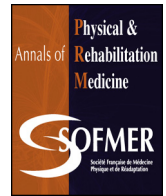




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Review

Contemporary issues regarding nutrition in cardiovascular rehabilitation

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ABSTRACT

In this article, we discuss certain contemporary and controversial topics in cardiovascular (CV) nutrition including recent data regarding the health benefits of the Mediterranean diet, the role of saturated fatty acids, red meat and the microbiome in CV disease and the current role of personalized CV nutrition. Findings from the PREDIMED study now demonstrate the health benefits of the Mediterranean diet even in the absence of heart disease. The study highlighted that even small, sustained and easily implementable changes to diet can provide significant health benefits even in Mediterranean regions. Likewise, observational data in secondary prevention show that increased adherence to the Mediterranean diet is associated with good long-term clinical outcomes among subjects with stable coronary heart disease. The role of saturated fats in the development of CV disease remains controversial, although data suggest that these fats are associated with modestly increased risk of CV events. In contrast, the obesity epidemic currently driving the CV risk worldwide is in large part due to excess consumption of refined carbohydrates. Furthermore, a growing body of evidence suggests that the intestinal microbiome is highly sensitive to lifestyle choices and may play a pivotal role in modulating CV disease development. For example, recent evidence linking processed and unprocessed meats to increased CV risk pointed to the gut microbial metabolite trimethylamine N-oxide as a potential culprit. Finally, given the high interindividual variability in response to interventions including diet, personalized nutrition has potential to play a major role in tailoring diets based on genetic make-up to maximize health benefits. This approach is still in its infancy but is highly promising.

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1. Introduction

Cardiovascular (CV) nutrition remains a cornerstone of a complete cardiac rehabilitation program. According to the most recent data from the World Health Organization, hypertension, high blood sugar, excess weight and hypercholesterolemia represent 4 of the 10 greatest risk factors for all-cause mortality worldwide [1]. These risk factors highlight the vital role that nutrition plays in health and disease. The same can be said at the individual level. The contemporary patient with CV disease (CVD) not only has underlying heart disease but most often has multiple

co-morbidities including obesity, diabetes, hypertension and dyslipidemia, all of which continue to play a role in long-term prognosis. Therefore, poor nutrition plays a major role in the initiation and maintenance of the atherosclerotic process, but diet has a major role in reversing heart disease.

In this article, we discuss several contemporary topics in CV nutrition, some of which are controversial, including recent findings regarding the Mediterranean diet (MED) and CV risk, the role of saturated fatty acids and red meat in CVD and personalized nutrition for CV prevention.

2. The Mediterranean diet: recent findings

Most dietary patterns that have been studied for their cardiometabolic properties (e.g. DASH, Mediterranean, Nordic diets) are based on similar principles, that natural, nutrient-rich

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foods should be prioritized over highly processed foods [2]. The widely known MED has been largely investigated since its first description by Keys et al. [3]. Briefly, this dietary pattern is rich in fruits and vegetables, legumes and grains, with moderate consumption of fish, low-fat dairy products, and alcohol and relies on extra-virgin olive oil (EVOO) as its main source of dietary fat [4]. The nutritional composition of the MED is thus rich in monounsaturated fatty acids (MUFAs), primarily oleic acid, dietary fibers, and antioxidant compounds such as polyphenols, in addition to a high ratio of omega-3 to omega-6 polyunsaturated FAs. This dietary pattern is also characterized by low consumption of highly processed foods, red meats and vegetable oils other than EVOO, so it is poor in saturated FAs (SFAs), industrially produced *trans* fats and simple sugars.

Epidemiological and accumulating clinical studies have demonstrated the benefits of the MED and its constituents that act in synergy to prevent the development of CVD and its risk factors in the primary prevention setting. For example, a recent meta-analysis of epidemiological and prospective trials concluded that a two-point increase in adherence to the MED, measured by the MED score elaborated by Panagiotakos et al. [5] was associated with a 10% reduction in all-cause mortality in healthy people of all age groups and in CV risk [6]. On a practical level, a two-point increase in MED score requires a modest increase in consumption of beneficial foods including fruits, vegetables, legumes, grains and fish combined with a modest decrease in detrimental foods such as processed and unprocessed red meats. Such dietary modifications are thus attainable and implementable at the population level. As noted below, data regarding the benefits of the MED in secondary prevention are more limited [7,8] but are wholly consistent with primary prevention studies.

The largely covered PREDIMED intervention trial and the plethora of post hoc-related analyses have revealed for the first time in a randomized controlled trial (RCT) the CV and cardiometabolic benefits of the MED in people without overt CVD but at high risk. The study involved 7447 Spanish participants with type 2 diabetes mellitus (T2DM) or at least 3 traditional CV risk factors who were randomized to receive a low-fat control diet or 1 of 2 MEDs (supplemented with large quantities of EVOO or mixed nuts). Adherence to a MED decreased the incidence of stroke, myocardial infarction (MI) or CV death by 30% [9]. As well, adherence to a MED (particularly in the increased nut-consumption group) significantly reduced the prevalence of metabolic syndrome and diabetes in the context of an ad libitum diet [10–12]. PREDIMED interventions positively affected other intermediate CV endpoints: they normalized levels of B-type natriuretic peptide, oxidized LDL, and lipoprotein(a) [13]; improved plasma antioxidant status [14]; and decreased the prevalence of hypertension [15].

However, conclusions from the PREDIMED trial require interpretation with caution [16]. In reality, all 3 groups had similar baseline diets, which reflected a high degree of adherence, on average, to the MED [9,17]. At the end of the trial, the proportion of energy intake from total fat was only slightly lower in the low-fat control group (37%) relative to the MED groups (41%), whereas that from saturated fat was similar among the groups [16]. Although adherence to the MED was increased in the olive oil and nut groups, the major differences in terms of the control diet were the higher MUFA content (from increased EVOO consumption and nut consumption) and PUFA content (from nut consumption). Thus, correctly speaking, PREDIMED demonstrated that consumption of significant quantities of EVOO or nuts in addition to a MED reduced fatal and non-fatal CV endpoints relative to a MED alone. Nonetheless, PREDIMED demonstrated that minor and thus sustainable dietary modifications to already “healthy” habits can benefit CV health and lower event rates.

Since the publication of both the GISSI-Prevenzione [7] and Lyon Diet Heart studies [8], no additional prospective RCTs have evaluated the impact of the MED or its constituents on the secondary prevention of CVD. Briefly, GISSI-Prevenzione demonstrated in 11,324 Italian subjects with recent MI that supplementation with fish oil (1 g EPA + DHA) reduced the risk of CV death relative to placebo by 17–30% after a mean follow-up of 3.5 years [7]. In contrast, in the Lyon Diet Heart study, 423 patients with recent acute MI were randomized to a control diet (prudent Western diet) or a MED and followed for 45 months, on average [8]. Similar to PREDIMED, the MED group received canola oil as a supplement to increase dietary content of alpha-linolenic acid. The study demonstrated that adherence to the MED reduced the composite endpoint of cardiac death and non-fatal MI by 72% ($P = 0.0001$) and risk of cardiac death alone by 65% ($P = 0.01$). Taken together, the results of PREDIMED, GISSI-Prevenzione and the Lyon Diet Heart studies demonstrate that as one moves from primary to secondary prevention of CVD and from targeted supplementation of a specific constituent to a holistic MED pattern, the benefits of a MED on hard clinical endpoints are even greater. Recent data from an observational study support this view. In a substudy of the STABILITY trial, which included over 15,000 patients with stable coronary heart disease (CHD), adherence to a MED was associated with reduced risk of major adverse cardiac events including CV death, non-fatal MI and non-fatal stroke in the context of optimal contemporary medical management [18]. In contrast, adherence to a Western-type diet rich in refined grains, carbohydrates and deep-fried foods was not associated with poorer outcomes. As noted by the authors, these data suggest that consumption of healthy foods is more important than avoidance of less healthy foods for secondary prevention of CV events [18].

3. Controversies in cardiovascular nutrition

3.1. Saturated fatty acids

In the past 2 years, much confusion has surrounded the role of SFAs in the pathogenesis of CHD because of the publication of meta-analyses that have suggested deleterious effects on CV health falsely attributed to these fats over the past 40 years [19,20]. The first meta-analysis of Chowdhury et al. concluded that their findings “did not yield clearly supportive evidence for current cardiovascular guidelines that encourage high consumption of polyunsaturated fatty acids and low consumption of saturated fats” [19]. However, many experts in the field have criticized the authors’ methodology, notably, that one study in particular, the Sydney Diet Heart Study [21], should not have been included in the meta-analysis because the supplemented source of w-6 PUFAs was a *trans* fat-based margarine [22]. Moreover, according to Dawczynski et al., in the analyses of circulating blood fatty acid composition, 2 studies [23,24] finding negative associations between SFAs from dairy products (pentadecanoic acid (15:0) and heptadecanoic acid (17:0)) and MI should not have been included because dairy sources of SFAs do not reflect total SFA intake [25]. By eliminating the 2 studies, Dawczynski et al. found a harmful association between SFA blood levels and coronary outcomes.

The meta-analysis by de Souza et al. also found no association between SFA intake and CV mortality or total CHD [20]. However, a positive trend association between SFA intake and CHD mortality was found. The methodology of this meta-analysis is arguable. Indeed, the study included observational studies, conducted over a very broad time range, from 1981 to 2014, and in very heterogeneous populations. Moreover, the studies included did not all consider which macronutrient replaced the SFAs [26]. In one

study that focused on which macronutrient replaced SFAs; the risk of fatal CHD was decreased with SFAs replaced by PUFAs [27]. Similarly, a pooled analysis of 11 prospective cohort studies found a 13% decrease in coronary events (hazard ratio [HR] 0.87, 95% CI 0.77–0.97) and a 26% decrease in coronary deaths (HR 0.74, 95% CI 0.61–0.89) with a 5% lower energy intake from SFAs and a concomitant higher energy intake from PUFAs [28]. A 7% increase in coronary events (HR 1.07, 95% CI 1.01–1.14) was found for intake of carbohydrates.

However, the meta-analysis of Mozaffarian et al., which included 8 RCTs and no observational studies, demonstrated a 10% reduction in risk of CHD events per 5% increase in energy intake from PUFAs, with absence of heterogeneity among studies [29]. Also, a recently updated Cochrane systematic review of 15 RCTs addressing the same question concluded that reduced SFA intake resulted in a 17% decrease in CV events, with the greatest benefit observed by substituting SFAs with PUFAs [30]. From these findings, the question is whether saturated fats are harmful and also whether in a balanced isocaloric diet, other types of fat or macronutrients are cardioprotective. To properly address this question, we need RCTs examining the replacement of saturated fat by other macronutrients as part of a globally cardioprotective diet. In fact, a recent RCT found an inverse association of SFAs replaced by MUFAs or PUFAs with CVD [31].

Adding to the complexity of this topic, SFAs appear to be a more heterogeneous group of FAs than was previously thought. According to a recent case-cohort study, the association of plasma phospholipid SFA intake and incident T2DM varied by length of the carbon chain of the fatty acid and number of carbon atoms (odd or even-chain) [32]. Intake of even-chain SFAs [myristic acid (14:0), palmitic acid (16:0) and stearic acid (18:0)] was positively associated with T2DM, with only a trend found for stearic acid in multivariable models (HR 1.06, 95% CI 1.00–1.13) and in half the sensitivity analyses. Conversely, intake of odd-chain SFAs [pentadecanoic acid (15:0), heptadecanoic acid (17:0)] and longer-chain SFAs [arachidic acid (20:0), behenic acid (22:0), tricosanoic acid (23:0), lignoceric acid (24:0)] was inversely associated with T2DM. However, intake of plasma phospholipid SFAs was not well correlated with food intake. Intake of even-chain SFAs was mostly positively associated with alcohol consumption. More studies are needed to assess the association between SFA subgroup intake and CV risk. In summary, we have limited high-quality data evaluating the exact role of SFAs in the development of CVD. At this time, intake of saturated fat overall appears to be modestly associated with CV risk, although some SFAs may be more harmful than others and others may be protective.

3.2. Cholesterol

According to a recent systemic review and meta-analysis, intervention trials showed that dietary cholesterol intake increases levels of total cholesterol, LDL-C (except for cholesterol doses >900 mg/day) and HDL-C cholesterol and the LDL to HDL ratio [33]. However, cohort studies show no association between cholesterol intake and the risk of CHD and stroke.

Whether cholesterol, saturated fat or both play a role in the development of CHD may remain unsolved. The first plausible explanation for the lack of convincing evidence is the complexity of measuring the food intake of individuals or populations. In observational studies, dietary intake is measured with food frequency questionnaires or dietary history interview [28]. Correlations between food frequency questionnaire data and diet records, considered more accurate, rarely exceed 0.7 [34]. Second, some nutrients may be more detrimental when eaten with other nutrients, cholesterol being eaten simultaneously with saturated fat, for example. In this context, food patterns may be more

appropriate in determining protective foods habits than nutrients studied separately. Indeed, as noted previously, the MED has been shown to protect against CVD [9]. Again, this dietary pattern is low in animal products and therefore low in cholesterol and saturated fat while being simultaneously high in MUFAs, primarily from olive oil [4]. In contrast, the Western diet, which is high in saturated fat, cholesterol, and refined sugars, has greatly contributed to the obesity epidemic and the major increase in prevalence of CVD [35]. In other words, the complete diet may have a more important role in health and disease than its individual constituents.

3.3. Carbohydrates

Total fat intake and types of fat have drawn much attention in the past years, but carbohydrates seem to be more detrimental. Carbohydrates, and especially refined starches such as white rice and major sources of added sugars, such as soft drinks, have been linked to the global obesity epidemic [35]. Indeed, Mozaffarian et al. observed an association between weight gain and foods rich in carbohydrates such as potato chips, potatoes and sugar-sweetened beverages in the US population [36]. As mentioned previously, CHD risk increases with SFAs replaced by carbohydrates [28]. However, carbohydrates from whole grains appear to decrease the risk of CHD as opposed to refined starches and added sugars [37]. This finding agrees with those from prospective cohort studies finding an association of sugar-sweetened beverages with CHD [38,39].

4. Red meat, processed meat and the microbiota

Although processed meat is clearly associated with all-cause mortality [40,41], CV mortality [40] and CHD risk [42], the association of unprocessed red meat and mortality remains conflicting [40–42]. The gut microbiota, this promising but still largely misunderstood organ, could explain in part these discrepancies. Indeed, Koeth et al. described a link between microbiota and synthesis of the proatherogenic compound trimethylamine-*N*-oxide (TMAO) from L-carnitine and choline present in red meats [43]. Dietary L-carnitine supplementation in mice was associated with modification of gut flora leading to increased production of TMAO and development of atherosclerosis. This mechanism was not observed in mice treated with antibiotics – and thus depleted in gut microbiota – which suggests an obligatory role of the gut microbiota in TMAO production [43]. Similarly, high plasma L-carnitine levels predicted prevalent CHD and incident major adverse cardiac events in humans [43]. Finally, increased TMAO level was found independently associated with CV events at 3 years [43–45]. Interestingly, a recent study found different gut microbiota composition in CHD patients and healthy subjects [46]. Emoto et al. demonstrated that gut microbiota composition could be a diagnostic marker of CHD [47], but several unresolved issues and contradictions remain.

For instance, unprocessed meats and other food items associated with cardioprotective diets such as seafood, eggs, and nuts contain L-carnitine and choline and might lead to TMAO production, which is puzzling [43,48]. Such inconsistencies could be explained by cardioprotective dietary patterns positively affecting the gut microbiota composition and mediating the production and cardiometabolic effect of TMAO. For instance, dietary habits that positively affect gut microbiota composition such as vegetarianism attenuated TMAO production with L-carnitine supplementation [43]. Fig. 1 illustrates the interaction between lifestyle factors, genetics, the intestinal microbiome and development of CVD or its risk factors.

5. Personalized cardiovascular nutrition: ready for prime-time?

Dietary recommendations emitted by government and other health agencies worldwide are meant to improve health at the population level. Furthermore, they are necessarily based on data from epidemiological studies and clinical trials showing that certain foods or nutrients are beneficial or deleterious, on average, to health. However, this approach does not consider the great interindividual variability in response to different treatments including diet. In other words, the response to a dietary intervention can vary considerably among individuals, with no benefit in some and substantial benefit in others. No doubt, this interindividual variability has among other factors a genetic basis resulting in functional differences in multiple biological systems. However, the situation is further complicated by most chronic diseases including CVD being polygenic, or complex traits, in which multiple genes have small but influential effects on disease processes. Despite this fact, better understanding the causes and

taking advantage of interindividual variability by personalizing nutritional recommendations to each individual's profile could increase the likelihood of successfully preventing and reversing chronic diseases. Furthermore, individuals given personalized dietary advice tend to be more compliant with recommendations and have greater drive to change habits, at least in the initial phase of an intervention program [49]. However, multiple interacting systems – notably genomics, epigenomics, transcriptomics, metabolomics, lipidomics and microbiota composition – can affect nutrient absorption, metabolism and excretion, thus affecting exposure to nutrients and their metabolites and affecting individuals' responses to nutritional interventions. Recent advances in high-throughput technologies and the sophistication of computational algorithms are increasingly allowing researchers to profile and dissect the flurry of omics data and pave the way toward personalized medicine and nutrition.

Genetics is the highest level that can explain interindividual variability in nutrition – referred to as nutrigenetics – whereby, for example, the genetic susceptibility to a CV risk factor can be mediated by dietary habits. Such gene–diet interactions were first identified in the apolipoprotein (APO) gene family, which codes for apolipoproteins that play a vital role in lipid metabolism and are thought to play a role in atherosclerosis [50]. One example is APOA1 gene. LDL-cholesterol levels were lowered to a greater degree with a high-PUFA diet in female carriers of the APOA1 A allele than women who were homozygous for the GG allele [51]. Interestingly, no gene–diet interaction was observed in men. In an observational study, high PUFA intake was associated with high HDL-C levels in female carriers of the APOA1 AA allele, but the opposite was true for female GG carriers [52]. Again, no such interactions were observed in men. These findings illustrate nicely how the response to diet varies greatly by genetic profile and sex. Recent findings from PREDIMED have uncovered other important gene–diet interactions. For instance, TT homozygotes for the rs7903146 polymorphism of transcription factor 7-like 2 gene (*TCF7L2*), one of the most important genetic predispositions to T2DM [53], did not show the expected higher fasting glycemia with high adherence to the MED relative to CC and CT carriers [54]. In contrast, low adherence to the MED was associated with significantly higher fasting glycemia among TT carriers. A gene–diet interaction has been identified for the *MLXIP* gene coding for carbohydrate response element binding protein. In fact, relative to CC carriers of allele *MLXIP*-rs3812316, G carriers had lower baseline triglyceridemia and, over the course of the PREDIMED study, significantly greater decrease in triglycerides level, and the incidence of MI was also reduced with high adherence to the MED [55]. Finally, the rs4580704 single nucleotide polymorphism (SNP) variant of the circadian locomotor output cycles protein kaput (*CLOCK*) gene, which plays a role in circadian regulation of glucose metabolism, mediated the interaction between MED and incidence of T2DM in non-T2DM participants in PREDIMED [56]. Moreover, presence of the rs4580704 SNP was associated with increased risk of stroke only in T2DM participants.

Gene–diet interactions have been identified in cohorts with pre-existing CVD. Indeed, CHD homozygotes for an allele of the apolipoprotein C-III gene (*APOC3*-455C) showed reduced response to the triglyceride-lowering effect of omega-3 PUFA supplementation [57]. In addition, CHD carriers of the rs4580704 SNP of the *CLOCK* gene on a low-fat diet showed marked reduction in inflammation markers and HDL to APOA1 ratio [58].

Epigenetic modifications can also account for gene–diet interactions in what can be referred to as nutri-epigenetics. Briefly, epigenetic modifications refer to transcriptional (i.e., histone modification, DNA methylation) or post-transcriptional (i.e., microRNA, small nucleolar RNA) modifications that regulate gene expression or protein synthesis, respectively. For example,

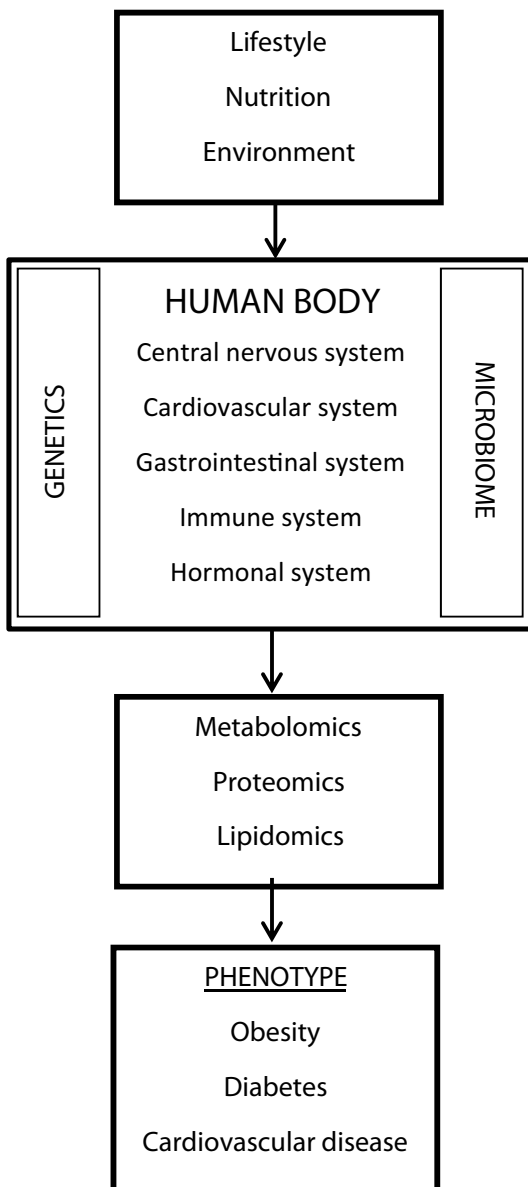


Fig. 1. Relationship between lifestyle factors, genetics, microbiome and the development of cardiovascular disease.

methylation of DNA promoter regions or changes in chromatin structure via histone modification can affect the access of the transcription machinery to DNA and thus modulate gene expression. Similarly, microRNAs can bind RNA and typically interfere with ribosomes to lower translation of RNA into proteins. All these events can be mediated by and affect the response to diets. In fact, foods and dietary habits that provide varying amounts of methyl donors such as methionine, choline, betaine, folate, vitamin B12 and zinc could affect DNA methylation [59] and in turn an individual's response to dietary intervention. This field is still in its infancy, but evidence of nutri-epigenetic interactions have been observed in C allele carriers of a microRNA target site variant (rs13702) of the lipoprotein lipase gene that modulates triglyceride levels and risk of stroke depending on level of adherence to the MED [60].

Although existing nutrigenetic evidence is highly intriguing, the current exploration of gene–diet interactions is only partial. In fact, the identification of single-gene polymorphisms probably cannot fully explain interindividual differences in response to diets, which results from the interaction between the many diverse nutritional components contained in each food item and multiple biological systems. Response to diets is presumably explained by the sum of multiple SNPs, most of which are probably still unknown or not fully characterized, each contributing modestly to the observed phenotype. However, the many biological processes that can be modulated by the known and yet to be discovered genetic polymorphisms can be functionally evaluated by the metabolites involved in such processes.

Indeed, untargeted metabolomics – which hereafter includes lipidomics – enables the quantification of chemical entities involved in cellular processes and that can in many instances be derived and/or affected by nutrient intake. Therefore, metabolites can often be considered intermediate phenotypes between genetic polymorphisms and metabolic response to nutrition and may help in our comprehension of the determinants of an individual's response to diet and contribute to personalized nutrition. Metabolomics can thus serve as a better proxy than genomics to functionally evaluate multiple biological pathways simultaneously, profile individuals' exposure to nutrients and their metabolites, thus globally capturing all features contributing to food response. Metabolomics profiling is usually conducted with biological fluids such as plasma or urine but can also be conducted with tissue or cells. Additionally, metabolomics improves the evaluation of dietary habits and the assessment of compliance to interventions better than traditionally used food frequency questionnaires and diaries. In doing so, it also accounts for the variability in nutritional composition between similar foods grown or produced in different environments or submitted to different storage and processing methodologies.

Metabolomic profiling has been used to detect early alterations in phospholipid metabolism in people without T2DM who carry the rs7903146 variant of the TCF7L2 gene [61]. This gene is strongly associated with the development of T2DM. In contrast, participants lacking the rs7903146 variant showed no abnormalities of phospholipid metabolism in the same study. Metabolomic profiling has also been successful in distinguishing metabolically healthy from metabolically unhealthy obese people [62] and assessing metabolic disturbances associated with heart failure [63]. In the PREDIMED trial, urinary metabolomic profiles reflected dietary habits and were affected by dietary interventions, so investigators could identify which of the three arms of the trial participants were in [64].

Another area that accounts in part for interindividual variability in response to diets is gut microbial diversity in composition and function. In fact, the intestinal tract is lined with a highly dynamic microbial community that is affected by multiple and still largely

misunderstood factors ranging from host genotype, health condition, life stage, dietary habits and lifestyles [65]. Various microbial species will differently interact and metabolize ingested nutrients and thus affect host exposure to their derivatives. Gut microbiota composition can be characterized from fecal samples but is only a non-functional proxy of the microbial composition of the distal intestinal tract. Alternatively, by measuring circulating metabolites, metabolomics is a more relevant proxy of gut microbiota composition and function because some of the measured compounds would be derived from the microbiome. For instance, TMAO can be quantified in plasma to help identify individuals with an unfavorable microbiota composition that would be at increased risk of atherosclerosis and thus in whom food items rich in choline and L-carnitine should be largely avoided.

Ultimately, dynamic assessment of individual metabolomic profiles over time and over the course of different nutritional and lifestyle interventions could help demystify the causes of interindividual variability to diets and tailor appropriate interventions. However, further progress is still required for such an approach to be fully beneficial to personalized nutrition. Importantly, not all entities that can be quantified by metabolomics technologies have been characterized or mapped onto biological pathways, so their interpretation is difficult. Also, most metabolomic studies have involved plasma or urine samples, which may not be fully representative of tissue-specific functionality.

From the current state of knowledge, the soundest approach is to group individuals by similar metabolomic profiles or metabolotypes. Individuals who share metabolotypes may respond similarly to diets or nutrients such as that observed with vitamin D supplementation [66] or to red wine polyphenols in people at high CV risk [67]. Metabolotypes were also successfully identified and used to deliver personalized recommendations to people with high cardiometabolic risk [68]. However, in this trial, unsupervised algorithms only needed anthropometric and traditional cardiometabolic markers (i.e., BMI, waist circumference, fasting glycemia and lipemia, blood pressure) to identify clusters of similar individuals, which questions the added value of using further metabolomics. Similarly, one of the first, albeit imperfect and incomplete, examples of the use of multiple levels of data to personalize nutritional advice was recently described [69]. In this trial, for 800 healthy participants, baseline anthropometric data, dietary habits and gut microbiota composition was evaluated, and plasma glucose content was continuously monitored over 7 days. On the basis of these parameters, a machine-learning algorithm was able to accurately predict individual postprandial glycemic response to standardized meals. With validation in a second cohort, this algorithm relied on meal-related and some microbiota-related characteristics to deliver personalized dietary recommendations to minimize postprandial glycemia.

In summary, omics technologies appear attractive; however, current knowledge is too limited for these technologies to move out of the research domain and be fully applied to the clinical and personalized nutrition fields. Further exploration of gene regulation of protein expression and its functional impact on biological pathways as well as integration of multiple levels of omics is needed to capture all features of interindividual variability [59,70,71]. Other major challenges facing this approach include optimizing clinical study design (e.g., cohort vs. case-control studies), dealing with varying sample sizes, data analysis, statistical considerations including the use of many biomarkers in small samples, and standardization of analytic techniques and nomenclature [36] (Table 1). Furthermore, a multidisciplinary approach is required. Current initiatives of omics profiling of large numbers of individuals with varying health statuses are moving in this direction and will, once completed, lead the field toward more

Table 1
Personalized cardiovascular nutrition: current challenges and limitations.

Cardiovascular diseases are polygenic, complex traits
Limited number of gene variants identified
Choice of clinical study design
Optimization of data analysis techniques
Choice of sample size
Statistical considerations for multimarker studies with small sample size
Standardization of analytic techniques
Nomenclature
Requires a multidisciplinary approach

effective personalized nutrition [71]. The figure illustrates the interaction between lifestyle factors, genetics, the intestinal microbiome and the development of CVD or its risk factors.

6. Conclusions

Large clinical studies continue to demonstrate the significant health benefits associated with adherence to the MED in both the primary and secondary prevention of CHD. Even among regions surrounding the Mediterranean sea, increased adherence to the MED provides additional benefits, so even small, sustained, and easily implementable changes to diet can have a major impact on highly relevant clinical outcomes. Controversy remains regarding the exact role of SFAs in the development of atherosclerosis and vascular disease. Data must be interpreted with caution given the extreme heterogeneity of study populations, type of study design, interventions, and data analysis techniques, notwithstanding that some SFAs may be more harmful than others and others may even provide benefit. What is more apparent is that in both the developing and developed world, the driving factor behind CV risk is excess weight, induced largely by the consumption of excessive quantities of refined carbohydrates. A multi-pronged approach will be required to tackle this problem, with public education and increased awareness, government policies to discourage the production and utilization of refined sugar and grain products, and changes in the food industry, which needs to be made more accountable for the health of the general public.

Beyond clinical outcomes, emerging data is now illustrating how response to the MED can vary significantly among individuals depending on their genetic make-up and the presence or absence of gene variants, so-called gene–diet interactions or nutrigenetics. This and other omics technologies continue to be evaluated to develop a robust and standardized personalized nutrition approach. Given that this approach is still in its early stages and must overcome many challenges, it cannot be recommended for clinical use at this time, despite commercial interests. Rather, a phenotypic and metabotypic approach appears more useful, whereby individuals with a similar metabotype can respond to an intervention in a similar fashion. Nevertheless, the future of personalized CV nutrition remains bright.

Disclosure of interest

The authors declare that they have no competing interest.

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