The impact of low-fat and full-fat dairy on symptoms of gastroesophageal reflux disease.

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Abstract

The impact of low-fat and full-fat dairy on symptoms of gastroesophageal reflux disease.

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Background: Gastroesophageal Reflux Disease (GERD) is a widely prevalent chronic condition. There is evidence to suggest an association between dairy consumption and symptoms of GERD, even though this is inconsistent and mostly based on observational studies. High dietary fat intake is also associated with symptoms of GERD; however, the current literature does not distinguish between different sources of dietary fat, which may include dairy fat. The purpose of this study was to investigate the impact of dairy consumption, and the fat content of dairy consumed, on the symptoms of GERD, specifically the frequency of acid reflux and the frequency and severity of heartburn, using data collected from a completed randomized controlled dietary intervention trial.

Methods: 72 participants with the metabolic syndrome were enrolled in this study. Participants first completed a 4-week wash-in diet period during which their dairy intake was limited to a maximum of 3 servings of skim milk per week. Participants were then randomized to either continue on the limited dairy arm, or switch to a diet containing an average of 3.3 servings per

day of either low-fat or full-fat dairy products (milk, yogurt and cheese) for a 12-week period. A questionnaire was administered before and after the 12-week intervention to assess the frequency of acid reflux and the frequency and severity of heartburn experienced.

Results: In the *per-protocol* analysis (n=63), there was no effect of the dairy interventions on a cumulative heartburn score (p=0.443 for the time by diet interaction in the overall repeated measures analysis of variance). The dairy interventions similarly did not predict the odds of experiencing acid regurgitation in a binomial logistic regression model (p>0.2 for all three dietary intervention groups). Results were identical in the *intent-to-treat* analysis (n=72).

Discussion: This study suggests that consuming three servings of dairy per day, regardless of fat content, may not affect the common symptoms of GERD, heartburn and acid regurgitation, in men and women with the metabolic syndrome. These findings are limited because this was an exploratory analysis of data collected from a trial not designed to specifically study effects on GERD-related outcomes. To conclusively rule out a role of dairy foods in GERD, adequately-powered long-term intervention trials among participants who have been clinically diagnosed with GERD are warranted.

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INTRODUCTION (BACKGROUND SUMMARY)

Gastroesophageal Reflux Disease (GERD) is a very common chronic disease, with prevalence in the USA ranging from 18.1% to 27.8%[1]. Per the Montreal definition, GERD is the mild presentation of heartburn and acid regurgitation at least twice weekly, or moderate to severe presentation at least once weekly[2]. The pathogenesis of GERD is multifactorial – contributing factors include decreased lower-esophageal sphincter (LES) pressure, higher frequency of transient LES relaxations (TLESRs), and structural changes at the gastro-esophageal junction[3,4]. Patients with GERD suffer from impaired quality of life due to reduced functioning and sleep, and are at increased risk for the development of functional bowel diseases[5]. It has been estimated that the average medical cost for a patient with GERD is double that of a healthy individual, and that the total annual economic cost of GERD in the USA is close to $24 billion, 60% of which is to pay for medications[5].

Medical treatment includes the use of antacids, proton pump inhibitors (PPIs) and histamine 2-receptor antagonists (H_2RAs)[6]. Discontinuation of treatment often results in relapse of symptoms, however, because these drugs do not reverse the pathogenesis of GERD[7]. Lifestyle factors like obesity, smoking, and strenuous physical activity, and dietary factors like large meals, high fat intake, and specific foods like chocolate, coffee, and spicy foods have all been identified as risk factors for the development and progression of GERD[5,7,8]. Lifestyle and dietary modifications are currently regarded as the first line of therapy, and are almost always offered to patients experiencing GERD symptoms, even though there is little evidence behind some of

the specific recommendations given[7]. This knowledge gap highlights the need for more studies designed to better understand how specific dietary factors influence symptoms of GERD.

Dairy is one dietary factor that a limited number of mostly observational studies has linked to GERD. Ndebia et al.[9] found that milk and milk products are a risk factor for acid regurgitation. Caselli et al.[10] proposed food intolerance as a potential pathogenic pathway to explain milk as a risk factor for GERD, based on their pilot study in which avoidance of dairy by people with a positive leukocytotoxic test reaction to dairy foods improved their GERD symptoms. On the other hand, some findings suggest that dairy has a protective effect on GERD as frequent consumption of milk has also been associated with reduced risk of GERD symptoms[11,12]. Again other studies report a positive correlation between fat content of milk and heartburn[13,14].

Taken together, there is some evidence for an association between dairy consumption and symptoms of GERD. However, this evidence is almost entirely based on data from observational studies, and is inconsistent. To our knowledge, no study has investigated the effect of both low-fat and full-fat dairy on symptoms of GERD using a randomized controlled design. The purpose of this study was to investigate the impact of dairy consumption, and the fat content of dairy consumed, on the symptoms of GERD, specifically the frequency of acid reflux and the frequency and severity of heartburn, using data from a completed randomized controlled dietary intervention trial.

BACKGROUND

Gastroesophageal Reflux Disease

Gastroesophageal Reflux Disease (GERD) is a chronic disease and one of the most frequently encountered conditions by primary care physicians and gastroenterologists[15]. The Montreal definition of GERD is an evidence-based global consensus that defines the disease as presenting symptoms of mild heartburn and/or regurgitation at least twice weekly, or symptoms of moderate to severe heartburn and/or regurgitation at least once weekly[2]. According to the Montreal definition, heartburn is defined as a burning sensation in the retrosternal area (behind the breastbone), and regurgitation is defined as the perception of a flow of refluxed gastric content into the mouth or hypopharynx[2]. Historically, GERD has been approached as a continuous spectrum of disease and has been classified as non-erosive reflux disease (NERD), also called endoscopy negative reflux disease, and erosive reflux disease (ERD), or reflux esophagitis (RE)[4,15]. NERD is thought to be at the beginning of the spectrum, and is defined by the presence of troublesome reflux-associated symptoms, while ERD is defined endoscopically by visible breaks of the distal esophageal mucosa[2]. Of the various classification systems that have been developed to grade the severity of ERD, the Los Angeles (LA) classification system is the most commonly referred to in the literature. Toward the extreme end of the spectrum lies the most severe form of the condition, known as Barrett's columnar lined esophagus[4]. At this stage, there is a delayed presentation of comparatively mild symptoms due to the relative insensitivity of the mucosal lining to acid. More recent evidence has called into question the assumption that NERD leading to ERD leading to Barrett's is the natural progression of the

disease, and instead suggests that these three types of GERD are categorically different and do not often naturally progress from one grade to another along the spectrum[4].

A well-documented patient history of presenting with typical symptoms of heartburn and/or regurgitation is sufficient for a clinical diagnosis of NERD, but an upper endoscopy, which evaluates the esophageal mucosa, is required for a clinical diagnosis of ERD[16]. A more objective diagnostic tool for NERD is ambulatory esophageal pH monitoring, which allows for a direct measurement of esophageal acid exposure and reflux episode frequency[15]. Some atypical symptoms of GERD include nausea, bloating, belching, epigastric pain, and fullness[15]. Generally, these symptoms are more common immediately after a meal and are worsened by leaning back or lying down. The presence of atypical symptoms can be indicative of GERD, but can also suggest the presence of other conditions such as peptic ulcer disease or gastroparesis. Patients with GERD can also present with extra-esophageal symptoms like chronic cough, wheezing, sore throat, asthma, and dental erosions.

GERD is a widely prevalent condition, with one study reporting the prevalence of GERD to be between 10 to 48% in western countries[17]. The wide prevalence range has been attributed to the lack of consensus on the definition of GERD in the literature[18]. Most epidemiological studies define GERD using the Montreal definition, and symptoms are most often assessed via a self-reported questionnaire or a clinician diagnosis[18]. A systematic review of 15 population-based epidemiological studies of GERD indicate that the prevalence of GERD in the USA ranges from 18.1% to 27.8%[18]. Globally, the prevalence of GERD in Europe ranges from 8.8% to 25.9%, with

a trend of higher prevalence in Northern Europe, when compared to Southern Europe[18]. Prevalence in the Middle East ranges from 8.7% to 33.1%, and East Asia 2.5% to 7.8%[18]. In considering symptoms of GERD, a recent meta-analysis of 108 community-based cross-sectional surveys report the global pooled prevalence of heartburn and acid regurgitation to be 14.8%[19]. These figures are higher when considering only the USA: 44% of the population suffers from GERD symptoms at least once monthly, 17% at least once weekly, and 7% at least once daily[20]. While these statistics indicate that a large number of individuals experience symptoms of GERD on a regular basis, there is a possibility that the true prevalence of acid reflux and heartburn may be higher as many individuals choose to self-medicate and not seek advice or support for dealing with these symptoms[21]. Although only three epidemiological studies of GERD from pre-1995 exist, a comparison between studies conducted before and after 1995 indicated a statistically significant increase in the prevalence of GERD worldwide over the last two decades[18].

The pathogenesis of GERD is thought to be multifactorial, with a combination of altered physiological factors leading to the development of the disease[22]. One contributing factor is decreased lower-esophageal sphincter (LES) pressure, which allows for stomach contents to reflux up into the esophagus when the pressure in the stomach exceeds the LES pressure. Other patients with GERD may have normal LES resting tone, but have a higher frequency of transient LES relaxations (TLESRs) associated with reflux, which are brief periods of LES relaxation unrelated to swallowing or peristalsis. Some patients with GERD also have structural changes at the gastro-esophageal junction, which reduces the resistance to reflux[4]. As these changes

become more pronounced, the frequency and severity of reflux symptoms increase, and in over 90% of patients with severe GERD, a hiatal hernia is present[4,22]. This further exacerbates the symptoms because it disrupts LES function, and allows large volumes of gastric contents to pass into the hiatal sac without any barriers. Some other factors that can lead to the onset of GERD include impaired esophageal acid clearance, impaired esophageal mucosal resistance, and delayed postprandial gastric emptying.

Complications associated with GERD include impaired quality of life due to effects on patients' functioning and sleep, as well as the development of functional bowel diseases[4,5]. Patients with severe ERD also have an increased risk of developing peptic strictures. Barrett's esophagus can lead to severe complications like esophageal ulcerations and strictures, and have a high potential for progressing to malignancy, resulting in adenocarcinoma. The presence of GERD can also lead to the manifestation of other conditions like pulmonary diseases, laryngitis, and sinusitis, but exact etiologies remain unclear[22]. One proposed hypothesis is that gastric acid reflux may reach the larynx and pharynx, making these respiratory structures more prone to acid-induced injuries.

GERD is thought to be the most expensive digestive disease in the USA as it has the highest annual direct costs[23]. The total annual economic cost of GERD is the USA, which includes both direct and indirect costs, is approximately $24 billion, with 60% of the cost being spent on medications[5]. Direct costs include hospital facilities (inpatient, outpatient clinics, and emergency rooms), physician services, and medications, while indirect costs are primarily

incurred due to loss of work productivity. It has also been estimated that the average medical costs for an individual diagnosed with GERD is double that of a healthy individual due to additional hospitalizations, visits to outpatient clinics and emergency rooms, and medication use[5].

Since GERD is a chronic disease, and no cure is currently known, long-term management of symptoms in the form of lifestyle modification and medical therapy is required[15]. The most common forms of medical treatment include the use of antacids, proton pump inhibitors (PPIs) and histamine 2-receptor antagonists (H_2RAs). Antacids are bases that act to neutralize the acidic content of the stomach, while both PPIs and H_2RAs work to block gastric acid secretions. Discontinuation of treatment often results in relapse of symptoms because these drugs do not reverse the pathogenesis of GERD[7]. Additionally, there is some evidence to suggest that long-term PPI treatment is associated with weight gain in patients with GERD[24]. Long-term use of PPIs has also been linked to multiple adverse effects – increased risk of bone fractures related to reduced calcium absorption, hypomagnesaemia, vitamin B12 deficiency, and a potentially increased risk of dementia, renal disease, cardiovascular disease, and pneumonia[25]. Although underlying biological mechanisms are plausible for many of these adverse effects, most are associations based on observational data and conclusive evidence from clinical studies remains weak.

Lifestyle and Gastroesophageal Reflux Disease

Certain lifestyle and dietary factors have been identified as risk factors for the development and progression of GERD. Multiple studies have reported evidence supporting obesity as a strong risk factor for development of GERD symptoms. In one meta-analysis of epidemiological studies, an association was found between GERD symptoms and being overweight (BMI 25-29.9 kg/m^2) (OR = 1.43, 95% CI 1.158-1.774) or obese (BMI 30-34.9 kg/m^2) (OR = 1.94, 95% CI 1.468-2.566)[26]. A large case-control study reported the risk of reflux to be three times higher among severely obese (BMI>35 kg/m^2) men (OR 3.3, 95% CI 2.4-4.7) and six times higher among severely obese women (OR 6.3, 95% CI 4.9-8.0) when compared with normal weight participants (BMI 18.5-24.9 kg/m^2)[27]. Additionally, elevated sagittal abdominal diameter ($\geq$ 26 cm), a measure of visceral obesity, was found to be a risk factor for reflux symptoms (OR = 1.85, 95% CI 1.55-2.21) after adjusting for BMI in a cross-sectional study of 80,110 participants[28]. Although the mechanism behind this association is not fully understood, it is hypothesized that visceral adiposity could be associated with increased intra-abdominal pressure, which can promote GERD via increased intra-gastric pressure[29]. Increased intra-gastric pressure can lead to increased episodes of TLESR. Wu et al reported a significantly ($P<0.001$) higher rate of TLESR episodes, as well as TLESR episodes with acid reflux, among overweight and obese participants when compared to their normal-weight counterparts[30]. Another suggested pathogenic pathway involves observed associations between obesity and a separation between the LES and extrinsic crural diaphragm, which is a predisposition to hiatal hernia[29].

Smoking and physical activity are two other lifestyle factors that have been linked to GERD. Individuals who had ever smoked, smoked more than 20 cigarettes daily, or had smoked for over 20 years are at a higher risk for developing symptoms of GERD[31,32]. With regards to physical activity, vigorous or strenuous exercise, but not moderate physical activity, has been suggested to acutely induce GERD symptoms in some cases[29].

With regards to dietary factors, various dietary patterns as well as specific foods have been associated with development or exacerbation of GERD symptoms. In a population-based cross-sectional study, Mone et al. found that participants who closely followed a Mediterranean style diet had a reduced risk of GERD after adjustment for age, sex, lifestyle factors, BMI, and socio-economic characteristics[33]. Dietary fiber intake has also been inversely associated with the risk of GERD symptoms, after adjusting for BMI, total energy intake, and demographics (OR = 0.72, 95% CI 0.53-0.99, P = 0.04) in a cross-sectional study that investigated the relationship between GERD symptoms and specific dietary components [34]. This study used GERD questionnaires to assess symptoms of GERD and food frequency questionnaires (FFQs) to assess dietary intake. Nilsson et al also reported similar findings from their case-control study designed to investigate the relationship between lifestyle habits and GERD symptoms[32]. The authors observed a statistically significant inverse linear trend (P < 0.0001) between fiber content of bread and GERD symptoms – participants who consumed bread with at least 7% dry weight of fiber had a 50% risk reduction when compared to those who ate bread with 1-2 % fiber content (OR = 0.5, 95% CI 0.4-0.7).

Evidence also suggests that both dietary fats and dietary carbohydrates could play a role[7]. The association between high dietary fat intake and GERD symptoms stems from physiological studies that were carried out to determine the mechanisms of action[7]. It has been hypothesized that meals high in fat trigger the secretion of a larger amount of cholecystokinin (CCK), which acts to cause gastric distention, thereby increasing TLESRs[35]. However, there is mixed evidence to support this hypothesis. Evidence from a study conducted on healthy participants suggested that high-fat meals increase esophageal acid exposure 3 hours post-consumption, and that subjective reflux symptoms are more frequent when a high-fat diet was administered[36]. An epidemiological study conducted by El-Serag et al. reported that participants with weekly GERD symptoms had significantly higher daily intake of total fat, a higher average number of fat servings per day, and a higher percentage of energy from dietary fat when compared to participants without GERD symptoms[37]. However, the association between fat and GERD symptoms disappeared when the statistical analyses were adjusted for BMI. The current literature on dietary fat intake and GERD does not distinguish between different sources of dietary fat.

In the case of dietary carbohydrates, a few studies demonstrate that limiting carbohydrate intake resulted in the resolution of GERD symptoms. Case reports of five obese individuals following a very low-carbohydrate diet for weight loss reported complete disappearance of their GERD symptoms within one week of beginning the diet[38]. It should be noted that these participants also eliminated chocolate and coffee from their diets. A study of eight obese individuals who were allowed to eat unlimited amounts of meat and eggs, but limited amounts

of hard cheeses, and were restricted to only 20 g of carbohydrates per day also reported similar findings[39]. In this study, both self-reported GERD symptoms and the total time with a measured pH < 4 in the distal esophagus saw a statistically significant decrease after four to six days on the diet.

Specific foods and beverages that have been associated with worsening symptoms of GERD include, but are not limited to, coffee, peppermint, citrus, carbonated drinks, chocolate, spicy foods, and alcohol[5,7]. While there seems to be plenty of anecdotal evidence to support these associations, there is a lack of evidence derived from rigorous scientific studies. It is common to see patients with GERD avoid specific foods that they perceive can induce their GERD symptoms, and this list of foods often differs from one patient to the other.

Caselli et al. hypothesized that food intolerances may contribute to the development of GERD symptoms based on their pilot study of leukocytotoxic test-based exclusion diets[40]. Thirty-eight participants exhibiting GERD symptoms were recruited, and the severity of symptoms was assessed using the GERD Impact Scale (GIS) questionnaire. Participants were randomized to receive either the “true” diet, which excluded all foods presenting a moderate to severe reaction on the leukocytotoxic test, or the control diet that included these foods. Follow-up at one month showed that both groups experienced a significant reduction in GIS scores, but the “true” diet group’s mean GIS score was significantly lower than that of the control group. At one month, all participants on the control diet were also given the “true” diet, and symptoms were re-assessed after three months. At this point, participants who were switched over from

control to “true” diet experienced a further significant reduction in GIS scores, while participants who continued on the “true” diet only experienced a slight reduction in GIS scores. The authors concluded that leukocytotoxic test-based exclusion diets may be effective in reducing the severity of GERD symptoms, especially in patients not responding to pharmacological treatment. Milk was most frequently involved in inducing positive leukocytotoxic test reactions, followed by lettuce, Brewer’s yeast, pork, coffee and rice. These findings suggest that dairy foods may be a major culprit, at least for some people, and indicate that many other foods that are not commonly considered in the literature or clinical setting may play a role in the development of GERD symptoms.

There has been some evidence to suggest that coffee consumption may be a risk factor for GERD symptoms[7]. A study of healthy participants reported that regular coffee consumption resulted in a significant decrease in LES pressure and a significant increase of time with esophageal pH < 4[41]. Coffee also modifies gastric acid secretion by inducing a higher acid response[42]. On the contrary, a meta-analysis of 15 case-control studies, which included a mix of community-based and hospital-based studies, and one nested-case control study, concluded that there was no significant relationship between coffee intake and GERD[43].

Lifestyle modifications to alleviate symptoms include weight loss, smoking cessation, sleeping with the head elevated, eating smaller meals, eating slower and not lying down for at least three hours postprandial[15]. A systematic review of 16 randomized controlled trials that evaluated the impact of lifestyle measures on GERD concluded that only weight loss and

sleeping with the head elevated consistently demonstrated improvement of GERD symptoms[44]. Although the role of diet in the pathogenesis and management of GERD is still poorly understood, dietary modification is currently regarded as the first line of therapy[5]. Therefore, dietary and lifestyle advice is almost always offered to patients experiencing GERD symptoms, even if there is little evidence behind some of the specific recommendations given[7].

Dairy and Gastroesophageal Reflux Disease

One category of foods that has been commonly associated with symptoms of GERD is dairy. Cross-sectional data from a Korean study by Nam et al. suggest a protective effect of milk on NERD, defined as at least weekly symptoms of acid reflux or heartburn[11]. Healthy participants who were in the third and fourth quartile for milk consumption (> 66.7 g/d) had reduced NERD when compared with participants in the first quartile (third quartile OR = 0.8, 95% CI 0.68-0.95, P = 0.01; fourth quartile OR = 0.78, 95% CI = 0.65-0.95, P = 0.009). However, milk consumption was positively associated with increased reflux esophagitis in women. This study did not distinguish milk consumption by its fat content. Another study from Korea, which was designed to investigate the frequency of heartburn produced by beverages, reported that full-fat milk consumption was associated with a significantly higher heartburn score, calculated from self-reported severity of heartburn, when compared to the heartburn score associated with low-fat milk consumption (P = 0.008)[45].

An additional study reported that all types of milk were associated with significantly more self-reported heartburn episodes when compared with water[13]. A positive correlation was observed

between fat content of milk and self-reported prevalence of frequent heartburn: 19.4% of participants reported an increased frequency of regular heartburn after consuming full-fat milk, 9.3% of participants reported an increased frequency of regular heartburn after consuming low-fat milk, and 7% of participants reported an increased frequency of regular heartburn after consuming skim milk. Babka and Castell conducted an observational study, where they measured the changes in intraluminal LES pressure continuously for 15 minutes before and 60 minutes after the administration of different foods using an infused open-tipped system[14]. They observed slight, but significant decreases in LES pressure after the consumption of full-fat milk. On the other hand, the consumption of nonfat milk was associated with significant increases in LES pressure, which alludes to an association between dairy fat and GERD.

Ndebia et al. found that milk and milk products were one of the most commonly consumed foods, with an average of 26 times per month, among 57 healthy South African participants who were recruited for a study that investigated the relationship between reflux and diet[9]. Reflux was assessed using 24-hour ambulatory esophageal impedance pH monitoring, which allowed investigators to identify the type and extent of reflux. Dietary intake over the past month was assessed using FFQs. Milk and milk product consumption was the most influential dietary component, as it was associated with six reflux parameters, including more total reflux ($P = 0.022$), more weak acid reflux ($P = 0.015$), and less the time that gastric pH was higher than 4 ($P = 0.030$). The next most commonly associated food domain was fat intake, with associations with 4 reflux parameters, including increase in acid reflux ($P = 0.046$).

Another study examined whether diet habits affect the prevalence of reflux esophagitis (RE) among a Chinese population, using a case-control design[20]. In this study, 268 patients newly diagnosed with RE were recruited as cases. The extent of esophageal mucosal damage was assessed using the Los Angles grading system, and 96.3% of patients were classified as having mild RE (grade A or grade B). 269 individuals who had no reflux symptoms and had normal upper GI endoscopies acted as controls. Data on dietary intake for the past year was collected using FFQs. Daily intake of milk and dairy products was significantly higher in cases compared to controls, and there was a significant relationship between milk and dairy product intake and RE (OR = 1.34, 95% CI 1.09-1.65, P = 0.01). When adjusted for waist circumference, waist-to-hip ratio, total energy intake, and demographics (sex, age, education level), this relationship was attenuated (OR = 1.20, 95% CI 1.00-1.44, P = 0.06). In the adjusted analysis, a positive relationship between RE and calcium intake was observed (OR = 1.63, 95% CI = 1.26-2.11, P < 0.01).

Stake-Nilsson et al. conducted a prospective study with an 18-year follow-up by enrolling a subset of participants from the 1990 Swedish Dyspepsia Study in order to investigate the natural course of GI symptoms over time and the impact of lifestyle factors on reported GI symptoms[46]. Participants enrolled in the original study were those who were seeking medical care for unpleasant abdominal symptoms or any other symptoms assumed to be related to the digestive system. The authors found that there was a significant decrease in milk drinking (P = 0.008) over time. Participants also reported a significantly decreased frequency of acid regurgitation, but a stable frequency of heartburn, over time. When associations between

symptom changes and lifestyle changes were analyzed, statistically significant associations were reported between reduced acid regurgitation and increased levels of exercise (OR = 3.05, 95% CI 1.23-7.56, P = 0.016) and decreased smoking (OR = 3.45, 95% CI 1.22-9.80, P = 0.02). It remained unclear from the paper whether there was a significant association between decreased acid regurgitation and reduced milk consumption over time because the authors either failed to analyze or report this association.

A recently published community-based study from southern India to identify potential factors associated with GERD reported that milk consumption had a protective effect on heartburn and regurgitation symptoms[12]. Participants were interviewed by physicians to establish presence of GERD symptoms, and were also asked about the frequency of their meat and milk consumption. A multivariate analysis revealed that drinking milk less than three times per week was associated with an increased risk of GERD symptoms (OR = 1.6, 95% CI 1.3-1.9, P <0.001) when compared to drinking milk three or more times per week.

On the other hand, two observational studies conducted with participants from the USA observed no associations between risk for GERD and milk or dairy foods. The first was a prospective cohort study that used data collected from 43,308 women enrolled in the Nurses' Health Study II and with no reported symptoms of GERD at baseline[47]. FFQs were used to assess dietary intakes and a simple questionnaire was used to determine frequency of either acid regurgitation or heartburn, and women reporting at least weekly symptoms were considered cases. There was no association between number of servings of milk consumption per day and

risk of GERD symptoms in multivariate analyses (p=0.79). The second was a cross-sectional study among 915 employees at a Veterans Affairs Medical Center that investigated associations between GERD symptoms and intakes of different dietary components using FFQs and the validated 32-question Gastroesophageal Reflux Questionnaire[34]. Again, there was no association between servings of dairy consumed per day and risk of GERD symptoms (OR=1.09, 95% CI 0.70-1.57, p=0.58).

Summary and Knowledge Gaps

Taken together, there is some evidence for an association between dairy consumption and symptoms of GERD, but this evidence is currently inconsistent and mostly based on observational evidence. Most published studies on this topic rely on self-reported food intake and self-reported frequency and severity of GERD symptoms to assess acid reflux and heartburn symptoms. Almost all studies employ an observational study design, which has many limitations. Issues of temporality and reverse causality make it difficult to establish causation. In most instances of studies that enroll participants with GERD, it is possible that experiencing frequent GERD symptoms influence participants' dairy consumption. Cross-sectional and case-control studies that use FFQs are also subject to recall bias. To our knowledge, there is no study in the current literature that investigated the relationship between symptoms of GERD and both dairy consumption and fat content of dairy using a randomized controlled design. Additionally, there is little to no evidence on this topic among a primarily North American population.

Our lab conducted a pilot study that tested the effects of an Anti-Inflammatory Milieu (AIM) diet, which excluded dairy products, on low-grade chronic inflammation in adipose tissue. During the final group session, almost all participants stated that they saw improvements in symptoms of heartburn and acid regurgitation after following the AIM diet for 12 weeks (unpublished observation). Several cases had been free of heartburn symptoms on the AIM diet, in many cases after suffering from heartburn for many years. In one case, a participant was free of symptoms even after discontinuing PPIs, which she had been taking for more than 2 years. This very consistent, albeit anecdotal participant feedback, along with the suggestive evidence from the published literature, motivated the present study. The purpose of this project is to investigate the impact of dairy consumption, and the fat content of dairy consumed, on the symptoms of GERD, specifically the frequency and severity of acid reflux and heartburn, using data from a completed randomized controlled dietary intervention trial.

METHODS

Study Participants

The clinical portion of this study was completed between January 2016 and October 2018. We aimed to recruit men and women living in the greater Seattle area who suffered from the metabolic syndrome. See **Appendix 1** for a complete list of inclusion and exclusion criteria. We identified potentially eligible participants through an automated screening of the University of Washington (UW) electronic medical record (EMR) system. We sent a letter to 4,277 potentially eligible individuals inviting them to participate in the study. Three hundred and fifty-four interested potential participants completed a telephone screening interview. Of these, 130 individuals were invited to attend in-person screening visits at the Fred Hutchinson Cancer Research Center (FHCRC). During this screening visit, anthropometric measurements were taken, and individuals were asked to complete medical, nutritional and medication history questionnaires. Eligible participants then returned for a study initiation visit, where they provided consent for the intervention, were weighed, and completed a modified Blair Physical Activity Questionnaire (PAQ) to assess habitual physical activity. We enrolled 76 men and women. Of these, four were excluded or withdrew during the wash-in phase, and 72 participants were randomized to one of three intervention arms.

Study design and diets

Following the study initiation visit, all eligible participants completed a 4-week wash-in diet period. During this period, participants were asked to consume a maximum of 3 servings of

nonfat milk per week, not to consume any other dairy products, and otherwise to consume their habitual diet *ad libitum*. Dietary compliance was assessed at a check–in visit during the wash-in diet period when participants came to FHCRC to pick up their dairy products. Participants were excluded from the trial for noncompliance if they had consumed more than three servings of non-study dairy products over the first 2 weeks of the study, failed to complete one or more daily dairy logs, or did not complete at least one of the two 24-hour dietary recall interviews during this period. Individuals who were excluded due to noncompliance or who dropped out during the wash-in period were not randomized, did not complete any clinic visits, did not count towards the recruitment goal, and were not included in any statistical analyses.

In the last week of the wash-in phase, participants completed clinic visit #1 at the UW Translational Research Unit (TRU), where they were asked to complete a GERD questionnaire to assess the frequency of acid regurgitation and the frequency and severity of heartburn, both during the day and at night (**Appendix 2**). We also collected anthropometric measurements, and participants completed a modified Blair PAQ and a health questionnaire to assess changes in physical activity, illness and medication/supplements.

Following completion of the wash-in diet phase and baseline assessments at clinic visit #1, participants were randomized to one of three intervention arms. We utilized a block randomization procedure stratified by gender and HOMA-IR (<5.0 vs. ≥ 5.0 or diagnosis of diabetes). Subjects either continued to consume a diet with little dairy ("limited dairy diet",

control), or switched to a diet including 3.3 servings/day of either nonfat/low-fat dairy products ("low-fat dairy diet") or full-fat dairy products ("full fat dairy diet"). Subjects were provided with all of their dairy products by the FHCRC Human Nutrition Laboratory (HNL).

The limited dairy diet included 3 servings/week of nonfat milk (skim milk). The low-fat dairy diet included 23.1 servings/week of nonfat or low-fat dairy products, for an average of 3.3 servings per day. These 23.1 weekly servings consisted of 8 servings of nonfat milk, 7.1 servings of nonfat yogurt, and 8 servings of low-fat cheese (11-21% fat). In the full-fat dairy diet arm, participants were also provided with 23.1 servings/week, consisting in this case of 8 servings of whole milk (3.25% milk fat), 7.1 servings of plain full-fat yogurt (3.1% milk fat), and 8 servings of full-fat cheese (21-33% fat). One serving of milk was 240mL, one serving of yogurt 170g, and one serving of cheese 42.5g. Participants randomized to the low-fat and full-fat dairy diets were asked to consume all of the dairy products that were provided to them for a given week. Consumption of the nonfat milk was optional for participants randomized to the limited dairy arm. All participants were asked to not consume any other dairy products. To assess compliance, participants were asked to keep a daily dairy log of any dairy foods eaten, including study and non-study dairy foods. Participants were also asked to record any change in medication or supplement intake as well as any illness. Participants visited the FHCRC HNL every 1-2 weeks to meet with a kitchen staff member, return any leftover dairy foods, and receive a 7-14-day supply of dairy products. Staff weighed all returned dairy products to assess the amount of dairy consumed. Additionally, the returned dairy logs were compared against the returned dairy foods and checked for compliance. We contacted participants by phone if

compliance was below the desired level (i.e. <90% of the study dairy foods were consumed, and/or non-study dairy foods were consumed regularly). During the intervention period, participants also completed two additional modified Blair PAQs at approximately 4-week intervals. Participants also completed three additional 24-hour recalls during the intervention phase.

Participants completed clinic visit #2 at the UW TRU 12 weeks ± 1 week after starting the intervention diet. During this visit, participants were asked to complete the same GERD questionnaire administered at clinic visit #1. All of the other data collected at clinic visit #1 were also collected at clinic visit #2.

Statistical Analysis

This was an exploratory analysis of data collected from a randomized controlled dietary intervention trial that was designed to test the impact of low-fat and full-fat dairy on glucose homeostasis. Statistical analyses were performed using SPSS for Windows (Version 26; IBM). All data are reported as means ± standard deviations for normally distributed variables, or medians (25th; 75th percentile) for non-normally distributed variables, or percentages for categorical variables. Key baseline characteristics that are relevant for GERD were compared by study arm to ensure that the randomization was successful, defined as a p value > 0.1 in statistical tests across the three dietary intervention groups. We conducted both an intent-to-treat (ITT) and a *per-protocol* analysis. For the ITT analysis, which included all randomized participants, we used multiple imputation to generate 5 complete datasets, and all analyses were run on all five. For

the per-protocol analysis, participants were included if they (a) completed the dietary intervention and all clinic visits, (b) were compliant with the dietary regimen (defined as consuming at least 90% of the study dairy foods provided, and consuming 10 or fewer servings of non-study dairy foods during the 12-week intervention period), and (c) were with complete data from the GERD questionnaire.

Primary outcome 1: Heartburn Score: A heartburn score was calculated by adding the products of frequency score (0-4) and severity score (0-3) for heartburn during the day and at night, resulting in a score ranging from 0 to 24 for each participant. The heartburn score was analyzed using a repeated measures analysis of variance (RM-ANOVA) with *time* (clinic visit #1 vs. #2) as the within-subjects variable and *diet group* (limited dairy vs. low-fat dairy vs. full-fat dairy) as the between-subjects variable, to determine whether there was a significant *time x diet group* interaction. Logarithmic transformations were performed on all outcome variables that were not normally distributed.

Primary outcome 2: Frequency of Acid Regurgitation: Frequency of acid regurgitation was dichotomized as "never", for participants who indicated they did not experience acid regurgitation, and "ever", for participants who indicated they experienced any frequency of acid regurgitation. We created a binomial logistic regression model to analyze the effect of the dietary interventions on acid regurgitation at the conclusion of the intervention period (CRC #2), using baseline acid regurgitation (CRC #1) as a co-variate in the model.

We also conducted sensitivity analyses for both primary outcomes 1 and 2, excluding participants who had ever been diagnosed with GERD or who used medication for GERD (antacids, PPIs or H_2RAs) at any time point. Similarly, we conducted sensitivity analyses adjusting for changes in GERD medication use during the intervention period of the study (decreased use, stable use, increased use). We also conducted sensitivity analyses adjusting for changes in body weight, waist circumference, total energy intake, physical activity, and dietary fiber intake. This was done by re-running the overall RM-ANOVA model (for heartburn score) and binomial logistic regression model (for frequency of acid regurgitation), including each of these baseline or change variables as a co-variate. The alpha-error level was set to 5%.

RESULTS

Description of participants

All 72 participants randomized to one of the three intervention groups (n=24 in all three groups) were included in the ITT analysis. Nine subjects were excluded from the *per-protocol* analysis for a total of 63 participants. Three of the nine excluded participants dropped out of the study prior to the final clinic visit, two were excluded for non-compliance with the dietary intervention, and four participants did not have complete data from the GERD questionnaire collected at one or both of the two clinic visits. Fourteen of the 72 participants indicated a past medical history of GERD on the medical questionnaire completed at the screening visit and 10 were taking GERD-related medications at baseline (clinic visit #1). During the intervention period, one participant reported a reduction in GERD medication use, and three participants began using GERD medications. There were no significant differences in baseline characteristics between the intervention groups in both ITT and *per-protocol* analyses. **Table 1** shows baseline characteristics of participants included in the *per-protocol* analysis.

Adherence of Intervention

Based on data from the Human Nutrition Laboratory on administered and returned study dairy foods as well as participants' entries of consumption of non-study dairy foods on their dairy logs, *per protocol* participants (n=63) consumed 98.3 $\pm$ 1.7% and 98.0 $\pm$ 2.8% (mean $\pm$ SD) of the study dairy foods provided to them during the low-fat and full-fat dairy intervention diet periods, respectively. During the limited dairy intervention period, participants consumed an average of 76.5 $\pm$ 33.6% of the provided (non-mandatory) nonfat milk. Consumption of non-

study dairy foods was 0.6 ± 1.0, 0.6 ± 0.9, and 1.3 ± 2.3 total servings during the 12 weeks of the limited, low-fat, and full-fat dairy diet periods respectively. Consistent data (not shown) on total consumption of dairy foods were obtained from the average of three unannounced 24-hour dietary recall interviews conducted during the intervention period.

Effects of the intervention on heartburn and acid regurgitation

In the *per-protocol* analysis, there was no effect of the dairy interventions on heartburn, as assessed by the heartburn score (**Figure 1**). The dairy interventions were not significantly associated with acid regurgitation, adjusted for baseline (CRC #1) acid regurgitation ($p = 0.492$ for limited dairy; $p = 0.851$ for low-fat dairy; $p = 0.263$ for full-fat dairy) (**Table 2**). Sensitivity analyses adjusting for changes in GERD medications during the intervention, or excluding participants with a past medical history of GERD or taking GERD-related medications did not impact the overall intervention effect on frequency of acid regurgitation or heartburn score. Similarly, sensitivity analyses adjusting for changes in body weight, waist circumference, total energy intake, fiber intake (in g/1,000 kcal), or physical activity also did not impact the overall intervention effect on both primary outcomes. These findings were identical in the ITT analyses including all 72 randomized participants.

DISCUSSION

In this exploratory analysis of data from a completed randomized controlled dietary intervention trial, we found that consumption of neither low-fat nor full-fat dairy products, including milk, yogurt and cheese, had an effect on heartburn (HB) or acid regurgitation (AR) symptoms in men and women with the metabolic syndrome. These findings were consistent in both ITT and *per protocol* analyses, and remained robust in sensitivity analyses that adjusted for past medical history of GERD, use of GERD medications, changes in GERD medications during the intervention period, and other potential anthropometric, dietary, and lifestyle changes that may mediate GERD symptoms.

To our knowledge, this is the first study to investigate the effects of both low-fat and full-fat dairy consumption on GERD symptoms using data from a randomized controlled trial, where participants received all of the dairy products to be consumed, no other dairy consumption was allowed, and adherence was closely monitored. Our results are consistent with findings from two observational studies also conducted with participants from the USA that observed no associations between risk for GERD and milk[47] or dairy foods[34]. Both of these studies used FFQs to assess dietary intakes and did not distinguish between the different fat contents of dairy products, or what products constituted the dairy food group. GERD symptoms were assessed by a simple questionnaire to determine frequency of either HB or AR[47], or a 32-question validated Gastroesophageal Reflux Questionnaire[34]. In comparison, we used a questionnaire with 5 questions to assess frequency of AR and both frequency and severity of HB during the day and

at night. Another trial[48] that is consistent with our findings of no effect of dairy on HB and AR tested specifically the effect of milk fermented with a strain of *Bifidobacterium bifidum* using a 4-week double-blind randomized, placebo-controlled trial among healthy Japanese participants. Findings from two other East Asian observational studies are also consistent with our findings, reporting no association between the use of milk with coffee over 80% of the time[49] or milk consumption[20] and GERD in multivariate analyses. It should be noted that the latter involved participants with newly diagnosed reflux esophagitis based on endoscopic findings, which may not always be accompanied by presentation of HB and AR symptoms[11,49].

On the other hand, our results contradict findings from several other observational studies. Ndebia et al.[9] reported milk and milk products to be a risk factor for AR among healthy South African adults. They found that milk product consumption was associated with the greatest number of reflux parameters, as measured by 24-hour esophageal pH-impedance monitoring, which is a more objective measure of AR compared to a questionnaire. These findings oppose those of Nam et al.[11] and Chowdhury et al.[12], both of which reported milk as a protective factor for symptoms of GERD. The former, a case-control study from South Korea, analyzed data collected from 3-day food records and GERD questionnaires to find that the third and fourth quartiles of milk consumption were associated with a reduced risk of GERD symptoms. The latter was a cross-sectional study from South India, where a survey was employed to assess GERD symptoms, lifestyle factors, and specific dietary intakes. These authors found that consuming milk less than 3 times per week was associated with GERD symptoms.

Although we found no difference in the effect of low-fat vs. full-fat dairy on GERD symptoms, findings from two other studies suggest that there may be a relationship between the fat content of dairy and GERD. Feldman & Barnett[13] observed a significant positive correlation between fat content of milk and self-reported frequency of HB in a cross-sectional study. Babka and Castell[14] observed a decrease in LES pressure following ingestion of whole milk and an increase in LES pressure with nonfat milk when they measured changes in the LES pressure of six young, healthy adults (19-24 years) in response to various beverages. Given that decreased LES pressure is hypothesized to contribute to the pathogenesis of GERD[50], these data suggest that dietary fat intake could affect GERD symptoms. However, these findings are only generalizable to young adults, which is an important limitation given that GERD is more prevalent among adults older than 50 years[19]. Additionally, consumption of a high fat diet delays gastric emptying and leads to gastric distention, a suggested trigger of TLESRs, which is another factor linked to the pathogenesis of GERD[7]. Although both total fat and saturated fat intake have been associated with risk for GERD symptoms[34], the literature has not distinguished between the different sources of saturated fat, so it is unclear what role, if any, dairy fat may play.

In summary, the literature on the impact of dairy on symptoms of GERD is very inconsistent. Some of these inconsistencies could be attributed to the large heterogeneity of studies in terms of study population, outcomes measured, and tools used to collect data. There are several discrepancies about the criteria used to define GERD symptoms[19], and multiple studies, including ours, used different forms of GERD questionnaires to assess symptoms. These

questionnaires rely on self-reported data from participants; therefore, are subject to recall bias, and the rating scales employed could be open to interpretation. Some studies opted for more objective measurement tools like esophageal pH-impedance monitoring and intraluminal pressure measurements, but made no observations on how these findings compared to clinical symptoms experienced by participants. Another hypothesis that may explain these inconsistencies is the potential role of food intolerances in the development of GERD. Caselli et al.'s[10], double-blind, randomized, controlled pilot trial of leukocytotoxic test-based exclusion diets with GERD patients provides compelling evidence for this theory. Interestingly, this study found that milk was the most frequent food type to induce leukocytotoxic test positivity. While this may indicate that individuals with GERD symptoms may more likely be intolerant to milk, it also suggests that the relationship between diet and GERD may be more individualized than previously thought.

Strengths of this study include the randomized, controlled study design; strong adherence rates; the standardized wash-in diet limited in dairy; and the inclusion of a wide variety of dairy foods, including fermented vs. non-fermented and full-fat vs. low-fat versions. However, our study also had several limitations. Data was collected from a study that was not designed to specifically test the impact of dairy foods on GERD symptoms. Thus, the study may not have been adequately powered to detect differences in GERD symptoms between the three study arms, especially in the sensitivity analyses. It is possible that some selection bias may be present, as individuals who are aware of GERD symptoms in response to dairy may have chosen not to participate. Additionally, the generalizability of our findings to populations other than

those with the metabolic syndrome is uncertain, and the duration of the intervention may have been insufficient to fully capture dairy effects on GERD symptoms.

In conclusion, our study indicates that consuming three servings of dairy per day, regardless of fat content, does not have an effect on AR or HB in men and women with the metabolic syndrome. This suggests that consuming dairy may not necessarily worsen or alleviate the common symptoms of GERD. Given that GERD is a widely prevalent condition, and clinicians often offer dietary advice as a first line of therapy, it is important to better understand the role of specific dietary factors in the pathogenesis and management of GERD. Future intervention studies should investigate the effects of different types of dairy foods on AR and HB among participants that have been clinically diagnosed with GERD. Such studies may also benefit from considering the role of individual food intolerances and other lifestyle or dietary factors that may mediate symptoms of GERD, like meal size, macronutrient composition of meals, and the time lapse between eating meals and lying down.

REFERENCES

1. El-Serag H, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut.* 2014;63:871-880.
2. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Group GC. The Montreal Definition and Classification of Gastroesophageal Reflux Disease: A Global Evidence-Based Consensus. *American Journal of Gastroenterology.* 2006;101:1900-1920.
3. De Giorgio F, Palmiero M, Esposito I, Mosca F, Cuomo R. Pathophysiology of gastro-oesophageal reflux disease. *Acta Otorhinolaryngologica Italica.* 2006;26:241-246.
4. Fox M, Forgacs I. Gastro-oesophageal reflux disease. *BMJ.* 2006;332:88-93.
5. Sethi S, Richter JE. Diet and gastroesophageal reflux disease: role in pathogenesis and management *Current Opinion in Gastroenterology.* 2017;33:107-111.
6. Badillo R, Francis D. Diagnosis and treatment of gastroesophageal reflux disease. *World Journal of Gastrointestinal Pharmacology and Therapeutics.* 2014;5(3):105-112.
7. Surdea-Blaga T, Negrutiu DE, Palage M, Dumitrascu DL. Food and Gastroesophageal Reflux Disease. *Current Medicinal Chemistry.* 2017;24:1-14.
8. Festi D, Scaioli E, Baldi F, et al. Body weight, lifestyle, dietary habits and gastroesophageal reflux disease. *World Journal of Gastroenterology.* 2009;15(14):1690-1701.
9. Ndebia EJ, Sammon AM, Umapathy E, Iputo JE. Diet affects reflux in a rural African Community. *Acta Gastro-Enterologica Belgica.* 2017;LXXX:357-360.

10. Caselli M, Zuliani G, Cassol F, et al. Test-based exclusion diets in gastro-esophageal reflux disease patients: A randomized controlled pilot trial. *World Journal of Gastroenterology.* 2014;20(45):17190-17195.

11. Nam SY, Park BJ, Cho Y-A, et al. Different effects of dietary factors on reflux esophagitis and non-erosive reflux disease in 11,690 Korean subjects *Journal of Gastroenterology.* 2017;52:818-829.

12. Chowdhury SD, George G, Ramakrishna K, et al. Prevalence and factors associated with gastroesophageal reflux disease in southern India: A community-based study. *Indian Journal of Gastroenterology.* 2019;38(1):77-82.

13. Feldman M, Barnett C. Relationships between the acidity and osmolality of popular beverages and reported postprandial heartburn. *Gastroenterology.* 1995;108(1):125-131.

14. Babka JC, Castell DO. On the genesis of heartburn: The effects of specific foods on the lower esophageal sphincter. *The American Journal of Digestive Diseases.* 1973;18(5):391-397.

15. Badillo R, Francis D. Diagnosis and treatment of gastroesophageal reflux disease. *World Journal of Gastrointestinal Pharmacology and Therapeutics.* 2014;5(3):105-112.

16. DeVault KR, Castell DO. Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease. *American Journal of Gastroenterology.* 2005;100:190-200.

17. Ebrahimi-Mameghani M, Sabour S, Khoshbaten M, Arefhosseini SR, Saghafi-Asl M. Total diet, individual meals, and their association with gastroesophageal reflux disease *Health Promotion Perspectives.* 2017;7(3):155-162.

18. El-Serag H, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review *Gut.* 2014;63:871-880.

19. Eusebi LH, Ratnakumaran R, Yuan Y, Solaymani-Dodaran M, Bazzoli F, Ford AC. Global prevalence of, and risk factors for, gastro-oesophagal reflux symptoms: a meta-analysis. *Gut.* 2018;67(3):430-440.

20. Wu P, Zhao X-H, Ai Z-S, et al. Dietary Intake and Risk for Reflux Esophagitis: A Case-Control Study *Gastroenterology Research and Practice.* 2013;2013:9 pages.

21. Oliver K, Davies G, Dettmar P. Diet and lifestyle as trigger factors for the onset of heartburn . *Nursing Standard.* 2011;25(36):44-48.

22. De Giorgi F, Palmiero M, Esposito I, Mosca F, Cuomo R. Pathophysiology of gastro-oesophageal reflux disease. *Acta Otorhinolaryngol Ital.* 2006;26(5):241-246.

23. Rubenstein JH, Chen JW. Epidemiology of Gastroesophageal Reflux Disease. *Gastroenterology Clinics of North America.* 2014;43(1):1-14.

24. Yoshikawa I, Nagato M, Yamasaki M, Kume K, Otsuki M. Long-term treatment with proton pump inhibitor is associated with undesired weight gain. *World Journal of Gastroenterology.* 2009;15(38):4794-4798.

25. Eusebi LH, Rabitti S, Artesiani ML, et al. Proton pump inhibitors: Risks of long-term use. *Journal of Gastroenterology and Hepatology.* 2017;32(7):1295-1302.

26. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: Obesity and the risk for gastroesophageal reflux disease and its complications. *Annals of Internal Medicine.* 2005;143(3):199-211.

27. Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. *Journal of the American Medical Association* 2003;290(1):66-72.

28. Corley DA, Kubo A, Zhao W. Abdominal obesity, ethnicity and gastro-oesophageal reflux symptoms. *Gut.* 2007;56(6):756-762.

29. Festi D, Scaioli E, Baldi F, et al. Body weight, lifestyle, dietary habits and gastroesophageal reflux disease. *World Journal of Gastroenterology.* 2009;15(14):1690-1701.

30. Wu JC, Mui LM, Cheung CM, Chan Y, Sung JJ. Obesity is associated with increased transient lower esophageal sphincter relaxation. *Gastroenterology.* 2007;132(3).

31. Zheng Z, Nordenstedt H, Pedersen NL, Lagergren J, Ye W. Lifestyle factors and risk for symptomatic gastroesophageal reflux in monozygotic twins. *Gastroenterology.* 2007;132(1):87-95.

32. Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Lifestyle related risk factors in the aetiology of gastro-oesophageal reflux. *Gut.* 2004;53(12):1730-1735.

33. Mone I, Kraja B, Bregu A, et al. Adherence to a predominantly Mediterranean diet decreases the risk of gastroesophageal reflux disease: a cross-sectional study in a South Eastern European population *Diseases of the Esophagus.* 2016;29:794-800.

34. El-Serag HB, Satia JA, Rabeneck L. Dietary intake and the risk of gastro-oesophageal reflux disease: a cross sectional study in volunteers. *Gut.* 2005;54:11-17.

35. Lacy BE, Carter J, Weiss JE, Crowell MD. The effects of intraduodenal nutrient infusion on serum CCK, LES pressure, and gastroesophageal reflux. *Neurogastroenterology and Motility.* 2011;23(7):631-e256.

36. Iwakiri K, Kobayashi M, Kotoyori M, Yamada H, Sugira T, Nakagawa Y. Relationship between post-prandial esophageal acid exposure and meal volume fat content. *Digestive Diseases and Sciences.* 1996;41(5):926-930.

37. El-Serag HB, Satia JA, Rabeneck L. Dietary intake and the risk of gastro-oesophageal reflux disease: a cross sectional study in volunteers *Gut.* 2005;54:11-17.

38. Yancy WSJ, Provenzale D, Westman EC. Improvement of gastroesophageal reflux disease after initiation of a low-carbohydrate diet; five brief case-reports. *Alternative Therapies in Health and Medicine.* 2001;7(6):116-119.

39. Austin GL, Thiny MT, Westman EC, Yancy WSJ, Shaheen NJ. A very low-carbohydrate diet improves gastroesophageal reflux and its symptoms. *Digestive Diseases and Sciences.* 2006;51(8):1307-1312.

40. Caselli M, Zuliani G, Cassol F, et al. Test-based exclusion diets in gastro-esophageal reflux disease patients: A randomized controlled pilot trial *World Journal of Gastroenterology.* 2014;20(45):17190-17195.

41. Gudjonsson H, McAuliffe TL, Kaye MD. The effect of coffee and tea upon lower esophageal sphincteric function. *Laeknabladid.* 1995;81(6):484-488.

42. Cohen S, Booth GHJ. Gastric acid secretion and lower-esophageal-sphincter pressure in response to coffee and caffeine. *New England Journal of Medicine.* 1975;293(18):897-899.

43. Kim J, Oh SW, Myung SK, et al. Association between coffee intake and gastroesophageal reflux disease: a meta-analysis. *Diseases of the Esophagus.* 2014;27(4):311-317.

44. Kaltenbach T, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. *Archives of Internal Medicine.* 2006;166(9):965-971.

45. Kim YK, Moon JS, Ryu SH, Lee JH, Kim YS. The relationship between the popular beverages and reported post-prandial heartburn. *Korean Journal of Gastroenterology.* 2010;55(2):109-118.

46. Stake-Nilsson K, Hultcrantz R, Unge P, Wengstrom Y. Changes in symptoms and lifestyle factors in patients seeking healthcare for gastrointestinal symptoms: an 18-year follow-up study. *European Journal of Gastroenterology & Hepatology.* 2013;25(12):1470-1477.

47. Mehta RS, Song M, Staller K, Chan AT. Association between beverage intake and incidence of Gastroesophageal Reflux Symptoms. *Clinical Gastroenterology and Hepatology.* 2019.

48. Gomi A, Yamji K, Watanabe O, et al. Bifidobacterium bifidum YIT 10347 fermented milk exerts beneficial effects on gastrointestinal discomfort and symptoms in healthy adults: A double-blind, randomized, placebo-controlled study. *Journal of Dairy Science.* 2018;101(6):4830-4841.

49. Wei T-Y, Hsueh P-H, Wen S-H, Chen C-L, Wang C-C. The role of tea and coffee in the development of gastroesophageal reflux disease. *Tzu Chi Medical Journal.* 2019;31(3):169-176.

50. De Giorgi F, Palmiero M, Esposito I, Mosca F, Cuomo R. Pathophysiology of gastro-oesophageal reflux disease. *Acta Otorhinolaryngologica Italica.* 2006;26(5):241-246.

TABLES AND FIGURES

Table 1. Baseline characteristics of study participants included in the *per protocol* analysis

Variable	Limited	Low-fat	Full-fat	P-value
	N = 20	**N = 23**	**N = 20**	
Age (y)	56 (45; 69)	63 (58; 71)	64 (57; 67)	0.328
Male sex (%)	60	57	60	0.965
Caucasian race (%)*	70	78	75	0.631
Body Mass Index (kg/m^2)	33.2 (28.7; 36.2)	31.4 (26.8; 40.0)	31.0 (27.4; 35.4)	0.876
Waist circumference (cm)	112 ± 10	110 ± 17	111 ± 13	0.944
Total energy intake (kcal)	1968 (1621; 2269)	2029 (1505; 2428)	1805 (1399; 2113)	0.429
Total fat intake (% of total energy)	34.1 ± 58.4	34.3 ± 7.9	34.8 ± 9.2	0.963
Total fiber intake (g)	23.9 ± 9.3	25.1 ± 8.7	21.6 ± 9.3	0.435
Fiber (g/1,000 kcal)	12.5 ± 5.2	12.6 ± 3.5	11.9 ± 4.2	0.847
Physical activity level (MET-h/wk)	38.0 (26.0; 55.8)	40.5 (24.5; 92.7)	36.3 (18.9; 48.1)	0.311
Has past medical history of GERD (%)	10	17	25	0.464

Is taking GERD medication (%)	15	13	15	0.978
Never experienced acid regurgitation (%)	95	87	80	0.368

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

*Sample size for Caucasian Race: limited n= 20, low-fat n= 22, full-fat n= 20

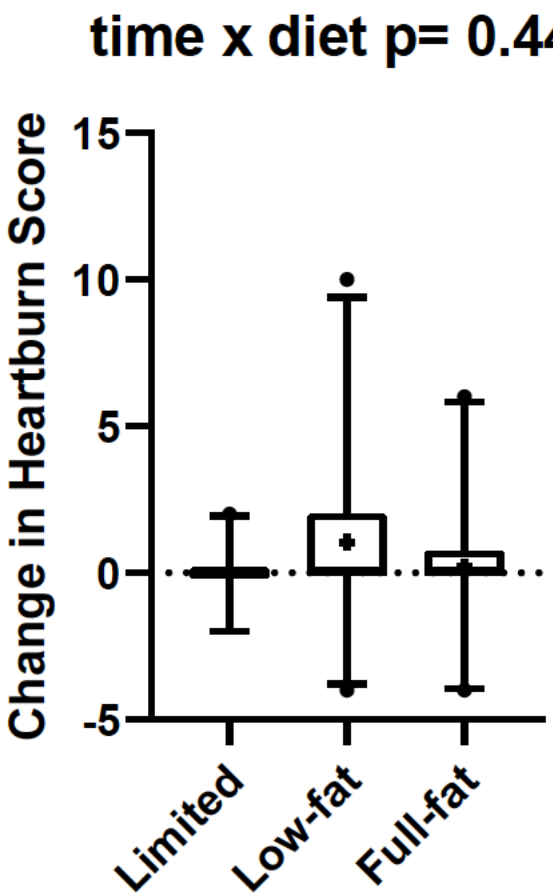
Table 2. Presence of Acid Regurgitation in the *per protocol* analysis

	Never experienced Acid Regurgitation	**Experienced Acid Regurgitation***
Limited Dairy (n=20)		
CRC 1	19 (95)	1 (5)
CRC 2	17 (85)	3 (15)
Low-fat Dairy (n=23)		
CRC 1	20 (87)	3 (13)
CRC 2	19 (83)	4 (17)
Full-fat Dairy (n=20)		
CRC 1	16 (80)	4 (20)
CRC 2	18 (90)	2 (10)

Data are n (%)

*Experienced Acid Regurgitation include participants who indicated experiencing acid regurgitation either 0-1 times/month, 2-4 times/month, 1-6 times/week, or 1+ times/day

Figure 1. Change in the Heartburn Score in the three dietary intervention groups (*per protocol* analysis, n=63). Boxes represent 25th-75th percentiles, and whiskers 5th and 95th percentiles, with outliers represented by a solid dot. Medians are represented by horizontal bars across the boxes and means are represented by crosses. The p-value for the time by diet interaction from the overall repeated measures analysis of variance is displayed at the top.



APPENDIX 1: Inclusion and exclusion criteria

Inclusion criteria:	Exclusion criteria:

• Age 18 – 75 years
• Three of the following five criteria:
  ◦ Increased waist circumference:
  ▪ In Asians: ≥ 90 cm in men, ≥ 80 cm in women
  ▪ In all other races: ≥ 102 cm in men, ≥ 88 cm in women
  ◦ Fasting plasma triglycerides ≥ 150 mg/dL, or drug treatment for elevated triglycerides
  ◦ High-density lipoprotein (HDL)-cholesterol <40 mg/dL in males or <50 mg/dL in females, or drug treatment for reduced HDL-cholesterol
  ◦ Systolic blood pressure ≥ 135 mm Hg or diastolic blood pressure ≥ 85 mm Hg or drug treatment for hypertension
  ◦ Fasting plasma glucose ≥ 100 mg/dL or previous diagnosis of diabetes
• Body weight within 10% of current weight over the last 6 months before starting the study
	• Antidiabetic medications or insulin within the last 6 months
	• Uncontrolled diabetes, defined as HbA_{1c} > 8.0%
	• Allergic to milk protein
	• Presence of major chronic inflammatory or autoimmune disease (with acute symptoms or CRP > 10 mg/L), or malabsorption syndromes
	• Presence or history of liver disease or end-stage renal disease requiring dialysis
	• Uncontrolled thyroid disease
	• Inability or unwillingness to eat the provided foods
	• Any contraindications for MRI scan other than body size
	• Intake of drugs likely to interfere with study endpoints, including, but not limited to; corticosteroids, anabolic steroids, anti-psychotic medications, antiretroviral drugs, and immunosuppressive drugs (within 3 months of starting the study)
	• Regular high-dose use of non-steroidal anti-inflammatory drugs (more than 3 times per week

• Able to come to the FHCRC for all scheduled study visits including picking up study foods and materials • Able and willing to attend a study initiation meeting of ~1.5 hour duration, two clinic visits of ~5 hours duration each at the University of Washington (UW) Medial Center Translational Research Unit (TRU), and two clinic visits of ~2 hours duration each at the UW Bio-Molecular Imaging Center (BMIC) • Willing to follow the dietary regimen • Able to provide informed consent	and more than 600 mg per day, within 3 months of starting the study) • Presence or recent history of anemia (within 3 months of starting the study) • History of bariatric surgery • Participation in an intervention study or weight-loss program (within 3 months of starting the study) • Alcohol intake > 2 drinks per day (within 12 months of starting the study) • Use of tobacco products, eCigarettes, or recreational drugs on more than 2 days per month (within 12 months of starting the study) • Current or recent (within 12 months of starting the study) pregnancy or breastfeeding, or intention of becoming pregnant in the next 6 months • Fasting Triglycerides >1000mg/dL • Any cancer other than non-melanoma skin cancer in the last 3 years • Other significant health condition, as determined by researcher and Physician of Record, that makes the individual unfit to participate

APPENDIX 2: Gastroesophageal Reflux Disease (GERD) Questionnaire

Did you experience any acid regurgitation since you started the study (visit 1) / started the intervention (visit 2)?

□ Yes (complete the following section) □ No (skip to the next section)

How often did you experience acid regurgitation?

→ ***Regurgitation is a sour taste from stomach contents backing up into your throat or mouth***

0-1 times/month □ 1 weekly/1-6 times/week □ 3

2-4 times/month □ 2 daily 1+ times/day □ 4

Did you experience any heartburn or reflux symptoms since you started the study (visit 1) / started the intervention (visit 2)?

□ Yes (complete the following section) □ No (finished with questionnaire)

How often (if ever) did you experience heartburn during the day?

→ ***Heartburn is a burning pain or discomfort behind your breastbone***

0-1 times/month □ 1 weekly/1-6 times/week □ 3

2-4 times/month □ 2 daily 1+ times/day □ 4

If you experienced heartburn during the day, how would you rate it?

mild □ 1 moderate □ 2 severe □ 3

How often (if ever) did you experience heartburn during the night?

0-1 times/month □ 1 weekly/1-6 times/week □ 3

2-4 times/month □ 2 daily 1+ times/day □ 4

If you experienced heartburn during the night, how would you rate it?

mild □ 1 moderate □ 2 severe □ 3