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Conference on 'Dietary strategies for the management of cardiovascular risk'

Dietary patterns and cardiovascular disease

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Despite strong prospective epidemiology and mechanistic evidence for the benefits of certain micronutrients in preventing CVD, neutral and negative outcomes from secondary intervention trials have undermined the efficacy of supplemental nutrition in preventing CVD. In contrast, evidence for the positive impact of specific diets in CVD prevention, such as the Dietary Approaches to Stop Hypertension (DASH) diet, has focused attention on the potential benefits of whole diets and specific dietary patterns. These patterns have been scored on the basis of current guidelines for the prevention of CVD, to provide a quantitative evaluation of the relationship between diet and disease. Using this approach, large prospective studies have reported reductions in CVD risk ranging from 10 to 60% in groups whose diets can be variously classified as 'Healthy', 'Prudent', Mediterranean' or 'DASH compliant'. Evaluation of the relationship between dietary score and risk biomarkers has also been informative with respect to underlying mechanisms. However, although this analysis may appear to validate whole-diet approaches to disease prevention, it must be remembered that the classification of dietary scores is based on current understanding of diet–disease relationships, which may be incomplete or erroneous. Of particular concern is the limited number of high-quality intervention studies of whole diets, which include disease endpoints as the primary outcome. The aims of this review are to highlight the limitations of dietary guidelines based on nutrient-specific data, and the persuasive evidence for the benefits of whole dietary patterns on CVD risk. It also makes a plea for more randomised controlled trials, which are designed to support food and whole dietary-based approaches for preventing CVD.

CVD: Diet and disease: Myocardial infarction: Mediterranean diet: Nutrient

Nutrient *v.* food and diet-based recommendations for health

The hierarchy of evidence to support the relationship between diet and disease can be viewed as a pyramid of study designs, from which the strength of evidence increases from relatively weak cross-cultural and observational studies at its base, through prospective cohort trials, to the much stronger intervention studies at its peak (Fig. 1). While prospective cohort studies have provided a wealth of evidence to support associations between specific nutrients and disease endpoints[1–3], the findings are prone to severe confounding by other categorical and continuous variables. Cohort studies[1,2] have also given little address to the impact of specific foods or whole diets, such that there is now a general lack information on how diets of different types influence cardiovascular health. In contrast, a relatively small number of dietary intervention trials have provided valuable information on mechanisms to support the cause and effect relationships with CVD; although the majority of interventions with individual nutrients have produced neutral or negative findings. Dietary

Abbreviation: DASH, Dietary Approaches to Stop Hypertension.

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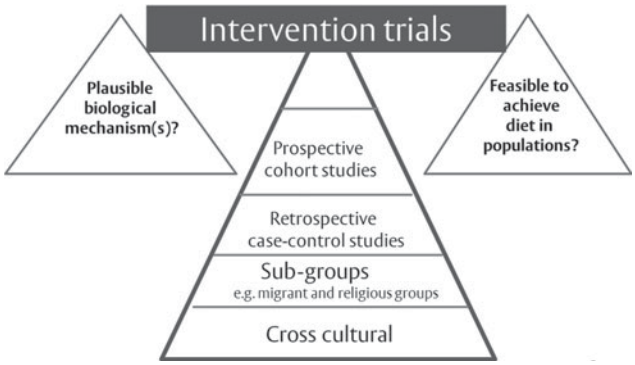

Fig. 1. Hierarchy of experimental designs.

interventions provide information relating to the feasibility of achieving dietary change within free-living populations, but are often restricted by their reliance on indirect biomarkers, rather than clinical endpoints of CVD.

Discordance between nutrient, food and dietary-based associations with CVD

Nutrients are ingested as complex mixtures in foods, which are consumed as mixed meals and diets. The biological effects of a nutrient in a food may be altered through interaction with other constituents within the food or other foods in the overall diet. It follows that because a food contains a nutrient, the food may not necessarily exert the effect typical of the single nutrient. This provides one obvious explanation for why associations between single nutrients and disease, which have been unequivocally confirmed in meta-analyses of observational cohort studies, do not necessarily translate into predictable outcomes in intervention studies with whole diets. The disparity between the impacts of single nutrients, foods and diets on health is highlighted by the potential health benefits of foods containing micronutrients, such as β-carotene and vitamin E[4,5], and the neutral and negative outcomes from secondary prevention intervention trials with these single antioxidant micronutrients[6–9]. It is also evident from the inconsistency between the established cholesterol-raising effects of dietary SFA in experimental feeding studies, and effects produced by some foods that are rich in saturated fat, such as dairy products. There is emerging evidence that certain dairy foods produce little or no significant effect on serum LDL cholesterol, and as a food group, are associated with lower CVD mortality and associated risk factors, such as blood pressure[10,11]. These findings suggest that recommendations based on single nutrients, particularly when additional nutrients are provided in the supplemental form, may be inappropriate for cardiovascular health. Guidelines based on foods, food groups and ultimately whole diets, may offer a more rational and comprehensive approach for the prevention of CVD. However, a stronger research base, grounded in a combination of observational and intervention data is required to substantiate the relationship between potentially beneficial diets and disease risk.

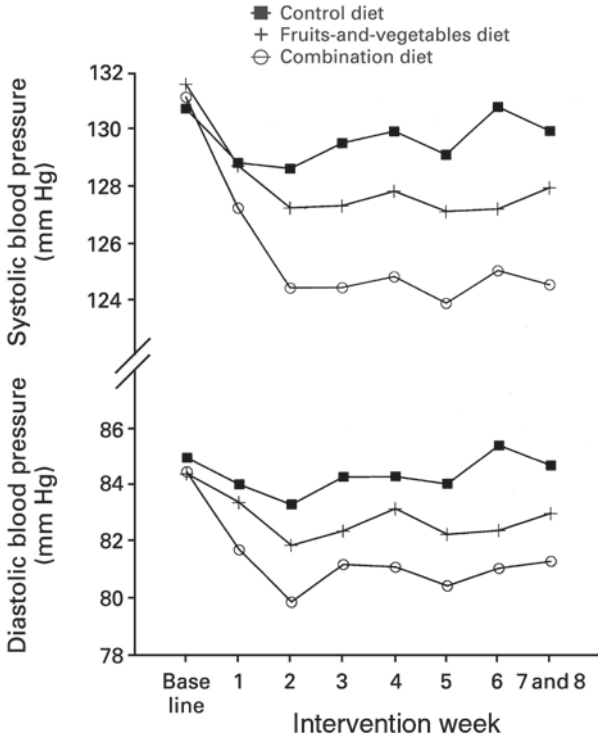

Fig. 2. Mean systolic and diastolic blood pressures at base line and during each intervention week, according to diet, for 379 subjects with complete sets of weekly blood pressure measurements[15].

Existing evidence for the benefits of dietary patterns in reducing CVD risk

The Lyon Heart Study is one of the most successful trials to date to demonstrate the benefit of a dietary pattern in preventing CVD. It was a randomly controlled, secondary prevention study designed to examine the effects of a Mediterranean type of diet over 5 years in 605 patients who had suffered a previous myocardial infarction[12]. When primary and secondary endpoints were combined, the Mediterranean diet which was characterised by increased bread, root and green vegetables, fruit, fish, less red meat and fats high in olive oil and α-linolenic acid, produced an impressive 76% reduction in risk relative to the control diet, which was typical of that consumed in the UK and North America. More recently, when a typical Mediterranean diet was supplemented with either extra-virgin olive oil or nuts in a Spanish population, both experimental diets (extra-virgin olive oil *n* 2543 and nuts *n* 2454) produced highly significant reductions in the primary endpoint, which was a composite of myocardial infarction, stroke and death from cardiovascular causes over a follow-up of 4·8 years, in comparison with a control diet (*n* 2450)[13]. However, in the Heart Institute of Spokane Diet Intervention and Evaluation Trial, in which an intervention with a Mediterranean-style diet was shown to be equivalent to a low-fat diet in increasing cardiovascular-event-free survival after myocardial infarction, close examination of the dietary data reveals that the Mediterranean-style diet targets were not achieved[14]. In particular, the target of a two-fold increase in monounsaturated fat intake was not

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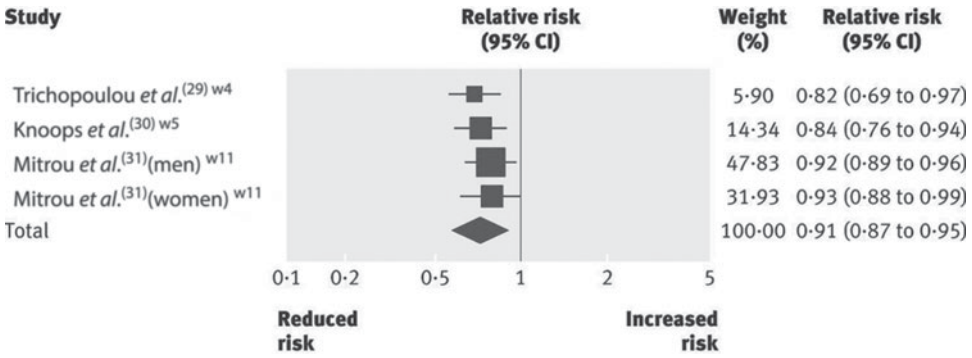

Fig. 3. Risk of mortality from CVDs associated with two-point increase in adherence score for Mediterranean diet. Squares represent effect size; extended lines show 95% CI; diamond represents total effect size[26]; superscripts w4, w5, w11 denote the three articles out of 12w1-w12 which fulfilled the inclusion criteria for the meta-analysis.

achieved, and at the end of the intervention with a Mediterranean-style diet, total fat intake and fatty acid profile were identical to that of the low-fat diet, apart from slightly higher intakes of 'omega-3 fats'. These data and the difficulties inherent in ensuring compliance with specified dietary targets over a prolonged period, amply illustrate the challenges faced with these types of studies.

The Dietary Approaches to Stop Hypertension (DASH) trial has produced some of the most conclusive evidence for the benefits of a dietary pattern on blood pressure and other CVD risk factors. DASH examined the effects of two experimental diets against a control diet for 8 weeks, in 459 adults a proportion of which suffered moderate hypertension. The experimental diets consisted of either a daily intake of between eight and ten servings of fruits and vegetables, or a combination of this diet, plus 2·7 portions of low-fat dairy products, and reduced total and saturated fat. Sodium and body weight were maintained throughout the intervention[15]. While both experimental diets produced dramatic reductions in systolic and diastolic blood pressure, the combination diet produced by far the greatest reductions in the total cohort (Fig. 2), and especially in a subgroup with hypertension. Other favourable effects included a significant increase in serum folate, and decreases in homocysteine[16] and total serum and LDL cholesterol, but notably a potentially detrimental lowering of HDL cholesterol[17]. Predictably, the later addition of a low sodium intake to a DASH-type diet, showed even greater efficacy in lowering blood pressure, the population-wide application of which was estimated to translate into decreased risk of CHD and stroke of 15 and 27%, respectively[18]. The impact of the DASH diet on the predicted 10-year risk of developing CHD has been calculated by the Framingham risk equations[19]. In comparison with the control and fruit and vegetable-rich diets, the DASH diet (rich in fruits, low-fat dairy, reduced total and saturated fat) was shown to reduce estimated 10-year CHD risk by 18 and 11% respectively, with evidence of a significantly greater reduction in CHD risk in Black African Americans. These findings provide further evidence to underpin national dietary guidelines in North America, which had already adopted the principles of the DASH diet some 5 years before this report.

Dietary pattern analysis: a new direction in nutritional epidemiology?

There are two main approaches for examining the relationship between dietary patterns and CVD. The first relies on the empirical application of cluster and principal components analyses to identify associations between dietary patterns and disease. This method has been used widely in cross-sectional studies to generate hypotheses on the potential effectiveness of dietary patterns on CVD reduction[20]. The second approach is based on the calculation of a dietary score or index that provides a summary of diet quality or adherence to specific dietary recommendations, the most established examples of which are scores for the DASH and Mediterranean diets. To investigate the long-term efficacy of the DASH diet on endpoints of CHD and stroke, a DASH diet score based on eight foods and nutrients[21] was calculated from FFQ on seven occasions, over 24 years in the Nurses' Health Study. In this prospective, cohort study of 88 517 female nurses aged 34–59 years, the DASH diet was found to be associated with reductions in the relative risk for non-fatal and fatal CHD of 22 and 34%, respectively, and a 17% reduction in risk of stroke, across increasing quintiles of the DASH-diet score, after adjustment for age, smoking and other CVD risk factors. Other dietary scores include the Healthy Eating Index[22] and Recommended Food Score[23]. Diet Quality Index[24] and the Mediterranean Diet Score[25]. A recent systematic review concluded that greater adherence to a Mediterranean-like dietary pattern was associated with significant reductions in overall mortality (9%) and mortality from CVD (9%; Fig. 3), cancer (6%), Parkinson's and Alzheimer's diseases (13%)[26].

Despite impressive evidence for the efficacy of dietary scores, one major drawback is their dependence on the current understanding of the relationship between diet and disease, making it impossible to identify and account for previously unknown factors. While it might seem intuitive that the overall effects of diet on CVD will be greater than that of single nutrients, there are coherent statistical and biological reasons to support this view. False-positive associations between a single nutrient and CHD can arise because the former acts as surrogate marker for other

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dietary components. A classic example of this would be dietary cholesterol in eggs. While consumption of eggs has been shown to be unrelated to CHD and stroke[27,28], positive associations persist, in part, because eggs represent an easily quantified marker of a diet that is invariably energy dense and high in saturated fat. Likewise, multiple analyses of individual nutrients may also lead to false-positive findings simply by chance. Conversely, false-negative findings may arise when the effects of a single nutrient are confounded by other nutrients in the foods in which they are contained, through errors associated with its measurement and by misclassification of foods in FFQs. Although diet scores are less susceptible to confounding, they are subject to the same measurement errors, misclassifications and recording biases that characterise all diet and nutrient assessments, as well as an inherent inability to identify mechanisms that underlie the relationship between diet and disease. However, the classification of individuals according to dietary patterns which quantify the sum total effects of dietary bio-actives, is likely to result in the estimation of larger effect sizes due to the dietary exposure representing the cumulative, and possibly, synergistic effects of individual components. From a statistical perspective, there is also likely to be smaller measurement error, risk of confounding and greater chance of observing significant associations.

From a biological standpoint, atherosclerosis and thrombosis are complex, multi-factorial processes, which may be affected by nutrients, acting synergistically within whole diets, at numerous sites and at various stages of the disease. As well as their high potential for confounding and measurement type errors, investigation of single nutrient–disease relationships are aiming to delineate a single cause–effect pathway amongst an array of diet-related pathological processes. It is therefore unsurprising to find that many single nutrient intervention studies have failed to confirm the hypothetical relationship that has been demonstrated in observational studies.

What is the future for nutrition research?

Given the very strong evidence from cohort studies for the benefits of specific dietary patterns in prevention of CVD, the paucity of well-designed interventions with hard endpoints, and major implications for public health, there is arguably an urgent need for more research in this area. Dietary intervention trials, using approaches which can be feasibly achieved in free-living populations are required, not only to elucidate mechanisms of action of nutrients and food bio-actives in health and disease, but also to underpin future nutritional policy, which must recognise the limitations of single nutrient-based recommendations for cardiovascular health. High-quality randomised controlled dietary-intervention studies will always face the inevitable challenges associated with their prohibitive cost, and the feasibility of delivering a lifestyle modification in a free-living setting. To succeed, they must overcome behavioural barriers to dietary change, and the confounding influence of inter-individual variation in dietary response. Ideally they should include disease endpoints as the primary outcome, and above all, involve whole-diet interventions.

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Author contribution

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