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Dietary and policy priorities to reduce the global crises of obesity and diabetes

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The world faces a global nutrition crisis, most clearly evidenced by the twin pandemics of obesity and type 2 diabetes (T2DM). Yet, substantial confusion and controversy exist about optimal dietary priorities and policy approaches to address these challenges. This paper reviews the evolution of nutritional evidence, emerging areas and corresponding policy lessons to address obesity and T2DM. This includes the complexity of diet–health pathways for long-term weight maintenance and metabolic health; a need to focus on both increasing protective foods (for example, minimally processed, phytochemical-rich foods) and reducing detrimental factors (for example, refined starches, added sugars and processed meats); and critical assessment of popular diets for weight-loss and metabolic health. Emerging evidence highlights areas for further research, including those related to food processing, non-nutritive sweeteners, emulsifiers, the microbiome, flavonoids and personalized nutrition. Evidence-based, multi-sectoral policy actions to address the global nutrition crisis are shown to span several domains, including health systems, economic incentives, school and workplace environments, quality and labelling standards, and innovation and entrepreneurship.

The 'double burden' of undernutrition and chronic diseases causes enormous economic losses and lost human potential across the lifespan[1]. Globally, poor nutrition is responsible for 41% of all deaths (3.2 million per year from child and maternal undernutrition, 10.9 million per year from chronic diseases) and 48% of lost quality-adjusted life years (327 and 255 billion per year, respectively)[2,3]. The food system also exacerbates diet-related health disparities, creating a vicious cycle of illness, poor work and school performance, and stunted potential[4]. The food sector causes 25% of greenhouse gas emissions, 32% of global energy use, 69% of freshwater consumption, 80% of deforestation, and loss of resilience of our soil and oceans[5–8]. The scope of these health, economic, equity and sustainability impacts are staggering—yet have remained under-recognized or accepted as status quo by governments, the public, health systems and businesses. This lack of prioritization is, however, rapidly changing—at least partly driven by recognition of the escalating health and economic costs of diet-related obesity and type 2 diabetes (T2DM). Since 1980, the number of adults with obesity has increased from 100 million to 671 million worldwide; and with T2DM, from 108 million to 422 million[9,10]. This is a global phenomenon: not a single nation worldwide has experienced a decline in obesity or T2DM; prevalence of T2DM in Japan (8.4%), India (9.1%) and China (9.9%) exceeds that of the United States (8.2%)[10]; and 55% of the rise in adiposity globally (80% in some low- and middle-income regions) is due to increases in rural, not urban, areas[11]. Left unchecked, these twin global pandemics will decimate population health, economic productivity and health-system capacity worldwide.

While the importance of good nutrition for health and curbing diet-related disease is appreciated, many people are confused about what constitutes a healthy diet. Like other scientific fields, nutritional science is rapidly evolving, with continuously improving methods and an increasing evidence-base[12]. Unlike many fields, these scientific advances in nutrition combine with deep personal and sociocultural overlays and conflicting information sources, intensifying scepticism and confusion. In addition, this evolution has occurred over less than 100 years[13]. The first half of the twentieth century was marked by discovery and synthesis of all the major vitamins, documentation of their roles in nutrient deficiency diseases, and recognition of a growing global population that required massive increases in food production. Together with the food shortages of the Great Depression and World War II, these scientific advances converged to emphasize the role of food as a delivery vehicle for selected vitamins and staple calories. The subsequent Green Revolution[14] intentionally crafted a modern food system to maximize inexpensive commodity crops and their derivative shelf-stable, starch-rich, vitamin-fortified foods. The successes of this approach should not be understated, including remarkable reductions in global hunger and classical nutrient-deficiency diseases.

It was not until the 1980s that nutrition science and policy began to meaningfully recognize and turn toward chronic diseases. The previous reductionist strategy, so successful for nutrient-deficiency diseases, was naturally extended—for example, creating isolated focus on total fat, saturated fat and sugar. However, in the past two decades, an explosion of new studies and methodologies demonstrate that specific foods and diet quality, rather than nutrient-focused metrics, are most relevant for addressing chronic diseases like obesity and T2DM. This evolution of modern nutrition science clarifies much about the state of the field today, including the current directions of nutritional research, guidelines, policies, and areas of debate and confusion.

This paper reviews evidence, emerging areas and corresponding lessons for modern dietary and policy priorities to address obesity and T2DM. Given the scope of these issues, this Review is not intended to be exhaustive, but a synthesis of key relevant topics.

Diet quality versus diet quantity

A simplistic focus on calorie counting may achieve some success, but does not account for the complex interplay of foods and dietary patterns, on long-term weight control and metabolic health. Foods should be considered as not merely energy, but information—biologic inputs to multiple pathways that help or hinder the body's

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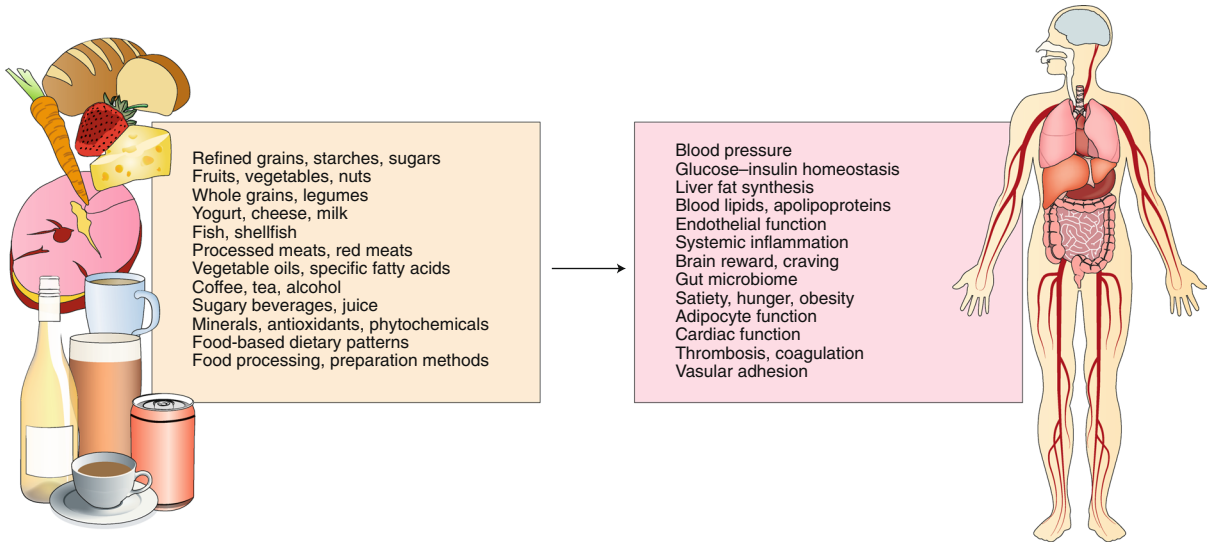

Fig. 1 | Nutrition-related biologic pathways for weight and metabolic health. Diverse aspects of the diet influence numerous risk factors, making it important to consider multiple pathways as well as clinical outcomes when making conclusions and recommendations about different foods. Reproduced from ref. [24], AHA.

diverse and overlapping pathways for long-term weight control. In other words, diet quality influences energy consumption and weight gain[15–20]. In one controlled metabolic unit trial, the availability of highly processed foods, compared to minimally processed foods, resulted in substantially greater ad libitum energy intake (+508 kcal d^{-1})—even when diets were otherwise matched in available energy, macronutrients, energy density, sugar, sodium and fibre—and, over just two weeks, the highly processed foods resulted in 0.9 kg spontaneous weight gain, while the minimally processed foods led to 0.9 kg spontaneous weight loss[20].

Diet quality also influences energy expenditure[21,22]. In a controlled feeding trial among overweight adults who had achieved 12% initial weight loss, total energy expenditure after 20 weeks was nearly 100 kcal d^{-1} higher on a moderate carbohydrate diet and more than 200 kcal d^{-1} higher on a low carbohydrate diet, compared to a high carbohydrate diet[22]. These differences were largest among those with higher insulin secretion at baseline, supporting the relevance of carbohydrate handling and sensitivity in these effects. Explanatory mechanisms require further study and could include insulin-induced partitioning of metabolic fuels away from oxidation (and heat production) and toward storage (in adipose tissue); changes in brown fat metabolism (and subsequent heat generation); and alterations in microbiome composition, mass, nutrient utilization and thermogenesis.

Thus, diet quality appears to be a major determinant of long-term diet quantity, suggesting that long-term obesogenic effects of foods cannot be judged on the basis of caloric content alone, but also physiologic and metabolic effects that drive subsequent long-term energy intake and expenditure. In addition, diet quality influences health through a diversity of physiologic effects and biologic pathways beyond obesity (Fig. 1)[23–26]. While the global obesity pandemic has appropriately highlighted the central role of nutrition in health, a focus on obesity as the most relevant endpoint misses the many other health consequences of dietary habits—obesity is just one mediating pathway. Rather than diet quantity or obesity alone, the primary targets and metrics of success for clinical and population actions on nutrition should be overall diet quality and health.

Complexity and pleiotropic effects of foods

For much of its history, nutrition science leveraged a reductionist strategy that emphasized isolated nutrients and their impact on single diseases or pathways[13]. Scientific advances make clear that foods represent complex matrices of nutrients, ingredients and processing characteristics, each with pleotropic effects on vascular, hepatic, adipocyte, pancreatic, cardiac, intestinal and brain tissues. For example, while dietary fats are commonly considered as concentrated sources of energy, they are also highly physiologically active molecules, regulating gene transcription, altering the structure and function of cellular membranes, modifying ion channel activity and electrophysiology, and influencing numerous inflammatory and other pathways through their downstream metabolites[23,26]. These complex physiologic effects do not fit neatly within the conventional nutritional classification of fats as saturated, monounsaturated or polyunsaturated, due to additional structural and biologic differences among fatty acids within these groups. Health effects of dietary fats appear to further vary depending on the specific food source, further complicating simplistic predictions of their potential effects on obesity, T2DM and related health outcomes[26,27].

As another example, thousands of different trace phytonutrients are now being documented in foods, including more than 5,000 flavonoids with wide-ranging molecular and physiologic effects (Fig. 2; also see 'Flavonoids', below), which separately and together may contribute to health effects of cocoa, tea, coffee, fruits, nuts, seeds, vegetables, beans and their oils[25]. Similarly, metabolic effects of dairy foods have generally been considered in relation to a limited set of nutrients, such as total saturated fat, calcium and vitamin D, and a limited set of pathways, such as blood cholesterol and bone health. Yet, diverse compounds in the matrix of dairy influence a wide range of molecular and physiologic pathways[25]. Further complexity is evidenced in emerging areas of nutrition science related to the gut microbiome, food processing and personalized nutrition. Together, these scientific advances highlight new, food-based dietary priorities to reduce risk of obesity and T2DM, as further described in the sections below.

Dietary priorities and protective foods

The current evidence indicates that a maximally beneficial diet pattern incorporates high intake of minimally processed, bioactive foods like fruits, nuts, seeds, non-starchy vegetables, beans/legumes, oils from these plants, whole grains, yogurt and fish; moderation in unprocessed red meats, poultry, eggs and milk; and avoidance of refined starches and sugars, processed meats, and other highly

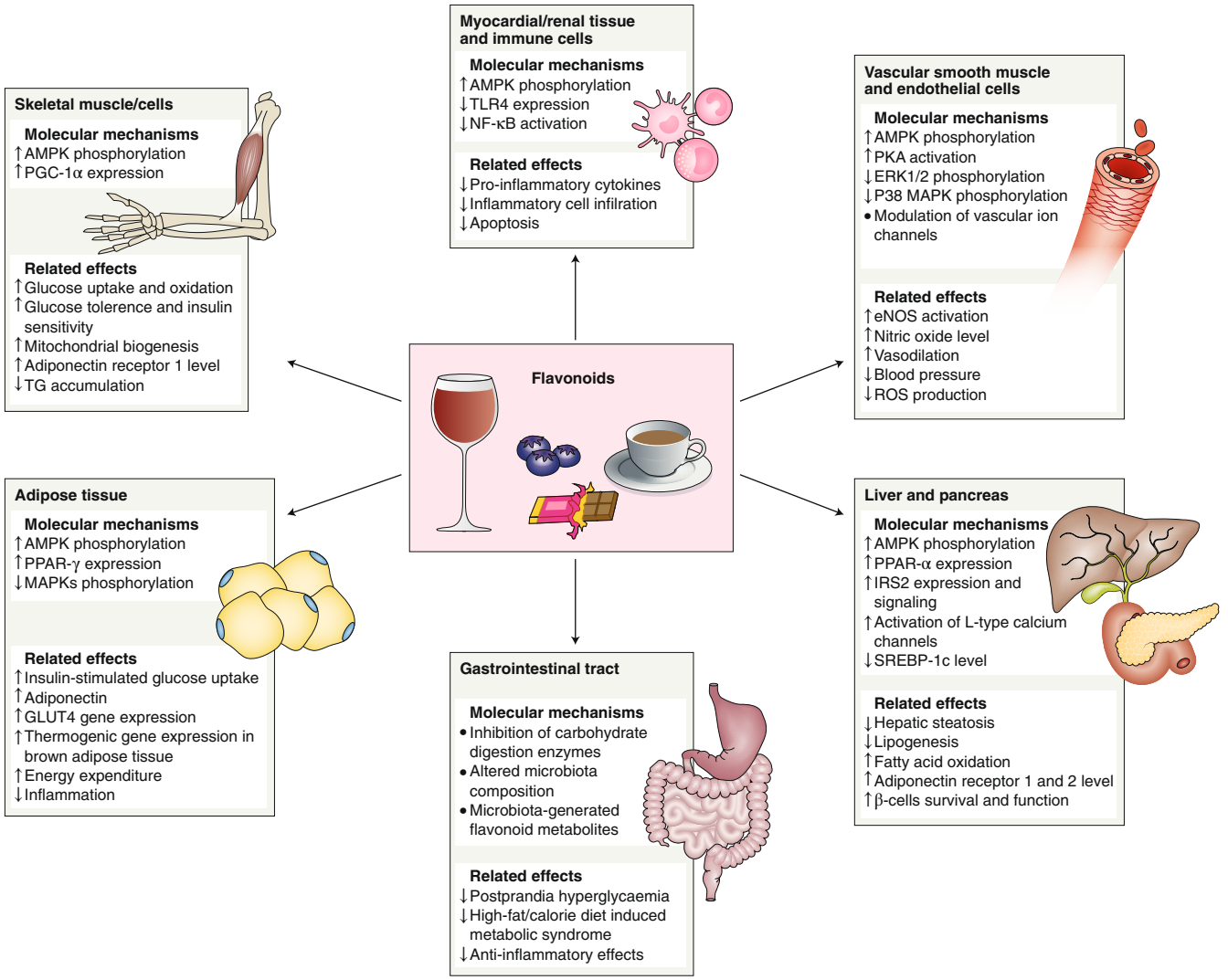

Fig. 2 | Selected physiologic pathways and molecular mechanisms for metabolic effects of flavonoids. These diverse compounds and their emerging complexities are likely to contribute to several of the metabolic benefits of minimally processed, phytochemical rich foods. AMPK, 5′ AMP-activated protein kinase; ERK1/2, extracellular signal-regulated kinases 1 and 2; eNOS, endothelial nitric oxide synthase; GLUT4, glucose transporter type 4; IRS2, insulin receptor substrate-2; MAPK, mitogen activated protein kinase; NF-κB, nuclear factor-κB; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; PKA; protein kinase-A; PPAR-α/γ, peroxisome proliferator-activated receptor-α/γ; ROS, reactive oxygen species; SREBP-1c, sterol regulatory element–binding protein-1c; TG, triglycerides; and TLR4, Toll-like receptor 4. Reproduced from ref. [25], AHA.

processed foods high in sodium, added sugars or trans-fat (Fig. 3)[24,28]. While no simple label can incorporate all the relevant characteristics of this maximally beneficial diet pattern, the most straightforward description may be a high-fat, Mediterranean-type diet emphasizing minimally processed, phytonutrient-rich foods.

Such a dietary pattern promotes weight maintenance—fruits, non-starchy vegetables, nuts, beans, yogurt, fish and whole grains each appear to protect against chronic weight gain: the more of these foods consumed, the lower the average weight gain[15,17–19]. In contrast, increased intakes of refined grains and sugars, sugar-sweetened beverages (SSBs), potatoes, processed meats and unprocessed red meats each associate with long-term weight gain[15,17–19]. Consistent with this observational evidence, in controlled trials Mediterranean diet patterns produce significant weight loss and reduced visceral adiposity[29–31].

Such minimally processed, bioactive foods are also consistently linked to better cardiometabolic outcomes[28]. In the large Women's Health Initiative, women who consumed healthier overall diet patterns rich in protective foods experienced significantly lower risk of T2DM[32]. In contrast, the randomized low-fat intervention did not reduce onset of T2DM or improve insulin resistance over 8.5 years[33]. These observed long-term benefits are supported by controlled trials utilizing dietary patterns rich in these foods[24,34]. For example, in the PREDIMED clinical trial, participants assigned to Mediterranean-type diets supplemented with extra-virgin olive oil or mixed nuts had less visceral adiposity and lower incidence of T2DM and cardiovascular disease, compared with a control low-fat diet[31,35,36].

While effects of specific subcategories of protective foods are less well established, those richest in phytochemicals (for example, nuts, berries and virgin olive oil) appear to be particularly potent. For example, a meta-analysis of controlled trials of tree nuts or peanuts identified favourable effects on insulin resistance and fasting insulin, although not statistically significant changes in HbA1c (glycated haemoglobin) or fasting glucose[37]. A meta-analysis of controlled trials of berries found modest but significant improvements in HbA1C, body mass index, systolic blood pressure, low-density lipoprotein (LDL)-cholesterol and tumour necrosis factor-α[38]. Similarly,

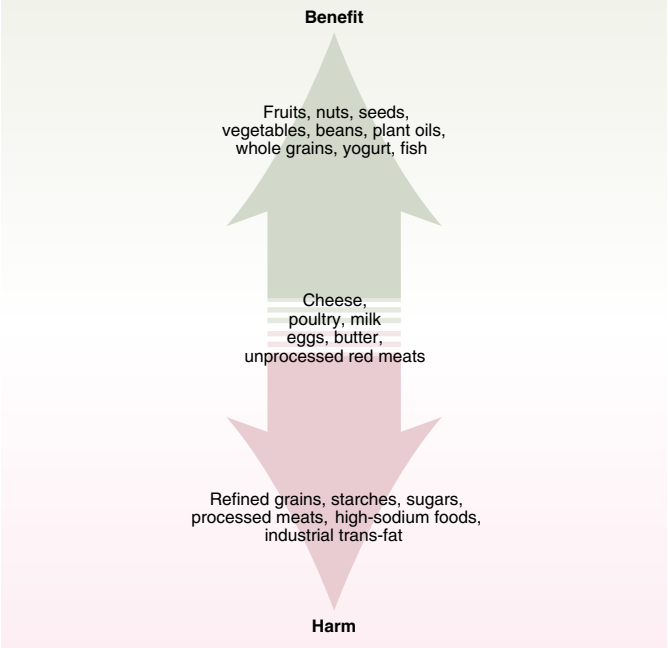

Fig. 3 | Dietary priorities to reduce obesity and T2DM. Various foods appear protective, relatively neutral or harmful for obesity and T2DM. An interesting central feature of many protective foods is their role in germinating new plant life—that is, fruits, nuts, seeds, beans, whole grains and many 'vegetables' that are actually fruits (such as tomatoes, cucumbers, olives, squash, eggplant, peppers). The myriad of phytonutrients in these foods, jointly evolved and optimized to nurture and support new life, may be relevant to humans for optimal development and aging. Other characteristics of certain protective foods—for example, probiotics in yogurt or long-chain omega-3 fats in fish—likely contribute to their health benefits. Adapted from ref. [24], AHA

Box 1 | Factors that jointly improve carbohydrate quality for metabolic health

- Lower absolute doses of refined starch and/or added sugar.
- Lower flux of carbohydrate (that is, slower digestion and absorption, for example as measured by glycaemic load), based on less processing and more intact food structure, which shields the intrinsic carbohydrate from digestive enzymes. This low flux diminishes postprandial spikes in blood glucose, insulin and other counter-regulatory hormones; and reduces hepatic de novo lipogenesis and accumulation of visceral fat.
- Higher dietary fibre, including foods providing soluble (for example, from barley, beans, legumes, oats, nuts, seeds, and certain fruits and vegetables) and insoluble (for example, from wheat, other whole grains and certain vegetables) fibre.
- Higher levels of protective phytochemicals (for example, flavonoids, other phenolics and vitamins), such as in fruits, vegetables and beans.
- More whole-grain content, providing bran and germ, and their fibre, minerals and fatty acids.
- Less milling/refining and more intact food structure, which reduces carbohydrate flux and may augment delivery of nutrients to the gut microbiome.
- Avoidance of liquid added sugars, such as sugar-sweetened sodas and energy drinks, that provide little to no nutritional value.
- Replacement of other, more highly processed carbohydrate-rich foods, which have correspondingly adverse effects related to each of the pathways above.

a meta-analysis of controlled trials supports glycaemic benefits of extra-virgin olive oil, compared with various control fats or low-fat diets, on fasting glucose and HbA1c in diabetic patients[39].

Carbohydrate quality. As a proportion of the diet, refined starches and sugars from processed foods represent one of the largest global challenges for obesity and T2DM. Major sources include white bread, white rice, white potatoes, breakfast cereals and crackers, refined pastas, chips and fries, soda, candy, muffins and sweet bakery products. Across diverse foods and beverages, those richest in starches and sugars most strongly associate with long-term weight gain[15] and T2DM risk[40]. Together with evidence from metabolic feeding studies on harms of processed, rapidly digestible carbohydrates[41], and interventional trials demonstrating substantial weight loss and improved glycaemia on low-carbohydrate (low-carb) diets[42–44], these findings make clear that poor-quality carbohydrates should be avoided to optimize weight and metabolic health.

Long-term health effects of simple and refined complex carbohydrates in foods appear similarly adverse[15,24,45]. Both are rapidly digested and produce very similar dose-dependent glycaemic responses. These similarities are consistent with adverse metabolic associations of high-glycaemic-load diets[40]. Thus, from a health perspective, refined complex carbohydrate (that is, starch, which is essentially 100% glucose) may be considered similar to 'hidden sugar'—pervasive and insidious in the global food supply. Added sugars in beverages appear even more deleterious, with adverse effects on weight gain and, independently, body composition, fatty liver and T2DM, perhaps owing to a combination of large portion sizes, rapid intake patterns and limited effects on satiety[24]. Yet, not all carbohydrates should be avoided. For example, fruits, bean, legumes, whole grains and yogurt all contain some sugar or starch, yet are linked to metabolic and cardiovascular benefits as well as long-term weight maintenance[24]. These benefits appear related to a combination of factors (Box 1), rather than any one characteristic[24,46]. Glycaemic responses of carbohydrates can be further mitigated by food order or mixed meals, such as by adding fats or proteins preceding or accompanying the meal, or even by a healthier long-term background diet[47,48].

Foods containing whole grains or dietary fibre are associated with lower risk of T2DM and weight gain[24,28,46]. While some of these benefits are likely related to displacement of poor-quality carbohydrates in the diet, evidence supports additional metabolic benefits of whole grains and dietary fibre, such as related to the germ in whole grains (containing minerals, fatty acids and phytochemicals) and to microbial fermentation of dietary fibre (for example, related to production of bioactive short-chain fatty acids such as acetate, butyrate and propionate)[49].

Resistant starches are also of growing interest but are understudied. Starches can be resistant to digestion due to physical inaccessibility (for example, intact whole grains), crystalline form (for example, raw potatoes, green bananas high amylose maize), retrogradation (realignment of cooked, gelatinized starches during cooling, for example, stale bread or cold rice) or chemical modification (for example, many emulsifiers, stabilizers and thickening agents)[50]. Like dietary fibre, resistant starches reach the large intestine where bacterial fermentation produces short-chain fatty acids and other metabolites. Two recent meta-analyses identified only small, short-term trials of resistant starch, conducted in mixed patient populations[51,52]. Evaluating body weight, satiety and glucose-insulin homeostasis, some benefits were identified, but of uncertain

relevance given the small number of studies, heterogeneity and uncertain risk of bias.

Because an array of different factors may influence carbohydrate quality, there is no single accepted metric or definition of a healthy carbohydrate-rich food. Contents of total carbohydrate, soluble fibre, insoluble fibre, resistant starch, net carbs, whole grains, added sugar, glycaemic index and glycaemic load may each be relevant but also not tell the whole story. A holistic approach should first focus on food categories to be encouraged (for example, fruits and beans) versus avoided (such as sugar-sweetened beverages, white bread, white rice and sugary breakfast cereals). Secondarily, for distinguishing among processed and packaged foods (such as different types of commercially produced whole-grain breads, cereals, crackers, granola bars, energy bars and bakery products), the ratio of total carbohydrate to fibre is empirically useful. While not perfect, a ratio of 10:1 or lower succeeds as a practical 'rule-of-thumb' by implicitly balancing the relative proportion of starch and sugar versus whole grain, bran and added fibre[53,54].

Dietary fats. For decades, low-fat diets and foods were the cornerstone of recommendations for weight loss and weight control. Based on multiple lines of new evidence, several organizations including the 2015 United States Dietary Guidelines Advisory Committee have concluded that evidence no longer supports any upper limit on total fat consumption[34]. However, other organizations like the World Health Organization have not yet discarded outdated perspectives on harms of total fat[27], contributing to public and policy confusion.

Dietary fats comprise highly diverse compounds with robust and complex effects on cell membrane structure and function, transmembrane receptors and ion channels, gene expression, and regulatory metabolites[23,26]. Health effects of fats appear further modified by the food source, for example due to accompanying nutrients, food matrices, intramolecular and supramolecular lipid structures, and processing[26,27,55]. Consistent with this complexity, total dietary fat consumption is not related to risk of T2DM (or other major health outcomes) across large ranges (~20–40%) of energy[56]. Low-fat diets are inferior to low-carb diets for weight loss and glycaemic control[42–44].

Among major fat subclasses, total saturated fat intake has similar effects on glycaemic responses as total carbohydrate[57] and is not associated with risk of T2DM[58]. In contrast, unsaturated fats reduce both HbA1c and HOMA-IR (homeostatic model assessment of insulin resistance), whether compared to saturated fat or carbohydrate; while polyunsaturated fats further improve insulin secretion capacity[57]. Consistently, estimated dietary consumption and circulating blood biomarkers of linoleic acid (the predominant dietary omega-6 polyunsaturated fat) are associated with lower incidence of T2DM, with 35% lower risk across the interquintile range of blood linoleic acid levels[59,60]. These benefits are further supported by a recent Mendelian randomization study of genetic variants associated with higher linoleic acid levels[61]. Together, these finding support the benefits of foods rich in unsaturated fats, such as nuts, seeds, avocados, and oils from fruits (for example, olive and avocado), beans (such as soybean or canola) and seeds (for example, safflower and grapeseed), to improve glycaemic control, reduce insulin resistance and lower risk of T2DM.

Circulating biomarkers of dairy fat consumption, including both odd-chain saturated fats and a natural ruminant trans-fat, are also consistently associated with lower risk of T2DM, with about 20–35% lower risk across their interquintile ranges[62]. While such objective biomarkers have several advantages, they cannot distinguish between different food sources, and such benefits could relate to other aspects of foods rich in dairy fat[25].

Metabolic effects of omega-3 fatty acids remain uncertain. In meta-analyses of trials, seafood-derived (long-chain) omega-3 fats reduce triglycerides, heart rate and blood pressure; improve endothelial function; and increase adiponectin[23]. However, long-chain omega-3 fats do not significantly affect glycaemia or insulin sensitivity in trials[63]. Prospective cohort studies generally find little to no association of long-chain omega-3 consumption from fish with risk of T2DM, except for protective associations in Asian populations[64]. Few trials have evaluated effects of plant-derived omega-3 fats on glucose-insulin homeostasis; and their associations with T2DM risk in observational studies remain inconsistent[64].

Other minor fatty acids may influence risk of T2DM. For instance, very long-chain saturated fats (20 to 24 carbons) are of growing interest, with significant inverse associations between their circulating levels and risk of T2DM[65], as well as other health outcomes. Very long-chain saturated fats can be endogenously synthesized through elongation of long-chain saturated fats or consumed from a handful of foods such as canola oil, peanuts and macadamia nuts. These fats are key components of, and may alter the biologic effects of, ceramides and sphingomyelin, which play roles in insulin resistance, inflammation and liver homeostasis[66].

Dietary protein. Increased dietary protein plus strength-training increases muscle mass and strength more than strength-training alone in generally healthy, middle-aged and older populations[67,68]. Given the relevance of lean muscle mass for insulin sensitivity, this suggests that protein consumption with strength training could improve metabolic health. However, studies of dietary protein and satiety, weight control or metabolic health show mixed findings. In meta-analysis of randomized trials, increased protein consumption had little effect on metabolic risk factors, including adiposity, lipids, blood pressure, inflammation or glucose[69]. And, in a meta-analysis of 21 prospective cohorts including 487,956 participants with 38,350 incident cases of T2DM, total protein intake was associated with higher risk of T2DM[70]. When food sources were separately evaluated, animal protein was associated with higher risk, while plant protein was associated with a trend toward lower risk. In interventional studies, high-protein diets induce variable effects on the gut microbiome, again with differences for animal compared to plant sources[71]. Given the broadly similar amino acid profiles of animal and plant proteins (indeed, the former are typically more complete and bioavailable), the difference in risk suggests effects on T2DM of animal compared to plant foods are unrelated to protein content. This is not unexpected: similar to total dietary fat or carbohydrate, dietary protein is derived from highly diverse food sources with divergent health effects. Based on current evidence, a focus on dietary protein per se appears less relevant than on specific types of foods to encourage or avoid; and the addition of strength training may modify effects.

Red and processed meats. Intakes of red and processed meat are each linked to higher incidence of T2DM, with about double the risk, gram-for-gram, for processed compared to unprocessed meats[72]. Given their otherwise generally similar nutrient profiles, this risk difference implicates harms of preservatives (for example, sodium and nitrites) or other aspects of processing (for example, high-temperature cooking)[73–75]. For unprocessed red meats, harms may relate to excess haeme iron, a generally underappreciated risk for T2DM based on animal experiments, studies of gestational diabetes and genetic disorders of iron metabolism[76,77]. In experimental studies, iron generates oxidative stress, impairs pancreatic β-cell and mitochondrial function, and may increase skeletal muscle and adipose tissue insulin resistance[77]. Both unprocessed red and processed meat intake are also positively associated with long-term weight gain[15,18]. Based on these findings, processed meats should be avoided, while unprocessed red meats should be minimized (for example, up to 1–2 servings per week) to optimize metabolic health. Interestingly, the particular harms of processed meats appear underrecognised—

in the United States, for example, consumption of unprocessed red meat has declined by nearly 20% since 2000, while consumption of processed meat remains unchanged[78].

Dairy foods. While dairy foods are often grouped together, the health effects of different subtypes (milk, cheese, yogurt or butter) appear to vary[25]. Implicated compounds include probiotics, vitamin K_1 and K_2 (menoquinones), milk fat globule membrane (MFGM), specific amino acids, medium-chain triglycerides, odd-chain saturated fats, unsaturated fats, branched-chain fats, natural trans-fats, vitamin D and calcium. For example, growing evidence supports benefits of probiotics, such as those in yogurt, fermented milk and certain cheeses, for weight control, glycaemia and perhaps non-alcoholic fatty liver disease[79–81]. Cheese is also a rich source of menoquinones, produced by bacterial fermentation, which have higher bioavailability and longer half-lives than vitamin K_1. Through carboxylation of osteocalcin, menoquinones may influence β-cell proliferation, insulin expression and adiponectin production[82]. Uniquely found in dairy, MFGM is a fascinating tri-layered membrane that naturally encloses milk triglyceride globules during extrusion from the mammary gland. Rich in bioactive polar lipids (phospholipids and sphingolipids) and proteins, MFGM at usual levels in cheese or cream reduces intestinal absorption of dietary cholesterol, blunts rises in blood LDL-cholesterol and alters gene expression[83–85], while higher doses of MFGM actually improve blood lipids and reduce post-prandial insulin[86–88]. In contrast to cream or cheese, butter contains very little MFGM, which is discarded as buttermilk during its production.

In short-term randomized trials, consumption of total dairy or milk products increases lean muscle mass and reduces body fat, especially in the setting of energy-restricted weight-loss diets[89]. Among children, observational studies suggest that dairy consumption associates with lower risk of obesity, with limited and mixed findings by type of dairy[89]. No long-term trials have been performed in children, other than rare multi-component interventions that preclude inference on dairy alone[90]. Among adults, observational relationships between dairy intake and long-term weight and T2DM vary by food type not dairy fat content[15,17,18,91,92]. For example, consumption of yogurt and fermented milk, but not regular reduced-fat or whole milk, associates with lower incidence of T2DM; while cheese associates with lower incidence of T2DM in many but not all studies[91–94]. Consistent with this, neither reduced-fat milk nor whole milk appreciably relates to long-term weight gain among adults[15,17,18]; changes in milk fat appear unconsciously compensated with carbohydrates long-term[18]. Cheese intake is associated with less long-term weight gain when replacing refined carbohydrates, but with weight gain when accompanied by refined carbohydrates[18]. Yogurt consistently associates with lower long-term weight gain[15,17,18], even for sugar-sweetened yogurts, although with about half the benefits lost compared with unsweetened yogurt[18].

Coffee and tea. Both coffee and tea are observationally associated with modest improvements in long-term weight maintenance[16] and lower risk of T2DM[95,96]. Emerging studies suggest that phytonutrients, rather than caffeine, in these bean, leaf and fruit extracts may be most relevant[25]. However, controlled trials have not yet confirmed physiologic effects to account for the magnitude of these associations, with mixed and inconsistent findings for coffee and tea and glycaemia[97–99]. Green and black tea may modestly lower blood pressure[100] and LDL-cholesterol[101,102], while green tea may improve glycaemia[99]. Mendelian randomization studies of genetic variants linked to coffee intake did not find associations with cardiometabolic risk factors or T2DM[103,104]. Overall, observational studies support potential cardiometabolic benefits of coffee and tea, but further research is needed to confirm such benefits and corresponding mechanisms.

Popular diets to treat obesity and T2DM

Among diet patterns evaluated and advocated for weight-loss and glycaemic control, increasing attention is being paid to Mediterranean, low-carb, ketogenic and paleo diets. For diet patterns, health effects cannot be attributed to any single food or nutrient, but to the overall pattern.

Mediterranean diets. In a network meta-analysis of 56 randomized trials evaluating popular diet patterns (for example, low-fat, vegetarian, Mediterranean, paleo, low-carb, low glycaemic and high-protein) in patients with T2DM, Mediterranean, paleo, and vegetarian diets appeared most effective to reduce fasting glucose; while low-carb, Mediterranean and paleo diets appeared most effective to reduce HbA1c[105]. In subgroup analyses, low-carb diets appeared more effective in shorter-term studies, smaller studies and older individuals (age 60+ years), while Mediterranean diets appeared more effective in longer-term studies, larger studies and younger adults (age <60 years). For weight loss in patients with T2DM, a meta-analysis of 20 randomized trials of various popular diets found significant weight loss only with a Mediterranean diet[30]. Most of these trials did not exceed one year, raising questions about long-term effects. The PREDIMED trial supports long-term benefits of a Mediterranean diet; after 5 years, the Mediterranean-type diet supplemented with extra-virgin olive oil or nuts reduced visceral adiposity as well as risks of T2DM and cardiovascular disease, compared with a low-fat diet[36,106,107].

The health effects of individual foods (Fig. 3), together with the above results, provide strong evidence for a Mediterranean-type diet for long-term weight control and metabolic health. The key characteristics of such a diet pattern are not any specific regional cuisine but an abundance of minimally processed foods and plant oils rich in phytochemicals, moderate fish and dairy, occasional meat, and low intakes of highly processed foods including refined starches, sugars and salt. The specific choices of foods meeting these criteria can be adapted to local availability and culture.

Low-carb and ketogenic diets. In trials with equal-intensity dietary interventions, low-carb (high-fat) diets produce similar or greater weight-loss than low-fat (high-carb) diets, with corresponding improvements in blood pressure, lipids and glycaemic control[42,43]. Meta-analyses further suggest that low-carb diets may be superior to low-fat diets for glycaemic control in patients with T2DM[44,108,109]. Such benefits occur even though most low-carb (for example, Atkins) diets lack calorie guidance or restriction, while low-fat diets include the additional interventions of portion control and calorie-restriction. In one trial comparing ad libitum low-carb versus low-fat diets (that is, testing the effects of diet composition alone), the low-carb diet reduced body weight and body fat, while the low-fat diet had small effects on weight and reduced lean muscle mass[110].

A 'low-carb' focus can be a simple rule to help reduce exposure to ultra-processed foods rich in refined starches and sugars, which likely explains HbA1c reductions[105]. Yet, carbohydrate food sources and other characteristics (that is, processing, food structure, accompanying nutrients, dose and flux) are also relevant. For example, both low-carb–high-fat and high-carb–low-fat diets lead to weight loss, without calorie counting, when they emphasize minimally processed, bioactive-rich foods[20,111]. Overall, a Mediterranean-type diet, rich in minimally processed foods and healthy fats, and low in ultra-processed foods and refined starches and sugars, appears optimal.

Extreme low-carb (that is, ketogenic) diets can lead to meaningful weight loss and metabolic benefits[112]. However, such diets may be challenging to sustain and do not leverage health benefits of fruits, non-starchy vegetables, beans/legumes and minimally processed whole grains. Also, the specific long-term requirement for ketosis per se (versus simply reducing refined starches and sugars) remains unclear. Extreme low-carb diets may be most useful

for initial weight-loss (for example, over 6–12 months), followed by transitions toward slowly incorporating carbs from minimally processed, bioactive-rich foods as tolerated. Potential long-term health effects require further investigation.

Paleo diets. Paleo diets aim to conform to foods consumed during human evolution over millennia. Benefits include avoidance of poor quality carbohydrates (refined starches and sugars) and other ultra-processed foods; and positive emphasis on non-starchy vegetables, nuts and fish; which together can produce weight-loss and corresponding metabolic benefits[113]. Yet, some interpretations of paleo diets include liberal intakes of red meats (including non-paleo processed meats), lard and salt, as well as avoidance of protective plant oils, legumes and dairy; which may reduce net benefits.

Selected emerging areas

Many exciting scientific areas relating to nutrition and metabolic health are in their relative infancy. In the coming years, rigorous further investigation of such topics will greatly expand our understanding and armamentarium to better address obesity, T2DM and other diet-related disorders. Four of these areas are highlighted below.

Food processing. Over the past 70 years, changes in plant and livestock breeding, agricultural practices and food processing methods have transformed the global food supply. The potential health implications of the new processing and manufacturing techniques are receiving increasing attention[20,114–117], with certain food classification systems and even national guidelines advocating for avoidance of highly processed foods[118,119]. Processed meats and refined grains, starches and sugars are convincingly linked to metabolic harms[28]. However, nearly all foods must undergo some form of processing for human consumption—for example, milling, refining, heating, cooking, smoking, drying, salting, fermenting or preserving (some exceptions include fruits, nuts, seeds and certain vegetables). Thus, rather than focusing on processing per se, the key issue is to understand which aspects of modern processing are detrimental and define optimal processing of different foods for health.

Processing can increase palatability, nutrient bioavailability, shelf life and convenience, and reduced risk of food-borne pathogens. Processing may also reduce fibre, phenolics, minerals, fatty acids, vitamins and other bioactives; increase the doses and flux of starch and sugar; and introduce compounds such as sodium, other preservatives and additives, trans-fats, heterocyclic amines and advanced glycation end-products (AGEs). Pathways related to the microbiome—including prebiotics, probiotics, non-nutritive sweeteners, emulsifiers and thickeners—are reviewed in the next section.

Health effects of AGEs represent a promising but substantially understudied area. AGEs, formed during high-temperature cooking and browning, are experimentally implicated in pathways related to cardiometabolic risk[73,120]. A few small studies suggest benefits of low-AGE diets in subjects with overweight, obesity and prediabetes[120]. In the largest trial, among 100 subjects with obesity and metabolic syndrome, a low- versus high-AGE diet for one year significantly reduced body weight, waist circumference, insulin resistance, and biomarkers of oxidative stress and inflammation[121].

On average, most highly processed food products have adverse metabolic effects (for example, SSBs, refined grains and cereals, and processed meats), while most minimally processed foods are protective (for example, fruits, nuts and seeds) (Fig. 3). On the other hands, certain more 'natural' foods such as eggs, butter and unprocessed red meats do not appear to improve metabolic health, while other more processed products (for example, yogurt, cheese, plant oils and margarines, canned fish, nut and fruit-rich snacks) are beneficial. In addition, while newer industrial processing methods have received the most media and public attention, certain traditional processing methods may also have adverse health effects. For example, the centuries-old practice of making butter removes MFGM, a potentially beneficial compound[83–88,122,123]. And, as described above, AGEs are formed during cooking and heating, used by humans for millennia.

Overall, seeking minimally processed, phytochemical-rich foods, and avoiding more processed foods, is a strong general—but not absolute rule—for good health. Given the size, expertise and reach of the global agriculture and food industry, a major increase in private and public research investment is needed to better define and understand pathways for optimal food processing.

Gut microbiome. Nutritional choices exert large, rapid effects on gut microbial composition and function, with implications on host health[124–127]. For example, several protective foods (Fig. 3) have prebiotic or probiotic characteristics. Prebiotics feed the microbiome, such as dietary fibres, fructans (for example, inulin in chicory root) and other oligosaccharides, resistant starch, and certain phenolics (for example, cocoa-derived flavonols)[46,126]. Probiotics are live bacteria or yeasts that favourably alter gut microbial composition[127], found in fermented foods like yogurt; cheddar, cottage, gouda and mozzarella cheeses; and kefir (milk), kimchi (cabbage and other vegetables), kombucha (tea), miso (soybeans), natto (soybeans), sauerkraut (cabbage) and tempeh (soybeans). Trials of probiotic-containing foods and supplements demonstrate benefits on weight control, glycaemia and possibly non-alcoholic fatty liver disease[79–81].

Conversely, metabolic harms of highly processed foods may partly relate to adverse microbial effects. Common processing methods (for example, milling and refining) strip away key prebiotics. Even if reconstituted (for example, added bran and fibre), the loss of intact food structure (termed 'acellular nutrition') may alter digestion and absorption in the proximal gut[117] and also deprive the (dominant) distal gut microbiome of relevant prebiotics[128]. Foods can also be intentionally processed to retain or supplement prebiotic contents.

Food additives like non-nutritive sweeteners, emulsifiers and thickeners may also influence the microbiome[117,128]. In some animal models and limited human experiments, artificial sweeteners alter host microbial composition and adversely influence satiety, glucose–insulin homeostasis, caloric intake and weight gain[129,130]. Non-nutritive sweeteners may also influence taste preferences and learned behaviours, especially among children; and trigger digestive tract sweet-taste receptors that influence glucose absorption and insulin secretion[131]. In a meta-analysis of short-term trials, non-nutritive sweeteners significantly reduced postprandial blood glucose at 2 to 3.5 hours, compared with baseline[132]. The long-term implications of such effects, which could induce counter-regulatory hunger or other hormonal responses, are unclear. In one small trial, participants who consumed a drink with non-nutritive sweeteners, compared with a sugar-sweetened drink, ate significantly more one hour later when provided ad libitum lunch, eliminating (but not overtaking) the initial caloric deficit of the non-nutritive-sweetened drink[133]. Some long-term observational studies find that baseline frequency of diet soda intake associates positively with weight gain and T2DM[134], but studies of changes in intake (less susceptible to bias and reverse causation) find very small inverse associations[16]. In sum, evidence on harms of artificial sweeteners is mixed, while no long-term studies have assessed the newer, natural non-nutritive and low-calorie sweeteners. Based on the breadth and depth of their use and uncertain long-term effects, the global food sector may be said to have "embarked on a massive, uncontrolled, and inadvertent public health experiment"[134]. Further research on their effects is urgently needed. For now, these compounds may best be considered a bridge for consumers and the food sector away from added sugars and toward naturally sweet or unsweetened foods, rather than a final destination.

Emulsifiers and thickeners are used to alter the appearance, texture or mouthfeel of processed foods[135]. Common emulsifiers include carrageenan, guar gum, lecithin (soy, egg), mono- and diglycerides, and polysorbates. Food thickeners include proteins (for example, collagen, egg whites and gelatin), starches (for example, cornstarch, potato starch, sago, wheat flour and tapioca), sugar polymers (such as agar and pectin), and vegetable gums (for example, guar and xanthan). In some experimental models, emulsifiers and thickeners influence the gut microbiome, the gut mucosa and related inflammatory pathways[135]. For example, in a mouse model, two common emulsifiers disrupted the gut mucosal barrier, altered microbial composition and increased bacterial translocation, leading to low-grade inflammation, weight gain and metabolic syndrome[136]. Such effects appear partly mediated by direct effects on microbial composition and pro-inflammatory potential[137]. As with artificial sweeteners, the long-term metabolic effects of emulsifiers and thickeners remain uncertain and controversial.

Flavonoids. Flavonoids represent more than 5,000 different compounds in fruits, nuts, seeds, vegetables, beans and their oils, with wide-ranging molecular and physiologic effects[25]. Oleocanthal is a flavonoid in extra-virgin olive oil that causes the common burning sensation at the back of the throat when the oil is directly consumed. The similarity of this sensation to swallowing a chewed uncoated aspirin is no coincidence: oleocanthal binds the same irritant transient receptor potential A1 channel in the throat as many non-steroidal anti-inflammatory drugs[138,139]. Likewise, oleocanthal inhibits cyclooxygenase 1 and 2 isoenzymes throughout the body, with stronger dose-dependent anti-inflammatory effects than ibuprofen at equimolar concentrations[138,139]. Thus, while metabolic effects of olive oil are often considered only through the lens of its monounsaturated fat content, trace phytonutrients such as oleocanthal are likely also important.

Individual foods and diet patterns rich in dietary flavonoids and other phytochemicals consistently associate with better weight control and lower risk of T2DM[24,140,141]. Animal and experimental studies demonstrate effects of flavonoids on a number of pathways related to metabolic health (Fig. 2). Supplementation with flavonoids prevents diet-induced weight gain in several animal models[25], even on calorie-matched diets[142–145], suggesting possible additional effects on pathways related to energy expenditure, such as in the gut microbiome or brown fat.

Given the diversity of naturally occurring flavonoids identified to date[146], observed effects on molecular pathways for certain flavonoids are unlikely to be generalizable to others. The complexities in flavonoid bioavailability and metabolism, including effects of microbiome-produced flavonoid metabolites, which often have longer half-lives and achieve higher circulating concentrations[147], remain to be fully explored. Based on their promise for metabolic health, additional mechanistic, experimental and clinical studies of flavonoids and their metabolites are urgently needed to further elucidate their typology, bioavailability, metabolism and health effects.

Personalized nutrition. The investigation of gene–diet interactions for obesity and T2DM has resulted in many findings, but disappointingly small effect sizes and reproducibility[148,149]. Personalization based on other characteristics—for example, sociodemographics, cultural factors, the microbiome, medical history, physiologic parameters and epigenetics—appears more promising[150–154]. For example, glycaemic responses to poor quality carbohydrates may be especially detrimental in women[155] compared with men. Similarly, patients with T2DM, insulin resistance or atherogenic dyslipidaemia may benefit most from reducing refined carbs and increasing dietary fibre, proteins and plant oils[22,153,154,156,157]. The gut microbiome is also promising for personalization: an individual's gut microbial composition may help predict personalized glycaemic and weight responses to different foods[152,158–161]. This could relate, for example, to differential digestion of dietary fibres by *Bacteroides*, *Prevotella* and other gut species, with corresponding varying production of short-chain fatty acids[161].

In addition to identifying optimal foods, personalized nutrition could theoretically inspire larger or more sustained behavioural changes compared with more general recommendations. For example, strategies that assess and incorporate a person's cognitive–behavioural stages, and cultural and socioeconomic background, may increase effectiveness of general behaviour-change strategies[162,163]—but limited evidence currently supports this concept for nutrition behaviours[164]. Moreover, personalized interventions could increase health disparities if they are costly or difficult to access due to required genomic, metabolomic and other high-dimensional data[150].

Overall, personalized nutrition remains an interesting concept deserving of greater investigation. However, the massive, rapid global shifts in obesity and T2DM across and within populations[165] demonstrate the dominant influence of generalized environmental determinants and the corresponding importance of population approaches to address these factors. Such systems strategies can also reduce health disparities, compared with individual-based approaches[166,167].

Multisectoral policies and best-buy priorities

Given the core role of nutrition in health, healthcare costs, disparities and sustainability, multi-sectoral policies for better nutrition should be a top priority for governments, businesses, health systems and payers[168–171]. Effective actions span several domains: health systems, economic incentives for consumers and industry, school and workplace environments, government quality standards and labeling, and innovation and entrepreneurship (Table 1)[171–185].

For most of human history and through the twentieth century 'Green Revolution'[14], governments aimed to combat the challenge of insufficient calories by promoting production and distribution of staple crops. With the unprecedented recent rise in global diet-related chronic diseases, government policies have largely failed to adapt, emphasizing agricultural production of major commodities and support for large food companies as motivated by traditional trade and economic perspectives. However, the continued double burden of diet-related illness plus a new sustainability agenda has begun to shift this dynamic—for example, the majority of the United Nations 2030 Sustainable Development Goals incorporate or are heavily influenced by food and nutrition[186].

In formulating dietary policies to address obesity and T2DM, many governments and public health experts have adapted principles from the World Health Organization 2005 Framework Convention on Tobacco Control, the first contemporary framework convention with specific public health objectives[187]. This includes an emphasis on taxation, warning labels, marketing restrictions, access constraints and limitations on content levels of harmful compounds. For example, SSB taxes have now passed in seven United States jurisdictions and multiple nations, including Barbados, Belgium, Brunei, Chile, Dominica, Ecuador, France, India, Ireland, Kiribati, Mauritius, Mexico, Norway, Peru, the Philippines, Portugal, Saudi Arabia, South Africa, Spain (Catalonia), St Helena, St Vincent and the Grenadines, Sri Lanka, Thailand, the United Arab Emirates, the United Kingdom and Vanuatu[188]. While such tax policies can be fiscally regressive, they are progressive for improving health disparities. Fiscal regressivity can be further offset by utilizing the tax revenues for subsidies on healthier foods, an approach that has been recommended[189] but not yet implemented by any nation. A diversity of countries have also implemented mandatory or voluntary food front-of-package or other warning labels[190], including Chile's notorious new 'black box' warning labels[191]. Several nations, including Belgium, Canada (Quebec), Chile, Ireland, Israel, France, Mexico, Sweden, Taiwan and the United Kingdom, have also instituted

Table 1 | Effective multi-sectoral actions to improve nutrition[a]

Health systems	Economic incentives	Schools	Worksites	Quality and labelling standards	Innovation and entrepreneurship
Electronic health record standards: for example, nutrition vital sign, nutrition annual physical	Taxes on sugary drinks, added sugar and salt	School meals: strong nutrition standards	Procurement standards for worksite cafeterias, snacks and catering	Limits on additives such as trans-fat, salt and sugar	Coordinated government leadership and funding for fundamental and translational research (for example, a new National Institute of Nutrition)
Medical education: nutrition in physician and other provider licensing exams, specialty certifications and continuing education	Retail consumer subsidies or other incentives for protective foods	Competitive foods: strong nutrition standards[b]	Cafeteria built-environment nudges (behavioural economics)	Marketing standards or restrictions, especially relating to children	Public–private partnerships for research and development, for example, on optimal agricultural practices or food processing
Healthy food prescriptions covered by health insurance	Government feeding programs: strong nutritional incentives and/or standards	Free provision of fruits and vegetables	Multicomponent wellness platforms including a strong nutritional focus	Nutrient content labels, front-of-pack icons and restaurant menu labelling	Academic convening of investors and start-ups to facilitate evidence-based, mission oriented innovation
Medically tailored meals for highest-risk patients with complex chronic conditions	Tax incentives (agricultural, retail, manufacturing and restaurant) for development and marketing of healthier foods	School gardens with coordinated educational programming	Employee incentives for purchasing healthier foods at or outside work	Warning labels	Global pooling of research dollars for top nutrition priorities; for example, obesity, T2DM, cancer, brain health, microbiome, phytochemicals, data science and policy translation
Provider quality metrics and payer reimbursement for nutritional evaluation and intervention	Changes in shareholder criteria (for example, B-Corps) and investment vehicles to reward companies for tackling obesity and T2DM	—	Procurement standards for hospital cafeterias and food	Health claims	—

[a]Another domain of interest is the built food environment: that is, neighbourhood availability of different food retail stores and restaurants 'food deserts'. The evidence for dietary or health effects of changes in this domain remains surprisingly limited[171–185], perhaps because the built food environment is at least partly determined by prevailing consumer demand. Actions in the table above may be market-based approaches to increase demand, availability and affordability of healthier foods and, thereby, the presence, type and product inventory of neighbourhood retail stores and restaurants. [b]Foods sold outside of regular school meals, for example, before or after school, in vending machines or at school stores.

restrictions on food marketing to children[192,193]. Countries such as the United States and Mexico constrain access to soda and/or junk food in schools; while Canada, Denmark, Switzerland, Turkey, the United Kingdom and the United States aim to limit contents of additives such as trans-fats, sodium or added sugars[194,195].

This 'tobacco playbook' makes sense for certain food categories (for example, soda and junk foods) and additives (for example, trans fats, sodium and added sugars). However, such policies have much less relevance for increasing the consumption of protective foods. Insufficient intakes of such foods cause at least as much disease as excess intakes of harmful foods and nutrients[2,28]. This can represent an important positive message for the public, policy makers and industry—one that celebrates the power of good nutrition. To increase the availability, affordability and consumption of protective foods, a more nuanced, multi-sectoral set of actions will be required (Table 1). For instance, the Rockefeller Foundation recently outlined a set of priorities toward such goals, including smart investments in value chain infrastructure and efficiency, advances in the use of artificial intelligence and data analytics, increased investments in research and innovation, and coordinated efforts for public awareness and innovation to increase demand for, and desirability of, protective foods[196]. Given the Rockefeller Foundation's central role in the 'Green Revolution' more than 70 years ago, a highly successful effort that increased global food production and reduced global hunger, this new recognition and focus on protective foods represents a powerful new chapter in the effort to reduce diet-related illness and its consequences.

Conclusions

The food system is crucial for well-being, healthcare costs, health disparities and planetary sustainability. While diet influences many diseases, the global pandemics of obesity and T2DM are particularly notable. In less than a century, modern nutrition science has advanced remarkably, highlighting key priorities to address obesity and T2DM. The significant impacts of the food system on health, the economy, equity and the environment, together with mounting public and food-industry recognition of these issues, have created an opportunity for leadership to create meaningful and lasting solutions. Such efforts must be catalyzed by multi-sectoral policies, with governments playing a special role. This includes an urgent need for greatly expanded food and nutrition discovery and innovation, that is coordinated and mission-oriented toward the health of people and the planet.

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Competing interests

Tufts University holds patents US8889739 and US9987243 (unlicensed), listing D.M. as a co-inventor, for use of trans-palmitoleic acid to prevent and treat insulin resistance, type 2 diabetes and related conditions, as well as reduce metabolic risk factors.

Additional information

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