

Clinical and scientific debates on atherosclerosis

The ketogenic diet: Pros and cons

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HIGHLIGHTS

- Most diets are supported by little rigorous scientific evidence.
- The ketogenic diet requires a firm restriction of carbohydrates and allows liberal ingestion of fats.
- The ketogenic diet induces a rapid weight loss and reduction in hemoglobin A1c, but raises LDL cholesterol.
- Other diets are as effective, more sustainable and safer.

ABSTRACT

Diets have been at the center of animated debates for decades and many claims have been made in one direction or the other by supporters of opposite camps, often with limited evidence. At times emphasis has been put on a single new aspect that the previous diets had overlooked and the new one was to embrace in order to improve weight loss and well-being. Unfortunately, very few randomized clinical trials involving diets have addressed the combined question of weight loss and cardiovascular outcomes. The recently introduced ketogenic diet requires a rigorous limitation of carbohydrates while allowing a liberal ingestion of fats (including saturated fats) and has generated a flurry of interest with many taking the pro position and as many taking the cons position. The ketogenic diet causes a rapid and sensible weight loss along with favourable biomarker changes, such as a reduction in serum hemoglobin A1c in patients with diabetes mellitus type 2. However, it also causes a substantial rise in low density lipoprotein cholesterol levels and many physicians are therefore hesitant to endorse it. In view of the popular uptake of the keto diet even among subjects not in need of weight loss, there is some preoccupation with the potential long-term consequences of a wide embrace of this diet by large segments of the population. On the contrary, numerous lines of evidence show that plant-based diets are associated with reduction in oncological and cardiovascular diseases and a prolonged life span. The debate reproduced in this article took place during a continuous medical education program between two cardiologists with largely differing views on the matter of effectiveness, sustainability, and safety of the ketogenic diet compared to alternative options.

1. Pro: Dr. Blair O'Neill

1.1. The ketogenic diet is safe and more effective than other diets

It has been said that: “The illiterate of the 21st century will not be those who cannot read and write, but those who cannot learn, unlearn, and relearn.” [1] Despite nearly 50 years of clinging to the dogma that saturated fat is detrimental to health, that total cholesterol is associated with mortality, and despite developing extremely effective therapies to reduce cholesterol, we continue to see an ever-expanding epidemic of obesity, diabetes, and increasing incidence of coronary heart disease (CHD). Reversing decades of decreasing coronary heart disease incidence and prevalence, for the past decade trends are now increasing, especially in those under 50 years-old male and female [2]. Lead by the United States Department of Agriculture, we have developed healthy food guidelines globally that counsel us to reduce fat intake,

particularly saturated fat, in order to reduce our future risk of heart disease (<https://health.gov/dietaryguidelines/2015/guidelines/>). Our population has listened and supported by the food industry has reduced our intake of fat, and particularly saturated fats, and as a consequence increased our consumption of carbohydrates which of course are broken down into sugars in our bodies [3]. There has been a direct correlation with the reduction of fat intake and the increase in carbohydrate intake with the obesity epidemic and the concordant increase in type II diabetes that we have witnessed over the past several decades (<https://www.cdc.gov/obesity/data/prevalence-maps.html>).

Dr. Ancel Keys, the most influential nutrition scientist in modern history, was an effective proponent of the so-called “diet heart hypothesis” [4]. Yet, the diet heart hypothesis remains in search of evidence-based validation. There was no evidence from randomized control trials to support the concept that fat is harmful at the time of the introduction of food guidelines in the late 1970s and early 1980s, nor

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has any more evidence that saturated fats are harmful accumulated since [5,6]. There is universal agreement that trans fats are detrimental to health and these have been phased out of foods as a consequence [7].

There is evidence that the decades-long trend to reduce the incidence and prevalence of CHD is ending. Decreased CHD rates have been largely attributed to successful public policy which reduced smoking rates across the Western world [8]. Unfortunately, over the past decade, we have seen that trend reverse. The incidence of CHD has been increasing. Even more concerning is the finding that premature myocardial infarction in subjects in their 40s and 50s occur often in patients with obesity, hypertension, and diabetes mellitus [2]. This is despite Americans following the low-fat recommendations since the 1980's with the consequence of consuming more carbohydrates and the population gaining more weight than ever before [3]. Indeed, unlike smoking, nutritional guidelines appear to have been a public policy failure.

What was the evidence that has created the past half century of nutritional advice? Indeed, it was shaky from the start. The principle proponent of the diet heart hypothesis, Dr. Ancel Keys and his team, performed the Minnesota Coronary Experiment from 1968 to 1972 replacing the standard American diet of the time which was approximately 45% fat with polyunsaturated oils, chiefly linoleic acid, and demonstrated as predicted that there was a decrease in total cholesterol [9]. Unfortunately, there was no change in mortality, although there was a signal of increased mortality in patients at highest risk, over age 65. However, because the investigators did not believe their own results, it was not until 2016 that these results were published. Had they been published at the time and associated with the totality of other evidence, it is quite probable that the guidelines to reduce fat and increase carbohydrates in the diet would not have been accepted and we might have avoided the current epidemic of obesity and diabetes.

Why is obesity such a major risk factor for CHD? It is most likely secondary to the development of visceral obesity, associated with hyperinsulinemia/insulin resistance, leading to enhanced local and systemic production of inflammatory cytokines/adipokines, and the ensuing dyslipidemia characterized by high-circulating triglycerides and low HDL [10,11]. Inflammation in vessel walls leads to medium vessel hypertrophy and hypertension that is present in 80% of overweight and obese individuals. Inflammation in small and medium arteries of the legs, kidneys and the heart leads to peripheral arterial disease, nephrosclerosis and CHD. A heightened systemic inflammatory state leads to insulin resistance and higher circulating insulin levels. Higher fasting insulin levels have been associated with higher risk of CHD in subjects without overt diabetes mellitus [12].

In cardiovascular science there has been increasing interest in inflammation as an explanation for the so called “residual risk” after patients' LDL cholesterol is controlled by statins. The REGARD registry showed that patients with an LDL cholesterol ≤ 1.8 mmol/L who had a high-sensitivity CRP (hsCRP) serum level ≥ 2 mg/L had a higher stroke risk, as well as all-cause and CHD mortality than patients with a hsCRP level < 2 mg/L [13]. The higher the fasting insulin the greater the likelihood of having an elevated hsCRP; at least one study showed that patients with an insulin level greater than 15 uIU/mL had a 30% greater risk of having an hsCRP ≥ 2 mg/dl [14].

Perspectives on better understanding lipid profile and CHD risk are changing. It is now recognized that it is not simply the LDL cholesterol, but the composition of the lipoprotein that more accurately determines risk [15–17]. Again, there is a relationship between LDL particle size and obesity and insulin resistance [18]. Patients with high small dense LDL particles have a much higher risk of CHD events compared with those who have larger more buoyant LDL particles. This situation often creates a discordance with patients with lower LDL cholesterol levels but higher particle counts demonstrating a higher risk of CHD events, while patients with higher LDL cholesterol but lower particle counts have a lower risk of events. Macronutrient studies have shown that a diet high in saturated fatty acids actually increases LDL particle size

compared to low-fat high carbohydrate diets that guidelines have encouraged the public to consume [19].

Thus, it appears that LDL must be modified to become atherogenic [20]. How it is packaged by its lipoprotein moiety and how that package is modified in the circulation and vessel wall determines its role in atherosclerosis. Modified or oxidized LDL has less affinity for LDL receptors and, therefore, longer circulation times. In the vessels wall, scavenger receptors on macrophages have a higher affinity for oxidized LDL leading to increased uptake, foam cell transformation and apoptosis, essential ingredients for the formation of vulnerable atherosclerotic plaques. Oxidized LDL concentrations are higher in insulin resistance, the metabolic syndrome, and diabetes mellitus type 2 [21].

Insulin, itself, has a dichotomous impact on the vessel wall. In metabolically healthy individuals in an insulin sensitive state, low levels of insulin are associated with healthy nitric oxide production, vasodilation, lower monocyte adhesion, lower local and systemic inflammation, and less oxidative stress. In the metabolically unwell patient with chronically high insulin levels due to insulin resistance, insulin exerts the opposite effect once it interacts with its receptor, increasing levels of plasminogen activator-1, and endothelin leading to a pro-vasoconstrictive state, smooth muscle proliferative state and a milieu that promotes migration of monocytes and smooth muscle cells [22].

Is there a way to reverse the diabetes and obesity epidemic? Certainly, the last 5–10 years of research have suggested that low carbohydrate, high-fat diets are associated with significantly greater weight loss compared with low-fat diets in head to head randomized control trials [23]. Similarly, for patients most metabolically unwell, those with diabetes mellitus type 2, the most effective treatment has been bariatric surgery [24]. Can obesity, a lifestyle disease, only be reversed by surgical intervention? More research is confirming that very low carbohydrate diets can effectively reverse the metabolic abnormalities of patients with diabetes mellitus type 2. Compared with low fat diets, carbohydrate restriction produces significantly greater reduction in hemoglobin A1c, and weight loss in patients with diabetes mellitus type 2. In a non-randomized clinical trial in patients with type 2 diabetes mellitus, 262 patients received a very low carbohydrate diet and 87 controls received a diet based on standard guidelines [25]. The intervention group was treated with a ketogenic diet with blood measurements confirming nutritional ketosis, with beta-hydroxybutyrate levels between 0.4 and 0.6 mmol/L. Patients lost between 10 and 15% of body weight. Inflammatory responses, as measured by hsCRP and white blood cell count, decreased significantly while they did not change or continued to increase in the usual care group. Virtually every important biomarker changed in a positive direction including triglycerides, HDL, small dense LDL particle count, and, most importantly, the 10-year risk of atherosclerotic cardiovascular disease decreased despite an increasing LDL cholesterol level. Indeed, the observation that LDL-C rises but its apolipoprotein B (apoB) does not, suggests that the particles have favorably transformed, which is confirmed by the increase in LDL particle size and the dramatic fall in the far more atherogenic small dense LDL-P. This would portend an event free advantage for those treated with a ketogenic diet. Conversely, in the usual care group, virtually every biomarker continued to deteriorate over follow-up including the predicted 10-year risk of cardiovascular events [26]. The LDL cholesterol, however, decreased. Unfortunately, the usual care low-fat diet also further reduced LDL particle size in these metabolically challenged diabetic patients. Have we been focusing on the wrong biomarker of risk? Is there any wonder why we have considered type 2 diabetes mellitus to be a largely progressive irreversible disease? Not surprisingly, in the intervention cohort, average hemoglobin A1c decreased from baseline 7.6%–6.3% at one year. From a cost perspective, medication utilization was dramatically reduced with half the patients completely discontinuing insulin, and all coming off sulfonylureas as opposed to the usual care group where insulin doses and sulfonylurea use continued to increase.

It is time for a paradigm shift in the thinking about risk factors for CHD. The epidemiological experiment to decrease fat in the diet has failed and has only made the population sick. We are seeing the adverse outcomes of misguided dogma that focused only on LDL cholesterol levels. It has been too simplistic and has led to an increased prevalence of heart disease in young people, who have been exposed to the toxic refined carbohydrate diet for their entire lives. It is sugar and processed carbohydrates that lead to insulin resistance, and then to a pro-inflammatory state that leads to many chronic conditions of our era, including hypertension, peripheral arterial disease, CHD, atrial fibrillation, heart failure with or without preserved ejection fraction, chronic renal insufficiency among many others. With 7/10 adults and 4/10 children, now overweight or obese, we need an urgent call to action to use science and not dogma to drive recommendations. Recommendations should not be based on nutritional and scientific bias. Indeed, we are now seeing the convergence of environmentalism, animal rights activism, plant-based dietism using weak association data to drive policy agenda. If we don't get this right, we will continue to witness an ever-expanding epidemic of obesity and its consequences in the population, with escalating astronomical costs both to individuals and to society. It is time for transparent science to drive agendas not dogma.

2. Cons: Dr. Paolo Raggi

2.1. *There is no scientific proof of the superiority, safety and sustainability of the ketogenic diet*

It is hard to image a debate more animated and scientifically weaker than any debate centered around diets. The ketogenic diet (keto for short) may happen to have some merits, but the excessive fervor with which it is often defended by its proponents makes it appear as another of the fads we have lived through, all too often unsupported by good evidence. The paucity of scientifically rigorous trials renders the debate over diets tentative, confusing, very opinionated and -at times- a bitter confrontation between opposing camps. Keto makes no exception to this rule, and in fact it may represent a perfect case in point. It is worth noting and discussing some of the objections the proponents of the keto diet advance. The main thrust of the keto campaign rests on the tenet that carbohydrates are noxious to the health of the population. Additionally, they stress that the low-fat diets advocated by professional associations for decades have no scientific basis and have induced the current epidemic of obesity and diabetes mellitus. Such emphasis on carbohydrates inducing obesity seems a bit misplaced when in the early 1860s William Banting already warned of the dangers of sugars in the *Letter on Corpulence?* [27] In his opening statement Banting wrote: *"Of all the parasites that affect humanity, I do not know of, nor can I imagine, any more distressing than that of Obesity, and, having just emerged from a very long probation in this affliction I am desirous in circulating my humble knowledge and experience ..."*. He then proceeded to describe a long list of failures to lose weight at the advice of luminaries who counselled him to be more physically active, rest better, take Turkish baths etc.. all leading to insignificant results. The failures continued until the day he met an illuminated physician who advised him *"to abstain as much as possible [from] ... bread, butter, milk, sugar, beer and potatoes."* In adherence with such a diet he lost 2–3.5 pounds per week and became a slim 165-pound man from his corpulent 202 pounds just a few months earlier. Later in the letter he describes a typical breakfast in his new diet and states: *"For breakfast, I take four or five ounces of beef, mouton, kidneys, broiled fish, bacon or cold meats of any kind except pork, a large cup of tea without milk or sugar and a small biscuit ..."* I would say Banting introduced the notion that obesity is a chronic ailment and proposed a ketogenic approach to weight loss long before we even started talking about it! So, here are a few facts no one may be able to dispute: [a] restricting calories of any type induces weight loss; [b] a diet rich in fats and proteins causes early satiety therefore a

reduction in ingestion of calories; [c] limiting or eliminating carbohydrates is a major contributor to weight loss; [d] introducing a keto diet mostly, or almost exclusively, based on animal products induces rapid weight loss. But toward the end Banting warns the reader of another important fact: *"I am now in that happy, comfortable state, that I should not hesitate to indulge in any fancy in regard to diet, but if I did so, should watch the consequences, and not continue any course which might add to weight or bulk and consequent discomfort."* That is to say, weight loss is to be preserved and the effectiveness of any diet is to be measured in the potential for maintenance. Having been born in a southern European country I find it hard to believe that keto may be a sustainable, healthy and affordable approach to fight obesity and its consequences, or become a lifestyle. I am even less convinced that it may be a safe diet in patients with established cardiovascular disease or at very high risk for it. In the next several paragraphs I will address these concerns and review some observational data as well as the limited randomized trials available to date in support of dietary preferences.

2.1.1. *Of myths and dogma*

Despite accusing mainstream medicine to be fraught with dogma, keto supporters appear to apply a dogmatic approach to their assertions without a good base for their arguments. One of the frequent arguments brought forward by keto followers is that western populations have been ingrained with various wrong dogma for several decades. Among others: the negative effects of saturated fats have never been demonstrated; Ancel Keys misrepresented the truth in the Seven Countries Study [28]; guidelines that invited the population to observe a low-fat diet, induced an increase in ingestion of carbohydrates with a subsequent epidemic of obesity. Furthermore, there is a large industry interest behind this plot. Honestly, I cannot see how industry may not (and does not) benefit from either excess: too many carbohydrates or too much beef, eggs, chicken, dairy etc. Why would the sugar industry be smarter and slicker than the meat industry? We are currently facing a serious environmental challenge with the increasing greenhouse gas emitted by cattle (<http://www.fao.org/gleam/results/en/>), and many are willing to close an eye on it. Because food is a global commodity, what is consumed in one country can impact another. One of the most devastating effects of the global increase in demand for animal products (beef in particular) is the ever-expanding deforestation we are witnessing. I don't see how this is not evidence of an industry interest.

The assertion that Dr. Keys misrepresented the results of the Seven Countries Study and obliterated the truth about the benign nature of saturated fats consumption is -to say the least- a gross manipulation of the facts (reviewed elegantly here [29]).

It is also hard to believe that the guidelines induced a switch toward a larger ingestion of dangerous carbohydrates. Going back decades, in 1980 the US Department of Agriculture and the Department of Health and Human Services (<https://health.gov/dietaryguidelines/1980thin.pdf>) warned of the dangers of obesity, encouraged the population to eat a variety of foods (including meat, fish, eggs, dairy etc..), suggested that people eat mostly complex carbohydrates, whole grains and beans, not refined carbohydrates. The guidelines did not prohibit but suggested limiting the ingestion of saturated fats and acknowledged that a diet low in fat may not help everyone, in fact people can still have a high serum cholesterol even when eating a low-fat diet. The reality however is very different: North Americans are eating low quantities of complex carbohydrates, vegetables, legumes and fruit and eat too many refined, simple sugars (<https://health.gov/dietaryguidelines/2015/guidelines/chapter-2/a-closer-look-at-current-intakes-and-recommended-shifts/>). So, the population is not observing the guidelines, and it appears odd that keto supporters would accuse the guidelines and their writers of inducing an epidemic of obesity. Caution is therefore in order.

2.1.2. *Weight loss and its sustainability*

Keto can induce a rapid -mostly due to water losses- and gratifying weight loss but, like any other diet, it must be sustained to keep weight

off. The studies completed so far have been very short and have not convincingly demonstrated that the keto diet is more sustainable and that the effects are more durable than those of others. In a metaanalysis comparing low-fat vs low-carbohydrate diets, Bueno et al. [30] reviewed 9 studies of 12-month duration and 4 additional studies lasting 24 months. They concluded that keto provided on average 0.9 kg additional weight loss compared to low-fat diets, along with a significant reduction in triglycerides, and diastolic blood pressure, in the face of a significant increase in HDL-c and LDL-c. While these results are encouraging it should be remarked that the studies in the metaanalysis included a very small number of patients (60–200 patients, with one study including 305 patients), and there was no report on the long-term outcome of the enrolled subjects. In an experiment conducted in a metabolic inpatient unit, Hall et al. [31] exposed 17 overweight or obese subjects to isocaloric low-fat vs low-carbohydrate diets in 2 subsequent study periods. The energy loss (in Kcal per day) induced by the two diets was not different. Although keto induced a substantial decrease in insulin secretion along with increasing circulating free-fatty acids and ketones, it did not induce a greater body fat loss than the low-fat diet. It is important to remember that a strict keto diet includes no more than 10% of the total daily calorie intake in the form of carbohydrates, 20% as proteins and the remaining as fats. Many may find this restriction too limiting and unpalatable, despite the freedom to ingest as much butter and bacon as desired and may deviate from such enforcement with the simple ingestion of one apple a day (one medium size apple contains about 22 gm of carbohydrates, Fig. 1). Halitosis, constipation and diarrhea, muscle cramps, headaches, vitamin deficiencies, nephrolithiasis and other side effects may also deter many patients from persevering on the keto diet.

2.1.3. Safety and long-term benefits

Despite the well-advertised weight loss and the reduction in insulin requirements and hemoglobin A1c, the long-term benefits of keto have not been demonstrated. A study often reported as demonstrating the superiority of keto compared to low fat diets in reducing hemoglobin A1c and inducing weight loss in patients with diabetes mellitus type 2, was an open-label, non-randomized study during which patients were exposed to 1-year of a continuous care intervention or usual care [25]. Notably, all patients, who elected to participate in the “intervention arm” (i.e. keto diet), received extensive counseling and tools to measure their adherence to the diet as well as their progress. These included: a cellular-connected body weight scale, a finger-stick blood glucose and

ketone meter, a blood pressure cuff, access to a web-based application for biomarker reporting and monitoring, education, and communication with a remote care team consisting of a health coach, a medical provider and social support via an online peer community. The patients who volunteered to adhere to usual care simply continued to see their family doctors and received advice on diet. One can hardly imagine this to be a balanced trial and fair a comparison. Furthermore, a systematic review of trials comparing the effect of low-carbohydrate diets, diets with high intake of saturated fats, high intake of monounsaturated fats or high intake of polyunsaturated fats (PUFA), showed the best results in terms of reduction of hemoglobin A1c, insulin secretion and resistance with a diet rich in PUFA [32].

It is worrisome that virtually every study involving keto, several metaanalyses of keto as a weight losing diet [33,34], and a controlled experiment in healthy subjects [35] demonstrated a significant increase in LDL-c. Healthy, normal weight volunteers exposed to a 3-week long keto diet demonstrated a 44% increase in serum LDL-c and a 30% reduction in the expression of the LDL-c receptor on the surface of peripheral blood mononuclear cells [35]. In a pediatric study, 141 children with intractable seizure disorder (the ketogenic diet was introduced as a treatment for this disorder numerous decades ago) were treated with the keto diet and strictly monitored for development of a ketogenic state [36]. Total cholesterol, LDL, VLDL, non-HDL cholesterol, triglycerides and total apoB increased significantly while the HDL level decreased significantly after 6 months of treatment. Although attenuated, a significant increase in all apoB containing lipoproteins persisted at 12 and 24 months from treatment inception.

The supporters of keto maintain that a very-low carbohydrate, high-fat diet increases the number of large buoyant LDL particles but not that of the noxious small-dense LDL particles. However, several issues should be remarked upon. First, the total apoB concentration increases (as discussed above) and independent of any other consideration this should be taken as an ominous harbinger. It has been clearly demonstrated in epidemiological and genetic studies as well as clinical trials that LDL is the cause of atherosclerosis [37], and none of the many international guidelines on risk reduction differentiates between large and small LDL particle size. This is likely due to the weak and conflicting evidence that LDL particle size matters more than LDL mass [15]. Importantly, the number of particles and the serum level of apoB containing lipoproteins have been clearly shown to increase cardiovascular risk, not the size of the LDL particles [38–40]. In a sub-study of the Multi-Ethnic Study of Atherosclerosis (MESA), small and large LDL

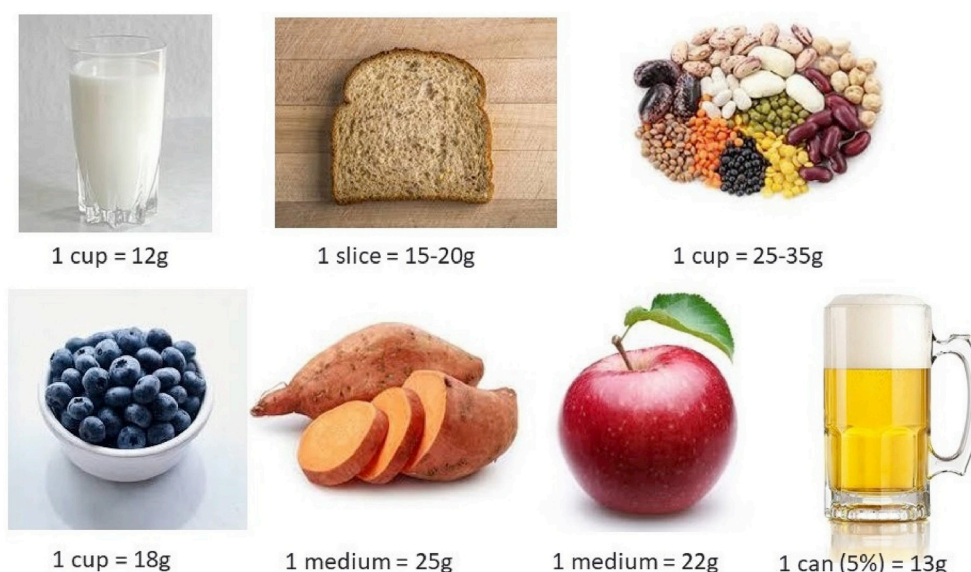


Fig. 1. Representative carbohydrate content of frequently consumed foods.

particles were equally associated with increased carotid intima media thickness after adjustment for confounding [41]. As a result, none of international or national guidelines focus on small LDL levels but on LDL mass, non-HDL and/or apoB. Ultimately, the number of apoB containing lipoproteins circulating in the arterial lumen will determine the number of particles infiltrating the arterial wall and the number of particles retained in the subintimal space, where they will promote atherosclerosis plaque growth. Paradoxically, small dense LDL may even protect against repeat cardiovascular events [42].

Contrary to the above observations, the benefits of lower fat, mostly plant-based diets have been demonstrated both in large observational studies and a few randomized trials. Two recent long-term prospective observational studies reported on the comparison of plant-based vs animal-based diets. In a north American study [43], the long-term (several decades) all-cause and cardiovascular mortality of 131,342 health care professionals was assessed after animal and plant-based energy intake was gauged with validated and regularly updated food frequency questionnaires. Animal protein intake was not associated with increased all-cause mortality but was associated with a significant increase in cardiovascular mortality (8% increased risk per 10% increase in animal-based energy intake). On the contrary, plant-based diets were associated with a significant reduction in all-cause and cardiovascular mortality (10% and 12% decrease respectively per 3% increase in plant-based energy intake). A switch from an animal to a plant-based diet was associated with a 34% reduction in all-cause mortality when 3% of energy from plant protein was substituted for an equivalent amount of protein from processed red meat, 12% from unprocessed red meat, and 19% from eggs. A more recent Japanese study [44] confirmed and reinforced the above findings. Among 70,696 adults participating in the Japan Public Health Center-based Prospective Cohort, 12,381 total deaths were recorded over a 20-year follow-up period after collecting food frequency questionnaires to assess plant vs animal-based protein intake between 1995 and 1999. Again, animal protein intake was not associated with total or cause-specific mortality. However, intake of plant protein was associated with a significantly lower all-cause mortality (11–13% according to quintile of intake), and lower cardiovascular mortality (16–30% reduction according to quintile of intake). As in the north American observation, isocaloric substitution of 3% energy derived from red meat proteins with plant-based proteins was associated with a 34% lower all-cause mortality, 42% lower cardiovascular mortality and even a 39% lower cancer related mortality. Despite the observational nature of these studies the findings were undeniably impressive, especially in view of the large sample size and length of follow-up. An older observation in a sample of 6500 Chinese adults living in rural areas reported almost identical findings [45]. The fat intake in rural China was less than half that in the United States, fiber intake was 3 times higher and animal protein intake about 10% of the US intake. The mean serum total cholesterol was 3.2 mmol/L in rural China versus 5.25 mmol/L in the United States. As a reflection, coronary artery disease mortality was almost 17-fold greater for American men and 6-fold greater for American women. Mortality from coronary artery disease in rural China was inversely associated with the frequency of intake of green vegetables and positively associated with salt intake and plasma apolipoprotein B levels. Of course, the living conditions were also very different between the populations studied, and what is frequently missing in observational studies are the associated lifestyle differences between populations (as discussed a little later in this review). The merits of a Mediterranean type diet (high intake of olive oil, fruit, nuts, vegetables, and cereals; moderate intake of fish and poultry; low intake of dairy products, red meat, processed meats, and carbohydrates; moderate wine consumption, Fig. 2) were addressed both in secondary and in primary prevention trials.

The Lyon Heart Study was designed to compare the impact of the Mediterranean diet vs a traditional Western prudent diet in 605 patients with prior myocardial infarction. Despite the originally planned 5 years

duration, the study was reported after a mean follow-up of 27 months due to a highly statistically significant reduction in the rate of re-infarction and death in the patients following the Mediterranean diet (risk ratio: 0.27; 95% CI 0.12–0.59, $p = 0.001$) [46]. These results were confirmed in the extension study (adjusted risk ratios varying between 0.28 and 0.53) [47]. The nutrients intake was substantially different between groups: patients following the Mediterranean diet consumed significantly less lipids, saturated fat, cholesterol, and linoleic acid but more oleic and alpha-linolenic acids.

In the primary prevention PREDIMED study [48], 7477 patients at high risk for cardiovascular disease were randomized to a low-fat (AHA style) diet, or a Mediterranean diet supplemented with either extra-virgin olive oil (MEDIevoo) or nuts (MEDInuts). After a median follow-up of 4.8 years there was a significant 31% reduction in the primary combined endpoint of myocardial infarction, stroke, or death in the MEDIevoo and 28% reduction in the MEDInuts cohorts compared to the low-fat diet cohort. Of note, at baseline 50% of the patients enrolled had diabetes mellitus, the mean BMI was 30 and over 70% of the patients had dyslipidemias. Adherence to the Mediterranean diet based on the number of recommended food items consumed per week, was strongly and inversely associated with risk of developing obesity [49]. Higher consumption of red meat was associated with a higher prevalence and incidence of the metabolic syndrome and central obesity [50]. Conversely, liberal consumption of unsaturated fats was not associated with weight gain or increase in waist circumference [51].

2.1.4. Summary of the cons position

Naturally, there are numerous opinions on what constitutes a “healthy diet” and often confusion reigns [52]. As an example, the same authors of the large five continent PURE observational study reported conflicting associations, at times favouring fat intake [53–55], and at times sugar intake [56,57]. However, there are many other aspects besides diet that affect cardiovascular health at a population level, such as smoking and regular exercise [58]. The French paradox, that extends to most of the southern European nations, has been talked about and dissected extensively: despite a high fat intake, the cardiovascular morbidity and mortality are very low. However, what differentiates Mediterranean populations from others is not only the proportional intake of fat, vegetables, olive oil, nuts and wine. Diet in those counties is a lifestyle; a way of living that involves pleasure in eating; it entails seeing a meal as an opportunity to enjoy friends, family and a tasty portion of food, without too much preoccupation as to the caloric content of each item on the menu. Exercise is an integral part of life in Europe where people often commute on foot or by bicycle, and often stroll after a meal. The benefit of exercise along with a Mediterranean-style diet has been shown recently. Salas-Salvado et al. [59] randomized 626 adults with the metabolic syndrome to a calorie restricted Mediterranean diet, plus counseling on daily exercise *versus* dietary advice only. The patients who received dietary and exercise counseling achieved a significant 2.5 kg weight loss in excess of patients given isolated dietary advice. The keto diet offers several potential benefits such as substantial weight loss, reduction in insulin secretion and reduced hemoglobin A1c among others [60]. Nonetheless, there is currently no scientific evidence of its ultimate clinical benefit. It is however reassuring that [ClinicalTrail.gov](https://clinicaltrials.gov) lists over 70 ongoing trials involving the keto diet that should shed some light on the ultimate question of long-term benefit.

I am, and always have been, open to innovation but I respect the scientific discourse. Such approach does not value strong personal opinions and values facts that stand the rigour of peer review. Beyond adopting a different feeding approach for the purpose of weight loss, the keto lifestyle has been embraced by large segments of the population with no need to lose weight and without a solid base for it. Adopting the keto diet beyond the scope of weight loss begs the question of its sustainability and long-term safety, but also enjoyment in life. One can't help but wonder if the attentiveness to labelling certain foods

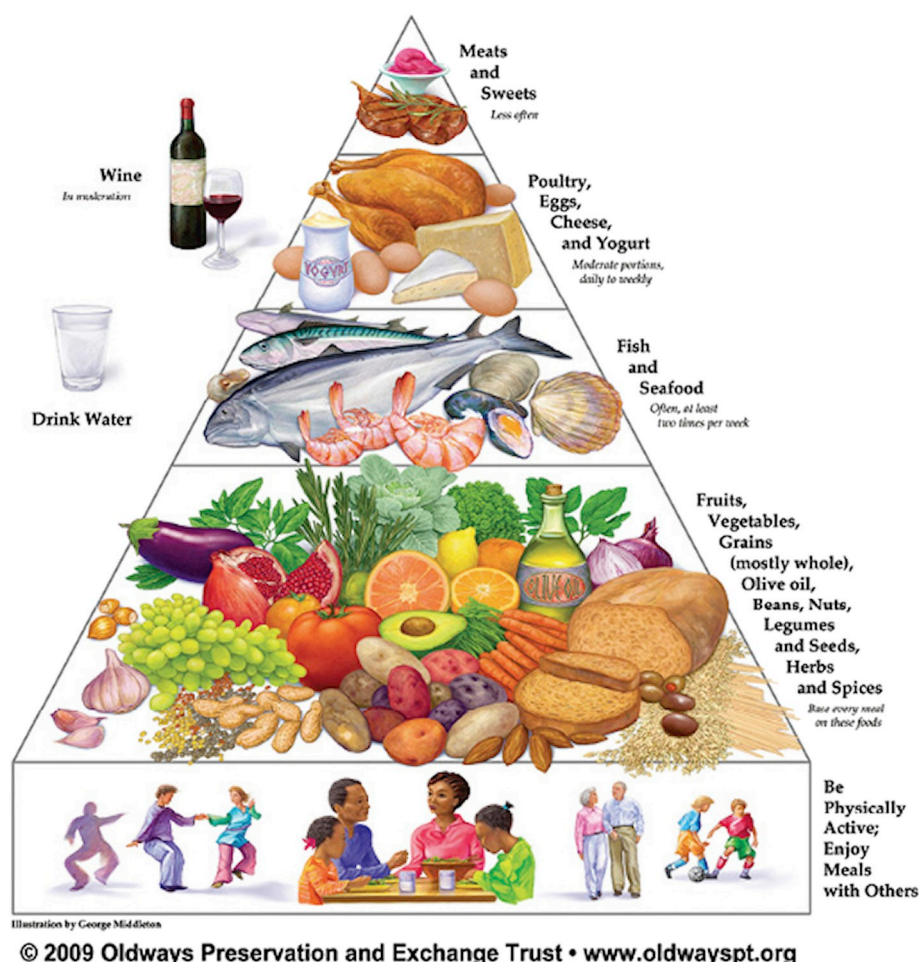


Fig. 2. Simplified graphical description of the Mediterranean diet.

The pyramid shows food items typically consumed in this diet in order of least frequently (apex) to most frequently consumed (base of the pyramid) (reproduced with permission from Oldways Preservation and Exchange Trust).

as ‘bad’ and to be avoided, or ‘good’ and to be consumed induces an unhealthy preoccupation with food and enhances latent behavioural eating disorders. Developing a healthy relationship with food is a necessary part of life. Personally, I am not in favour of any restrictive approach, and will always support moderation, enjoyable diets and the promotion of healthy lifestyle habits. After all, dancing the hula may be all we need to do to improve our cardiovascular health and do so happily (<https://newsroom.heart.org/news/native-hawaiians-lowered-blood-pressure-with-hula-dancing?preview=1094>; Kaholokula et al. personal communication [61]).

3. Conclusions

These closing remarks try to summarize in an objective way the state of the current knowledge on this topic. The ketogenic diet induces a rapid weight loss. It is not entirely clear if the loss is due to water loss, a special effect of the diet itself (i.e. fat burning) or a reduction in total calorie intake; in fact, the keto diet is known to induce a quick sense of satiety that has a potential to reduce total calorie intake. In-house, controlled studies comparing low-fat *versus* low-carbohydrate diets did not demonstrate the superiority of either dietary approach for weight loss. Other potentially relevant effects of the keto diet are the improvement in glycemic control and reduction in triglycerides and small-dense LDL lipoprotein particles concentration attainable with this nutritional approach. However, the total number of apoB containing lipoproteins is substantially increased in patients adopting the ketogenic diet. In view of the risk of cardiovascular disease associated with an

elevation in apoB containing lipoproteins, subjects without diabetes and the metabolic syndrome should think carefully whether this lifestyle is advisable for any protracted period of time. In contrast, plant-based diets allowing a daily moderate content of non-saturated fats, and small amounts of red meats and saturated fats hold for now the best epidemiological and randomized clinical trial evidence that they are safe and associated with reduction in several chronic diseases, including atherosclerotic cardiovascular disease. Numerous ongoing randomized clinical trials are addressing many unanswered questions about the keto diet and should provide some of the much-needed evidence many are waiting for.

Declaration of competing interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

References

- [1] Alvin Toffler, *Future Shock*, Random House, New York, 1970.
- [2] S. Aurora, G.A. Stouffer, A.M. Kucharska-Newton, A. Qamar, M. Vaduganathan, A. Pandey, M.C. Caughey, Twenty-year trends and sex differences in young adults hospitalized with acute myocardial infarction: the ARIC community surveillance study, *Circulation* 139 (2018) 1047–1056, <https://doi.org/10.1161/CIRCULATIONAHA.118.037137>.
- [3] E. Cohen, M. Cragg, J. deFonseka, et al., Statistical review of US macronutrient consumption data, 1965–2011: Americans have been following dietary guidelines, coincident with the rise in obesity, *Nutrition* 31 (5) (2015) 727–732.
- [4] A. Keys, Diet and the epidemiology of coronary heart disease, *J. Am. Med. Assoc.*

- 164 (1957) 1912–1919, <https://doi.org/10.1001/jama.1957.62980170024007e>.
- [5] Z. Harcombe, J.S. Baker, S.M. Cooper, B. Davies, N. Sculthorpe, J.J. DiNicolantonio, F. Grace, Evidence from randomised controlled trials did not support the introduction of dietary fat guidelines in 1977 and 1983: a systematic review and meta-analysis, *Open Heart* 2 (2015), <https://doi.org/10.1136/openhrt-2014-000196> e000196.
 - [6] P.W. Siri-Tarino, Q. Sun, F.B. Hu, R.M. Krauss, Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease, *Am. J. Clin. Nutr.* 91 (2010) 535–546, <https://doi.org/10.3945/ajcn.2009.27725>.
 - [7] I. Ascherio, M.B. Katan, P.L. Zock, M.J. Stampfer, W.C. Willett, Trans fatty acids and coronary heart disease, *N. Engl. J. Med.* 340 (1999) 1994–1998, <https://doi.org/10.1056/NEJM199906243402511>.
 - [8] Z. Kabir, G.N. Connolly, L. Clancy, H.K. Koh, S. Capewell, Coronary heart disease death and decreased smoking prevalence in Massachusetts, 1993–2003, *Am. J. Public Health* 98 (2008) 1468–1469, <https://doi.org/10.2105/AJPH.2007.129924>.
 - [9] C.E. Ramsden, D. Zamora, S. Majchrzak-Hong, K.R. Faurot, S.K. Broste, R.P. Frantz, J.R. Hibbeln, Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968–73), *BMJ* 353 (2016) i1246, <https://doi.org/10.1136/bmj.i1246>.
 - [10] A. Gómez-Hernández, N. Benoit, S. Díaz-Castroverde, Ó. Escribano, Differential role of adipose tissues in obesity and related metabolic and vascular complications, *Internet J. Endocrinol.* 2016 (2016) 1216783, <https://doi.org/10.1155/2016/1216783>.
 - [11] N. Tahara, H. Kai, S. Yamagishi, M. Mizoguchi, H. Nakaura, M. Ishibashi, H. Kaida, K. Baba, N. Hayabuchi, T. Imaizumi, Vascular inflammation evaluated by [18F]-fluorodeoxyglucose positron emission tomography is associated with the metabolic syndrome, *J. Am. Coll. Cardiol.* 49 (2007) 1533–1539, <https://doi.org/10.1016/j.jacc.2006.11.046>.
 - [12] M. Pyörälä, H. Miettinen, M. Laakso, K. Pyörälä, Hyperinsulinemia predicts coronary heart disease risk in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study, *Circulation* 98 (1998) 398–404, <https://doi.org/10.1161/01.cir.98.5.398>.
 - [13] P.E. Penson, D.L. Long, G. Howard, P.P. Toth, P. Muntner, V.J. Howard, M.M. Safford, S.R. Jones, S.S. Martin, M. Mazidi, A.L. Catapano, M. Banach, Associations between very low concentrations of low density lipoprotein cholesterol, high sensitivity C-reactive protein, and health outcomes in the Reasons for Geographical and Racial Differences in Stroke (REGARDS) study, *Eur. Heart J.* 39 (2018) 3641–3653, <https://doi.org/10.1093/eurheartj/ehy533>.
 - [14] J.S. Yang, J.N. Gerber, H.J. You, Association between fasting insulin and high-sensitivity C reactive protein in Korean adults, *BMJ Open Sport & Exerc Med* 3 (2017), <https://doi.org/10.1136/bmjsem-2017-000236> e000236.
 - [15] J.D. Otvos, S. Mora, I. Shalaurova, P. Greenland, R.H. Mackey, D.C. Goff Jr., Clinical implications of discordance between low-density lipoprotein cholesterol and particle number, *J Clin Lipidol* 5 (2011) 105–113, <https://doi.org/10.1016/j.jacl.2011.02.001>.
 - [16] P.P. Toth, M. Grabner, R.S. Punekar, R.A. Quimbo, M.J. Cziraky, T.A. Jacobson, Cardiovascular risk in patients achieving low-density lipoprotein cholesterol and particle targets, *Atherosclerosis* 23 (2014) 585–591, <https://doi.org/10.1016/j.atherosclerosis.2014.05.914>.
 - [17] P. Manickam, A. Rathod, S. Panaich, P. Hari, V. Veeranna, A. Badheka, S. Jacob, L. Afonso, Comparative prognostic utility of conventional and novel lipid parameters for cardiovascular disease risk prediction: do novel lipid parameters offer an advantage? *J Clin Lipidol* 5 (2011) 82–90, <https://doi.org/10.1016/j.jacl.2010.12.001>.
 - [18] J. Hulthe, L. Bokemark, J. Wikstrand, B. Fagerberg, The metabolic syndrome, LDL particle size, and atherosclerosis: the Atherosclerosis and Insulin Resistance (AIR) study, *Arterioscler. Thromb. Vasc. Biol.* 20 (2000) 2140–2147, <https://doi.org/10.1161/01.ATV.20.9.2140>.
 - [19] R.M. Krauss, P.J. Blanche, R.S. Rawlings, H.S. Fernstrom, P.T. Williams, Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia, *Am. J. Clin. Nutr.* 83 (2006) 1025–1031, <https://doi.org/10.1093/ajcn/83.5.1025>.
 - [20] G. Maiolino, G. Rossitto, P. Caielli, V. Bisogni, G.P. Rossi, L.A. Calò, The role of oxidized low-density lipoproteins in atherosclerosis: the myths and the facts, *Mediat. Inflamm.* 2013 (2013) 714653, <https://doi.org/10.1155/2013/714653>.
 - [21] W. Ali, U.P. Kushwaha, M. Wamique, P. Vishwakarma, M. Tasleem, et al., Oxidized LDL as a biomarker in metabolic syndrome, *J Diabetes Metab* 8 (2017) 764, <https://doi.org/10.4172/2155-6156.1000764>.
 - [22] G.L. King, K. Park, Q. Li, Selective insulin resistance and the development of cardiovascular diseases in diabetes: the 2015 Edwin Bierman Award Lecture, *Diabetes* 65 (2016) 1462–1471, <https://doi.org/10.2337/db16-0152>.
 - [23] J. Sackner-Bernstein, D. Kanter, S. Kaul, Dietary intervention for overweight and obese adults: comparison of low-carbohydrate and low-fat diets. A Meta-Analysis, *PLoS One* (2015), <https://doi.org/10.1371/journal.pone.0139817>.
 - [24] P.R. Schauer, D.L. Bhatt, J.P. Kirwan, et al., Bariatric surgery versus intensive medical therapy for diabetes — 5-year outcomes, *N. Engl. J. Med.* 376 (2017) 641–651, <https://doi.org/10.1056/NEJMoa1600869>.
 - [25] J. Sarah, S.J. Hallberg, A.L. McKenzie, P.T. Williams, et al., Effectiveness and safety of a novel care model for the management of type 2 diabetes at 1 year: an open-label, non-randomized, controlled study, *Diabetes Ther* 9 (2018) 583, <https://doi.org/10.1007/s13300-018-0373-9>.
 - [26] N.H. Bhanpuri, S.J. Hallberg, P.T. Williams, et al., Cardiovascular disease risk factor responses to a type 2 diabetes care model including nutritional ketosis induced by sustained carbohydrate restriction at 1 year: an open label, non-randomized, controlled study, *Cardiovasc. Diabetol.* 17 (2018) 56, <https://doi.org/10.1186/s12933-018-0698-8>.
 - [27] William Banting, Letter on Corpulence, Addressed to the Public, University Library of San Francisco, 1865.
 - [28] A. Keys, A. Menotti, M.J. Karvonen, C. Aravanis, H. Blackburn, R. Buzina, B.S. Djordjevic, A.S. Dontas, F. Fidanza, M.H. Keys, et al., The diet and 15-year death rate in the seven countries study, *Am. J. Epidemiol.* 124 (1986) 903–915, <https://doi.org/10.1093/oxfordjournals.aje.a114480>.
 - [29] K.D. Pett, W.C. Willett, E. Vartiainen, D.L. Katz, The seven countries study, *Eur. Heart J.* 38 (42) (2017) 3119–3121, <https://doi.org/10.1093/eurheartj/ehx603>.
 - [30] N.B. Bueno, I.S. de Melo, S.L. de Oliveira, T. da Rocha Ataíde, Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials, *Br. J. Nutr.* 110 (2013) 1178–1187, <https://doi.org/10.1017/S0007114513000548>.
 - [31] K.D. Hall, K.Y. Chen, J. Guo, Y.Y. Lam, R.L. Leibell, L.E. Mayer, M.L. Reitman, M. Rosenbaum, S.R. Smith, B.T. Walsh, E. Ravussin, Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men, *Am. J. Clin. Nutr.* 104 (2016) 324–333, <https://doi.org/10.3945/ajcn.116.133561>.
 - [32] F. Imamura, R. Micha, J.H. Wu, M.C. de Oliveira Otto, F.O. Otite, A.I. Abioye, D. Mozaffarian, Effects of saturated fat, polyunsaturated fat, monounsaturated fat, and carbohydrate on glucose-insulin homeostasis: a systematic review and meta-analysis of randomised controlled feeding trials, *PLoS Med.* 13 (7) (2016), <https://doi.org/10.1371/journal.pmed.1002087> e1002087.
 - [33] A.J. Nordmann, A. Nordmann, M. Briel, U. Keller, W.S. Yancy Jr., B.J. Brehm, H.C. Bucher, Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials, *Arch. Intern. Med.* 166 (2006) 285–293, <https://doi.org/10.1001/archinte.166.3.285>.
 - [34] N. Mansoor, K.J. Vinknes, M.B. Veierød, K. Retterstøl, Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials, *Br. J. Nutr.* 115 (2016) 466–479, <https://doi.org/10.1017/S0007114515004699>.
 - [35] K. Retterstøl, M. Svendsen, I. Narverud, K.B. Holven, Effect of low carbohydrate high fat diet on LDL cholesterol and gene expression in normal-weight, young adults: a randomized controlled study, *Atherosclerosis* 279 (2018) 52–61, <https://doi.org/10.1016/j.atherosclerosis.2018.10.013>.
 - [36] P.O. Kwiterovich Jr., E.P. Vining, P. Pyzik, R. Skolasky Jr., J.M. Freeman, Effect of a high-fat ketogenic diet on plasma levels of lipids, lipoproteins, and apolipoproteins in children, *J. Am. Med. Assoc.* 290 (2003) 912–920, <https://doi.org/10.1001/jama.290.7.912>.
 - [37] B.A. Ference, H.N. Ginsberg, I. Graham, K.K. Ray, C.J. Packard, E. Bruckert, R.A. Hegele, R.M. Krauss, F.J. Raal, H. Schunkert, G.F. Watts, J. Borén, S. Fazio, J.D. Horton, L. Masana, S.J. Nicholls, B.G. Nordestgaard, B. van de Sluis, M.R. Taskinen, L. Tokgözoğlu, U. Landmesser, U. Laufs, O. Wiklund, J.K. Stock, M.J. Chapman, A.L. Catapano, Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel, *Eur. Heart J.* 38 (2017) 2459–2472, <https://doi.org/10.1093/eurheartj/ehx144>.
 - [38] S. Ip, A.H. Lichtenstein, M. Chung, J. Lau, E.M. Balk, Systematic review: association of low-density lipoprotein subfractions with cardiovascular outcomes, *Ann. Intern. Med.* 150 (2009) 474–484, <https://doi.org/10.7326/0003-4819-150-7-200904070-00007>.
 - [39] P.P. Toth, M. Grabner, R.S. Punekar, R.A. Quimbo, M.J. Cziraky, T.A. Jacobson, Cardiovascular risk in patients achieving low-density lipoprotein cholesterol and particle targets, *Atherosclerosis* 235 (2014) 585–591, <https://doi.org/10.1016/j.atherosclerosis.2014.05.914>.
 - [40] AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices, T.G. Cole, J.H. Contois, G. Csako, J.P. McConnell, A.T. Remaley, S. Devaraj, D.M. Hoefner, T. Mallory, A.A. Sethi, G.R. Warnick, Association of apolipoprotein B and nuclear magnetic resonance spectroscopy-derived LDL particle number with outcomes in 25 clinical studies: assessment by the AACC Lipoprotein and Vascular Diseases Division Working Group on Best Practices, *Clin. Chem.* 59 (5) (2013 May) 752–770, <https://doi.org/10.1373/clinchem.2012.196733>.
 - [41] S. Mora, M. Szklo, J.D. Otvos, P. Greenland, B.M. Psaty, D.C. Goff Jr., D.H. O'Leary, M.F. Saad, M.Y. Tsai, A.R. Sharrett, LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA), *Atherosclerosis* 192 (2007) 211–217, <https://doi.org/10.1016/j.atherosclerosis.2006.05.007>.
 - [42] Y. Pokharel, Y. Tang, B. Bhardwaj, K.K. Patel, M. Qintar, J.H. O'Keefe Jr., K.R. Kulkarni, P.H. Jones, S.S. Martin, S.S. Virani, J.A. Spertus, Association of low-density lipoprotein pattern with mortality after myocardial infarction: insights from the TRIUMPH study, *J Clin Lipidol* 11 (2017) 1458–1470, <https://doi.org/10.1016/j.jacl.2017.09.002> e4.
 - [43] M. Song, T.T. Fung, F.B. Hu, W.C. Willett, V.D. Longo, A.T. Chan, E.L. Giovannucci, Association of animal and plant protein intake with all-cause and cause-specific mortality, *JAMA Intern Med* 176 (2016) 1453–1463, <https://doi.org/10.1001/jamainternmed.2016.4182>.
 - [44] S. Budhathoki, N. Sawada, M. Iwasaki, T. Yamaji, A. Goto, A. Kotemori, J. Ishihara, R. Takachi, H. Charvat, T. Mizoue, H. Iso, S. Tsugane, Japan Public Health Center-based Prospective Study Group. association of animal and plant protein intake with all-cause and cause-specific mortality, *JAMA Intern Med* (2019 Aug 26), <https://doi.org/10.1001/jamainternmed.2019.2806>.
 - [45] T.C. Campbell, B. Parpia, J. Chen, Diet, lifestyle, and the etiology of coronary artery disease: the Cornell China study, *Am. J. Cardiol.* 82 (10B) (1998) 18T–21T, [https://doi.org/10.1016/S0002-9149\(98\)00718-8](https://doi.org/10.1016/S0002-9149(98)00718-8).
 - [46] M. de Lorgeril, S. Renaud, N. Mamele, P. Salen, J.L. Martin, I. Monjaud, J. Guillelmet, P. Touboul, J. Delaye, Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease, *Lancet* 343 (8911) (1994)

- 1454–1459, [https://doi.org/10.1016/S0140-6736\(94\)92580-1](https://doi.org/10.1016/S0140-6736(94)92580-1).
- [47] M. de Lorgeril, P. Salen, J.L. Martin, I. Monjaud, J. Delaye, N. Marnette, Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study, *Circulation* 99 (1999) 779–785, <https://doi.org/10.1161/01.cir.99.6.779>.
- [48] R. Estruch, E. Ros, J. Salas-Salvadó, et al., Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra virgin olive oil or nuts, *N. Engl. J. Med.* 378 (2018) e34, <https://doi.org/10.1056/NEJMoa1800389>.
- [49] M.A. Martínez-González, A. García-Arellano, E. Toledo, J. Salas-Salvadó, P. Buil-Cosiales, D. Corella, M.I. Covas, H. Schröder, F. Arós, E. Gómez-Gracia, M. Fiol, V. Ruiz-Gutiérrez, J. Lapetra, R.M. Lamuela-Raventós, L. Serra-Majem, X. Pintó, M.A. Muñoz, J. Wärnberg, E. Ros, R. Estruch, PREDIMED Study Investigators, A 14-item Mediterranean diet assessment tool and obesity indexes among high-risk subjects: the PREDIMED trial, *PLoS One* 7 (2012), <https://doi.org/10.1371/journal.pone.0043134> e43134.
- [50] N. Babio, M. Sorlí, M. Bulló, J. Basora, N. Ibarrola-Jurado, J. Fernández-Ballart, M.A. Martínez-González, L. Serra-Majem, R. González-Pérez, J. Salas-Salvadó, Nureta-PREDIMED Investigators, Association between red meat consumption and metabolic syndrome in a Mediterranean population at high cardiovascular risk: cross-sectional and 1-year follow-up assessment, *Nutr. Metab. Cardiovasc. Dis.* 22 (2012) 200–207, <https://doi.org/10.1016/j.numecd.2010.06.011>.
- [51] R. Estruch, M.A. Martínez-González, D. Corella, J. Salas-Salvadó, M. Fitó, G. Chiva-Blanch, et al., PREDIMED Study Investigators. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: a prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial, *Lancet Diabetes Endocrinol* 7 (2019) e6–e17.
- [52] N.J. Temple, Fat, sugar, whole grains and heart disease: 50 years of confusion, *Nutrients* 10 (1) (2018) E39, <https://doi.org/10.3390/nu10010039> pii.
- [53] M. Dehghan, A. Mente, X. Zhang, S. Swaminathan, W. Li, V. Mohan, et al., Prospective Urban Rural Epidemiology (PURE) study investigators. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study, *Lancet* 390 (10107) (2017) 2050–2062, [https://doi.org/10.1016/S0140-6736\(17\)32252-3](https://doi.org/10.1016/S0140-6736(17)32252-3).
- [54] M. Dehghan, A. Mente, S. Rangarajan, P. Sheridan, V. Mohan, R. Iqbal, et al., Prospective Urban Rural Epidemiology (PURE) study investigators. Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study, *Lancet* 392 (10161) (2018) 2288–2297, [https://doi.org/10.1016/S0140-6736\(18\)31812-9](https://doi.org/10.1016/S0140-6736(18)31812-9).
- [55] A. Mente, M. Dehghan, S. Rangarajan, M. McQueen, G. Dagenais, A. Wielgosz, et al., Prospective Urban Rural Epidemiology (PURE) study investigators. Association of dietary nutrients with blood lipids and blood pressure in 18 countries: a cross-sectional analysis from the PURE study, *Lancet Diabetes Endocrinol* 5 (2017) 774–787, [https://doi.org/10.1016/S2213-8587\(17\)30283-8](https://doi.org/10.1016/S2213-8587(17)30283-8).
- [56] V. Miller, A. Mente, M. Dehghan, S. Rangarajan, X. Zhang, S. Swaminathan, et al., Prospective Urban Rural Epidemiology (PURE) study investigators. Fruit, vegetable, and legume intake, and cardiovascular disease and deaths in 18 countries (PURE): a prospective cohort study, *Lancet* 390 (10107) (2017) 2037–2049, [https://doi.org/10.1016/S0140-6736\(17\)32253-5](https://doi.org/10.1016/S0140-6736(17)32253-5).
- [57] V. Miller, S. Yusuf, C.K. Chow, M. Dehghan, D.J. Corsi, K. Lock, et al., Availability, affordability, and consumption of fruits and vegetables in 18 countries across income levels: findings from the Prospective Urban Rural Epidemiology (PURE) study, *Lancet Glob Health* 4 (2016) e695–703, [https://doi.org/10.1016/S2214-109X\(16\)30186-3](https://doi.org/10.1016/S2214-109X(16)30186-3).
- [58] K. Teo, S. Lear, S. Islam, P. Mony, M. Dehghan, W. Li, et al., PURE Investigators. Prevalence of a healthy lifestyle among individuals with cardiovascular disease in high-, middle- and low-income countries: the Prospective Urban Rural Epidemiology (PURE) study, *J. Am. Med. Assoc.* 309 (2013) 1613–1621, <https://doi.org/10.1001/jama.2013.3519>.
- [59] J. Salas-Salvadó, A. Díaz-López, M. Ruiz-Canela, J. Basora, M. Fitó, D. Corella, et al., PREDIMED-Plus investigators. Effect of a lifestyle intervention program with energy-restricted Mediterranean diet and exercise on weight loss and cardiovascular risk factors: one-year results of the PREDIMED-Plus Trial, *Diabetes Care* 42 (2019) 777–788, <https://doi.org/10.2337/dc18-0836>.
- [60] P.N. Hyde, T.N. Sapper, C.D. Crabtree, R.A. LaFountain, M.L. Bowling, A. Buga, et al., Dietary carbohydrate restriction improves metabolic syndrome independent of weight loss, *JCI Insight* 4 (12) (2019) 128308, <https://doi.org/10.1172/jci.insight.128308> pii.
- [61] J.K. Kaholokula, T.M. Mabellos, S.Y. Choi, T.B. Seto, T. Wills, M. de Silva, A. Dillard, J. Gonsalves, A.A.A. Seabury, J.K. Vegas, S.J. Haumea, D.M. Palakiko, M.A. Look, A cultural dance program proves efficacious for hypertension control: a randomized controlled trial, *Hypertension* 74 (2019) AP3054, https://doi.org/10.1161/hyp.74.suppl_1.P3054.