follow-up or who always reported implausible calorie intake (<800 or >4200 kcal/d for men and <500 or >3500 kcal/d for women). Participants

the NHS, and 81,597 women (25-42 y) in the NHS II were included in the analysis. In the three cohorts, dietary information was collected and updated every 4 years. The change in yogurt consumption updated every 4 years was used as the exposure to estimate the risk of type 2 diabetes in the subsequent 4 years. During a total of 2,783,210 person-years, 11,906 incident cases of type 2 diabetes were documented (2,300 in the HPFS, 5,993 in the NHS, and 3,613 in the NHS II). In a multivariate analysis adjusted for confounders,[106] compared with maintaining a stable yogurt consumption, women in the NHS who increased their daily yogurt consumption by > 0.50 serving per day had a statistically significant reduced risk of type 2 diabetes (HR = 0.86; 95% CI: 0.78, 0.95). However, women in NHS II and men in the HPFS who increased their daily yogurt consumption by > 0.50 serving per day did not have a statistically significantly reduced risk of type 2 diabetes (HR = 0.89; 95% CI: 0.77, 1.02 and HR = 1.10; 95% CI: 0.85, 1.42, respectively). In a further analysis of pooled data from these three cohorts, increased daily yogurt consumption by > 0.50 serving per day was statistically significantly associated with a reduced risk of type 2 diabetes as compared with maintaining a stable yogurt consumption (HR = 0.89; 95% CI: 0.82, 0.96). However, decreasing yogurt consumption by > 0.50 serving per day was not statistically significantly associated with a reduced risk of type 2 diabetes among the individual three cohorts or in a pooled analysis.

Yuzbashian et al. (2021) investigated the association between changes in low-fat and high-fat yogurt consumption and incidence of type 2 diabetes among prediabetic men and women in the TLGS prospective cohort.[107] After applying the exclusion criteria,[108] data from 639 subjects with prediabetes and a mean age of 47.3 ± 11 y at baseline, were examined in this high methodological quality study. The assessment of dietary data was conducted every 3 years. Changes in yogurt consumption from the fourth (2009–2011, baseline) to fifth (2011–2014) cycles were used to predict the incidence of type 2 diabetes risk in the sixth (2015–2018) cycle. At the sixth follow-up cycle, 161 cases of type 2 diabetes were identified. In a multivariate analysis adjusted for confounders,[109] compared with maintaining a stable consumption, increasing low-fat yogurt consumption by > 0.20 serving per day was statistically significantly associated with a reduced risk of type 2 diabetes (OR = 0.55; 95% CI 0.33, 0.93). No statistically significant association was observed with increased consumption of high-fat yogurt (> 0.20 serving per day) and reduced risk of type 2 diabetes as compared to maintaining a stable consumption (OR = 1.35; 95% CI: 0.86, 2.10).

---

without baseline information on dairy consumption or follow-up information on diabetes diagnosis data were also excluded.

[106] The analysis was adjusted for age and stratified by calendar year in 4-y intervals, race (Caucasian, non-Caucasian), family history of diabetes, updated history of hypercholesterolemia and high blood pressure, menopausal status and postmenopausal hormone use, oral contraceptive use, initial and change in smoking status, initial and change in physical activity level, initial BMI, initial and changes in energy and alcohol intakes, initial and change in Alternative Healthy Eating Index (AHEI) score, and initial intake of the type of dairy product used as the main exposure, and adjusted for initial and change in intakes of other dairy products.

[107] See *supra*, note 71.

[108] Subjects were excluded if they reported a history of myocardial infarction, stroke, or cancer at baseline. Those missing covariates and dietary data at follow-up were excluded. Also excluded were participants who reported implausible calorie intake (<800 or >4200 kcal/d for men and <600 or >3500 kcal/d for women). Participants were excluded if they had type 2 diabetes in the fifth cycle, or they missed the final follow-up.

[109] Multivariate model was adjusted for age, sex, physical activity, change in BMI, family history of diabetes, total energy intake, and dietary factors, including whole grain and energy from protein and carbohydrate.

Yogurt Intake and Surrogate Endpoints of Type 2 Diabetes

Prospective Cohort Studies

Pereira et al. (2002) investigated the association between the consumption of yogurt and abnormal glucose homeostasis[110] among overweight young adults (18-30 y, BMI ³ 25 kg/m^2) from the multi-center prospective CARDIA study.[111] This study was of a moderate methodological quality. In this 10-year follow up study, a stratified analysis adjusted for confounders[112] showed that the intake of one daily eating occasion of yogurt among individuals who were overweight at baseline (n= 923) was not statistically significantly associated with a reduction in abnormal glucose homeostasis (OR = 0.44; 95% CI: 0.12, 1.62).

Babio et al. (2015) investigated the association between the total consumption of yogurt, consumption of low-fat and consumption of whole-fat yogurt, and fasting blood glucose among non-diabetic elderly men (55-80 y) and women (60-80 y) at high cardiovascular risk from the PREDIMED (Prevención con Dieta Mediterránea) study in Spain.[113] This study was of a high methodological quality. Out of 1,868 subjects without metabolic syndrome at baseline, 1,268 subjects did not have the metabolic syndrome component of high fasting blood glucose.[114] During a median follow up of 3.2 (1.9 to 5.8) years, 41.4% of 1,268 subjects developed high fasting blood glucose. In a multivariate analysis adjusted for confounders,[115] men and women in the highest tertile (median intake) of total yogurt (127 grams per day), whole-fat yogurt (46 grams per day), and low-fat yogurt (124 grams per day) were statistically significantly associated with reduced risk of high fasting blood glucose as compared with those in the lowest tertile of intakes (0 to 7 grams per day) (HR = 0.72; 95% CI: 0.61, 0.85, HR = 0.79; 95% CI: 0.66, 0.94, and HR = 0.81; 95% CI: 0.68, 0.96, respectively).

---

[110] Abnormal glucose homeostasis was defined as a fasting plasma insulin concentration of at least 20 μU/mL (approximately the 90th percentile of the fasting insulin distribution), fasting glucose concentration of at least 110 mg/dL (6.1 mmol/L), or use of medications to control blood glucose.

[111] The Coronary Artery Risk Development in Young Adults (CARDIA) Study is a multicenter population-based prospective study aimed to identify factors that begin in young adulthood, which is two to three decades before the onset of cardiovascular disease in later life in a US cohort of black and white young adults (age ranges: 18-24 and 25-30 years old). Pereira et al. 2002 included the analysis the first 10 years beginning with baseline in 1985, in which 51% of the 5,115 eligible participants underwent the baseline examination.

[112] Adjusted for age, sex, race, calorie intake per day, study center, BMI, educational level, daily alcohol intake, current smoking status, physical activity, use of vitamin supplement, caloric percentage of daily polyunsaturated fat consumption, caffeine intake, fiber, whole and refined grains, meat, fruit, vegetables, soda, caloric percentage of protein and saturated fat, dietary intake of magnesium, calcium, potassium, and vitamin D.

[113] See *supra*, note 77.

[114] See *supra*, note 38.

[115] The multivariate analysis was adjusted for intervention group, sex, age, leisure time physical activity, BMI, current smoker, former smoker, hypoglycemic, hypolipidemic, antihypertensive, and insulin treatment at baseline. Additionally, it was adjusted for mean consumption during follow-up of vegetables, fruit, legumes, cereals, fish, red meat, cookies, olive oil, and nuts, alcohol, as well as the prevalence of metabolic syndrome components at baseline, including abdominal, obesity, hypertriglyceridemia, low HDL cholesterol, hypertension, and high fasting plasma glucose.

Sayón-Orea et al. (2015) analyzed data from the SUN cohort study[116] for the relationship between total consumption of yogurt, consumption of low-fat yogurt, and consumption of whole-fat yogurt and impaired glucose metabolism as an individual component of metabolic syndrome[117]. 8,063 men and women (mean age of 36.4 ± 11.6 y and mean BMI 22.7 ± 2.7 kg/m^2) without at least one criterion of metabolic syndrome at baseline were followed up for six years. In a multivariate analysis adjusted for confounders,[118] consumption of both types of yogurts, as well as consumption of the individual whole-fat and low-fat yogurts at a level of ³ 875 grams per week (³ 7 servings per week) as compared to £ 250 g per week (0 to 2 servings per week) was not statistically significantly associated with a reduction in risk of impaired glucose metabolism. The results for the individual components of metabolic syndrome, including impaired glucose metabolism, were presented in a forest plot. The study was of a moderate methodological quality.

Hruby et al. (2017) analyzed data from the Framingham Heart Study Offspring Cohort[119] for the relationship between yogurt[120] intake and incidence of prediabetes[121] among 1,884 individuals (mean age of 54 ± 9.7 y) with normoglycemia at baseline. This study was of a moderate methodological quality. During the 10.5 ± 4.1 years follow up, 902 cases of incidence of prediabetes were reported. Thirty-six percent of participants did not report consuming yogurt during the entire follow-up period. In a multivariate analysis adjusted for confounders,[122] yogurt consumption demonstrated a non-linear association with prediabetes, in which the third quartile of intake (1 to < 3 servings per week[123]) showed a statistically significant association with reduced risk of type 2 diabetes (HR = 0.76; 95% CI: 0.62, 0.92), but not the highest quartile of intake (³ 3 servings per week) (HR = 0.95; 95% CI: 0.72, 1.26) as compared with the lowest quartile of intake (0 gram per week).

---

[116] The SUN ("Seguimiento Universidad de Navarra) Project is a prospective cohort study of Spanish alumni with the aim of identifying dietary determinants of stroke, hypertension, diabetes, coronary heart disease and other chronic diseases. Methods were adapted from the Nurses' Health Study and Health Professionals Follow-up Study in collaboration with some investigators from the Harvard School of Public Health. Recruitment of the cohort started in December 1999, and it is permanently open with participants followed-up every two years (Martínez-Gonzalez et al., 2002).

[117] See *supra*, note 38.

[118] The multivariate model was adjusted for age, sex, baseline weight, total energy intake, alcohol intake, soft drinks, red meat, French fries, fast food, Mediterranean diet, physical activity, sedentary behavior, hours sitting, smoking status, snacking between meals, following special diet.

[119] See *supra*, note 81.

[120] See *supra*, note 42.

[121] Incident prediabetes was defined as the first incident measurement of FG ≥5.6 to <7.0 mmol/L (≥100 to <126 mg/dL).

[122] The multivariate model was adjusted for age, sex, and energy intake, parental history of diabetes, baseline smoking status, dyslipidemia or treatment, and hypertension or treatment, means of other dietary characteristics, including intake of coffee, nuts, fruits, vegetables, meats, alcohol, fish; the glycemic index (used as a measure of carbohydrate quality); and other dairy intake, as appropriate (for example, for associations of low-fat dairy intake, high-fat dairy intake was included in the model), baseline BMI and weight change over follow-up.

[123] One serving of yogurt = 227 grams.

Slurink et al. (2022a) evaluated the association of yogurt intake and incidence of prediabetes from the prospective Hoorn studies, Hoorn Study 1 (HS1) and Hoorn Study 2 (HS2).[124] A total of 2,262 (997 from HS1 and 1,265 from HS2) middle-aged Dutch men and women (mean age of 55.9 ± 7.3 y, mean BMI 25.7 ± 3.4 kg/m^2) who were without prediabetes or type 2 diabetes at baseline were included in this moderate methodological quality study. During a mean follow-up of 6.4 ± 0.7 years, 811 participants developed prediabetes. The analysis was performed for total consumption of yogurt, consumption of high-fat, and consumption of low-fat yogurt.[125] In a regression analysis adjusted for confounders,[126] intake of total yogurt among men and women was not statistically significantly associated with a reduced risk of prediabetes when comparing those in the highest quartile (1 serving per day) versus those in the lowest quartile (0 serving per day) of yogurt intake (RR = 1.05; 95% CI: 0.90, 1.23). Because many participants reported no intake of high-fat or low-fat yogurt, the analysis for high-fat and low-fat yogurt was performed among non-consumers and consumers divided into tertiles of intake. Individuals in the highest tertile of high-fat (median intake of 0.8 servings per day) and low-fat (median intake of 0.9 servings per day) yogurt intake were not statistically significantly associated with a reduced risk of prediabetes when compared with non-consumers (RR = 1.11; 95% CI: 0.92, 1.34), and RR = 0.99; 95% CI: 0.85, 1.15, respectively). Analyzing the data in a continuous scale of one serving per day (*i.e.*, 150 ml per day) of total intake of yogurt , and high-fat and low-fat yogurt intakes were also not statistically significantly associated with a reduced risk of prediabetes (RR = 1.06; 95% CI: 0.94, 1.18), RR = 1.12; 95% CI: 0.94, 1.34, and RR = 1.01; 95% CI: 0.89, 1.14, respectively).

Slurink et al. (2022b) investigated the association of yogurt intake and incidence of prediabetes and longitudinal insulin resistance from the three sub-cohorts of the Rotterdam Study (RS-I, RS-II, and RS-III) among Dutch men and women 45 y and older.[127] All three sub-cohort studies were of moderate methodological quality. Data from 6,053 participants (RS-I: n= 2,617, RS-II: n = 1,250, and RS-III: n= 2,186) without type 2 diabetes and prediabetes at baseline or without follow-up data on prediabetes were included in the analysis. During a mean follow-up of 11.4 ± 4.8 years, 1,139 cases of incident prediabetes out of 6,053 participants were identified. Among the individual sub-cohorts, total intake of yogurt, and intakes of low-fat or high-fat yogurt were

---

[124] The Hoorn Study 1 (HS1) included individuals aged 50–75 years at baseline, it began enrollment in 1989–1992 with a follow-up period between 1996–1998. The Hoorn Study 2 (HS2) included individuals aged 40–65 years and it began enrollment between 2006–2007 with a follow-up period between 2013–2015.

[125] High-fat yogurt included full fat yogurt, full fat fruit yogurt, whereas low-fat yogurt included semi-skimmed yogurt, skimmed yogurt, skimmed fruit yogurt.

[126] Adjusted for age, sex, follow-up duration, enrollment wave (1989-1992 (HS1) and 1996-1998 (HS2)), energy intake, education, smoking, physical activity, alcohol consumption and family history of diabetes, food groups associated with type 2 diabetes, including intakes of fruit, vegetables, tea, coffee, grains (whole and refined), meat (processed and red) and sugar-sweetened beverages, BMI, blood pressure (systolic and diastolic) and LDL cholesterol. The model also included an interaction term and stratified associations by enrolment wave to assess if associations differed for each wave of the Hoorn Studies. The effect modification by age, sex and BMI was examined, and associations were stratified in case of significance.

[127] The Rotterdam study (RS) is comprised of middle-aged and elderly persons living in the district Ommoord in Rotterdam, the Netherlands. The first sub-cohort (RS-I) was established in 1989–1993 among inhabitants aged 55 and over (n = 7,983). The second sub-cohort (RS-II) was recruited in January 2000 among people who had become 55 years of age or moved into the study district (n = 3,011). The third sub-cohort (RS-III) was initiated in 2006 for which subjects aged 45 years and older were recruited (n = 3,932). These three sub-cohorts of the Rotterdam Study comprised of 14926 subjects at baseline. Examinations were repeated every 3–5 years.

not statistically significantly associated with reduced risk of prediabetes when the model was fully adjusted for confounders for total yogurt (RS-I: HR = 0.89; 95% CI: 0.73, 1.07, RS-II: HR = 0.95; 95% CI: 0.76, 1.20, and RS-III: HR = 0.92; 95% CI: 0.77, 1.09); low-fat yogurt (RS-I: HR = 0.97; 95% CI: 0.78, 1.21, RS-II: HR = 1.03; 95% CI: 0.82, 1.29, and RS-III: HR = 0.98; 95% CI: 0.83, 1.16); and high-fat yogurt (RS-I: HR = 0.76; 95% CI: 0.54, 1.07), RS-II: HR = 0.47; 95% CI: 0.20, 1.10), and RS-III: HR = 0.55; 95% CI: 0.29, 1.04). No other statistically significant association was observed between total intake of yogurt, and intakes of low-fat and high-fat yogurts, and reduced risk of prediabetes in the individual sub-cohorts as analyzed in a continuous scale of 150 mL per day. However, in a pooled multivariate analysis (all three sub-cohorts) adjusted for confounders,[128] consumption of high-fat yogurt was statistically significantly associated with a reduced risk of prediabetes when comparing the highest quartile (median intake of 0.7 servings per day) with the lowest quartile (median intake of 0 servings per day) (HR= 0.70; 95% CI: 0.54, 0.91), as well as in a continuous scale of one serving per day (*i.e.,* 150 mL per day) (HR= 0.67; 95% CI: 0.51, 0.89). Total intake of yogurt also showed a statistically significant association with reduced risk of prediabetes for those in the highest versus the lowest quartile of intake (HR = 0.84; 95% CI: 0.71, 0.99) in a pooled analysis, however, this association was not statistically significant when the data was analyzed in a continuous scale of 150 mL of total yogurt intake per day (HR = 0.92; 95% CI: 0.82, 1.02). No statistically significant associations were observed between consumption of low-fat yogurt and reduced risk of prediabetes when comparing the highest versus the lowest quartile of intake (HR= 0.99; 95% CI: 0.83, 1.17) or in a continuous scale of 150 mL low-fat yogurt intake per day (HR= 0.99; 95% CI: 0.88, 1.11) in a pooled analysis.

For the insulin resistance analysis, participants were excluded if they had no data on the homeostatic model assessment of insulin resistance (HOMA-IR) at baseline and follow-up, resulting in 6,593 participants (RS-I: n = 2,892, RS-II: n = 1,391, RS-III: n = 2,310). The results of the longitudinal insulin resistance, only high-fat yogurt intake was statistically significantly inversely associated with reduced risk of insulin resistance. In a pooled (all three sub-cohorts) multivariate analysis adjusted for confounders,[129] consumption of high-fat yogurt was statistically significantly associated with a lower log-transformed HOMA-IR when comparing the highest with the lowest quartile of intake (median intake of 0.7 and 0 serving per day, respectively) (β = -0.10; 95% CI: -0.16, -0.05), as well as, in a continuous scale of 150 mL per day (β = -0.08; 95% CI: -0.13, -0.03).

Slurink et al. (2023) investigated the association between total consumption of yogurt and reduced risk of prediabetes by analyzing data from the Australian Diabetes, Obesity and Lifestyle (AusDiab) prospective cohort.[130] The study was of a moderate methodological quality. 4,891 participants (mean age of 49.0 ± 12.3 y, mean BMI 26.1 ± 4.3 kg/m^2) were followed for 5 and 12 years, who were without prediabetes or type 2 diabetes at baseline or had no missing information on diabetes and prediabetes at the two follow-up periods. A total of 765 incidence of

[128] Adjusted for age, sex, energy intake, education, smoking, physical activity, alcohol consumption, family history of diabetes (RS-I and RS-II only) and food groups associated with type 2 diabetes, including intakes of fruit, vegetables, wholegrains, legumes, nuts, tea, coffee, red meat, and sugar-sweetened beverages.
[129] See, *supra*, note 128.
[130] The Australian Diabetes, Obesity and Lifestyle (AusDiab) study is a national, population-based survey of 11,247 adults aged 25 y and older at baseline (1999–2000) with follow-up measurements in 2004–2005 and 2011–2012.

prediabetes cases were identified, 408 at the 5-year follow-up and 357 at the 12-year follow-up. In a multivariate analysis adjusted for confounders,[131] total intake of yogurt was not statistically significantly associated with reduced risk of prediabetes when comparing those in the highest tertile (median intake of 0.36 servings per day) with those in the lowest tertile (median intake, 0 serving per day) of yogurt intake (RR = 0.99; 95% CI: 0.84, 1.17) or as analyzed in a continuous scale of 150 mL of yogurt per day (RR = 1.14; 95% CI: 0.90, 1.43). Applying the ADA 2020 cut-offs for prediabetes did not change the outcome, total yogurt intake was still not statistically significantly associated with reduced risk of prediabetes when comparing those in the highest tertile (median intake of 0.36 servings per day) with those in the lowest tertile (median intake, 0 serving per day) of yogurt intake (RR = 1.10; 95% CI: 0.98, 1.22) or as analyzed in a continuous scale of 150 mL of yogurt per day (RR = 1.16; 95% CI: 1.00, 1.34).

Cross-Sectional Study

Drehmer et al. (2015) analyzed data cross-sectionally from 10,010 men and women (mean age of 50.7 ± 8.7 y and mean BMI 26.6 ± 4.5 kg/m^2) of the ELSA-Brasil cohort study[132] for the relationship between yogurt[133] intake and fasting blood glucose and HbA1c. In a multivariable linear regression analysis adjusted for confounders,[134] consumption of one serving (120 grams) per day increment of yogurt was statistically significantly inversely associated with HbA1c (-0.04%; 95% CI: -0.06%, -0.01%), but lowering fasting blood glucose did not reach statistical significance (-0.29; 95% CI: -1.03, 0.44 mg/dL). This study was of a moderate methodological quality.

<u>Change in Yogurt Intake and Surrogate Endpoint of Type 2 Diabetes</u>

Prospective Cohort Study

Trichia et al. (2020) investigated the association between changes in total consumption of yogurt, consumption of low-fat, and consumption of full-fat yogurt and HbA1c levels among men and women in the EPIC-Norfolk prospective cohort.[135] 15,612 participants aged 40-78 y old were included in the study after applying the exclusion criteria,[136] but only data from 6,224

---

[131] Multivariate model was adjusted for age, sex, energy intake, education, smoking, physical activity, alcohol consumption, family history of diabetes, and food groups associated with type 2 diabetes, including intakes of fruit, vegetables, grains, legumes, nuts, red and processed meat, tea, coffee, and fruit juice.

[132] ELSA-Brasil *(Estudo Longitudinal de Saúde do Adulto* – Brazilian Longitudinal Study for Adult Health) is a multicenter cohort study designed to investigate the development of chronic diseases, primarily diabetes and cardiovascular diseases and their risk factors over long-term follow-up. 15,105 women and men aged 35 to 74 years, civil servants (active employees and retirees) of six public universities and research institutions located in the Northeast, Southeast and South regions of Brazil, were enrolled with baseline data collected from 2008 to 2010 (Aquino et al., 2013).

[133] Yogurt included regular and low-fat yogurt.

[134] Adjusted for age, sex, race, occupational status, education, family income, and study center, menopause, family history of diabetes, smoking status, alcohol intake, physical activity, calorie intake, nondairy food groups, and anthropometric variables (height and waist and hip circumferences).

[135] See *supra*, note 60.

[136] Subjects were excluded if they did not undergo follow-up assessments, they were without dietary data, they had extreme values of dietary intakes based on total energy intake [<800 and >4000 kcal/d for men and <500 and >3500 kcal/d for women] or extreme changes in dairy consumption or cardiometabolic marker for each association

participants were evaluated for the endpoint HbA1c in this high methodological quality study. The dietary assessment was conducted at baseline (1993-1997) and followed up (1998-2000) for an average of 3.7 ± 0.7 y. Changes in consumption of total, low-fat, and full-fat yogurt were, respectively, 0.02 ± 0.41, 0.02 ± 0.40, and 0.00 ± 0.16 servings per day. In a multivariate linear regression analysis adjusted for confounders,[137] increased consumption by one serving per day of total, low-fat, and full-fat yogurt was not statistically significantly associated with lower levels of HbA1c (total yogurt: 0.21 (95% CI: -0.29, 0.71) mmol/mol; low-fat yogurt: 0.33 (95% CI: -0.23, 0.89) mmol/mol; and full-fat yogurt: -0.01 (-1.68, 1.66) mmol/mol.

III. Strength of the Scientific Evidence

Below, the agency rates the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (*e.g.*, intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of the evidence (number of the various types of studies and sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,[138] and the overall consistency[139] of the total body of evidence.[140] Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance/disease relationship and, if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship or to prevent the claim from being misleading in other ways.

As discussed in Section II, the totality of scientific evidence about a possible relationship between yogurt intake and risk of type 2 diabetes includes 28 observational studies from which scientific conclusions can be drawn.

<u>High Methodological Quality Studies</u>

Of these studies, there were a total of nine publications that were of a high methodological quality; six of them evaluated the intake of yogurt and reduced risk of type 2 diabetes, whereas three publications reported on the effect of change in yogurt intake and reduced risk of type 2 diabetes. Among the studies reporting on yogurt intake, three publications reported on four prospective cohorts from the U.S. (HPFS, NHS, NHS II, and WHS) with a large sample size (40,000 to 85,000 individuals) and a follow-up period ranging from 10 to 30 years (Choi et al., 2005, Liu et al., 2006, Chen et al., 2014). The other three publications involved analyses from one prospective cohort from Spain (PREDIMED) with a considerably smaller sample size (1,800 to 3,500 individuals) and a follow-up period ranging from 3.2 to 4.3 years, and included analyses of low-fat, high-fat, and total yogurt (Diáz-López et al., 2016, Guash-Ferre et al., 2017, Babio et al., 2015). Two large U.S. cohorts (HPFS and NHS II) did not show a statistically significant

examined (outside the range of 3 SDs from the mean).

[137] Multivariate model was adjusted for age, sex, education, socioeconomic status, physical activity, smoking status, clinical medication use, BMI, total energy intake, and food groups.

[138] See, *supra*, note 12.

[139] See, *supra*, note 13.

[140] See, *supra*, note 4.

association between yogurt intake and reduced risk of type 2 diabetes, whereas, among women in another two large U.S. cohorts (NHS and WHS) and all the other prospective cohorts from Spain, there was a statistically significant association between yogurt intake and reduced risk of type 2 diabetes. The doses of yogurt intake that showed statistical significance were ³ 2 servings per week among the U.S. prospective cohorts, and 120 grams per day for low-fat, 45 grams per day for high-fat, and 128 grams per day for total yogurt, in the prospective cohort from Spain.

The findings regarding changes in yogurt consumption and reduced risk of type 2 diabetes were inconsistent. Among the three health professionals' prospective cohorts in the U.S that increased consumption by > 0.50 serving per day, only the NHS cohort (n= 67,138), but not the NHS-II (n= 85,884) or HPFS (n= 41,479) cohorts, demonstrated a statistically significant association with reduced risk of type 2 diabetes (Drouin-Chartier et al., 2019). No statistically significant associations were observed with small changes in serving per day (0-0.02) of total, full-fat, and low-fat yogurt intake and HbA1c levels among men and women (n = 6,224) in the U.K. (Trichia et al., 2020). In a small prospective cohort from Iran (n= 639), an increased consumption of yogurt by > 0.20 serving per day was statistically significantly associated with a reduced risk of type 2 diabetes for low-fat yogurt, but not for high-fat yogurt (Yuzbashian et al., 2021).

In summary, among the high methodological quality studies, a significant association was observed for both outcomes: incidence of type 2 diabetes and the surrogate endpoint of fasting plasma glucose. The large observational studies from the U.S. did not investigate the consumption of yogurt according to their fat content. However, the observational studies from Spain did report their findings for low-fat, high-fat, and total yogurt, with all types of yogurts showing a statistically significant association with a reduced risk of type 2 diabetes and demonstrating no difference in terms of the fat content of yogurt and reduced risk of type 2 diabetes for that population. The effect of change in yogurt consumption and reduced risk of type 2 diabetes was investigated in prospective cohorts in the U.S. and Iran, but the findings were inconsistent.

Moderate Methodological Quality Studies

The moderate methodological quality studies consisted of a total of 19 publications involving 13 prospective cohorts, two nested case-control, and four cross-sectional studies.

The results were inconsistent among all four cross-sectional studies. One study demonstrated a statistically significant association between yogurt intake and reduced HbA1c, but not yogurt intake and fasting blood glucose (Drehmer et al., 2015). Another study demonstrated a statistically significant association between yogurt intake and reduced risk of type 2 diabetes among women, but not among men (Liang et al., 2017). In Eussen et al., (2016), yogurt intake was statistically significantly associated with reduced risk of newly diagnosed type 2 diabetes when analyzed in a continuous scale, but not when evaluated per tertile of yogurt intake; however, the opposite was true when the outcome was impaired blood glucose, where yogurt intake was statistically significantly associated with reduced risk of type 2 diabetes when analyzed per tertile of intake, but not when analyzed in a continuous scale. Lastly, Brouwer-Brolsma et al., (2018), investigating the various types of yogurts based on fat content, observed that intake of full-fat yogurt was statistically significantly associated with a higher risk of

prediabetes when comparing the highest (14 g median intake) versus the lowest tertile of intake, but when the data was analyzed on a continuous scale of 150 gram-serving, there was no statistically significant association between full-fat yogurt intake and reduced risk of type 2 diabetes. No statistically significant associations were observed between total intake of yogurt or skimmed yogurt with prediabetes or type 2 diabetes. Cross-sectional studies are considered to be less reliable than prospective cohorts and case-control studies and there is a potential to mislead as errors of interpretation are very common.[141] Overall, cross-sectional studies are considered to be a relatively weak method of studying diet-disease associations and the results of these particular cross-sectional studies were highly inconsistent.

Among the remaining 15 publications, 8 prospective cohorts and 2 nested case-control studies evaluated incidence of type 2 diabetes, and 6 prospective cohorts evaluated surrogate endpoints of type 2 diabetes.[142]

Regarding the studies that evaluated the incidence of type 2 diabetes, only 4 out of 10 studies—one nested-case control study from the U.K. and three prospective cohorts (one from U.S. and two from Korea)—showed a statistically significant association between yogurt intake and reduced risk of type 2 diabetes. Among the three prospective cohorts, two were very large cohorts: the WHI-OS from the U.S. involving 82,000 post-menopausal women followed up for 8 years and the Ansung-Ansan cohort from Korea including around 53,000 individuals followed up for over 4 years (Margolis et al., 2011, Zhang et al., 2022). The results from the Ansung-Ansan prospective cohort from Korea showed a statistically significant association for men, but not for women. The third prospective cohort, also from Korea, followed up with 8,000 individuals for 7 years (Jeon et al., 2019). The prospective cohort of post-menopausal women from the U.S. found a statistically significant association with low-fat and non-fat yogurt and reduced risk of incidence of type 2 diabetes, whereas the other studies showing an association investigated the effect of yogurt in general. Overall, the observational studies that showed an association had doses that ranged from an average of 45 to 128 grams per day, whereas studies that did not show an association ranged from an average of 60 to 276 grams per day. Therefore, there was no consistency in the findings regarding differences in gender, sample size, or dose.

Six observational studies evaluated the intake of yogurt and validated surrogate endpoints of type 2 diabetes. There was no statistically significant association between yogurt intake or change in yogurt intake and reduced risk of type 2 diabetes among the studies that evaluated the validated surrogate endpoints of type 2 diabetes, which included prediabetes, HbA1c levels, and high fasting blood glucose alone or as an individual component of metabolic syndrome.

Summary

Based on the findings of these 28 observational studies, FDA concludes that there is some credible evidence supporting a relationship between yogurt intake and reduced risk of type 2 diabetes. As noted in the petition, the credible scientific evidence found a statistically significant association between risk reduction of type 2 diabetes and yogurt as a food, rather than any single

[141] See, *supra*, note 4.

[142] One publication, Hruby et al. 2017, reported on both the incidence and a validated surrogate endpoint of type 2 diabetes.

nutrient or compound in yogurt, and irrespective of fat or sugar content. However, this evidence is based exclusively on observational studies which, despite controlling for relevant covariates, cannot exclude residual confounding due to unknown or unmeasured confounders. Consequently, observational studies measure associations instead of a cause-and-effect relationship between a substance and disease. Furthermore, the study findings were inconsistent. Most of the statistically significant associations between yogurt intake and reduced risk of type 2 diabetes were observed among the high methodological quality studies, however, most of the moderate quality studies did not observe a statistically significant association. For these reasons, FDA concludes that there is some credible evidence for a relationship between yogurt intake and reduced risk of type 2 diabetes, but this evidence is limited.

The petition proposed 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." As discussed in Section IV.A., based on the credible evidence supporting the relationship between yogurt and reduced risk of type 2 diabetes, FDA considers 2 cups (3 servings) per week of yogurt to be the minimum amount for a qualified health claim for the relationship between yogurt consumption and reduced risk of type 2 diabetes.

Based on the FDA's review of the strength of the total body of scientific evidence for the proposed claims, the agency has determined that qualifying language should be included to convey the limits on the strength of scientific evidence supporting the relationship. FDA thus intends to consider the exercise of enforcement discretion for a qualified health claim about yogurt and risk reduction of type 2 diabetes on the label or in the labeling of qualified products that include a truthful and non-misleading description of the strength of the body of scientific evidence, *i.e.*, "limited." Such a description is truthful and not misleading because, while there is some credible evidence for the claimed relationship, this evidence is limited.

Based on the above, FDA concludes that there is limited evidence for a relationship between yogurt and risk reduction of type 2 diabetes.

IV. Other Enforcement Discretion Factors

A qualified health claim on the label or in the labeling of a yogurt about consumption of yogurt and reduced risk of type 2 diabetes, for which FDA intends to consider the exercise of its enforcement discretion, is required to meet all applicable statutory and regulatory requirements under the Act, with the exception of the requirement that a health claim meet the significant scientific agreement standard and the requirement that the claim be made in accordance with an authorizing regulation.

Other exceptions to the general requirements for qualified health claims are discussed below, as well as enforcement discretion factors specific to qualified health claims about consumption of yogurt and reduced risk of type 2 diabetes.

A. Qualifying Level of Yogurt to Achieve the Claimed Effect

The general requirements for health claims provide that, if the claim is about the effects of consuming the substance at other than decreased dietary levels, the level of the substance must be sufficiently high and in an appropriate form to justify the claim. Where no definition for "high" has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect (21 CFR 101.14(d)(2)(vii)).

The agency considered the six observational studies that were determined to be of a high methodological quality to establish the minimum amount of yogurt to be considered as a factor in the exercise of its enforcement discretion for a qualified health claim about yogurt and reduced risk of type 2 diabetes (Choi et al., 2005; Liu et al., 2006; Chen et al., 2014; Dias-Lopez et al., 2016; Guash-Ferré et al., 2017; Babio et al., 2015). Three out of the six observational studies (Choi et al., 2005; Liu et al. 2006; Chen et al., 2014) evaluated data from four large prospective cohorts in the U.S., and the remaining three studies (Diáz-López et al., 2016; Guash-Ferré et al., 2017; Babio et al., 2015) analyzed data from a prospective cohort conducted in Spain. Data analysis from two U.S. prospective cohort (HPFS and NHS II) did not show a positive association (Choi et al., 2005 and Chen et al., 2014). Therefore, the lowest amount necessary to achieve the relevant benefits was based on two large U.S. prospective cohorts (NHS and WHS) and one prospective cohort (PREDIMED) from Spain. In the two U.S. prospective cohorts (Liu et al., 2006 and Chen et al., 2014), 2 servings per week of yogurt was reported to have a statistically significant association on reducing the risk of type 2 diabetes. In the FFQs that were administered, each serving was equivalent to one cup of yogurt (Salvini et al. 1989, Feskanich et al. 1993). Therefore, 2 servings per week (based on the scientific evidence) was translated into 2 cups of yogurt per week for a practical measure and consumer understanding. However, the recommended amount customarily consumed (RACC) for yogurt is 2/3 cup, and thus, 2 cups is equivalent to 3 servings. As a result, the agency considers the reported 2 cups per week (3 servings per week) of yogurt to be the minimum amount for a qualified health claim for the relationship between yogurt consumption and reduced risk of type 2 diabetes.

B. Disqualifying Nutrient Levels

Under the general requirements for health claims (21 CFR 101.14(e)(3)), a food may not bear a health claim if that food exceeds any of the disqualifying nutrient levels for total fat, saturated fat, cholesterol, or sodium established in § 101.14(a)(4), unless FDA establishes an alternative level. Section 101.14(e)(3) applies to all health claims regardless of types of diseases and health-related conditions. The disqualifying nutrient levels vary for individual foods, meal products, and main dishes. Disqualifying total fat levels for individual foods are 13 g per RACC and per label serving size, and for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying saturated fat levels for individual foods are 4 g per RACC and per label serving size, and for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying cholesterol levels for individual foods are 60 mg per RACC and per label serving size, and for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying sodium levels for individual foods are 480 mg per RACC and per label serving size, and for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g.

The general requirements for health claims also provide for FDA to authorize a health claim for a food despite the fact that a nutrient in the food exceeds the disqualifying level, if FDA finds that such a claim will assist consumers in maintaining healthy dietary practices (21 CFR 101.14(e)(3)). In such cases, a disclosure statement that complies with 21 CFR 101.13(h), highlighting the nutrient that exceeds the disqualifying level, would apply.

FDA intends to consider the exercise of enforcement discretion for yogurts bearing the claim that do not exceed the disqualifying nutrient levels. The agency finds that there is no basis for considering the exercise of enforcement discretion for yogurts bearing the claim that exceed the disqualifying nutrient levels because doing so would not assist consumers in maintaining healthy dietary practices. Note that FDA expects that many yogurts do not exceed the disqualifying levels in 21 CFR 101.14(a)(4). For example, the vast majority of yogurts do not exceed the cholesterol disqualifying level of 60 mg of cholesterol per RACC and per labeled serving, based on yogurts analyzed in USDA's FoodData Central. In addition, yogurts generally do not contain sodium at levels that would exceed the disqualifying level for sodium of 480 mg per RACC and per label serving size. However, a yogurt could feasibly be formulated to exceed the sodium disqualifying level (*e.g.*, salted caramel yogurt).

Furthermore, FDA expects that the vast majority of yogurts do not exceed the total fat disqualifying level of 13 g per RACC and per label serving size. Indeed, according to data analyzed for selected yogurts from FoodData Central, the yogurt with the highest fat content contained 8 g per RACC and per label serving size. Similarly, with a few exceptions, FDA expects that many yogurts do not exceed the saturated fat disqualifying level of 4 g per RACC and per labeled serving. However, the *Dietary Guidelines for Americans, 2020-2025* recommends limiting foods higher in saturated fat, and in particular, recommend that most dairy and dairy alternative choices, such as yogurt, be fat-free or low-fat, since excess intake of this nutrient is associated with chronic disease risk. Additionally, there are many fat-free and low and reduced fat yogurt options that are available to consumers.

FDA concludes that it would not assist consumers in maintaining healthy dietary practices if the claim were made on yogurts exceeding the disqualifying nutrient levels for total fat, saturated fat, cholesterol, or sodium. Therefore, FDA intends to consider the exercise of enforcement discretion for the use of the claim on yogurts that do not exceed the disqualifying nutrient levels for total fat, saturated fat, cholesterol, and sodium in accordance with 21 CFR 101.14(a)(4).

Added Sugars

Currently, FDA has not set a disqualifying nutrient level for added sugars and therefore it is not listed in 21 CFR 101.14(a)(4).[143] Moreover, as discussed above and noted in the petition, the credible scientific evidence found a statistically significant association between reduced risk of type 2 diabetes and yogurt as a food, irrespective of fat or sugar content. As such, the level of added sugars is not an enforcement discretion factor for a qualified health claim regarding the relationship between yogurt and type 2 diabetes at this time. However, we are concerned that the

[143] We plan to address, as appropriate and as time and resources permit, the impact of the changes in nutrient declarations in the May 2016 final rule on other regulations, such as 21 CFR 101.14(a)(4) and (e)(6), in other rulemaking actions (see 81 Fed. Reg. 33742 at 33751).

use of a qualified health claim on yogurts that contain a significant amount of added sugars could contribute empty calories to the diet. The *Dietary Guidelines for Americans, 2020-2025* recommend limiting added sugars to less than 10 percent of total calories and note that added sugars account on average for almost 270 calories, or more than 13 percent of total calories per day in the U.S. population.

We note that, based on nutrition science, the agency has taken several steps in recent years to assist consumers in identifying the amount of added sugars in foods, including requiring a declaration of both the gram amount and the percent Daily Value for added sugars on the Nutrition Facts label ("Food Labeling: Revision of the Nutrition and Supplement Facts Labels" 81 Fed. Reg. 33742; May 27, 2016). FDA also hosted a public meeting, in collaboration with other agencies in the U.S. Department of Health and Human Services and the U.S. Department of Agriculture, on strategies to reduce added sugars consumption in the U.S. Consequently, while there is currently no disqualifying level for added sugars, given that Americans are exceeding recommended limits on added sugars, and some yogurts on the market are high in added sugars, FDA encourages careful consideration of whether to use the claim on products that could contribute significant amounts of added sugars to the diet.

C. 10 Percent Minimum Nutrient Content Requirement

Under the general requirements for health claims, a conventional food may not bear a health claim unless it contains, prior to any nutrient addition, at least 10 percent of the Daily Value (DV) of certain nutrients per RACC (21 CFR 101.14(e)(6)). The purpose of this requirement is to prevent the use of health claims on foods with minimal nutritional value. The specific nutrients listed in 21 CFR 101.14(e)(6) are vitamin A, vitamin C, iron, calcium, protein, and fiber. We note that the final rule entitled "Food Labeling: Revision of the Nutrition and Supplement Facts Labels" (81 Fed. Reg. 33742; May 27, 2016) changed the mandatory declaration of vitamins and minerals as a percent of the RDI in 21 CFR 101.9(c)(8) from vitamin A, vitamin C, calcium, and iron to vitamin D, calcium, iron, and potassium. Therefore, vitamin D and potassium are now nutrients of public health significance.

FDA expects that all yogurts contain more than 5 g of protein per RACC (10 percent of the RDI for protein which is 50 g), and most of the yogurts that are fortified with calcium or vitamin D would also contain more than 10 percent of the RDI for calcium (1,300 mg) and the RDI for Vitamin D (20 µg). Therefore, for the purposes of this qualified health claim, the agency intends to consider the exercise its enforcement discretion with respect to 21 CFR 101.14(e)(6) for the qualified health claim to be used on yogurt food labels or labeling where the food contains 10 percent or more of the DV per RACC for any of the nutrients listed in 21 CFR 101.14(e)(6). Based on the reasoning provided above, FDA will also consider the exercise of its enforcement discretion if the food contains 10 percent or more of the DV per RACC for vitamin D or potassium.

V. Conclusions

Based on FDA's consideration of the scientific evidence and other information submitted with your petition, and other pertinent scientific evidence and information, FDA concludes that the current scientific evidence is appropriate for consideration of qualified health claims for consumption of yogurt and reduced risk of type 2 diabetes, provided that the qualified health claims are appropriately worded to avoid misleading consumers.

The petition proposed the following claims to be used on the labels or in the labeling of conventional foods:

> "Eating yogurt regularly may reduce the risk of type 2 diabetes. FDA has concluded there is limited information supporting this claim."
>
> "Eating yogurt regularly may reduce the risk of type 2 diabetes according to limited scientific evidence."
>
> The petition also proposed 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."

Qualifying language will inform consumers about the level of science supporting the claim and prevent them from being misled about the strength of the supporting evidence. As discussed in Section III of this letter, based on 28 observational studies from which conclusions could be drawn, the evidence suggesting that consumption of yogurt may reduce the risk of type 2 diabetes is limited.

Additionally, as discussed in Section IV.A., FDA considers 2 cups (3 servings) per week to be the minimum amount necessary to achieve the claimed effect of yogurt on the reduced risk of type 2 diabetes. This is based on data from two U.S. prospective cohorts, evaluated in high methodological quality studies, that reported that consumption of 2 servings per week of yogurt had a statistically significant association with reducing the risk of type 2 diabetes. In these cohorts, one cup was equivalent to one serving. However, the RACC for yogurt is 2/3 cup, and thus, 2 cups is equivalent to 3 servings. While the petitioner proposed including a recommended intake level as an optional phrase in the qualified health claims, limiting our consideration of enforcement discretion to claims that recommend consumption of yogurt in amounts that have been observed to reduce the risk of type 2 diabetes in some well-conducted scientific studies will ensure that consumers do not consume so little of the substance that it would be very unlikely to provide any health benefit. Therefore, the claims for which FDA intends to consider enforcement discretion must include the phrase "at least 2 cups (3 servings) per week" after the word "regularly."

Thus, FDA intends to consider exercising its enforcement discretion for the following qualified health claims:

> "Eating yogurt regularly, at least 2 cups (3 servings) per week, may reduce the risk of type 2 diabetes. FDA has concluded that there is limited information supporting this claim."

> "Eating yogurt regularly, at least 2 cups (3 servings) per week, may reduce the risk of type 2 diabetes according to limited scientific evidence."

FDA intends to consider exercising enforcement discretion for the above qualified health claims for when all other factors for enforcement discretion identified in Section IV of this letter are met.

Please note that scientific information is subject to change, as are consumer consumption patterns. In the event that new information is submitted to the agency, FDA intends to evaluate the new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support significant scientific agreement, that will no longer support the use of the above qualified health claims, or that may raise safety concerns about the substances that are the subject of the claims.

Sincerely,

/S/

Claudine Kavanaugh, PhD, MPH, RD
Director
Office of Nutrition
and Food Labeling
Center for Food Safety
and Applied Nutrition

REFERENCES

Abreu, S., Moreira, P., Moreira, C., Mota, J., Moreira-Silva, I., Santos, P. C., & Santos, R. (2014). Intake of milk, but not total dairy, yogurt, or cheese, is negatively associated with the clustering of cardiometabolic risk factors in adolescents. *Nutr Res, 34*(1), 48-57.

Alberti, K.G.M.M., Eckel, R.H., Grundy, S.M., Zimmet, P.Z., Cleeman, J.I., Donato, K.A., … (2009). Harmonizing the Metabolic Syndrome—A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation, 120*, 1640-1645.

Ali, H. I., Jarrar, A. H., El Sadig, M., & K, B. Y. (2013). Diet and carbohydrate food knowledge of multi-ethnic women: a comparative analysis of pregnant women with and without Gestational Diabetes Mellitus. *PLoS One, 8*(9), e73486.

Alvarez-Bueno, C., Cavero-Redondo, I., Martinez-Vizcaino, V., Sotos-Prieto, M., Ruiz, J. R., & Gil, A. (2019). Effects of Milk and Dairy Product Consumption on Type 2 Diabetes: Overview of Systematic Reviews and Meta-Analyses. *Adv Nutr, 10*(suppl_2), S154-S163.

American Diabetes Association (2017). Standards of Medical Care in Diabetes. *Diabetes Care, 40*.

Aquino, E.M.L., Araujo, M.J., Almeida, M.C.C., Conceição, P., Andrade C.R., Cade, N.V., Carvalho, M.S., Figueiredo, R.C., Fonseca, M.J.M., Giatti, L., Menezes, G.M.S., Nunes, M.A., Souza, A.G., Vasconcellos-Silva, P.R., Vigo, A. (2013). Participants recruitment in ELSA-Brasil (Brazilian Longitudinal Study for Adult Health). *Rev Saúde Pública, 47* (Supl 2).

Asemi, Z., Samimi, M., Tabassi, Z., Naghibi Rad, M., Rahimi Foroushani, A., Khorammian, H., & Esmaillzadeh, A. (2013). Effect of daily consumption of probiotic yoghurt on insulin resistance in pregnant women: a randomized controlled trial. *Eur J Clin Nutr, 67*(1), 71-74.

Aune, D., Norat, T., Romundstad, P., & Vatten, L. J. (2013). Dairy products and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies. *Am J Clin Nutr, 98*(4), 1066-1083.

Awwad, S. F., Abdalla, A., Howarth, F. C., Stojanovska, L., Kamal-Eldin, A., & Ayyash, M. M. (2022). Invited review: Potential effects of short- and long-term intake of fermented dairy products on prevention and control of type 2 diabetes mellitus. *J Dairy Sci, 105*(6), 4722-4733.

Azizi, F., Zadeh-Vakili, A., & Takyar, M. (2018). Review of Rationale, Design, and Initial Findings: Tehran Lipid and Glucose Study. *Int J Endocrinol Metab, 16*(4) Suppl:e84777.

Babio, N., Becerra-Tomas, N., Martinez-Gonzalez, M. A., Corella, D., Estruch, R., Ros, E., . . . Investigators, P. (2015). Consumption of Yogurt, Low-Fat Milk, and Other Low-Fat Dairy Products Is Associated with Lower Risk of Metabolic Syndrome Incidence in an Elderly Mediterranean Population. *J Nutr, 145*(10), 2308-2316.

Berthold, H. K., Schulte, D. M., Lapointe, J. F., Lemieux, P., Krone, W., & Gouni-Berthold, I. (2011). The whey fermentation product malleable protein matrix decreases triglyceride concentrations in subjects with hypercholesterolemia: a randomized placebo-controlled trial. *J Dairy Sci, 94*(2), 589-601.

Beydoun, M. A., Gary, T. L., Caballero, B. H., Lawrence, R. S., Cheskin, L. J., & Wang, Y. (2008). Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. *Am J Clin Nutr, 87*(6), 1914-1925.

Brouwer-Brolsma, E. M., Sluik, D., Singh-Povel, C. M., & Feskens, E. J. M. (2018). Dairy product consumption is associated with pre-diabetes and newly diagnosed type 2 diabetes in the Lifelines Cohort Study. *Br J Nutr, 119*(4), 442-455.

Brouwer-Brolsma, E. M., van Woudenbergh, G. J., Oude Elferink, S. J., Singh-Povel, C. M., Hofman, A., Dehghan, A., . . . Feskens, E. J. (2016). Intake of different types of dairy and its prospective association with risk of type 2 diabetes: The Rotterdam Study. *Nutr Metab Cardiovasc Dis, 26*(11), 987-995.

Brouwer-Brolsma, E.M., Perenboom C., Sluik, D., van de Viel, A., Geelen, A., Feskens, E. J., de Vries, J.H.M. (2022). Development and external validation of the "Flower-FFQ': a FFQ designed for the Lifelines Cohort Study. *Publ Health Nutr, 25(2),* 225-236.

Brunner, E., Stallone, D., Juneja, M., Bingham, S., & Marmot, M. (2001). Dietary assessment in Whitehall II: comparison of 7 d diet diary and food-frequency questionnaire and validity against biomarkers. *Br J Nutr, 86*(3), 405-414.

Burton, K. J., Rosikiewicz, M., Pimentel, G., Butikofer, U., von Ah, U., Voirol, M. J., . . . Vionnet, N. (2017). Probiotic yogurt and acidified milk similarly reduce postprandial inflammation and both alter the gut microbiota of healthy, young men. *Br J Nutr, 117*(9), 1312-1322.

Buziau, A. M., Soedamah-Muthu, S. S., Geleijnse, J. M., & Mishra, G. D. (2019). Total Fermented Dairy Food Intake Is Inversely Associated with Cardiovascular Disease Risk in Women. *J Nutr, 149*(10), 1797-1804.

Chang, B. J., Park, S. U., Jang, Y. S., Ko, S. H., Joo, N. M., Kim, S. I., . . . Chang, D. K. (2011). Effect of functional yogurt NY-YP901 in improving the trait of metabolic syndrome. *Eur J Clin Nutr, 65*(11), 1250-1255.

Chandan, R. C., Gandhi, A., & Shah, N. P. (2017). Yogurt: Historical background, health benefits, and global trade. In *Yogurt in health and disease prevention* (pp. 3-29). Academic Press.

Chen, M., Pan, A., Malik, V. S., & Hu, F. B. (2012). Effects of dairy intake on body weight and fat: a meta-analysis of randomized controlled trials. *Am J Clin Nutr, 96*(4), 735-747.

Chen, M., Sun, Q., Giovannucci, E., Mozaffarian, D., Manson, J. E., Willett, W. C., & Hu, F. B. (2014). Dairy consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. *BMC Med, 12*, 215.

Chlup, R., Jelenova, D., Kudlova, P., Chlupova, K., Bartek, J., Zapletalova, J., . . . Chlupova, L. (2006). Continuous glucose monitoring -- a novel approach to the determination of the glycaemic index of foods (DEGIF 1) -- determination of the glycaemic index of foods by means of the CGMS. *Exp Clin Endocrinol Diabetes, 114*(2), 68-74.

Choi, H. K., Willett, W. C., Stampfer, M. J., Rimm, E., & Hu, F. B. (2005). Dairy consumption and risk of type 2 diabetes mellitus in men: a prospective study. *Arch Intern Med, 165*(9), 997-1003.

Cormier, H., Thifault, E., Garneau, V., Tremblay, A., Drapeau, V., Perusse, L., & Vohl, M. C. (2016). Association between yogurt consumption, dietary patterns, and cardio-metabolic risk factors. *Eur J Nutr, 55*(2), 577-587.

Crichton, G. E., & Alkerwi, A. (2014). Whole-fat dairy food intake is inversely associated with obesity prevalence: findings from the Observation of Cardiovascular Risk Factors in Luxembourg study. *Nutr Res, 34*(11), 936-943.

Diaz-Lopez, A., Bullo, M., Martinez-Gonzalez, M. A., Corella, D., Estruch, R., Fito, M., . . . Salas-Salvado, J. (2016). Dairy product consumption and risk of type 2 diabetes in an elderly Spanish Mediterranean population at high cardiovascular risk. *Eur J Nutr, 55*(1), 349-360.

Dougkas, A., Minihane, A. M., Givens, D. I., Reynolds, C. K., & Yaqoob, P. (2012). Differential effects of dairy snacks on appetite, but not overall energy intake. *Br J Nutr, 108*(12), 2274-2285.

Drehmer, M., Pereira, M. A., Schmidt, M. I., Del Carmen, B. M. M., Alvim, S., Lotufo, P. A., & Duncan, B. B. (2015). Associations of dairy intake with glycemia and insulinemia, independent of obesity, in Brazilian adults: the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Am J Clin Nutr, 101*(4), 775-782.

Drouin-Chartier, J. P., Brassard, D., Tessier-Grenier, M., Cote, J. A., Labonte, M. E., Desroches, S., . . . Lamarche, B. (2016). Systematic Review of the Association between Dairy Product Consumption and Risk of Cardiovascular-Related Clinical Outcomes. *Adv Nutr, 7*(6), 1026-1040.

Drouin-Chartier, J. P., Li, Y., Ardisson Korat, A. V., Ding, M., Lamarche, B., Manson, J. E., . . . Hu, F. B. (2019). Changes in dairy product consumption and risk of type 2 diabetes: results from 3 large prospective cohorts of US men and women. *Am J Clin Nutr, 110*(5), 1201-1212.

Ejtahed, H. S., Mohtadi-Nia, J., Homayouni-Rad, A., Niafar, M., Asghari-Jafarabadi, M., & Mofid, V. (2012). Probiotic yogurt improves antioxidant status in type 2 diabetic patients. *Nutrition, 28*(5), 539-543.

Ejtahed, H. S., Mohtadi-Nia, J., Homayouni-Rad, A., Niafar, M., Asghari-Jafarabadi, M., Mofid, V., & Akbarian-Moghari, A. (2011). Effect of probiotic yogurt containing Lactobacillus acidophilus and Bifidobacterium lactis on lipid profile in individuals with type 2 diabetes mellitus. *J Dairy Sci, 94*(7), 3288-3294.

El Khoury, D., Brown, P., Smith, G., Berengut, S., Panahi, S., Kubant, R., & Anderson, G. H. (2014). Increasing the protein to carbohydrate ratio in yogurts consumed as a snack reduces post-consumption glycemia independent of insulin. *Clin Nutr, 33*(1), 29-38.

Ericson, U., Hellstrand, S., Brunkwall, L., Schulz, C. A., Sonestedt, E., Wallstrom, P., . . . Orho-Melander, M. (2015). Food sources of fat may clarify the inconsistent role of dietary fat intake for incidence of type 2 diabetes. *Am J Clin Nutr, 101*(5), 1065-1080.

Esmaillzadeh, A., Zakizadeh, E., Faghihimani, E., Gohari, M., & Jazayeri, S. (2015). The effect of purslane seeds on glycemic status and lipid profiles of persons with type 2 diabetes: A randomized controlled cross-over clinical trial. *J Res Med Sci, 20*(1), 47-53.

Eussen, S. J., van Dongen, M. C., Wijckmans, N., den Biggelaar, L., Oude Elferink, S. J., Singh-Povel, C. M., . . . Dagnelie, P. C. (2016). Consumption of dairy foods in relation to impaired glucose metabolism and type 2 diabetes mellitus: the Maastricht Study. *Br J Nutr, 115*(8), 1453-1461.

Feeney, E. L., O'Sullivan, A., Nugent, A. P., McNulty, B., Walton, J., Flynn, A., & Gibney, E. R. (2017). Patterns of dairy food intake, body composition and markers of metabolic health in Ireland: results from the National Adult Nutrition Survey. *Nutr Diabetes, 7*(2), e243.

Feng, Y., Zhao, Y., Liu, J., Huang, Z., Yang, X., Qin, P., . . . Zhang, M. (2022). Consumption of Dairy Products and the Risk of Overweight or Obesity, Hypertension, and Type 2 Diabetes Mellitus: A Dose-Response Meta-Analysis and Systematic Review of Cohort Studies. *Adv Nutr, 13*(6), 2165-2179.

Feskanich, D., Rimm, E.B., Giovannucci, E.L., Colditz, G.A., Stampfer, M.J., Litin, L.B., Willett, W. (1993). Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. *J Am Diet Assoc,* 93(7) 790-796.

Fisberg, M. & Machado, R. (2015). History of yogurt and current patterns of consumption. *Nutr. Rev*, *73* (1) Suppl., 4-7.

Frary, C. D., Johnson, R. K., & Wang, M. Q. (2004). Children and adolescents' choices of foods and beverages high in added sugars are associated with intakes of key nutrients and food groups. *J Adolesc Health, 34*(1), 56-63.

Fumeron, F., Lamri, A., Emery, N., Bellili, N., Jaziri, R., Porchay-Balderelli, I., . . . Group, D. S. (2011). Dairy products and the metabolic syndrome in a prospective study, DESIR. *J Am Coll Nutr, 30*(5 Suppl 1), 454S-463S.

Gao, D., Ning, N., Wang, C., Wang, Y., Li, Q., Meng, Z., . . . Li, Q. (2013). Dairy products consumption and risk of type 2 diabetes: systematic review and dose-response meta-analysis. *PLoS One, 8*(9), e73965.

Gibson, S. A. (2007). Dietary sugars intake and micronutrient adequacy: a systematic review of the evidence. *Nutr Res Rev, 20*(2), 121-131.

Gijsbers, L., Ding, E. L., Malik, V. S., de Goede, J., Geleijnse, J. M., & Soedamah-Muthu, S. S. (2016). Consumption of dairy foods and diabetes incidence: a dose-response meta-analysis of observational studies. *Am J Clin Nutr, 103*(4), 1111-1124.

Grantham, N. M., Magliano, D. J., Hodge, A., Jowett, J., Meikle, P., & Shaw, J. E. (2013). The association between dairy food intake and the incidence of diabetes in Australia: the Australian Diabetes Obesity and Lifestyle Study (AusDiab). *Public Health Nutr, 16*(2), 339-345.

Guasch-Ferre, M., Becerra-Tomas, N., Ruiz-Canela, M., Corella, D., Schroder, H., Estruch, R., . . . Salas-Salvado, J. (2017). Total and subtypes of dietary fat intake and risk of type 2 diabetes mellitus in the Prevencion con Dieta Mediterranea (PREDIMED) study. *Am J Clin Nutr, 105*(3), 723-735.

Heravifard, S., Neyestani, T. R., Nikooyeh, B., Alavi-Majd, H., Houshiarrad, A., Kalayi, A., . . . Gharavi, A. (2013). Regular consumption of both vitamin D- and calcium- and vitamin D-fortified yogurt drink is equally accompanied by lowered blood lipoprotein (a) and elevated apoprotein A1 in subjects with type 2 diabetes: a randomized clinical trial. *J Am Coll Nutr, 32*(1), 26-30.

Hobbs, D. A., Givens, D. I., & Lovegrove, J. A. (2018). Yogurt consumption is associated with higher nutrient intake, diet quality and favourable metabolic profile in children: a cross-sectional analysis using data from years 1-4 of the National diet and Nutrition Survey, UK. *Eur J Nutr*.

Hodge, A., Patterson, A. J., Brown, W. J., Ireland, P., & Giles, G. (2000). The Anti Cancer Council of Victoria FFQ: relative validity of nutrient intakes compared with weighed food records in young to middle-aged women in a study of iron supplementation. *Aust N Z J Public Health, 24*(6), 576-583.

Hove, K. D., Brons, C., Faerch, K., Lund, S. S., Rossing, P., & Vaag, A. (2015). Effects of 12 weeks of treatment with fermented milk on blood pressure, glucose metabolism and markers of cardiovascular risk in patients with type 2 diabetes: a randomised double-blind placebo-controlled study. *Eur J Endocrinol, 172*(1), 11-20.

Hruby, A., Ma, J., Rogers, G., Meigs, J. B., & Jacques, P. F. (2017). Associations of Dairy Intake with Incident Prediabetes or Diabetes in Middle-Aged Adults Vary by Both Dairy Type and Glycemic Status. *J Nutr, 147*(9), 1764-1775.

Hulston, C. J., Churnside, A. A., & Venables, M. C. (2015). Probiotic supplementation prevents high-fat, overfeeding-induced insulin resistance in human subjects. *Br J Nutr, 113*(4), 596-602.

Hutt, P., Songisepp, E., Ratsep, M., Mahlapuu, R., Kilk, K., & Mikelsaar, M. (2015). Impact of probiotic Lactobacillus plantarum TENSIA in different dairy products on anthropometric and blood biochemical indices of healthy adults. *Benef Microbes, 6*(3), 233-243.

Ibsen, D. B., Laursen, A. S. D., Lauritzen, L., Tjonneland, A., Overvad, K., & Jakobsen, M. U. (2017). Substitutions between dairy product subgroups and risk of type 2 diabetes: the Danish Diet, Cancer and Health cohort. *Br J Nutr, 118*(11), 989-997.

Ibsen, D. B., Overvad, K., Laursen, A. S. D., Halkjaer, J., Tjonneland, A., Kilpelainen, T. O., . . . Jakobsen, M. U. (2021). Changes in intake of dairy product subgroups and risk of type 2 diabetes: modelling specified food substitutions in the Danish Diet, Cancer and Health cohort. *Eur J Nutr, 60*(6), 3449-3459.

Ikram, M.A., Brusselle G, Ghanbari, M., Goedegebure, A., Ikram, M.K., Kavousi, M., Kieboom, B.C.T., Klaver, C.C.W., de Knegt, R.J., Luik, A.I., Nijsten, T.E.C., Peeters, R.P., van Rooij, F.J.A., Stricker, B.H., Uitterlinden, A.G., Vernooij, M.W., Voortman, T. (2020). Objectives, design and main findings until 2020 from Rotterdam Study. *Eur J Epidemiol* 35:483-517.

Institute of Medicine (IOM), National Academy of Sciences, 2005. Dietary Supplements: A Framework for Evaluating Safety. Chapter 7, Categories of Scientific Evidence – *In Vitro* Data. The National Academies Press, Washington, D.C.

Ivey, K. L., Hodgson, J. M., Kerr, D. A., Lewis, J. R., Thompson, P. L., & Prince, R. L. (2014). The effects of probiotic bacteria on glycaemic control in overweight men and women: a randomised controlled trial. *Eur J Clin Nutr, 68*(4), 447-452.

Jafari, T., Faghihimani, E., Feizi, A., Iraj, B., Javanmard, S. H., Esmaillzadeh, A., . . . Askari, G. (2016). Effects of vitamin D-fortified low fat yogurt on glycemic status, anthropometric indexes, inflammation, and bone turnover in diabetic postmenopausal women: A randomised controlled clinical trial. *Clin Nutr, 35*(1), 67-76.

Jeon, J., Jang, J., & Park, K. (2018). Effects of Consuming Calcium-Rich Foods on the Incidence of Type 2 Diabetes Mellitus. *Nutrients, 11*(1).

Johnson, R. K., Appel, L. J., Brands, M., Howard, B. V., Lefevre, M., Lustig, R. H., . . . Prevention. (2009). Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. *Circulation, 120*(11), 1011-1020.

Kim, D., & Kim, J. (2017). Dairy consumption is associated with a lower incidence of the metabolic syndrome in middle-aged and older Korean adults: the Korean Genome and Epidemiology Study (KoGES). *Br J Nutr, 117*(1), 148-160.

Kim, J. (2013). Dairy food consumption is inversely associated with the risk of the metabolic syndrome in Korean adults. *J Hum Nutr Diet, 26 Suppl 1*, 171-179.

Kirii, K., Mizoue, T., Iso, H., Takahashi, Y., Kato, M., Inoue, M., . . . Japan Public Health Center-based Prospective Study, G. (2009). Calcium, vitamin D and dairy intake in relation to type 2 diabetes risk in a Japanese cohort. *Diabetologia, 52*(12), 2542-2550.

Klipstein-Grobusch, K., den Breeijen, J. H., Goldbohm, R. A., Geleijnse, J. M., Hofman, A., Grobbee, D. E., & Witteman, J. C. (1998). Dietary assessment in the elderly: validation of a semiquantitative food frequency questionnaire. *Eur J Clin Nutr, 52*(8), 588-596.

Liang, J., Zhang, Y., Xue, A., Sun, J., Song, X., Xue, B., . . . Ning, F. (2017). Association between fruit, vegetable, seafood, and dairy intake and a reduction in the prevalence of type 2 diabetes in Qingdao, China. *Asia Pac J Clin Nutr, 26*(2), 255-261.

Liu, S., Choi, H. K., Ford, E., Song, Y., Klevak, A., Buring, J. E., & Manson, J. E. (2006). A prospective study of dairy intake and the risk of type 2 diabetes in women. *Diabetes Care, 29*(7), 1579-1584.

Madjd, A., Taylor, M. A., Mousavi, N., Delavari, A., Malekzadeh, R., Macdonald, I. A., & Farshchi, H. R. (2016). Comparison of the effect of daily consumption of probiotic compared with low-fat conventional yogurt on weight loss in healthy obese women following an energy-restricted diet: a randomized controlled trial. *Am J Clin Nutr, 103*(2), 323-329.

Magliano, D. J., Barr, E. L., Zimmet, P. Z., Cameron, A. J., Dunstan, D. W., Colagiuri, S., . . . Shaw, J. E. (2008). Glucose indices, health behaviors, and incidence of diabetes in Australia: the Australian Diabetes, Obesity and Lifestyle Study. *Diabetes Care, 31*(2), 267-272.

Maki, K. C., Nieman, K. M., Schild, A. L., Kaden, V. N., Lawless, A. L., Kelley, K. M., & Rains, T. M. (2015). Sugar-sweetened product consumption alters glucose homeostasis compared with dairy product consumption in men and women at risk of type 2 diabetes mellitus. *J Nutr, 145*(3), 459-466.

Marette, A., & Picard-Deland, E. (2014). Yogurt consumption and impact on health: focus on children and cardiometabolic risk. *Am J Clin Nutr, 99*(5 Suppl), 1243S-1247S.

Margolis, K. L., Wei, F., de Boer, I. H., Howard, B. V., Liu, S., Manson, J. E., . . . Women's Health Initiative, I. (2011). A diet high in low-fat dairy products lowers diabetes risk in postmenopausal women. *J Nutr, 141*(11), 1969-1974.

Martínez-Gonzalez, M. A., Sayon-Orea, C., Ruiz-Canela, M., de la Fuente, C., Gea, A., & Bes-Rastrollo, M. (2014). Yogurt consumption, weight change and risk of overweight/obesity: the SUN cohort study. *Nutr Metab Cardiovasc Dis, 24*(11), 1189-1196.

Martínez-Gonzalez, M. A., Sánchez-Villegas, A., De Irala, J., Marti, A., & Martínez, J.A. (2002). Mediterranean diet and stroke: objectives and design of the SUN cohort project. *Nutr Neurosci., 5*(1), 65-73.

Mena-Sanchez, G., Babio, N., Martinez-Gonzalez, M. A., Corella, D., Schroder, H., Vioque, J., . . . investigators, P.-P. (2018). Fermented dairy products, diet quality, and cardio-metabolic profile of a Mediterranean cohort at high cardiovascular risk. *Nutr Metab Cardiovasc Dis, 28*(10), 1002-1011.

Micha, R., Shulkin, M. L., Penalvo, J. L., Khatibzadeh, S., Singh, G. M., Rao, M., . . . Mozaffarian, D. (2017). Etiologic effects and optimal intakes of foods and nutrients for risk of cardiovascular diseases and diabetes: Systematic reviews and meta-analyses from the Nutrition and Chronic Diseases Expert Group (NutriCoDE). *PLoS One, 12*(4), e0175149.

Mistura, L., D'Addezio, L., Sette, S., Piccinelli, R., & Turrini, A. (2016). Diet quality of Italian yogurt consumers: an application of the probability of adequate nutrient intake score (PANDiet). *Int J Food Sci Nutr, 67*(3), 232-238.

Mitri, J., Mohd Yusof, B. N., Maryniuk, M., Schrager, C., Hamdy, O., & Salsberg, V. (2019). Dairy intake and type 2 diabetes risk factors: A narrative review. *Diabetes Metab Syndr, 13*(5), 2879-2887.

Mohamadshahi, M., Veissi, M., Haidari, F., Shahbazian, H., Kaydani, G. A., & Mohammadi, F. (2014). Effects of probiotic yogurt consumption on inflammatory biomarkers in patients with type 2 diabetes. *Bioimpacts, 4*(2), 83-88.

Moslehi, N., Shab-Bidar, S., Mirmiran, P., Sadeghi, M., & Azizi, F. (2015). Associations between dairy products consumption and risk of type 2 diabetes: Tehran lipid and glucose study. *Int J Food Sci Nutr, 66*(6), 692-699.

Mozaffarian, D., Hao, T., Rimm, E. B., Willett, W. C., & Hu, F. B. (2011). Changes in diet and lifestyle and long-term weight gain in women and men. *N Engl J Med, 364*(25), 2392-2404.

Nabavi, S., Rafraf, M., Somi, M. H., Homayouni-Rad, A., & Asghari-Jafarabadi, M. (2014). Effects of probiotic yogurt consumption on metabolic factors in individuals with nonalcoholic fatty liver disease. *J Dairy Sci, 97*(12), 7386-7393.

Nakamura, T., Hitomi, Y., Yoshida, M., Shirasu, Y., Tsukui, T., & Shimasaki, H. (2002). Effect of yogurt supplemented with brewer's yeast cell wall on levels of blood lipids in normal and hypercholesterolemic adults. *J Oleo Sci, 51*, 323-334.

National Research Council. 2011. Reference Manual on Scientific Evidence: Third Edition. The National Academies Press, Washington, DC, page 220.

Nazare, J. A., de la Perriere, A. B., Bonnet, F., Desage, M., Peyrat, J., Maitrepierre, C., . . . Laville, M. (2007). Daily intake of conjugated linoleic acid-enriched yoghurts: effects on energy metabolism and adipose tissue gene expression in healthy subjects. *Br J Nutr, 97*(2), 273-280.

Neuenschwander, M., Ballon, A., Weber, K. S., Norat, T., Aune, D., Schwingshackl, L., & Schlesinger, S. (2019). Role of diet in type 2 diabetes incidence: umbrella review of meta-analyses of prospective observational studies. *BMJ, 366*, l2368.

Neyestani, T. R., Nikooyeh, B., Kalayi, A., Zahedirad, M., & Shariatzadeh, N. (2015). A Vitamin D-Calcium-Fortified Yogurt Drink Decreased Serum PTH but did not Affect Osteocalcin in Subjects with Type 2 Diabetes. *Int J Vitam Nutr Res, 85*(1-2), 61-69.

Nikooyeh, B., Neyestani, T. R., Farvid, M., Alavi-Majd, H., Houshiarrad, A., Kalayi, A., . . . Zahedirad, M. (2011). Daily consumption of vitamin D- or vitamin D + calcium-fortified yogurt drink improved glycemic control in patients with type 2 diabetes: a randomized clinical trial. *Am J Clin Nutr, 93*(4), 764-771.

Nikooyeh, B., Neyestani, T. R., Tayebinejad, N., Alavi-Majd, H., Shariatzadeh, N., Kalayi, A., . . . Salekzamani, S. (2014). Daily intake of vitamin D- or calcium-vitamin D-fortified Persian yogurt drink (doogh) attenuates diabetes-induced oxidative stress: evidence for antioxidative properties of vitamin D. *J Hum Nutr Diet, 27 Suppl 2*, 276-283.

Niu, K., Kobayashi, Y., Guan, L., Monma, H., Guo, H., Cui, Y., . . . Nagatomi, R. (2013). Low-fat dairy, but not whole-/high-fat dairy, consumption is related with higher serum adiponectin levels in apparently healthy adults. *Eur J Nutr, 52*(2), 771-778.

O'Connor, L. M., Lentjes, M. A., Luben, R. N., Khaw, K. T., Wareham, N. J., & Forouhi, N. G. (2014). Dietary dairy product intake and incident type 2 diabetes: a prospective study using dietary data from a 7-day food diary. *Diabetologia, 57*(5), 909-917.

Ostman, E. M., Liljeberg Elmstahl, H. G., & Bjorck, I. M. (2001). Inconsistency between glycemic and insulinemic responses to regular and fermented milk products. *Am J Clin Nutr, 74*(1), 96-100.

Panagiotakos, D. B., Tzima, N., Pitsavos, C., Chrysohoou, C., Papakonstantinou, E., Zampelas, A., & Stefanadis, C. (2005). The relationship between dietary habits, blood glucose and insulin levels among people without cardiovascular disease and type 2 diabetes; the ATTICA study. *Rev Diabet Stud, 2*(4), 208-215.

Panahi, S., Doyon, C. Y., Despres, J. P., Perusse, L., Vohl, M. C., Drapeau, V., & Tremblay, A. (2018). Yogurt consumption, body composition, and metabolic health in the Quebec Family Study. *Eur J Nutr, 57*(4), 1591-1603.

Panahi, S., Fernandez, M. A., Marette, A., & Tremblay, A. (2017). Yogurt, diet quality and lifestyle factors. *Eur J Clin Nutr, 71*(5), 573-579.

Pasin, G., & Comerford, K. B. (2015). Dairy foods and dairy proteins in the management of type 2 diabetes: a systematic review of the clinical evidence. *Adv Nutr, 6*(3), 245-259.

Patterson, R. E., Kristal, A. R., Tinker, L. F., Carter, R. A., Bolton, M. P., & Agurs-Collins, T. (1999). Measurement characteristics of the Women's Health Initiative food frequency questionnaire. *Ann Epidemiol, 9*(3), 178-187.

Pereira, M. A., Jacobs, D. R., Jr., Van Horn, L., Slattery, M. L., Kartashov, A. I., & Ludwig, D. S. (2002). Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA Study. *JAMA, 287*(16), 2081-2089.

Rajala, S. A., Salminen, S. J., Seppanen, J. H., & Vapaatalo, H. (1988). Treatment of chronic constipation with lactitol sweetened yoghurt supplemented with guar gum and wheat bran in elderly hospital in-patients. *Compr Gerontol A, 2*(2), 83-86.

Ranganathan, R., Nicklas, T. A., Yang, S. J., & Berenson, G. S. (2005). The nutritional impact of dairy product consumption on dietary intakes of adults (1995-1996): the Bogalusa Heart Study. *J Am Diet Assoc, 105*(9), 1391-1400.

Rautiainen, S., Wang, L., Lee, I. M., Manson, J. E., Buring, J. E., & Sesso, H. D. (2016). Dairy consumption in association with weight change and risk of becoming overweight or obese in middle-aged and older women: a prospective cohort study. *Am J Clin Nutr, 103*(4), 979-988.

Rehm, C. D., Penalvo, J. L., Afshin, A., & Mozaffarian, D. (2016). Dietary Intake Among US Adults, 1999-2012. *JAMA, 315*(23), 2542-2553.

Rizkalla, S. W., Luo, J., Kabir, M., Chevalier, A., Pacher, N., & Slama, G. (2000). Chronic consumption of fresh but not heated yogurt improves breath-hydrogen status and short-chain fatty acid profiles: a controlled study in healthy men with or without lactose maldigestion. *Am J Clin Nutr, 72*(6), 1474-1479.

Romaguera, D., Angquist, L., Du, H., Jakobsen, M. U., Forouhi, N. G., Halkjaer, J., . . . Sorensen, T. I. (2011). Food composition of the diet in relation to changes in waist circumference adjusted for body mass index. *PLoS One, 6*(8), e23384.

Rosenberg, L., Robles, Y. P., Li, S., Ruiz-Narvaez, E. A., & Palmer, J. R. (2020). A prospective study of yogurt and other dairy consumption in relation to incidence of type 2 diabetes among black women in the USA. *Am J Clin Nutr, 112*(3), 512-518.

Salas-Salvado, J., Guasch-Ferre, M., Diaz-Lopez, A., & Babio, N. (2017). Yogurt and Diabetes: Overview of Recent Observational Studies. *J Nutr, 147*(7), 1452S-1461S.

Salvini, S., Hunter, D.J., Sampson, L., Stamper, M.J., Colditz, G.A., Rosner, B., Willett, W.C. (1989) Food-based validation of a dietary questionnaire: The effects of week-to-week variation in Food Compsotion. *Int J Epidemiol*, 18(4), 858-867.

Samara, A., Herbeth, B., Ndiaye, N. C., Fumeron, F., Billod, S., Siest, G., & Visvikis-Siest, S. (2013). Dairy product consumption, calcium intakes, and metabolic syndrome-related factors over 5 years in the STANISLAS study. *Nutrition, 29*(3), 519-524.

Santiago, S., Sayon-Orea, C., Babio, N., Ruiz-Canela, M., Marti, A., Corella, D., . . . Martinez, J. A. (2016). Yogurt consumption and abdominal obesity reversion in the PREDIMED study. *Nutr Metab Cardiovasc Dis, 26*(6), 468-475.

Sayon-Orea, C., Bes-Rastrollo, M., Marti, A., Pimenta, A. M., Martin-Calvo, N., & Martinez-Gonzalez, M. A. (2015). Association between yogurt consumption and the risk of metabolic syndrome over 6 years in the SUN study. *BMC Public Health, 15*, 170.

Sayon-Orea, C., Martinez-Gonzalez, M. A., Ruiz-Canela, M., & Bes-Rastrollo, M. (2017). Associations between Yogurt Consumption and Weight Gain and Risk of Obesity and Metabolic Syndrome: A Systematic Review. *Adv Nutr, 8*(1), 146S-154S.

Schaafsma, G., Meuling, W. J., van Dokkum, W., & Bouley, C. (1998). Effects of a milk product, fermented by Lactobacillus acidophilus and with fructo-oligosaccharides added, on blood lipids in male volunteers. *Eur J Clin Nutr, 52*(6), 436-440.

Scholtens, S., Smidt, N., Swerts, M.A., Bakker, S.J.L., Dotinga, A., Vonk, J.M., van Dijk, F., van Zon, S.K.R., Wijmenga, C., Wolffenbuttel, B.H.R., Stolk, R.P. (2015). Cohort Profile: LifeLines, a three-generation cohort study and biobank. *Int J Epidemiol 44*, 1172-1180.

Schram, M.T., Sep, S.J.S., Van der Kallen, C.J., Dagnelie, P.C., Koster, A., Schaper, N., Henry, R.M.A., Stehouwer, C.D.A. (2014). The Maastricht Study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. *Eur J Epidemiol 29*:439-451.

Schwingshackl, L., Hoffmann, G., Schwedhelm, C., Kalle-Uhlmann, T., Missbach, B., Knuppel, S., & Boeing, H. (2016). Consumption of Dairy Products in Relation to Changes in Anthropometric Variables in Adult Populations: A Systematic Review and Meta-Analysis of Cohort Studies. *PLoS One, 11*(6), e0157461.

Shab-Bidar, S., Neyestani, T. R., Djazayery, A., Eshraghian, M. R., Houshiarrad, A., Gharavi, A., . . . Haidari, H. (2011). Regular consumption of vitamin D-fortified yogurt drink (Doogh) improved endothelial biomarkers in subjects with type 2 diabetes: a randomized double-blind clinical trial. *BMC Med, 9*, 125.

Shin, H., Yoon, Y. S., Lee, Y., Kim, C. I., & Oh, S. W. (2013). Dairy product intake is inversely associated with metabolic syndrome in Korean adults: Anseong and Ansan cohort of the Korean Genome and Epidemiology Study. *J Korean Med Sci, 28*(10), 1482-1488.

Shively, C. A., Apgar, J. L., & Tarka, S. M., Jr. (1986). Postprandial glucose and insulin responses to various snacks of equivalent carbohydrate content in normal subjects. *Am J Clin Nutr, 43*(3), 335-342.

Sialvera, T. E., Pounis, G. D., Koutelidakis, A. E., Richter, D. J., Yfanti, G., Kapsokefalou, M., . . . Zampelas, A. (2012). Phytosterols supplementation decreases plasma small and dense LDL levels in metabolic syndrome patients on a westernized type diet. *Nutr Metab Cardiovasc Dis, 22*(10), 843-848.

Sigman-Grant, M., Warland, R., & Hsieh, G. (2003). Selected lower-fat foods positively impact nutrient quality in diets of free-living Americans. *J Am Diet Assoc, 103*(5), 570-576.

Sluijs, I., Forouhi, N. G., Beulens, J. W., van der Schouw, Y. T., Agnoli, C., Arriola, L., . . . InterAct, C. (2012). The amount and type of dairy product intake and incident type 2 diabetes: results from the EPIC-InterAct Study. *Am J Clin Nutr, 96*(2), 382-390.

Slurink, I. A., Chen, L., Magliano, D. J., Kupper, N., Smeets, T., & Soedamah-Muthu, S. S. (2023). Dairy product consumption and incident prediabetes in the Australian Diabetes, Obesity and Lifestyle Study with 12 years follow up. *J Nutr*.

Slurink, I. A. L., den Braver, N. R., Rutters, F., Kupper, N., Smeets, T., Elders, P. J. M., . . . Soedamah-Muthu, S. S. (2022a). Dairy product consumption and incident prediabetes in Dutch middle-aged adults: the Hoorn Studies prospective cohort. *Eur J Nutr, 61*(1), 183-196.

Slurink, I. A. L., Voortman, T., Ochoa-Rosales, C., Ahmadizar, F., Kavousi, M., Kupper, N., . . . Soedamah-Muthu, S. S. (2022b). Dairy Product Consumption in Relation to Incident Prediabetes and Longitudinal Insulin Resistance in the Rotterdam Study. *Nutrients, 14*(3).

Smith, J. D., Hou, T., Ludwig, D. S., Rimm, E. B., Willett, W., Hu, F. B., & Mozaffarian, D. (2015). Changes in intake of protein foods, carbohydrate amount and quality, and long-term weight change: results from 3 prospective cohorts. *Am J Clin Nutr, 101*(6), 1216-1224.

Snijder, M. B., van der Heijden, A. A., van Dam, R. M., Stehouwer, C. D., Hiddink, G. J., Nijpels, G., . . . Dekker, J. M. (2007). Is higher dairy consumption associated with lower

body weight and fewer metabolic disturbances? The Hoorn Study. *Am J Clin Nutr, 85*(4), 989-995.

Soedamah-Muthu, S. S., Masset, G., Verberne, L., Geleijnse, J. M., & Brunner, E. J. (2013). Consumption of dairy products and associations with incident diabetes, CHD and mortality in the Whitehall II study. *Br J Nutr, 109*(4), 718-726.

Spilker B. (1991) Guide to Clinical Studies. Raven Press, New York, New York, pp. 59-64.

Struijk, E. A., Heraclides, A., Witte, D. R., Soedamah-Muthu, S. S., Geleijnse, J. M., Toft, U., & Lau, C. J. (2013). Dairy product intake in relation to glucose regulation indices and risk of type 2 diabetes. *Nutr Metab Cardiovasc Dis, 23*(9), 822-828.

Stuber, J. M., Vissers, L. E. T., Verschuren, W. M. M., Boer, J. M. A., van der Schouw, Y. T., & Sluijs, I. (2021). Substitution among milk and yogurt products and the risk of incident type 2 diabetes in the EPIC-NL cohort. *J Hum Nutr Diet, 34*(1), 54-63.

Tong, X., Dong, J. Y., Wu, Z. W., Li, W., & Qin, L. Q. (2011). Dairy consumption and risk of type 2 diabetes mellitus: a meta-analysis of cohort studies. *Eur J Clin Nutr, 65*(9), 1027-1031.

Tremblay, A., Doyon, C., & Sanchez, M. (2015). Impact of yogurt on appetite control, energy balance, and body composition. *Nutr Rev, 73 Suppl 1*, 23-27.

Tremblay, A., & Panahi, S. (2017). Yogurt Consumption as a Signature of a Healthy Diet and Lifestyle. *J Nutr, 147*(7), 1476S-1480S.

Trichia, E., Luben, R., Khaw, K-T., Wareham, N.J., Imamura, F., Forouhi, N.G. (2020). The associations of longitudinal changes in consumption of total and types of dairy products and markers of metabolic risk and adiposity: findings from the European Investigation into Cancer and Nutrition (EPIC)–Norfolk study, United Kingdom. *Am J Clin Nutr, 111*:1018–1026.

Trichia E., Luben, R., Khaw, K-T, Wareham, N.J., Imamura, F., Forouhi, N.G. (2020) The associations of longitudinal changes in consumption of total and types of dairy products and markers of metabolic risk and adiposity: findings from the European Investigation into Cancer and Nutrition (EPIC)-Norfolk study, United Kingdom. *AJCN* 111:1018-1026.

U.S. Centers for Disease Control and Prevention (2017). *National Diabetes Statistics Report*. Retrieved from Atlanta, GA: https://www.cdc.gov/diabetes/data/statistics-report/index.html

U.S. Department of Health and Human Services and U.S. Department of Agriculture. "Dietary Guidelines for Americans 2015-2020", 8th ed. Washington, DC: U.S. Government Printing Office, 2015-2020. Retrieved from: *http://health.govldietaryguidelines/2015/guidelinesA*

U.S. Department of Agriculture and U.S. Department of Health and Human Services. "Scientific Report of the 2015 Dietary Guidelines Advisory Committee", Advisory Report to the Secretary of Health and Human Services and the Secretary of Agriculture. Washington, DC, 2015. Retrieved from: *http://health.govldietaryguidelines/2015-scientific-report PDFs/Scientific-Report-of-the-2 015-Dietary-G uidelines-Advisory-ommittee.pdf*.

U.S. Department of Health and Human Services and U.S. Department of Agriculture. "Dietary Guidelines for Americans 2015-2020", 8th ed. Washington, DC: U.S. Government Printing Office, 2015-2020. Retrieved from: *http://health.govldietaryguidelines/2015/guidelinesA*

U.S. Food and Drug Administration (2020). Memorandum to the File (Docket No. FDA-2019-P-1594) "Valid surrogate endpoints and criteria for the diagnosis of type 2 diabetes, to be used in the evaluation of a health claim petition received by CFSAN on the relationship between yogurt consumption and reduced risk of diabetes.

U.S. Food and Drug Administration (2024). Memorandum to the File (Docket No FDA-2022-Q-0051) "Criteria for the diagnosis of type 2 diabetes and valid surrogate endpoints for increased risk of type 2 diabetes".

Vergnaud, A. C., Peneau, S., Chat-Yung, S., Kesse, E., Czernichow, S., Galan, P., . . . Bertrais, S. (2008). Dairy consumption and 6-y changes in body weight and waist circumference in middle-aged French adults. *Am J Clin Nutr, 88*(5), 1248-1255.

Vien, S., Luhovyy, B. L., Patel, B. P., Panahi, S., El Khoury, D., Mollard, R. C., . . . Anderson, G. H. (2017). Pre- and within-meal effects of fluid dairy products on appetite, food intake, glycemia, and regulatory hormones in children. *Appl Physiol Nutr Metab, 42*(3), 302-310.

Van Dongen, M.C.J.M., Wijckmans-Duysens, N.E.G., den Biggelaar, L.J.C.J., Ocké, M.C., Meijboom, S., Brants, H.A.M., de Vries, J.H.M., Feskens, E.J.M., Bueono-de-Mesquita, H.B., Geelen, A., Stehouwer, C.D.A., Dagnelie, P.C., Eussen, S.J.P.M. (2019). The Maastricht FFQ: Development and validation of a comprehensive food frequency questionnaire for the Maaastricht study. *Nutr, 62*, 39-46.

Wang, H., Livingston, K. A., Fox, C. S., Meigs, J. B., & Jacques, P. F. (2013). Yogurt consumption is associated with better diet quality and metabolic profile in American men and women. *Nutr Res, 33*(1), 18-26.

Wang, H., Troy, L. M., Rogers, G. T., Fox, C. S., McKeown, N. M., Meigs, J. B., & Jacques, P. F. (2014). Longitudinal association between dairy consumption and changes of body weight and waist circumference: the Framingham Heart Study. *Int J Obes (Lond), 38*(2), 299-305.

Watanabe, D., Kuranuki, S., Sunto, A., Matsumoto, N., & Nakamura, T. (2018). Daily Yogurt Consumption Improves Glucose Metabolism and Insulin Sensitivity in Young

Nondiabetic Japanese Subjects with Type-2 Diabetes Risk Alleles. *Nutrients, 10*(12).

Weaver, C. M. (2014). How sound is the science behind the dietary recommendations for dairy? *Am J Clin Nutr, 99*(5 Suppl), 1217S-1222S.

Webb, D., Donovan, S. M., & Meydani, S. N. (2014). The role of yogurt in improving the quality of the American diet and meeting dietary guidelines. *Nutr Rev, 72*(3), 180-189.

White, K. M., Bauer, S. J., Hartz, K. K., & Baldridge, M. (2009). Changes in body composition with yogurt consumption during resistance training in women. *Int J Sport Nutr Exerc Metab, 19*(1), 18-33.

Yuzbashian, E., Asghari, G., Mirmiran, P., Chan, C. B., & Azizi, F. (2021). Changes in dairy product consumption and subsequent type 2 diabetes among individuals with prediabetes: Tehran Lipid and Glucose Study. *Nutr J, 20*(1), 88.

Zhang, J., Lim, K., & Shin, S. (2022). Dairy product consumption and type 2 diabetes among Korean adults: a prospective cohort study based on the Health Examinees (HEXA) study. *Epidemiol Health, 44*, e2022019.

Zhang, K., Bai, P., & Deng, Z. (2022). Dose-Dependent Effect of Intake of Fermented Dairy Foods on the Risk of Diabetes: Results From a Meta-analysis. *Can J Diabetes, 46*(3), 307-312.

Zhu, Y., Wang, H., Hollis, J. H., & Jacques, P. F. (2015). The associations between yogurt consumption, diet quality, and metabolic profiles in children in the USA. *Eur J Nutr, 54*(4), 543-550.