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Food for thought

The science and politics of nutrition

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SCIENCE AND POLITICS OF NUTRITION

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Foreword

Jeffrey R Bohn, head of Swiss Re Institute

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Swiss Re is dedicated to making the world more resilient by working with the market, policy makers, and partners to reach people who are underinsured. Creating, collecting, and curating risk knowledge is critical to realise this vision. The Swiss Re Institute provides the research and development platform to expand Swiss Re's position as the thought leader in the re/insurance industry by developing and sharing industry relevant research from internal experts and external partners.

In the area of life and health insurance, the institute explores ways to help people live longer and healthier lives and close the gap between the insurance coverage individuals have and the coverage needed to ensure they are resilient to typical life and health risks (the insurance protection gap). We also engage with various stakeholders by sharing insights, tailored services, and products to enable risk focused decision making and smarter solutions to manage risk.

Considering the effect that nutrition has on diseases like diabetes, obesity, and cancer, we are pleased to partner with *The BMJ* and its impressive ambition to drive good science and research in the nutrition space. With sponsorship from Swiss Re Institute, *The BMJ* has commissioned a series of articles authored by nutrition and research experts. These articles cover a range of topics, including key macronutrients such as dietary fat, personalised nutrition, gut microbiota, nutritional approaches to disease prevention, and management of type 2 diabetes. Several articles focus on broader issues such as hunger, malnutrition, and evidence in nutritional science. Each article has multiple authors (often with conflicting views) to foster open and honest debate around what we know and, more importantly, what we don't.

In this spirit, we are hosting a related launch event, "Food for thought: the science and politics of nutrition." By convening top researchers in nutrition, we aspire to uncover ideas on how best to move forward and develop a better understanding of the studies needed to resolve conflicting recommendations. A good example is what we're told about fat consumption: the American Heart Association and World Health Organization both advise a limit on overall, and particularly saturated, fat. However, the PURE study published last year suggests increased consumption of total fat is associated with lower risk of mortality and that increased saturated fat consumption is not associated with detrimental health outcomes.

As noted in the article in this series by John Schoonbee and Emile Elefteriadis, diabetes and obesity have a devastating effect on health systems, insurers, and, most importantly, people. By developing a better understanding of nutrition and resolving long standing disagreements with respect to key health research questions, we can develop much better dietary guidelines and related policies. This cannot happen too soon.

Swiss Re Institute will be involved in a number of research initiatives and events over the next several years to broaden and deepen our collective understanding of this critical topic. As a scientist who does not have specific training in nutrition research but tries to stay informed about how I can improve my health, I look forward to this research and related discussions to cut through the confusion. We all benefit from this increased clarity.

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Food for thought

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What should we eat in order to stay healthy and avoid disease? Nutrition is one of the biggest drivers of chronic diseases, including obesity and diabetes, yet the answer to this seemingly simple question remains a subject of heated debate. A new series of articles in *The BMJ* aims to cut through the confusion and controversy to bring the latest evidence on nutrition to clinicians.[1]

The number of studies exploring the link between food and health has grown substantially over the past 50 years,[2] but the extent to which the growth in information has been matched by greater understanding is questionable. Navigating the vast evidence base is challenging, even more so when concerns about weak science, vested interests, and conflicting or distorted media messages also muddy the waters. Nor do people eat for purely utilitarian ends. Food is central to culture and identity, which leads to strongly held preferences, beliefs, and biases.

Our goal at *The BMJ* is to advance understanding through research and debate, but we recognise that sometimes additions to the literature can generate more heat than light. This series is our attempt to take a different approach. We have brought together some of the world's most thoughtful and influential voices in the field of nutrition and health, representing a range of backgrounds and perspectives, to help make sense of the state of current knowledge, the quality of the evidence on key issues, the extent and implications of potential disagreements between experts, and the agenda for further research.

Guided by our series advisers, Dariush Mozaffarian and Nita Forouhi, we have chosen topics covering priority areas of clinical interest and unresolved controversy. The articles consider questions that will help doctors offer clarity and sensible advice to patients and guide policy makers towards effective actions. Is there a link between saturated fat and heart disease? What are the best diets for weight loss, and how good is the evidence to support them? Can a particular dietary pattern help prevent or reverse type 2 diabetes? Will interventions focused on personalised nutrition and the gut microbiome be beneficial for health? How can we address the urgent global problems of hunger and malnutrition? And what is the role of government and the food industry in tackling ill health related to food? The articles lay out what we know and what we've yet to learn in these areas and more. Following the initial launch, more articles are planned in the coming months covering topics ranging from the relation between food and cancer to the quality of dietary guidelines.

In a field notable for strong opinions and, often, polarised debate, a key ambition of the series is to bring together authors with a range of viewpoints and ensure a balanced approach to the evidence as far as possible. Authors have been tasked with outlining areas of consensus and uncertainty, and have been encouraged to discuss their disagreements in the text rather than come to forced compromise.

To bring the series to as wide an audience as possible we have partnered with The Swiss Re Institute to fund open access publication for the articles. The series will be launched at a meeting co-hosted by *The BMJ* and the Swiss Re Institute in Zurich, bringing together nutritional researchers, clinicians, and policy makers to discuss themes such as dietary fats and health, the role of bias in nutritional research, and the role of commercial food systems in promoting health.

These articles won't of course be the last word on nutrition and health. When the science is so contested and opinions so deeply held, debates will continue, new research will be done, and knowledge will evolve. But we hope these articles achieve a new approach in bringing together different perspectives, establishing consensus where possible, spelling out uncertainty where necessary, and moving the field forward. They set out a credible future research agenda, meaningful evidence based policy actions, and clearer messages for clinicians to help improve the health of their patients and the public.

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History of modern nutrition science—implications for current research, dietary guidelines, and food policy

Dariush Mozaffarian and colleagues describe how the history of modern nutrition science has shaped current thinking

Although food and nutrition have been studied for centuries, modern nutritional science is surprisingly young. The first vitamin was isolated and chemically defined in 1926, less than 100 years ago, ushering in a half century of discovery focused on single nutrient deficiency diseases. Research on the role of nutrition in complex non-communicable chronic diseases, such as cardiovascular disease, diabetes, obesity, and cancers, is even more recent, accelerating over the past two or three decades and especially after 2000.

Historical summaries of nutrition science have been published, focusing on dietary guidelines, general scientific advances, or particular nutritional therapies.[1-4] Carl Sagan said, "You have to know the past to understand the present;" and Martin Luther King, Jr, "We are not makers of history. We are made by history." This article describes key historical events in modern nutrition science that form the basis of our current understanding of diet and health and clarify contemporary priorities, new trends, and controversies in nutrition science and policy.

KEY MESSAGES

- Modern nutrition science is young: It is less than one century since the first vitamin was isolated in 1926
- The first half of the 20th century focused on the discovery, isolation, and synthesis of essential micronutrients and their role in deficiency diseases
- This created strong precedent for reductionist, nutrient focused approaches for dietary research, guidelines, and policy to address malnutrition
- This reductionist approach was extended to address the rise in diet related non-communicable diseases—eg, focusing on total fat, saturated fat, or sugar rather than overall diet quality
- Recent advances in nutrition science have shown that foods and diet patterns, rather than nutrient focused metrics, explain many effects of diet on non-communicable disease
- Lower income countries are recognising a growing "double burden" (combined undernutrition and non-communicable disease)
- Nutrition policy should prioritise food based dietary targets, public communication of trusted science, and integrated policy, investment, and cultural strategies to create systems level change across multiple organisations and environments

1910s to 1950s: era of vitamin discovery

The first half of the 20th century witnessed the identification and synthesis of many of the known essential vitamins and minerals and their use to prevent and treat nutritional deficiency related diseases including scurvy, beriberi, pellagra, rickets, xerophthalmia, and nutritional anaemias. Casimir Funk in 1913 came up with idea of a "vital amine" in food, originating from the observation that the hulk of unprocessed rice protected chickens against a beriberi-like condition.[5] This "vital amine" or vitamin was first isolated in 1926 and named thiamine, and subsequently synthesised in 1936 as vitamin B1. In 1932, vitamin C was isolated and definitively documented, for the first time, to protect against scurvy,[6] some 200 years after ship's surgeon James Lind tested lemons for treating scurvy in sailors.[7]

By the mid-20th century all major vitamins had been isolated and synthesised (fig 1). Their identification in animal and human studies proved the nutritional basis of serious deficiency diseases and initially led to dietary strategies to tackle beriberi (vitamin B1), pellagra (vitamin B3), scurvy (vitamin C), pernicious anaemia (vitamin B12), rickets (vitamin D), and other deficiency conditions. However, the chemical synthesis of vitamins quickly led to food based strategies being supplanted by treatment with individual vitamin supplements. This presaged modern day use and marketing of individual and bundled multivitamins to guard against deficiency, launching an entire vitamin supplement industry.

This new science of single nutrient deficiency diseases also led to fortification of selected staple foods with micronutrients, such as iodine in salt and niacin (vitamin B_3) and iron in wheat flour and bread.[8-10] These approaches proved to be effective at reducing the prevalence of many common deficiency diseases, including goitre (iodine), xerophthalmia (vitamin A), rickets (vitamin D), and anaemia (iron). Foods around the world have since been fortified with calcium, phosphorus, iron, and specific vitamins (A, B, C, D), depending on the composition of local staple foods.[10-13]

As one of the great accidents of nutrition history, this new science and focus on single nutrients and their deficiencies coincided with the Great Depression and second world war, a time of widespread fear of food shortages. This led to even further emphasis on preventing deficiency diseases. For example, the first recommended dietary allowances (RDAs) were a direct result of these concerns, when the League of Nations, British Medical Association, and the US government separately commissioned scientists to generate new minimum dietary requirements to be prepared for war.[14] In 1941, these first RDAs were announced at the National Nutrition Conference on Defence, providing new guidelines for total calories and selected nutrients including protein, calcium, phosphorus, iron, and specific vitamins.[15] These historical events established a precedent for nutrition research and policy recommendations to focus on single nutrients linked to specific disease states.

1950s to 1970s: fat versus sugar and the protein gap

During the next 20 to 30 years, calorie malnutrition and specific vitamin deficiencies fell sharply in high income countries because of economic development and large increases in low cost processing of staple foods fortified with minerals and vitamins. At the same time, the rising burdens of diet related non-communicable diseases began to be recognised, leading to

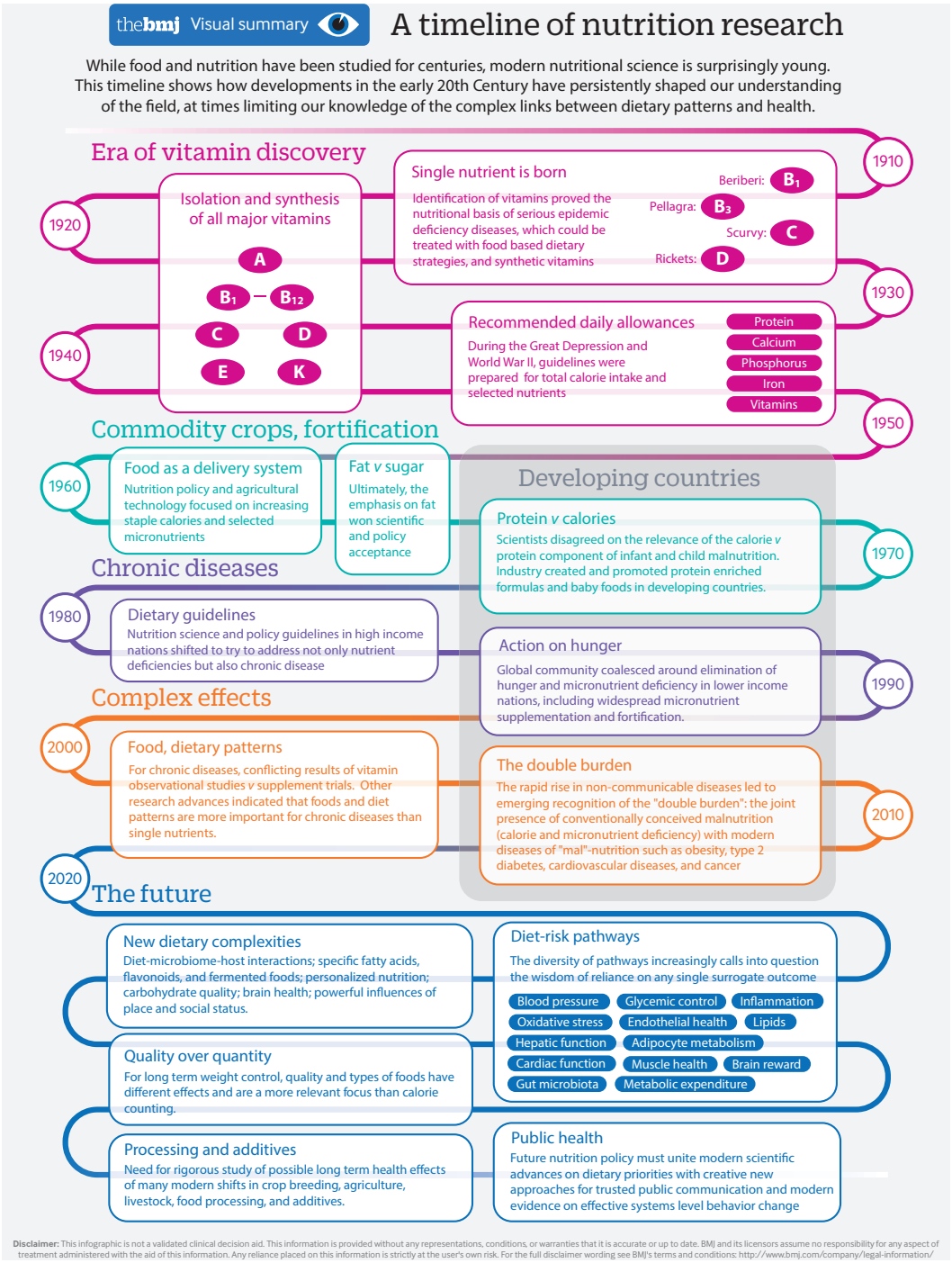

Fig 1 | Key historical events in modern nutrition science, with implications for current science and policy

new research directions. Attention included two areas: dietary fat and sugar.[16-19]

Early ecological studies and small, short term interventions, most prominently by Ancel Keys, Frederick Stare, and Mark Hegsted, contributed to the widespread belief that fat was a major contributor to heart disease. At the same time, work by John Yudkin and others implicated excess sugar in coronary disease, hypertriglyceridemia, cancer, and dental caries. Ultimately, the emphasis on fat won scientific and policy acceptance, embodied in the 1977 US Senate committee report *Dietary Goals for the United States*, which recommended low fat, low cholesterol diets for all. This was not without controversy: in 1980, the US National Academy of Sciences Food and Nutrition Board reviewed the data and concluded that insufficient evidence existed to limit total fat, saturated fat, and dietary cholesterol across the population.[20]

Some interpret these controversies as evidence of industry influence, and others as natural disagreement and evolution of early science.[16-19] More relevant is that both the dietary fat and sugar theories relied on a nutritional model developed to address deficiency diseases: identify and isolate the single relevant nutrient, assess its isolated physiological effect, and quantify its optimal intake level to prevent disease. Unfortunately, as subsequent research would establish, such reductionist models translated poorly to non-communicable diseases.

In less wealthy countries, the main objectives of nutrition policy and recommendations during this period remained on increasing calories and selected micronutrients. In many ways, foods became viewed as a delivery vehicle for essential nutrients and calories. Accordingly, agricultural science and

technology emphasised production of low cost, shelf stable, and energy dense starchy staples such as wheat, rice, and corn, with corresponding breeding and processing to maximally extract and purify the starch. As in high income nations, these efforts were accompanied by fortification of staple foods[10-13] as well as food assistance programmes to promote survival and growth of infants and young children in vulnerable populations.

Scientists focused on malnutrition disagreed on the relative role of total calories and protein in infant and child diseases such as marasmus and kwashiorkor—also termed "the protein-calorie deficiency diseases."[21 22] Support for the "protein gap" concept led to extensive industrial development of protein enriched formulas and complementary foods for developing countries. Other scientists supported the primary role of calorie insufficiency and believed that protein enriched formulas and foods should not replace breast milk. As one prominent scientist wrote in 1966, "Millions of dollars and years of effort... into developing these [high protein] foods would have been better spent on efforts to preserve the practice of breast feeding... being abandoned everywhere."[22]

The debate essentially ended when in 1975 leading scientists in the US and London independently concluded from the scientific evidence that a lack of food was the main problem:[22] "The concept of a worldwide protein gap... is no longer tenable... the problem is mainly one of quantity rather than quality of food."[23]

This conclusion influenced subsequent efforts to tackle malnutrition in developing countries. For example, a formal UK advisory committee on international nutrition aid recommended that, "the primary attack on malnutrition should be through the alleviation of poverty... aid should be directed to projects that will generate income among the poor, even where such projects do not have any marked effect on the national income of the country concerned."[22]

However, the earlier decades of uncertainty had fostered a multinational industry that continued to promote formula and baby foods in low income countries based on their protein content and nutrient fortification. In addition, nutrient supplementation strategies remained effective at preventing or treating endemic deficiency diseases. Thus, despite the shift in scientific thinking to focus on economic development, substantial emphasis remained or even accelerated on providing sufficient calories, most often as starchy staples, plus vitamin fortification and supplementation.

1970s to 1990s: diet related chronic diseases and supplementation

Accelerating economic development and modernisation of agricultural, food processing, and food formulation techniques continued to reduce single nutrient deficiency diseases globally. Coronary mortality also began to fall in high income countries, but many other diet related chronic diseases were increasing, including obesity, type 2 diabetes, and several cancers.

In response, nutrition science and policy guidelines in high income nations shifted to try to deal with chronic disease. Building on the 1977 Senate report, the 1980 Dietary Guidelines for Americans was one of the earliest such national guidelines.[24] Many of the available data were derived from less robust types of evidence, such as from crude cross-country (ecological) comparisons and short term experiments using surrogate outcomes, mostly in healthy middle aged men. More importantly, these studies followed the deficiency disease model, largely considering isolated single nutrients. Accordingly, the 1980 dietary guidelines remained heavily nutrient focused: "avoid too much fat, saturated fat, and cholesterol; eat foods with adequate starch and fiber; avoid too much sugar; avoid too much sodium."[24] International guidelines were similarly nutrient focused.[25] This led to a proliferation of industrially crafted food products low in fat, saturated fat, and cholesterol and fortified with micronutrients, as well as expansion of other nutrient focused technologies to reduce saturated fat such as partial hydrogenation of vegetable oils.

At the same time the global community prioritised action to eliminate hunger and micronutrient deficiency in lower income nations. Major micronutrient targets during this period were iron, vitamin A, and iodine. Evidence was increasing that vitamin A supplements could prevent child mortality from infection, such as measles, as well as preventing night blindness and xerophthalmia.[26] Field trials provided a basis for WHO recommendations for widespread micronutrient supplementation, especially during pregnancy, with iron and vitamin A, and for fortification of salt with iodine to prevent goitre and developmental abnormalities such as congenital hypothyroidism and hearing loss.

Based on these priorities, the UN, national governments, and other international groups adopted portfolios for preventing micronutrient deficiencies through supplementation and fortification and integration of the growing relevant evidence. Scientific investigations further focused on other environmental factors that may interact with micronutrients and dietary protein, such as infection and related poor sanitation, leading to concepts such as subclinical enteritis or malabsorption called first "tropical enteritis," then "environmental enteropathy," and currently "environmental enteric dysfunction."[27-29]

Thus, in both lower and higher income nations, for partly overlapping reasons, a nutrient specific focus continued to shape both scientific inquiry and policy interventions.

1990s to the present: evidence debates, diet patterns, the double burden

Among the most important scientific development of recent decades was the design and completion of multiple, complementary, large nutrition studies, including prospective observational cohorts, randomised clinical trials, and, more recently, genetic consortiums. Cohort studies provided, for the first time, individual level, multivariable adjusted findings on a range of nutrients, foods, and diet patterns and a diversity of health outcomes. Clinical trials allowed further testing of specific questions in targeted, often high risk populations, in particular effects of isolated vitamin supplements and, more recently, specific diet patterns. Genetic consortiums provided important evidence on genetic influences on dietary choices, gene-diet interactions affecting disease risk factors and endpoints, and Mendelian randomisation studies of causal effects of nutritional biomarkers.

These advances were not without controversy, in particular the general discordance of findings between cohort studies and those of supplement trials for specific vitamins on cardiovascular and cancer endpoints.[30 31] Some experts interpreted the discordance as evidence for irredeemable shortcomings of observational studies (inherent residual confounding). Others believed it showed the limitations of single nutrient approaches to chronic diseases as well as potentially reflecting the different methodological designs, with trials often focused on short term, supraphysiological doses of vitamin supplements in high risk patients, while observational studies often focused on habitual intake of vitamins from food in general populations.

In contrast to single nutrients, physiological intervention trials, large cohort studies, and randomised clinical trials provided more consistent evidence for diet patterns, such as low fat diets (few significant effects) or Mediterranean and similar food based patterns (consistent benefits).[32 33] This concordance was

supported by advances in research methods and better understanding of the complementary strengths of different study designs.[34-39]

Together, these advances suggested that single nutrient theories were inadequate to explain many effects of diet on non-communicable diseases. This pushed the field beyond the RDA framework and other nutrient metrics designed to identify thresholds for nutrient deficiency diseases, and towards complex biological effects of foods and diet patterns.[40-44] Such factors were increasingly seen to reflect joint contributions and interactions between carbohydrate quality (eg, glycaemic index, fibre content), fatty acid profiles, protein types, micronutrients, phytochemicals, food structure, preparation and processing methods, and additives.

Prospective cohorts and dietary intervention trials showed that a focus on total fat, a mainstay of dietary guidelines since 1980, produced little measurable health benefit; conversely, nutrient based recommendations for specific foods such as eggs, red meats, and dairy products (eg, based on dietary cholesterol, saturated fat, calcium) belied the observed relations of these foods with health outcomes.[32 33] For weight loss and glycaemic control, decades of emphasis on low fat diets were questioned by the results of a series of prospective cohort studies, metabolic feeding studies, and randomised trials, which showed that foods rich in healthy fats produced benefit, while foods rich in starch and sugar caused harm.[33 45-47] This progress was extended to recognition of the relevance of diet patterns such as traditional Mediterranean or vegetarian diets that emphasised minimally processed foods such as fruits, vegetables, nuts, beans, whole grains, and plant oils and low amounts of highly processed foods rich in starch, sugar, salt, and additives.[32 33]

These recent scientific shifts help explain many uncertainties and controversies in nutrition today. After decades of focus on simple, reductionist metrics such as dietary fat, saturated fat, nutrient density, and energy density, the emerging true complexities of different foods and diet patterns create genuine challenges for understanding influences on health and wellbeing. For several categories of foods, meaningful numbers of prospective observational or interventional studies have become available only recently.[33 38] Growing realisation of the importance of overall diet patterns has stimulated not only scientific inquiry but also a deluge of empirical, commercial, and popular dietary patterns of varying origin and scientific backing.[48] These range, for example, from flexitarian, vegetarian, and vegan to low carb, paleo, and gluten-free. Many of these patterns have specific aims (eg, general health, weight loss, anti-inflammation) and are based on differing interpretations of current evidence.

In lower income countries, concerns about vitamin supplementation have emerged, such as harms associated with higher dose vitamin A supplements, risk of exacerbating infections such as malaria with iron, and safety concerns about folic acid fortification of flour, which might exacerbate neurological and cognitive deficits among people with low vitamin B_{12} levels.[49-52] In addition, a precipitous rise in non-communicable diseases in these countries has led to new focus on the "double burden"—both conventionally conceived malnutrition (insufficient calories and micronutrients) leading to poor maternal and child health and modern malnutrition (poor diet quality) leading to obesity, type 2 diabetes, cardiovascular diseases, and cancer. These dual global burdens are increasingly found within the same nation, community, household, and even person.[53-55]

Yet, after decades of focus in the international nutrition community on vitamin supplements, food fortification, and starchy staples to provide calories, the necessary shift towards diet quality is slowed by considerable inertia. This is seen, for example, in the reductionist, single nutrient focus of many of the UN sustainable development goals. Even when non-communicable diseases are considered, the predominant focus is on obesity rather than the diverse risk pathways and conditions affected by nutrition—facilitating a misleading concept of "overnutrition" rather than unhealthy dietary composition as the root problem.[55]

Future of nutrition science

Building on the evidence for multifaceted effects of different foods, processing methods, and diet patterns,[32 33] new priorities for research are emerging in nutrition science. These include optimal dietary composition to reduce weight gain and obesity; interactions between prebiotics and probiotics, fermented foods, and gut microbiota; effects of specific fatty acids, flavonoids, and other bioactives; personalised nutrition, especially for non-genetic lifestyle, sociocultural, and microbiome factors; and the powerful influences of place and social status on nutritional and disease disparities.[33 56-60]

For lower income nations and populations, rigorous investigation is required to understand the optimal dietary patterns to jointly tackle maternal health, child development, infection risk, and non-communicable diseases.

Our understanding of diet related biological pathways will continue to expand (fig 1),[33 57 61] highlighting the limitations of using single surrogate outcomes to determine the full health effects of any dietary factor. In addition, future conclusions about diets and health should be based on complementary evidence from controlled interventions of multiple surrogate endpoints, mechanistic studies, prospective observational studies, and, when available, clinical trials of disease outcomes.[35-39] This will require moving away from the current simplistic belief that reliable nutritional evidence can be derived only from large scale randomised trials.

Given the large and continuing global rise in agribusiness and manufactured foods, nutrition science must keep pace with and systematically assess the long term health effects of new food technologies. Relatively little rigorous evaluation has been done on potential long term health consequences of modern shifts in agricultural practices, livestock feeding, crop breeding, and food processing methods such as grain milling and processing; plant oil extraction, deodorisation, and interesterification; dairy fat homogenisation; and use of emulsifiers and thickeners.

Additional complexity may arise in nutritional recommendations for general wellbeing versus treatment of specific conditions. For example, dietary recommendations for treating obesity are now particularly controversial. Many scientists continue to support a basic "energy imbalance" concept of obesity, wherein calories from different foods are all considered equal.[62] Conversely, growing evidence suggests that, over longer periods, diet composition may be a more relevant focus than calories because of the varied influences of different foods on overlapping pathways for weight control such as satiety, brain reward, glycaemic responses, the microbiome, and liver function.[56 63-65] Over months to years, some foods may impair pathways of weight homeostasis, others may have relatively neutral effects, and others may promote integrity of weight regulation. These long term effects will be especially relevant as anti-obesity efforts shift from secondary prevention (weight loss in people with obesity) towards primary prevention (avoidance of long term weight gain in populations).

Recognition of complexity is a key lesson of the past. This is common in scientific progress whether in nutrition, clinical medicine, physics, political science, or economics: initial observations lead to reasonable, simplified theories that achieve certain practical benefits, which are then inevitably advanced by

new knowledge and recognition of ever-increasing complexity.[35]

Nutrition policy

Like nutrition science, policy needs to move from simplistic reductionist strategies to multifaceted approaches. Nutrition policy to reduce non-communicable diseases has so far generally relied on consumer knowledge—simply inform the public through education, dietary guidelines, product nutrition labels, etc, and people will make better choices. However, it is now clear that knowledge alone has relatively limited effects on behaviour, and that broader systems, policy, and environmental strategies are needed for effective change.[66 67]

Compounding these challenges, many current strategies remain focused on reductionist constructs such as total fat or total saturated fat,[41 68] overlooking the importance of food type and quality, processing methods, and diet patterns. Another example of policy lag involves energy balance. Policy makers continue to promote total calorie labelling laws for menus and packaging and other calorie reduction policies, rather than aiming to increase calories from healthy foods and reduce calories from unhealthy foods.

The public is understandably bewildered by these evolving dietary messages. Many food companies compound the confusion by marketing products rich in refined flours, sugar, salt, and industrial additives, exploiting added micronutrients or terms such as "organic," "local," or "natural" to supply a false aura of healthiness. Public uncertainty is amplified by competing nutritional messages from varied media sources, online and social networks, cultural thought leaders, and commercial outlets, whose messages vary depending on underlying goals, expertise, perspectives, and competing interests.[35]

Although reductionist policies may have some value to reduce specific additives—eg, trans fats, sodium, added sugar—whole food based policies will be crucial to fully address diet related illnesses. Most policy innovation has focused on sugar sweetened drinks, following the model of the WHO Framework Convention on Tobacco Control: tax, restrict places of sale, restrict marketing, use warning labels. This construct breaks down for incentivising consumption of healthy foods. Integrated policy, investment, and cultural strategies are needed to create change in food production and manufacturing, worksites, schools, healthcare systems, quality standards and labelling, food assistance programmes, research and innovation, and public-private partnerships.

To be effective, future nutrition policy must unite modern scientific advances on dietary priorities (specific foods, processing methods, additives, diet patterns) with trusted communication to the public and modern evidence on effective systems level change. This includes a shift from the global medicalisation of health towards addressing the interconnected personal, community, sociocultural, national, and global determinants of food environments and choices.[66 67] In both lower and higher income countries, interventions must consider the double burdens of food insecurity and chronic disease, and their links to disparities in education, income, and opportunity. This will require substantially more funding for research, both from government sources and through appropriately fashioned, transparent public-private partnerships.[69 70] Guided by knowledge of the past, creative new approaches are needed for accelerated scientific investigation, coordination, and translation of current and future advances.

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Dietary fat and cardiometabolic health: evidence, controversies, and consensus for guidance

Although difficulties in nutrition research and formulating guidelines fuel ongoing debate, the complexities of dietary fats and overall diet are becoming better understood, argue **Nita G Forouhi and colleagues**

In past decades, dietary guidance has almost universally advocated reducing the intake of total and saturated fat, with the emphasis shifting more recently from total fat to the replacement of saturated fat with polyunsaturated fats and the elimination of trans fat. These recommendations and the link between fat consumption and the risk of cardiovascular disease have been among the most vexed issues in public health: are dietary fats "villains," are they benign, or are they even "heroes" that could help us consume better overall diets and promote health? And, which dietary fats fit into which category?

The medical literature is still full of articles arguing opposing positions. For example, in 2017, after a review of the evidence, the American Heart Association Presidential Advisory strongly endorsed that "lowering intake of saturated fat and replacing it with unsaturated fats, especially polyunsaturated fats, will lower the incidence of CVD".[1] Three months later, the 18-country observational Prospective Rural Urban Epidemiology (PURE) Study concluded much the opposite: "Total fat and types of fat were not associated with cardiovascular disease, myocardial infarction, or cardiovascular disease mortality".[2] The devil, as always, is in the detail, including the inherent complexity of human diets, methodological considerations, and the role of bias and confounding.

This article takes a critical look at the evolution of scientific understanding about dietary fats and health, the difficulties of establishing public health dietary guidelines, and what the current advice should be for dietary fat consumption. Although the focus is on cardiovascular disease, we also consider other outcomes, including weight gain and obesity, type 2 diabetes, and cancer.

History, evolution, and current understanding of dietary fat and health

The public health debate about dietary fats and health has been ongoing for over 60 years. The "diet-heart hypothesis" (box 1) has been the focus of discussions on dietary fat and health because coronary heart disease has been and remains the main cause of death worldwide.

Fat is not just fat

Despite decades of dietary advice that the lower the total fat content, the healthier the diet, researchers and public health authorities now agree that to consider the effect of total fat intake alone on health is meaningless; different types of fats must be considered (box 2).

To produce public health guidelines on which foods to eat or avoid to reduce the risk of chronic disease is complicated because dietary fats are typically mixtures of different types of fatty acids. Animal fats, for instance, are the main sources of saturated fats in many modern diets, but some animal fats are higher in monounsaturated fats than saturated fats, and polyunsaturated fats in vegetable oils will typically contain both omega 3 and omega 6 fatty acids in different concentrations. Hence, conclusions about the health effects of saturated and polyunsaturated fatty acids are unlikely to consistently translate to the health effects of the fats, oils, and foods in which those fatty acids are present.

Foods are not just nutrients

The scientific investigation of nutrients (both macro- and micronutrients) is essential for understanding pathophysiological mechanisms of disease. However, people

KEY MESSAGES

- For cardiovascular health, substantial evidence supports the importance of the type of fat consumed, not total fat intake, and the elimination of industrially produced trans fats
- Much of the evidence suggests that the risk of coronary heart disease is reduced by replacing saturated fat with polyunsaturated fats (including plant oils) but not when carbohydrate is the replacement nutrient
- Controversies remain about long term health effects of specific plant oils and of high fat, low carbohydrate diets, and research is needed to resolve these
- The focus of dietary advice must be on the consumption of foods and overall dietary patterns, not on single nutrients

Box 1: Diet-heart hypothesis

The seemingly simple diet-heart hypothesis was first proposed by nutritionist Ancel Keys in the early 1950s. The hypothesis outlined a sequence of relationships in which a fatty diet elevates serum cholesterol levels, leading to atherosclerosis and myocardial infarction. The focus of the hypothesis soon shifted from the total fat consumed in the diet to the more nuanced idea that saturated fats should be replaced by polyunsaturated fats and the benefits of replacing animal fats with vegetable fats were advocated. Total cholesterol as the atherogenic biomarker was later replaced by cholesterol subfractions: the cholesterol in low density lipoproteins and high density lipoproteins, and serum levels of triglycerides. That science, too, has continued to evolve in complexity with further research (fig 1).

Pathophysiological and genetic studies and randomised clinical trials with different cholesterol lowering drugs have led to a consensus that low density lipoprotein (LDL) particles are a cause of coronary heart disease.[3] The effect of saturated fat on LDL cholesterol levels[1 4 5] and the association of LDL with coronary heart disease[1 3] have led to the inference that dietary saturated fat directly promotes the development of coronary heart disease. However, direct evidence of the benefits of lowering cholesterol or LDL cholesterol by changing the fat content of the diet is lacking. Meta-analyses and systematic reviews still place emphasis on the results of a few small trials done 40 to 50 years ago, supplemented by the observations of prospective epidemiological cohort studies.[4 6-9] This evidence has not been sufficient to resolve controversies as both the randomised trials and the observational evidence have many methodological and interpretive problems. Moreover, as the science has evolved, fat consumption itself and its relation with health have become more complex.

Box 2: Dietary fats and their food sources

- Dietary fats are mostly triglycerides, with each triglyceride molecule containing three fatty acids on a glycerol backbone
- The structure and function of dietary fatty acids can vary greatly depending on chain length (6-24 carbon units); number of double bonds—saturated (with no double bonds), monounsaturated, or polyunsaturated; and whether the double bonds are in a cis (same side) or trans (opposite side) position
- Polyunsaturated fats with double bonds that are 3 carbon atoms or 6 carbons from the n-terminal end of the fatty acid (n-3 or n-6, respectively) are considered essential—that is, they must be obtained from the diet because they are not synthesised in the body. Both have important structural and physiological functions
- Different fatty acids have distinct biochemical properties and can therefore produce different metabolic and physiological effects with different clinical manifestations, such as cardiovascular, neurological, or other

Food sources of dietary fats

- Food sources of individual fatty acids vary within each class. For instance, within the omega 3 polyunsaturated fatty acid class, alpha linolenic acid comes from plants, including some nuts and seeds such as walnuts and linseed, whereas eicosapentaenoic acid and docosahexaenoic acid come mostly from fish and other marine sources
- Many food sources contain different types of fatty acids. For example, olive oil is a good source of monounsaturated fatty acids but also contains saturated and polyunsaturated fatty acids in smaller proportions. Animal products are rich in saturated fats but some also contain large proportions of monounsaturated and polyunsaturated fatty acids

do not consume isolated nutrients and the foods they eat are more than the sum of their nutrients.

Synergism and interactions between different components of foods together with the degree of processing and preparation or cooking methods lead to a "food matrix" effect which is not captured by considering single nutrients. Different types of food that are high in saturated fats are likely to have different effects on health. For example, dairy products and processed meats, both high in saturated fats, are differentially associated with many health outcomes in prospective epidemiological studies, often in opposite directions.[10] One explanation for this divergence is that despite their similar fat content, other components of these two food groups are associated with different health effects. For example, dairy products contain minerals such as calcium and magnesium and have probiotic features if fermented, whereas processed red meat has a high salt and preservative content.

The potential for residual confounding from lifestyle, dietary, and socioeconomic factors and bias in observational research limits causal interpretation. However, it is also unlikely that randomised clinical trials of individual foods or food groups for disease endpoints will be possible, not least because of the problems of sample size, adherence, dose, duration, and cost. For this reason, dietary guidance is usually derived from analysis and synthesis of different types of evidence.

Nutrient replacement

Within overall diets, eating less of one macronutrient implies eating more of others to keep calorie intake the same. Dietary manipulations in clinical trials always involve multiple variables. If total fat reduction is the intervention in a randomised trial, any effect observed could depend on the replacement source of energy, whether it is mainly carbohydrate or protein or a combination of the two. The quality of the replacement macronutrient (for instance, highly refined grains versus whole grains) can also influence the observed effect. If reduction of saturated fat but not total fat is the intervention, the effect will differ depending on whether the replacement fat is a mostly polyunsaturated fat, in which case whether an omega 3 or omega 6 polyunsaturated fatty acid, or a mostly monounsaturated fat such as from olive oil.

The same principles apply to observational studies, when statistical models of associations between diet and disease need to adjust for total energy intake. In recent years, most observational studies have done this, but the comparison sources of energy (eg, carbohydrate or unsaturated fats) are often not specified.

In meta-analyses of observational studies that adjust for total calorie intake, higher intakes of polyunsaturated fatty acids in place of saturated fatty acids were associated with a lower risk of coronary heart disease.[6 11 12] Similar findings were seen for total and cardiovascular mortality in 128 000 men and women followed for up to 32 years with repeated measures of diet.[13] Replacing saturated fatty acids with polyunsaturated fatty acids has been part of dietary guidelines since the 1970s and has led to modest reductions in saturated fat intake and an increase in plant oil consumption in the US (eg, polyunsaturated fatty acid intake increased from about 3% to 7% of energy intake) at a time when coronary heart disease mortality fell by nearly 75%.[14] At a minimum, these findings support the safety of these dietary changes, although the benefits of changing the type of fat are difficult to quantify because of changes in other factors such as other aspects of diet, smoking, and emergency medical services.

A global perspective on the health effects of dietary fats and other macronutrients was provided by the PURE study, which included 135 335 individuals in 18 countries.[2] Higher intakes of total fat and saturated, monounsaturated, and polyunsaturated fatty acids individually were associated with lower total mortality but not with cardiovascular disease mortality or incidence, except for inverse associations of saturated fatty acids with the incidence of stroke. In contrast, higher carbohydrate intake was non-linearly associated with increased total mortality; in nutrient substitution analyses, only the replacement of carbohydrate with polyunsaturated fats was associated with lower mortality. Although limited by the observational study design, these findings add to the concern about guidelines that focus on limiting the intake of total and saturated fats, particularly without considering the replacement nutrient.

Taken together, a single nutrient approach can be misleading both in the interpretation of research findings and in the health implications of translating results into dietary guidelines and public health programmes.

Importance of lipid components in the diet-heart hypothesis

As the diet-heart hypothesis evolved in the 1960s and 1970s, the focus shifted from the effect of dietary fat on total cholesterol to LDL cholesterol. However, changes in LDL cholesterol are not an actual measure of heart disease itself. Any dietary intervention might influence other, possibly unmeasured, causal factors that could affect the expected effect of the change in LDL cholesterol. This possibility is clearly shown by the failure of several categories of drugs to reduce cardiovascular events despite significant reductions in plasma LDL cholesterol levels.[15-17] LDL cholesterol can also be reduced through diet in ways that do not reduce the risk of coronary heart disease; for instance, when saturated fat is replaced by carbohydrates, this lowers LDL cholesterol but also reduces HDL cholesterol and increases triglycerides.[5] In the past, these effects were considered less important as researchers and the

pharmaceutical industry focused on the effect of the reduction of LDL cholesterol.

Since the 1980s, studies on the LDL cholesterol biomarker itself and the effects of dietary fats on other biomarkers of disease have revealed a more complicated situation. Researchers now widely recognise the existence of a range of LDL particles with different physicochemical characteristics, including size and density, and that these particles and their pathological properties are not accurately measured by the standard LDL cholesterol assay.[18] Hence assessment of other atherogenic lipoprotein particles (either LDL alone, or non-HDL cholesterol including LDL, intermediate density lipoproteins, and very low density lipoproteins, and the ratio of serum apolipoprotein B to apolipoprotein A1) have been advocated as alternatives to LDL cholesterol in the assessment and management of cardiovascular disease risk.[17 19-21] Moreover, blood levels of smaller, cholesterol depleted LDL particles appear more strongly associated with cardiovascular disease risk than larger cholesterol enriched LDL particles,[22] while increases in saturated fat intake (with reduced consumption of carbohydrates) can raise plasma levels of larger LDL particles to a greater extent than smaller LDL particles.[22] In that case, the effect of saturated fat consumption on serum LDL cholesterol may not accurately reflect its effect on cardiovascular disease risk. While polyunsaturated fats and monounsaturated fats reduce LDL cholesterol levels, their effects on cardiovascular disease risk factors that are associated with lipoprotein particles are less clear. Although uncertainty exists about the causal role, if any, of elevated triglycerides or low HDL cholesterol levels in coronary heart disease, there has been continued interest because of their association with insulin resistance and metabolic syndrome, and their relevance in global populations.[19 23] Notably, these lipid markers improve—that is, triglycerides decrease or HDL cholesterol increases—when saturated, monounsaturated, or polyunsaturated fats replace carbohydrates.

Trans unsaturated fatty acids (trans fats) are an example of a fatty acid category whose effects on lipid biomarkers of cardiovascular disease risk are consistent with their association with cardiovascular disease events in prospective cohort studies. When substituted for other macronutrients, these fatty acids, such as those in industrially produced hydrogenated oils, have been shown to increase levels of LDL cholesterol and the number of atherogenic lipoproteins (LDL and very low density lipoproteins), while also increasing triglycerides and reducing HDL cholesterol and LDL particle size.[24]

To complicate the relation further, dietary fatty acid composition may affect the risk of cardiovascular disease independently of these lipid biomarkers, specifically through the effects on inflammation, endothelial function, thrombosis, ventricular arrhythmias, and blood pressure. However, as reviewed recently,[25] insufficient evidence exists to draw firm conclusions about the effects of fatty acid type on these factors (fig 1).

Finally, consideration must be given to the role of personal factors that may alter the effect of dietary fat on LDL cholesterol and other lipids. For example, evidence from clinical trials suggests that saturated fat may have little effect on LDL cholesterol levels in people with obesity.[26 27] Moreover, the possibility of differing effects of dietary fats on lipids in racial and ethnic subgroups has not been systematically evaluated.

Beyond cardiovascular disease

Cancer

In the 1960s and 1970s, national per capita intakes of total and saturated fat correlated with rates of cancers of the breast, colon, prostate, and other common cancers in Western countries. Although the ecological findings were potentially confounded by many aspects of diet and lifestyle, and no clear biological basis was shown, these findings were used to support widespread dietary recommendations to reduce total fat intake.[28] Later prospective cohort studies with follow-up of up to 20 years have not found positive associations between total fat intake and the incidence of these cancers,[29] nor have large clinical trials, most notably, the Women's Health Initiative.[30] However, the Women's Health Initiative may not be informative because the blood lipid fractions of participants randomised to a low fat diet did not change, which raises questions about adherence to the diet. In another trial in which participants did show the expected change in blood lipids with a low fat diet, no effect on breast cancer incidence was observed.[31] A comprehensive review of the literature by the World Cancer Research Fund and the American Institute for Cancer Research concluded that no convincing or probable relation exists between intakes of total or saturated fat and risk of any form of cancer.[32] An association between omega 6 intake and cancer incidence is also not supported.

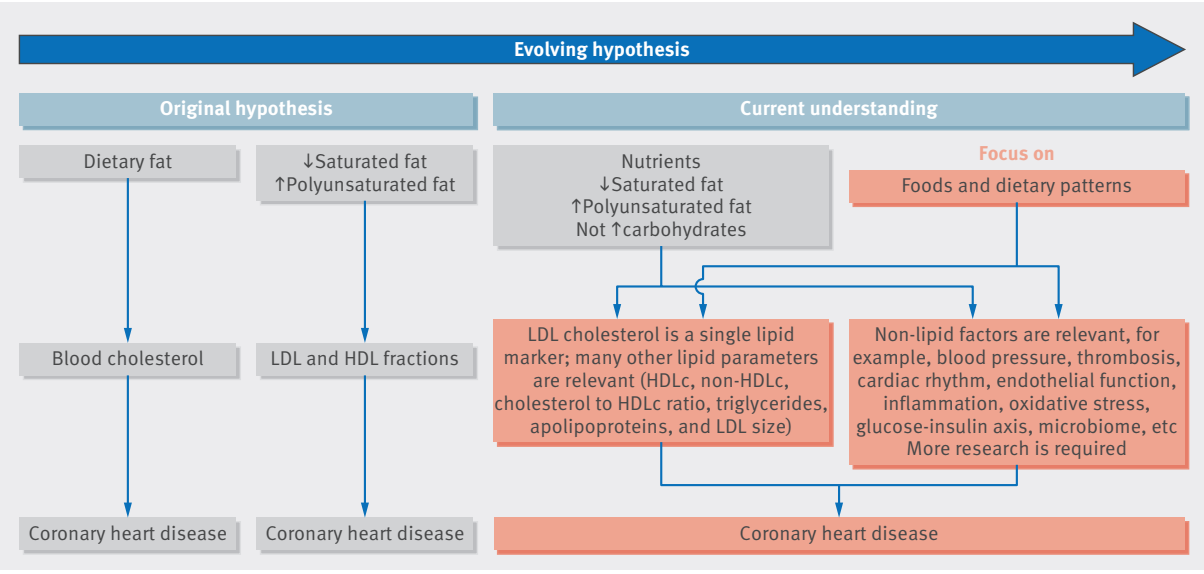

Fig 1 | Diet-heart hypothesis and current understanding. HDL: high density lipoprotein, HDLc: high density lipoprotein cholesterol, LDL: low density lipoprotein

Weight gain and obesity

The assumption that diets high in fat promote weight gain is based on the relative energy density of macronutrients—9 kcal/g for fat compared with 4 kcal/g for carbohydrate or protein. This assumption, however, ignores the important role of macronutrients in hunger and satiety and in pathways regulating fuel partitioning, fat storage, and fatty acid metabolism. Randomised trials of diet and weight loss are easier to conduct than trials that have chronic disease as the outcome because they can be shorter and require far fewer participants. However, several design issues are important in interpreting trial findings. For example, many people initially comply with the intervention diets when they start in a trial and lose weight but regain much of that weight by one year. Because long term weight control is of interest, trials should last a minimum of one year and ideally two years or longer. Moreover, dietary interventions such as counselling, monitoring, feedback, and support can help with weight loss independently of the specific dietary advice because of healthier eating, and this complicates interpretation. Control diet groups should receive a similar intervention.

In studies where the intensity of intervention was similar for the diets tested, participants randomised to low carbohydrate, high fat diets lost about 1.5 kg more weight than those in the low fat group.[33] Diets higher in fat and restricted in carbohydrate seem to help weight loss[28] but dietary adherence is a critical factor in the effectiveness of any diet.[34] Another relevant factor for weight loss is diet quality. A trial comparing diets high in carbohydrates or fats showed an equal amount of weight loss by participants when consuming whole and natural food sources while avoiding sugar, sugary drinks, refined grains, trans fats, and processed foods in general.[35]

Maintaining a healthy weight to prevent obesity is also important. The typical weight gain in many Western countries is about 0.5 kg a year, which seems small but by age 50 this results in weight levels that are associated with important health risks.[36] Few randomised trials have examined the effects of diet on long term weight gain in people who are initially not overweight. In prospective observational studies, a simple design assessing baseline diet in relation to long term weight change is not optimal because many people change their diet during follow-up; a longitudinal design examining the change in diet with change in weight is preferable. Evidence is sparse, but an analysis in the Nurses' Health Study suggested that intakes of saturated and trans fat were positively associated with weight gain in women who were normal weight at the start, while intakes of mono and polyunsaturated fat (mainly omega 6) were not; total fat intake was only weakly associated with weight gain.[37]

Taken together, the evidence does not support a benefit of low fat diets for weight loss or prevention of overweight compared with low carbohydrate diets. Other aspects of diet may have a greater influence on long term weight control, including the quantity and quality of carbohydrate intake; thus any effect of fat is likely to depend on its food source and the overall dietary pattern.

Type 2 diabetes

A combination of insulin resistance and an inadequate capacity to secrete insulin leads to the development of type 2 diabetes, with adiposity a critical risk factor. Prospective studies report little association between total fat consumption and risk of diabetes but an association may exist, as with cardiovascular disease, for type of fat. The findings of a few short term feeding trials (usually lasting four weeks, with some up to 16 weeks) that assessed intermediate endpoints support this evidence. Evidence from randomised controlled trials suggests that industrially produced trans fats increase inflammatory factors and adversely affect lipid levels, but no or inconclusive evidence was found for an effect on markers of glucose homoeostasis.[38 39] Evidence from prospective studies suggests that intake of industrially produced trans fats is positively associated with the incidence of type 2 diabetes, while the intake of polyunsaturated fatty acids is inversely associated.[4 40] More specifically, a blood biomarker of the most abundant omega 6 fatty acid, linoleic acid, is inversely associated with the incidence of type 2 diabetes.[41 42] Despite promising studies in animals, diets rich in marine omega 3 fatty acids have not been shown in humans to reduce insulin resistance or the incidence of type 2 diabetes. However, biomarker studies point to an inverse association between blood omega 3 fatty acids (alpha linolenic acid) derived from plants and type 2 diabetes.[41 43] Because the type of dietary carbohydrate may also affect the risk of diabetes, any relation between dietary fat and type 2 diabetes may depend on the quantity and quality of carbohydrate as well.

Moving from controversy to consensus

Two related issues have caused the most controversy about the relative roles of saturated fats and polyunsaturated fats and the evidence for making public health recommendations.

Since the 1960s, the evidence has suggested that replacing saturated fats in the diet with polyunsaturated fats reduces the risk of chronic disease and premature death. In practice this means replacing red and processed meat and high fat dairy with fish, nuts, and seeds, and replacing animal fats such as butter and lard with vegetable oils such as corn, sunflower, soy, rapeseed, or olive oils. The PREDIMED study, a large primary prevention randomised controlled trial on people at high risk of cardiovascular disease, reported that increased intake of extra virgin olive oil or nuts with a Mediterranean diet significantly reduced the incidence of cardiovascular disease compared with a low fat dietary advice group.[44] However, while the intake of unsaturated fats increased in both the olive oil and nut arms and may therefore have contributed to the clinical outcomes, there was no nutrient substitution for saturated fats and their intake was not reduced compared with the low fat dietary advice group. How this evidence should be interpreted and applied remains controversial.

Since 2000, clinical trials lasting up to two years have suggested that low carbohydrate diets in which total and saturated fat replaces the carbohydrate content of the diet have beneficial effects on overweight as well as on lipid risk factors such as HDL cholesterol and triglycerides (but not LDL cholesterol) and on risk factors for type 2 diabetes.[45 46] Here, we ourselves disagree on the significance and interpretation of these trials because long term trial evidence is not available, definitions of low carbohydrate vary substantially across studies, and few clinical trial data exist on the incidence of clinical endpoints (see related article in this series on diet and management and prevention of type 2 diabetes).[47]

These controversies arise largely because existing research methods cannot resolve them. In the current scientific model, hypotheses are treated with scepticism until they survive rigorous and repeated tests. In medicine, randomised controlled trials are considered the gold standard in the hierarchy of evidence because randomisation minimises the number of confounding variables. Ideally, each dietary hypothesis would be evaluated by replicated randomised trials, as would be done for the introduction of any new drug. However, this is often not feasible for evaluating the role of diet and other behaviours in the prevention of non-communicable diseases.

One of the hypotheses that requires rigorous testing is that changes in dietary fat consumption will reduce the risk of non-communicable diseases that take years or decades to manifest. Clinical trials that adequately test these hypotheses require thousands to tens of thousands

Box 3: Prevention strategies

Public health preventive measures can be divided into two main categories.

Subtractive—Rose described this as "the removal of an unnatural factor and the restoration of biological normality".[49] For coronary heart disease, this would include smoking prevention or cessation and, more recently, the near elimination of industrially produced trans fatty acids through a combination of information, advice, and regulation. Despite the absence of long term randomised controlled trials to support the benefits of these interventions, the evidence from observational studies and, in the case of trans fats, short term feeding trials is considered sufficiently consistent to support these public health interventions.

Additive—Rose described this as "not removing a supposed cause of disease but adding some other unnatural factor, in the hope of conferring protection".[49] Additive measures for coronary heart disease would include a high intake of polyunsaturated fats and long term medication. Rigorous testing would be required as for any pharmaceutical therapy to ensure long term safety and that harm does not outweigh benefit.

of participants randomised to different dietary interventions and then followed for years or decades until significant differences in clinical endpoints are observed. As the experience of the Women's Health Initiative suggests, maintaining sufficient adherence to assigned dietary changes over long periods (seven years in the Women's Health Initiative) may be an insurmountable problem. For this reason, among others, when trials fail to confirm the hypotheses they were testing, it is impossible to determine whether the failure is in the hypothesis itself, or in the ability or willingness of participants to comply with the assigned dietary interventions. This uncertainty is also evident in diet trials that last as little as six months or a year.

In the absence of long term randomised controlled trials, the best available evidence on which to establish public health guidelines on diet often comes from the combination of relatively short term randomised trials with intermediate risk factors (such as blood lipids, blood pressure, or body weight) as outcomes and large observational cohort studies using reported intake or biomarkers of intake to establish associations between diet and disease.[48] Although a controversial practice, many, if not most, public health interventions and dietary guidelines have relied on a synthesis of such evidence. Many factors need to be considered when using combined sources of evidence that individually are inadequate to formulate public health guidelines, including their consistency and the likelihood of confounding, the assessment of which

Box 4: Role of omega 6 and omega 3 polyunsaturated fatty acids in health

Both omega 6 and omega 3 are essential fatty acids and are intrinsic to cell membranes and the structure of the central nervous system. They are precursors of eicosanoids, which are involved in inflammation, cardiac rhythm, thrombosis, vascular function, and many other processes. Evidence suggests, but is inconsistent, that adequate intake of omega 3 fatty acids reduces cardiac arrhythmias and sudden cardiac death. Concerns have been raised that omega 6 polyunsaturated fats are pro-inflammatory but this is not supported by controlled feeding studies and large cross sectional observations.[50] In a follow-up study of over 128 000 men and women for up to 32 years, higher intake of linoleic acid (the most abundant omega 6 fatty acid) was associated with lower risks of coronary heart disease, cancer, and total mortality.[13] The inverse association between linoleic acid intake and risk of cardiovascular disease and overall death is approximately linear up to about 8% of energy, beyond which data are lacking.[13] Notably, linoleic acid levels in blood, a direct marker of dietary intake, were inversely associated, with the incidence of type 2 diabetes in prospective studies but arachidonic acid was not.[41 51] In contrast, blood omega 3 polyunsaturated fatty acids were modestly inversely associated with coronary heart disease[52] but the association with type 2 diabetes varied by subtype: plant origin omega 3 fatty acid (alpha linolenic acid) was inversely associated while marine origin omega 3 fatty acids were not.[41]

Use of plant oils to replace saturated fatty acids

With the exception of the cardiovascular benefit[44] of extra virgin olive oil (comprised predominantly of oleic acid, a monounsaturated fat), which has been used for thousands of years in Mediterranean countries, most of the literature on the effects of plant oils on the risk of cardiovascular disease and other outcomes has examined intakes of specific fatty acids. These oils contain a combination of saturated, monounsaturated, and omega 6 and omega 3 fatty acids but the proportions vary greatly. Plant oils also contain other minor constituents, including polyphenols and antioxidants, which may influence the effect of oil consumption on disease risk. A reduction in cardiovascular mortality was observed in the older randomised trials that used plant oils containing both omega 6 and omega 3 fatty acids to replace saturated fat.[53] Recent publications from the Sydney Diet Heart Study and the Minnesota Coronary Trial raise questions about very high intakes of plant oils containing only omega 6 fatty acids.[53 54] The concerns raised are complex and discussed elsewhere.[1] The safety of long term use of polyunsaturated plant oils was supported by a significant inverse association between the intake of polyunsaturated plant oils and all-cause mortality at 32 years of follow-up; no increase in risk was seen for any outcome.[13] Evidence also exists that rapeseed (canola) oil reduces the risk of coronary heart disease: most notably, rapeseed oil was the primary intervention in the Lyon Heart Study of secondary prevention of coronary heart disease, which reduced recurrent cardiovascular disease or death by about 70%.[55] Other specific types of oil, including corn, sunflower, coconut oil, and palm oils, have not been well studied. Although a recent report suggests that coconut oil compared with butter results in a more favourable lipid profile (lower LDL, higher HDL cholesterol), and compared with olive oil was equivalent in lipid effects,[56] further research is needed in large long term trials and current recommendations on caution about use should be upheld.[1] Some plant oils, including corn and sunflower oil, have little omega 3 content. If these are the primary oils consumed and intake of omega 3 fatty acids from fish and other sources is low, this could result in inadequate intake of these essential fatty acids with possible adverse effects on cardiovascular disease and other outcomes. Also, to benefit from the use of unsaturated oils assumes that they are not partially hydrogenated as this (and some other industrial processes such as deodorisation if done improperly) produces trans fats.

In summary, evidence exists of the long term safety and benefit of many of the commonly consumed unsaturated plant oils. Further research is needed to define more precisely the long term effects and optimal intakes of specific fatty acids and plant oils, and their interactions with genetic and other dietary factors, including the amount and type of carbohydrate intake.

is not shared universally. The level of evidence required for public health guidelines may differ depending on the nature of the guideline itself.

The controversies over the effects of replacing saturated fatty acids with polyunsaturated fatty acids—reduced consumption of animal fats, increased consumption of vegetable oils—and the significance of the evidence from trials of very low carbohydrate, high fat diets suggest both "additive" and "subtractive" nutritional approaches to prevention of cardiovascular disease (box 3). Both depend on assumptions about the nature of biological normality in human diets. The replacement of saturated fats with polyunsaturated fats implies that saturated fat as a nutrient causes disease and is being reduced and/or that the consumption of vegetable oils is healthy and without long term risks. Box 4 appraises the debate about the role of omega 6 and omega 3 polyunsaturated fatty acids and the use of plant oils. The consumption of very low carbohydrate, high fat diets assumes that high levels of dietary fat and saturated fat can be consumed for a lifetime without the risks outweighing the benefits. A point of controversy is whether such assumptions can be accepted without long term clinical trials of the kind that would be required for a pharmaceutical means of prevention. This controversy might be resolved by longer term clinical trials, but the cost and methodological and ethical challenges of such dietary trials suggest they may never be done.

Although authorities still disagree, most consider that public health decisions should be made on the weight of the available evidence, acknowledging its limitations, and seeking to obtain further, better evidence when indicated. Equally important is to acknowledge when evidence is insufficient to formulate any guidance, in which case all the relevant options should be clearly outlined to enable informed choice.

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Dietary carbohydrates: role of quality and quantity in chronic disease

David S Ludwig and colleagues examine the links between different types of carbohydrate and health

Carbohydrate is the only macronutrient with no established minimum requirement. Although many populations have thrived with carbohydrate as their main source of energy, others have done so with few if any carbohydrate containing foods throughout much of the year (eg, traditional diets of the Inuit, Laplanders, and some Native Americans).[1 2] If carbohydrate is not necessary for survival, it raises questions about the amount and type of this macronutrient needed for optimal health, longevity, and sustainability. This review focuses on these current controversies, with special focus on obesity, diabetes, cardiovascular disease, cancer, and early death.

Role of carbohydrate consumption in human development

The large brain of modern humans is energetically expensive, requiring a disproportionate share of dietary energy compared with that of other primates. The first hunting and gathering societies were characterised by greater consumption of not only animal foods but also plant foods with greater carbohydrate availability than leaves—including ripe fruit, honey, and eventually cooked starchy foods.[3 4] The higher nutrient and energy density of this diet allowed for evolution of a smaller gastrointestinal tract, offsetting the energy demands of the brain.[5]

KEY MESSAGES

- Human populations have thrived on diets with widely varying carbohydrate content
- Carbohydrate quality has a major influence on risk for numerous chronic diseases
- Replacing processed carbohydrates with unprocessed carbohydrates or healthy fats would greatly benefit public health
- The benefit of replacing fructose containing sugars with other processed carbohydrates is unclear
- People with severe insulin resistance or diabetes may benefit from reduction of total carbohydrate intake

As a result of selective pressures related to dietary changes, two major gene adaptations occurred affecting carbohydrate digestion: average salivary amylase gene copy number (AMY1) increased more than threefold, with substantial variation among populations related to starch consumption[6]; and lactase persistence into adulthood developed in multiple geographically distinct populations, facilitating digestion of the milk sugar lactose.[7] After our transition to an agrarian lifestyle in the Neolithic period, beginning 12 000 to 14 000 years ago, total carbohydrate intake increased substantially as grains became a dietary staple, but archaeological evidence shows that diet related problems also emerged, including endemic nutrient deficiencies, a decrease in mean height, and dental caries.[8-10]

Relation between carbohydrate types and health outcomes

Carbohydrates are formally defined as containing carbon, hydrogen, and oxygen in the ratio of 1:2:1. In practice, dietary carbohydrates comprise compounds that can be digested or metabolically transformed directly into glucose, or that undergo oxidation into pyruvate, including some sugar alcohols (eg, sorbitol). Several systems for classifying carbohydrates have been in use, with varying relevance to health outcomes.

Chain length

Carbohydrates can be categorised according to degree of polymerisation into monosaccharides (monomers), disaccharides, oligosaccharides, and polysaccharides (starch). Conventionally, carbohydrate polymer length is believed to determine the rate of digestion and absorption, and therefore the rise in blood glucose after eating. People with diabetes were therefore instructed to avoid sugars and emphasise starchy foods.[11] However, research beginning 50 years ago showed no meaningful relation between carbohydrate chain length and postprandial glycaemia or insulinaemia.[12 13] Modern starchy foods such as bread, potatoes, and rice raise blood glucose and insulin substantially more than some high sugar foods (eg, whole fruits).[14] By contrast, some traditionally consumed starches (legumes, whole kernel grains, pasta, long fermentation sourdough bread) release glucose more slowly because the starch is protected from digestion by the food matrix (gelatinised) or because the presence of organic acids slows gastric emptying.

Glycaemic index and glycaemic load

Although carbohydrates are the only food constituents that directly increase blood glucose (the main determinant of insulin secretion), population studies suggest that the total amount of carbohydrate as a percentage of dietary energy is less important than the carbohydrate type for risk of chronic disease. Refined grains, potatoes, and sugar sweetened beverages are associated with increased risk,[15] whereas minimally processed grains, legumes, and whole fruits are associated with reduced risk.[16] This distinction may be explained partly by differences in how specific carbohydrates affect postprandial hyperglycaemia and hyperinsulinaema, which are causally related to the development of type 2 diabetes, coronary heart disease, and perhaps obesity.[17]

Two empirical metrics have been introduced to rank foods according to effects on blood glucose: glycaemic index (GI) and glycaemic load (GL) (table 1). The GI compares foods based on a standardised amount of available carbohydrate. Glycaemic load (GI multiplied by the amount of carbohydrate in a typical serving) allows the glycaemic effect of foods, meals, and whole diets to be compared as realistically consumed, and it has been shown to be a better predictor of glycaemic response than the amounts of carbohydrate, protein, and fat in food.[18] Prospective observational studies have reported that higher energy adjusted GI or total GL is an independent risk factor for type 2 diabetes in men and women[19]; cardiovascular morbidity and mortality, including stroke, in women[20-22]; and certain types of cancers in both sexes,[23 24] though some have questioned the strength and consistency of these findings.[25]

Fibre and resistant starch

Fibre or non-starch polysaccharide is plant carbohydrate that is not digestible by human enzymes. Fibre and resistant starch provide, to varying degrees, substrate for

Table 1 | Carbohydrate content and glycaemic index of representative foods

Food	Serving size (g)	Available carbohydrate* (g) per serving	Glycaemic index†	Glycaemic load
Rice, jasmine, boiled	120	32	86	28
Instant oat porridge/oatmeal	250	26	79	21
Rice, basmati, boiled	120	30	57	17
Potato, boiled	150	20	78	16
Breakfast cereal, flaked	30	22	72	16
Pasta, white or brown, boiled	120	31	49	15
Bread, white or brown	40	19	75	14
Traditional oat porridge	250	24	55	13
Fruit juice	250 mL	24	50	12
Fruit, tropical	120	16	58	9
Barley, boiled	120	34	28	9
Bread, wholemeal	40	13	54	7
Legumes, boiled	150	22	31	7
Fruit, temperate	120	14	42	6
Pumpkin, boiled	75	8	64	5
Milk	250 mL	12	32	4
Nuts	30	7	25	2

*Available carbohydrate may vary depending on specific brand or country of origin
†GI data are average values adapted from Atkinson et al[14] and unpublished observations from the Sydney University Glycemic Index Research Service, 2018.

colonic microbial fermentation, leading to the production of short chain fatty acids that provide a direct energy source for colonic epithelium and influence hepatic insulin sensitivity.[26] Fibre can be classed as soluble (viscous or non-viscous) and non-soluble, properties that influence gastrointestinal absorption and metabolic effects. Viscous fibres such as vegetable gums and those derived from fruits, legumes, and psyllium slow down digestion and reduce postprandial glycaemia and cholesterol absorption, whereas insoluble fibres (eg, from wheat bran) have limited metabolic actions.

Added and free sugar

Added sugars are defined as sugars that are added to foods during food processing, manufacturing, or preparation. The newer term, "free sugars," also includes sugars naturally present in unsweetened fruit juices: otherwise, these two terms are interchangeable. Under this definition, only lactose naturally present in milk products and sugars contained within the cellular structure of foods (eg, whole fruits) would be excluded.[27]

Most health authorities agree that overconsumption of added sugars, and particularly sugar sweetened drinks, has contributed to the obesity epidemic.[27] In the higher quality prospective observational studies, changes in consumption of sugary drinks are directly associated with changes in energy intake[28] and body weight.[29] Furthermore, two large randomised controlled trials found that elimination of sugary drinks reduced body weight among adolescents at one year[30] and among younger children at 18 months.[31] In meta-analyses of trials in adults consuming unrestricted diets, reduced intake of added sugars is associated with a modest decrease in body weight, while higher intake is associated with a comparable gain. Isocaloric substitution of sugars for other carbohydrate, however, did not affect body weight.[32]

The potential mechanisms relating sugar to weight gain remain a topic of debate. Several investigators have highlighted the potential role of fructose.[33-39] Fructose is metabolised primarily in the gut and liver and, under certain experimental conditions, can stimulate de novo lipogenesis, inflammation, and insulin resistance. However, the relevance of these findings to typical consumption patterns has been questioned.[40 41] Moreover, high intakes of fruits with relatively high amounts of fructose are associated with good metabolic health, suggesting that the food source of fructose is also important.[42]

The relative contribution of added sugar versus other carbohydrates to the obesity epidemic remains unknown. Indeed, high GL starchy foods (without fructose) contribute substantially more calories to typical Western diets than added sugar.[43] In Australia, intakes of added sugars and sugar sweetened drinks have progressively declined since the 1990s, even as mean body mass index in adults and children has risen sharply.[44]

Beyond body weight, meta-analyses of randomised trials indicate that higher intakes of added sugars raise triglycerides, total cholesterol, blood pressure, and other risk factors for cardiovascular disease.[38 45-47] Of special concern is non-alcoholic fatty liver disease, an obesity related condition that has emerged as a major public health threat. Reduction of fructose or sugar consumption in several clinical trials resulted in lower intrahepatic fat.[48-50] However, each of these studies has design limitations, such as lack of a control group and confounding by unintended weight loss. In a six month trial, people consuming sugar sweetened drinks had higher levels of liver and ectopic fat than those consuming drinks without added sugar, even though body weight did not differ by diet group.[47]

Based on the finding that "increasing or decreasing free sugars is associated with parallel changes in body weight … regardless of the level of intake of free sugars," the 2015 WHO guidelines recommended that consumption of free sugars should be less than 10% of energy intake for both adults and children, with potential additional benefits below 5%.[27] The Scientific Advisory Committee on Nutrition in the UK recommended a 5% upper limit, noting potential benefits at this lower level for dental health and total energy intake.[51] (Modern starchy foods may also contribute to dental carries.[52]) The *2015-2020 Dietary Guidelines for Americans* recommend a limit on added sugars of 10% total energy.[53]

Composite quality indices

Beyond the mechanisms implied by these broad classification systems, carbohydrate containing foods may influence health in various other ways. Whole plant foods contain myriad compounds with demonstrably beneficial (vitamins, minerals, and antioxidant and anti-inflammatory phytochemicals) or possibly adverse [54] (lectins, phytates) actions. Ultimately, diet must be considered in an integrated fashion, with changes in consumption of one category of food affecting others. The nature of these exchanges will determine the apparent healthfulness of specific foods in population studies. Recognising this challenge, several indices for carbohydrate quality (based on GI, fibre, whole:total grain consumption, and other factors) and total diet quality have been proposed.

How do carbohydrate containing foods affect health?

Grains

Grains—the seeds of cereal grasses and similar plant families—are staple foods and a major source of dietary carbohydrate worldwide. Minimally processed whole grains retain all three components of the seed. Refined grains are processed to remove the protein and fat rich germ and fibre rich bran, leaving only the starchy endosperm. Meta-analyses of randomised clinical trials indicate that, compared with diets without them, whole grains produce small but significant reductions in low density lipoprotein (LDL) cholesterol, total

cholesterol, and percentage body fat; they also improve postprandial glucose levels and glucose homeostasis.[55-57]

Prospective cohort studies have also shown significant inverse associations between whole grain intake and incidence of type 2 diabetes, coronary heart disease, ischaemic stroke, total cardiovascular disease, and several cancers, as well as risk of death from all causes.[58-62] Conversely, greater refined grain intake, especially from white rice, is associated with an increased risk of type 2 diabetes.[59 63] Whole kernel or coarsely milled grains tend to have lower GI than refined grains and contain higher amounts of fibre and phytochemicals with potential anti-inflammatory and antioxidant properties.

However, the relative health benefits of whole grains and wholemeal foods compared with other categories of whole foods with lower carbohydrate content (eg, nuts, seeds, legumes, avocado, olives) has not been well studied. Furthermore, most whole grains in processed foods do not contain the intact whole grain kernel but have been milled into a fine particle size (thus higher GI) flour, with varying amounts of bran and germ reincorporated. Therefore, food labelled as whole grain may not have the same health benefits as intact or minimally processed whole kernel grains (wheat berries, steel cut oats, quinoa), and some whole grain foods contain high amounts of added sugar.

Potatoes

Potatoes, the leading vegetable food in most countries, are another major source of dietary carbohydrate. Although potatoes have some nutrients (such as vitamin C, potassium, and fibre), they contain predominantly starch with a high GI as typically eaten.[14] In three cohorts of US men and women, increased intake of potatoes was associated with greater weight gain[64] and higher risk of type 2 diabetes, even after adjustment for body mass index and other diabetes risk factors.[65] In the same cohorts, higher intake of baked, boiled, or mashed potatoes and French fries was independently associated with an increased risk of developing hypertension.[66] Thus, the health effects of potatoes more closely resemble those of refined grains than those of other vegetables.

Legumes

Legumes such as beans, peas, and lentils, like whole grains, improve nutritional quality and health outcomes when included in typical dietary patterns. Legumes contain low GI carbohydrate and relatively high amounts of protein, fibre, and other nutrients.[14 67] A meta-analysis of randomised clinical trials found a significant decrease in total and LDL cholesterol for non-soy legume dietary interventions compared with control diets.[68] Another meta-analysis found a 10% lower risk of cardiovascular disease comparing the highest with the lowest categories of consumption.[69] In a Costa Rican population, increasing the ratio of beans to white rice was associated with lower cardiometabolic risk factors, including blood lipids and blood pressure.[70]

Fruits

Whole fruits are high in fibre, vitamins, minerals, and phytochemicals and typically have moderate to low GL.[14] Regular consumption of fruits is associated with lower risk of type 2 diabetes, cardiovascular disease, cancer, and all-cause mortality in prospective cohort studies.[71-73] Greater consumption of whole fruits (especially blueberries, grapes, and apples) is significantly associated with lower risk of diabetes, whereas greater consumption of fruit juices is associated with a higher risk in three US cohorts.[74] Compared with whole fruits, fruit juices tend to have less fibre, fewer micronutrients, and higher GI,[75] and for these reasons, classifying whole fruits and juices together in dietary recommendations is controversial.

What are the metabolic effects of carbohydrates in populations?

Residents in places associated with extreme longevity have traditionally consumed high carbohydrate diets, although associated healthy lifestyle factors may confound a causal interpretation.[76] By contrast, the PURE study in 18 countries reported that higher carbohydrate intake was associated with increased mortality, but here too, confounding is possible (eg, many people in low income countries subsist predominantly on starchy foods such as white rice).[77 78] In long term large cohorts studied in the US, total carbohydrate intake is also associated with higher mortality, though the type of dietary fat importantly modified risk.[79] Analogously, substitution of saturated fat with low GI carbohydrate is associated with lower risk of myocardial infarction, whereas substitution with high GI carbohydrates is associated with higher risk.[80]

Clinical trials have shown that low carbohydrate diets produce greater weight loss than lower fat diets in the short term, but this difference diminishes with time because of poor long term compliance.[81-85] The recent DIETFITs study reported a non-significant advantage for a healthy low carbohydrate versus healthy low fat diet, but both groups were counselled to limit sugar, refined grains, and processed foods in general.[86] Thus evidence suggests that the type of carbohydrates may have a greater effect on health outcomes than total amount for the general population. However, specific groups may respond differently to the carbohydrate quantity and quality.

Insulin resistance, metabolic syndrome, and diabetes

The metabolic syndrome (characterised by central adiposity, hypertension, dyslipidaemia, hyperglycaemia, and chronic inflammation) contributes importantly to risk of diabetes and cardiovascular disease worldwide. An underlying cause of this syndrome is insulin resistance and the associated increase in circulating insulin levels. Since insulin resistance reflects diminished ability to promote uptake of glucose into target organs, some investigators have proposed a reduced carbohydrate diet as part of treatment.[87] Observational and experimental data suggest that people with low levels of physical activity or obesity (major contributors to insulin resistance) may be especially sensitive to the adverse metabolic effects of diets high in sugar or GL[88 89]—perhaps explaining how Asian farming societies can maintain low adiposity and cardiovascular disease rates on white rice based diets.

People with diabetes may particularly benefit from reducing consumption of foods that increase postprandial blood glucose. Preliminary evidence suggests improved glycaemic control, lower triglycerides, and other metabolic advantages from low carbohydrate or low GI diets in both type 1[90] and type 2 diabetes,[91] though long term data on efficacy and safety are lacking.

Early insulin secretion

Early insulin secretion reflects the tendency of the pancreatic □ cells to release insulin rapidly after carbohydrate ingestion. This clinical measure, distinct from insulin resistance, can be assessed as the blood insulin concentration 30 minutes into a standard oral glucose tolerance test (insulin 30).[92] According to the carbohydrate-insulin model of obesity, people with high insulin secretion would be especially susceptible to weight gain on a high GL diet, a hypothesis with some support from laboratory, observational, and clinical research.[93-95] High insulin action in adipose tissue may have an anabolic effect that promotes fat deposition, leading to increased hunger and lower energy expenditure. A recent Mendelian randomisation study found that genetically determined insulin 30 results strongly predicted body mass index.[96] However, neither insulin 30 nor genetic risk was found to modify response to diet in DIETFITS, although GL was notably low in both diet groups of that study.[86]

Box 1: Carbohydrate controversies

- Would reduction in total carbohydrate intake (currently typically 45-65% of total energy) help control body weight in general population and susceptible subgroups?
- What is the role of a low carbohydrate diet in prevention and treatment of metabolic syndrome and type 2 diabetes, and in management of type 1 diabetes?
- Does ketosis induced by severe carbohydrate restriction provide any unique metabolic benefits and, if so, in what clinical settings would this diet be advisable?
- To what level should added (or free) sugars be restricted for optimum individual health and for the population as a whole?
- Would substitution of fructose in added sugars with glucose based sweeteners provide metabolic benefit or harm?
- Would substitution of free sugars with poorly digestible sugars, sugar alcohols, or artificial sweeteners provide health benefits or harms (eg, unexpected effects on the microbiome)?
- Would increased intake of resistant starch provide health benefits?
- What are the health effects of substituting whole grains with other high carbohydrate (fruits, legumes) or high fat (nuts, seeds, avocado) whole plant foods?
- What are the long term effects of different types of carbohydrates on population risk of cancer, neurodegenerative diseases, and cognitive function?
- Which carbohydrate based foods will provide an optimal combination of health benefits, environmental sustainability, cost, and public acceptability?

Salivary amylase

The diploid copy number of the salivary amylase gene (AMY1) varies widely, affecting amylase protein concentration in saliva. People with higher copy numbers have higher postprandial glycaemia after consumption of starchy (but not sugary) foods.[97] High AMY1 copy number may have provided a survival advantage, but its relevance to obesity and metabolic disease today remains unclear.[98-100] A recent study reported a diet-gene interaction such that the lowest body mass index was observed among people with high starch intake and low AMY1 copy number (reflecting low genetic capacity to digest starch).[99]

Conclusions

Although human populations have thrived on diets with widely varying macronutrient ratios, the recent influx of rapidly digestible, high GI carbohydrates in developed nations has contributed to the epidemics of obesity and cardiometabolic disease. Moreover, the traditional starch based diets of some developing nations have likely contributed to rising risk of chronic disease, with the decrease in physical activity and higher body mass index associated with rapid urbanisation.

However, carbohydrate quality seems to have a more important role in population health than carbohydrate amount. A strong case can be made for consumption of high GL grains, potato products, and added sugars (especially in drinks) being causally related to obesity, diabetes, cardiovascular disease, and some cancers; whereas non-starchy vegetables, whole fruits, legumes, and whole kernel grains appear protective. Nevertheless, the metabolic effects of total and high GI carbohydrate may vary among individuals, depending on the degree of insulin resistance, glucose intolerance, or other inherited or acquired biological predispositions.

Despite much new knowledge about the metabolic effects of carbohydrate and areas of broad consensus, many controversies remain. Most long term data derive from observational studies, which may be affected by confounding and other methodological problems. Most randomised controlled trials are short, rely on proxy measures, lack blinding, do not control for treatment intensity between dietary groups, and have limited compliance. Additional relevant considerations in effectiveness studies include the behavioural and environmental factors (eg, food availability and affordability) affecting compliance. The resolution of these controversies (summarised in box 1) will require mechanistically oriented feeding studies and long term clinical trials, prospective observational research, and examination of economic and environmental impacts.

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Food based dietary patterns and chronic disease prevention

Matthias B Schulze and colleagues discuss current knowledge on the associations between dietary patterns and cancer, coronary heart disease, stroke, and type 2 diabetes, focusing on areas of uncertainty and future research directions

Can specific foods provide health benefits? Will adopting a specific food pattern prevent major chronic diseases such as type 2 diabetes, cardiovascular disease, or cancer? Are exclusion diets—vegetarian or vegan diets or avoidance of foods containing gluten, lactose, or fructose—the key to good health? Should doctors advise patients to follow a paleolithic diet? The wide range of popular diet plans and concepts seems to continuously expand.[1] But to what extent are their purported benefits supported by scientific evidence?

We have qualitatively assessed the available evidence from recent systematic reviews of long term studies to summarise current understanding of foods or dietary patterns and risk of major chronic diseases. Given that nutrition research has been criticised for providing apparently implausible results,[2 3] which might contribute to the range of different popular diet concepts, we also discuss methodological approaches and specific challenges of conducting research on food intake patterns and health.

KEY MESSAGES

- Food based prevention of chronic disease risk should prioritise fruits, vegetables, whole grains and fish and lower consumption of red and processed meats and sugar sweetened drinks
- Higher consumption of nuts, legumes, vegetable oils, fermented dairy products, and coffee are further likely to confer benefit
- Evidence comes from prospective observational and intervention studies, each study design having different strengths and limitations. Both types of studies should contribute to the evidence base
- New analytical approaches are needed for nutrition research; eg, to account for measurement error, standardisation of exposure definitions, replication efforts, and the use of repeated dietary assessments

Evaluation of food patterns in nutrition studies

Given the relative stability of caloric intake by individual people, changes in dietary habits are generally characterised by substitution effects, where high consumption of some foods is associated with lower intake of other foods. This makes inferences about individual foods particularly challenging. For this reason, researchers also study food patterns, which account for inter-relations of food choices, represent the cumulative exposure to different diet components, and may have stronger effects on health than any single component.[4]

Food patterns can be defined as the quantities, proportions, variety, or combination of different foods and drinks in diets, and the frequency with which they are habitually consumed.[5] Given that food intake is a multi-dimensional exposure, there are obviously numerous different combinations of foods to potentially investigate. How these combinations are defined in nutrition research largely depends on the research question and study design. In intervention studies food intake is directly manipulated, but in observational studies exposure to food patterns is derived from self reported intake. Two main research methods have been used in this context.[4 6] The first is using a priori defined indices intended to capture specific dietary patterns, such as measuring conformity to dietary guidelines. The second is using data driven (exploratory) statistical methods (predominantly cluster analysis,[7] principal component and factor analysis,[4 8] and reduced rank regression[6 9]) to characterise major patterns of food intake. Both approaches allow ranking and quantifying adherence of study participants to these patterns, which is needed to evaluate their association with disease risk. Both approaches and the corresponding statistical methods have their own specific strengths and limitations (table 1).

An evidence based approach can be used to investigate causality between the intake of individual foods or dietary patterns and human health. This approach considers factors such as temporality, consistency, and sources of bias.[10] The strongest evidence is usually derived from randomised controlled trials because this design minimises confounding bias. But most of the data available come from observational studies on food intake and risk of chronic diseases. Prospective cohort studies have contributed substantially over the past 60 years to what is known today. Systematic reviews have summarised data from such studies and highlighted the importance of individual foods and dietary patterns in the prevention of chronic diseases.[11-14]

Health benefits and risks related to food intake and food patterns

Individual foods and health outcomes

Table 2 shows foods and beverages consistently associated in the literature with risk of cancer, type 2 diabetes, coronary heart disease, or stroke. Higher consumption of whole grains is related to lower risk for most endpoints,[11-14] whereas processed meat and unprocessed red meat consumption is associated with an increased risk.[11-14] Evidence for other foods is less consistent and might be disease specific— for example, fruits and vegetables are associated with lower risk of cancer,[14] coronary heart disease, and stroke,[12 13] but not type 2 diabetes.[12] The role of dairy foods remains unclear, with fermented dairy products being more convincingly related to lower cardiometabolic disease risk than others[11 12] and total dairy consumption seems relevant to colorectal cancer.[14] Sugar sweetened drinks are associated with increased risk of type 2 diabetes,[11 12] coronary heart disease,[12 13] and stroke,[13] and coffee consumption is associated with lower risk of type 2 diabetes,[11 12] cardiovascular disease,[12 18] and several cancers,[14 18] with beneficial effects being most prominent at consumption of 3-5 cups a day.[18]

Healthy food patterns and health outcomes

In prospective cohort studies the Mediterranean diet has been associated with lower risk for cancer, type 2 diabetes, and cardiovascular disease.[19 20] Similar findings were reported for the PREDIMED study, a randomised controlled trial of the Mediterranean diet supplemented with extra

virgin olive oil or nuts (fig 1).[21 22] The primary endpoint of cardiovascular events was about 30% lower in the intervention groups than in the control group,[21] and analyses of secondary endpoints support benefits for peripheral artery disease,[23] atrial fibrillation,[24] type 2 diabetes,[22] and breast cancer.[25] The Mediterranean diet generally refers to a diet encouraging high intake of fruits, nuts and seeds, vegetables, fish, legumes, and cereals and limiting the intake of meat and dairy products. Moderate intake of alcohol and olive oil as a major fat source have also been considered key components.[26]

Several other defined food patterns have been evaluated in terms of chronic disease risk. Indices measuring adherence to the Healthy Eating Index,[27] Alternative Healthy Eating Index,[28] and the Dietary Approaches to Stop Hypertension trial (DASH)[29 30] have been associated with lower risk of cardiovascular events, cancer, and type 2 diabetes (fig 2).[19 31]Table 3 shows the composition of these diets in comparison to the Mediterranean diet. Heterogeneity regarding the actual composition of these food scores exists between studies.[19] Although these diets may be recommendable, only the Mediterranean diet has been shown both in observational studies and a randomised trial to lower disease risk.

Notably, none of the diet plans captures fully the known benefits or detrimental effects of single foods; for example, the Mediterranean diet has traditionally not focused on whole grains or red meat.[32] Low fat dairy consumption is encouraged in the DASH diet, but discouraged in the Mediterranean diet, although the evidence for limiting dairy is sparse.[29] The Mediterranean diet emphasises olive oil, whereas the DASH diet discourages intake of fats and the Alternative Healthy Eating Index refers to high polyunsaturated fatty acid intakes, which would largely reflect vegetable fat sources other than olive oil. Still, these data corroborate previous findings that increased adherence to dietary patterns that emphasise fruits,

Box 1 Limitations of observational nutrition studies on foods and dietary patterns and suggestions for further research

Semiquantitative dietary data
- Use new assessment methods; eg, multiple sources to estimate usual intake
- Evaluate relative versus quantitative scores for dietary patterns and implications of differences in absolute intake levels

Measurement error
- Develop and use measurement error correction methods
- Investigate measurement error influences on dietary pattern composition
- Investigate validity and reliability of dietary patterns
- Develop new biomarkers of food intake and pattern adherence

Correlation of food intake and substitution
- Investigate specific food substitution by statistical modelling
- Investigate influence of energy adjustment in exploratory pattern analysis

Long term variability of intake
- Repeat diet assessments
- Investigate change in intake and subsequent risk

Varying scoring systems for defined food patterns
- Investigate influences of scoring alternatives
- Standardise scoring systems

Population specificity of exploratory patterns
- Replicate pattern associations in independent study populations with varying dietary habits

Different food classification and grouping
- Evaluate influence of food grouping on pattern structure
- Standardise food grouping

Unclear contribution of individual components to pattern association
- Systematically evaluate contribution of each component

Table 1 | Strengths and limitations of approaches to measuring food patterns

	Exploratory patterns		
Defined patterns	**Cluster analysis**	**Principal component and factor analysis**	**Reduced rank regression**
Strengths:			
Information on a variety of food items can be described by a single score	Information on a variety of food items can be described by a few mutually exclusive clusters of people	Information on a variety of food items can be described by a few underlying uncorrelated patterns	Information on a variety of food items can be described by a few underlying uncorrelated patterns
Easily reproducible and comparable	Does not require prior theory; based only on the data	Does not require prior theory; based only on the data	Combines pathophysiological knowledge (hypothesis oriented biomarkers) with study data (exploratory evaluation of food intake)
Particularly useful for evaluating associations between diet and disease endpoints		Particularly useful for identifying existing patterns of food consumption	Particularly useful for identifying patterns related to disease endpoints
Limitations:			
Subjective selection of components and cut-offs	Subjective decisions regarding cluster methods, numbers, distance measure	Subjective decisions regarding number of patterns	Subjective decisions regarding number of patterns
Single components are considered as independent	Descriptive analysis necessary to characterise patterns	Unclear which food items characterise the pattern	Unclear which food items characterise the pattern
Dependent on strengths of evidence for hypothesis	Procedure not related to outcomes	Procedure not related to outcomes	Dependent on knowledge and availability of response variables (eg, disease biomarkers)
Assumes additive effects		Only a low to moderate proportion of intake explained	Only a low to moderate proportion of response variation explained

Box 2 Limitations of randomised controlled trials on food intake and health

- Recruiting participants for long term changes to diets is difficult, and dropout rates are high
- Dietary advice and actual dietary consumption differ
- Identifying appropriate control diets is challenging, and treatment intensity between intervention and control arms may be imbalanced
- Blinding dietary interventions is frequently unfeasible
- Adherence problems limit the difference in exposure between intervention arms
- Long term interventions to investigate effects on chronic disease risk are costly

vegetables, whole grains, nuts, legumes, vegetable oils, and fish and minimise red meat, processed meat, and added sugars are associated with decreased risk of cardiovascular events, cancer, and type 2 diabetes.[5]

Controversies and research gaps in observational studies

Evidence for the benefits of fruits, vegetables, whole grains, fish, nuts, legumes, vegetable oils, dairy, coffee, and tea—and for a lower intake of red and processed meats and sugar sweetened drinks— comes largely from observational studies, which have multiple limitations (box 1).

Semiquantitative nature of food intake data in observational studies

Most prospective cohort studies use semiquantitative food frequency questionnaires. These instruments are not designed to provide an accurate estimate of absolute intake. In studies that use quantitative cut-offs to assign points for individual components of the pattern, uncertainty accumulates. Many pattern indices or scores are based on relative cut-offs, which might better reflect the semiquantitative nature of the underlying assessment instrument.[4] Such approaches usually evaluate intakes relative to the average consumption level in the studied population; for example, indices to capture exposure to the Mediterranean diet usually assign points for components based on centiles of population intake.[42] Similarly, pattern scores from principal component or factor analysis are based on food variables standardised to the population mean. Consequently, the average and variation in absolute intake of individual components may vary largely among populations investigated for the same dietary pattern. This is a substantial challenge for making inference on specific dose-response relations.

Measurement error

Measurement error is a major limitation of observational nutrition studies.[43] Researchers have tried to tackle the varying validity and reliability of dietary questionnaires to assess different components of a dietary pattern,[44] but their results have hardly been used in investigations of dietary patterns and health outcomes. Studies evaluating the validity and reliability of dietary patterns are also scarce.[45 46] New biomarkers of food intake or food pattern exposure may complement or even substitute traditional dietary assessments.[47] The use of repeated measurements of food intake over the follow-up period in cohort studies improves accuracy.

Table 2 Associations between intake of foods and chronic disease risk based on published meta-analyses and reviews

Food	Cancer	Type 2 diabetes	Coronary heart disease	Stroke
Whole grains	↓14	↓11 12	↓12 13	
Vegetables	↓14		↓12 13	↓12 13
Fruits	↓14		↓12 13	↓12 13
(Fermented) dairy products	↓14	↓11 12		↓12
Red meat	↓14	↑11 12	↑13	↑12 13
Processed meat	↓14	↑11 12	↑12 13	↑12 13
Fish			↓12 13	↓12 13
Olive oil		↓15		↓16
Eggs		↑12		
Nuts		↓12	↓12 13	
Cocoa/chocolate			↓17	↓17
Coffee	↓14 18	↓11 12 18	↓12 18	↓12 18
Tea		↓12	↓12	↓12
Sugar sweetened beverages		↑11 12	↑12 13	↑13

Variation in pattern scoring systems

Many studies have evaluated a priori defined dietary patterns, but the composition of patterns has varied considerably.[19 20 31] This limitation also applies to randomised trials, where differences in the definition of intervention diets are a major challenge.[48] Investigations of both single food groups and food patterns are frequently constrained by the information collected in food frequency questionnaires. Although it seems clear that foods with similar characteristics can be put into aggregated groups, broader groups are less homogeneous than narrower ones. The influence of regional foods and of food classifications in the definition and categorisation of food patterns is still understudied.[4 49] Comparing different definitions for conceptually similar diets would be an important step forward; for example, Tong and colleagues compared different indices of the Mediterranean diet and cardiovascular disease.[50]

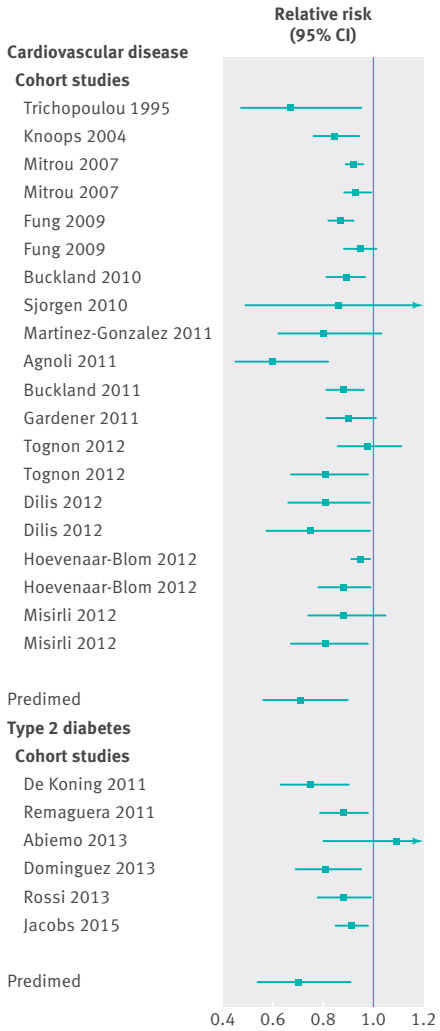

Fig 1 | Mediterranean diet and risk of cardiovascular events and type 2 diabetes in cohort studies according to systematic reviews[19 20] and the PREDIMED randomised trial.[21 22]

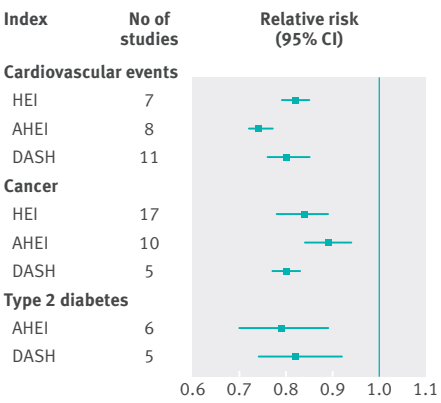

Fig 2 | Dietary patterns and risk of cardiovascular events,[31] cancer,[31] and type 2 diabetes[19] in meta-analyses of prospective cohort studies. AHEI=Alternative Healthy Eating Index; DASH=Dietary Approaches to Stop Hypertension; HEI=Healthy Eating Index.

Food patterns versus individual food components

Food patterns pre-empt potential dietary confounding by other aspects of the diet, increase the ability to assess stronger effects due to the cumulative effects of many features of the diet, and allow assessment of the interaction among synergistic components. But observed associations could be due to single components rather than the overall dietary pattern. This can be tackled by systematic analysis of the effect of single components for the overall association; for example, the reduced diabetes risk observed for the Mediterranean diet in the Europe-wide EPIC-InterAct study was partly attributable to moderate alcohol, higher olive oil, and lower meat consumption.[51] The evaluation of overall dietary patterns could also mask the effects of individual foods; for example, exploratory patterns including whole grains as components showed only marginal inverse association with diabetes risk,[52-57] whereas whole grains were inversely associated.[58 59] Also, dietary patterns usually capture only a fraction of variation in food intake, which leaves a large space of potential effects related to foods not included as components of the pattern.

Generalisability of data driven food patterns

Exploratory patterns are specific to the population investigated, so the contribution of single study findings to evidence based recommendations is limited. Although exploratory food patterns might have similar components, clear criteria for their consistency needed to summarise observations in meta-analysis are lacking. Replicating study findings in other populations is important, as has been applied in studies using reduced rank regression.[60] A common element of exploratory pattern methods is that investigators must make arbitrary decisions when, for example, selecting the appropriate number of patterns to investigate further (table 1).

Confounding by diet—food substitution

Observational studies are more prone to confounding bias than randomised controlled trials. Confounding is not only related to other lifestyle factors and general risk factors, but to additional food exposures. Food intake is characterised by combinations and substitutions, so appropriate control of correlated foods is essential in studies investigating individual foods as potential risk factors. Cohort studies provide the possibility to model specific isocaloric food substitutions—an underused approach. When evaluating reductions in red meat intake, for example, taking into account the substitution of other protein sources can be informative.[61] Pattern analysis might account for intercorrelations among foods.

Timescale of dietary assessment in long term studies

Inferences from observational studies are usually based on comparisons between different groups that differ in baseline intake; for example, comparing study participants who consume sugar sweetened drinks daily with those who consume them less frequently. Cohort studies can, however, evaluate changes in food consumption if repeated measures of intake are available. Increasing diet quality, assessed as adherence to the Alternative Healthy Eating Index, DASH, or Mediterranean diets, has been found to decrease mortality risk compared with unchanged adherence.[62] Observational designs that use repeated measurements to assess changes in food patterns can almost simulate interventional trials and provide strong evidence on causality if relevant confounders are controlled.

Potential and limitations of randomised trials

Randomised controlled trials are less prone to confounding bias and have the ability to control exposure differences between groups, allowing for quantification of dose-response relations. But randomised controlled trials testing dietary interventions are considerably more challenging than standard drug trials (box 2).[63]

One challenge is the difficulty of identifying an appropriate control when evaluating foods or food patterns.[64] If control participants do not receive a placebo or a comparative intervention, there is strong potential for expectation bias (expected benefit in the intervention group versus expected lack of benefit in the control group). The Women's Health Initiative Dietary Modification Trial, for example, compared a low fat intervention group with intensive behaviour modification counselling to increase fruit, vegetable, and grain consumption with a "usual diet" group receiving diet related education materials only.[65] Although active controls can be designed, such trials are difficult to blind.

Studies depending on dietary advice may not result in sufficiently large differences in food consumption between intervention and control groups due to suboptimal

Table 3 Key components of the Mediterranean, DASH (Dietary Approaches to Stop Hypertension), and Alternative Healthy Eating dietary pattern scores

Food	Mediterranean diet[26 32]	DASH[29 30]	Alternative Healthy Eating Index[28]
Cereals*	Encouraged	Encouraged (whole grain)	Encouraged (whole grain)
Vegetables	Encouraged	Encouraged	Encouraged
Fruits	Encouraged	Encouraged	Encouraged
Nuts, legumes	Encouraged	Encouraged	Encouraged
Fish	Encouraged	Encouraged	Encouraged
Meat†	Discouraged	Fatty meat discouraged	Red and processed meat discouraged
Dairy products	Discouraged	Encouraged (low fat)	-
Fats	Olive oil	Discouraged	Fat sources high in long chain omega3 and total polyunsaturated fatty acids, low in trans fatty acids
Sweets/sweetened beverages	Discouraged	Discouraged	Discouraged
Alcohol	In moderation	-	In moderation
Sodium¶	-	Restricted	Restricted

*Related to total cereals or whole grain cereals, depending on score.
†Related to total meats or red and processed meats, depending on score.
¶Considered in some scores

compliance of participants—this critique has been raised for large randomised dietary trials, such as the PREDIMED study[66] and the Women's Health Initiative Dietary Modification Trial.[67] For large trials with thousands of participants, changing people's habitual dietary patterns demands an unparalleled workload. In addition, the high costs of running long term intervention studies makes it unlikely that associations for multiple foods, food substitutions, and food patterns can be tested for hard outcome endpoints. Still, randomised controlled trials can support or refute observations using surrogate markers of disease. The DASH trial, for example, was a controlled feeding trial with a dietary pattern rich in fruits, vegetables, and low fat dairy products, which reduced blood pressure.[29] This could be extrapolated to a reduction in cardiovascular event risk, although no randomised trial has been conducted to evaluate if the DASH diet affects incidence of cardiovascular disease. Surrogate (intermediate) markers such as blood pressure can be important mediating factors between food intake, food pattern, and disease risk.

Shorter term randomised trials are not only a tool to support (or refute) the biological causality of observations but can also be used to determine potential effect sizes. But the triangulation of evidence from different sources[63] might be difficult owing to the different timing and duration of exposures in long term cohort studies versus short term randomised controlled trials of intermediate endpoints, as well as the choice of diet sensitive surrogate markers.[68] Still, this approach is useful for the popular diet concepts for which evidence on their long term relevance for chronic disease prevention is currently lacking.

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Dietary and nutritional approaches for prevention and management of type 2 diabetes

Common ground on dietary approaches for the prevention, management, and potential remission of type 2 diabetes can be found, argue **Nita G Forouhi and colleagues**

Dietary factors are of paramount importance in the management and prevention of type 2 diabetes. Despite progress in formulating evidence based dietary guidance, controversy and confusion remain. In this article, we examine the evidence for areas of consensus as well as ongoing uncertainty or controversy about dietary guidelines for type 2 diabetes. What is the best dietary approach? Is it possible to achieve remission of type 2 diabetes with lifestyle behaviour changes or is it inevitably a condition causing progressive health decline? We also examine the influence of nutrition transition and population specific factors in the global context and discuss future directions for effective dietary and nutritional approaches to manage type 2 diabetes and their implementation.

Why dietary management matters but is difficult to implement

Diabetes is one of the biggest global public health problems: the prevalence is estimated to increase from 425 million people in 2017 to 629 million by 2045, with linked health, social, and economic costs.[1] Urgent solutions for slowing, or even reversing, this trend are needed, especially from investment in modifiable factors including diet, physical activity, and weight. Diet is a leading contributor to morbidity and mortality worldwide according to the Global Burden of Disease Study carried out in 188 countries.[2] The importance of nutrition in the management and prevention of type 2 diabetes through its effect on weight and metabolic control is clear. However, nutrition is also one of the most controversial and difficult aspects of the management of type 2 diabetes.

The idea of being on a "diet" for a chronic lifelong condition like diabetes is enough to put many people off as knowing what to eat and maintaining an optimal eating pattern are challenging. Medical nutrition therapy was introduced to guide a systematic and evidence based approach to the management of diabetes through diet, and its effectiveness has been demonstrated,[3] but difficulties remain. Although most diabetes guidelines recommend starting pharmacotherapy only after first making nutritional and physical activity lifestyle changes, this is not always followed in practice globally. Most physicians are not trained in nutrition interventions and this is a barrier to counselling patients.[4 5] Moreover, talking to patients about nutrition is time consuming. In many settings, outside of specialised diabetes centres where trained nutritionists/educators are available, advice on nutrition for diabetes is, at best, a printed menu given to the patient. In resource poor settings, when type 2 diabetes is diagnosed, often the patient leaves the clinic with a list of new medications and little else. There is wide variation in the use of dietary modification alone to manage type 2 diabetes: for instance, estimates of fewer than 5-10% of patients with type 2 diabetes in India[6] and 31% in the UK are reported, although patients treated by lifestyle measures may be less closely managed than patients on medication for type 2 diabetes.[7] Although systems are usually in place to record and monitor process measures for diabetes care in medical records, dietary information is often neglected, even though at least modest attention to diet is needed to achieve adequate glycaemic control. Family doctors and hospital clinics should collect this information routinely but how to do this is a challenge.[5 8]

Progress has been made in understanding the best dietary advice for diabetes but broader problems exist. For instance, increasing vegetable and fruit intake is recommended by most dietary guidelines but their cost is prohibitively high in many settings: the cost of two servings of fruits and three servings of vegetables a day per individual (to fulfil the "5-a-day" guidance) accounted for 52%, 18%, 16%, and 2% of household income in low, low to middle, upper to middle, and high income countries, respectively.[9] An expensive market of foods labelled for use by people with diabetes also exists, with products often being no healthier, and sometimes less healthy, than regular foods. After new European Union legislation, food regulations in some countries, including the UK, were updated as recently as July 2016 to ban such misleading labels. This is not the case elsewhere, however, and what will happen to such regulation after the UK leaves the European Union is unclear, which highlights the importance of the political environment.

Evidence for current dietary guidelines

In some, mostly developed, countries, dietary guidelines for the management of diabetes have evolved from a focus on a low fat diet to the recognition that more important considerations are macronutrient quality (that is, the type versus the quantity of macronutrient), avoidance of processed

KEY MESSAGES

- Considerable evidence supports a common set of dietary approaches for the prevention and management of type 2 diabetes, but uncertainties remain
- Weight management is a cornerstone of metabolic health but diet quality is also important
- Low carbohydrate diets as the preferred choice in type 2 diabetes is controversial. Some guidelines maintain that no single ideal percentage distribution of calories from different macronutrients (carbohydrates, fat, or protein) exists, but there are calls to review this in light of emerging evidence on the potential benefits of low carbohydrate diets for weight management and glycaemic control
- The quality of carbohydrates such as refined versus whole grain sources is important and should not get lost in the debate on quantity
- Recognition is increasing that the focus of dietary advice should be on foods and healthy eating patterns rather than on nutrients. Evidence supports avoiding processed foods, refined grains, processed red meats, and sugar sweetened drinks and promoting the intake of fibre, vegetables, and yoghurt. Dietary advice should be individually tailored and take into account personal, cultural, and social factors
- An exciting recent development is the understanding that type 2 diabetes does not have to be a progressive condition but instead there is potential for remission with dietary intervention

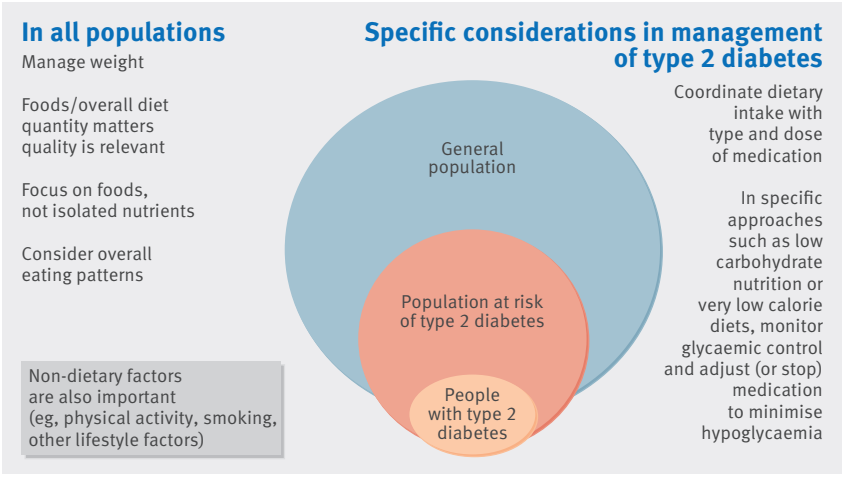

Fig 1 | Dietary advice for different populations for the prevention and management of type 2 diabetes

foods (particularly processed starches and sugars), and overall dietary patterns. Many systematic reviews and national dietary guidelines have evaluated the evidence for optimal dietary advice, and we will not repeat the evidence review.[10-18] We focus instead in the following sections on some important principles where broad consensus exists in the scientific and clinical community and highlight areas of uncertainty, but we begin by outlining three underpinning features.

Firstly, an understanding of healthy eating for the prevention and management of type 2 diabetes has largely been derived from long term prospective studies and limited evidence from randomised controlled trials in general populations, supplemented by evidence from people with type 2 diabetes. Many published guidelines and reviews have applied grading criteria and this evidence is often of moderate quality in the hierarchy of evidence that places randomised controlled trials at the top. Elsewhere, it is argued that different forms of evidence evaluating consistency across multiple study designs including large population based prospective studies of clinical endpoints, controlled trials of intermediate pathways, and where feasible randomised trials of clinical endpoints should be used collectively for evidence based nutritional guidance.[19]

Secondly, it is now recognised that dietary advice for both the prevention and management of type 2 diabetes should converge, and they should not be treated as different entities (fig 1). However, in those with type 2 diabetes, the degree of glycaemic control and type and dose of diabetes medication should be coordinated with dietary intake.[12] With some dietary interventions, such as very low calorie or low carbohydrate diets, people with diabetes would usually stop or reduce their diabetes medication and be monitored closely, as reviewed in a later section.

Thirdly, while recognising the importance of diet for weight management, there is now greater understanding[10] of the multiple pathways through which dietary factors exert health effects through both obesity dependent and obesity independent mechanisms. The influence of diet on weight, glycaemia, and glucose-insulin homeostasis is directly relevant to glycaemic control in diabetes, while other outcomes such as cardiovascular complications are further influenced by the effect of diet on blood lipids, apolipoproteins, blood pressure, endothelial function, thrombosis, coagulation, systemic inflammation, and vascular adhesion. The effect of food and nutrients on the gut microbiome may also be relevant to the pathogenesis of diabetes but further research is needed. Therefore, diet quality and quantity over the longer term are relevant to the prevention and management of diabetes and its complications through a wide range of metabolic and physiological processes.

Areas of consensus in guidelines

Weight management

Type 2 diabetes is most commonly associated with overweight or obesity and insulin resistance. Therefore, reducing weight and maintaining a healthy weight is a core part of clinical management. Weight loss is also linked to improvements in glycaemia, blood pressure, and lipids and hence can delay or prevent complications, particularly cardiovascular events.

Energy balance

Most guidelines recommend promoting weight loss among overweight or obese individuals by reducing energy intake. Portion control is one strategy to limit energy intake together with a healthy eating pattern that focuses on a diet composed of whole or unprocessed foods combined with physical activity and ongoing support.

Dietary patterns

The evidence points to promoting patterns of food intake that are high in vegetables, fruit, whole grains, legumes, nuts, and dairy products such as yoghurt but with some cautions. Firstly, some dietary approaches (eg, low carbohydrate diets) recommend restricting the intake of fruits, whole grains, and legumes because of their sugar or starch content. For fruit intake, particularly among those with diabetes, opinion is divided among scientists and clinicians (see appendix on bmj.com). Many guidelines continue to recommend fruit, however, on the basis that fructose intake from fruits is preferable to isocaloric intake of sucrose or starch because of the additional micronutrient, phytochemical, and fibre content of fruit. Secondly, despite evidence from randomised controlled trials and prospective studies[10] that nuts may help prevent type 2 diabetes, some (potentially misplaced) concern exists about their high energy content. Further research in people with type 2 diabetes should help to clarify this.

There is also consensus on the benefits of certain named dietary patterns such as the Mediterranean diet for prevention and management of type 2 diabetes. Expert guidelines also support other healthy eating patterns that take account of local sociocultural factors and personal preferences.

Foods to avoid

Consensus exists on reducing or avoiding the intake of processed red meats, refined grains and sugars (especially sugar sweetened drinks) both for prevention and management of type 2 diabetes, again with some cautions. Firstly, for unprocessed red meat, the evidence of possible harm because of the development of type 2 diabetes is less consistent and of a smaller magnitude. More research is needed on specific benefits or harms in people with type 2 diabetes. Secondly, evidence is increasing on the relevance of carbohydrate quality: that is that whole grains and fibre are better choices than refined grains and that fibre intake should be at least as high in people with type 2 diabetes as recommended for the general population, that diets that have a higher glycaemic index and load are associated with an increased risk of type 2 diabetes, and that there is a modest glycaemic benefit in replacing foods with higher glycaemic load with foods with low glycaemic load. However, debate continues about

the independence of these effects from the intake of dietary fibre. Some evidence exists that consumption of potato and white rice may increase the risk of type 2 diabetes but this is limited and further research is needed.

Moreover, many guidelines also highlight the importance of reducing the intake of in foods high in sodium and trans fat because of the relevance of these specifically for cardiovascular health.

Areas of uncertainty in guidelines

Optimal macronutrient composition

One of the most contentious issues about the management of type 2 diabetes has been on the best macronutrient composition of the diet. Some guidelines continue to advise macronutrient quantity goals, such as the European or Canadian recommendation of 45–60% of total energy as carbohydrate, 10–20% as protein, and less than 35% as fat,[13 20] or the Indian guidelines that recommend 50-60% energy from carbohydrates, 10-15% from protein, and less than 30% from fat.[21] In contrast, the most recent nutritional guideline from the American Diabetes Association concluded that there is no ideal mix of macronutrients for all people with diabetes and recommended individually tailored goals.[12] Alternatively, a low carbohydrate diet for weight and glycaemic control has gained popularity among some experts, clinicians, and the public (reviewed in a later section). Others conclude that a low carbohydrate diet combined with low saturated fat intake is best.[22]

For weight loss, three points are noteworthy when comparing dietary macronutrient composition. Firstly, evidence from trials points to potentially greater benefits from a low carbohydrate than a low fat diet but the difference in weight loss between diets is modest.[23] Secondly, a comparison of named diet programmes with different macronutrient composition highlighted that the critical factor in effectiveness for weight loss was the level of adherence to the diet over time.[24] Thirdly, the quality of the diet in low carbohydrate or low fat diets is important.[25 26]

Research to date on weight or metabolic outcomes in diabetes is complicated by the use of different definitions for the different macronutrient approaches. For instance, the definition of a low carbohydrate diet has ranged from 4% of daily energy intake from carbohydrates (promoting nutritional ketosis) to 40%.[15] Similarly, low fat diets have been defined as fat intake less than 30% of daily energy intake or substantially lower. Given these limitations, the best current approach may be an emphasis on the use of individual assessment for dietary advice and a focus on the pattern of eating that most readily allows the individual to limit calorie intake and improve macronutrient quality (such as avoiding refined carbohydrates).

Fish

Regular fish intake of at least two servings a week, including one serving of oily fish (eg, salmon, mackerel, and trout) is recommended for cardiovascular risk prevention but fish intake has different associations with the risk of developing type 2 diabetes across the world—an inverse association, no association, and a positive association.[27] It is thought that the type of fish consumed, preparation or cooking practices, and possible contaminants (eg, methyl mercury and polychlorinated biphenyls) vary by geographical location and contributed to this heterogeneity. More research is needed to resolve whether fish intake should be recommended for the prevention of diabetes. However, the current evidence supports an increase in consumption of oily fish for individuals with diabetes because of its beneficial effects on lipoproteins and prevention of coronary heart disease. Most guidelines agree that omega 3 polyunsaturated fatty acid (fish oil) supplementation for cardiovascular prevention in people with diabetes should not be recommended but more research is needed and the results of the ASCEND (A Study of Cardiovascular Events in Diabetes) trial should help to clarify this.[28]

Dairy

Dairy foods are encouraged for the prevention of type 2 diabetes, with more consistent evidence of the benefits of fermented dairy products, such as yoghurt. Similar to population level recommendations about limiting the intake of foods high in saturated fats and replacing them with foods rich in polyunsaturated fat, the current advice for diabetes also favours low fat dairy products but this is debated. More research is needed to resolve this question.

Oils

Uncertainty continues about certain plant oils and tropical oils such as coconut or palm oil as evidence from prospective studies or randomised controlled trials on clinical events is sparse or non-existent. However, olive oil, particularly extra virgin olive oil, has been studied in greater detail with evidence of potential benefits for the prevention and management of type 2 diabetes[29] and the prevention of cardiovascular disease within the context of a Mediterranean diet[30] (see article in this series on dietary fats).[31]

Difficulties in setting guidelines

Where dietary guidelines exist (in many settings there are none, or they are adapted from those in developed countries and therefore may not be applicable to the local situation), they vary substantially in whether they are evidence based or opinion pieces, and updated in line with scientific progress or outdated. Their accessibility—both physical availability (eg, through a website or clinic) and comprehensibility—for patients and healthcare professionals varies. They vary also in scope, content, detail, and emphasis on the importance of individualised dietary advice, areas of controversy, and further research needs. The quality of research that informs dietary guidelines also needs greater investment from the scientific community and funders. Moreover, lack of transparency in the development of guidelines and bias in the primary nutritional studies can undermine the development of reliable dietary guidelines; recommendations for their improvement must be heeded.[32]

Reversing type 2 diabetes through diet

Type 2 diabetes was once thought to be irreversible and progressive after diagnosis, but much interest has arisen about the potential for remission. Consensus on the definition of remission is a sign of progress: glucose levels lower than the diagnostic level for diabetes in the absence of medications for hyperglycaemia for a period of time (often proposed to be at least one year).[33 34] However, the predominant role of energy deficit versus macronutrient composition of the diet in achieving remission is still controversial.

Remission through a low calorie energy deficit diet

Although the clinical observation of the lifelong, steadily progressive nature of type 2 diabetes was confirmed by the UK Prospective Diabetes Study,[35] rapid normalisation of fasting plasma glucose after bariatric surgery suggested that deterioration was not inevitable.[36] As the main change was one of sudden calorie restriction, a low calorie diet was used as a tool to study the mechanisms involved. In one study of patients with type 2 diabetes, fasting plasma glucose normalised within seven days of following a low calorie diet.[37] This normalisation through diet occurred despite simultaneous withdrawal of metformin therapy. Gradually over eight weeks, glucose stimulated insulin secretion returned to normal.[37] Was this a consequence of calorie restriction or composition of the diet? To achieve the degree of weight loss obtained (15 kg), about 610 kcal a day was provided—510 kcal as a liquid formula diet and about 100 kcal as non-starchy vegetables. The formula diet consisted of 59 g of carbohydrate (30 g as sugars), 11.4 g of fat, and 41 g of protein, including required vitamins and minerals.

This high "sugar" approach to controlling blood glucose may be surprising but the critical aspect is not what is eaten but the gap between energy required and taken in. Because of this deficit, the body must use previously stored energy. Intrahepatic fat is used first, and the 30% decrease in hepatic fat in the first seven days appears sufficient to normalise the insulin sensitivity of the liver.[37] In addition, pancreatic fat content fell over eight weeks and beta cell function improved. This is because insulin secretory function was regained by re-differentiation after fat removal.[38]

The permanence of these changes was tested by a nutritional and behavioural approach to achieve long term isocaloric eating after the acute weight loss phase.[39] It was successful in keeping weight steady over the next six months of the study. Calorie restriction was associated with both hepatic and pancreatic fat content remaining at the low levels achieved. The initial remission of type 2 diabetes was closely associated with duration of diabetes, and the individuals with type 2 diabetes of shorter duration who achieved normal levels of blood glucose maintained normal physiology during the six month follow-up period. Recently, 46% of a UK primary care cohort remained free of diabetes at one year during a structured low calorie weight loss programme (the DiRECT trial).[40] These results are convincing, and four years of follow-up are planned.

A common criticism of the energy deficit research has been that very low calorie diets may not be achievable or sustainable. Indeed, adherence to most diets in the longer term is an important challenge.[24] However, Look-AHEAD, the largest randomised study of lifestyle interventions in type 2 diabetes (n=5145), randomised individuals to intensive lifestyle management, including the goal to reduce total calorie intake to 1200-1800 kcal/d through a low fat diet assisted by liquid meal replacements, and this approach achieved greater weight loss and non-diabetic blood glucose levels at year 1 and year 4 in the intervention than the control group.[41]

Considerable interest has arisen about whether low calorie diets associated with diabetes remission can also help to prevent diabetic complications. Evidence is sparse because of the lack of long term follow-up studies but the existing research is promising. A return to the non-diabetic state brings an improvement in cardiovascular risk (Q risk decreasing from 19.8% to 5.4%)[39]; case reports of individuals facing foot amputation record a return to a low risk state over 2-4 years with resolution of painful neuropathy[42 43]; and retinal complications are unlikely to occur or progress.[44] However, other evidence highlights that worsening of treatable maculopathy or proliferative retinopathy may occur following a sudden fall in plasma glucose levels,[45 46] so retinal imaging in 4-6 months is recommended for individuals with more than minimal retinopathy if following a low calorie remission diet. Annual review is recommended for all those in the post-diabetic state, and a "diabetes in remission" code (C10P) is now available in the UK.[34]

Management or remission through a low carbohydrate diet

Before insulin was developed as a therapy, reducing carbohydrate intake was the main treatment for diabetes.[47 48] Carbohydrate restriction for the treatment of type 2 diabetes has been an area of intense interest because, of all the macronutrients, carbohydrates have the greatest effect on blood glucose and insulin levels.[49]

In a review by the American Diabetes Association, interventions of low carbohydrate (less than 40% of calories) diets published from 2001 to 2010 were identified.[15] Of 11 trials, eight were randomised and about half reported greater improvement in HbA1c on the low carbohydrate diet than the comparison diet (usually a low fat diet), and a greater reduction in the use of medicines to lower glucose. Notably, calorie reduction coincided with carbohydrate restriction in many of the studies, even though it was not often specified in the dietary counselling. One of the more highly controlled studies was an inpatient feeding study,[50] which reported a decline in mean HbA1c from 7.3% to 6.8% (P=0.006) over just 14 days on a low carbohydrate diet.

For glycaemia, other reviews of evidence from randomised trials on people with type 2 diabetes have varying conclusions.[51-56] Some concluded that low carbohydrate diets were superior to other diets for glycaemic control, or that a dose response relationship existed, with stricter low carbohydrate restriction resulting in greater reductions in glycaemia. Others cautioned about short term beneficial effects not being sustained in the longer term, or found no overall advantage over the comparison diet. Narrative reviews have generally been more emphatic on the benefits of low carbohydrate diets, including increased satiety, and highlight the advantages for weight loss and metabolic parameters.[57 58] More recently, a one year clinic based study of the low carbohydrate diet designed to induce nutritional ketosis (usually with carbohydrate intake less than 30 g/d) was effective for weight loss, and for glycaemic control and medication reduction.[59] However, the study was not randomised, treatment intensity differed substantially in the intervention versus usual care groups, and participants were able to select their group.

Concerns about potential detrimental effects on cardiovascular health have been raised as low carbohydrate diets are usually high in dietary fat, including saturated fat. For lipid markers as predictors of future cardiovascular events, several studies found greater improvements in high density lipoprotein cholesterol and triglycerides with no relative worsening of low density lipoprotein cholesterol in patients with type 2 diabetes following carbohydrate restriction,[15] with similar conclusions in non-diabetic populations.[57 60-62] Low density lipoprotein cholesterol tends to decline more, however, in a low fat comparison diet[61 63] and although low density lipoprotein cholesterol may not worsen with a low carbohydrate diet[63] in the short term, the longer term effects are unclear. Evidence shows that low carbohydrate intake can lower the more atherogenic small, dense low density lipoprotein particles.[57 64] Because some individuals may experience an increase in serum low density lipoprotein cholesterol when following a low carbohydrate diet high in saturated fat, monitoring is important.

Another concern is the effect of the potentially higher protein content of low carbohydrate diets on renal function. Evidence from patients with type 2 diabetes with normal baseline renal function and from individuals without diabetes and with normal or mildly impaired renal function has not shown worsening renal function at one or up to two years of follow-up, respectively.[22 65-67] Research in patients with more severely impaired renal function, with or without diabetes, has not been reported to our knowledge. Other potential side effects of a very low carbohydrate diet include headache, fatigue, and muscle cramping but these side effects can be avoided by adequate fluid and sodium intake, particularly in the first week or two after starting the diet when diuresis is greatest. Concern about urinary calcium loss and a possible contribution to increased future risk of kidney stones or osteoporosis[68] have not been verified[69] but evidence is sparse and warrants further investigation. The long term effects on cardiovascular disease and chronic kidney disease in patients with diabetes need further evaluation.

Given the hypoglycaemic effect of carbohydrate restriction, patients with diabetes who adopt low carbohydrate diets and their clinicians must understand how to avoid hypoglycaemia by appropriately reducing glucose lowering medications.

Finally, low carbohydrate diets can restrict whole grain intake and although some low carbohydrate foods can provide the fibre and micronutrients contained in grains, it may require greater effort to incorporate such foods. This has led some experts to emphasise restricting refined starches and sugars but retaining whole grains.

Nutrition transition and population specific factors

Several countries in sub-Saharan Africa, South America, and Asia (eg, India and China) have undergone rapid nutrition transition in the past two decades. These changes have paralleled economic growth, foreign investment in the fast food industry, urbanisation, direct-to-consumer marketing of foods high in calories, sale of ultraprocessed foods, and as a result, lower consumption of traditional diets. The effect of these factors on nutrition have led to obesity and type 2 diabetes on the one hand, and co-existing undernutrition and micronutrient deficiencies on the other.

Dietary shifts in low and middle income countries have been stark: in India, these include a substantial increase in fat intake in the setting of an already high carbohydrate intake, with a slight increase in total energy and protein,[70] and a decreasing intake of coarse cereals, pulses, fruits, and vegetables[71]; in China, animal protein and fat as a percentage of energy has also increased, while cereal intake has decreased.[72] An almost universal increase in the intake of caloric beverages has also occurred, with sugar sweetened soda drinks being the main beverage contributing to energy intake, for example among adults and children in Mexico,[73] or the substantial rise in China in sales of sugar sweetened drinks from 10.2 L per capita in 1998 to 55.0 L per capita in 2012.[74] The movement of populations from rural to urban areas within a country may also be linked with shifts in diets to more unhealthy patterns,[75] while acculturation of immigrant populations into their host countries also results in dietary shifts.[76]

In some populations, such as South Asians, rice and wheat flour bread are staple foods, with a related high carbohydrate intake (60-70% of calories).[77] Although time trends show that intake of carbohydrate has decreased among South Asian Indians, the quality of carbohydrates has shifted towards use of refined carbohydrates.[71] The use of oils and traditional cooking practices also have specific patterns in different populations. For instance, in India, the import and consumption of palm oil, often incorporated in the popular oil *vanaspati* (partially hydrogenated vegetable oil, high in trans fats), is high.[78] Moreover, the traditional Indian cooking practice of frying at high temperatures and re-heating increases trans fatty acids in oils.[79] Such oils are low cost, readily available, and have a long shelf life, and thus are more attractive to people from the middle and low socioeconomic strata but their long term effects on type 2 diabetes are unknown.

Despite the nutrition transition being linked to an increasing prevalence of type 2 diabetes, obesity and other non-communicable diseases, strong measures to limit harmful foods are not in place in many countries. Regulatory frameworks including fiscal policies such as taxation for sugar sweetened beverages need to be strengthened to be effective and other preventive interventions need to be properly implemented. Efforts to control trans fatty acids in foods have gained momentum but are largely confined to developed countries. To reduce consumption in low and middle income countries will require both stringent regulations and the availability and development of alternative choices of healthy and low cost oils, ready made food products, and consumer education.[80] The need for nutritional labelling is important but understanding nutrition labels is a problem in populations with low literacy or nutrition awareness, which highlights the need for educational activities and simpler forms of labelling. The role of dietary/nutritional factors in the predisposition of some ethnic groups to developing type 2 diabetes at substantially lower levels of obesity than European populations[81] is poorly researched and needs investigation.

Conclusion

Despite the challenges of nutritional research, considerable progress has been made in formulating evidence based dietary guidance and some common principles can be agreed that should be helpful to clinicians, patients, and the public. Several areas of uncertainty and controversy remain and further research is needed to resolve these. While adherence to dietary advice is an important challenge, weight management is still a cornerstone in diabetes management, supplemented with new developments, including the potential for the remission of type 2 diabetes through diet.

Web Extra: Extra material supplied by the author.

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Contributors and sources: The authors have experience and research interests in the prevention and management of type 2 diabetes (NGF, AM, VM, RT, WY), in guideline development (NGF, AM, VM, WY), and in nutritional epidemiology (NGF, VM). Sources of information for this article included published dietary

Future directions

- Nutritional research is difficult. Although much progress has been made to improve evidence based dietary guidelines, more investment is needed in good quality research with a greater focus on overcoming the limitations of existing research. Experts should also strive to build consensus using research evidence based on a combination of different study designs, including randomised experiments and prospective observational studies
- High quality research is needed that compares calorie restriction and carbohydrate restriction to assess effectiveness and feasibility in the long term. Consensus is needed on definitions of low carbohydrate nutrition. Use of the findings must take account of individual preferences, whole diets, and eating patterns
- Further research is needed to resolve areas of uncertainty about dietary advice in diabetes, including the role of nuts, fruits, legumes, fish, plant oils, low fat versus high fat dairy, and diet quantity and quality
- Given recent widespread recommendations (such as from the World Health Organization[82] and the UK Scientific Advisory Committee on Nutrition[83]) to reduce free sugars to under 10% or even 5% of total energy intake in the general population and to avoid sugar sweetened drinks, we need targeted research on the effect of non-nutritive sweeteners on health outcomes in people with diabetes and in the whole population
- Most dietary guidelines are derived from evidence from Western countries. Research is needed to better understand the specific aetiological factors that link diet/nutrition and diabetes and its complications in different regions and different ethnic groups. This requires investment in developing prospective cohorts and building capacity to undertake research in low and middle income settings and in immigrant ethnic groups. Up-to-date, evidence based dietary guidelines are needed that are locally relevant and readily accessible to healthcare professionals, patients, and the public in different regions of the world. Greater understanding is also needed about the dietary determinants of type 2 diabetes and its complications at younger ages and in those with lower body mass index in some ethnic groups
- We need investment in medical education to train medical students and physicians in lifestyle interventions, including incorporating nutrition education in medical curricula
- Individual, collective, and upstream factors are important. Issuing dietary guidance does not ensure its adoption or implementation. Research is needed to understand the individual and societal drivers of and barriers to healthy eating. Educating and empowering individuals to make better dietary choices is an important strategy; in particular, the social aspects of eating need attention as most people eat in family or social groups and counselling needs to take this into account. Equally important is tackling the wider determinants of individual behaviour—the "foodscape", sociocultural and political factors, globalisation, and nutrition transition

guidelines or medical nutrition therapy guidelines for diabetes, and systematic reviews and primary research articles based on randomised clinical trials or prospective observational studies. All authors contributed to drafting this manuscript, with NGF taking a lead role and she is also the guarantor of the manuscript. All authors gave intellectual input to improve the manuscript and have read and approved the final version.

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Role of the gut microbiota in nutrition and health

Ana M Valdes and colleagues discuss strategies for modulating the gut microbiota through diet and probiotics

Microbiome refers to the collective genomes of the micro-organisms in a particular environment, and microbiota is the community of micro-organisms themselves (box 1). Approximately 100 trillion micro-organisms (most of them bacteria, but also viruses, fungi, and protozoa) exist in the human gastrointestinal tract[1 2]—the microbiome is now best thought of as a virtual organ of the body. The human genome consists of about 23 000 genes, whereas the microbiome encodes over three million genes producing thousands of metabolites, which replace many of the functions of the host,[1 3] consequently influencing the host's fitness, phenotype, and health.[2]

Box 1: Glossary

- *Microbiome*—the collective genomes of the micro-organisms in a particular environment
- *Microbiota*—the community of micro-organisms themselves
- *Microbiota diversity*—a measure of how many different species and, dependent on the diversity indices, how evenly distributed they are in the community. Lower diversity is considered a marker of dysbiosis (microbial imbalance) in the gut and has been found in autoimmune diseases and obesity and cardiometabolic conditions, as well as in elderly people
- *Operational taxonomic unit*—a definition used to classify groups of closely related organisms. DNA sequences can be clustered according to their similarity to one another, and operational taxonomic units are defined based on the similarity threshold (usually 97% similarity) set by the researcher
- *Colonocytes*—epithelial cells of the colon
- *Germ-free animals*—animals that have no micro-organisms living in or on them
- *Short chain fatty acids*—fatty acids with two to six carbon atoms that are produced by bacterial fermentation of dietary fibres

Studying the gut microbiota

Twin studies have shown that, although there is a heritable component to gut microbiota, environmental factors related to diet, drugs, and anthropometric measures are larger determinants of microbiota composition.[4 5]

Gut microbes are key to many aspects of human health including immune,[6] metabolic[5] and neurobehavioural traits (fig 1).[7 8] Different levels of evidence support the role of gut microbiota in human health, from animal models[9 10] and human studies.[4 11-13]

Animal models can help identify gut microbes and mechanisms, though the degree to which findings translate to humans is unknown. In humans, observational studies can show cross-sectional associations between microbes and health traits but are limited by the inability to measure causal relations. The strongest level of evidence is obtained from interventional clinical studies—in particular, randomised controlled trials.

The composition of gut microbiota is commonly quantified using DNA based methods, such as next generation sequencing of 16S ribosomal RNA genes or whole genome shotgun sequencing,

KEY MESSAGES

- Gut microbiota influences many areas of human health from innate immunity to appetite and energy metabolism
- Targeting the gut microbiome, with probiotics or dietary fibre, benefits human health and could potentially reduce obesity
- Drugs, food ingredients, antibiotics, and pesticides could all have adverse effects on the gut microbiota
- Microbiota should be considered a key aspect in nutrition; the medical community should adapt their education and public health messages
- Fibre consumption is associated with beneficial effects in several contexts

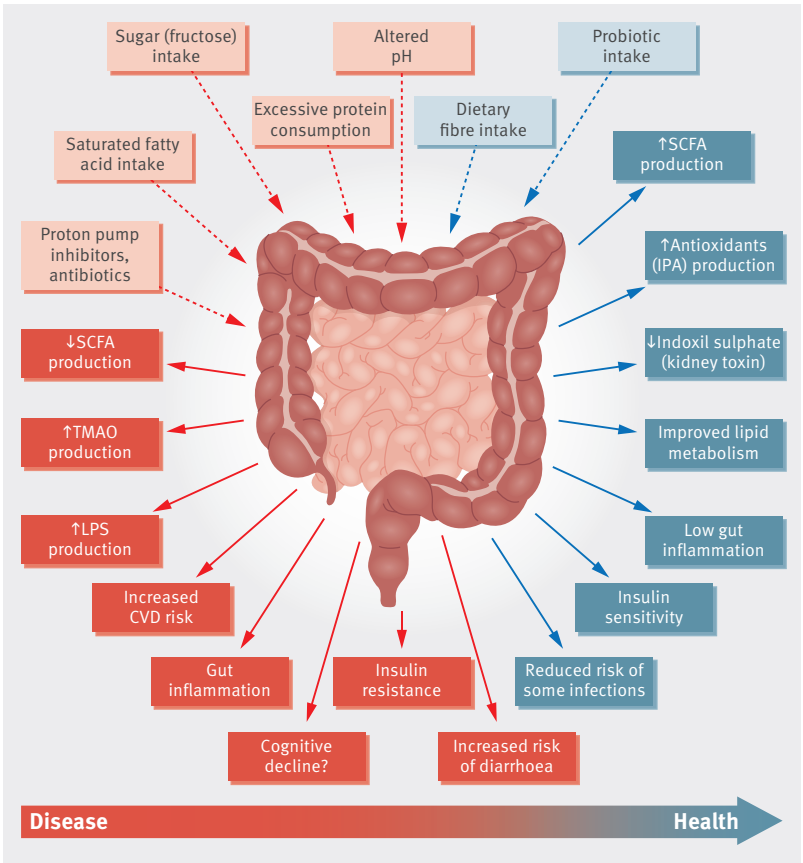

Fig 1 | Schematic representation of the role of the gut microbiota in health and disease giving some examples of inputs and outputs. CVD=cardiovascular disease; IPA=indolepropionic acid; LPS=lipopolysaccharide; SCFA=short chain fatty acids; TMAO=trimethylamine N-oxide

which also allow inference of microbiota functions.[14 15] Metabolic products of the microbiota are now measurable in stool and serum using metabolomic methods.[16]

What does the gut microbiota do?

The gut microbiota provides essential capacities for the fermentation of non-digestible substrates like dietary fibres and endogenous intestinal mucus. This fermentation supports the growth of specialist microbes that produce short chain fatty acids (SCFAs) and gases.[17] The major SCFAs produced are acetate, propionate, and butyrate.

Butyrate is the main energy source for human colonocytes, can induce apoptosis of colon cancer cells, and can activate intestinal gluconeogenesis, having beneficial effects on glucose and energy homeostasis.[18] Butyrate is essential for epithelial cells to consume large amounts of oxygen through β oxidation, generating a state of hypoxia that maintains oxygen balance in the gut, preventing gut microbiota dysbiosis.[19]

Propionate is transferred to the liver, where it regulates gluconeogenesis and satiety signalling through interaction with the gut fatty acid receptors [18] Acetate—the most abundant SCFA and an essential metabolite for the growth of other bacteria—reaches the peripheral tissues where it is used in cholesterol metabolism and lipogenesis, and may play a role in central appetite regulation.[20] Randomised controlled trials have shown that higher production of SCFAs correlates with lower diet-induced obesity[21] and with reduced insulin resistance.[22] Butyrate and propionate, but not acetate, seem to control gut hormones and reduce appetite and food intake in mice.[21] Gut microbial enzymes contribute to bile acid metabolism, generating unconjugated and secondary bile acids that act as signalling molecules and metabolic regulators to influence important host pathways.[23]

Other specific products of the gut microbiota have been implicated directly in human health outcomes. Examples include trimethylamine and indolepropionic acid. The production of trimethylamine from dietary phosphatidylcholine and carnitine (from meat and dairy) depends on the gut microbiota and thus its amount in blood varies between people. Trimethylamine is oxidised in the liver to trimethylamine N-oxide, which is positively associated with an increased risk of atherosclerosis and major adverse cardiovascular events.[24] Indolepropionic acid is highly correlated with dietary fibre intake[25] and has potent radical scavenging activity in vitro,[26] which seems to reduce the risk of incidence of type 2 diabetes.[25]

The gut microbiota and obesity

The gut microbiota seems to play a role in the development and progression of obesity. Most studies of overweight and obese people show a dysbiosis characterised by a lower diversity.[31-39] Germ-free mice that receive faecal microbes from obese humans gain more weight than mice that receive microbes from healthy weight humans.[4] A large study of UK twins found that the genus *Christensenella* was rare in overweight people and when given to germ free mice prevented weight gain.[4] This microbe and others such as *Akkermansia* correlate with lower visceral fat deposits.[12] Although much of the confirmatory evidence comes from mouse models, long term weight gain (over 10 years) in humans correlates with low microbiota diversity, and this association is exacerbated by low dietary fibre intake.[28]

Gut microbiota dysbiosis probably promotes diet induced obesity and metabolic complications by a variety of mechanisms including immune dysregulation, altered energy regulation, altered gut hormone regulation, and proinflammatory mechanisms (such as lipopolysaccharide endotoxins crossing the gut barrier and entering the portal circulation[29 30]; fig 1).

Microbiota diversity and health

Lower bacterial diversity has been reproducibly observed in people with inflammatory bowel disease,[31] psoriatic arthritis,[32] type 1 diabetes,[33] atopic eczema,[34] coeliac disease,[35] obesity,[36] type 2 diabetes,[37] and arterial stiffness,[38] than in healthy controls. In Crohn's disease smokers have even lower gut microbiome diversity.[39] The association between reduced diversity and disease indicates that a species-rich gut ecosystem is more robust against environmental influences, as functionally related microbes in an intact ecosystem can compensate for the function of other missing species. Consequently, diversity seems to be a generally good indicator of a "healthy gut."[40 41] But recent interventional studies indicate that major increases in dietary fibre can temporarily reduce diversity, as the microbes that digest fibre become specifically enriched, leading to a change in composition and, through competitive interactions, reduced diversity.[22]

The functional role of the gut microbiome in humans has been shown using faecal microbiota transplantation.[42] This procedure is effective in cases of severe drug refractory *Clostridium difficile* infection and is now routinely used for this purpose around the world.[43] For other pathologies, faecal transplants are not yet clinical practice but have been explored.[44] For example, transplanting faeces from a lean healthy donor (allogeneic) to recipients with metabolic syndrome resulted in better insulin sensitivity, accompanied by altered microbiota composition, than using autologous faeces.[45]

Effects of food and drugs on the gut microbiota

Specific foods and dietary patterns can all influence the abundance of different types of bacteria in the gut, which in turn can affect health (table 1).

High-intensity sweeteners are commonly used as sugar alternatives, being many times sweeter than sugar with minimal calories. Despite being "generally recognised as safe" by regulatory agencies, some animal studies have shown that these sugar substitutes may have negative effects on the gut microbiota.[46] Sucralose, aspartame, and saccharin have been shown to disrupt the balance and diversity of gut microbiota.[46] Rats given sucralose for 12 weeks had significantly higher proportions of *Bacteroides*, *Clostridia*, and total aerobic bacteria in their guts and a significantly higher faecal pH than those without sucralose.[47] Mice given sucralose for six months had an increase in the expression in the gut of bacterial pro-inflammatory genes and disrupted faecal metabolites.[48]

Food additives, such as emulsifiers, which are ubiquitous in processed foods, have also been shown to affect the gut microbiota in animals.[49] Mice fed relatively low concentrations of two commonly used emulsifiers—carboxymethylcellulose and polysorbate-80—showed reduced microbial diversity compared with mice not fed with emulsifiers. Bacteroidales and Verrucomicrobia were decreased and inflammation promoting Proteobacteria associated with mucus was enriched.[49]

Other areas of concern include the side effects of popular restrictive diets on gut health. These include some strict vegan diets, raw food or "clean eating" diets, gluten-free diets, and low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diets used to treat irritable bowel syndrome.

Vegans are viewed by some as healthier than omnivores. A study of 15 vegans and 16 ominvores found striking differences in serum metabolites generated by the gut microbes but very modest differences in gut bacterial communities.[50] A controlled feeding experiment of 10 human omnivores randomised to receive either a high fat and low fibre diet or a low fat and high fibre for 10 days found very modest effects on gut microbiome composition and no difference in short chain fatty acid production. Together these data support a greater role for diet influencing the bacterial derived metabolome than just the short term bacterial community.[50]

Table 1 | Examples of foods, nutrients, and dietary patterns that influence human health linked to their effect on the gut microbiota

Dietary element	Effect on gut microbiome	Effect on health outcomes mediated by gut microbiome	Human observational studies	Human interventional studies
Low FODMAP diet	Low FODMAP diet increased Actinobacteria; high FODMAP diet decreased abundance of bacteria involved in gas consumption[58]	Reduced symptoms of irritable bowel syndrome[56]	Yes	Yes
Cheese	Increased *Bifidobacteria*,[97 98] which are known for their positive health benefits to their host through their metabolic activities.[99] Decrease in *Bacteroides* and *Clostridia*, some strains of which are associated with intestinal infections[98]	Potential protection against pathogens.[100] Increased production of SCFA and reduced production of TMAO[99]	Yes	Yes
Fibre and prebiotics	Increased microbiota diversity and SCFA production[22 101 102]	Reduced type 2 diabetes[22] and cardiovascular disease[103]	Yes	Yes
Artificial sweeteners	Overgrowth of Proteobacteria and *Escherichia coli*.[104] *Bacteroides*, *Clostridia*, and total aerobic bacteria were significantly lower, and faecal pH was significantly higher[47]	Induced glucose intolerance[105]	No	No
Polyphenols (eg, from tea, coffee, berries, and vegetables such as artichokes, olives, and asparagus)	Increased intestinal barrier protectors (*Bifidobacteria* and *Lactobacillus*), butyrate producing bacteria (*Faecalibacterium prausnitzii* and *Roseburia*) and *Bacteroides vulgatus* and *Akkermansia muciniphila*.[107] Decreased lipopolysaccharide producers (*E coli* and *Enterobacter cloacae*)[106]	Gut micro-organisms alter polyphenol bioavailability resulting in reduction of metabolic syndrome markers and cardiovascular risk markers[108]	Yes	Yes
Vegan	Very modest differences in composition and diversity in humans and strong differences in metabolomic profile compared with omnivore diet in humans[50]	Some studies show benefit of vegetarian over omnivore diet,[109] others fail to find a difference[110]	Yes	Yes

FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides and polyols; SCFA=small chain fatty acids; TMAO= trimethylamine N-oxide

Animal and in vitro studies indicate that gluten-free bread reduces the microbiota dysbiosis seen in people with gluten sensitivity or coeliac disease.[51 52] But most people who avoid gluten do not have coeliac disease or proved intolerance, and a recent large observational study showed an increased risk of heart disease in gluten avoiders, potentially because of the reduced consumption of whole grains.[53] One study showed that 21 healthy people had substantially different gut microbiota profiles after four weeks on a gluten-free diet. Most people showed a lower abundance of several key beneficial microbe species.[54]

The low FODMAP diet has been shown in six randomised controlled trials to reduce symptoms of irritable bowel syndrome.[55 56] It is associated with a reduced proportion of *Bifidobacterium* in patients with irritable bowel syndrome, and responsiveness to this diet can be predicted by faecal bacterial profiles.[57] Low FODMAP diets lead to profound changes in the microbiota and metabolome, the duration and clinical relevance of which are as yet unknown.[58 59]

In addition to diet, medication is a key modulator of the gut microbiota composition. A large Dutch-Belgian population study showed that drugs (including osmotic laxatives, progesterone, TNF-□ inhibitors and rupatadine) had the largest explanatory power on microbiota composition (10% of community variation).[13] Other studies have shown major effects of commonly prescribed proton pump inhibitors on the microbial community, which could explain higher rates of gastrointestinal infection in people taking these drugs.[60] Antibiotics clearly have an effect on gut microbes, and low doses are routinely given to livestock to increase their growth and weight. A large proportion of antibiotic use in many countries is for agriculture—particularly intensive farming of poultry and beef.[61] Several observational human studies as well as many rodent studies have pointed to an obesogenic effect of antibiotics in humans even in tiny doses found in food.[61] But humans have very variable responses to antibiotics, and intervention studies have not shown consistent metabolic consequences.[62] Pesticides and other chemicals are commonly sprayed on foods, but, although levels can be high, solid evidence for their harm on gut health and the effects of organic food is currently lacking.[63]

Insufficient clinical evidence exists to draw clear conclusions or recommendations for these or other dietary preferences based on gut microbiota. But future studies of food additives, drugs, and the safety and efficacy of dietary modifications must take into account these advances and their effect on the gut microbiota. This is becoming clear in patients with cancer treated with immunochemotherapy, bone marrow recipients, and patients with autoimmune disorders on biologics, where small changes in their microbiota can cause major changes in their response.[64] Moreover, animal experiments have shown the protective effects of phytoestrogens on breast cancer depend on the presence of gut microbes (such as *Clostridium saccharogumia, Eggerthella lenta, Blautia producta,* and *Lactonifactor longoviformis)* that can transform isoflavones into the bioactive compounds.[65]

Box 2 summarises our current knowledge on the interactions between gut microbiota, nutrition, and human health.

Box 2: Consensus and uncertainties

What we know

- Probiotic supplementation has several beneficial effects on human health
- The microbes in our gut influence and human energy metabolism[22-45]
- Diet and medication have a strong influence on gut microbiota composition
- Microbiota composition influences response to chemotherapy and immunotherapy[96]
- Microbiome composition defines glucose response to foods and can be used to personalise diet[94]
- Dietary fibre intake influences gut microbiota composition and is related to better health[86 87 104]

What we don't know

- Are natural probiotics in food better than probiotic supplements? Should we take them preventively?
- Can microbes influence food choices and appetite?
- Do low dose antibiotics in food affect human health?
- What is the effect of pesticides in food on the gut microbiome? Is organic food better for the gut microbiota?
- Should all new drugs and food chemicals be tested on the gut microbiota?

Manipulating the gut microbiota through diet

Changes to the gut microbiota can occur within days of changing diet; remarkable differences were found after African Americans and rural Africans switched diets for only two weeks.[66] Increased abundance of known butyrate producing bacteria in the African Americans consuming a rural African diet caused butyrate production to increase 2.5 times and reduced synthesis of secondary bile acid.[66] Another study comparing extreme shifts between plant and animal protein based diets showed these changes after only five days.[67] But healthy microbiota are resilient to temporal changes by dietary interventions, meaning that homeostatic reactions restore the original community composition, as recently shown in the case of bread [68]

Prebiotic foods and dietary fibre

Most national authorities define dietary fibre as edible carbohydrate polymers with three or more monomeric units that are resistant to the endogenous digestive enzymes and thus are neither hydrolysed nor absorbed in the small intestine.[69] A subset of dietary fibre sources is fermentable, which means that they serve as growth substrates for microbes in the distal bowel.[70] Some non-digestible carbohydrates have been referred to as "prebiotics," which are defined as food components or ingredients that are not digestible by the human body but specifically or selectively nourish beneficial colonic micro-organisms (box 3).[71] The prebiotic concept has been criticised for being poorly defined and unnecessarily narrow,[72] and some scientists prefer the term "microbiota accessible carbohydrates,"[11] which are essentially equivalent to fermentable dietary fibre in that they become available as growth substrates for gut microbes that possess the necessary enzymatic capacity to use them.[70]

Consuming resistant starches has been shown to enrich specific bacterial groups (*Bifidobacterium adolescentis, Ruminococcus bromii*, and *Eubacterium rectale*) in some people.[74 75] The taxa enriched differ depending on the type of resistant starches and other dietary fibres,[75] indicating that shifts are dependent on the carbohydrate's chemical structure and the microbes' enzymatic capacity to access them. Microbes need also to "adhere" to a substrate and tolerate the conditions generated from fermentation (such as low pH).[76]

The effect of microbiota accessible carbohydrates on the gastrointestinal microbiome composition can be substantial, with specific species becoming enriched to constitute more than 30% of the faecal microbiota.[75 77] Thus, microbiota accessible carbohydrates provide a potential strategy to enhance useful minority members of the microbiome. These changes only last as long as the carbohydrate is consumed, and they are highly individual, which provides a basis for personalised approaches. Many short term feeding trials with purified dietary fibres or even whole plant based diets either have no effect on microbiota diversity or reduce it,[22] but can still have clinical benefits, potentially through metabolites such as small chain fatty acids.[22 67]

Low fibre intake reduces production of small chain fatty acids and shifts the gastrointestinal microbiota metabolism to use less favourable nutrients,[78] leading to the production of potentially detrimental metabolites.[79 80] Convincing evidence shows that the low fibre Western diet degrades the colonic mucus barrier, causing microbiota encroachment, which results in pathogen susceptibility[81]and inflammation,[82] providing a potential mechanism for the links of Western diet with chronic diseases. Two recent studies showed that the detrimental effects of high fat diets on penetrability of the mucus layer and metabolic functions could be prevented through dietary administration of inulin.[83 84] Overall, these findings, together with the role of butyrate in preventing oxygen induced gut microbiota dysbiosis,[19] provide a strong rational to enrich dietary fibre consumption to maintain intact mucosal barrier function in the gut.[85]

Considerable observational evidence shows that fibre intake is beneficial for human health. Two recent meta-analyses found clear links between dietary fibre and health benefits in a wide range of pathologies,[86 87] and a recent intervention study found dietary fibres significantly reduced insulin resistance in patients with type 2 diabetes, with clear links to the shifts in the microbiota and beneficial metabolites (such as butyrate).[45]

Probiotic foods

Probiotics are live micro-organisms that, when administered in adequate amounts, confer a health benefit on the host).[88] Probiotics (mostly *Bifidobacterium* and *Lactobacillus* species) can be included in a variety of products, including foods, dietary supplements, or drugs.

There are concerns that most microbe supplements are unable to establish themselves in the gut and fail to exert an effect on the resident community.[89 90] But probiotics can affect health independently of the gut microbiota through direct effects on the host; for example, through immune modulation or the production of bioactive compounds. The therapeutic effect of probiotic supplementation has been studied in a broad range of diseases.

We searched the Cochrane library of systematic reviews for "probiotic*", yielding 39 studies, and searched Medline for "systematic review" or "meta-analysis" and "probiotic*", yielding 31 studies. We included information on systematic reviews of randomised controlled trials published in the past five years where the main treatment was probiotics (not dietary supplements in general). Only studies that focused on comparisons of probiotics with a control group, that contained at least some moderate or high quality randomised controlled trials in the estimation of the authors of the systematic review, which resulted in a total of 22 systematic reviews (table 2). The analysis of 313 trials and 46 826 participants showed substantial evidence for beneficial effects of probiotic supplementation in preventing diarrhoea, necrotising enterocolitis, acute upper respiratory tract infections, pulmonary exacerbations in children with cystic fibrosis, and eczema in children. Probiotics also seem to improve cardiometabolic parameters and reduced serum concentrationof C reactive protein in patients with type 2 diabetes. Importantly, the studies were not homogeneous and were not necessarily matched for type or dose of probiotic supplementation nor length of intervention, which limits precise recommendations. Emerging areas of probiotic treatment include using newer microbes and combinations, combining probiotics and prebiotics (synbiotics),[91] and personalised approaches based on

Box 3: What are prebiotics and probiotics?

Dietary amounts of protein, saturated and unsaturated fats, carbohydrates, and dietary fibre influence the abundance of different types of bacteria in the gut. The microbiota can also be modified by adding live micro-organisms to food or by periods of fasting.

- Probiotics are live bacteria and yeasts that, when administrated in a viable form and in adequate amounts, are beneficial to human health. They are usually added to yoghurts or taken as food supplements.
- Prebiotics are defined as a substrate that is selectively used by host micro-organisms conferring a health benefit. Although all compounds considered prebiotics are microbiota accessible carbohydrates or fermentable dietary fibre, the reverse is not true. The prebiotic concept is an area of current debate[70]
- Synbiotics contain a mixture of prebiotics and probiotics

Table 2 | Summary of systematic reviews analysing the role of probiotics on clinical outcomes

Outcome	Reference	No of studies/ participants	Evidence of benefit?	Results/conclusions
Clostridium difficile associated diarrhoea in adults and children	Goldenberg et al (2017)[111]	39/9955	Yes	Moderate quality evidence that probiotics are safe and effective for preventing *C difficile* associated diarrhoea. (RR 0.30, 95% CI 0.21 to 0.42)
Necrotising enterocolitis	Al Faleh et al (2014)[112] Rees et al (2017)[113]	17/5338	Yes	Enteral supplementation of probiotics prevents severe necrotising enterocolitis (RR 0.43, 95%CI 0.33 to 0.56) and all cause mortality in preterm infants (RR 0.65, 95% CI 0.25 to 0.81)
Antibiotic associated diarrhoea in children	Goldenberg et al (2015)[114]	26/3898	Yes	Moderate evidence of a fall in the incidence of antibiotic associated diarrhoea in the probiotic *v* control group (RR 0.46, 95% CI 0.35 to 0.61; I^2=55%, 3898 participants)
Probiotics for preventing acute upper respiratory tract infections	Hao et al (2015)[115]	12/3720	Yes	Probiotics were better than placebo in reducing the number of participants experiencing episodes of acute upper respiratory tract infections, the mean duration of an episode, antibiotic use, and related school absence (12 trials, 3720 participants including children, adults, and older people)
Urinary tract infections	Schwenger et al (2015)[116]	9/735	No	No significant benefit for probiotics compared with placebo or no treatment
Prevention of asthma and wheeze in infants	Azad et al (2013)[117]	6/1364	No	No evidence to support a protective association between perinatal use of probiotics and doctor diagnosed asthma or childhood wheeze
Prevention of eczema in infants and children	Mansfield et al (2014)	16/2797	Yes	Probiotic supplementation in the first several years of life did have a significant impact on development of eczema (RR 0.74, 95% CI 0.67 to 0.82)
Prevention of invasive fungal infections in preterm neonates	Agrawal et al (2015)[119]	19/4912	Unclear	Probiotic supplementation reduced the risk of invasive fungal infections (RR 0.50, 95% CI 0.34 to 0.73, I^2=39%) but there was high heterogeneity between studies. Analysis after excluding the study with a high baseline incidence (75%) showed that probiotic supplementation had no significant benefits (RR 0.89, 95% CI 0.44 to 1.78)
Prevention of nosocomial infections	Manzanares et al (2015)[120]	30/2972	Yes	Probiotics were associated with a significant reduction in infections (RR 0.80, 95%CI 0.68 to 0.95, P=0.009; I^2=36%, P=0.09). A significant reduction in the incidence of ventilator associated pneumonia was found (RR 0.74, 95% CI 0.61 to 0. 90, P=0.002; I^2=19%)
Treatment of rotavirus diarrhoea in infants and children	Ahmadi et al (2015)[121]	14/1149	Yes	Probiotic supplementation resulted in a mean difference of −0.41 (CI 95% −0.56 to −0.25; P<0.001) in the duration of diarrhoea. Probiotics exert positive effect on reducing the duration of acute rotavirus diarrhoea compared with control
Prevention and treatment of Crohn's disease and ulcerative colitis	Saez Lara et al (2015)[122]	14/821 ulcerative colitis 8/374 Crohn's disease	Yes	The use of probiotics and/or synbiotics has positive effects in the treatment and maintenance of ulcerative colitis, whereas in Crohn's disease clear effectiveness has only been shown for synbiotics (no meta- analysis was performed)
Pulmonary exacerbations in children with cystic fibrosis	Ananathan et al (2016)[123]	9/275	Yes	Significant reduction in the rate of pulmonary exacerbation (two parallel group randomised controlled trials and one crossover trial: RR 0.25, 95% CI 0.15 to 0.41; P< 0.00001)
Type 2 diabetes (fasting glucose, glycated haemoglobin test)	Akbari et al (2016)[124]	13/805	Yes	Probiotics significantly reduced fasting blood glucose compared with placebo (8 studies; standardised mean difference −1.583; 95% CI −4.18 to 4.18; P=0.000). Significant reduction in HbA_{1c} was also seen (6 studies; SMD −1.779; 95% CI, −2.657 to −0.901; P=0.000)
Type 2 diabetes (insulin resistance, insulin levels)	Zhang et al (2016)[125]	7/425	Yes	Probiotic therapy significantly decreased homeostasis model assessment of insulin resistance (HOMA-IR) and insulin concentration (WMD: −1.08, 95% CI −1.88 to −0.28; and weighted mean difference −1.35mIU/L, 95% CI -−2.38 to −0.31, respectively
Necrotising enterocolitis in pre-term neonates with focus *on Lactobacillus reuteri*	Athalye-Jape et al (2016)[126]	6/1778	Yes	Probiotic reduced duration of hospitalisation (mean difference = −10.77 days, 95% CI −13.67 to −7.86; in 3 randomised controlled trials), and late onset sepsis (RR 0.66; 95% CI, 0.52 to 0.83; 4 RCTs) were reduced in the
Reduction of serum concentration of C reactive protein	Mazidi et al (2017)[127]	19/935	Yes	Significant reduction in serum C reactive protein after probiotic administration with a WMD −1.35 mg/L, (95% CI −2.15 to −0.55, I^2 65.1%)
Cardiovascular risk factors in patients with type 2 diabetes	Hendijani et al (2017)[128]	11/641	Yes	Probiotic consumption significantly decreased systolic blood pressure (−3.28 mm Hg; 95% CI −5.38 to −1.18), diastolic (WMD −2.13 mm Hg; 95% CI −4.5 to 0.24), low density lipoprotein cholesterol (WMD 8.32 mg/dL; 95% CI −15.24 to −1.4), total cholesterol (WMD −12.19 mg/dL; 95% CI −17.62 to −6.75) and triglycerides(WMD −24.48 mg/dL; 95% CI −33.77 to −11.18) compared with placebo
Reduction of total cholesterol and low density lipoprotein cholesterol	Wu et al (2017)[129]	15/976	Yes	*Lactobacillus* consumption significantly reduced total cholesterol by 0.26 mmol/L (95% CI −0.40 to −0.12) and LDL-C by 0.23 mmol/L (95% CI, −0.36 to −0.10)
Depressive symptoms	Wallace and Milev (2017)[79,130]	6/1080	Yes	No quantitative analysis was performed. Most studies found positive results, and the authors conclude that compelling evidence shows that probiotics alleviate depressive symptoms
Vulvovaginal candidiasis in non-pregnant women	Xie et al (2018)[131]	10/1656	Yes	Probiotics increased the rate of short term clinical cure (RR 1.14, 95% CI 1.05 to 1.24, low quality evidence) and mycological cure (RR 1.06, 95% CI 1.02 to 1.10, low quality evidence) and decreased relapse rate at one month (RR 0.34, 95% CI 0.17 to 0.68, low quality evidence)
Chronic periodontitis	Ikram et al (2018)[132]	7/220	Yes	The overall mean difference for gaining clinical attachment level gain between probiotics and placebo was significant (weighted mean difference 1.41, 95% CI 0.15 to 2.67, P=0.028)

RR=risk ratio, SBP systolic blood pressure, DBP= diastolic blood pressure, TC= total cholesterol, TG=serum triglycerides, SMD=standardised mean difference, WMD=weighted mean difference' CI=confidence interval

profiles of the candidate microbes in inflammation, cancer, lipid metabolism, or obesity.[92] Stable engraftment of a probiotic *Bifidobacterium longum*, for example, has been shown to depend on individualised features of the gut microbiota, providing a rationale for the personalisation of probiotic applications.[93]

Personalised nutrition and future directions

Given the variation in the gut microbiota between people, the optimal diet of a person may need to be tailored to their gut microbiota. Zeevi et al.[94] obtained a multidimensional microbiota profile in 900 people and monitored food intake, continuous blood glucose levels, and physical activity for one week. The researchers devised a machine learning algorithm to predict personalised glucose responses after meals based on clinical and gut microbiome data and showed that it achieved significantly higher predictions than approaches such as carbohydrate counting or glycaemic index scores. In a follow-up double blinded randomised crossover trial of 26 participants, personalised dietary interventions based on the algorithm successfully normalised blood glucose levels.[94]

A study on response to bread[68] using a randomised crossover trial of one week long dietary interventions showed significant interpersonal variability in the glycaemic response to different bread types. The type of bread that induced the lower glycaemic response in each person could be predicted based solely on microbiome data collected before the intervention.[68] Much more research is needed to establish whether these kinds of personalised approaches are feasible, sustainable, and have a positive effect on clinical outcomes.

Conclusions

We are entering an era where we can increasingly modify health through food and measure the effects through our microbes or metabolites. Fibre is a key nutrient for a healthy microbiome and has been overlooked while debates have raged about sugar and fat. The adverse effects on the microbiome of drugs and processed food ingredients can no longer be ignored. Given the current gaps in knowledge, we need clinical evidence that can be translated into clinical practice, ideally through randomised controlled studies that use consistent matrices of prebiotics or probiotics or faecal microbiota transplantation to assess changes in gut microbiota composition and in health outcomes.

Contributors and sources: AMV studies the molecular basis of ageing and complex disease and has recently investigated the role of gut microbiome composition on cardiometabolic disorders. JW has studied and reported widely on the microbial ecology of the gut microbiota, its role in host health, and how it can be modulated by diet. ES heads a multidisciplinary lab of computational biologists and experimental scientists focusing on nutrition, genetics, microbiome, and their effect on health and disease. His aim is to develop personalised nutrition and medicine. TDS leads the TwinsUK registry and British gut project as the head of a multidisciplinary team studying the genetic, dietary, and lifestyle determinants of human gut microbiome composition and its relationship to common diseases. All authors contributed, read, and approved the final version.

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Personalised nutrition and health

Jose Ordovas and colleagues consider that nutrition interventions tailored to individual characteristics and behaviours have promise but more work is needed before they can deliver

Dietary factors are well recognised contributors to common diseases, including heart disease, stroke, type 2 diabetes and cancer.[1-3] Despite the known link between dietary patterns and disease, interventions to alter dietary habits and to improve public health and wellbeing have had limited impact. Personalisation of interventions may be more effective in changing behaviour[4] that will affect health outcomes.[5] In this article we consider the evidence for personalised nutrition.

What is personalised nutrition and what is it used for?

There is no agreed definition of personalised nutrition. For the purposes of this review, we define it as an approach that uses information on individual characteristics to develop targeted nutritional advice, products, or services. Gibney et al[6] describe it as an approach that "assists individuals in achieving a lasting dietary behaviour change that is beneficial for health." Personalised nutrition partially overlaps with related terms such as precision nutrition, nutrigenomics, nutrigenetics, nutritional genomics, etc (box 1).

The overall goal of personalised nutrition is to preserve or increase health using genetic, phenotypic, medical, nutritional, and other relevant information about individuals to deliver more specific healthy eating guidance and other nutritional products and services (table 1). Personalised nutrition is equally applicable to patients and to healthy people who may or may not have enhanced genetic susceptibilities to specific diseases.

Personalised nutrition can be applied in two broad areas: firstly, for the dietary management of people with specific diseases or who need special nutritional support—for example, in pregnancy or old age, and, secondly, for the development of more effective interventions for improving public health. It has traditionally focused on maximising the benefits and reducing the adverse effects of dietary changes for the individual. However, this focus on the individual may have limited impact on populations. To have a wider impact, it must be deployed at a scale and in a

KEY MESSAGES

- Personalised nutrition uses information on individual characteristics to develop targeted nutritional advice, products, or services to assist people to achieve a lasting dietary change in behaviour that is beneficial for health
- Personalised nutrition is based on the concept that individualised nutritional advice, products, or services will be more effective than more traditional generic approaches
- This personalisation may be based on biological evidence of differential responses to foods/nutrients dependent on genotypic or phenotypic characteristics, and/or based on current behaviour, preferences, barriers and objectives
- Most of the available evidence in support of personalised nutrition has come from observational studies with risk factors as outcomes, rather than from randomised controlled trials using clinical end points
- The overall consensus is that much research and regulation is required before personalised nutrition can deliver the expected benefits

Box 1: Descriptors and definitions

In common with other scientific fields in their early development, multiple concepts and descriptors are used in personalised nutrition, sometimes without rigorous definition. In addition to the term personalised nutrition, many other terms are used—for example, precision nutrition, stratified nutrition, tailored nutrition, and individually tailored nutrition. We have attempted to group the descriptors as follows:

- Stratified and tailored nutrition are similar (if not synonymous). These approaches attempt to group individuals with shared characteristics and to deliver nutritional intervention/advice that is suited to each group
- Personalised nutrition and individually tailored nutrition mean similar things and go a step further by attempting to deliver nutritional intervention/advice suited to each individual
- Precision nutrition is the most ambitious of the descriptors. It suggests that it is possible to have sufficient quantitative understanding about the complex relationships between an individual, his/her food consumption, and his/her phenotype (including health) to offer nutritional intervention/advice, which is known to be individually beneficial. The degree of scientific certainty required for precision nutrition is much greater than that required for the other approaches
- Nutrigenetics is an aspect of personalised nutrition that studies the different phenotypic responses (ie, weight, blood pressure, plasma cholesterol, or glucose levels) to a specific diet (ie, low fat or Mediterranean diets), depending on the genotype of the individual
- Nutrigenomics involves the characterisation of all gene products affected by nutrients and their metabolic consequences
- Exposome is the collection of environmental factors, such as stress, physical activity and diet, to which an individual is exposed and which may affect health

As one moves from stratified to personalised to precision nutrition, it becomes necessary to apply more and more dimensions or characteristics to achieve the desired goal. For example, stratification could be undertaken using one, or a few, dimensions such as age, gender, or health status. In contrast, given the complexity of relationships between individual diet and phenotype, deployment of a wide range of dimensions/characteristics, perhaps including "big data" approaches, would be necessary to achieve the goal of precision nutrition. An exception to this broad generalisation is the management of inborn errors of metabolism such as phenylketonuria, where "precision nutrition" can be achieved using information on a single characteristic—that is, genotype.

- Epigenomics is a branch of genomics concerned with the epigenetic changes (methylation, histone modification, microRNAs) that modify the expression and function of the genetic material of an organism
- Metabolomics is the scientific study and analysis of the metabolites (usually restricted to small molecules, ie, <900 daltons) produced by a cell, tissue, or organism
- Microbiomics is the study of the microbiome, the totality of microbes in specific environments (ie, the human gut)

way that reduces (rather than increases) health disparities. Individuals may also wish to use personalised nutrition to achieve personal goals/ambitions that are less directly related to health—for example, to deal with preferences for, and dislikes of, specific foods, to attempt to achieve a desired body size or shape, or for competitive sports.[7]

What are the conceptual bases for personalised nutrition?

Personalised nutrition is based on the idea that individualising nutritional advice, products, or services will be more effective than more generic approaches.

Personalisation can be based on:

- Biological evidence of differential responses to foods/nutrients dependent on genotypic or phenotypic characteristics
- Analysis of current behaviour, preferences, barriers, and objectives and subsequent delivery of interventions, which motivate and enable each person to make appropriate changes to his or her eating pattern.

Personalisation based on biological characteristics of the individual

Differences in the response of people to dietary components have been well documented for almost a century.[8-10] This provides the basis, and motivation, for developing personalised nutrition strategies. The trend towards personalisation is the result of: firstly, nutrition research that provides a better understanding of how diet affects health; secondly, new technology that enables better and continuous measurements of markers of individual health and fitness; and thirdly, new analytical tools that interpret this flow of data and transform it into user friendly practical information. Moreover, personal nutrition integrates with the change in bioscience and public health programmes towards preventing rather than mitigating existing disease. Response to food is variable and has multiple forms. These include differential responses in plasma cholesterol concentration to dietary saturated fat intake, food allergies or intolerances (eg, lactose intolerance or gluten sensitivity), or more severe forms such as phenylketonuria and other inborn errors of metabolism. Moreover, personalised nutritional advice may be appropriate for some key factors, such as age (teenager, elderly, child, adult), stage of life (pregnant, lactating, etc), sex, BMI, disease or health status, ethnicity, and cultural or religious backgrounds that dictate particular diets

Nutrigenetics has been defined as "the discipline that studies the different phenotypic response to diet depending on the genotype of each individual."[11] It is a classic example of an attempt to characterise the response of an individual to a dietary intervention based on genetic factors. To a large extent, this is based on accumulating evidence of the phenotypic consequences of interactions between interindividual differences in genetic make up and nutrition.[12] Nutrigenetics has evolved from using a unique single nucleotide polymorphism at a candidate gene locus to examine interaction with a specific nutrient (eg, saturated fat) to a more comprehensive whole genome approach analysing interactions with dietary patterns.[13]

More recently, new technology has enabled multiple endogenous and exogenous factors to be studied at the same time and used to predict the response to intervention. These include epigenomics, metabolomics, microbiomics (box 1), and the individual's environment,[14] also known as the exposome.[15] The ability to measure "everything that matters" is becoming a reality with the increasing availability of fitness trackers, mobile apps, and other devices. These enable individuals to monitor continuously multiple health related factors, such as physical activity, sleep, and vital signs—for example, blood pressure, heart rate, and stress levels. The usefulness of these devices remains controversial.[16 17] However, in theory, such information could be used to develop algorithms that, in combination with genetic and other biological information, may provide a sound basis for personalised recommendations.

Potentially just as important is the belief that easy access to indices of health provided frequently, and in real time, will be a driver for beneficial, and sustained behaviour change. Thus, an individual will acquire data on his/her genotype and multiple phenotypic characteristics on which the personalised nutrition is based. Periodic physiological and biochemical analyses and microbiome tests will enable tracking of their health metrics in response to dietary, and other personalised, behavioural changes in real time. Relatively little has been published on the development and validation of the algorithms for personalised nutrition. The Food4Me Study published algorithms to integrate information based on current diet, phenotypic characteristics, and genotypic characteristics.[18] However, other approaches—for example, using machine-learning[19] or artificial intelligence,[20] might offer additional advantages.

For example, Zeevi et al[21] used the connection between a raised concentration of postprandial blood glucose and the risk of type 2 diabetes risk. They monitored glucose concentrations in 800 people continuously for 1 week. They then used the variability in glycaemic response to identical test meals to devise a machine-learning algorithm that integrated blood parameters, dietary habits, anthropometrics, physical activity, and gut microbiota to predict an individual's postprandial glycaemic response to real meals. The predictive algorithm was validated in an independent cohort (n=100). These investigators conducted a small randomised controlled dietary intervention study that suggested that personalised diets may successfully modify raised postprandial blood glucose.

The potential role of microbiome based information in developing personalised nutrition has been emphasised in more recent work from the same group. They used a small intervention study to show that an individual's glycaemic response to a test meal can be predicted from microbiome data before the intervention.[22] These results highlight the importance of information about individual people in understanding the effects of dietary factors on metabolism and health. The results suggest that interindividual differences in responses to dietary challenges may be particularly informative, but we need evidence from larger scale studies to know whether such personalised interventions based on a "challenge test" offer significant advantages.

This approach was illustrated more recently by Price et al.[23] They collected personal data, including whole genome sequences, clinical tests, blood metabolome and proteome, physical activity, and fecal microbiome, on three occasions over 9 months from 108 people. They used these data to generate correlation networks that disclosed communities of related analytes associated with physiology and disease. They also used some of the personal data (genotype and clinical markers) to implement behavioural coaching to help participants to improve biomarkers of health. This study showed, firstly, that some highly motivated people are willing to collect personal data over extended periods; secondly, that more information can help to confirm existing knowledge about the connectedness of human physiology and to expose new connections; and, thirdly, with intense measurement in highly motivated people, "personalised coaching" may help to change behaviour. However, it is not clear how much of the detailed measurement undertaken in the study was essential in developing the "personalised coaching." As the participants were self-selected, it is unclear whether this approach would be acceptable to larger populations.

Personalisation based on analysis of current behaviour, preferences, barriers, and objectives

Most researchers, and other stakeholders in personalised nutrition, have focused on the capture of genotypic or phenotypic characteristics. The implicit assumption is that, the more we can measure, the more effective will be the outcomes of personalisation.[24] There is increasing realisation that, unlike with medication, dietary changes require individuals to make daily, sometimes hourly, choices. The adoption of these lifestyle changes (including but not limited to changes in dietary patterns) is highly dependent on effective collaboration with participants who are being helped to take responsibility for their behaviour, and, ultimately, health. Increasing technology is available that can motivate healthy eating. However, such applications usually adopt a "one-size-fits-all" approach that is biased towards specific cultures or population subgroups. Evidence suggests that it is possible to facilitate a change in behaviour using genetic testing or personalised advice as the catalysts.[25 26] More emphasis is needed to develop behavioural approaches that will best motivate particular individual and cultural groups.

There may be benefits in moving from a decision framework based on health professionals' perspectives of effectiveness to one of shared decision making. An intervention based on shared decision making between the provider and the recipient becomes personalised and may increase acceptance and adherence. In this regard, the Food4Me Study stands out. It was a randomised controlled trial (RCT) involving >1600 participants from seven European countries, which showed that personalised nutrition was more effective than a conventional one-size-fits-all approach as control (box 2).[27] A limitation of the study is that no information is available on outcomes beyond 6 months. However, findings from an earlier systematic review and meta-analysis suggest that, if changes are apparent at 6 months, they are likely to be sustained for at least a year.[28]

None the less, many questions remain, and the conceptual framework underpinning this type of personalisation is poorly defined.

Implementation challenges

Personalised nutrition has raised expectations similar to the excitement that has surrounded other scientific developments in their early stages. Scientists working in this area have expressed concerns about overpromising,[29 30] individually[31 32] as well as through institutional guidelines and statements.[33-38] Highest expectations arise from the suggestion that genetic information might be used to define personalised dietary recommendations. For example, the Academy of Nutrition and Dietetics states that "nutritional genomics provides insight into how diet and genotype interactions affect phenotype. The practical application of nutritional genomics for complex chronic disease is an emerging science and the use of nutrigenetic testing to provide dietary advice is not ready for routine dietetics practice." The consensus is that much research is needed before personalised nutrition can deliver the expected benefits.[36]

Gaps in the evidence base—Firstly, most studies, many of which are nutrigenetic, have used retrospective or observational approaches. Those studies that have used interventions are small and have focused on intermediate biomarkers. Only a few reports have studied gene-diet interactions in large, randomised, long term dietary intervention studies with clinical events as endpoints.[39 40] Stronger evidence for causality may come from well designed dietary RCTs that use prospective genotyping when randomising participants to treatments, as in the FINGEN Study[41] (box 3). The latter study investigated the effects of supplementation with fish oil on cardiovascular risk markers. For the design and implementation of an RCT, such an approach is much less complex than trials involving whole foods or which attempt to change eating patterns. Randomised controlled trials are essential to providing proof of concept and to giving scientific credibility to the concept of personalised nutrition. We envisage that ethical providers will build delivery systems in which elements of the system are evidence based but for which it would be difficult or impossible to test the whole system with an RCT.

Applying evidence for populations to individuals—Most of our evidence in populations is probabilistic. The personalised nutrition approach wants to use this evidence for individuals. To take a simple example, there is evidence that an interaction between a variant in *APOA2* and intake of saturated fatty acids has an effect on obesity and, by extrapolation, on the risk of cardiovascular disease.[42 43] Lowering saturated fatty acid intake in those carrying this variant would be expected to lower obesity and thus the risk of cardiovascular disease in populations. However, for individuals, there is no guarantee of any benefit. This is because, in common with most health outcomes, the risk of cardiovascular disease is multifactorial and includes the effects of stochastic factors. Available evidence allows us to predict mean outcomes from a given intervention and genotype, but it is impossible to predict health outcomes for individuals. Thus, the current interest is in studies that measure multiple parameters at the same time. Alternatively, others have advocated single subject studies in personalised nutrition.[44] Single subject, or n-of-1, trials can potentially assess the usefulness of personalised interventions by integrating emerging technology and biomarkers.[45] Analytical approaches to n-of-1 studies are being developed in related fields—for example, health

Box 2: Food4Me Study

The Food4Me Study[27] is the largest randomised controlled trial to have investigated the efficacy of personalised nutrition.

The study asked two key questions:

- Is personalised nutrition more effective in changing diet than a conventional one-size-fits-all approach?
- Does the basis used for personalisation matter? (With particular interest in the benefit of personalisation based on phenotypic and genotypic characteristics)

After 6 months, the answer was clear. Personalisation of dietary advice assisted and/or motivated consumers to eat a healthier diet and follow a healthier lifestyle (in comparison with "impersonal" (conventional) dietary advice). The Healthy Eating Index was used as the global measure of "healthfulness" of eating patterns and change was measured after 3 and 6 months.

Personalisation based on analysis of current diet was more effective in assisting and/or motivating study participants to make, and to sustain, appropriate healthy changes to their usual (habitual) diet and lifestyle. However, there was no evidence of any additional benefit from using more sophisticated, and expensive, bases for personalisation, such as phenotypic and genotypic information.

The Food4Me Study was implemented as an internet based intervention to emulate commercial personalised nutrition aids. The intervention was delivered to >1600 adults in seven European countries and used several new approaches to collection and validation of data and biological samples.[47-58] This study provides a model for the use of the internet in delivering personalised interventions. It demonstrates the opportunities to scale up and to make potentially significant cost effective improvements in public health.

Box 3: Personalised nutrition

Strengths

- Interindividual variability in response to dietary factors is a real phenomenon
- Some studies have shown that personalisation results in greater improvements in diet than universal approaches
- Personalisation may foster sustained change in behaviour
- The personalised nutrition approach mirrors the rise in personalised, or precision, medicine, which is likely to drive scientific developments beneficial for personalised nutrition, and, therefore, public health

Weaknesses

- Scientific evidence for personalised nutrition is mostly based on observational studies with a low level of reproducibility
- The theoretical basis for personalised nutrition is underdeveloped
- The factors responsible for interindividual differences in response to dietary factors, their persistence over time within the same individual, and their heritability are mostly unknown[59]
- There are few well-designed randomised controlled trial that demonstrate the efficacy and safety of personalised nutrition
- Most commercial offerings in the personalised nutrition area are based on direct to consumer tests that are unregulated and have limited published evidence of benefit

psychology, and may be suitable for use in personalised nutrition.[46]

Effect on health disparities—The use of most new technology (such as n-of-1 trials) for predicting and measuring the response to specific dietary changes may be prohibitively expensive if deployed at scale.[5] This may increase health disparities. The challenge for research will be to define the minimum set of measurements/biomarkers that predicts individual response to personalised nutrition.

Encouraging shared decision making—Face-to-face consultations with a health professional or lifestyle coach might enable shared decision making, but is relatively expensive. In the Food4Me Study, personalisation was implemented by nutrition researchers[52 7 47] using decision trees. This guided the personalised advice and ensured that it was standardised across study sites. This process could be used to build algorithms that "tailor" the advice/support offered to an individual, based on preferences, barriers, ambitions, etc. Such algorithms can also incorporate techniques for behaviour change to help maximise the (health) benefit.[48] These algorithms could be automated and could operate in "real time" using the internet. They provide an opportunity for large scale, cost effective shared decision making that may minimise possible increases in health disparities.

Is personalised nutrition more effective than alternative approaches?

Despite studies supporting personalised nutrition, most evidence has come from observational studies with risk factors as outcomes, rather than from RCTs using clinical end points.

There are two key related questions. Firstly, can personalised nutrition produce greater, more appropriate and sustained changes in behaviour than conventional approaches? Secondly, do these changes result in better health and wellbeing?

We have limited information that the answer to the first of these questions is yes.[27 49] However, evidence for the usefulness of communicating genetic risks of a disease itself on risk-reducing health behaviour is weak.[50] A recent systematic review studied genetic testing and lifestyle behaviour change. It concluded that behaviour change can be facilitated using genetic testing as the catalyst. The authors argued that to promote such change the theory of planned behaviour should be deployed when communicating the results of genetic testing.[26]

The second question remains unanswered. No personalised nutrition study has been carried out at a large scale, in an appropriate population group and over a sufficiently long time. For this reason, and because of the importance of lifestyle change for large sections of the population, other investigators advocate a universal, rather than targeted, approach to lifestyle intervention for disease prevention and treatment.[51] The logistical complexity, practical challenges, and financial costs of nutrition intervention studies with disease risk as outcomes are large and likely to be increased in personalised nutrition interventions. Thus further testing will probably use outcomes such as changes in diet, adiposity, or established biomarkers of disease such as blood pressure, HbA_{1c}, or cognitive function. In addition, there are major opportunities to test the usefulness of personalised nutrition in the response to disease management and treatment. This would be cost effective and logistically feasible.

Personalised nutrition in the marketplace

The potential market for personalised nutrition is huge. Firstly: as indicated above, it applies to both diseased and healthy people; secondly, eating is a daily activity, and thus opportunities for personalisation are continuous; thirdly, through personalisation a person may feel able to enhance or maintain health. Most commercial personalised nutrition interventions are provided directly to the consumer through the internet. The reliability of the evidence used by such companies is uncertain.[52 53] The business has developed without regulatory oversight, defined standards, and consumer protection.[54] Moreover, there are no educational resources or guidelines for how the outcomes of research into personalised nutrition should be implemented. To protect the public, advice should be based on robust scientific evidence. A framework for testing evidence for the scientific validity of nutrigenetic knowledge has been published.[38] It is intended to be used for developing transparent and scientifically sound advice to the public founded on nutrigenetic tests. This is based on the assumption that scientifically valid, properly regulated information delivered through the internet will be less expensive and more pervasive and may help to reduce health inequalities.

Suggestions for the future

Advancement of personalised nutrition will be facilitated by a number of factors. Firstly, the development of a strong theoretical basis, including identification of the most important individual characteristics on which to base personalisation. Secondly, the evidence for efficacy and cost effectiveness from well designed intervention studies. Thirdly, the introduction of a regulatory framework designed to protect the public and to give confidence to health professionals and policy makers. This will require a substantial increase in the scientific evidence. This implies:

- More robust study designs ranging from RCTs enrolling participants based on preselected genotypes, to n-of-1 trials and aggregated n-of-1 trials. Such research will benefit from multidisciplinary research teams, comprising, for example, behavioural psychologists, computer scientists, biomedical scientists, and nutritionists.
- Integration of other "omics" to provide greater mechanistic interpretation of the evidence. This is likely to include emphasis on epigenomics, metabolomics, and microbiomics. In this respect, proof of principle of the role of the microbiome in shaping interindividual variability in response to diet has been established.

A first step in developing guidelines for using genotype based advice in personalised nutrition has been proposed by the

Table 1 | Different levels of recommendation for women (not pregnant or lactating)

Global recommendation	Personalised dietitian recommendation based on an individual's history and preferences	Personalised recommendation based on individual history, preferences, and genetic information
Zn (8 mg/day): Consume a wide variety of foods containing zinc. Red meat and poultry provide the majority of zinc in the American diet. Other good food sources include beans, nuts, certain types of seafood, whole grains, fortified breakfast cereals, and dairy products	Recommendations vary according to age, sex, pregnancy and lactation (2-13 mg). Personalisation will account for these individual characteristics. In addition, consideration should be given to: • People who have had gastrointestinal surgery, such as weight loss surgery, or who have digestive disorders, such as ulcerative colitis or Crohn's disease. Both these conditions can decrease the amount of zinc that the body absorbs and increase the amount lost in the urine • Vegetarians, because they do not eat meat, which is a good source of zinc. Also, the beans and grains they typically eat contain compounds that prevent complete absorption of zinc by the body. For this reason, vegetarians might need to eat as much as 50% more zinc than the recommended amounts • Older infants who are breastfed because breast milk contains insufficient zinc for infants aged >6 months. Infants taking formula receive sufficient zinc. Older infants who do not take formula should be given foods that contain zinc, such as pureed meats • Alcoholics, because alcoholic beverages decrease the amount of zinc absorbed by the body and increase the amount lost in the urine. Also, many alcoholics eat a limited amount and variety of food, so they may not get enough zinc • People with sickle cell disease, because they might need more zinc	SLC30A8: Carriers of the A allele at the rs11558471 SLC30A8 (zinc transporter) variant need supplements containing zinc in addition to a healthy diet to maintain proper glucose homoeostasis.[55] Knowledge of this genetic information will trigger a recommendation for Zn supplementation
Dietary fat and cholesterol: Choose a diet low in fat, saturated fat, and cholesterol	Use fats and oils sparingly. Use the nutrition facts label to help you choose foods lower in fat, saturated fat, and cholesterol Eat plenty of grain products, vegetables, and fruits Choose low fat milk products, lean meats, fish, poultry, beans, and peas to get essential nutrients without substantially increasing calories and intake of saturated fat	*TCF7L2:* For carriers of the T allele at the TCF7L2-rs7903146 polymorphism a Mediterranean diet reduces its adverse effect on cardiovascular risk factors and incidence of stroke, but not so a low fat diet. Therefore carriers of the T allele will be recommended to: • Eat primarily plant based foods, such as fruits and vegetables, whole grains, legumes, and nuts • Replace butter with healthy fats such as extra virgin olive oil • Use herbs and spices instead of salt to flavour foods • Limit red meat to a few times a month • Eat fish and poultry at least twice a week • Drink red wine in moderation (optional)[39]
Vitamin B2 (riboflavin): Consume the appropriate recommended dietary allowance (RDA) from a variety of foods	Recommendations vary according to age, sex, pregnancy, and lactation (0.3-1.6 mg/day) Personalisation will take account of these individual characteristics. In addition, consideration should be given to: • Vegetarian athletes, as exercise produces stress in the metabolic pathways that use riboflavin People who are vegan or consume little milk, or both, are also at risk of riboflavin inadequacy	*MTHFR:* Carriers of the TT genotype at the MTHFR C677T polymorphism are at higher risk of hypertension, which may not reach targets (systolic blood pressure <120 mmHg) with medication. However, they particularly benefit from riboflavin supplementation (~1.6 mg/day)[56] *SLC52A3:* Brown-Vialetto-Van Laere syndrome is caused by mutations in the *SLC52A3* gene, which encodes the intestinal riboflavin transporter. As a result, these patients have riboflavin deficiency. Riboflavin supplementation can be life saving in this population[57]

Food4Me consortium.[38] It will be important for research and regulatory communities to evaluate the proposed guidelines. This may lead to the development of more generic guidelines that could be valuable for national (and international) regulators. However, given the diversity of approaches to personalised nutrition, it is likely to be difficult to agree on the principles for such generic guidelines. Experience shows that commercial providers are keen to proceed before the scientific evidence is established. This would be unimportant if the commercial offerings were harmless. However, inappropriate dietary change may harm the consumer's health and finances. It will be important to find ways of curbing the more extravagant claims, which are likely to tarnish the emerging science of personalised nutrition.

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Hunger and malnutrition in the 21st century

Despite record food output globally, hunger is still with us. **Patrick Webb and colleagues** argue that key policy actions are urgently needed to tackle this scourge and must focus on improving diet quality for all

Today's world is characterised by the coexistence of agricultural bounty and widespread hunger and malnutrition.[1] Recent years have seen a reversal of a decades old trend of falling hunger, alongside the re-emergence of famine.[1] National and global evidence shows that ensuring an adequate food supply is still an important contribution to eradicating hunger. However, generating more food in the form of staple grains or tubers is not enough. Good nutrition and an end to hunger both require everyone to have an appropriate diet. How can that be achieved?

Characterising the problem

A recent report for the World Committee on Food Security argued that "malnutrition in all its forms—not only hunger, but also micronutrient deficiencies, as well as overweight and obesity—is ... a critical challenge not only in the developing but also in the developed countries. Resolving malnutrition requires a better understanding of the determinants and processes that influence diets."[1] Malnutrition ranges from extreme hunger and undernutrition to obesity (box 1).[2 3] Furthermore, malnutrition is found in all countries, irrespective of their economic development, where people lack high quality diets.[4-6] Thus, solutions to hunger and to all forms of malnutrition need to focus on ensuring an adequate supply of food, but equally, on the quality of diets. Today, risk factors for ill health associated with poor quality diets are the main causes of the global burden of disease.[5 6] Low quality diets lack key vitamins, minerals (micronutrients), and fibre or contain too many calories, saturated fats, salt, and sugar.[7] In 2010, dietary risk factors combined with physical inactivity accounted for 10% of the global burden of disease (measured as disability adjusted life years, which reflect the number of years lost due to ill health, disability, or early death).[8] By 2015, six of the top 11 global risk factors were related to diet, including undernutrition, high body mass index (BMI), and high cholesterol.[9 10] Where governments have invested the economic gains derived from rising productivity in safety nets and services accessible to the poor, this has resulted in national growth.[11-13] However, where poverty persists, including in rich nations, hunger also persists.

Several faces of hunger

Hunger is a broad unscientific term that relates to nutrition and health outcomes in various ways. The proportion of people defined as hungry over the long term (usually termed "chronically undernourished") fell from 18.6% globally in 1990-2002 to under 11% in 2014-16 (table 1). That was a decline of 211 million people while the

KEY MESSAGES

- Despite record levels of food production globally, hunger and many forms of malnutrition still affect billions of people
- While traditionally associated with a lack of food, hunger, and malnutrition (which includes overweight and obesity as well as undernutrition) are associated with low quality diets
- Poor diet quality is a problem in every country—high and low income alike. A high quality diet meets most key nutrient needs, mainly through nutrient rich foods
- Securing high quality diets for all, comprising sufficiency, diversity, balance, and safety, is necessary to resolve hunger and malnutrition in all its forms
- Policy makers must urgently implement evidence based, cost effective actions that have a triple purpose: eradicate hunger, resolve all forms of undernutrition, and tackle obesity
- Governments must consider how policies across multiple sectors influence the functioning of food systems from farm to fork. They must identify changes that will help all consumers to have healthy diets
- The challenge is huge, but the urgency has never been so great

Box 1: Terms and definitions[1-3]

- *Hunger*—is characterised in many ways. It encompasses individual sensations and household behavioural responses, food scarcity (actual or feared) and national food balance sheets that focus on supply of energy (kilocalories) in any country in relation to a minimum threshold of need. The food balance sheet approach is the only standard of measurement used globally. It is based on data collated by the Food and Agriculture Organization of the United Nations. This organisation has replaced its previous use of the word "hunger" in describing this metric with the phrase "chronic undernourishment". This today is defined as "a person's inability to acquire enough food to meet daily minimum dietary energy requirements during 1 year" [1]
- *Malnutrition*—An all inclusive term that represents all manifestations of poor nutrition. It can mean any or all forms of undernutrition, overweight, and obesity
- *Undernutrition*—Refers to any form of nutritional deficiency, particularly those manifest in maternal underweight, child stunting, child wasting, or micronutrient deficiencies. It does not include reference to overweight and obesity
- *Maternal underweight*—A body mass index (BMI) of <18.5 among women of reproductive age. This typically reflects chronic energy deficiency coupled with a lack of other key macronutrients or micronutrients, ill health, or energy expenditure higher than consumption. A prevalence >20% indicates a serious public health problem
- *Child stunting*—Height for age ≤ −2 standard deviations of the median for children aged 6-59 months, according to World Health Organization child growth standards
- *Child wasting*—Weight for height ≤ −2 standard deviations of the median for children aged 6-59 months, according to WHO child growth standards
- *Micronutrient deficiencies*—A lack of various key vitamins and minerals leads to a range of symptoms that are of global concern. These include anaemia due to iron deficiency and risk of child mortality associated with clinical vitamin A deficiency. Such deficiencies are measured in several ways, including biomarkers (assessed using blood, serum, urine, etc), clinical manifestations, or proxy measures of diet quality
- *Overweight and obesity*—For non-pregnant adults, a BMI ≥25 represents being overweight. The threshold for obesity is a BMI ≥30. Child obesity is of increasing concern and was included in the latest global nutrition goals for 2030 ("no increase in childhood obesity")[4]

Table 1 | Numbers (millions) and prevalence (%) of people with chronic undernourishment, stunting, and wasting* by year and geographical region[2 14]

	Undernourished		Stunted (6-59 million)		Wasted† (6-59 million)	
Region	1990-2002	2014-16	1990-2002	2014-16	1990-95	2014-16
World	1010 (19)	795 (11)	254 (40)	155 (24)	50†(9)	52 (7)
Sub-Saharan Africa	176 (33)	220 (19)	38 (42)	59 (32)	8 (7)	14 (7)
Asia	742 (24)	512 (12)	190 (48)	88 (25)	40 (11)	36 (10)
Latin America and Caribbean	66 (15)	34 (6)	14 (26)	6 (12)	2 (3)	1 (1)
Oceania	1 (16)	1 (14)	<1 (36)	<1 (38)	<1 (6)	<1 (9)

* These are the three main metrics relating to hunger that can be reported globally, comparably and over time. Other measures (relating to food security, obesity, and micronutrient deficiencies) are not standardised in this way. This suggests an urgent need for the development of global data systems.
† No global dataset is available for wasting estimates covering the early 1990s. The data presented here for 1990-95 were calculated by de Onis et al 1993[15] and by de Onis and Blössner 2000[16] for developing countries only.

world's population increased by 2 billion.[2] Big gains were made in large countries like China and in Brazil, Ethiopia, and Bangladesh (box 2). South America was particularly successful, reducing undernourishment by over 50% in 25 years.[1] Such gains were made possible largely by rapid reduction of poverty, rising levels of literacy, and health improvements that reduced preventable child mortality.[17]

However, despite such progress the world still has unacceptably high numbers of undernourished people. Of the roughly 800 million undernourished, 780 million are in low income countries, especially in sub-Saharan Africa and South Asia.[1] The continents of Africa and Asia have the greatest number of people living in extreme poverty, and it is here that extreme hunger and poverty together present the greatest risk of famine.

Box 2: Successful resolution of undernutrition: Brazil, Ethiopia, and Bangladesh

Hunger (chronic undernourishment) has remained static at around 800 million people for several decades. This is largely because of rising populations in fragile states and the escalation of armed conflict in numerous parts of the world.[12] Nevertheless, child undernutrition has been falling. In 2000, roughly 200 million children under 5 years of age were stunted, but this has fallen to less than 151 million today. Rapid improvements in nutrition have been concentrated in several large nations, which have shown the way with policy success stories

- *Brazil* saw its prevalence of child stunting decline from 37% in 1974–1975 to 7% in 2006-7.[17] It achieved these gains through a sustained commitment to expand access to maternal and child health services (reaching into previously underserved geographical regions). This was coupled with large scale investment in social reform and safety net programmes that supported a narrowing of the income gap (through equitable poverty reduction), rising numbers of girls in school, declining fertility, and greater stability in income flows and food consumption among the poor. Stable food consumption was achieved through food supplementation targeted at mothers and children, and with cash transfers targeted at the poorest groups. All of this was helped by improved stability of governance. Few of these actions focused explicitly on nutrition, but many were driven by a policy agenda called "zero hunger." Even with recent economic challenges and changes of government, the gains made over past decades persist
- *Ethiopia* has faced famines many times between the 1980s and the early 2000s. It has also reduced child stunting from 58% in 2000 to <40% by 2014.[18] Although this figure is still unacceptably high, it represents a fall of about 1.2% a year.[19] Ethiopia also increased enrolment and retention of girls in schools during this period, increased agricultural productivity, and implemented a huge employment based safety net (one of the largest social protection programmes in Africa). However, two other important drivers improved nutrition in this period. Firstly, a move by government to treat nutrition as a multisector challenge (met by numerous line ministry responsibilities) and, secondly, improved sanitation, focused on eradicating open defecation, which was a major impediment to health and the retention of nutrients in the diet[18 19]
- *Bangladesh* is a modern nutrition superstar. It emerged from famine in the 1970s. Successive governments have worked alongside an unusually vibrant non-governmental sector to deal with underlying problems and visible symptoms of malnutrition. While service delivery remains generally weak, widespread targeted interventions were combined with a variety of nutritional measures that deal with underlying problems.[20] Such actions included economic growth policies aimed at the poor, girls' education, improved sanitation, and a significant turnaround in the agricultural sector, which moved Bangladesh from being a net importer of food to a significant exporter.[18 21] As a result, child stunting fell from almost 57% in 1997 to around 36% in 2014[18 19]

Famine is the most acute face of hunger. Over 70 million people died in famines during the 20th century.[22-24] Most deaths occurred in human induced crises, in which political mismanagement, armed conflict, and discrimination of marginalised political or ethnic groups compounded the effects of environmental shocks, such as droughts or locust invasions.[25] Deaths from famine fell from the mid-1980s onwards. However, as of 2017 four countries were again struggling to cope: Somalia, Yemen, South Sudan, and Nigeria.[26] In each case, instability induced by conflict, terrorism, drought and decades of failed governance have left over 20 million people facing famine, including 1.4 million children "at imminent risk of death."[27]

A major cause of mortality in famines is children becoming severely wasted. Around 52 million children were wasted in 2016, of whom around 70% (36 million) resided in Asia (table 1).[14] Roughly 12.6% of deaths among children under 5 are attributed to wasting worldwide.[28] Although wasting has declined, progress has been slow and some countries have seen a rise, including Pakistan and India.[29] Many of the drivers of wasting are often the same as for stunting—namely, low birth weight, lack of exclusive breast feeding, poor hygiene and sanitation, and infectious disease.[30] While wasting is one sign of acute hunger, stunting (being too short for one's age) represents chronic distress. Around 151 million preschool children were stunted in 2017, down from 200 million at the turn of the 20th century.[14] Improvements were made in east Asia, including China (today reporting a prevalence of only 6% compared with the global mean of 23%) and Bangladesh as well as in Latin America (table 1).[31] Nevertheless, South Asia and East and Central Africa all still had rates over 32% in 2017.

Coexisting forms of malnutrition related to diet

The coexistence of multiple forms of malnutrition is a global phenomenon. That is, wasting often coexists with stunting in the same geographical areas, and can be found simultaneously in children.[32] For example,

around 9% of children in India exhibit both conditions, while the rate in parts of Ghana is reported to be >3%.[32 33] Many countries with a high prevalence of stunting have made limited progress in achieving annual average rates of reduction required to meet global targets. For example, Timor Leste needs an annual reduction of around 5% to reduce stunting by 40% by 2030, but its current reduction rate is barely above zero.[9] Ethiopia also needs an annual average rate of reduction of 5%, but continues to remain at 3%.

Part of the reason for slow progress lies in overlapping micronutrient deficiencies. Inadequate supply of energy and protein both impair a child's growth, but micronutrient deficiencies also have a role. It has been estimated that roughly 2 billion people, or about 29% of the world's population, faced micronutrient deficiencies in 2010.[34-37] Micronutrient deficiencies are also widely present in high income countries. For example, childhood anaemia in 2010 was 26% in the Russian Federation and in Georgia, and 16%, on average, across the European Union.[38]

Obesity is conventionally associated with food excess, but it is also associated with micronutrient deficiencies and even with daily hunger, as shown for Malaysia,[39] Canada,[40] and Iran.[41] Indeed, people with obesity can be prone to deficiencies of micronutrients, such as zinc, iron, and vitamins A, C, D, and E.[42-46] Between 1990 and 2010, the prevalence of adults with a high BMI in sub-Saharan Africa tripled. At the same time, hypertension increased by 60%, and the prevalence of high blood glucose rose nearly 30%.[47]The prevalence of overweight and obesity among South Asian women is almost the same today as the prevalence of underweight.[6] Pacific and Caribbean islands and countries in the Middle East and Central America have reached extremely high rates of adult overweight and obesity. Some have a prevalence as high as 80% (eg, Tonga, 84% for men, 88% for women).[48]

Many countries today face the dual burden of rising rates of female obesity with continuing high rates of maternal underweight. The latter matters because of ill effects on the mother and on the unborn child. Roughly 30% of stunting by a child's 3rd birthday can be attributed to being born small for gestational age, which is linked to nutrition before birth and health problems of the mother.[28] Not only is maternal underweight still more prevalent than overweight in rural parts of South Asia and sub-Saharan Africa but adult female underweight rose recently in Senegal, Madagascar, and Mali, mainly in urban settings.[49]

Thus, actions are needed in all countries around the world to deal with undernutrition, micronutrient deficiencies, and overweight and obesity simultaneously. No country is exempt. "Triple duty" investments are needed everywhere because wealth and food sufficiency will not in themselves resolve the problems of low quality of diets.

Effective actions to tackle hunger and malnutrition

In 2016, the world hit a new record by producing over 2.5 billion metric tons of cereal grains—up from 1.8 billion tons 20 years earlier.[50] But hunger persists because an increased supply of food alone is neither the solution to hunger nor an answer to malnutrition. Countries that have made recent progress in reducing hunger and improving nutrition have a core set of common characteristics. Firstly, they tend to be politically stable countries that have pursued relatively equitable growth policies (not only increasing wealth for some but reducing poverty overall). Secondly, they employ targeted safety nets for the poor and invest in accessible services (education, clean water, healthcare). Thirdly, they assume responsibility for responding to shocks (economic, environmental, or due to conflict) in timely ways that mitigate human suffering.

Successful actions typically include a mix of targeted so called nutrition specific programming (aimed at preventing or resolving defined nutrition and health problems in individuals) and nutrition sensitive interventions for the whole population that deal with the underlying causes.[9 32 35] Table 2 provides details of evidence based policies and programmes in a variety of sectors, which are known to reduce hunger and deal with malnutrition.[32] In food and agriculture, these may include national price support interventions that increase the supply and accessibility of nutrient rich foods (often perishables, like dairy, fruits and fresh meats), coupled with technical and financial support for women farmers to produce nutrient rich vegetables in their gardens. In health, national policies to support accessible high quality services are critical to ensuring antenatal and postnatal care, particularly combined with targeted nutrition, exclusive breast feeding, and infant feeding messaging. Measures directed at underweight mothers are important for good birth outcomes, as well as varied forms of micronutrient supplementation.[1] In other words, the quality of services, scale of coverage, and the singling out of nutritionally vulnerable

Table 2 | Examples of actions to tackle hunger and malnutrition across sectors[3 20 47 51]

Sectors of intervention	Sensitive to nutrition (dealing with underlying causes)	Specific for nutrition (dealing with specific symptoms)
Agriculture	Promotion and support of smallholder horticulture production; investments in research and extension supporting productivity gains in foods rich in nutrients; promoting food market development to increase smallholder farmer incomes and price accessibility to diets rich in nutrients	Enhanced agriculture extension with messaging on optimal diet choices; facilitating access to rural finances for farmers, food processors and traders (particularly focusing on women's involvement); interventions supporting optimal levels of consumption of foods rich in nutrients (eg, poultry promotion/vaccination, egg marketing, fruit/vegetable cold chain marketing)
Health	Establishment of high quality, high coverage health services, including nutrition counselling and reproductive health; effective reduction of the burden of infectious diseases; promotion of evidence based dietary guidelines to the population	Promotion and facilitation of exclusive breast feeding and early child development, targeted food supplementation of underweight mothers; cash transfers for populations at risk; micronutrient supplementation; management of diseases (access to impregnated bed nets, reduction of household air pollution through improved stoves and fuel); maternal deworming (which may improve anaemia)
Education	Universal enrolment and retention of girls in schools; use of schools to provide instruction on nutrition and health; promotion of awareness of a healthy diet through school gardening; enhanced curricular initiatives on diet, and physical activity	Healthy meals/snacks provided in schools (and other institutions), using locally procured foods, as appropriate; deworming and vaccination at school; after-school outreach education programmes for adolescent girls, focusing on antenatal nutrition and health
Water and sanitation	National and local programmes that eliminate open defecation; universal provision of clean water; promotion of good sanitation and hygiene practices	Promotion of hygiene and sanitation best practices in households; use of improved water sources; facilitating access to improved toilets
Market development	Micronutrient fortification of widely accessible foods, including salt iodisation; quality and food safety regulation	Development of rural feeder roads and other infrastructure (facilitating sale of produce and access to a diversity of fresh produce at markets)
Resilience building	Implementing effective social safety nets that smooth income flows and food consumption among vulnerable groups	Preparedness for rapid establishment of targeted management/treatment of acute malnutrition; targeted use of specialised nutritious food products to individuals at risk in emergencies

demographic groups are all keys to success.[20 47]

Good nutrition and eradication of hunger comes at a price, but pays for itself in the longer term. Donor funding for nutrition sensitive programmes rose between 2003 and 2015, from 11.8% to 19.4%, reaching around $19bn (£14bn, €16bn) in 2015.[48] Such assistance is deemed to be effective, in that a 10% increase in overall nutrition sensitive aid delivers an estimated 1.1% "decrease in hunger" (measured as chronic undernourishment).[48] The World Bank has argued that a "priority package" of evidence based nutritional interventions that could be readily scaled up would require roughly $23bn over a decade, or $5 per child.[51 52] The World Bank emphasises that while international donor agencies should increase spending to achieve global nutrition goals, national governments and citizens themselves need to increase spending and act appropriately. The role of individuals and families comes largely in the form of preferences and constraints.[52] People make choices that shape dietary patterns and physical activity but also the uptake of healthcare services, spending on smoking and hygiene, as well as investments in schooling for their children and agricultural productivity (if farmers).

The value of such large investments to future human and economic development has long been understood in high income countries, such as Europe and the United States. European countries deploy a wide range of policies to combat residual hunger. These include promoting more diverse local food production and diversified diets, the latter "encouraged through nutrition education targeting school children and mothers of young children."[38] The United States also supports large state food provisioning through nutrition programmes aimed at women and children. For example, spending on the federal food stamp programme in 2017 reached $68bn ($126 per person).[53] Similarly, spending on the Women Infants and Children programme, which targets low income families nutritionally at risk with food supplements, nutrition education, and health system referrals, reached $6.5bn in 2017.[54]

Conclusions

The sustainable development goals require all countries and their citizens to act together to end hunger and all forms of malnutrition by 2030.[13] Setting targets is a good first step, but actions need to follow quickly. Urgent attention to achieve such goals is seriously overdue. Policy action must be designed to reduce malnutrition in all its forms, and be adequately funded. Measures must be evidence based, implemented at scale, and include both broad based and targeted actions aimed at the most nutritionally vulnerable people. The evidence to support such actions is growing, but it is already plentiful and compelling; there is no need for delay. The rapidly escalating threats posed by malnutrition represent a planetary challenge on a par with poverty and climate change. An appropriate response at the required scale is top priority for decision makers globally. It cannot wait.

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Nutrition disparities and the global burden of malnutrition

Strategies to tackle stunting, obesity, and micronutrient deficiencies must take into account the inequities in which these diseases are rooted, argue **Rafael Perez-Escamilla and colleagues**

Social determinants of health are understood to be key to grasping why inequalities in health outcomes exist within, and between, populations. They are also implicated in the differences in dietary intake, dietary patterns, and dietary quality seen in some groups, leading to an unequal burden of disease and morbidity. Nutrition disparities are reflected in the higher prevalence of undernutrition; overweight and obesity (overnutrition); or both, in inequitable social conditions, such as poverty. They happen more often in low and middle income countries (LMICs) compared with high income countries (HICs), and also in subpopulations within these countries. The double burden of malnutrition (DBM) refers to the coexistence of under- and overnutrition that can happen at the individual, household, or population level.

Tackling the coexistence of stunting and overweight (including obesity) has been identified as a formidable challenge for LMICs, requiring integrated, multisectoral actions.[1 2] These two DBM components have common elements rooted in the social determinants of health (SDoH). For example, household food insecurity, a condition related to poverty that limits access to a nutritious and safe diet, has been consistently associated with both undernutrition in children and overweight in women.[3-5] The first 1000 days of life offer a window of opportunity to prevent both stunting and obesity, and are a worthwhile focus for strategies to tackle nutrition disparities.

KEY MESSAGES

- As a feature of the double burden of malnutrition (DBM), child undernutrition and adult obesity coexist in low and middle income countries (LMICs)
- The DBM in LMICs and obesity in high income countries (HICs) are concentrated among the poor
- Nutrition specific interventions alone have not been able to make a significant dent on the DBM in LMICs
- Multisectoral policies that tackle the social determinants of health are needed to prevent and reduce inequities in undernutrition and obesity globally

The main objectives of this article are to: describe nutrition disparities in stunting in LMICs and obesity in both LMICs and HICs; discuss disparities in micronutrient malnutrition using anaemia as an example; describe the critical role of breastfeeding for maternal-child health and identify challenges to its practice; and consider whether an integrated, equity focused, multisectoral approach, focused on the SDoH, could tackle both stunting and obesity.

The maternal-child life course

Nutritional disparities and the DBM must be considered from a life course perspective. Research focusing on women of childbearing age living in socioeconomically deprived circumstances has documented the intergenerational transmission of both stunting and obesity.[6-8] Albeit less studied, paternal excessive body weight has also been associated with increased obesity risk in children.[9]

Over 2 billion people are overweight and almost two thirds live in LMICs.[2 10] Obesity among women of childbearing age and children is increasing globally.[11] Women who enter pregnancy overweight are more likely to gain excessive weight during pregnancy, develop gestational diabetes, deliver large for gestational age or premature newborns, and are less likely to breastfeed.[11] Children born to overweight women have increased risks of developing obesity that persist as they mature. Women then pass to their children an increased risk of obesity that persists into later life, perpetuating the cycle.[6 12 13]

Maternal stunting, underweight, and gaining less weight than recommended during pregnancy are associated with intrauterine growth restriction, which has also been associated with increased risk of stunting.[2] As with obesity, stunting is transmitted from one generation to the next, possibly through epigenetic mechanisms,[14] and stunting is a risk factor for the development of obesity.[15 16] This early onset risk is difficult to reverse after infancy, underscoring the high priority for very early intervention to achieve normal weight among all women and men.

Intergenerational transmission of risk for malnutrition is heightened in the presence of social, economic, and gender inequities.[6 17] The challenges associated with facilitating optimal pre-conception nutrition are rooted in many societal processes and sectors. These need to be tackled by equity focused policies and systems through changes in community capacity building, advocacy, and political will[7 18-20] (fig 1).

Patterns of nutrition disparities

To have a better understanding of socioeconomic inequities in nutrition outcomes across countries with different levels of economic development, this section first presents data on the distribution of stunting, obesity, and anaemia among LMICs, followed by the distribution of obesity in HICs as a function of family socioeconomic status.

Iron deficiency anaemia was chosen because it is the most common micronutrient deficiency related condition all over the world,[21] there are clear inequities in its distribution, and it has proven to be difficult to tackle through simple supplementation or fortification.[22 23]

Stunting, obesity, and anaemia in low and middle income countries

An analysis of 80 countries by world regions, as classified by UNICEF, shows that stunting and overweight are not randomly distributed within any given population. In all regions, stunting prevalence among children under 5 decreases as wealth increases (fig 2). The highest prevalence of stunting and widest wealth driven gaps are in south Asia, and the narrowest in eastern Europe and central Asia.

By contrast, child overweight (fig 3) is positively associated with wealth in all regions, with west and central Africa showing the smallest gaps. However, although absolute obesity prevalences are still higher among the wealthier in LMICs, obesity rates are growing much faster among the socioeconomically vulnerable, including indigenous groups defined as the original inhabitants of a region.[24 25]

Inequities are also present with respect to iron deficiency anaemia, which is highly prevalent among young children in LMICs. Demographic and Health Survey (DHS) data, collected between 2005 and 2016 from 52 low, lower-middle, and upper-middle countries, showed an overall

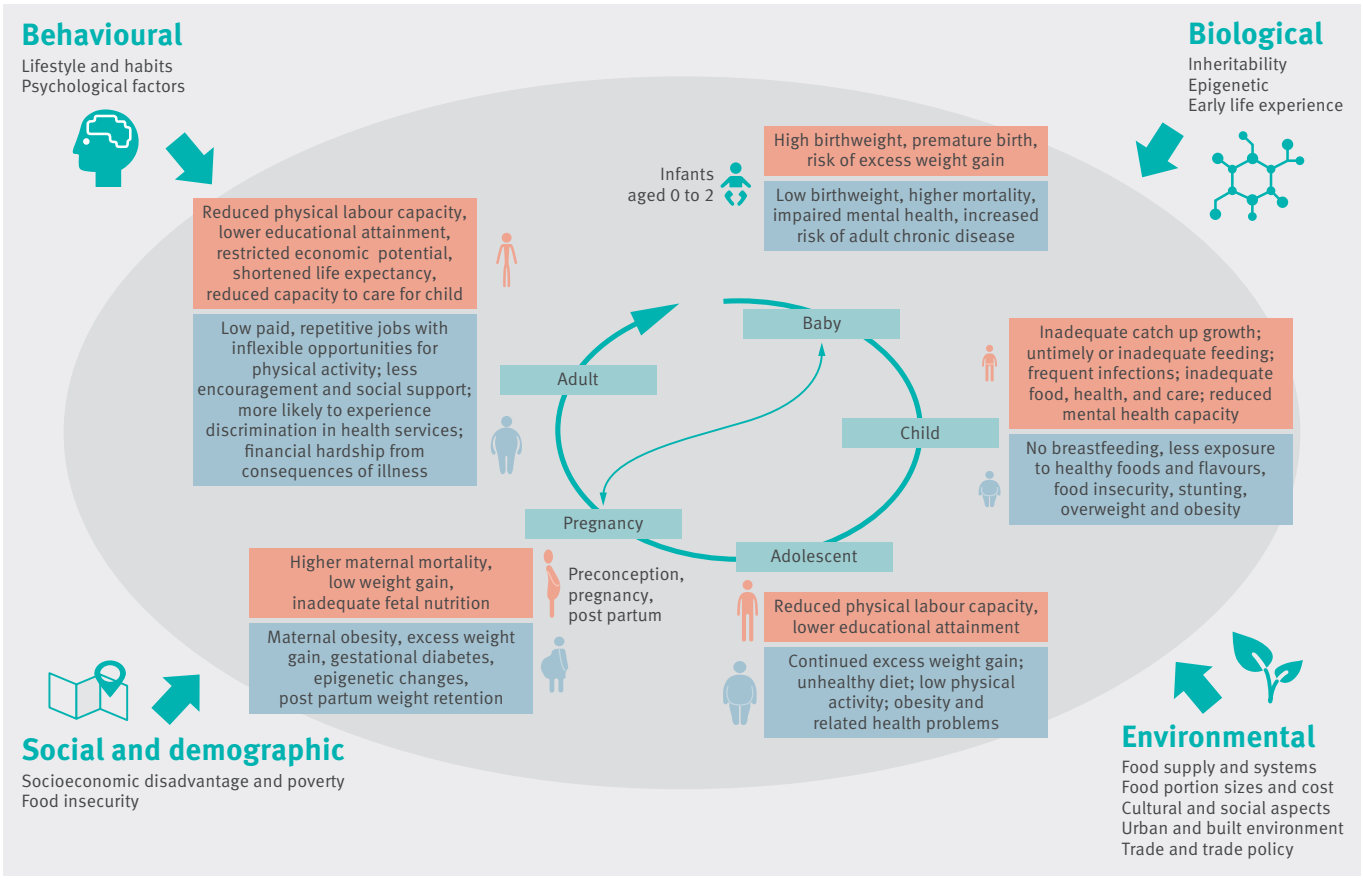
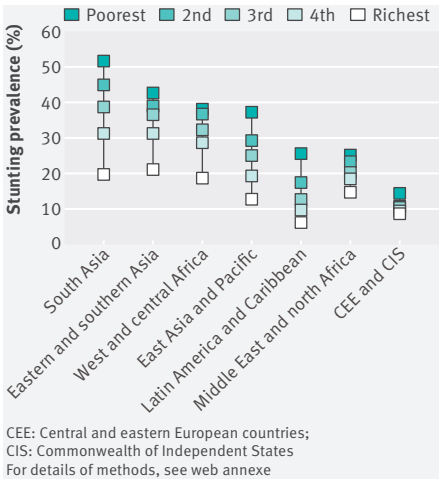


Fig 1 | The double burden of malnutrition through the life cycle and across generations and shared drivers[17 19]

anaemia prevalence of 54.2% among children less than 5 years old. Disparities were found as a function of both World Bank country income classification[26] and wealth index as defined by DHS.[27] The unweighted mean prevalence of anaemia was highest in the 22 lower income countries (61.7%) and lowest in the six upper-middle income countries (39.4%), and in between in 24 lower-middle income countries (51.7%). Consistent with these findings, in all three country income groupings, children in households in the poorest quintile had the highest anaemia prevalence and those in households in the wealthiest quintile had the lowest (fig 4).

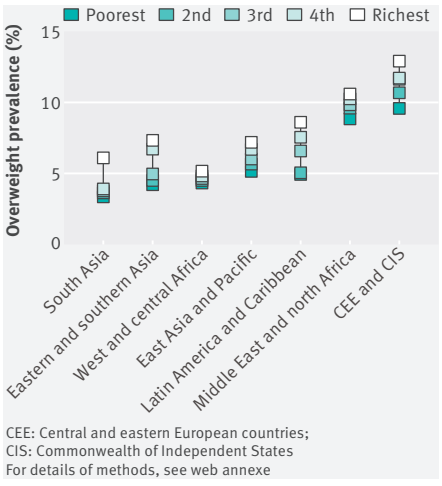
Obesity inequities in high income countries

Both maternal and child obesity are more prevalent among the poor in HICs.[28 29] However, an initial pattern of more obesity among the wealthy is seen where undernutrition among the poor is still the predominant problem.[30] As previously indicated, overweight prevalence is increasing rapidly among the poor, including in rural areas and indigenous communities.[31] Prevalence increases with social disadvantage, as illustrated for the US and England in figs 5 and 6.[32 33] Additionally, inequities affecting ethnic minority populations are pronounced (figs 7 and 8).[32 33] Children in ethnic minority populations living in HICs, including the US, often experience social inequities disproportionately.[34]



CEE: Central and eastern European countries;
CIS: Commonwealth of Independent States
For details of methods, see web annexe

Fig 2 | Stunting prevalence in children under 5 years old, according to wealth quintiles by world regions ordered by prevalence in the poorest quintile



CEE: Central and eastern European countries;
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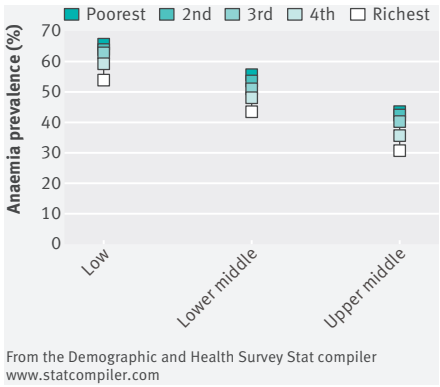
Fig 3| Overweight prevalence in children under 5 years according to wealth quintiles, by world regions ordered by prevalence in the poorest quintile



From the Demographic and Health Survey Stat compiler
www.statcompiler.com

Fig 4 | Percentage of children less than 5 years old with anaemia (Hb < 11 g/dL) by World Bank country income classifications and Demographic and Health Surveys wealth index

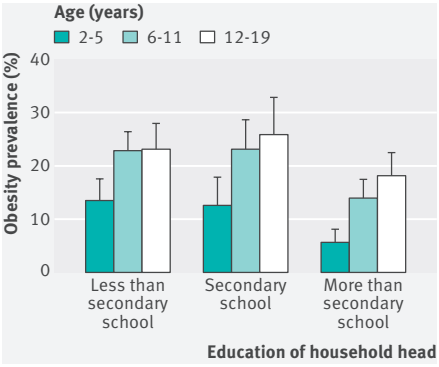


Fig 5 | Association of childhood obesity with educational attainment in the US

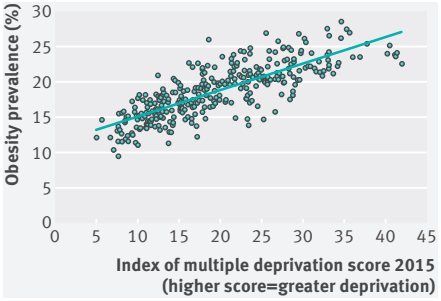


Fig 7 | Obesity prevalence among US children from diverse racial groups

Strategies for tackling undernutrition and overweight

Given the well established excessive stunting risk among the poor, and the growing concentration of overweight in socioeconomically vulnerable groups, it is important to explore potential solutions to the DBM in LMICs and the obesity epidemic in HICs at different levels of the socioecological model, taking into account other nutrition related problems, including anaemia (box 1).

There is increasing recognition that early life strategies to tackle undernutrition should take into account other forms of malnutrition, including obesity.[18 35] Otherwise, solving one problem can magnify another. Global food security initiatives, for example, often promote the production and availability of specific staple crops such as grains or starchy vegetables. Such programmes have succeeded in increasing the availability of plant protein and food energy,[36] but have been criticised for distorting markets and potentially promoting obesity and non-communicable disease (NCD) risk by making healthier foods less affordable for consumers, leading to less varied, more energy dense diets for consumers.[37] International initiatives for food security are now considering balancing programmes focused on protein energy malnutrition and micronutrient deficiency with obesity prevention initiatives.[5 35 38]

Undernutrition

Stunting

Prevention of child stunting through nutrition specific interventions, such as lipid based nutrient spreads (LNSs), has been suggested, but effectiveness trials have had mixed results.[39-41] A recent review found that small quantity (SQ)-LNS are generally well accepted but remain unproven for efficacy in improving linear growth or preventing growth faltering.[39] These findings are consistent with an expert review of eight pregnancy and early childhood randomised controlled trials (RCTs) conducted in Asia, Africa, the Caribbean, and Latin America.[41] Thus, drawing on insights from the social ecological model, which postulates that health behaviours are shaped by the interactions of people with their larger social, cultural, economic, and environmental contexts,[42] tackling stunting simply as a food problem to be solved with nutrition specific interventions in the absence of tackling SDoH is not enough.[43]

As described above, stunting in children is more concentrated in LMICs where living standards are suboptimal—these environments asssre characterised by poor environmental sanitation, poverty, food insecurity and hunger, and lack of access to quality healthcare and education. Countries like Brazil, Chile, and Peru have been successful at tackling chronic malnutrition through more equitable social and economic policies.[44-46] The case study of Brazil illustrates the value of nutrition sensitive interventions in concert with those focused on SDoH (box 2). Tackling stunting does require effective and equitable policies and civil society participation in governance structures that facilitate inclusive, equitable, and sustainable economic growth: multisectoral strategies that tackle cultural diversity, eating styles, and both local and global food systems,[47] as well as access to clean water and sanitation, healthcare, and education.[48]

Anaemia

Systematic reviews of several RCTs of micronutrient powders (MNPs) in Africa, Asia, and the Caribbean have found a reduction in the risk of anaemia and iron deficiency of around 30% and 50%, respectively.[49 50] A recent Cochrane review that included 13 RCTs from Africa, Asia, and Latin America found that provision of MNPs (containing between 2 and 18 vitamins and minerals) to young children led to lower risk of anaemia and iron deficiency.[51] However, although MNP interventions were overall well accepted, adherence was context specific and in several studies comparable to the same benefit as using standard iron supplementation interventions.[50] In addition, the effect of MNPs on diarrhoea risk needs to be further examined.[51] LNS interventions havsse also reduced anaemia prevalence[40 41] although it is unclear if either MNPs or LNSs provide benefits above and beyond standard approaches.[50] As with stunting,[48] sustainable reductions in anaemia prevalence require well coordinated, effective, multisectoral policies that include health, nutrition, agriculture, water and sanitation, education, and social protection sectors.[52]

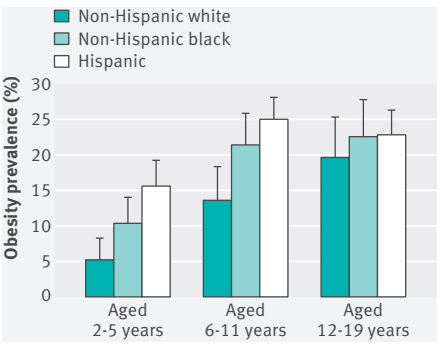


Fig 6 | Association of overweight children with neighbourhood deprivation, 10-11 year old children in England

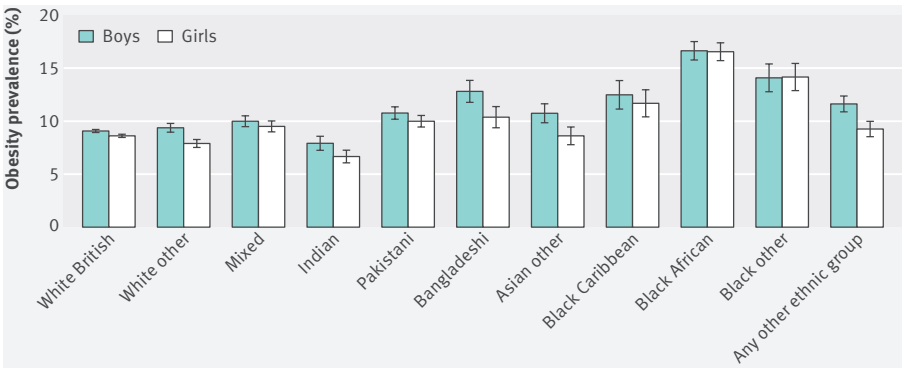


Fig 8 | Prevalence of child overweight among 4-5 year olds in diverse ethnic groups in England

Box 1: Nutrition disparities: where do we go from here?

Context

- Poverty and other social inequities are associated with poor nutrition in both LMICs and HICs, also among certain population subgroups within countries
- The double burden of malnutrition (DBM), defined as the coexistence of undernutrition (for example, stunting) and overnutrition (overweight or obesity) at the population, family, or individual level, is highly prevalent in LMICs
- HICs are experiencing a major obesity epidemic. Socioeconomic inequities have been associated with both under- and overnutrition within HICs

What is known

- In all regions where LMICs are located, stunting prevalence among children under 5 is inversely associated with family wealth
- The prevalence of adult obesity continues to concentrate more among the poor in LMICs and in the US
- The obesity epidemic continues to be unabated in HICs. Multisectoral life course strategies are needed to tackle it
- DBM occurs in the context of widespread micronutrient deficiencies
- LMICs do not have well coordinated strategies to effectively tackle the DBM

Areas of consensus

- Tackling inequities in the distribution of the DBM in LMICs and the obesity epidemic in HICs requires also tackling the social determinants of health, including access to food security, healthcare, education, and jobs that pay reasonable wages
- Nutrition specific interventions during the first 1000 days of life including preconceptional nutrition, nutrition during pregnancy, and optimal breastfeeding and complementary feeding are key for tackling the prevention of infectious diseases and non-communicable diseases globally.
- The DBM requires avoiding strategies that solve one nutrition problem while magnifying another one such as the use of sugar as a vehicle for micronutrient fortification.

Areas of controversy

- We don't know if micronutrient specific interventions such as lipid nutrient supplements reduce the risk of stunting in low income countries
- It's unclear how to improve access to social determinants of health in different contexts given that this requires equitable and sustainable economic growth which is lacking among the populations that are most vulnerable to experiencing nutrition inequities

Future directions in this field

- Implementation of science research based on complex systems frameworks is needed for understanding how to scale up cost effective, multisectoral interventions that can simultaneously tackle stunting, overweight, and micronutrient deficiencies

Box 2: How did Brazil reduce levels of stunting and change breastfeeding practices?

Brazil has shown impressive improvements in stunting levels and breastfeeding practices since the mid-1970s.[46 109] Stunting prevalence among children younger than 5 years has dropped from 37% in 1975 to 19% in 1989 and to 7% in 2007. Exclusive breastfeeding (< 6 months) underwent a remarkable improvement from 4.7% in 1986 to 37% in 2006 and relative stabilisation between 2006 and 2013[109]; during the same period, the median duration of breastfeeding increased from around 2.5 months to 14 months.[46]

This progress is derived from a strong political commitment in reducing malnutrition and corresponding inequities following a socioecological approach. Up to the mid-2010s, Brazil had tackled three key components of social determinants of health and nutrition through well thought out multisectoral policies[46] reflected in: more equitable wealth distribution; improved social protection and public health programmes (for example, conditional cash transfer programme Bolsa Família and improvements in water and sanitation); restructuring and strengthening of the health sector by expanding coverage and quality of public health programmes (promotion of breastfeeding, oral rehydration, and immunisations), universal healthcare coverage, and implementing multiple national and state-wide effective maternal and child health and nutrition programmes and policies, including paid maternity leave.

This case study illustrates that improving breastfeeding and reducing stunting require both nutrition sensitive and nutrition specific approaches delivered though a socioecological, multisectoral, well coordinated framework.[79ss]

Overweight

The social ecological model has also widened our understanding of the causes of obesity beyond biomedical or psychological paradigms. Population level obesity is recognised as the result of the complex, multilevel interplay of biology, behaviour, and environments.[53] For management of obesity and prevention in high risk groups, there is a role for individual level intervention in clinical and community settings. However, relative increases in inequities associated with social disadvantage indicate that current individually focused obesity prevention efforts in the absence of structural changes to facilitate behaviour changes may be doing harm by widening wealth driven inequities.[12] To be broadly effective, population level obesity prevention must account for the wider social and environmental contexts in which people make food choices.[54] Specifically, obesity prevention requires collectively tackling behavioural, biological, environmental, social, and demographic drivers from the individual level to the population level, paying strong attention to equity (fig 1).

Consumer oriented policies are an important focus of strategies to tackle obesity. In HICs, reconciling the roles and responsibilities of individuals, communities, governments, and markets has been a major challenge.[55] Although there is consensus that tackling unhealthy eating behaviours is fundamental for curbing the obesity and NCDs epidemics,[1056 57] there is limited agreement on how this should be achieved. The dominant paradigm of placing responsibility with the consumer, exemplified by individually focused education, is now shifting to population level consumer information based interventions, such as menu labels in restaurants,[58] labels on manufactured foods,[59] and nutrition oriented shelf labels in supermarkets.[60] The impact of informational approaches has been limited, in part because the majority of food related decisions are not the result of rational reflection and deliberation, but rather automatic and habitual behaviours, cued by the food retailing environment and reinforced by cultural norms.[61] Moreover, information based approaches can potentially widen inequalities, because they generally work best in higher socioeconomic status populations, which have more psychosocial and material resources to act upon health related information.[62] This reinforces the importance of tackling these epidemics through multisectoral policies that tackle the SDoH.[38]

Critical role of breastfeeding

Whereas above we discussed the highly specific micronutrient fortification

interventions as a way to tackle anaemia, it is important to also take into account that there are key nutrition specific interventions, such as breastfeeding, that involve complex maternal-infant behaviours and their interactions within the context of their surrounding social, economic, and cultural environments. Breastfeeding is an example of an early life nutrition behaviour that has implications for both undernutrition and infectious diseases, as well as obesity and chronic diseases in the child, and also offers major health benefits to the mother.

There are also exclusive breastfeeding inequities that need to be tackled through the socioecological model lens.[63] Sufficient duration of breastfeeding is critical for maternal and child health[64] and also facilitates obesity prevention, especially for children at high biological risk of excess weight gain.[65-67] Breastfeeding may also help to break the cycle of intergenerational transmission by facilitating maternal postpartum weight loss,[68-70] decreasing the mother's risk of being more overweight in a subsequent pregnancy. This applies especially in HICs but is becoming relevant to those LMICs where the majority of women of reproductive age are overweight or obese.[69 71] Overall, breastfeeding prevalence and duration are lower and obesity rates higher in HICs than in LMICs[64 68 72]; obesity is more common among women in low income and ethnic minority populations in HICs[32 73]; and breastfeeding is less common among women with obesity.[68 74]

Breastfeeding traditions in some indigenous and established or new immigrant racial or ethnic minorities in HICs may be associated with higher breastfeeding prevalence compared with the host population but may not be sustained with continued exposure to contexts that favour formula feeding.[75] Breastfeeding promotion involves "baby friendly" initiatives in hospitals and various education and counselling approaches to motivate and support breastfeeding in community and family settings.[76] Studies in diverse countries indicate that such interventions typically improve one or more key breastfeeding outcomes—initiation, duration, or exclusivity[77]—in some cases with relatively larger effects among women in less educated or ethnic minority populations that have especially low breastfeeding rates.[76] Breastfeeding in LMICs tends to last longer among poorer and rural women than in the rest of the population, and breastfeeding is one of the few healthy behaviours that are more common among the poor. However, in several middle income countries breastfeeding rates are increasing among high income women while declining among low income and indigenous women.[78]

Improving breastfeeding duration and exclusivity require policy based interventions that empower women and their families.[76 79] Relevant policy targets include: infant formula marketing regulation through enforcement of the international code of marketing of breastmilk substitutes and subsequent relevant World Health Assembly resolutions[80]; pre-service breastfeeding education and training in medical, nursing, and allied health schools; breast pump access; family leave policies; flexibility of work hours or locations, and protections for women in informal work sectors; and accommodations for breastfeeding mothers in workplaces and childcare settings.[74 79] Empirical evidence for the effectiveness of such policy approaches relies primarily on observational studies but is consistent with the underlying known structural factors affecting breastfeeding.[79 81] The case of Brazil illustrates how nutrition sensitive and nutrition specific interventions through a social ecological, multisectoral, well coordinated framework can have an impact on improving breastfeeding outcomes[79] (box 2).

Tackling the social determinants of health

Given the central role that social determinants of health play in nutrition and health outcomes across the life course, strategies that tackle social determinants will be key to tackling the DBM in LMICs and the obesity epidemic in HICs. The social ecological model has been used to understand the aetiology of child undernutrition[82] and overweight across the life course,[42 83] without recognising that both may have common structural determinants. The common pathways suggest the potential for integrated SDoH strategies.[1 35 84] The recent trend of tackling economic and environmental determinants of unhealthy diets will likely result in greater equity in obesity prevention in HICs and may also be effective for tackling obesity in LMICs.[66] In these countries, rising consumption of processed food products high in sugar, salt, and fats has been attributed largely to structural factors stemming from economic development, particularly rising incomes, urbanisation, and globalising economies enabling foreign investment, and imports of cheap, processed foods.[10 30 85 86] Food consumption is inherently an economic activity, with implications for the political economy of the food system, and the interests of powerful stakeholders within it. In the long term, agriculture sector policies that prioritise commodity crops that provide a cheap and steady source of starch, fat, and sugar in the food supply will need to change consistent with public health goals.[87] Fiscal incentives for the production of a variety of fruits, vegetables, and sustainable protein sources should be considered.[57 88]

Fiscal, demand side interventions are also important for tackling undernutrition in LMICs, but unintended consequences may arise. Conditional cash transfer programmes (CCTs), which provide cash to poor households that agree to participate in education and health promotion activities, have reduced child stunting in some settings and population subgroups.[89-91] However, CCTs have also been associated with increased risk of obesity and greater intake of sugar and sugar sweetened drinks among adults.[89 92 93] CCTs are designed to supplement the incomes of low income families and can be used for anything the family needs or wants, not only food, as long as they meet the programme conditions (participation in education and health services). Studies have shown, however, that CCT funds do help reduce food insecurity in target families.[91]

Another fiscal demand side intervention indicates that subsidies for healthy foods in the form of vouchers or discounts ranging from 10% to 50% can have beneficial effects on food purchasing in LMICs.[66 94-97] Targeted food taxes may also be effective. The tax on sugar sweetened beverages and energy dense snack foods in Mexico[98] has reduced the purchase of these products, with effects strongest in lowest income households.[66] Likewise, Hungary's tax, which is partly determined by sugar content of food and drink, has resulted in a substantial decline in consumption of the taxed products.[99] Preliminary evaluations of more recently implemented taxes on sugar sweetened drinks in Chile,[100] Barbados,[101] South Africa, and some US municipalities are showing promising results.[102]

Implications for dietary guidelines

Tackling the DBM requires taking into account food systems in the context of socioeconomic inequities. Therefore, it is key for influential policy instruments, such as government issued dietary guidelines, to take these inequities into account when selecting evidence based policies and programmes. The DBM demands a new strategy for dietary guidelines that seek to simultaneously curb the stunting, obesity, and micronutrient deficiency epidemics while taking into account the profound inequities upon which they are rooted. Food based dietary guidelines are needed not only for consumers but also for providers across sectors and for the development of evidence based policies and programmes.[103-105] Dietary guidelines and ancillary products are being issued

globally [106 107] but few tackle the importance of the first 1000 days for stunting and obesity prevention. Likewise, very few are grounded on the principles of responsive parenting and feeding which has been shown to be crucial for childhood obesity prevention.[107] Future guidelines will need to take this knowledge into account as well as the increasing evidence on effective policies to implement the WHO code on marketing of breastmilk substitutes[80] and subsequent relevant World Health Assembly resolutions, and to limit consumption of unhealthy foods and drinks, provide consumers with more information, and encourage product reformulation to reduce or eliminate added sugars and trans fats.[64]

Conclusions

Can an integrated multisector strategy can be designed to prevent both stunting and obesity in LMICs? International development agencies have identified the development of multicomponent strategies to tackle the coexistence of contrasting forms of malnutrition across the life course as a priority. This should be possible because, as the evidence presented here highlights, common drivers of the food and nutritional components of the DBM, and the obesity epidemic in HICs, are: intergenerational transmission; environmental and socioeconomic influences (for example, the ability to access nutritious foods and adopt healthier nutrition habits and behaviours); and a lack of shared multisectoral delivery platforms (fig 1). Common platforms for delivering actions can offer an opportunity for alignment and coordination of cost effective integrated actions and can be a catalyst for tackling policy challenges beyond health—including reducing health and social inequities within populations and raising educational attainment.[35] It is important to acknowledge that, even though multisectoral coordination is needed for delivery of effective programmes to prevent stunting, obesity, and micronutrient deficiencies through common interventions, recovery from stunting and obesity does require different sets of interventions once these conditions are established.

Our conclusions are congruent with the "double duty actions" recently proposed by WHO.[35] These actions call for policies and programmes that can simultaneously reduce the risk or burden of both undernutrition and overweight, obesity, or diet related to NCDs through common interventions following three levels of recommended actions[35 108]: ensuring that current interventions, policies, and programmes designed to tackle one form of malnutrition do not inadvertently increase the risk of another (for example, sugar fortification with micronutrients, or agricultural policies that foster the consumption of energy dense foods and sugar sweetened beverages); leveraging existing actions designed to tackle one type of malnutrition to simultaneously reduce other types, especially maternal-child nutrition programmes during the first 1000 days; and identifying the shared upstream nutrition sensitive drivers between different forms of malnutrition (such as food systems). Tackling the double burden of malnutrition through double duty equitable actions will be of critical importance in achieving both the ambitions of the UN's Decade of Action on Nutrition and the Sustainable Development Goals.[108] Implementation science research based on complex systems frameworks is needed for understanding how to scale up cost effective, multisectoral interventions that can simultaneously tackle stunting, overweight, and micronutrient deficiencies.

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Making progress on the global crisis of obesity and weight management

Food and obesity are undoubtedly linked but the relation is complex. **Michael Lean and colleagues** discuss what we know, and what we don't know, about weight management

Obesity is an unsolved crisis, generating long term distress and disabilities, reducing human capital, and increasing disease burdens and healthcare costs globally. Obesity has a complex aetiology, incurring controversies within both scientific and media arenas.[1] Poor education and socioeconomic situations are important drivers of severe obesity, confounding country analyses by racial or ethnic groups. Data collected by EUROSTAT show wide variations in prevalences of people with a body mass index (BMI) >30 across European states.[2] Age is important: by age 65-70, as many as 40% of all people in the UK reach a BMI >30, and 80% have a BMI >25.[3] Many with BMI >30 will experience secondary medical consequences, although overall life expectancies of populations have increased steadily despite obesity and the disabilities it brings.

Many factors have been associated with weight gain, difficulty achieving and maintaining weight loss, and secondary medical consequences of obesity. Some have causal influences, many are innocent bystanders, and some have no basis in science. We focus on those related to food.

KEY MESSAGES

- The balance between calorie intake and calorie expenditure determines body weight and body fat changes
- Different foods influence total energy consumption by modifying appetite, or by affecting energy expenditure, eg through diet induced thermogenesis
- Overweight people generally consume more food energy (calories) than thinner people to maintain their higher body weight weight
- Any diet plan that an individual is able to adhere to will cause weight loss, but different dietary patterns may influence adherence to different degrees in different subgroups
- Weight loss maintenance is a greater challenge than weight loss for many people because it requires adapting to permanently eating less energy despite living with in the same physical, social, cultural, and educational environments in which they developed obesity

Energy balance: is a calorie always a calorie?

The energy equation—that calories consumed=calories expended +/- calories stored (as body fat or glycogen)—is always true. Obesity develops if absorbed dietary energy (calories) from foods exceeds energy expenditure for a considerable period (box 1). Similarly, excess body fat is lost if energy intake falls below expenditure. However, numerous multilevel factors contribute to determining energy expenditure, intake, and absorption, and small mismatches with food consumption over a long period can lead to large cumulative weight changes.

Obesity is best considered not just as a state of excess of body fat or body mass index above an arbitrary cut-off, but as the disease process, of excess body fat accumulation that has interacting (epi-) genetic and environmental causes and multiple pathological consequences.[5] Although obesity tracks in families and has relatively high heritability,[6] intensive searches for genetic factors have been unfruitful, but environmental drivers may be augmented by epigenetic changes. Given that 20-30% of entire populations have become obese in only 50 years, the dominant cause of the current obesity epidemic clearly lies in environmental factors.

Science and controversies linking food, obesity, and weight management

Although declining physical inactivity contributes to obesity in populations, possibly through a disconnect between energy expenditure and appetite when physical activity falls below an individual threshold,[7 8] we consider here only the role of food.

Different aspects of the influences of specific foods on obesity are often confused. In some cases, commercial or political interests have distorted evidence and muddied the water. Individual foods seldom influence obesity. Instead, we consider food groups, overall diets, and the patterns of eating within them, resulting from food choices or restrictions. Diets are analysed in terms of their macronutrient contents (fat, protein, and carbohydrate), micronutrients (vitamins, minerals), and other bioactive molecules and food properties (eg, fibre and whole grain). A "healthy" diet (which confers health and helps prevent chronic diseases) will not necessarily prevent or treat obesity. Conversely, diets containing fewer calories may not always be healthy.

Managing obesity demands understanding how nutrients and diet compositions, foods, eating patterns, food cultures, and political and commercial systems are responsible for weight gain and obesity, and how they can contribute to effective weight loss and prevent weight regain. These elements (table 1) are not necessarily the same, and complex influences vary between subgroups. For

Box 1: Energy balance explained

Each kg of adipose tissue contains about 7000 kcal. Thus consuming just 100 kcal a day more than energy expenditure for a year could result in a gain of 5 kg adipose tissue (100×365/7000). A continued excess of half that size would be enough to reach 40-50 kg weight gain over 20-30 years. However, energy expenditure is not fixed and varies with diet and with weight changes:

- At any weight, a person whose body weight and physical activity remain stable must consume the same number of calories as are expended
- As weight (body mass) increases, basal metabolism and the cost of carrying the extra weight in activities both rise gradually, roughly in proportion to the weight gain.[4] So continued weight gain will occur only if the calories consumed continue to rise
- During active weight loss, basal metabolic rate falls and physical activity becomes more efficient, so fewer calories are expended in proportion to weight loss. Additionally, severe negative energy balance (ie, undereating) produces exaggerated adaptive changes. These changes protected people against food shortages during evolution, such that consuming a fixed calorie deficit below the baseline energy expenditure will lead to weight loss but with a plateau. For continued weight loss, to treat obesity, energy intake must fall further to remain at a level below the reduced energy expenditure.[4]

each, we must also consider potential effects on general health, and risks of other diseases. Effective public recommendations for weight loss or to avoid weight gain are all likely to also reduce the risks of secondary conditions such as diabetes, cardiovascular diseases, cancer, arthritis, depression, and dementia.

The lack of objective ways to establish what people are actually eating is a major problem for human nutrition and clinical sciences. Substantial misreporting of food consumption is usual, particularly under-reporting among people with obesity. Despite stated motivation to lose weight, and expert professional support, people often find it hard to change eating behaviours and revert towards their previous habitual diets. Changing the behaviours people consider normal is difficult, as a general principle. This is particularly true for diet because of the strong biological reward system that facilitates eating. Whether eating, or overeating, should be considered addictive is debated. There are at least parallels, with food cravings characteristically for energy dense foods that facilitate overeating,[9] and some of the neural mechanisms behind normal repetitive eating behaviours are shared with classical addictions. The evidence in more in keeping with a normal addiction to eating as a survival mechanism, which is sometimes exaggerated, than with true addictions to specific foods.[10]

Individual willpower versus societal responsibilities: gluttony and sloth?

The "victim blaming" view that individuals are responsible for their afflictions has been persistent and destructive. Although some people at risk can resist obesity through vigilance, external factors are hard to overcome. Evidence indicates a recent environmentally led global epidemic, mediated by obesogenic factors such as frequent eating out, large portion sizes, and the commercial normalisation of routinely consuming high sugar, high fat snacks and sweetened drinks between meals.

Sustained conscious effort and willpower are needed to lose weight and not regain it when food is easily available. However, that does not imply that lack of individual willpower—gluttony and sloth—is the cause or that insufficient motivation and engagement explains the failures of interventions. Hunger, greed, and temptation are sensations originating in the unconscious brain, which are affected by the food environment in ways that are resistant to willpower: the sight or smell of attractive food triggers a cascade of hormone and sympathetic nervous system responses that increase hunger and desire to eat. Thus calorie cutting strategies that increase hunger tend to fail because willpower is ineffective over the more potent lower brain functions. Individually directed willpower centric approaches towards prevention will therefore almost inevitably fail while the food environment is unregulated. Collective responsibility is therefore required for effective progress at a population level (box 2).

Current controversies in food and obesity

Eat less, or exercise more?

Many lay people believe that exercise is essential or sufficient for weight loss. However, although exercise has a small weight loss benefit when combined with an energy restricted food plan,[12] neither aerobic nor resistance exercise in typical amounts are effective as a sole strategy.[13 14] Recognising that reducing energy intake has the central role in weight loss and prevention of regain will help prevent discouragement and recidivism. Physical activity has a modestly greater role in maintain weight loss[15 16] and undoubted value for long term health and preserving muscle mass.[17]

Box 2: Failures of willpower centric view

- National behavioural recommendations for weight management are largely based on application of willpower and are poorly accepted because they are (accurately) viewed as difficult and ineffective
- Uniquely for a major disease causing multiple pathologies, the prevailing perception of obesity is as a cost to healthcare and a burden on society, rather than its disabling and distressing effect on individuals
- There is insufficient investment in effective treatments for obesity, thus numerous profitable non-evidence-based approaches are promoted, with inflated claims to meet popular desire for easier weight control
- Intense media coverage of commercial "treatments" that are not evidence based or are minimally effective contribute to mass confusion and undermine professional advice
- The view that food companies are not responsible for the obesity epidemic leaves them free to create and promote an increasing variety of tempting obesogenic products
- Less obesogenic food products tend to be more expensive per calorie, which is a barrier to population shifts towards healthier eating habits
- Willpower centricity leads to an underdevelopment of population directed measures that avoid individual accountability
- Government funding for obesity treatment is less than for other diseases relative to numbers of resulting disability or deaths[11]

Table 1 | Four roles of food and diet in obesity

Roles of food and diet	Strategy	Comment
Prevent weight gain (body fat gain)	Long term, population directed	Food and diet may have specific effects on metabolism or on appetite, generally for all people or for definable subgroups (personalised weight maintenance or obesity prevention diets)
Weight loss (body fat loss)	Short term, individual	Weight loss is aimed mainly at providing a vehicle to deliver the least number of calories for the longest possible time, for the greatest number of people to achieve targets. Individual preferences and cultures as well as metabolic charactistics mean that different foods and diets are preferred and more effective for some people
Prevent weight regain (body fat regain)	Long term, individual	In general, this role is likely to be similar to preventing weight gain
Optimal health for overweight/obese people during:		Nutrient content of the diet is less relevant or critical for health during short term weight loss, except for specific issues (eg, preventing gallstones by providing adequate dietary fat, postural hypotension by providing sufficient sodium and water) and for specific situations (eg, obese people with poor nutritional status preparing for surgery, where deficiencies of vitamin C or Mg might be problems)
Preventing weight gain	Long term	
Weight loss	Short term	
Preventing weight regain	Long term	

How many calories are needed for health and weight management?

The calorie requirements of adult humans are lower now than in the past. US reference values for healthy adult men and women in energy balance are 2500 and 2000 kcal/day respectively. Adults who are overweight or obese typically have higher (not lower) calorie requirements than those who are not obese.[18] During acute negative energy balance (such as on a restricted diet), energy expenditure is reduced substantially, by about 15%-30% on average,[19 20] but contrary to widespread belief, once someone has stopped losing weight, energy requirements are decreased relatively little, in direct proportion to weight loss.[21] The challenge of sustainable weight

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loss, therefore, is to reduce food intake below the already low normal energy requirements and then to maintain a permanently lower energy intake afterwards to prevent weight regain. This is difficult for people who have become obese leading what they have regarded as normal lives, when living under the same obesogenic conditions.

Historically, the prevailing advice for weight management has been to introduce a modest reduction in energy intake, to lose weight gradually, and avoid extreme diets, which were believed to cause "rebound" weight regain to a higher than baseline level. Accumulating evidence now suggests that the best long term successes are often among people who engage well and lose weight successfully in the early stages, whether by eating food based diets or following intensive programmes with nutritionally complete formula diets.[22 23] No particular dietary method for long term maintenance has so far been shown to achieve superior results to others when implemented with appropriate support, but individuals may have diet preferences, for multiple reasons, which permit better outcomes.

Special effect foods: are all calories equal?

There is no evidence that any single food carries special risks of weight gain and obesity. Some people can lose weight, and avoid regain, by focusing on restricting specific foods or food groups, including (for different people) bread and cereals, red meats or meat products, cakes and confectionery, milk and dairy foods, sugar, and alcohol. These strategies are effective for weight control as long as the foods are rich sources of energy, consumed frequently by the individual, easily identified, and their avoidance tolerated without compensation from other foods. However, such restrictive diets can be difficult to maintain because dietary variety seems to be innately attractive, persuasively marketed, and tends to increase energy consumption.[24] Broader measures, such as veganism, avoiding all packaged foods, or all gluten containing foods, can also help weight control, but these measures can lead to undesirable nutritional consequences—for example, iodine deficiency if dairy or seafoods are not consumed, or thiamine deficiency from avoiding cereals.[25]

Macronutrients and foods differ in their effects on appetite and satiation and on thermogenesis and in how efficiently they are digested. Thus, the total calories in a food are not the same as the calories available and absorbed after eating. For example, high protein diets reduce appetite more than other macronutrients, a potential hazard for people who are underweight[26] but a benefit for those wishing to lose weight. There is a hierarchy of obligatory diet induced thermogenesis from macronutrients (protein>carbohydrate>fat), so high protein and whole grain foods increase postprandial metabolism more than foods higher in carbohydrate or fat.[26-28] Foods rich in various fibres, dairy foods such as milk and yoghuts (perhaps related to calcium content),[29] and with structural integrity that resist digestion such as nuts, all show reduced absorption of energy from the gastrointestinal tract, likely by reducing the efficiency of fat absorption.[30] However, these are relatively small effects, easily overwhelmed by factors such as portion size,[31] so should not be considered in isolation when determining dietary recommendations.

Sugar and obesity

The role of sugar in obesity is hotly debated and much misunderstood. Sugar provides 3.75 kcal/g and has a relatively low GI. However, it is not essential to human diets, and its consumption, particularly in sweetened drinks between meals and in snack foods combined with fat (9 kcal/g), has risen steeply worldwide in parallel with rising rates of obesity.[32] Nevertheless, it is difficult to establish a causal relation between sugar consumption and obesity: much of the published research has been observational, and "reverse causality" may apply.[33 34]

The media are giving increasing attention to the view that sugar is uniquely to blame for obesity and its metabolic complications, based on the effect of glucose in raising serum insulin, which promotes fat synthesis. Some have extended this concern to all forms of carbohydrate. However, meta-analysis of randomised controlled trials and prospective cohort studies finds only modest effects. Design of randomised trials can affect the conclusions. For example, in studies into the effects of removing sugar from the diet the control group can either continue with the extra calories from sugar or remove the equivalent number of calories from another food source, and choosing fats or protein sources will affect outcomes. Alternatively, the intervention group may have the sugar calories replaced with calories from another source to the same level as controls. These manipulations are hard to interpret because changing the amount of one nutrient inevitably changes the proportions and metabolic influences or others and from the entire diet. In summary, the evidence is that adding a calorie source such as sugar will cause weight gain and adverse metabolic effects, cutting a calorie source such as sugar or sugar sweetened drinks reduces weight gain by 2-3 kg, but there is no detectable sugar specific effect on body weight, because body weight does not change when sugar is removed from the diet and replaced with the same calories from other carbohydrates.[35 36]

There is ongoing debate about whether sugar in liquids may bypass energy regulation and appetite control mechanisms. If consumed in large amounts, sugar increases weight by a small amount in overweight people.[37] A systematic review of all studies lasting over three weeks concluded that sugar sweetened drinks had no overall effect on the obesity epidemic, but they may pose difficulties once people had obesity.[38] A six month randomised controlled trial in people who were overweight found that adding one litre a day of a sugar sweetened beverage increased visceral fat, liver and muscle fat, and also raised triglycerides and total cholesterol, compared with a similar artificially sweetened drink, water, and milk.[39]

As well as being a calorie source, sugar may also have indirect influences on appetite and eating. Evidence in humans is weak, but frequent exposure to highly sweetened drinks and foods may induce tolerance to unnatural sweetness and so facilitate weight gain by promoting consumption of very sweet, energy dense foods.[40 41] In real life, a common dietary pattern associated with obesity is characterised by frequent consumption of sweetened drinks and sugary-fatty snacks between meals: theses habits are recent, heavily promoted by social marketing, and tend to travel together. Taxation on sugar sweetened drinks has led to greater promotion and consumption of artificially sweetened alternatives, but it is not yet known if that will reduce weight gain.[42]

Fructose (50% of table sugar or honey, and enriched in corn syrup sweeteners) is sweeter than glucose, so has been proposed as a calorie saving alternative to glucose or sucrose. However, it has several adverse metabolic effects when consumed in large amounts, including preferential de novo lipogenesis, lipoprotein remodelling, adverse changes in body fat distribution and low density lipoprotein fractions, and increased insulin resistance. These effects appear only when fructose is consumed as 25% of dietary energy, which would not occur if sucrose is its source, but could be a problem with high intakes of corn syrup.[43]

Intermittent fasting

Total fasting depletes essential nutrients and is unsustainable. Well designed intermittent modified fasting regimens for weight control[44] reflect many long estab-

lished religious practices and probably match conditions experienced throughout human evolution. Several models are under investigation, including alternate day fasting or 5:2 diet regimens, usually with "fasting" days restricted to about 500 kcal and either usual eating or some form of conventional healthy diet on other days. Current evidence suggests similar weight losses in completers but higher drop-out than with constant daily restriction.[45] Flexible approaches to suit individual preferences may be appropriate, but better long term evidence is needed for effectiveness and safety of intermittent fasting for maintaing weight.

Reducing dietary carbohydrate or fat?

Arguments abound as to whether carbohydrates or fats are to blame for obesity. Some carbohydrates act as a more potent stimulus for insulin, possibly to promote fat deposition, but fats contain two to three times as many calories per gram as carbohydrate and are more readily stored as body fat, without raising metabolic rate. Epidemiological and long term intervention studies are heavily confounded by other factors that also influence energy balance. For example, higher fat intakes are found in wealthier countries, where obesity is more common. Overweight people may consume more carbohydrate but must also eat more calories overall, and they commonly underreport their food consumption selectively.[46 47] Advice to restrict carbohydrate may be more effective in reducing energy consumption in populations where a high proportion of carbohydrate is visible as sugar, and with manufactured foods which also contain fat, whereas the fat content of foods is often more difficult to identify.

Evidence comparing low carbohydrate and low fat diets is not entirely consistent. A careful meta-analysis of 32 studies of isocaloric exchange between fat and carbohydrate concluded that the loss of body fat and increase in energy expenditure are slightly better with low fat diets.[48] However, longer term studies show better weight loss outcomes for both low carbohydrate and low fat diets when compared with habitual diet, with little difference between the two in weight and body fat loss.[49-51] Other meta-analyses find about 2 kg greater loss of body fat with low carbohydrate diets and also improved cardiometabolic risk factors,[52] but the effect sizes are generally small. The apparently conflicting outcomes of meta-analyses may be explained by differences in inclusion criteria for diets, study design, how the other dietary components of the diets were changed, and the characteristics of participants (box 3).

An isocaloric exchange design is less clinically relevant to the real life situation, where most of the effects of dietary composition on weight loss are indirect, through differential effects on hunger and satiety. It is also relevant that a very low carbohydrate diet will deplete body glycogen stores, which necessarily incurs a loss of the 2 kg of water that is combined with glycogen[53] and probably also reduces capacity for physical activity. Concerns have been raised that publication bias may favour studies supporting lower carbohydrate diet[s-54]

Personalised dietary management based on genetic or metabolic status?

Emerging evidence suggests that genetic or metabolic factors may affect a person's weight loss responsiveness to carbohydrate, such that normoglycaemic people achieve greater satiety on low fat diets despite a higher glycaemic load (GL), whereas more insulin resistant people do better with lower GLs.[55] Specifically, people who are more insulin resistant or diabetic may lose more weight, with benefits for glucose control, lipid levels, and blood pressure, when assigned to lower glycaemic load regimens.[56,] A low GL can be achieved either by selecting a diet that is lower in total carbohydrate or by choosing low glycaemic index (GI) carbohydrates. These findings may help explain discrepant results across different populations with different dietary profiles of carbohydrates, as well as assist personalisation of weight management regimens. The results are broadly consistent with another study in people with type 2 diabetes showing that even high carbohydrate consumptions of up to 65% of dietary energy can have metabolic benefit for glycaemia and lipids if the carbohydrate is largely from amylose rich wholegrain and legume sources.[57-60] These diets have not been studied for long periods to establish effects on weight. More evidence is required to define the best range of carbohydrate intakes to recommend on metabolic grounds for people with type 2 diabetes, or whether personal choice may be the dominant influence for long term adherence and weight control.

A recent large 12 month trial comparing healthy low fat and healthy low carbohydrate diets in overweight adults reported weight losses of 5-6 kg in both groups, with no significant difference in weight change between the two diets. In this study neither the presence of genes that have been proposed to confer benefit from low carbohydrate diets, nor baseline insulin secretion, helped to define which diet was better for specific subgroups, but low adherence to the diet prescriptions may have masked any possible effects.[61]

The evidence is incomplete, but it suggests that people with normal insulin sensitivity can achieve marginally greater success on low fat regimens, provided very high GLs are avoided. However insulin resistance or diabetes exaggerates the responses to glycaemic loads, making lower total carbohydrate intakes preferable in most cases since this is easier than adhering to a higher carbohydrate regimen with the necessary large amounts of dietary fibre and legumes.[55 62 63] These different dietary patterns still need to be compared in randomised trials, but outcomes seem likely to be affected more by adherence in real life settings, which in turn will relate to the effectiveness of behavioural support and cultural and social factors, than by individual underlying biology.

Box 3: Factors affecting outcome of meta-analyses

- *Inclusion criteria*—Diets referred to as "low carbohydrate" range from 15% to 45% of energy from carbohydrate
- *Study design*—Isocaloric diets administered under controlled metabolic ward conditions provide information on biological and metabolic effects, whereas studies under free living conditions and diets tell us about effects mediated by, or limited by, changes in appetite
- *Modification of dietary components*—Protein, fat, and fibre contents of the diet have different metabolic and satiating influences, and they also interact within a food matrix to affect palatability
- *Characteristics of participants*—Innumerable factors can modify how a particular diet composition will affect weight change in different individuals, including age, sex, smoking, and acquired knowledge, beliefs and attitudes towards foods and diet composition

Feeding the microbiota to combat obesity?

Evidence is emerging that organisms in the gut may have a role in obesity.[64] The gut microbiota in rodents can affect the efficacy of energy harvest from feed and affects secretion of gastrointestinal appetite hormones. In humans, certain bacteria metabolise dietary fibre to short chain fatty acids that are absorbed to provide fuel for the gut itself (2-3 kcal/g), and act as insulin sensitisers and satiety stimulants.[65] A Prevotella driven enterotype is predominant in people consuming more carbohydrate and fibre[66] and seems to help weight control. In a randomised trial, participants with high ratio of *Prevotella* spp to *Bacteroides* spp (P:B) experienced a 3.5 kg greater weight loss over 26 weeks on a Mediterranean/Nordic style diet (high in fibre and wholegrain) than those on an average Danish diet, whereas no weight loss difference was observed among people with low P:B.[67] The

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success of people with high P:B ratio is dependent on a high dietary fibre intake.[63] It remains to be determined if these associations are on the causal pathway, but the P:B ratio may prove predictive of successful weight loss.

Evolution, weight cycling and "paleo" diets

Assumptions that our evolutionary ancestors did not experience obesity, and rarely developed type 2 diabetes or other complications of overweight, have led to a profusion of popular diets based on notions about their eating patterns. Beliefs about high fat, high meat, low carbohydrate 'paleo' diets have attracted media interest. Evidence from archaeology, ethnology, biochemistry, physiology, and anatomy are not persuasive that this was the usual diet of human ancestors, and the life expectancy of palaeolithic ancestors was short—an insecure basis for modern dietary recommendations.

Humans do not have specialised carnivore anatomy but do possess the high levels of amylase necessary to digest starchy foods, and require dietary fibre and retrograded starch to maintain a healthy microbiome. While our ancestors were clearly omnivorous, evidence on hunter gatherers, even before agrarian settlement, points to considerable reliance on aquatic and plant foods.[68] As an example, the residual hunter forager Tsimane people of Bolivia, who have no obesity, diabetes, or cardiovascular disease, follow a very high carbohydrate plant based diet (73% of energy).[69] This demands, and supports, much more physical activity, averaging 10-15 000 steps/day, which allows appetite to match requirement better[8] than in modern populations. Humans probably had to adapt to seasonal and intermittent periods of food shortage during evolution, with different metabolic and behavioural strategies, some individuals responding by conserving energy and others by risking energy expenditure to seek foods.

Although we may have adapted through evolution to cope well with short-term and seasonal food shortages, body weight fluctuations may still harm longterm health. There is no convincing evidence that weight cycling from intentional dieting is a hazard for cardiovascular health, but there may be greater loss of bone mass than is restored during weight regain, and weight cycling has been associated with a more android body fat distribution and is linked with polycystic ovary syndrome.[70] Major weight loss will reduce fertility in normal weight women, but paradoxically it can restore fertility to many obese women.

The global obesity epidemic, dating only from the 1970s-90s in different countries, reflects multiple changes beyond the conditions to which humans adapted during evolution, with huge reductions in physical activity, an absence of food shortages, large out-of-home meal portions, and effective promotion of energy consumption through eating outside meals. Occasional grazing, on available plant foods, has probably always been normal, but frequent large meals of varied energy dense foods and modern snacking on energy dense "snack foods" combining high GI carbohydrates and fat (such as ice cream and chips), and highly sweetened drinks, seems particularly hazardous. Although many conceptions of paleolithic eating are almost certainly wrong, any diet regimen that disallows modern facilitators of overeating, such as varied meals and snack foods, creates favourable conditions for effective weight loss as long as these prohibitions are followed.

What policy actions are required?

Lack of progress against the obesity epidemic has several origins. Research on obesity has been hampered by the assumption that the solution lies in advice or support for individual decision making. Importantly, funding for research and treatment will be more rationally planned if conditions such as type 2 diabetes, hypertension, arthritis, asthma, depression can be reframed as complications of obesity (the disease process, as defined above) rather than independent diseases. Research to contribute to effective ways to prevent and reverse obesity is needed on a truly global scale. Obesity is increasing everywhere, and the negative effects of obesity in one country are exported to others through increased greenhouse gas emissions and reduced national economic productivity.

Food is fundamental to the stable function of individuals, families, and society as well as to economies, so ethical and political aspects must be considered. WHO defined the critical threshold for malnutrition, demanding government intervention, as a 15% prevalence. Obesity prevalence has already exceeded 25% in many post-industrial countries, so interventions are overdue.

Interventions with the potential to be effective include those aimed at food marketing and taxing foods (or food groups) that are dominant contributors to weight gain, reducing the price of alternative less obesogenic food products, and curbing excessive portion sizes in restaurants.[71] Existing legislation—for example, the EU Unfair Commercial Practices Directive—could be used against vendors of products with unsubstantiated and misleading claims (overt or implied) of effectiveness against obesity.[72] Several countries have recently instituted taxes on sugar sweetened beverages. Evidence is accruing, from Mexico and elsewhere, that in the short term there are behavioural shifts away from taxed foods,[42] but effects on weight gain or obesity have not yet been reported. The UK is beginning to tax sweetened drinks with sugar content above 8%, encouraging product reformulation with sugar content falling from 10% to under 8%.

One way for diet related health to be improved without widening health inequalities is through "health-by-stealth" approaches. This recognises that in addition to interventions aimed at individuals, there must be a permanent change to the food supply. This approach is in contrast to population directed educational methods, which preferentially benefit the better educated and better advantaged. To be effective, health-by-stealth approaches require reformulation of entire product portfolios, rather than just creating premium price "health foods" or low energy alternatives.

Countering misinformation

Many issues relating to the causes and treatment of obesity seem more controversial in the media than they are in the scientific community, partly because of commercial interests. While several emerging research fields offer new insights, and potential avenues for future action, uncontroversial opportunities for potentially effective and safe government intervention have existed for many years.[73] Fiscal and other government-led initiatives could facilitate reduced consumption of highly energy dense foods and drinks of low nutritional value, discourage excessive portion sizes in foods and meals consumed away from home, and between meal consumption.

Misinformation is also a problem. Governments can build platforms to foster culturally appropriate ways to maintain and healthy weight without further disadvantaging the more disadvantaged in society, distribute responsible information about obesity prevention weight management, and support more research to identify effective interventions. Teaching about calories and energy balance early in schools, together with prominent, ubiquitous, calorie labelling of foods, could provide valuable effects at low cost. Combined, these multiple initiatives could have a major effect on the global obesity epidemic and human health.

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Role of government policy in nutrition—barriers to and opportunities for healthier eating

Dariush Mozaffarian and colleagues review strategies governments can use to improve nutrition and health

For most of human history including much of the 20th century, insufficient food was the greatest nutritional challenge. To tackle this, government sought to stimulate the production and distribution of as much inexpensive food as possible, in particular starchy (high carbohydrate) staple commodities and their shelf stable processed products. At the time, a global pandemic of obesity and chronic diseases from the widespread availability of inexpensive, unhealthy food was inconceivable.

The relatively recent rise of diet related chronic diseases including obesity, type 2 diabetes, cardiovascular diseases, and several cancers is at least partly a byproduct of these historical approaches and the responses of industry and consumers. A separate article in this series reviews the trends in nutrition science over this period,[1] which have slowly shifted focus from undernutrition defined by calories and micronutrient deficiency to food based diet patterns and overall health effects of the food supply.

Even with the unprecedented rise in diet related chronic diseases, government policies have continued to emphasise agricultural production of staple commodities and support for the food industry motivated by conventional perspectives on food security, economics, and trade. While undernutrition has improved with government supported systems changes such as agricultural development and fortification programmes,[1] government has tended to use educational policy measures directed at individuals in response to the rise in chronic diseases. Such measures aim to influence diet quality by emphasising personal responsibility and choice through dietary guidelines, food labels, menu labelling, and clinical counselling.

Growing evidence makes clear that multiple, complex factors beyond personal decisions strongly influence dietary choices and patterns (fig 1).[2-7] Even at the individual level, dietary habits are determined by personal preference and also age, gender, culture, education, income, health status, and nutritional and cooking knowledge and skills.[8] Psychological influences include attitudes to food and health, incentives, motivation, and values.[9] Food preferences may also be influenced by early life exposures, including the mother's diet during pregnancy, infant feeding practices, and foods consumed in early childhood.[10-12] Broader sociocultural determinants of personal choices include household lifestyle patterns such as television watching and sleep,[13-16] family and community norms, social pressures, social class, social networks, and race/ethnicity.[17] The local environment also plays an important role.[2-7]

Importantly, wider commercial pressures also affect consumer choice, including food packaging, marketing, advertising, and sociocultural perceptions of norms, status, and prestige.[18-20] Each of these individual determinants is shaped by, and in turn shapes, much broader drivers of food choice such as food industry formulations and globalisation, farming policy and production practices, national and international trade agreements, and ecosystem influences.[21 22]

Uncoordinated, these many influences are powerful and are nearly insurmountable barriers to making healthy dietary choices for many people worldwide. They can introduce health inequities, and sustain or deepen existing ones. However, with thoughtful, evidence informed policy, each of these factors also provides an opportunity for governments to support improvements in diets, health, wellbeing, and equity.

Based on advances in behavioural and policy science, we review strategies and approaches that governments can use to directly improve nutrition. We appreciate that other nutrition policy frameworks have been considered.[5-7] We focus on a broad range of interventions and nutrition policies and discuss their strengths, limitations, uncertainties, and recommendations.

Types of policy interventions

Governments can use a spectrum of policies from voluntary to mandatory. These include a bill (proposed law), law/act/statute (approved by legislative and executive branches), agency implementation (interpretation, application, regulation), court decision, guideline (recommendation, not mandatory), or directive (internal to an institution).

By their nature, public health concerns such as nutrition are multifactorial. Even single or simple interventions induce effects within complex webs of interactions.[23] We focus on policies directly targeting nutrition rather than more indirect mechanisms related to, for example, trade, farming, food waste, general education, and economic empowerment. Each policy strategy can be classified according to different related characteristics (box 1) that need to be considered and defined in government policy design.[24]

Government food policy strategies

For the different government policy actions, we present a summary of their strengths, limitations, uncertainties, and recommendations (table 1). Implementation of policy actions must be accompanied by systematic surveillance and evaluation to assess progress and guide further efforts.

Some key findings can be highlighted. For example, population education and

KEY MESSAGES

- Despite the rise in diet related chronic diseases and associated costs, government policies continue to have conventional perspectives on agricultural production, industry support, food security, economics, and trade
- New, evidence informed government nutrition policies are needed to reduce the risk of chronic diseases and reduce dietary and health inequities
- The complementary and synergistic nature of different policies supports the need for an integrated, multicomponent government strategy that uses and adapts existing structures and systems
- To translate evidence into action, governments must have the appropriate knowledge, capacity, and will to act and the governance and partnership to support action
- Specific actions by major stakeholders should promote, facilitate, and complement policy efforts
- Strong government policy is essential to help achieve a healthy, profitable, equitable and sustainable food system that benefits all

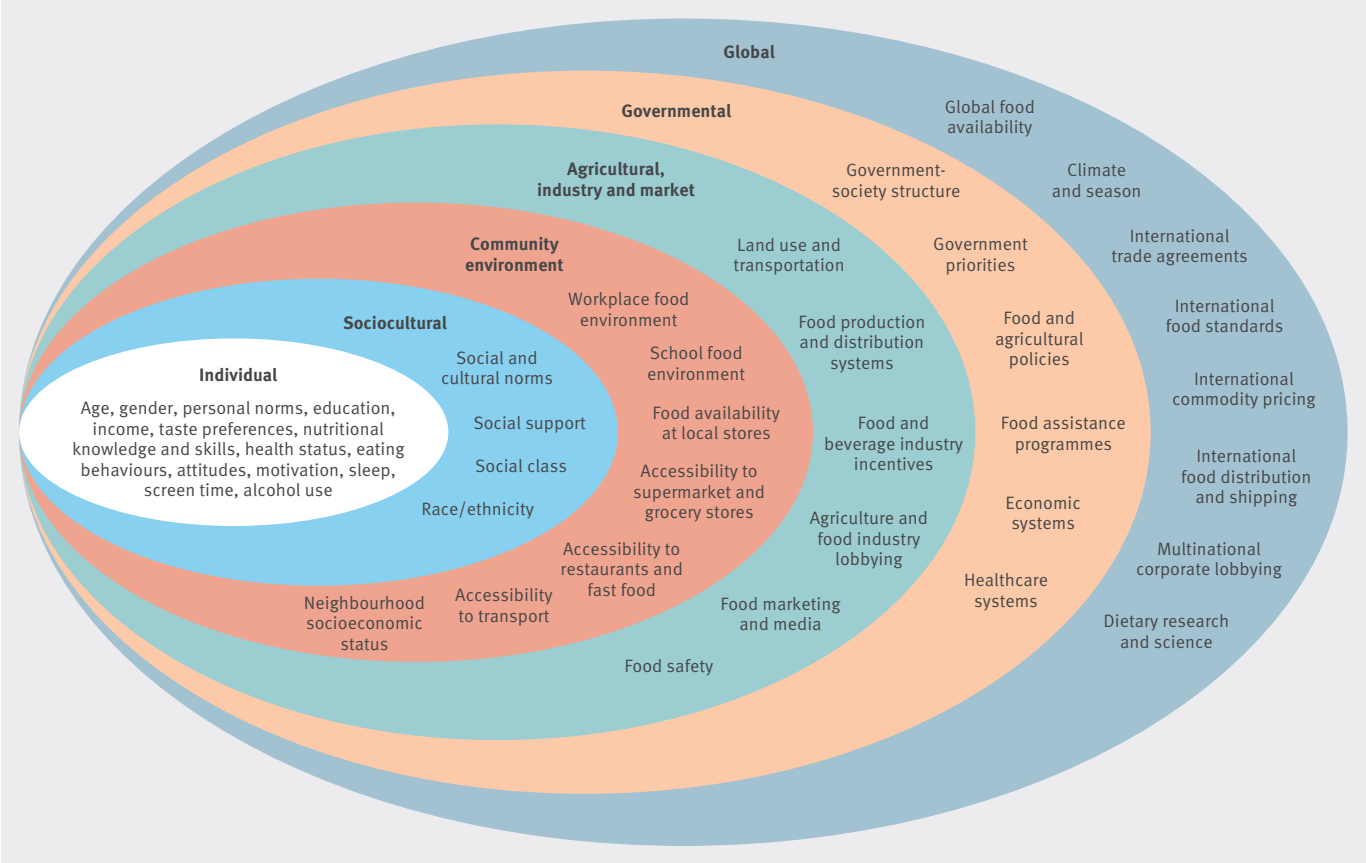

Fig 1 | Multilayered influences beyond personal knowledge and preference alter food choices. Government can consider these influences as potential targets, barriers, facilitators, and effect modifiers of food policies. Reproduced with permission from Ashfin et al[2]

point-of-purchase labelling are widely and increasingly used. Such "soft" policies place most responsibility on the individual consumer, with which industry is often more comfortable. The effectiveness of such policies on behaviour change overall and in specific population subgroups has been variable and they may have smaller effects in marginalised groups.[3 34 79 80] However, such approaches can also promote industry reformulations, which may have an important effect on longer term health beyond immediate consumer behaviour.[34] Overall, such approaches can be valuable as part of a broader, multicomponent government food and nutrition strategy.

In contrast to education and information, fiscal incentives and disincentives aimed at consumers, producers, and retailers have more consistent evidence of effectiveness.[2-7] Disincentives can include excise or sales taxes on unhealthy items such as sugar sweetened beverages and junk food[38-40] or removal of industry tax benefits for development and marketing of unhealthy products. Disincentives on specific foods can be politically difficult, however, the rapid international expansion of taxes on sugar sweetened beverages shows the growing acceptance of this approach.[81] Such taxes can be financially regressive for lower income individuals, but progressive because of benefits to nutrition and health. To reduce financial regressivity and increase the health effect, tax revenues can be used for other health promotion strategies including retail, manufacturing, or agricultural incentives to reduce the price of healthier food products.[41 42] Rather than being punitive, economic incentives and disincentives "normalise" the market by partly bringing the prices of different foods closer to their true societal cost.

Procurement and quality standards are relatively sustainable, low cost strategies for government to implement. For instance, limitations or standards on trans fat and sodium have been implemented in many countries and similar standards being considered for free or added sugars.[2-7] Because governments are often one of the largest buyers of food, nutrition procurement standards should be set for all their food purchases across agencies and programsmes.[82] In addition, vanguard local and national quality standards should be implemented on the use of food additives by industry such as trans fat, sodium, and sugar.[45-47 83-85]

Schools and worksites are natural and complementary settings for effective nutrition policies.[2-7] In schools, after school, and early childcare programmes, government should promote nutrition standards for both onsite meals and competitive foods as low cost, sustainable interventions—examples include standards in the US, Canada, Mexico, Europe, and New Zealand.[49] Free or low price provision of fruits and vegetables, farm to school

Box 1: Classification of policy interventions

- *Level*—city, state, or national government; international agencies; organisations (eg, school, worksite, healthcare facility); local neighbourhoods and communities
- *Target*—consumer, organisation (eg, school, worksite), health system, production (farming, agriculture), industry (manufacturer, retailer, restaurant)
- *Domain*—population education (eg, dietary guidelines, mass media), point-of-purchase information, fiscal policies, food quality standards, built environment changes, research and innovation
- *Mechanism*—altering consumer preferences or choice, food formulations, or food availability and accessibility

Table 1 | Key government related food policy strategies to improve diet quality*

Policy strategy	Examples	Strengths	Limitations	Uncertainties	Recommendations
Population education	National dietary guidelines.[25] Mass media "5 a day for better health" programme.[26] Population education components of the North Karelia project.[27] Use of cultural influencers. School curriculums focused on nutrition and culinary skills	Dietary guidelines can be promoted across the population[28] and be supported by rigorous and transparent reviews of evidence.[29] Dietary guidelines can directly influence government food service and assistance programmes. They are a "soft" policy with which industry is more comfortable and can indirectly promote industry reformulations	Mass media promotion of guidelines is costly, often with limited reach and sustainability. Large gaps exist between national dietary guidelines and actual public diets, indicating limited overall effectiveness. After decades of policy use, obesity and other chronic diseases continue to rise globally. Guidelines have smaller effects in marginalised subgroups	Optimal conditions in which population education can effect behaviour change, overall and in specific subgroups, remains unclear. Relative sustainability and cost effectiveness are uncertain especially compared with other environmental and systems based strategies	Can be helpful if accompanied by other measures, and if backed by government or semi-official bodies with influence. Cultural influencers (eg, celebrities, athletes, chefs) can help change social norms. Guidelines must be consistent with other official messages about food and health
Point-of-purchase labelling	Food package nutrition fact panels,[30] health claims. Restaurant calorie menu labelling.[31 32] Front-of-pack traffic light.[33] "Black box" warning labels in Chile	Such information can encourage industry to reformulate, especially for additives such as sodium, trans fat, and sugar.[34] Point-of-purchase strategies can be useful when consumers have knowledge or are more aware or motivated because of personal circumstances (eg, pregnancy, older age, with diabetes)	Evidence is mixed about effects on consumer behaviour, perhaps varying with nutrient or food targets.[34] Many approaches have not been rigorously studied or implemented and thoroughly evaluated. Confusion and controversy exist about optimal target nutrients/metrics. Consumer attention at point of purchase is slight; distractions can be high.[35 36] Official labels can be confused by product branding	Optimal dietary factors or standards to target are not well established (eg, many point-of-purchase approaches continue to include outdated targets such as total fat, total calories). Consumer attention and awareness may not translate to behaviour. Disparities might be exacerbated because of smaller effects on disadvantaged groups	These should be promoted because they are within the "consumer market" model. Promising options include front-of-pack (eg, UK, New Zealand), warning labels (eg, Chile, New York City's sodium menu label, California's proposed warning label on sugar sweetened beverages). For most such actions, relative healthfulness of different foods must be appropriately classified, perhaps using systems that combine food category classifications with multilevel nutrient criteria[37 38]
Fiscal incentives and disincentives	National soda and junk food taxes.[38-40] Subsidies for fruits and vegetables in national food assistance programmes.[41 42] Agricultural incentives for berry production[27]	Price has a strong influence on food choice. Such effects may also be stronger in low income groups, helping to reduce nutrition and health disparities. Publicity around price incentives and disincentives can bring about additional changes in attitudes and intake.	Consumption change in some foods may have unpredictable effects on overall dietary quality, depending on substitutes. Relatively large price differences may be needed to be effective and strong government support. Taxes and other financial disincentives often create strong opposition and lobbying by industry	How important are additional indirect effects on substitutes and complements (other foods)?	Fiscal incentives are effective and should be used by governments. This market based approach helps bring the price of foods closer to their true societal cost, including direct and indirect costs on health (and potentially the environment). Disincentives should be paired with incentives to reduce financial regressivity, maximise health benefits, and help reduce industry opposition
Food assistance programmes	Income based or other conditional food vouchers or cash transfers,[43] school meals, supplementation programmes	These improve purchasing power and access of low income groups, helping to tackle disparities. They use existing systems for improving nutrition, and align poverty reduction with health promotion and healthcare programmes[44]	These often have limited guidelines or standards around diet quality and health. Governments may consider them costly welfare programmes; short and long term benefits on health, healthcare costs, and productivity are often not estimated	The appropriate balance between participant choice and health promotion is unclear	All government food assistance programmes should have mechanisms, standards, and incentives for healthful, nutritious, and culturally appropriate choices, and also align with health promotion and healthcare programming
Procurement nutrition standards	Nutrition standards for food purchases for government offices, public schools, the military, food assistance programmes, and other government funded organisations	Governments are often large employers and food purchasers in their region. They are low cost and sustainable. In cases of high coverage food assistance programmes, nutrition standards may improve diets in large proportions of the population, including disadvantaged groups	Whereas setting standards is low cost, following them may substantially increase food purchasing costs where government budgets are limited.	Effects on diets are unclear eg, compensatory dietary changes may occur outside the organisation. Optimal dietary factors or standards to target are not well established, especially for packaged foods	Nutrition standards should guide all food purchases for government offices, public schools, the military, food assistance programmes, and other government funded organisations. National food assistance programmes can be used for diet quality and nutrition
Industry quality standards	Mandatory or government recommended limits and standards on use of additives, such as trans fat, salt, and sugar[45] (eg, limits on use of industrial trans fat,[46] UK salt reduction programme including public awareness[47])	These are low cost, sustainable, and more effective than consumer education and information.[48] They can be voluntary or mandatory; regulation and laws are stronger than voluntary guidance from government.	The food industry promotion of developing their own internal standards, and staunch opposition to government standards (see box 2). "Nanny state" concerns	Optimal targets for certain categories of product (eg, to balance health versus functionality, safety, and industry cost) are not known. Differences between 'natural' and 'industry' ingredients (eg, for sugar) are unclear. How to overcome political challenges is uncertain	These should be implemented by governments. They are most relevant, practical, and politically feasible for additives (eg, trans fat, sodium, and added sugar)

(*continued*)

Table 1 | Key government related food policy strategies to improve diet quality*

Policy strategy	Examples	Strengths	Limitations	Uncertainties	Recommendations
Schools, after school and early child care	Meal nutrition standards.[49] Nutrition standards for competitive food (products available outside regular meal times).[49] Free/reduced price provision of F&V.[49] School gardens, farm to school programmes. Nutrition education	With 1-2 meals eaten onsite each day, schools, after school, and early child care programmes are natural places to promote healthier eating in children. Nutrition standards for onsite meals and competitive foods are low cost and sustainable	Often budgets are limited for healthier meals. Loss of revenue is feared with strong standards for competitive foods, eg, from industry vending machines. Direct F&V provision, farm to school programmes, and gardens are more costly	Long term effects and cost-benefits are assumed but not yet rigorously evaluated or established	Government should set strong nutrition standards for school, after school, and early child care meals and competitive foods. Additional school based interventions should be implemented if fiscally feasible
Worksite wellness	Procurement standards for cafeterias and vending. Comprehensive wellness programmes. New technology platforms and incentives for healthier eating.[50] Built environment changes to encourage behavioural changes[51-53]	Time spent at work make worksites a natural place to promote healthier eating. Can focus on at-risk groups and high risk employees.[54] Can reduce absenteeism and medical costs.[55] Can be paired with government tax incentives for wellness programmes in private insurance and worksites	With increased turnover of the workforce, long term employment is becoming rare, reducing financial incentives for employers to improve long term health of their employees. Occupational health services tend to focus on immediate effects such as injuries	Long term effectiveness in improving diet is unclear; most evidence comes from shorter term intervention studies (up to one year). Few rigorous cost effectiveness analyses have been done, making it hard to promote the business case	Government guidelines or fiscal incentives are needed to promote the inclusion and evaluation of nutrition in private employer worksite wellness programmes and insurance plans
Health systems	Integrated lifestyle interventions by multidisciplinary teams (eg, Diabetes Prevention Program[56]). Medically tailored meals for patients with complex illness.[57 58] F&V prescriptions.[59] Nutrition counselling during pregnancy and early childhood.[2 60-62] Quality metrics and reimbursement systems that reward community engagement to address upstream causes of poor health.[63] Integration of healthcare with public health.[64] Worksite wellness and community leadership[65 66]	Consumers and policy makers continue to value and respect healthcare providers. Approaches can be synchronised with new care delivery investments in social determinants of health and community infrastructure. Health systems cannot be the only solution but they have an important role. Government and private healthcare systems often have considerable resources which can be used for better nutrition, returning value and savings to the system. Hospitals are often main community employers with an important local voice	The health system has limited reach, influence, and relevance for daily decisions such as food. Success has been higher for specific interventions such as promotion of breastfeeding. A cultural shift in needed and acceptance by providers and care systems of their role in basic behaviours	How to synchronise provider incentives for community engagement and health promotion in nutrition. How to reach disadvantaged groups	A variety of approaches is needed including integration of food and nutrition into the electronic health records, provider licensing and specialty exams, continuing medical education, and quality metrics and reimbursement standards; coverage of medically tailored meals and F&V prescriptions for relevant patients; testing of patient based inventive and education programmes for healthier eating using new technologies; payment reform that incentivises community health and engagement; systematic assessment and integration of healthcare with public health; and worksite wellness actions (see above) for staff, patients, and visitors
Food marketing standards	Limiting marketing to children of foods and beverages that do not meet nutrition standards[67-69]	These are low cost, can be sustained, and are recommended by many organisations, especially marketing to children up to 12 years	To be effective, they must restrict all marketing in any form to children, not just on children's programmes, because of widespread exposure of children to marketing in many formats[70]	Potential legal and political feasibility challenges exist. Nanny state concern. Non-traditional marketing through websites, social media, video games, television shows, and movies is growing, which is much more difficult to regulate.	Standards for marketing to children across all formats should be considered and implemented because of the evidence for effects of marketing on food preferences and dietary intakes, as well as inability of young children to discriminate between marketing and regular programming
Local built environment	Zoning restrictions on fast food outlets around schools.[71] Building of supermarkets in food deserts.[72] Expanding farmers' markets and mobile produce vendors	Clear conceptual frameworks support the importance of food access and availability. Public support and often (for increasing access) industry support is strong. Can advance equity goals where investments in infrastructure counter historical disparities in burden of disease and investments	Many such approaches have not been rigorously studied. Characterising availability and accessibility is complex, and often not simply related to geographical distance or density. Strong collaboration between town/city planning and businesses is needed	Cause and effect of many cross sectional relationships is uncertain. Optimal metrics to define access, availability, and types of stores are unclear	This is a promising approach. It relocates diet action within ecological public health, and reconnects with city planning.[73] More research is needed, including implementation and evaluation research

(*continued*)

Table 1 | Key government related food policy strategies to improve diet quality*

Policy strategy	Examples	Strengths	Limitations	Uncertainties	Recommendations
Research and innovation	Basic science, medical, and applied (including policy) nutrition research. Research and development incentives for agricultural producers and food manufacturers	Recognises that today's challenges often require tomorrow's solutions. Can promote and use industry innovation and economic success, eg, through tax breaks and government approval. Return on investment is often high	Is viewed as costly by some policy makers. Length of time to see benefits is uncertain	Recognition of benefits by policy makers and feasibility in era of constrained budgets. How to identify and minimise conflicts of interest for public-private partnerships (see box 2)	Government should substantially increase and sustain funding for research on food, nutrition, health, and policy implementation and evaluation is needed. Public-private partnerships (eg, research and development incentives) to promote development and marketing of healthier products are needed
Coordination of actions across ministries, agencies, and at local, national, and international levels	Coordination of school, after school, and early child care meal standards with national dietary guidelines.[49] Integration of food assistance programmes with healthcare for the poor. Public school lunch and breakfast programmes to improve military readiness and national security.[74] Agricultural and trade policy linked to nutrition and health.[75-77] Setting of nutrition guidelines, policy actions, and country goals by global economic and political institutions such as the World Bank, United Nations, and World Trade Organisation	A "nutrition and health in all" approach could greatly improve food systems and health outcomes, with large benefits on productivity, equity, and health costs. Uses and adapts existing government structures and systems	Expertise to combine and stage policy approaches is often limited. Jurisdiction for different aspects of policies may be divided across government sectors, who may also share unequally the costs and benefits. Factors driving policy for some outcomes (e., employment, business profits) may differ from those for nutrition and health	How to align different government sectors with historically different priorities, stakeholders, and cultures. Unclear time scale of risks and benefits for many actions	A ministerial or cabinet leadership position is needed with oversight and budgetary authority for cross agency food and nutrition policy.[78] Nutrition impact assessment for all major government policies (eg, similar to environmental impact assessment now done in many countries for environmental concerns). Agricultural and trade policies to promote cultivation, transport, storage, trade, and sale of healthier foods. Coordinated nutrition policies with bordering nations, close allies, and trade partners

F&V=fruits and vegetables.
*Based on advances in behavioural and policy science and our review and interpretation of the evidence, knowledge, and experiences. The policy strategies in this table are organised by domain of intervention. Variations of each strategy can be further characterised by level (eg, local, national, organisational), target (eg, consumer, industry), or mechanism (eg, altering consumer preference, food formulation, or food availability and accessibility) (box 1).

programmes, and school gardens are also promising strategies, although long term effects and cost-benefits are not yet rigorously evaluated. Worksite wellness programmes can not only improve health but also lower costs and increase productivity. In one analysis, every $1 spent on worksite wellness programming was estimated to generate about $3.27 in lower medical costs and $2.73 in less absenteeism.[55] However, relatively few long term worksite studies have evaluated the effects on diet, few rigorous cost effectiveness data are available, and increased employee turnover reduces the immediate incentives to businesses to invest in the health of their employees.[34] Governments should invest in their own employee worksite wellness programming and pursue policies, such as guidelines and tax incentives, to promote the implementation and evaluation by private employers of worksite efforts for healthier eating.

Ironically, one of the least used settings to promote better nutrition is the healthcare system. Individual providers and health organisations face several barriers to nutrition promotion. To overcome these difficulties, governments should promote policies that support implementation of evidence informed actions within the healthcare system and with relevant partners such as community health workers, pharmacies, and other community based organisations. Useful strategies include multidisciplinary lifestyle programmes for conditions such as prediabetes,[56] medically tailored meals for patients with complex chronic diseases,[57 58] prescriptions for fruit and vegetables for health promotion and disease prevention,[59] and nutrition counselling during pregnancy and early childhood. Other important actions include: educating healthcare providers on food and nutrition, systematically introduced through national reform of medical and specialty licensing exams and continuing medical education; expansion of nutrition counselling services through new reimbursement strategies and task sharing with community partners; and inclusion of standardised clinic and mobile assessments of diet quality and food insecurity in electronic health records, which are needed to assess and integrate nutrition into treatment plans, evaluate new health system interventions, and inform performance and reimbursement systems.[2 60-62] Expanding access to care through universal coverage or other national strategies can further increase the effect of nutrition policies on health. Hospitals should be incentivised by new quality measures and reimbursement guidelines to implement worksite wellness and engage in community public health.[63-66]

Standards for marketing, such as limiting advertising to children of foods and beverages that do not comply with basic nutrition, are recommended by the World Health Organization and Institute of Medicine.[67-69] Several countries currently implement different forms of marketing restrictions: for example, Chile has recently limited advertising and use of cartoon characters to market products to children that do not meet standards for added sugar, added saturated fats, and sodium.[70]

The media and policy makers have increasingly focused on the local food environment, such as clustering of fast food sellers around schools[71] and absence of supermarkets in many neighbourhoods (termed "food deserts").[72] However, the actual cause and effect of many of the observed cross sectional relationships and the appropriate ways to characterise the complex facets of availability and accessibility are poorly characterised.[2-7 73] Further investigation including implementation and evaluation research is needed to allow the development of

more concrete recommendations on how to improve the local food environment.

Modern nutritional science is young, especially in relation to the risk of the main chronic diseases.[1 86] Strong government funding for basic nutrition and applied research and innovation is essential to continue to develop evidence based priorities for dietary policies. Areas for investigation in the next decade, for example, include basic molecular pathways; diet-microbiome-host interactions; individual fatty acids and their lipid derivatives; prebiotics, probiotics, and fermentation; phenols and other bioactive compounds; personalised nutrition; and nutrition data ("big data"). Government funding should also make applied research a priority, including new technologies for nutritional assessment and behaviour change, and policy implementation and evaluation.

Governments should also promote the food industry's shift towards healthier foods, taking advantage of rapidly rising consumer demand. Tax incentives and other fiscal policies should promote research, development and marketing of healthier foods in the food industry, combined with (and potentially funded by) fiscal disincentives for marketing and promoting sugar sweetened beverages and junk foods. A programme of government funding and transparent public-private partnerships for nutrition research is also needed to help minimise conflicts of interest and perceived and real biases.[86 87]

No single intervention can tackle the complexities of the current food system, and different approaches can be complementary and synergistic.[2-7] For example, trade policy traditionally emphasises foreign direct investment, trade liberalisation, and privatisation to encourage private sector investment but the influence of such actions on the food environment can also have positive and negative effects on health.[75-77] These interconnections support the importance of an integrated, government strategy that uses and adapts existing structures and systems. Ideally, actions should be coordinated between ministries, agencies, and at local, national, and international levels. Upstream agricultural, trade, research, and industry measures can be integrated with midstream school, worksite, healthcare, and other environmental approaches as well as downstream consumer efforts. Such a "nutrition and health in all" policies could greatly improve food systems and health, national productivity, equity, and health savings. Strong government leadership is essential to help deliver such a comprehensive, sustained, multitarget, and multilevel approach.[78]

Translation of evidence to policy action: needs and difficulties

Local and national governments have important roles in bringing healthier food and food security to their populations. However, the path from knowledge to effective action requires capacity in several areas. To our knowledge no country has implemented a full range of updated, comprehensive, and evidence informed strategies to encourage a healthier and more equitable food system (table 1). Given the remarkable health and economic burden of diet related illness and the need for multistakeholder solutions, a coordinated national food and nutrition policy strategy should be a priority for all governments.

Government must have appropriate knowledge to translate evidence into policy action. This includes an evidence based assessment of what defines a healthy diet; an understanding of diet related health and risk distributions overall and in at-risk subpopulations; analyses of how poor diet affects non-health sectors such as private businesses or the military; and consideration of environmental and societal values such as sustainability, equity, and justice. Insufficient awareness of policy makers of these factors can be compounded by evolving science and conflicting media messages. For example, some policy strategies continue to emphasise reduction in total fat, total saturated fat, or total calories, rather than food type and quality, processing methods, additives, and diet patterns.[1 88 89] New metrics are needed that allow the healthiness of food products to be compared on multiple nutrient criteria.[37] In addition, tackling obesity is sometimes seen as the only goal of nutrition policy and programming, rather than improved diet quality and overall health and wellbeing. The evidence to support policy interventions is also different from that for interventions delivered to individuals.[2-7] Interventions on high risk individuals can often be studied in randomised placebo controlled trials; in contrast, policy interventions on populations often cannot. Thus, predictive modelling, observational, quasi-experimental, and interventional studies, and surveillance data must feature more heavily in the standards of evidence required for policy change.

Government must have the capacity to intervene. This includes having an evidence informed plan, access to technical experts for implementation and evaluation, and adequate resources and authority to act in the required areas. For many governments, developing a comprehensive nutritional policy will be new and unfamiliar, and require acknowledgement of certain limitations of the current system. The expertise to combine and phase different policy approaches can be lacking. Jurisdiction and funding for different aspects of policies may be spread across government sectors and ministries, which may share unequally the costs and benefits. Budgets for technical policy work on nutrition are often tied to resources allocated for the prevention of chronic diseases, which is underfinanced given their health and economic burden. Surveillance systems for monitoring and evaluating nutrition trends and disparities are under resourced. For some promising policy actions, relevant data demonstrating the links between food policies and health, healthcare costs, disparities, and economic problems are often unavailable to policy makers at the right time or in the right format for policy action.

Government must have the will to act and the governance and partnerships to support action. This requires support from civil society and relevant private and other non-government actors to implement and sustain appropriate policies. Political willingness to act can be undermined by several factors. For example, factors driving government food production policy (eg, employment, short term business profits, and international competition) may be different from those driving nutrition policy (eg, health and healthcare costs). Although dietary shifts can have rapid effects on health,[90-93] the perception that dietary interventions require long periods to achieve benefits may not coincide with political and budget cycles. Public opinion may also not support policies seen as intrusive.[94] Identified dietary priorities may not match public priorities and sentiment, nor agency authority for action. Industry opposition can be a major barrier, including political lobbying and marketing campaigns to fight policies they consider unfavourable.[95] When policies are passed, lack of implementation because of limited resources, management, and accountability can greatly limit their effect,[96] as in the case of school food standards in Mexico or quality standards to limit industrial trans fats in India.

Other stakeholders

Other stakeholders should promote, facilitate, and complement government policy

Box 2: Lessons from interactions between public and private stakeholders in food and nutrition

Engagement with multiple actors is essential for the implementation of effective policies and programmes to tackle obesity and other chronic diseases. Clear rules are needed to manage conflicts of interest.

A recent report of the UK Health Forum analysed examples of international public-private interactions for food and nutrition policies for the prevention of chronic diseases.[99] The report sheds light on relationships between government, civil society, academia, and the food and beverage industry and the need to strengthen governance for the identification and management of conflicts of interest that may arise.[100]

While the cases vary in their geographical and sociopolitical contexts and objectives, common themes are seen:

- Interactions between public and commercial sectors are numerous and diverse
- Transparency and documentation of these interactions are often limited
- Corresponding risks are neither assessed nor managed before or during such public-private interactions.

In Mexico a multistakeholder effort to monitor, evaluate and provide feedback on policies for the prevention and control of obesity and diabetes[101] showed that providing the commercial sector privileged access over public health and civil society led to biased conclusions influenced by commercial interests. Other cases in Chile, Brazil, Mexico, Fiji, Canada, Spain, and England show that conflicts of interest can undermine effective policy. Many examples exist of companies that produce sugar sweetened beverages and junk food putting up strong resistance and lobbying to counter national policy actions for obesity prevention. These include shifting the blame for obesity and chronic diseases away from specific products and towards physical inactivity and energy balance, and the use of multistakeholder coalitions to shape policy that benefits commercial interests. In Fiji and other countries industry self regulation was not effective and was used by the food industry to rebut government efforts to implement recommended public health policies.[102]

Specific lessons learnt about public-private interactions for policy and practice include:

- Need for governance principles in multistakeholder platforms. Governments have a duty to ensure that interests not in the public good do not influence the individuals or institutions responsible for public decision making, and preserving integrity and public trust. Multistakeholder platforms should have guidelines on conflict of interest identification, management, and protection. Governments should establish guidelines about participants in groups that are responsible for policy design. Otherwise, such platforms may stall regulation and policy by suggesting agreement among civil society, government, and industry when there are in fact disagreements.[101 103]
- Need for regulations on lobbying. Lobbying strategies can greatly affect health policy decisions.[104] In many countries, lobbying activities and corporate financing of politicians and political parties are loosely regulated. Strong regulations on transparency and activities are needed to maintain effective, unbiased policy making.
- Need for standards on public-private partnership. Given widespread recommendations for public-private alliances and partnerships to support the achievement of global health and development goals, governance of public-private partnerships is important to ensure that efforts to improve food and nutrition are in line with ethical, transparency, and accountability principles. For instance, the food and beverage industry should not participate in decision making on the design, implementation, or evaluation of obesity prevention policies. Their voice should be heard but decisions should be made by those without commercial interests.
- Need for more than self regulation. Industry self regulation is not sufficient to advance public health goals. Additional government regulation and standards are important to enforce the implementation of health related food and nutrition policies.

The case studies also highlight the need for scientific evidence free of conflicts of interest. Particularly in the cases of sugar sweetened beverages and junk foods, commissioning studies with strong ties to or funding from the food and beverage industry is a risk.[105] Independent, peer reviewed scientific research is important to help inform policy making with the best available evidence. When industry does play a role in research studies, the involvement should be transparent.

Analysis of these case studies indicates a need to address conflict of interest and industry influence in health and nutrition policy making. WHO recently published draft guidance for the prevention and management of conflicts of interest in policy development and implementation of national nutrition programmes.[106] Governments, academia and civil society all play an important role. In addition, further research is needed on how to identify, study, and minimise conflicts of interest in food and nutrition policy.

efforts.[2 5 21 97 98] Academia should prioritise research on optimal dietary targets and cost effective policies; monitor and evaluate health indicators and policy outcomes; engage with communities, advocacy groups, the media, business, and policy makers; and inform and evaluate government and industry efforts. Health systems, clinicians, and insurers should implement strategies on patient behaviour change; advocate for broad changes in health systems to support these efforts; and engage with local communities. Employers, communities, schools, hospitals, and religious congregations should implement organisational strategies for healthier eating. Advocacy groups should partner with scientists to disseminate best practices and hold government and industry accountable for meaningful action.

Large multinational companies frequently have a great influence because of their economic power, government lobbying, and communication and marketing resources. Unclear or variably enforced government provisions on conflicts of interest can further increase industry influence. More directly, certain food companies have actively opposed policies about healthier foods,[95] especially in low and middle income countries.[96] Because multiple actors must be involved in effective nutrition policies and programmes, transparent rules of engagement are needed for public-private interactions (box 2). The food industry must be a facilitator for, not a barrier to, healthy food policies and use their expertise, scale, innovation, and marketing to develop, distribute, and market healthier foods, and create transparent, sincere partnerships with academics, advocacy groups, and government.[87 100 101] To achieve this, the food industry's ultimate success ought to be linked to the distribution of healthy, optimally processed foods in a sustainable, equitable, and profitable way.

Given the scale of the problem and the multinational nature of the food industry, global public health efforts can complement national and local

Box 3: Recommended government roles and actions for a healthier food system

Systems can change when:

- Recognise that good nutrition is a priority for local, national, and global health, equity, and economic security
- Acknowledge the importance of multilevel approaches, not "magic bullets", in order to implement strategic, coordinated government action. Based on current evidence, the best approaches are:
  - Fiscal incentives/disincentives (eg, taxes and subsidies) for consumers, the food industry, and organisations (eg, worksites)
  - Prioritisation of both food security and nutritional quality in food assistance programmes
  - Appropriate standards for additives including trans fat, sodium, and added sugars
  - Procurement standards for all government food purchases and venues including food assistance programmes
  - Use of schools and worksites to promote healthier eating
  - Incorporation of food and nutrition into the healthcare system at all levels
  - Nutrition standards for marketing of foods and beverages to children
  - Front-of-pack labelling of evidence informed metrics such as overall fat quality (eg, unsaturated to saturated fat ratio), carbohydrate quality (eg, carbohydrate to fibre ratio), and sodium
- Implement policies using the best available evidence, which also provides an opportunity to build further evidence for better decision making by evaluation of the policies being implemented
- Emphasise strategies with the greatest potential to reduce social and racial/ethnic disparities from clustering of suboptimal diet habits, local environments, and disease risk factors
- Increase support for food and nutrition research to ensure that both dietary targets and policy efforts are scientifically sound
- Support public-private partnerships with the food industry and other major non-food businesses (eg, private health and life insurance, and self insured corporations) for research and development on healthier products, effective behaviour change, and other common aims. This must include development of clear and transparent policies to identify and minimise conflicts of interest (see box 2)
- Facilitate participation of other stakeholders in policy development, implementation, and evaluation
- Incorporate nutrition and health in all of government, for example, city planning, economic development, agricultural and trade policies, and nutrition impact assessment
- Link nutrition and food policies to economic and production indices such as the influence of diet related illness and health on production and the economy
- Create a ministerial or cabinet leadership position with oversight and budgetary authority for cross agency food and nutrition policy
- Support monitoring and evaluation of nutrition habits, food systems, and corresponding policies including for individuals, communities, and larger systems. Link to and use existing surveillance systems (eg, healthcare) as well as new technologies (eg, social media, and personal monitors)
- Identify and use complementary global public health activities (eg, the United Nations Sustainable Development Goals), including to bring stakeholders together and, where necessary, counter the food industry

government activities. International economic and political institutions, including the World Bank, United Nations, and World Trade Organisation, must play a more assertive role. Actions should include developing and measuring adherence to nutrition policy standards; coordinating efforts of member country; assisting governments as needed with design, implementation, and evaluation of food policies; bringing stakeholders together including global agribusiness, restaurant chains, and food manufacturers; and providing a countervailing force to multi-national food industry lobbying.

Conclusions and recommendations

Because multisectoral approaches are necessary to create healthier food systems,[5] governments should actively develop and implement policies to promote strategic and sustained change. We recommend several specific government roles and actions (box 3). For each, governments should assess whether the implemented strategies have the intended effects, identify and tackle disparities, and detect unintended consequences. This information should be made accessible to the public, academia, and other organisations.

The development and implementation of effective nutrition policies by governments have been hindered in the past by several factors, including insufficient knowledge, capacity, and will. Action and advocacy by many stakeholders are needed to overcome these barriers. Past successes that can point the way forward include effective public health approaches to complex problems such as tobacco use, motor vehicle crashes, and occupational safety. These have been achieved through a combination of scientific progress, public awareness and advocacy, consumer demand, industry innovation, government regulation, and cultural change. These successes provide a template for a healthier food system, that is: address the consumer, the product (agricultural commodities, foods, and beverages), the environment (retailers, cafeterias, and restaurants), and the culture (unhealthy eating, and marketing). To be successful, broad alliances are often required to maintain pressure, provide sound data, and bring about the desire for progress. Strong government policy is crucial to achieve a healthy, profitable, equitable, and sustainable food system that benefits all.

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Why would a leading global reinsurer be interested in nutrition?

The benefits of better diets extend beyond health, say **John Schoonbee** and **Emile Elefteriadis**

"Let food be thy medicine and medicine be thy food." More than 2000 years ago Hippocrates already recognised the link between nutrition and health. Today this link has an ever growing effect on our global society and, in particular, on insurers, who provide a financial safety net for people around the world. In the US, the world's largest life insurance market, insurers provide nearly $2tn in coverage for individual life policies.[1]

When determining long term mortality risk to provide this cover, actuaries have for decades factored in a price reduction based on the assumption that life expectancy will continue to increase. This is termed a "mortality improvement" assumption and can be locked in for many years when there are long term guarantees. If actual mortality improvements or the trend of living longer should slow down or reverse, it would have a substantial effect on the life insurance industry. Consumers too, would feel the pain, having to pay more for new life insurance than they do today.

In the UK, mortality has improved at a slower rate since 2011 than in the previous decade, according to the Continuous Mortality Investigation 2016 report.[2]

In the US, adult life expectancy in the general population has fallen for two consecutive years.[3] This has not occurred since the 1960s. The subsequent focus has been on the increase in deaths from non-natural causes such as opioid overdose. Yet the key contributing factors for many of the usual causes of death listed, like heart disease or stroke, are hard to determine and are typically not well recorded.

Diabetes

A recent study noted that diabetes is recorded as a cause of death in only 3.3-3.7% of deaths.[4] However, when the researchers examined the data more closely, the percentage of deaths attributable to diabetes was three times higher at 11.5-11.8%.

It is even more worrisome to see type 2 diabetes rates continue to soar not just in Western countries but also in developing countries, including many in Asia. India and China now have the highest number of people with type 2 diabetes. In China, almost 15% of adults living in cities today have type 2 diabetes,[5] and projections of global prevalence do not indicate a slowdown.[6]

In our ageing world, dementia and Alzheimer's disease are a growing concern and burden to families and society. The link between these diseases and diabetes and obesity (often referred to as diabetes type 3) should alarm us further.

Obesity

Obesity rates continue to climb,[7] and a recent study re-emphasised that increased obesity is associated with shorter longevity and significantly increased risk of cardiovascular morbidity and mortality.[8] Though rarely recorded as a cause of death, obesity is often linked to cardiovascular disease and significantly increases the risk of at least 13 cancers.[9]

Cancer Research UK states that after smoking, obesity is the biggest cause of cancer, linked to about 23 000 additional cases annually.[10] For the US, a 2017 report by the Centers for Disease Control and Prevention indicates that cancers associated with overweight and obesity make up 40% of cancers diagnosed.[11]

Nutrition

As much as genetics plays an important part in a person's susceptibility to overweight, obesity, or diabetes, nutrition is certainly the key driver. The evidence of what is or should be recommended to healthy people or those with metabolic disease is still confusing, contradictory, and, in fact, calamitous.

Recent studies show that weight loss and remission of diabetes can be achieved through dietary changes.[12-14] Our understanding of nutrition is often poor because of evidence that is conflicting and sometimes influenced by vested interests. This in turn leads to questionable downstream policy decisions that massively influence the outcome of world health, individual wellbeing, and the financial health of life insurance portfolios, not to speak of national health systems.

Swiss Re has developed a life insurance model to assess the population effect of reducing some of the longer term risk markers associated with type 2 diabetes, prediabetes, and metabolic syndrome through nutrition strategies. If all those affected followed such a nutrition strategy the model estimates an annual 13% reduction in total death claims.

For life insurers paying billions in death claims annually, a reduction of at least 13% would mean substantial gains. More importantly, for individuals and society it would reduce the premature loss of life from conditions that are preventable and reversible. May that be "food" for thought, and "medicine" to help make the world more resilient.

Competing interests: JS is a board member of the Nutrition Coalition. Both authors are employed by Swiss Re.

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