Uncovering Historic and Modern Discrepancies in the Paleo Diet

Dorothy Agoulnik, MS

Gerald J. and Dorothy R. Friedman School of Nutrition Science and Policy at Tufts University

Boston, MA USA Defense Date: April 29, 2019

Thesis Committee

Nicola M. McKeown, PhD (Advisor, Chair)

Elena Naumova, PhD

Mathieu Lalonde, PhD

Acknowledgements

Thank you to my Thesis Committee for their ongoing expertise and patience during this process: Dr. Elena Naumova, Dr. Lalonde, and especially to Dr. Nicola McKeown for her guidance as my Thesis Chair and Advisor.

Thank you to the ADAPT Research team, including Micaela Karlsen, Gail Rogers, Kara Livingston, and Akari Miki, who supported the data collection and analysis performed. I would also like to thank members of the Nutritional Epidemiology Program including Kenneth Chui who helped guide my analysis of the Paleo components. Finally, I would like to thank the Tufts Friedman School of Nutrition Science and Policy for their outstanding student support and promise for opportunity.

Abstract

Background:

The evolution of the human diet over the past century has led to an alarming increase in the incidence of adverse health effects in the general population. It is estimated that the typical Western diet (WD) is comprised of approximately 60% ultra-processed foods including: cereals, vegetable oils, and sugar (1). People employ a variety of dietary patterns to promote a healthier lifestyle or manage disease in an attempt to offset the deleterious health effects of the WD. Unfortunately, these newly adopted patterns often leave compliant followers with deficiencies in beneficial nutrients such as fiber. Dietary fiber intake is a key attribute of a healthy eating pattern and may have a significant impact on health markers affecting chronic health disease risk such as BMI, cholesterol, triglycerides, blood pressure, and inflammation (2). Current literature suggests the Paleolithic (Paleo) diet (PD), theoretically provides more dietary fiber compared to the WD, but it remains unclear if this is true in practice.

Aims:

The PD is primarily adopted to combat current maladaptation to industrialized diets, which contribute to chronic disease risk. The aims of this study are 1) to evaluate fiber and total energy intake among randomized controlled trials (RCTs) and observational studies using a PD 2) to evaluate fiber and total energy intake among self-reported adheres of the PD 3) to understand how populations are adhering to the principles of the PD by evaluating the PD with gluten-free and dairy-free diet groups. The following study demonstrates there are major discrepancies in the historic, hypothetical, and modern implementations of the PD.

Methods:

A literature search was performed to identify PD studies that reported energy intake and fiber intake. The search was done through PubMed and yielded 157 studies. A total of 7 studies were included in the review of the literature. The ADAPT Feasibility Survey, a cross sectional web-based survey of a convenience sample of U.S. adults was used to capture self-reported recipe and diet education. Nutrient data of the participants were analyzed from the ADAPT Pilot Study for both daily fiber and energy intake. The ADAPT Pilot Study was also used for analyzing daily fiber and energy intake in self-reported gluten-free and dairy-free adherers.

Results:

Subjects in RCTs and observational studies did not meet modern Paleo hypothetical intakes (19.3g/1000kcal), except for one RCT (20.2g/100kcal). Four out of seven studies did not meet USDA recommended daily fiber intakes of 14g/1000kcal. In all studies, calorie intakes were lower in the PD group, except for one study attempting to keep intervention groups isocaloric. It remains unclear if this was successful because adherence was not measured and the PD group lost more weight. Additionally, there is variation in the PD definition being used in research settings. Self -reported PD adherers from the ADAPT Pilot Study did not meet historic or modern hypothetical fiber or calorie intakes. This population also did not meet USDA fiber or calorie recommendations but did meet self-reported hypothetical PD bloggers fiber intakes. Finally, although no conclusion can be made based on the analysis, the PD had the lowest associated fiber intake compared to dairy-free or gluten-free diet followers.

Conclusions:

A lack of clear definition of the PD has led to modern discrepancies in the literature when performing PD interventions. The purported health benefits from these interventions further remains unclear due to the discrepancies in interpretation. Most likely, a reduction in calorie intake can be attributed to the health marker improvements in the studied populations. Future research should measure Paleo adherence while implementing the diet to discern the differences between adherence benefits versus reduction in energy intake. Additionally, it should aim to clarify the PD for intervention protocols so that data can be compared between studies. As we have seen in the literature, the best diet for weight loss is the one to which the patient can best adhere. Thus, the PD may only be more beneficial for some populations and specific dietary goals, such as improving metabolic syndrome biomarkers. Future studies should aim to understand which diet has the greatest nutrient density and can be successfully sustained for a prolonged period of time by the majority of the US population.

Table of Contents

Chapter 1. Introduction

For the greater part of the past hundred years, the major contributing factors to all-cause mortality in the United States have been cardiovascular disease (CVD) and cancer (3). Diabetes and obesity are major risk factors for both heart disease and cancer (4). The prevalence of obesity in United States adults was 39.8% between 2015-2016 (5). This represents a 5% increase in the prevalence of obesity over a span of 10 years. Obesity rates continue to remain high in the US and are expected to increase in some countries (5). In addition, it is estimated that over 30 million people, or 9.4%, of the US population had diabetes in 2017, with 23.8% of these diabetics being undiagnosed (6). The percentage of the US population with diabetes increased from 5.6% in 2005 to 7.4% in 2015, which represents an increase of approximately 7 million people (7). The increasing prevalence of potentially modifiable risk factors, such as diet, may foreshadow greater incidence of CVD and cancer.

The evolution of the human diet over the past century has increased adverse health effects at an alarming rate. A number of dietary parameters have been changing over the years, including: glycemic load, added sugars, fatty acid ratios, micronutrient composition, sodium/potassium ratios, and fiber content (8). Modern foods, a result of the industrial revolution, are often nutrient poor and ultra-processed (9). It is estimated that the typical Western diet (WD) is comprised of approximately 60% of ultra-processed foods including: cereals, vegetable oils, and sugar (1). This is in sharp contrast to the diet of humans during the Paleolithic era, which was comprised of vegetables, tubers, fruits, as well as animal flesh, bones, brains, and other organs (1). Genetic and human microbiota research suggest that WDs have strongly contributed to the rise of chronic disease in modern society due to a decrease in microbiota accessible carbohydrates (MACs) and an increase in refined sugars and processed foods (10–12).

People employ a variety of dietary patterns to promote a healthier lifestyle, or manage disease, in an attempt to offset the deleterious health effects of the WD. Unfortunately, these newly adopted patterns often leave compliant followers with deficiencies in beneficial nutrients such as fiber. Dietary fiber intake is a key attribute of a healthy eating pattern and may have significant impact on health markers affecting chronic health disease risk such as BMI, cholesterol, triglycerides, blood pressure, and inflammation (2). Current literature suggests the Paleolithic (Paleo) diet (PD) theoretically provides more dietary fiber compared to the WD, but it remains unclear if this is actually the case in practice.

It additionally remains unclear if caloric restriction or hypothetical increases in total daily fiber intake can explain the purported health benefits. Understanding how fiber and total energy intake vary among randomized control trials and observational studies will explain if a main constituent of the diet, such as an increase in fiber intake, is a predictor of beneficial outcomes on cardiovascular and metabolic disease markers. Further comparing the PD with gluten-free and dairy-free groups will help to understand how populations are adhering to the principles of the PD. The following study demonstrates there are major discrepancies in the historic, hypothetical, and modern implementations of the PD.

Chapter 2 reviews the history and dietary attributes of the PD. Chapter 3 provides an overview of observational and intervention studies that administered a PD and reported intake of dietary fiber. These studies were comprehensively reviewed and compared to the hypothetical modern intakes of dietary fiber discussed in Chapter 2. Chapter 4 reports the total fiber intake of individuals who self-reported adhering to a PD in the ADAPT Study and further compares these values to the hypothetical intakes of dietary fiber discussed in Chapter 2. Thus, Chapter 3 provides an overview of how researchers and study participants adhere to the diet, while Chapter 4 investigates how a modern American population adopts the dietary pattern. In Chapter 5, an analysis is performed using the ADAPT Study to understand how fiber intake differs among people who self-report adhering to a Paleo, gluten-free, or dairy-free diet. Finally, Chapter 6 outlines the discrepancies seen in the modern PD and provides future directions for research.

Chapter 2. Uncovering Discrepancies in the Paleo Diet: A Historic Perspective

2.1 Paleo Diet History

The Paleolithic period ended as agriculture began emerging in the Neolithic period, about 10,000 years ago. Up to that point, the human species consumed what it hunted or gathered. Later, they additionally consumed what they grew or manufactured. The PD, also known as the Stone-Age diet, first gained popularity in 1975 after the publication of 'The Stone Age Diet' by gastroenterologist Walter Voegtlin (8). The book aimed to answer the question: "Is modern man actually better or worse off nutritionally than was his Stone Age forbear?" (8). It wasn't until 1985, however, that the term "Paleolithic nutrition" was coined by Boyd Eaton and Melvin Konner (1). Thus, the PD is based on the premise that modern humans should eat like their ancestors to combat current maladaptation attributed to modern industrialized diets which lead to increased chronic disease risk (13). This premise of evolutionary discordance, as coined by Eaton and Konner (1), has been used to explain increasing rates of chronic disease such as cardiovascular disease and type 2 diabetes. Evolutionary discordance emphasizes the idea that modern agriculture and the introduction of processed foods is changing faster than Man's ability to adapt, thus leading to increased chronic disease risk.

2.2 Historic Discrepancies in the Paleo Diet

The evolutionary discordance theory coined in 1985 gave rise to academic and cultural interest in evolutionary nutrition. In 2002, Loren Cordain published a book entitled "The Paleo Diet". Cordain trademarked the term "Paleo diet", which quickly became extremely popular (11). The material in Cordain's book was based on research by Dr. Stanley Eaton, who produced a nutrient analysis from six groups of hunter-gatherers living in marginal habitats: 1) the Hadza of

Tanzania, 2) the !Kung, 3) the ≠Kade, 4) San of the Kalahari, 5) the Philippine Tasaday, and 6) Australian Aboriginals. The study locations were rather isolate, and data collected rarely included foods consumed outside of the study camp (10). Diets were highly dependent on the resources available in the particular environment of the study camp and therefore differed by latitude, climate, and season (14). It is estimated that hunter-gatherers consumed anywhere from 19%-35% of energy intake from animal protein, 22-40% from carbohydrates, and 28-58% from fat (15,16). The ranges are broad due to variation in the food supply. For example, energy intake in traditional Inuit diets in Alaska natives are high in dietary fat (50%), moderate in protein (30-35%), and low in total carbohydrate (15-20%) because their main food source is derived from seal and whale meat (17). In contrast, the diet of indigenous persons of New Guinea is high in dietary carbohydrates, approximately 70% of energy intake, which is derived mostly from potatoes and fruit (18). Using the *Ethnographic Atlas*, Cordain et al. later estimated that the diets of Paleo followers worldwide ranged between 45-65% of daily calories from animal sources with the remaining derived from plant-based sources (15). The limitations of using the *Ethnographic Atlas* to estimate energy intake from food sources is that its authors were not nutritional scientists and, therefore, not focused on diet. Furthermore, the authors of the *Ethnographic Atlas* lacked proper training in dietary collection techniques. It also remains unclear whether or not communities termed as “hunter-gatherers” in the Atlas were exclusively hunter-gatherers or included other, displaced, agricultural people (19). According to Cordain et al., portions of the Atlas have been verified. However, Neil Mann, a co-author of a paper by Dr. Eaton where the Atlas’s data was employed, commented that he was unaware of any study that validated the food records in the Ethnographic Atlas (20). Thus, the nutrient estimates of the ‘Paleo Diet’ obtained using data from the *Ethnographic Atlas* are controversial at best. Although Cordain et al. were able to estimate the percentage of diet composition from animal or plant sources, they note the macronutrients to be highly variable ranging from 19-35% protein, 22-40% carbohydrate, and 28-58% fat (15). This does not change the nutrient quality of the diet, which remains constant and very high.

Historic and current versions of the PD concur it is based on human ancestral intake from the Paleolithic period, which excludes farmed and processed grains and dairy. The following section will introduce incongruities.

2.3 Modern Discrepancies in the Paleo Diet: Research and Society

The modern PD allows all fruits/vegetables, lean game, eggs, fish, shellfish, nuts & seeds, animal fats, and unrefined oils. It excludes dairy, grains and pseudocereals (thus, gluten), legumes, processed foods, sugar, artificial sweeteners, vegetable oils, margarine, and synthetic trans fats resulting from partial hydrogenation (21). Since 2002, popularity in the PD has grown and is currently one of the top diet trends. In fact, in 2013 and 2014 the PD was the most searched diet using the Google engine (22,23). A 2014 survey of over 500 registered dietitians, predicted that the PD would be the top diet trend of the year (24).

Eaton JC and Iannotti note that the current world food system makes adopting a true PD unachievable (25). To help consumers in the trending marketplace, the Paleo Foundation has released a Certified Paleo logo that brands can adopt for shoppers to easily locate adherent brands (26). Unfortunately, food companies have been quick to profit from the diet’s popularity by flooding the shelves of local grocery stores with processed foods that are made from “Paleo” ingredients. As mentioned previously, the preliminary basis of the PD is the removal of all processed items in order to eat like indigenous peoples who walked the earth 10,000 years ago.

The introduction of “Paleo” processed food makes adopting a true PD even less achievable as followers of the regime are now tempted with “Paleo” versions of their favorite desserts and snacks.

The modern PD has undergone various revisions based on the adhering population. For example, a modified PD was created by Dr. Wahls for people with Multiple Sclerosis (27). The Autoimmune Paleo Diet is another version of the PD, outlined by Dr. Loren Cordain, who discovered certain foods can trigger inflammatory reactions in people with autoimmune disease (28). Additionally, Chris Kresser has published his own Personal Paleo Code that allows for the reintroduction of dairy and legumes, assuming they are tolerated by the individual (29). The lack of a clear PD definition in present times has led intervention studies to adopt versions that include/exclude certain foods, as summarized in Chapter 3 Table 2. A two-year study of the PD by Mellberg et al. (2014) excluded dairy, cereals, added salt, refined fats, and sugar but not legumes. It was based on a macronutrient profile of 30% total calories from protein, 40% from fat, and 30% from carbohydrate (30). A short intervention with the PD by Österdahl et al. (2008) eliminated all dairy, grains, legumes, charcuterie, canned food, sugar, liquor, and salt (31). It also limited consumption of dried fruit, salted seafood, honey, cured meats, potatoes, mineral water, and fatty cuts of meat. A study by Otten et al. (2018) eliminated dairy, cereals, legumes, added sugar and salt (32). Another study by Jönsson et al. (2009) excluded dairy, cereals, beans, refined fats, sugar, candy, soft drinks, beer, and added salts (33) while limiting eggs, nuts, dried fruit, potatoes, rapeseed or olive oil, and wine. There is profound variation in the definition of the PD in the current literature. The terms cereal and grain are used inconsistently, leaving confusion as to the exact nature of the difference and the incorrect impression that the terms are interchangeable. Alcohol is only sometimes mentioned as excluded whereas some studies allow wine consumption (33).

The abstract definition of the PD complicates the comparison of results generated from RCT and observational studies that examined the effects of the PD diet versus control diets (RCT) or the association of low compared to high PD diets (observational studies using scoring method). Additionally, the criteria used to determine the degree of 'adherence' to the PD are unclear. A group of researchers have developed and applied a Paleo adherence score in three different study populations. This score was created in 2014 by Whalen et. al. and has since been replicated twice, in 2016 and 2017, by the same group (34–36). The authors created Paleolithic and Mediterranean diet (MD) scores in a similar manner: foods and point values were determined using published guidelines for each diet (34). Higher scores were given to foods characteristic of the diet pattern and for when foods not characteristic of the diet were consumed less or not at all. Interestingly, the Paleolithic score was created based on Dr. Eaton and Konner's historic PD from 1985, whose questionable methodology was previously described in section 2.2. It was originally created to investigate the interactions between multiple, weak associations of foods and nutrients with colorectal adenoma risk. The latter applications investigated all-cause and cause-specific mortality as well as biomarkers of inflammation and oxidative balance in adults. All three studies (34–36) compared the Paleo adherence score with the Mediterranean adherence score and observed that both dietary patterns were inversely associated with colorectal adenoma risk, all-cause and cause-specific morbidity, inflammation, and oxidative balance. This is the only research group, to our knowledge, that has created and applied a PD score to observational data.

The PD is loosely defined by researchers with little understanding of adherence. It is futile to compare results between studies without accepted standard definitions. The current climate suggests large variation between professionals, bloggers, and society. In order to standardize results, future research should clearly define the PD and apply this definition consistently to future studies. Furthermore, a validated PD score could be created and applied to facilitate degree of adherence to the PD and better understand individual differences to PD interpretation (peanuts, pseudo-cereals, potatoes, etc.).

2.4 Purported Health Benefits of Paleo Diets

People follow the PD for a variety of reasons including chronic disease prevention (9) or the treatment of disease. The Paleo Diet has been employed in an attempt to treat type 2 diabetes (37,38), IBD (39), metabolic syndrome (40), and autoimmune conditions such as Multiple Sclerosis (41). Few RCTs have been conducted to compare the health effects of adhering to a PD. Typically, the main outcomes of interest in randomized controlled trial studies include a change in body fat distribution (ex. waist circumference, fat mass), blood pressure, glucose metabolism markers (ex. fasting glucose, fasting insulin), serum lipids, and high/low density lipoprotein cholesterol. It has been reported that people adhering to a PD consume less energy per day and feel more satiated per calorie consumed than those following Mediterranean-like diets (42)(38).

2.5 Two Beneficial Attributes of the Paleo diet – Dietary Fiber and Energy Density

As the relationship between PD and health benefits remains unclear it is important to consider two key health-promoting attributes of these diets – (1) dietary fiber and (2) energy density.

Comparing these two components within PD studies in the literature will help to explain whether the purported health benefits of the PD may be attributed to the dietary pattern or are an independent effect of caloric restriction.

2.5.1 Dietary Fiber: Definition, Current Recommendation, Historic Theoretical Fiber, Modern Theoretical Fiber

According to the Food and Drug Administration, fiber is defined as a nondigestible carbohydrate with more than 3 monomeric units that are inherent in food and isolated or synthetic fibers with shown physiologic benefit (43,44). The 2015-2020 Dietary Guidelines for Americans recommends 14 g dietary fiber per day per 1,000 kcal (45). The recommendation varies between 22.4-25.2 g/day for adult females and 30.8-33.6 g/day for adult males, depending on age (45). Historically, when the PD was described by Eaton et al. in 1997, the theoretical dietary fiber intake was 104 g/day or about 3.47% total daily energy (46). The contemporary PD created by Loren Cordain in 2002, based on the top consumed Paleolithic food groups in the United States, had a theoretical fiber intake of 42.5 g/day or about 1.93% energy (21). In 2014, NHANES reported the average daily dietary fiber intake of the American population was 16 g/day (47). This modern estimation of fiber by Cordain is almost 1.8 times less than the estimation based on the historic model and yet 2.7 times the average fiber intake per day of the American population. The estimate of dietary fiber is questionably high in the historic PD model and it is prudent to assume the average American will successfully consume a diet with almost 3 times more fiber. Thus, understanding the fiber intake of the population studies thus far will help explain how the diet is being adopted in modern times. Again, these concepts will help to explain whether the purported health benefits of the PD can be attributed to the dietary pattern or are independently an effect of reduced caloric intake.

2.5.2 Caloric Energy: Definition, Current Recommendation, Historic Theoretical Caloric Intake, Modern Theoretical Caloric Intake

Energy density is a reflection of the number of calories within a unit of volume. A calorie is used to measure the energy content of food and the amount of energy expended by bodily functions. The 2015-2020 Dietary Guidelines for Americans recommends males aged 19+ consume between 2,000- 3,000 kcal per day depending on age and physical activity level (45). Adult women are recommended to consume 1,600-2,400 kcal per day depending on age and physical activity level. When the PD was described by Eaton et al. in 1997, the theoretical daily caloric intake was 3,000 calories for males based on historic PD measurements from indigenous groups (46). In 2002 Loren Cordain created a contemporary PD based on the top consumed Paleolithic food groups in the United States. Although Cordain does not recommend a specific daily caloric intake, the nutrient analysis presented was based on a daily caloric intake of 2,200 calories (21).

2.6 Conclusion

Historic understanding of the PD carries numerous limitations in data including improper sourcing and analysis of nutrient intakes. A lack of clear definition of the PD has led to modern discrepancies in the literature when performing PD interventions. The purported health benefits from these interventions further remain unclear due to differences in interpretation. It is possible the purported health benefits of the PD are independently associated with weight loss due to decrease caloric intake, rather than the dietary pattern.

Chapter 3. Variation in Dietary Fiber Intake and Caloric Intake in Paleo Diets in Research Settings

3.1 Methods

A literature search was performed to identify PD studies that reported energy intake and fiber intake. The search was done through PubMed and yielded 157 studies, as summarized in Flow Chart 1 (see Appendix). The search terms were "Diet, Paleolithic", "Paleo diet", "Paleolithic Diet", "caveman diet", "cavemen diet", "Paleoenvironment", "stone age diet", "stone-age diet", excluding the terms "fossil" or "Archaeolog*" and only including human studies. Using EndNote's search feature, the full-text as well as the citation info exported from PubMed were for the following terms: fiber, fibre, fruit, fruits, vegetable, vegetables and yielded 102 studies after removing duplicates. Five additional sources were included in the full-text assessment, which were identified through hand search. Exclusion criteria included (1) studies not in English (2) populations with a non-normal life course (3) duplicate study populations and acquisition techniques (4) no reports of fiber consumption, or (5) populations from undeveloped countries (such as aborigines). A total of 7 studies were finally included in the review, because dietary fiber intake was reported in the text. Of these, 5 were randomized control trials (RCTs) and 2 were observational studies. These studies are summarized in Table 1.

Table 1. Paleo Diet Literature with Reported Calorie and Fiber Intake

	Study Design	Duration	Sample Size	Intervention Group Size, Age (yrs)	Baseline Calories (kcal)	Calorie Intake After Intervention (kcal)	Baseline Fiber (g)	Fiber Intake After Intervention (g)	Fiber After Intervention (g/1000 kcal)	Meets Modern Paleo Hypothetical (19.3g/1000 kcal)
Lindeberg et al. 2007	RCT, Parallel	12 weeks	29	PD=14, 65±10	Unknown	After 15±5 days, 1,344 ± 521	Unknown	After 15±5 days, 21.4 ± 13.2	15.92	N
				MD=15, 57±7	Unknown	After 15±5 days, 1,795 ± 306	Unknown	After 15±5 days, 26.8 ± 7.4	14.93	N
Osterdahl et al. 2008	Run-In Intervention	3 weeks	14	14, 20-40	2478 (269)	1584 (208)	31.3	32.0	20.20	Y
Jonsson et al. 2009	RCT, Cross Over	6 months	13	13, 64 ± 6	Unknown	PD= 1581 ± 295	Unknown	21 ± 8	13.28	N
						DD= 1878 ± 379		26 ± 8	13.84	N
Boers et al. 2014	RCT, Parallel	2 weeks	32	PD=18, 52 (SD 10.2)	2080	NA	34	NA	16.35	N
				DH=14, 55.4 (SD 9)	2080	NA	28	NA	13.46	N

Mellberg et al. 2014	RCT, Parallel	24 months	49	PD=27, 59 ± 5.5	2000 ± 59.0	−401 ± 89.5	24.6 ± 1.03	−2.70 ± 1.36	13.70	N
				NNR=22, 60.3 ± 5.9	2019 ± 59.1	−251 ± 62.2	21.9 ± 0.97	−0.77 ± 1.15	11.95	N
Whalen et al. 2016	Observational	NA, Data from 1994-1997 and 2002	642	PD Q5=60.4 ± 7.9, Q1=54.5 ± 9.4	Q1=2074 ± 709	Q5= 1808 ± 619	Q1=18.0 ± 7.6	Q5=26.2 ± 11.1	14.49	N
				MD Q5=57.9 ± 8.1, Q1=55.2 ± 9.4	Q1= 1794 ± 717	Q5= 1986 ± 596	Q1= 16.5 ± 8.1	Q5=27.1 ± 10.8	13.65	N
Otten et al. 2017	RCT, Parallel	12 weeks	37	PD=15, 60 (53-64)	2022 (1583–2268)	−291 (−587, −66)	21 (18–26)	23 (15–30)	13.29	N
				PD+Ex=14, 61 (58-66)	1595 (1428–2257)	−530 (−863, −157)	20 (18–22)	14 (13–17)	13.15	N
				Obs=8, 65 (57-67)	1743 (1652–1844)	193 (−80, 393)	22 (18–23)	20 (13–26)	10.33	N
Whalen et al. 2017	Observational	NA, Data from 2003-2007	21,423	PD Q5=66.1 ± 8.8, Q1=63.1 ± 9.4	Q1=1905 ± 723	Q5= 1540 ± 591	Q1=13.3 ± 6.2	Q5=19.8 ± 9.8	12.86	N
				MD Q5=65.3 ± 8.9, Q1=64.3 ± 9.5	Q1= 1628 ± 736	Q5= 1776 ± 625	Q1= 11.7 ± 6.6	Q5=21.2 ± 9.0	11.82	N

3.2 Diets Controlled for Fiber and Calorie Intake

Of the 8 studies, only one study did not allow participants to consume fiber and calories ad libidum. Boers et al. restricted participants to a PD or control diet of approximately 2,080 calories during their two-week, parallel and randomized intervention study (48). The target dietary fiber of the PD group (PD=18) was 34 g fiber/day (3% energy), and the control diet group (DH=14), based on the Dutch Health council guidelines, was 28 g fiber/day (2.7% energy). Despite efforts to keep weight stable in both groups, body weight decreased in the PD group significantly compared to control diet (-2.9 lbs, p=0.012). The study design did not include a run-in period, and thus, the weight loss observed in this initial short-term PD intervention may be due to poor study design. The authors included weight loss in a separate fixed effect model, to determine if the observed beneficial effects on inflammation, intestinal permeability, and cortisol remained significant in the PD arm. While these differences remained statistically significant, the small sample size, short follow up time and the lack of statistical comparison between changes in cardiometabolic risk factors in exposure compared to control arm are major limitations of the study. Furthermore, although compliance was measured through daily food records, it was not reported. Clearly, as a result of the significant difference in weight loss, it is unclear how compliant the participants were to the protocols. A nutrient analysis was only reported for the recommended dietary intervention; thus, the range of dietary fiber actually consumed remains ambiguous. It is unclear whether the significant weight loss in the PD group contributed to the purported beneficial effects when compared to the reference group.

3.3 Diets Consumed Ad Libidum: Observational

Seven of the studies allowed participants to consume their diets ad libidum. Two of these studies were observational studies, both by Whalen et al. using their created PD pattern score (35,36). The limitations with this diet score were previously addressed in section 2.3. The first observational study investigated the cross-sectional association between PD scores and MD scores and biomarkers of inflammation and oxidative balance in adults. The data was gathered from two sources from 1994-1997 and 2002, and the final analysis included 642 participants. The highest adherers to the PD consumed 1,808 ± 619 kcal per day and 26.2 ± 11.1 g fiber/day. Similarly, the highest adherers to the MD consumed 1,986 ± 596 kcal per day and 27.1 ± 10.8 g fiber/day. Although this is significantly different from the lowest adherers to the diets (PD: 18.0 ± 7.6 g fiber/day; MD: 16.5 ± 8.1 g fiber/day), there is no significant difference between groups. The study found an inverse association between the PD or MD and inflammation biomarkers, consistent with other cross-sectional studies observing that higher fiber intake is associated with lower inflammation (49). In 21,423 participants followed for 4 years, both the PD and MD score (35) were inversely associated with all-cause and cause-specific mortality in adults. Similar to the previous observational study, those who were most adherent to the PD diet consumed significantly less calories (1540 ± 591 kcal/day) than those who were least adherent (1905 ± 723 kcal/day). The highest adherers also consumed more fiber (19.8 ± 9.8 g fiber/day) than the lowest adherers (13.3 ± 6.2 g fiber/day). In the MD group, the highest adherers to the diet consumed slightly more fiber than the PD group per day (21.2 ± 9.0 g fiber/day) but also consumed slightly more calories (1776 ± 625 kcal/day). Both diet patterns were associated with lower risk of all-cause, cardiovascular, cancer, noninjury, or accident mortality. Of note, these relative scoring dietary patterns indicated that under free-living situations, few people are adhering to the dietary principles of true Mediterranean or Paleolithic diets.

3.4 Diets Consumed Ad Libidum: RCTs

The remaining five studies consisted of one randomized cross over intervention, one run-in intervention trial, and three parallel randomized controlled interventions. In 2009, Jönsson et al. (33) performed a randomized cross over intervention in 13 adults (3 women; 10 men) who had diabetes, on average, for 9 years, to investigate the effects of the PD on cardiovascular risk factors over 3 months. Participants were randomized to either a PD diet (n=7) or a Diabetes Diet (DD) (n=6). Participants ate significantly less calories on the PD (1,577 ± 287 kcal/day compared to 1,888 ± 382 kcal/day, p=0.005). The difference in fiber intake between diet groups was not significant when comparing fiber as percentage of total energy intake and, thus, controlling for the variation in caloric intake (2.5 ± 0.7 % E from fiber in PD or 2.7 ± 0.7 % E from fiber in DD; p=0.4). When comparing the total fiber intake and not controlling for energy intake, the PD consumed significantly less fiber (21 ± 8 g/day in PD or 26 ± 8 g/day in DD; p=0.02). However, this significant difference can be explained by the difference in caloric intake. Thus, this study concludes that fiber does not vary significantly between the PD and the DD and that the mean caloric intake while adhering to the PD is significantly less than while adhering to the DD. In comparison to the DD diet, the PD resulted in significantly lower mean values of BMI (-1 kg/m_2, p=0.04), diastolic blood pressure, HbA1c, and triglycerides, and higher values for HDL. Carry over in HbA1c and period effects of glucose metabolism biomarkers may suggest a lower calorie or higher fiber intake contributing to the observed beneficial effects cardiovascular risk factors in the PD. As such, these attributes could be considered confounders in this relationship.

One run-in intervention trial has been performed reporting caloric intake and fiber intake. Osterdahl et al. investigated the effects of 3 weeks on the PD following a 7-day run-in period. Although 20 participants began, only 14 fulfilled the dietary intervention, and dietary data could only be retained from 6 participants. Thus, 30% of the recruited sample completed the study which introduces substantial bias. Although the study is underpowered, it does show that participants ate 894 kcal (95% CI: -1133; -656) less kcal on the PD compared to their baseline intake of 2,478 (SD= 269) kcal. Regardless of this significant decrease in caloric intake, participants increased daily fiber intake from 31.3g to 32g. It is unclear if this daily fiber intake, when expressed as E%, is significantly different between groups. Weight, BMI, and systolic blood pressure significantly decreased. It is unclear whether these results were an effect of the 36% reduction in caloric intake, or the increased percentage of diet from daily fiber.

Dietary fiber and energy intake were reported in 3 other parallel RCTs. The first was performed by Lindeberg et al. in 2007 to investigate if the PD improved glucose tolerance more than the MD in people with ischaemic heart disease after 12 weeks (50). The control group was advised to follow the MD (n=15) while the intervention group followed the PD (n=14). Those in the PD group consumed significantly less calories, 1,344 ± 521 compared to 1,795 ± 306 (p=0.01), and fiber did not differ significantly between groups (21.4 ± 13.2 g PD; 26.8 ± 7.4 g MD; p=0.2). The PD group lost 5 ± 3.3 kg while the MD group lost 3.8 ±2.4 kg, but this difference was not significant between groups (p=0.3), only within (p=0.0001). The authors report a significant change in AUC Glucose in the PD group independent of changes in weight or weight circumference. This result is unexpected because earlier studies show weight loss is a major determinant of improved glucose tolerance (51,52). However, in a meta-analysis of the efficacy of lifestyle education to prevent type 2 diabetes, weight loss did not explain all observations of glucose improvements (51). The authors explain their results are, thus, reasonable. It should be noted that the MD group was significantly younger (57±7 yrs) compared to the PD group 65±10 (p=0.01), and the PD group had a slightly higher dropout rate (three compared to none). The authors note the higher dropout rate does not appear to be a source of bias and that the greater glucose improvements in the PD were likely due to higher motivation rather than food patterns. Thus, it seems that motivation rather than caloric intake or fiber intake may have a greater impact in glucose improvements. Additionally, diet recall was only collected once through a consecutive 4 day weighed food record with at least one weekend day. This diet recall was collected 15 ± 5 days after starting the 12-week intervention study. It is unclear what the participants were consuming at baseline, or after 12 weeks of the study.

The RCT by Mellberg et al. in 2014 used a parallel, block randomized design (30). Both the PD group and the control group, which followed Nordic Nutrition Recommendations (NNR), enrolled 35 participants in each diet arm of the study. After the two-year intervention, the dropout rate was 22.9% and 37.1% in the PD and NNR group, respectively. Both groups at baseline were consuming about 2,000 kcal. After 2 years, the PD was eating 20% or −401 ± 89.5 (−1.68 ± 0.38) kcal less than baseline. The NNR group was eating 12% or −251 ± 62.2 (−1.05 ± 0.26) kcal less than baseline. There was no significant change in fiber over the course of the intervention in either groups (PD Baseline: 2.45 ± 0.06%, 24 mo.: 0.29 ± 0.10% dietary fiber E%; NNR Baseline: 2.18 ± 0.08% , 24 mo.: 0.24 ± 0.13%, dietary fiber E%). The results of the study indicate the PD had a greater benefit on triglycerides in this obese postmenopausal women population after 24 months (PD Baseline: 1.22 ± 0.09 mmol/L, 24 mo.: -0.23 ± 0.07 mmol/L; NNR Baseline: 1.27 ± 0.10 mmol/L, 24 mo.: -0.01 ± 0.06 mmol/L). The PD also had greater benefit on fat mass and abdominal obesity, but the effects were not sustained at 24 months.

Interestingly, the PD group had poor adherence to goal protein intakes, as measured by reported protein intake and nitrogen excretion in urine. Although the long-term effects of the PD had greater benefit on triglycerides, it again remains unclear if this was due to the greater initial weight loss due to a more profound decrease in caloric intake rather than the composition of the dietary pattern itself. Again, as the authors note, the PD had poor adherence to protein goals; thus, it is unclear if they were fully adhering to the protocols.

Lastly, Otten et al. in 2017 conducted a 3 month intervention trial with 16 participants assigned to a PD group or a PD + exercise group (PDEX) and 8 participants in an observational control group, following usual diet (38). The purpose of the study was to see if there were benefits of the PD with or without exercise on fat mass, insulin sensitivity, and glycemic control in individuals with type 2 diabetes. Fifteen participants in the PD group completed the study and 14 in the PDEX. Both groups consumed significantly less calories compared to baseline (PD: -291 (-587, -66) kcal and PDEX: -530 (-863, -157) kcal). The observational group ate 193 (−80, 393) kcal more compared to baseline: 1,743 (1,652–1,844) kcal. Interestingly, the PDEX not only consumed less calories over the course of the intervention, but also at baseline (PD: 2,022 (1,583–2,268) kcal and PDEXL: 1,595 (1,428–2,257) kcal). This potentially suggests the added effects of exercise or motivation in this group is biasing the results. Fiber increased from 21 (18-26) g/day at baseline to 23 (15-30) g/day at 12 weeks in the PD group. In contrast, fiber increased significantly from 14 (13-17) g/day at baseline to 34 (31-41) g/day at 12 weeks in the PDEX group. Fiber did not change significantly in the observational group 22 (18–23) g/day to 20 (13–26) g/day. As fiber is not expressed as an E% in this study, it is unclear if the significance would remain within the PDEX group before and after the intervention and between the PDEX and PD group after 12 weeks. When dietary fiber was standardized to g/1000kcal, none of the groups were meeting the 2015-2010 Dietary Guidelines for Americans recommended 14 g dietary fiber per day per 1,000 kcal. Other than heart rate, likely due to the exercise treatment, there were no significant differences between the PD and PDEX groups after the intervention. Compared to the observational groups, both groups following the PD had improved fat mass, HOMA-IR, fasting insulin, HbA1c, and systolic and diastolic blood pressure. Unlike the previous 2 year study by Mellberg et al., triglycerides did not decrease compared to the observational group (30). Again, it remains unclear if the PD improves insulin sensitivity and glycemic control independently from reduced energy intake.

As you can see, the metabolic improvements observed following PD interventions vary across the limited number of published studies. None of these above-mentioned studies were able to keep participants at weight maintenance. Daily fiber intake is correlated with higher dietary quality. The PD is a higher diet quality diet than the WD, due to an emphasis of vegetables and fruit intake which increases hypothetical fiber intake (46). Daily fiber intake did not increase significantly in any of the studies and decreased significantly in one (38). Table 1 summarizes that only one study (31) was able to meet the hypothetical modern PD intake (19.3 g/1,000kcal/day). In four of the 7 studies, the USDA recommendation of 14 g/1,000kcal/day of dietary fiber was not achieved in the PD intervention group. Thus, it is prudent to say that the purported health benefits of the PD are a result of the diet composition, which is a higher diet quality, rather than a reduction in caloric intake.

3.5 Supporting Evidence of Energy Restriction and Previously Reported Health Benefits of Paleo

As mentioned previously, one of the key attributes of these diets is their effect on energy intake. Evidence suggests that energy restriction itself may explain the previously reported health benefits. A recent review of 10 observational studies and 1 randomized controlled trial demonstrates a reduction in energy intake significantly improved blood pressure and insulin sensitivity (53). Another review of the literature including 13 human models and 14 rodent models demonstrated that a reduction in energy intake may be a strategy to improve vascular dysfunction in metabolic disorders by decreasing bodyweight, leptin, triglycerides, LDL-c, CRP, oxidative stress, and increasing insulin sensitivity (54). A vast number of biomarkers can be improved by reducing energy intake, independent of diet composition. Thus, the purported health benefits of the PD may be attributed to caloric restriction rather than the diet itself. Lindeberg et al. previously found improved glucose tolerance and lower energy intake in people with ischemic heart disease (IHD) with impaired glucose tolerance or type 2 diabetes following a PD as compared to a Mediterranean-like diet (50). Twenty- nine male IHD patients with impaired glucose tolerance or type 2 diabetes and a waist circumference greater than 94cm were randomized to ad libidum consumption of either the PD or a Mediterranean-like diet. Specific guidelines of these PD protocols are reported in Table 2. A follow up report of the same study investigated the subjective ratings of satiety at meals and data on the satiety hormone leptin. In this study, the PD group consumed less energy per day than the MD Diet (1,386 kcal versus 1,816 kcal, p=0.04). The authors conclude there is no difference in subjectively assessed satiation between diet groups. However, because the quotients of mean change in satiety were higher in the PD group and there was a stronger trend for greater satiety quotient, the authors conclude that the PD is more satiating compared to a Mediterranean like diet in people with ischemic heart disease (42). Another finding was that leptin levels decreased to a greater degree relative to the PD group. This conclusion is prudent based on the presented evidence. Firstly, it has been previously demonstrated that plasma leptin levels decline in response to severity of food restriction (55). As the PD consumed less calories, a correlated greater trend in decreased leptin levels should be expected and does not support the reported conclusion that the PD is more satiating per calorie than a Med-like diet. Secondly, the Satiety Quotient is the change in satiety at initiation to 30 mins after meal initiation and the consumed energy or weight of food and drink for that specific meal. This formulation has limitations concerning the lack of linearity between energy consumed and time until the return of hunger (56). Thus, it is best used with fixed size meals to provide a quantitative measure produced by different foods. Jonsson et al. report no significant difference in SQ for weight (RS/kg, p=0.5), and a SQ for energy (RS/MJ, p=0.057) that becomes significant (p=0.02) once an outlier is excluded. Given the lack of strength with these data and knowledge of the effects of reduced energy intake on leptin levels, it is prudent to conclude the PD is more satiating than the Mediterranean diet.

In a systematic review of the effect of the PD on metabolic disease, Manheimer et al. conclude that it was not clear whether the avoidance of whole grains and dairy products offer a benefit to metabolism (40). This review of 4 randomized controlled trials (2 weeks to 2 yrs. duration) showed that those on the PD had greater short-term improvements in waist circumference, triglycerides, fasting blood sugar, and BP than control diets. Three out of four RCTs allowed participants to consume diet ad libidum (30,33,50). All three RCTs also reported less calories consumed in the PD group than the control. Boers et al. (2014) provided isocaloric meals and allowed snacks for participants who lost more than 2 kg body weight. In this RCT, the study duration was 2 weeks and included a total of 37 total participants (n=18 Paleo, n=16 reference). The reference group followed the Dutch Health council dietary guidelines. At baseline, the Paleo group had a significantly higher BMI (33.7 kg/m^2 versus 29.8, p=0.01) and greater number of characteristics of the metabolic syndrome (3.7 versus 2.7, p=0.02). In addition, the Paleo group had a larger proportion of patients with harmful HDL levels (p=0.001), worse fasting glucose (p=0.04) and higher bodyweight (p=0.04) at baseline. As mentioned previously, the greatest benefits of reduction in energy intake are usually observed in the sickest patients (53). Although the PD resulted in greater short-term improvements in metabolic syndrome components than control diets, it is unclear if the improvements are a result of reduced caloric intake or the PD composition.

Lastly, a systematic review and meta-analysis of controlled clinical trials by Mohammadi et al. investigated the effects of the PD on glycemic markers (57). They conclude that the Paleo dietary pattern had no significant effects on glucose metabolism, although there was a reduction in fasting blood glucose levels. The authors also note that when caloric intake and weight is held constant, the PD is as efficient as any standard diet in improving glucose, insulin, or HOMA-IR. This is in line with previous studies showing even very short deficits in energy balance can improve metabolic markers regardless of the diet's macronutrient composition (58,59). Thus, weight loss rather than the PD pattern may have more significant impact on metabolic health status.

Table 2. Comparison of Paleo Diet Definitions Used Amongst Studies

	Lean Meat	**Fish/Seafood**	**Eggs**	**Vegetables**	**Fruits**	**Berries**	**Nuts**	**Dairy**	**Cereals**	**Added Salt**	**Refined Fat**	**Sugar**	**Legumes**
Lindeberg et al. 2007[3]	✓	✓	✓	✓[3]	✓		✓	X	X			X	X[8]
Osterdahl et al. 2008[1]	✓[1]	✓[2]		✓	✓		✓[5]	X	X[6]	X		X	X
Jonsson et al. 2009[4]	✓	✓	✓	✓[4]	✓		✓	X	X	X	X	X	X[8]

Boers et al. 2014	✓	✓	✓	✓[3]	✓		✓	X	X	X	X	X	X
Mellberg et al. 2014	✓	✓	✓	✓	✓	✓	✓	X	X	X	X	X	
Whalen et al. 2016[5]	✓	✓		✓	✓		✓	X	X[7]	X			
Otten et al. 2017[2]	✓	✓	✓	✓	✓	✓	✓	X	X	X	X	X	X
Whalen et al. 2017[5]	✓	✓		✓	✓		✓	X	X[7]	X			

✓=included. X= excluded. blank= not mentioned. Superscript denotes variation or more details provided for definition within specific food groups. Subscript denotes more details provided for food allowances and restrictions.

1 fresh or frozen unsalted lean meats and minced meat; 2 fresh or frozen unsalted fish and seafood; 3 leafy and cruciferous vegetables, root vegetables; 4 leafy and cruciferous vegetables, root vegetables (including restricted amounts of potatoes); 5 unsalted nuts (except peanuts); 6 all grain products (including maize and rice); 7 grains and starches; 8 beans

1 Allowed canned tomatoes without additives except for citric acid, fresh squeezed lemon or lime juice (as dressing), flaxseed or rapeseed oil (as dressing), coffee and tea (without sugar, honey, milk or cream), all salt-free spices. Allowed food in restricted quantity: Dried fruit (ad lib 2 days/ week), salted seafood (one meal/week), fat meat (one meal/ week), potatoes (two medium sized/day), honey (used in marinade once/week), cured meats (as entree once/week), mineral water (only when drinkable tap water was not available). Restricted foods: charcuterie products (for example, sausages, pates and so on), canned food (except tomatoes, see above) and all forms of candy, ice cream, sorbet, soft drinks, juices, syrups, liquor.

2 Allowed canned fish and cold cuts like ham ad libitum, with restrictions of the following: eggs (1–2/day but a maximum of 5/week), potatoes (1 medium sized/day), dried fruit (130 g/day), and nuts (60 g/day). Rapeseed or olive oil (maximum 15 g/day) and small amounts of honey and vinegar were allowed as flavoring in cooking. Participants were instructed to drink mainly still water. Coffee and tea were restricted to a maximum of 300 g/day, and red wine to a maximum of one glass/week.

3 Avoid bakery products, soft drinks, and beer. Restrictions of the following: eggs (one or fewer per day), nuts (preferentially walnuts), potatoes (two or fewer medium-sized per day), rapeseed or olive oil (one or fewer tablespoons per day).

4 Avoid candy, soft drinks, beer. Limited amounts for the Paleolithic diet: eggs (≤2 per day), nuts (preferentially walnuts), dried fruit, potatoes (≤1 medium-sized per day), rapeseed or olive oil (≤1 table- spoon per day), wine (≤1 glass per day)

5 Additionally, included in PD Score for higher intake best: Fruit + Vegetable diversity, Calcium. Additionally, included for lower intake best: Red and processed meats, baked goods, sugar sweetened beverages, alcohol.

3.6 Conclusion

The PD differs extremely in history, literature, and between study populations. To say that people adopting the PD will reap benefits from the nutrient quality is primitive. Most likely, a reduction in calorie intake can be attributed to the health marker improvements in the studied populations. As Manheimer et al. report, it is not clear whether the avoidance of whole grains and dairy products offer a benefit to metabolism (40). Future research should measure Paleo adherence while implementing the diet to discern the differences between adherence benefits versus reduction in energy intake.

Chapter 4. ADAPT Study

4.1 Introduction

During Paleolithic times, humans did not have access to the overabundance of dietary options we now have. These people were restricted to a handful of foods that they were forced to eat with no other option. Thus, we hypothesize there will be extreme variation in the dietary adherence patterns of modern society to the PD. These variations in adherence patterns are likely to influence the purported health benefits and expected decrease in chronic disease burden outlined in Chapters 2 and 3. Therefore, it is important to understand how the American population will adopt the PD in our industrialized time.

To our knowledge, the Adhering to Dietary Approaches for Personal Taste (ADAPT) Study is the first observational study on individuals reporting adherence to a variety of popular diet intakes. The purpose of this analysis is to compare the dietary intakes of self-reported Paleo adherers to six of their reported most popular resources for Paleo recipes. The information gathered from this cohort will help to understand how self-identified Paleo followers are adhering to their reported sources for cooking and nutrition.

4.2 Methods

4.2.1 Hypothetical Historic Estimates of Dietary Fiber

We established hypothetical historic and modern PD estimates from the following resources respectively: 1) Eaton S. (1997) 2) Cordain L. (2002). Dr. Eaton produced the historically known PD from a nutrient analysis of six groups of hunter-gatherers living in marginal habitats (46). Loren Cordain further describes the contemporary PD based upon modern day popular Paleolithic food groups to examine the nutritional characteristics of a modern PD and to determine the potential impact of chronic disease risk (21). This original publication was used in his most popular publication, which Web of Science reports has been cited 903 times. Daily mean fiber intake and total calories were extracted from these historic and modern PD reports, as shown in Table 3.

4.2.2 ADAPT Hypothetical Modern Estimates

The Adhering to Dietary Approaches for Personal Taste (ADAPT) Feasibility Survey (FS) was started by the Jean Mayer USDA Human Nutrition Research Center on Aging in 2015 (60). It is a cross sectional web-based survey of U.S. non-institutionalized civilian adults aged 18 years or older. Of the 7,300 ADAPT FS individuals consenting to be contacted for a large-scale longitudinal study, 2,624 responded to an invitation and completed the ADAPT Pilot Study (PS). Of these respondents, data was successfully collected from 2,475 participants. Self-reported recipe and sources of dietary information were captured from the ADAPT FS. This data was used to create a hypothetical energy and fiber intake, based on the reported books and websites. Nutrient data of the participants were analyzed from the ADAPT PS. This data was used to create the actual energy and fiber intake in order to compare to historical, modern, and surveyed hypothetical PDs.

4.2.3 ADAPT Methods

4.2.3.1 Top Self-Reported Sources of Recipes

Top sources of diet and recipe information were captured from the ADAPT FS. The survey included an open-text question: “What are your main sources of information on nutrition and cooking for the diet you currently eat?” (books or websites) for their self-identified diet. A total of 6,372 respondents of the ADAPT FS answered this optional question with at least one source.

A random sample of 200 participants was used to collect data of the top sources of cooking and nutrition information. The top six sources of recipes were 1) The Paleo Solution by Robb Wolf 2) Whole 30 by Doug and Melissa Hartwig 3) Nom Nom Paleo by Michelle Tan 4) The Primal Blueprint by Mark Sisson 5) Practical Paleo by Diane Sanfilipo 6) The Paleo Mom.

4.2.3.2 Selection of Recipes

Survey responses to the open-text question on top sources of information were coded for each unique source. Books and websites authored by the same expert or organization were grouped. The majority of responses included two or more unique sources. Meal plans were created using the top three books and top three websites mentioned by at least 5% of the selected random sample. The meal plans were five days from each of six sources, for a total of 30 representative days. Nutrient collection and analysis was performed using Nutrition Data System for Research software version 2016 (NDSR 2016) developed by the Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN. Top sources of information on nutrition and cooking were weighted based on the percent of mentions within the PD group. The weighting was calculated as the number of mentions of the source out of the total number of mentions of the top six sources. Because most participants reported multiple sources, this weighting approach captures a more representative estimate of the most popular sources.

When inputting recipes, ingredients were entered based on the instructions when possible. If instructions were not precise, NDSR data-entry protocols were used for generic choices with standard portion sizes for consistency. Recipes were entered and divided by the number of servings to obtain single serving nutrient data. Accuracy of the recipes and meal plans entered were confirmed by a second reviewer. Finally, the meal plan data was standardized to

2,000 kcal/day. Supplementation of fiber by the participants was not included in any of the nutrient analysis for comparison.

4.2.3.3 Estimation of Dietary Fiber and Energy Intake in Those Who Self-Report Adherence to The Paleo Diet

Nutrient data of the participants were analyzed from the ADAPT PS. Of 2,475 who completed the ADAPT PS, 212 self-identified as PD followers and were used in this analysis (60). Data was cleaned and merged using SAS version 9.4 (61). Mean daily fiber intake and daily caloric intake was collected using R-Studio 3.4.3 (62).

4.3 Results

Of all participants who completed the ADAPT PS, only those who self-reported adherence to the PD were included. The mean caloric intake of this group (n=212) was 1,308.5 kcal/day, and the mean daily fiber intake was 16.6 g fiber/day. As shown in Table 3, this was standardized to a 1,000 kcal diet and compared to historic and modern hypothetical Paleo intakes. Standardized actual intake from the ADAPT Study was 12.7 g fiber/1000kcal, which is below the 2015-2020 Dietary Guidelines for Americans recommendation, 14g fiber/1000kcal.

Table 3. Hypothetical Historic and Modern Paleo Diets Compared to ADAPT Study and Hypothetical Intake Based on Reported Primary Recipe Sources

	Hypothetical Historic	Hypothetical Modern	Hypothetical Modern from Bloggers	Actual Intake from ADAPT Study
Mean Calorie Intake (kcal)	3000	2200	2000	1308.5

Mean Daily Fiber Intake (g/fiber/day)	104	42.5	24.37	16.6
Standardized Daily Fiber Intake (g/1000kcal)	34.7	19.3	12.18	12.7

4.4 Discussion

Mean caloric intake was significantly lower in participants of the ADAPT Study (1,308.5 kcal/day) as compared to historic (3,000 kcal/day) and modern (2,200 kcal/day) PD estimates. As previously described in Chapter 1, it remains unclear if this significant decrease in calories when adhering to the PD is the main component of the purported health benefits in literature. Additionally, fiber intake was significantly lower (12.7 g fiber/day/1000kcal) than historic (34.7 g fiber/day/1000kcal) and modern (19.3g fiber/day/1000kcal) PD estimates. Actual fiber intakes of participants from the ADAPT Study (12.7g fiber/day/1000kcal) were similar to their reported top 6 sources (12.2 g fiber/day/1000kcal) as well as the literature (Table 1). Overall, this shows that similar to controlled trials in literature, the PD is lower in fiber than hypothetical estimates and is associated with lower calorie intake.

The top six sources of recipes were The Paleo Solution by Robb Wolf, Whole 30 by Doug and Melissa Hartwig, Nom Nom Paleo by Michelle Tan, The Primal Blueprint by Mark Sisson, Practical Paleo by Diane Sanfilipo, and The Paleo Mom. Interestingly, the top six sources of information for those who are adhering to the PD were not all Paleo sources. Whole 30 (Hartwigs) and the Primal diet (Sisson) may include or restrict items foods that are not in the PD. For example, the Primal diet allows the use of dairy and Whole 30 further excludes honey, maple, and other sources of added sugar. Thus, it is possible there is confusion as to what the PD is for ADAPT Study participants. This confusion is further exemplified in Chapter 3 Table 2, which illustrates the differences of the PD used by researchers.

4.5 Conclusion

This is the first observational study of self-reported PD followers to compare adherence to self-reported sources of recipes and derived meal plan estimates. Actual intake of dietary fiber in participants of the ADAPT Study was 63% lower than the hypothetical historical PD and 34% lower than hypothetical modern PD reports. The actual intake of dietary fiber in self-reported PD adherers in the ADAPT Study (12.7 g fiber/day/1000kcal) was less than the RDA for the American population (14 g fiber/day/1000kcal). Future research should aim to clarify a PD definition that can be systematically applied to intervention protocols and isolate whether the purported health benefits are a result of lowered caloric intake or dietary pattern. It is important to understand how the population adheres to and adopts the PD for sustainability and measures of dietary behavior change success.

Chapter 5. Dietary Fiber Intake Amongst Followers of Paleolithic, Dairy Free, and Gluten Free Diets in the ADAPT Study

5.1 Abstract

Background: Gluten-free and dairy-free diets are associated with nutritional deficiencies, including fiber. Theoretically, the Paleolithic diet (PD) is reported to increase fiber intake even though gluten and dairy products are eliminated from the diet. The purpose of this data analysis is to compare total fiber intake across three diet types: gluten-free, dairy-free, and Paleo in a cross-sectional web-based sample of adults claiming adherence to specific diets.

Methods: Total daily fiber intakes of 610 adults participating in the Adhering to Dietary Approaches for Personal Taste (ADAPT) Study were examined using multivariate linear regression models adjusted for covariates age, BMI, gender, education, alcohol, and exercise. Total daily fiber intakes were also examined in those who adhered to three diet types: gluten-free (n=133), dairy-free (n=425), and Paleo (n=156). The groups were yielded from the same cohort of 610 adults, but were not independent of each other.

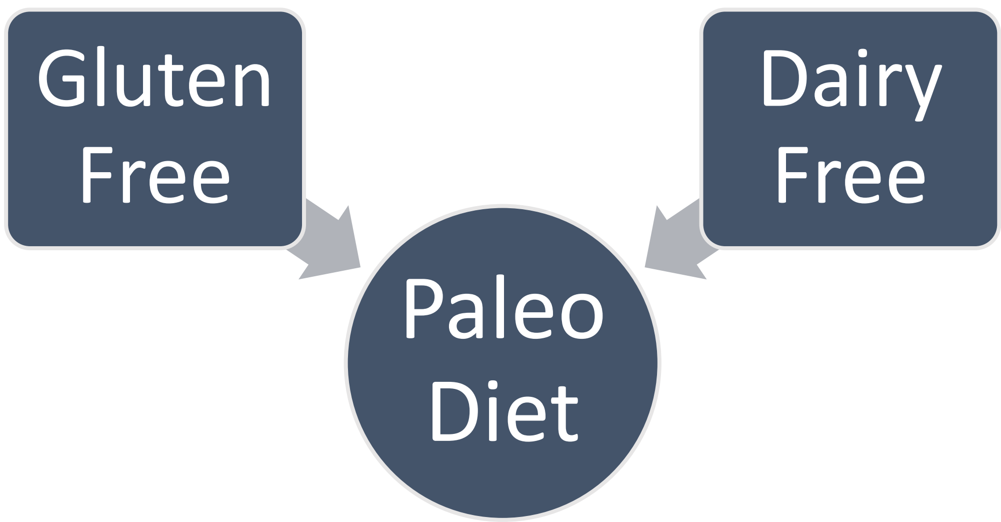
Results: Compared to the dairy-free and gluten-free groups, people who reported practicing the PD consumed on average 12 less grams of daily fiber (95% CI: -16.69, -7.23; $p<0.05$). Those who reported practicing a dairy-free diet consumed 6.07 more grams of daily fiber compared to the gluten-free and Paleo groups (95% CI: 1.06, 11.08; $p<0.05$).

Conclusion: In this convenience sample of US adults, daily fiber intake increased, respectively, with the following diet types: Paleo, gluten-free, and dairy-free. Further research should aim to delineate differences in specific dietary patterns and adherence when following the PD and its components.

5.2 Background

The human diet has undergone a dramatic change in food quality and quantity over the past century which has deeply influenced the number of adverse health effects at an alarming rate. People follow a variety of dietary patterns in an attempt to offset the deleterious health effects linked to the typical WD, promote a healthier lifestyle, or manage disease. These newly adapted patterns can often leave compliant followers with deficiencies in extremely beneficial nutrients, including dietary fiber. The 2015-2010 Dietary Guidelines for Americans recommends 14 g dietary fiber per day per 1,000 kcal. Recognizing fiber discrepancies in dietary patterns will allow practitioners to better advise patients and promote healthy dietary behaviors. As seen in Figure 1, the dairy-free diet and gluten-free diet are two components of the PD. Current literature suggests this encompassing diet, Paleo, has a greater fiber intake than either of its constituents (dairy-free or gluten-free). Fiber intake is a key determinant of a healthy eating pattern and may have a significant impact on biomarkers of health.

Figure 1. Two Dietary Components of the Paleolithic Diet



5.2.1 Gluten-Free Diet

The gluten-free diet was first reported to be used in the dietary treatment of celiac disease in 1941 by Dr. Willem Karl Dicke (63). The gluten-free diet eliminates all items containing the protein gluten such as wheat, soy sauce, bread and cakes. People with celiac disease follow the gluten-free diet to prevent progression of disease and control symptoms. Non-celiac gluten sensitivity (NCGS) has been reported and may also lead to diet adoption. Although the topic remains controversial, the estimated prevalence of NCGS in the United States was estimated to be 0.548% in 2013. This is about half the reported prevalence of celiac disease (64). Other populations who note relief include those with autoimmune diseases, IBS, and athletes.

Although the gluten-free diet is known to promote intestinal healing in people with gluten-related disorders, there may be long-term consequences to dietary adherence. This is likely a result of decreased nutrient content in gluten-free alternatives (65). Studies show these foods may have twice the amount of fat as well as higher carbohydrate and sodium content depending on the base flour used and product type (66).

Most notably, gluten-free products have lower fiber content than their gluten-containing counterparts (65,66). Whether this translates to lower fiber intake while adhering to a gluten-free diet remains unclear. One study demonstrated that individuals with celiac disease consumed diets with less fiber, but more fat and sugar compared to the diets of healthy adults (67). Similar results have been observed (68), but it is unclear whether this is due to dietary habits rather than the gluten-free diet.

One study performed in people adhering to gluten-free diets suggested that nutritional inadequacies are modified by gender, but the sample size was too small to create meaningful impact (69). There is little evidence to illustrate the diet's effect on BMI. Although celebrity endorsements and advertisements of the gluten-free diet show positive impacts of lowering BMI, there is little research to support this for a healthy population (70,71). Most studies involve people with celiac disease and show an increase in BMI when adopting the diet (68). However, this is likely due to a decrease in gastrointestinal symptoms, healing of the tract, and a return to an increased, healthier BMI for that population.

Overall, there is unclear evidence for the association between gluten-free diets and fiber intake or BMI.

5.2.2 Dairy-Free Diet

The dairy-free diet eliminates any whey or casein protein-based products such as milk, butter, cream, cheese, yogurt, and ice cream. People follow a dairy-free diet for a variety of reasons; lactose intolerance, an allergy, or to abstain from animal products. Lactose intolerance affects as much as 75% of the world's adult population (72). It is estimated that about 2% of US adults suffer from milk allergy (73). In dairy-free diets, the main nutrient deficiency concerns are calcium and vitamin D.

There is little research investigating fiber intake as a primary outcome of any dairy-free diet intervention. In studies reporting fiber intake, there is no difference between those adhering to a dairy-free diet and those consuming dairy (74,75).

Although there are many established health benefits of dairy-containing diets, the association between dairy-free diets and BMI remains unclear. Most studies do not completely eliminate dairy from the intervention group's diet. For example, Anderson et al. studied a soy-based or milk-based liquid meal replacement (76). The milk-based group was allowed to consume fruits, vegetables, and two servings of lean meat such as chicken breast or turkey. The soy-based group was only encouraged to include fruits or vegetables, but their supplement product had more fiber, protein, and calcium. Caveats like this, newly suggested implications of gene-nutrient interaction (77), and no long-term data, have made it very difficult to isolate the effect of the dairy-free diet on BMI. A recent review of evidence for weight loss strategies concluded from two meta-analyses that dairy is a useful component to weight loss but has no effect without caloric restriction (78). Thus, there is unclear evidence for the association between dairy-free diets and fiber intake or BMI.

5.2.3 Paleo Diet (extensively described in Chapter 1)

The PD, also known as the Stone-Age diet, first gained popularity in the mid- 1970s. The Paleolithic period ended as agriculture began emerging in the Neolithic period, about 10,000 years ago. Thus, the PD is based on the premise that modern humans should eat like their ancestors to combat current maladaptation to modern industrialized diets which manifest into a suite of chronic diseases. Previous hunter-gatherer studies show animal foods (lean game, eggs, fish, shellfish) contribute to about 35% of their total diet. The rest (65%) was filled by plant foods (fruits, vegetables, nuts, honey) (9). The modern PD allows all fruits/vegetables, lean game, eggs, fish, shellfish, nuts/seeds, animal fats, and unrefined oils. It excludes dairy, grains (thus, gluten) and pseudo cereals, legumes, processed foods, sugar, artificial sweeteners, vegetable oils, margarine, and trans fats. People adhere to the PD for a variety of reasons including: fad diet following, chronic disease prevention, and lessening the symptoms of autoimmune conditions.

The PD has a high consumption of fruits and vegetables, and thus it may be expected to have increased intake of fiber (30). However, this has not been thoroughly tested in research. Some studies show no change in short-term fiber intake on Paleo adherence (79). Compared to a Diabetes diet, a PD showed lower total dietary fiber intake (33). Compared to a Mediterranean diet, a PD did not change fiber intake (50). Although the PD should be higher in fiber based on dietary premise, it remains unclear through the literature if this is the case. Mellberg et al. conducted a two-year randomized trial in obese postmenopausal women (n=70) to understand the long-term effects of a PD. The researchers found a statistically significant decrease in BMI at 6 months, but this difference was attenuated after 24 months (30). Studies on the PD suggest positive metabolic health effects (80), but it is unknown if these favorable effects are from caloric restriction or the PD composition itself.

There is an ever-clear urgency to change current western dietary habits and reduce onset of chronic disease in the United States. There is inconclusive evidence to explain how total dietary fiber intake differs in dairy-free, gluten-free, or PDs. The Adhering to Dietary Approaches for Personal Taste (ADAPT) Study was started in 2017 by the Jean Mayer USDA Human Nutrition Research Center on Aging. The study aimed to understand the impact of dietary patterns, exercise, and behavior in disease prevention to provide individuals with better support to maintain specific dietary practices and how these long-term practices may influence healthy aging.

The presented analysis aims to determine and compare the total fiber intake in three groups that claim to adhere to a specific diet. Based on published literature described previously, we anticipate fiber intake is lowest in people adhering to the gluten-free and dairy-free diet. The objective of this research is to 1) investigate the association of total fiber intake within each diet type (gluten-free, dairy-free, Paleo) 2) investigate the association between total fiber intake among diet groups by creating a multiple linear regression model adjusting for covariates 3) further test if BMI and diet type interact, and if so, report the fiber intakes broken down by group. Results from this analysis will be important for educating practitioners and the public to improve dietary habits, given the critical health state of western culture.

5.3 Methods

5.3.1 Participants and Design

We abstracted 954 records from 2017 ADAPT Cycle 1 for all individuals claiming adherence to specific dietary patterns. Only respondents with complete data for Paleo, fiber, alcohol, gfAlways, dfAlways, bmi, education, exercise, gender, and age were included in the analysis.

Thus, 610 records remained in the final analysis. Mean data in Table 2 has 714 records because groups are not independent of each other. This is described further in 2.2.6.

5.3.2 Measures

ADAPT, Cycle 1 was conducted from January through May 2017 using a self-administered online questionnaire. Dietary intake was measured using the Diet History Questionnaire II from the National Cancer Institute.

5.3.3 BMI Assessment

The standard formula for Body Mass Index (kg/m^2) was calculated based on participants' self-reported height and weight using the following formula: BMI = (Weight in Pounds / Height in $inches^2$) x 703.

5.3.4 Demographic Covariates

Any persons with missing data for the variables used in this analysis were excluded. Education was collapsed from 5 categories (Less than 9^{th} grade, 9-11th grade, High school grad / GED or equivalent, Some college or Associate's degree, College graduate or above) into 3 categories to describe sample characteristics: High School Graduate or Less, Some College, Bachelor's Degree or Above. It was further collapsed into 2 categories to increase group size and model stability for the analysis: Some College or Less and Bachelor's Degree or Above.

5.3.5 Fiber Intake

Total fiber intake was calculated using the Diet History Questionnaire and United States Department of Agriculture nutrient database in total grams of fiber per day. The USDA database is based on the AOAC methods for measuring dietary fiber (81).

5.3.6 Exercise

Exercise was calculated based on self-reported priority in one question with five options, with 5 being 'very much a priority' and 1 being 'not a priority at all'.

5.3.7 Smoking and Alcohol

Smoking and alcohol use have also been established through literature to be potential confounders. The majority of people in this data set did not smoke (98.9%), and thus smoking was excluded as a covariate. The drinking status variable was created with binary variables, based on if the participant has had alcohol in the past year. Although this is a questionable indicator of alcohol status, it was a significant predictor in both models and thus included.

5.3.8 Diet Type

PD was determined by self-reported best description of eating preferences. Respondents were allowed to choose 1 out of 21 options that best described their typical dietary pattern. The options were: I haven't followed any diet, No particular diet but I have tried to eat healthy, Mediterranean-type diet, Paleo diet, Vegan diet, Raw vegan diet, Vegetarian diet, Pescatarian diet, Gluten-free diet, Whole food diet, Whole food, plant-based diet, Locavore / local food diet, Weston A. Price diet, High-protein diet, Low-carb diet, Low-fat diet, Dairy-free, Diet specifically for weight loss, such as Weight Watchers or similar program/diet, Doctor/practitioner recommended (diabetic sugar-free diet, DASH, NCEP, low-calorie, or other), Other diet (the diet I have followed is not listed here), or Prefer not to answer. PD was recoded to 1, and all else was recoded to 0.

Additionally, respondents were allowed to choose if any of the following were important to them in making their food choice: Organic, Raw, Free-range meat, Hormone-free meat, Unpasteurized dairy, Gluten-free, Superfoods, Dairy-free, Nut-free, Soy-free, or Prefer not to answer. If gluten-free or dairy-free options were chosen, a follow-up question asked how often do you eat gluten-free? The choices were 1 to 5, respectively: Always, Very Often, Sometimes, Rarely, Never. Those who responded always to the gluten-free follow-up question were recoded to 1, and all else to 0. Those who responded always to the dairy-free follow-up question were recoded to 1, and all else to 0. Thus, a binary variable was created for those who self-reported the PD, always adhered to a dairy-free diet, and always adhered to a gluten-free diet. This also means that people may belong to multiple groups. For example, a PD adherer may be dairy-free and gluten-free, while another individual could have been vegan, but chosen dairy-free. Another individual could have reported no specific dietary adherence but reported being gluten-free for other reasons.

5.4 Data Analysis

Data was cleaned and merged using SAS version 9.4 (61). Linear and multiple linear regression analyses regressed comparative associations between diet type and total fiber intake using R-Studio 3.4.3 and packages gmodels, car, and tableone (62). Total dietary fiber intake was the primary dependent variable in the linear regression model. Three hundred and forty-four participants with negative or missing values for any of the predictor values were completely excluded. None of the covariates were established as colliders in the causal directed acyclic graph (DAG) pathway. The remaining cohort consisted of 610 subjects.

A linear regression model was used to examine the association between total fiber intake within each diet type. A multiple linear regression model was then examined in the entire sample (n=610), while controlling for all covariates (age, gender, BMI, education, and alcohol). Linearity was assessed for total fiber intake, BMI, and age using Loess curves as well as component residual plots. A Q-Q plot was used to assess normality of the error of the adjusted model. Influential data were assessed using a leverage against standardized residual plot and Cook's distance. Outliers were defined as cases $\pm$ 4 standard deviations away from the mean that were also significantly influential based on the leverage against residual plot previously described. As a sensitivity analysis, outliers were further removed to assess their impact on the model. Results where compared to the original model to determine if they should be excluded. Collinearity was assessed in the multivariable model using VIF. The F-test was performed to confirm the effect of the extra predictors in the full model. BMI and diet type were further tested for interaction as part of the third study objective.

BMI, fiber, and age were assessed for linearity using Loess curves as well as component residual plots. All three variables maintain the linearity assumption. Figure 2 (see appendix) illustrates the Q-Q plot of fiber. The scatterplot shows both sets of quantiles came from normal distributions. The distribution shows no evidence of extreme values that would skew the data. Figure 3 (see appendix) shows the leverage against standardized residual plot, with Cook's distance shown in black, red, or green. Two of 610 subjects were identified as potential outliers. Both subjects had high residual and high leverage. Removing them from the model does not change the results significantly, so they were kept in the model. None of the univariate predictors suggested collinearity (VIF=2.72 or below).

To further explore whether BMI and diet type interacts, the interaction term for diet type and BMI was included in the multivariate model. The interaction terms were not significant and thus not included in the full model.

5.5 Results

After removing missing data for any of the univariate predictors completely, 610 subjects were left in the analysis. The characteristics of the sample population are summarized in Table 4. Study participants were 78.4% female, and the mean age was 51.8 ± 13.6 (SD) years. Sixty-eight percent (n=414/610) had a normal BMI, below 25 kg/m2, and 32 % (n=196/610), were overweight or obese. The average total fiber intake was 33.6 g/day ± 20.3 (SD).

Table 5 summarizes the mean fiber intake in each diet group. The diet groups were not independent of each other, and the analysis was performed using the 610 subjects. Those who reported eating a PD (n=133) had a mean daily fiber intake of 19.5g/day ± 10.8 (SD). Participants who self-identified as adhering to a gluten-free diet (n=156) had a mean daily fiber intake of 24.9 g/day± 16.2(SD), on average. Those who self-identified as adhering to a dairy-free diet (n=425) had a mean daily fiber intake of 38.8 g/day ± 20.7 (SD).

Of those who self-reported adhering to a PD, 2.35% were also gluten-free and dairy-free. Twenty-six percent of participants who reported being Paleo, also reported being always gluten-free, but not always dairy-free. Thirty-six percent who reported being Paleo, also reported not being always gluten-free and not always dairy-free. Of those who reported being Paleo, 1.65% also reported not always gluten-free and always dairy-free. Thus, 28.8% of those who reported being Paleo also reported being gluten-free, while only 4% of those who reported being Paleo also reported being always dairy-free.

The results of unadjusted and adjusted regression models of the associations between total daily fiber intake and diet type, BMI, age, gender, education, drinking status, and exercise are summarized in Table 6. The reported adherence to PD was associated with the reduction in total daily fiber intake of 18.01g (95% CI: -21.66, -14.36; $p<0.05$). Similarly, a reported adherence to the gluten-free diet was associated with the reduction of 11.64g (95% CI: -15.23, -8.05; $p<0.05$). As expected for the dairy-free diet, the intake was 17.14g (95% CI: 13.89, 20.38; $p<0.05$) higher as compared to two other groups. After controlling for age, gender, alcohol, education and exercise in the multivariable model, the reductions remained significant for Paleo and dairy-free diets, but not gluten-free: -11.59g (95% CI: -16.38, -6.80; $p<0.05$) for the PD, 6.47 (95% CI: 1.39, 11.55; $p<0.05$) for the dairy-free diet, and -3.71 (95% CI: -7.85, 0.441; $p=0.08$) for the gluten-free diet.

Those who make exercise very much a priority are associated with greater fiber intakes than those who do not. Those who do drink are associated with less fiber intake than those who do not. Those who have a bachelor's degree or above are associated with lower fiber intake than those who have some college education or less. The number of people with a high school diploma or less (108) was much smaller than the number of people with some college or more (502). This likely explains the large confidence interval and resulting beta-coefficient.

Table 4. Characteristics of the Study Sample

Variable	Overall Number (%) (n=610)	Number (%) Paleo (n=133)	Number (%) Gluten-Free (n=156)	Number (%) Dairy-Free (n=425)
Age (years) (Mean ± SD)	51.8 ± 13.6	47.8 ± 12.6	50.9 ± 13.2	52.6 ± 13.9
BMI (kg/m2) (Mean ± SD)	24.3 ± 5.0	25.4 ± 5.1	24.6 ± 5.1	23.7 ± 4.7
Fiber (g/day) (Mean ± SD)	33.6 ± 20.3	19.5 ± 10.8	25.0 ± 16.2	38.8 ± 20.7
Sex				
Male	132 (21.6)	32 (24.1)	22 (14.1)	95 (22.3)
Female	478 (78.4)	101 (75.9)	134 (85.9)	330 (77.6)
Education				
High School Graduate or Less	13 (2.1)	3 (2.2)	5 (3.2)	9 (2.1)
Some College	95 (15.6)	12 (9)	17 (10.9)	72 (16.9)
Bachelor's Degree or Above	503 (82.3)	118 (88.7)	134 (86)	344 (80.9)
Drinking Status				
Non-drinker	142 (23.3)	21 (15.8)	35 (22.4)	108 (25.4)
Consumed Alcohol in the Past Year	468 (76.7)	112 (84.2)	121 (77.6)	317 (74.6)
Exercise				
Not at All a Priority	23 (3.8)	4 (3)	11 (7.0)	12 (2.8)
A Little Bit of a Priority	57 (9.3)	6 (4.5)	16 (10.3)	41 (9.6)
Somewhat a Priority	105 (17.2)	28 (21.1)	28 (17.9)	64 (15.1)
A Priority	145 (23.8)	23 (17.3)	29 (18.6)	114 (26.8)
Very Much a Priority	280 (45.9)	72 (54.1)	72 (46.2)	194 (45.6)

Table 5. Average Fiber Intake of Each Diet Group

	Paleo (n=133)		Gluten-Free (n=156)		Dairy-Free (n=425)	
	Yes (n=133)	No (n=477)	Yes (n=156)	No (n=454)	Yes (n=425)	No (n=185)
Mean Fiber Intake (g/day) ± SD	19.55 ± 10.82	37.57 ± 20.62	24.94 ± 16.16	36.61 ± 20.77	38.83 ± 20.66	21.69 ± 13.34

Table 6. Factors Associated with Fiber Intake

Variable	Univariate Model B (95% CI), p-value	Multivariable Model 1* B (95% CI), p-value	F-Test Sum Sq. (p-value)
Paleo	-18.01 (-21.66, -14.36) **	-11.59 (-16.38, -6.80) **	-28912 **
Gluten-Free	-11.64 (-15.23, -8.05) **	-3.71 (-7.85, 0.441)	-46903 **
Dairy-Free	17.14 (13.89, 20.38) **	6.47 (1.39, 11.55) **	-24788 **
Age	0.16 (0.04, 0.28) **	0.05 (-0.06, 0.16)	-59823 **
BMI	-0.67 (-0.99, -0.35) **	-0.26 (-0.57, 0.05)	-55650 **
Gender (Male)	-6.90 (-10.79, -3.01) **	-6.39 (-9.90, -2.87) **	-57720 **
Education			
Some College or Less	Ref	Ref	-62035 **
Bachelor's Degree or Above	-23.12 (-34.20, -12.04) **	-1.76 (-5.56, 2.05)	
Drinking Status (None)	-7.74 (-11.52, -3.96) **	-5.64 (-9.05, -2.23) **	-56122 **
Exercise			
Not at All a Priority	Ref	Ref	-51969 **
A Little Bit of a Priority	3.80 (-5.89, 13.48) p=0.44	-0.20 (-8.88, 4.42)	
Somewhat a Priority	3.49 (-5.53, 12.51) p=0.45	1.90 (-6.29, 4.17)	
A Priority	12.46 (3.66, 21.26) **	8.02 (0-0.03, 4.10) p=0.051	
Very Much a Priority	11.95 (3.45, 20.46) **	8.29 (0.38, 4.03)**	

B, regression coefficient. Ref, reference. BMI: Body Mass Index (kg/m_2)
* Model includes covariates age, BMI, gender, education, alcohol, and exercise.
** p<0.05

5.6 Discussion

Among a convenience sample of predominately white and female US adults self-reporting dietary patterns, the PD was associated with lower total daily fiber intake than dairy-free or gluten-free. As explained in 2.2.6, a subject in the PD group could have also been in the dairy-free group. The groups were intended to represent components of the PD, however it is difficult to make conclusions between diet groups given the method of variable derivation. Only 2.35% who were adhering to the PD also reported being always gluten-free and always dairy-free. It appears the historic definition of the PD which includes being both gluten and dairy-free, is not being adhered to by modern society. Thus, the results should be interpreted as comparing each distinct group of study participants, keeping in mind the overlap described in the results.

The results from this study disagree with previous findings, although the literature does not present consistent findings either. In those with celiac disease, studies have demonstrated a gluten-free diet has less fiber than a gluten-containing diet in healthy adults (67,68). However, fiber intake in a gluten-free diet has not been studied in a healthy population, such as that presented in this study. A dairy-free diet has been previously associated with no change in fiber intake (74,75). A PD has shown conflicting evidence of no change, lower, or higher dietary fiber intake (30,33,50,79). Thus, our findings further illustrate the complex relationship between diet type, PD adherence, and fiber intake.

We propose the uncovered association can be explained by the following:

First, the method of variable derivation for the PD was different from the gluten-free and dairy-free variable. This was initially done because most of the ADAPT Study respondents were plant-based or vegan. Among respondents with complete demographic data in the ADAPT Study, 25% were whole-food, plant-based and 19% were vegan and raw vegan (60). If the participant was vegan, they could be strictly adhering to the dairy-free diet but would not have been able to respond to this option in the first diet type question asked, as a vegan diet best explains their overall habits. The method of variable derivation was used to include more study subjects but could have affected the results.

Second, the gluten-free and dairy-free variables allowed an adherence component to be included. Only people who were always following a gluten-free or dairy-free diet were included. Alternatively, a respondent could have chosen a PD to best represent their dietary habits but had low adherence.

This study is the first to compare PD, dairy-free, and gluten-free diets to understand the relationship of fiber intakes within each diet type, and adherence to the PD. The current finding illustrates the fact that dietary patterns are far more variable than the names imply. This could be due to a variety of factors including adherence, personal choice, and personal definition of each diet type. A possible restriction of the study is that adherence to PD was not included and it is unclear whether external factors, such as being vegan/vegetarian drove the dairy-free diet to have the highest fiber intakes. Due to the extremely healthy population (60), it is also difficult to generalize the results to other populations who may not be adhering to other healthy habits. The mean BMI of this sample was 24.3 ± 5.0 kg/m^2, while the US age-adjusted mean for women in 2015-2016 was 29.6 kg/m^2 and for men, 29.1 kg/m^2 (82). Finally, it should be noted that it is unclear how informative total daily fiber intake is to health outcomes without knowing the type of fiber. For example, ratios of soluble versus insoluble or fermentable versus non-fermentable may influence cardiovascular and metabolic biomarkers differently. Future studies should aim to create a precise study design that would further distinguish between the dietary habits within each group and better explain dietary choices within and between each diet type. In these future studies, enrollment strategy may be a potential limitation as social media recruitment may target people who follow these 'healthier' diets.

5.7 Conclusion

This study is the first to compare PD, dairy-free, and gluten-free diets to understand the relationship of fiber intakes within each diet type, and adherence to the PD. The PD was associated with the lowest daily fiber intake among the three diet types: Paleo, gluten-free, and dairy-free. The dairy-free diet group had the highest daily fiber intake. It remains unclear why the PD has a different daily fiber intake than dairy-free or gluten-free diets. The current finding illustrates the fact that dietary patterns are far more variable than the names imply. This could be due to a variety of factors including adherence, personal choice, and personal definition of each diet type. Future studies should carefully consider study design to address the differences. Through this research, more specific nutritional recommendations can be recommended for people adhering to these diets.

Chapter 6. Further Research

There is a clear need to identify and define what the PD is for research purposes. Additionally, longer term studies will help to understand if initial weight loss, which may be achieved through caloric restriction rather than the PD, is the main reason for purported health benefits in the literature. Another useful study could be performed in healthy individuals with normal BMI and no caloric restriction to understand if it possible to improve metabolic and cardiovascular biomarkers through PD adherence. This eludes to the idea that the healthiest diet for an individual is one they can adhere to most to, simply to achieve weight loss. Further research should clearly identify the purpose of using the PD rather than another diet such as Mediterranean which may similarly result in caloric restriction.

Conclusion

Historic understanding of the PD carries numerous limitations in data including improper sourcing and analysis of nutrient intakes. A lack of clear definition of the PD has led to modern discrepancies in the literature when performing PD interventions. The purported health benefits from these interventions further remains unclear due to the discrepancies in interpretation.

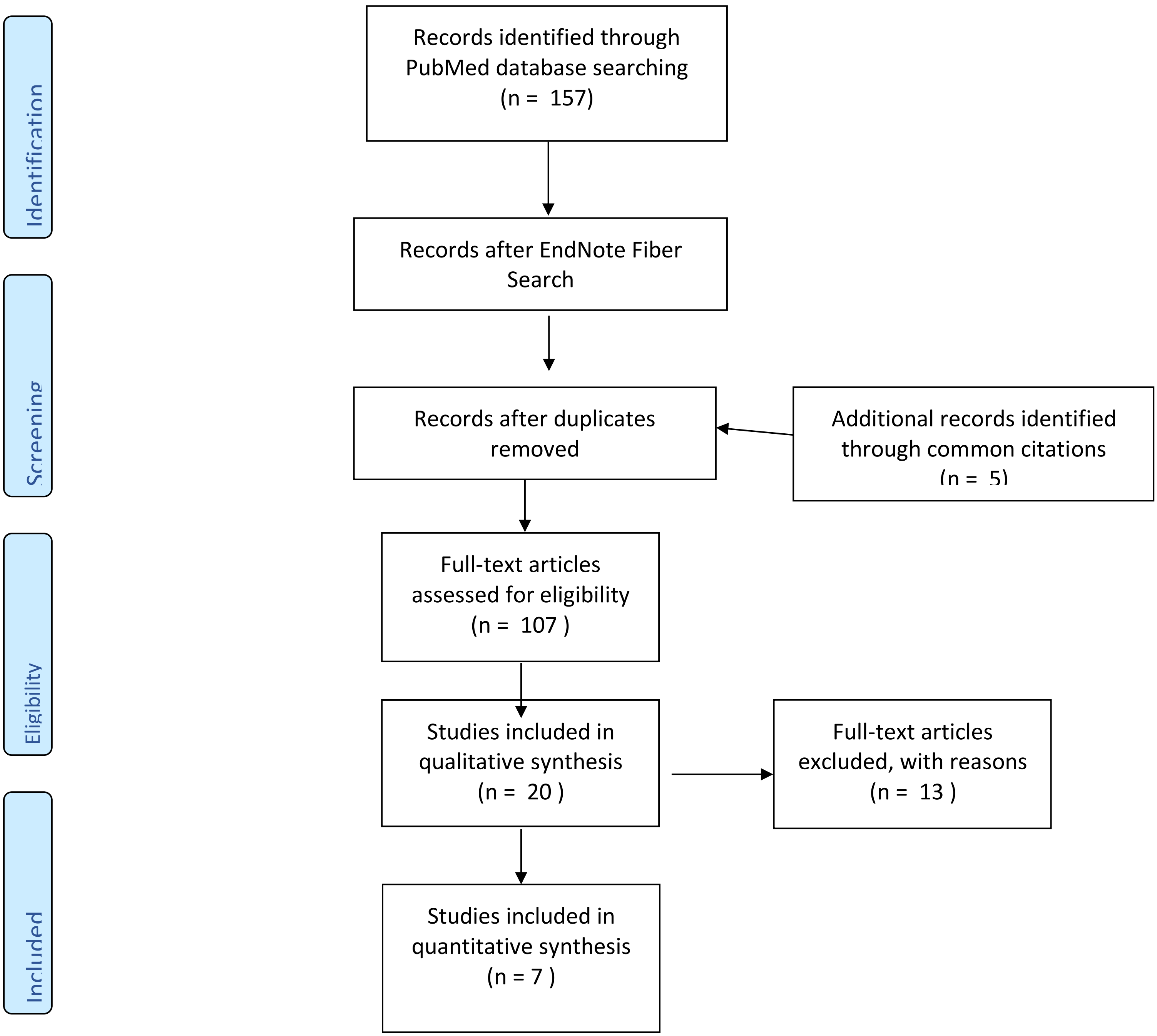
Most likely, a reduction in calorie intake can be attributed to the health marker improvements in the studied populations. Future research should measure Paleo adherence to discern the differences between adherence benefits versus reduction in energy intake. Additionally, it should aim to clarify the PD for intervention protocols so that data can be compared between studies. It is important to understand how the population adheres to and adopts the PD for sustainability and measures of dietary behavior change success.

It further remains unclear why the PD has a lower daily fiber intake than two of its components, the dairy-free and gluten-free diets. Future studies should carefully consider study design to address the differences. Through this research, more specific nutritional recommendations can be made for people adhering to these diets.

Finally, as we have seen in literature, the best diet for weight loss is the one the patient can adhere best to. Thus, the PD may only be more beneficial for some populations and specific dietary goals (such as increasing metabolic syndrome biomarkers). However, we must understand which diet the majority of the population has an easier time adhering to, long-term. Thus, an analysis comparing health benefit success across multiple diets in a long-term study is recommended.

Appendix

Flow Chart 1.



References

1. Eaton SB, Konner M. Paleolithic Nutrition: A Consideration of Its Nature and Current Implications. New England Journal of Medicine. 1985 Jan 31;312(5):283–9.

2. Chen J-P, Chen G-C, Wang X-P, Qin L, Bai Y. Dietary Fiber and Metabolic Syndrome: A Meta-Analysis and Review of Related Mechanisms. Nutrients. 2017 Dec 26;10(1):24.

3. Hoyert DL. 75 years of mortality in the United States, 1935-2010. NCHS Data Brief. 2012 Mar;(88):1–8.

4. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared Risk Factors in Cardiovascular Disease and Cancer. Circulation. 2016 Mar 15;133(11):1104–14.

5. Craig M Hales. Prevalence of Obesity Among Adults and Youth: United States, 2015–2016. NCHS data brief. 2017;(288):8.

6. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. 2017;20.

7. Centers for Disease Control and Prevention. Long-term Trends in Diabetes. 2016 Apr;6.

8. Voegtlin WL. The stone age diet: based on in-depth studies of human ecology and the diet of man. 1st ed. New York: Vantage Press; 1975. 277 p.

9. Jew S, AbuMweis SS, Jones PJH. Evolution of the Human Diet: Linking Our Ancestral Diet to Modern Functional Foods as a Means of Chronic Disease Prevention. Journal of Medicinal Food. 2009 Oct;12(5):925–34.

10. Ungar PS, Teaford MF, editors. Human diet: its origin and evolution. Westport, Conn: Bergin & Garvey; 2002. 206 p.

11. RD, CD and Kristal Lowe. A dissenting view on the Paleo Diet [Internet]. The Seattle Times. 2014 [cited 2019 Mar 2]. Available from: https://www.seattletimes.com/seattle-news/health/a-dissenting-view-on-the-paleo-diet/

12. Barone M, Turroni S, Rampelli S, Soverini M, D'Amico F, Biagi E, et al. Gut microbiome response to a modern Paleolithic diet in a Western lifestyle context. bioRxiv [Internet]. 2018 Dec 14 [cited 2019 Mar 8]; Available from: http://biorxiv.org/lookup/doi/10.1101/494187

13. Eaton SB. The ancestral human diet: what was it and should it be a paradigm for contemporary nutrition? Proceedings of the Nutrition Society. 2006 Feb;65(01):1–6.

14. Cordain L, Eaton SB, Sebastian A, Mann N, Lindeberg S, Watkins BA, et al. Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr. 2005 Feb;81(2):341–54.

15. Cordain L, Miller JB, Eaton SB, Mann N, Holt SH, Speth JD. Plant-animal subsistence ratios and macronutrient energy estimations in worldwide hunter-gatherer diets. Am J Clin Nutr. 2000 Mar;71(3):682–92.

16. Kuipers RS, Luxwolda MF, Dijck-Brouwer DAJ, Eaton SB, Crawford MA, Cordain L, et al. Estimated macronutrient and fatty acid intakes from an East African Paleolithic diet. Br J Nutr. 2010 Dec;104(11):1666–87.

17. Nobmann ED, Byers T, Lanier AP, Hankin JH, Jackson MY. The diet of Alaska Native adults: 1987-1988. Am J Clin Nutr. 1992 May;55(5):1024–32.

18. Lindeberg S, Berntorp E, Carlsson R, Eliasson M, Marckmann P. Haemostatic variables in Pacific Islanders apparently free from stroke and ischaemic heart disease--the Kitava Study. Thromb Haemost. 1997 Jan;77(1):94–8.

19. Milton K. Hunter-gatherer diets-a different perspective. Am J Clin Nutr. 2000 Mar;71(3):665–7.

20. Brumley C-L. Evolutionary nutrition and optimal human health: an integrative perspective for contemporary Australia. :538.

21. Cordain L. The Nutritional Characteristics of a Contemporary Diet Based Upon Paleolithic Food Groups. 2002;10.

22. Paleo Diet Tops Most Googled Diets Of 2013 | HuffPost Life [Internet]. 2013 [cited 2019 Mar 2]. Available from: https://www.huffpost.com/entry/most-googled-diets-of-2013_n_4426726

23. Friedman M. The Paleo Diet and the Insanity Workout Dominated Google Search in 2014 [Internet]. Redbook. 2014 [cited 2019 Mar 2]. Available from: https://www.redbookmag.com/health-wellness/body-blog/paleo-diet-insanity-workout-top-google-search-2014

24. Lara. 14 TOP DIET TRENDS FOR 2014 [Internet]. Pollock Communications. 2014 [cited 2019 Mar 2]. Available from: https://www.lpollockpr.com/in-the-news/14-top-diet-trends-2014-2/

25. Eaton JC, Iannotti LL. Genome–nutrition divergence: evolving understanding of the malnutrition spectrum. Nutrition Reviews. 2017 Oct 6;75(11):934–50.

26. Paleo, Keto, and Grain Free Product Certification • Paleo Foundation [Internet]. Paleo Foundation. [cited 2019 Mar 2]. Available from: https://paleofoundation.com/

27. Wahls T, Scott MO, Alshare Z, Rubenstein L, Darling W, Carr L, et al. Dietary approaches to treat MS-related fatigue: comparing the modified Paleolithic (Wahls Elimination) and low saturated fat (Swank) diets on perceived fatigue in persons with relapsing-remitting multiple sclerosis: study protocol for a randomized controlled trial. Trials [Internet]. 2018 Dec [cited 2019 Mar 2];19(1). Available from: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-018-2680-x

28. Ballantyne S. The Paleo Approach: reverse autoimmune disease and heal your body. Las Vegas: Victory Belt Publishing Inc; 2013. 432 p.

29. Kresser C. Your personal paleo code: the 3-step plan to lose weight, reverse disease, and stay fit and healthy for life. First edition. New York: Little, Brown and Company; 2013. 402 p.

30. Mellberg C, Sandberg S, Ryberg M, Eriksson M, Brage S, Larsson C, et al. Long-term effects of a Palaeolithic-type diet in obese postmenopausal women: a 2-year randomized trial. European Journal of Clinical Nutrition. 2014 Mar;68(3):350–7.

31. Österdahl M, Kocturk T, Koochek A, Wändell PE. Effects of a short-term intervention with a paleolithic diet in healthy volunteers. European Journal of Clinical Nutrition. 2008 May;62(5):682–5.

32. Otten J, Stomby A, Waling M, Isaksson A, Söderström I, Ryberg M, et al. A heterogeneous response of liver and skeletal muscle fat to the combination of a Paleolithic diet and exercise in obese individuals with type 2 diabetes: a randomised controlled trial. Diabetologia. 2018 Jul;61(7):1548–59.

33. Jönsson T, Granfeldt Y, Ahrén B, Branell U-C, Pålsson G, Hansson A, et al. Beneficial effects of a Paleolithic diet on cardiovascular risk factors in type 2 diabetes: a randomized cross-over pilot study. Cardiovascular Diabetology. 2009;8(1):35.

34. Whalen KA, McCullough M, Flanders WD, Hartman TJ, Judd S, Bostick RM. Paleolithic and Mediterranean diet pattern scores and risk of incident, sporadic colorectal adenomas. Am J Epidemiol. 2014 Dec 1;180(11):1088–97.

35. Whalen KA, Judd S, McCullough ML, Flanders WD, Hartman TJ, Bostick RM. Paleolithic and Mediterranean Diet Pattern Scores Are Inversely Associated with All-Cause and Cause-Specific Mortality in Adults. The Journal of Nutrition. 2017 Apr;147(4):612–20.

36. Whalen KA, McCullough ML, Flanders WD, Hartman TJ, Judd S, Bostick RM. Paleolithic and Mediterranean Diet Pattern Scores Are Inversely Associated with Biomarkers of Inflammation and Oxidative Balance in Adults. The Journal of Nutrition. 2016 Jun 1;146(6):1217–26.

37. Masharani U, Sherchan P, Schloetter M, Stratford S, Xiao A, Sebastian A, et al. Metabolic and physiologic effects from consuming a hunter-gatherer (Paleolithic)-type diet in type 2 diabetes. European Journal of Clinical Nutrition. 2015 Aug;69(8):944–8.

38. Stomby A, Otten J, Ryberg M, Nyberg L, Olsson T, Boraxbekk C-J. A Paleolithic Diet with and without Combined Aerobic and Resistance Exercise Increases Functional Brain Responses and Hippocampal Volume in Subjects with Type 2 Diabetes. Frontiers in Aging Neuroscience [Internet]. 2017 Dec 4 [cited 2019 Mar 2];9. Available from: http://journal.frontiersin.org/article/10.3389/fnagi.2017.00391/full

39. Ruemmele FM. Role of Diet in Inflammatory Bowel Disease. Annals of Nutrition and Metabolism. 2016;68(1):33–41.

40. Manheimer EW, van Zuuren EJ, Fedorowicz Z, Pijl H. Paleolithic nutrition for metabolic syndrome: systematic review and meta-analysis. The American Journal of Clinical Nutrition. 2015 Oct 1;102(4):922–32.

41. Masullo L, Papas MA, Cotugna N, Baker S, Mahoney L, Trabulsi J. Complementary and Alternative Medicine Use and Nutrient Intake Among Individuals with Multiple Sclerosis in the United States. Journal of Community Health. 2015 Feb;40(1):153–60.

42. Jönsson T, Granfeldt Y, Erlanson-Albertsson C, Ahrén B, Lindeberg S. A paleolithic diet is more satiating per calorie than a mediterranean-like diet in individuals with ischemic heart disease. Nutr Metab (Lond). 2010 Nov 30;7:85.

43. FDA.gov. [Internet]. Washington (DC): US Department of Health and Human Services, Food and Drug Administration, Center for Food Safety and Applied Nutrition. c. Nov 2016 [cited 2017 May 23]. Draft guidance: scientific evaluation of the evidence on the beneficial physiological effects of isolated or synthetic non-digestible carbohydrates submitted as a citizen petition (21 CFR 10.30): guidance for industry Available from: https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM528533.pdf.

44. Food and Drug Administration Health and Human Services. Federal Register. Food labeling: revision of the nutrition and supplement facts labels [Internet]. Available from: https://www.federalregister.gov/documents/2016/05/27/2016-11867/food-labeling-revision-of-the-nutrition-and-supplement-facts-labels.

45. 2015-2020 Dietary Guidelines for Americans. :144.

46. Eaton S, Eaton S, Konner M. Review Paleolithic nutrition revisited: A twelve-year retrospective on its nature and implications. European Journal of Clinical Nutrition. 1997 Apr;51(4):207–16.

47. Dietary Fiber Intake of the U.S. Population. 2014;(12):6.

48. Boers I, Muskiet FA, Berkelaar E, Schut E, Penders R, Hoenderdos K, et al. Favourable effects of consuming a Palaeolithic-type diet on characteristics of the metabolic syndrome: a randomized controlled pilot-study. Lipids in Health and Disease [Internet]. 2014 Dec [cited 2019 Mar 2];13(1). Available from: https://lipidworld.biomedcentral.com/articles/10.1186/1476-511X-13-160

49. King DE, Egan BM, Geesey ME. Relation of dietary fat and fiber to elevation of C-reactive protein. Am J Cardiol. 2003 Dec 1;92(11):1335–9.

50. Lindeberg S, Jönsson T, Granfeldt Y, Borgstrand E, Soffman J, Sjöström K, et al. A Palaeolithic diet improves glucose tolerance more than a Mediterranean-like diet in individuals with ischaemic heart disease. Diabetologia. 2007 Sep;50(9):1795–807.

51. Yamaoka K, Tango T. Efficacy of lifestyle education to prevent type 2 diabetes: a meta-analysis of randomized controlled trials. Diabetes Care. 2005 Nov;28(11):2780–6.

52. Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care. 2006 Sep;29(9):2102–7.

53. Rachel Nicoll, Michael Henein. Caloric Restriction and Its Effect on Blood Pressure, Heart Rate Variability and Arterial Stiffness and Dilatation: A Review of the Evidence. International Journal of Molecular Sciences. 2018 Mar 7;19(3):751.

54. García-Prieto C, Fernández-Alfonso M. Caloric Restriction as a Strategy to Improve Vascular Dysfunction in Metabolic Disorders. Nutrients. 2016 Jun 15;8(6):370.

55. Wadden TA, Considine RV, Foster GD, Anderson DA, Sarwer DB, Caro JS. Short- and Long-Term Changes in Serum Leptin in Dieting Obese Women: Effects of Caloric Restriction and Weight Loss 1. The Journal of Clinical Endocrinology & Metabolism. 1998 Jan;83(1):214–8.

56. Blundell J, de Graaf C, Hulshof T, Jebb S, Livingstone B, Lluch A, et al. Appetite control: methodological aspects of the evaluation of foods. Obes Rev. 2010 Mar;11(3):251–70.

57. Mohammadi M, Mohammadi H, Ghaedi E, Ramezani-Jolfaie N, Salehi-Abargouei A. Effects of Paleolithic Diet on Glucose Control in Adults: A Systematic Review and Meta-analysis of Controlled Clinical Trials. Journal of Nutrition and Food Security [Internet]. 2019 Jan 30 [cited 2019 Mar 2]; Available from: http://publish.kne-publishing.com/index.php/JNFS/article/view/399

58. Gannon MC, Nuttall FQ. Control of blood glucose in type 2 diabetes without weight loss by modification of diet composition. Nutr Metab (Lond). 2006 Mar 23;3:16.

59. Gannon MC, Nuttall FQ, Lane JT, Fang S, Gupta V, Sandhofer CR. Effect of 24 hours of starvation on plasma glucose and insulin concentrations in subjects with untreated non-insulin-dependent diabetes mellitus. Metab Clin Exp. 1996 Apr;45(4):492–7.

60. Karlsen MC, Lichtenstein AH, Economos CD, Folta SC, Rogers G, Jacques PF, et al. Web-Based Recruitment and Survey Methodology to Maximize Response Rates from Followers of Popular Diets: the Adhering to Dietary Approaches for Personal Taste (ADAPT) Feasibility Survey. Current Developments in Nutrition [Internet]. 2018 May 1 [cited 2019 Mar 23];2(5). Available from: https://academic.oup.com/cdn/article/doi/10.1093/cdn/nzy012/4931706

61. SAS Institute Inc. [Internet]. Cary, NC: SAS Institute Inc.; 2013 [cited 2019 Mar 23]. (SAS/ACCESS® 9.4 Interface to ADABAS: Reference.). Available from: https://documentation.sas.com/?docsetId=acadbas&docsetTarget=acadbas.pdf&docsetVersion=9.4&locale=en

62. RStudio Team. RStudio: Integrated Development for R. Boston, MA: RStudio, Inc.; 2015.

63. van Berge-Henegouwen GP, Mulder CJ. Pioneer in the gluten free diet: Willem-Karel Dicke 1905-1962, over 50 years of gluten free diet. Gut. 1993 Nov;34(11):1473–5.

64. DiGiacomo DV, Tennyson CA, Green PH, Demmer RT. Prevalence of gluten-free diet adherence among individuals without celiac disease in the USA: results from the Continuous National Health and Nutrition Examination Survey 2009–2010. Scandinavian Journal of Gastroenterology. 2013 Aug;48(8):921–5.

65. Fry L, Madden AM, Fallaize R. An investigation into the nutritional composition and cost of gluten-free versus regular food products in the UK. J Hum Nutr Diet. 2018;31(1):108–20.

66. Miranda J, Lasa A, Bustamante MA, Churruca I, Simon E. Nutritional differences between a gluten-free diet and a diet containing equivalent products with gluten. Plant Foods Hum Nutr. 2014 Jun;69(2):182–7.

67. Barone M, Della Valle N, Rosania R, Facciorusso A, Trotta A, Cantatore FP, et al. A comparison of the nutritional status between adult celiac patients on a long-term, strictly gluten-free diet and healthy subjects. Eur J Clin Nutr. 2016 Jan;70(1):23–7.

68. El Khoury D, Balfour-Ducharme S, Joye IJ. A Review on the Gluten-Free Diet: Technological and Nutritional Challenges. Nutrients. 2018 Oct 2;10(10).

69. Thompson T, Dennis M, Higgins LA, Lee AR, Sharrett MK. Gluten-free diet survey: are Americans with coeliac disease consuming recommended amounts of fibre, iron, calcium and grain foods? J Hum Nutr Diet. 2005 Jun;18(3):163–9.

70. Marcason W. Is there evidence to support the claim that a gluten-free diet should be used for weight loss? J Am Diet Assoc. 2011 Nov;111(11):1786.

71. Kim H-S, Demyen MF, Mathew J, Kothari N, Feurdean M, Ahlawat SK. Obesity, Metabolic Syndrome, and Cardiovascular Risk in Gluten-Free Followers Without Celiac Disease in the United States: Results from the National Health and Nutrition Examination Survey 2009-2014. Dig Dis Sci. 2017;62(9):2440–8.

72. Silanikove N, Leitner G, Merin U. The Interrelationships between Lactose Intolerance and the Modern Dairy Industry: Global Perspectives in Evolutional and Historical Backgrounds. Nutrients. 2015 Aug 31;7(9):7312–31.

73. Gupta RS, Warren CM, Smith BM, Jiang J, Blumenstock JA, Davis MM, et al. Prevalence and Severity of Food Allergies Among US Adults. JAMA Network Open. 2019 Jan 4;2(1):e185630.

74. Drouin-Chartier J-P, Gigleux I, Tremblay AJ, Poirier L, Lamarche B, Couture P. Impact of dairy consumption on essential hypertension: a clinical study. Nutr J. 2014 Aug 14;13:83.

75. Rideout TC, Marinangeli CPF, Martin H, Browne RW, Rempel CB. Consumption of low-fat dairy foods for 6 months improves insulin resistance without adversely affecting lipids or bodyweight in healthy adults: a randomized free-living cross-over study. Nutr J. 2013 May 2;12:56.

76. Anderson JW, Hoie LH. Weight loss and lipid changes with low-energy diets: comparator study of milk-based versus soy-based liquid meal replacement interventions. J Am Coll Nutr. 2005 Jun;24(3):210–6.

77. Smith CE, Follis JL, Dashti HS, Tanaka T, Graff M, Fretts AM, et al. Genome-Wide Interactions with Dairy Intake for Body Mass Index in Adults of European Descent. Mol Nutr Food Res. 2018;62(3).

78. Clifton P. Assessing the evidence for weight loss strategies in people with and without type 2 diabetes. World J Diabetes. 2017 Oct 15;8(10):440–54.

79. Osterdahl M, Kocturk T, Koochek A, Wändell PE. Effects of a short-term intervention with a paleolithic diet in healthy volunteers. Eur J Clin Nutr. 2008 May;62(5):682–5.

80. Popp CJ, Bohan Brown MM, Bridges WC, Jesch ED. The Effectiveness of MyPlate and Paleolithic-based Diet Recommendations, both with and without Exercise, on Aerobic Fitness, Muscular Strength and Anaerobic Power in Young Women: A Randomized Clinical Trial. Int J Exerc Sci. 2018;11(2):921–33.

81. Lee M. Official methods of analysis of AOAC International. Trends in Food Science & Technology.; 1995 11):382. Report No.: 16th edn.

82. National Health Statistics Reports, Number 122, December 20, 2018. 2018;(122):16.