NURTURING SUSTAINABLE NUTRITION THROUGH INNOVATIONS IN FOOD SCIENCE AND TECHNOLOGY

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NURTURING SUSTAINABLE NUTRITION THROUGH INNOVATIONS IN FOOD SCIENCE AND TECHNOLOGY

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Table of Contents

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Editorial: Nurturing sustainable nutrition through innovations in food science and technology

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Editorial on the Research Topic
Nurturing sustainable nutrition through innovations in food science and technology

Introduction

Nutrition Science and Food Science and Technology (FS&T) are at the heart of disruptive evolutionary processes, and exponential progresses in science, health, innovation and digital technology. Suitable knowledge of these advances is still evolving. Hence, a paradigm shift and novel curricula are required. Such an attempt was made in the 2020/21 International Master Michele Ferrero 8th edition program offered by the Ferrero Foundation and Soremartec in collaboration with the University of Turin and the Catholic University of the Sacred Heart, Milan. A series of nine-webinars by more than 30 invited eminent scientists and key industrial leaders was tailored-made, offering a wide spectrum of the state of the art knowledge and views.

This Research Topic directly stems from the 8th Master edition, with a Research Topic of papers comprehensively covering all FS&T-related key and novel topics elaborated during the Course. In light of the plethora of reviews published on the selected topics, challenging to read and digest by many practitioners, special efforts have been placed on offering concise yet comprehensive contributions.

a. Position paper

"*A need for a paradigm shift in healthy nutrition research*" by Aleta et al..

Research in sustainable and healthy nutrition requires the application of the latest advances in seemingly unrelated domains, such as complex systems and network sciences on one hand and big data and artificial intelligence on the other. Focusing here primarily on nutrition and health, the methodological changes needed to open current disciplinary boundaries to the methods, languages, and knowledge of the digital age are discussed, laying the groundwork for the development of a systems thinking approach. Specifically, a paradigm shift is required toward adoption of interdisciplinary, complex-systems-based research to tackle the immense challenges required for dealing with an evolving interdependent multiple scale systems. The latter are ranging from the metabolome to the population level, heterogeneous and more often than not contained incomplete data. Also, population changes subject to many behavioral and environmental pressures. To illustrate the importance of this methodological innovation, the paper focuses on the consumption aspects of nutrition rather than production. Nevertheless, the importance of system-wide studies that involve both these components of nutrition are recognized. Specific research directions that would make it possible to find new correlations and, possibly, causal relationships across scales, and in addition, answering pressing questions in the area of sustainable and healthy nutrition are furnished.

b. Perspective articles

"Plant-based: A perspective on nutritional and technological issues. Are we ready for "precision processing?"" by Menta et al..

Nutrition science is facing challenging times due to accelerated changes and fast-growing global population in the coming years. Innovation in raw materials, processes, science and digital capabilities seems to be the key to address this new era, and, in this context, a plant-based approach to nutrition could meet the needs of these new challenges. Particular attention is focused on highlighting the differences in quality and functionality of animal and plant proteins, along with a call to unite global efforts and to offer suitable available solutions.

"*Food products and digital tools: The unexpected interconnections*" by Marra.

The current advances and future directions in the use of science-based digital tools in food product design are highlighted, first, an overview of studies exploring food related apps and social media for understanding consumers' perception and preferences, and, second, a discussion on the integration of the derived data. A wider scheme for food product design based on predictive features is needed, using advanced multiscale and hybrid methods. Linking product features with the understanding of consumers' needs and preferences offers significant benefits for start-uppers and researchers who develop tools for reinventing food product design.

c. Mini reviews with a particular focus on:

- Health and consumers behavior impact

"*Impact of dietary palmitic acid on lipid metabolism*" by Murru et al..

Palmitic acid (PA) is ubiquitously present in dietary fat guaranteeing the relative high requirement and content in the human body, with a crucial physiological role. Lower placental transfer of PA strongly induces its endogenous biosynthesis from glucose *via de novo* lipogenesis (DNL), securing a tight homeostatic control of PA tissue concentrations. Unbalanced body composition and reduced physical fitness might be either cause or consequence of DNL. Unbalanced saturated fats/polyunsaturated fatty acids intake may further impact the energetic and metabolic balance.

"*Dietary fats, human nutrition, and the environment: Balance and sustainability*" by Meijaard et al..

Optimization of oil or fat choices that most benefit health and the environments in areas where these are produced, is undermined by a significant lack of data. The article reviews current knowledge about the sustainability impacts of oils and fats, focusing the role of biodiversity in their production. Gaps in knowledge and analytical to address them are highlighted.

"*Oxysterols as reliable markers of quality and safety in cholesterol containing food ingredients and products*" by Canzoneri et al..

Cholesterol is a lipid of functional value that easily undergoes oxidation, leading to a wide variety of cholesterol oxidation products, named oxysterols. Recent research points to oxysterols as highly reliable markers of food quality, before/after industrial processes and storage. Survey of relevant literature highlighted the advantages of quantifying oxysterols as quality markers of food and food ingredients. Further, bioavailability, metabolism, and pathophysiological features of measured oxysterols are fully discussed.

"*A2 milk and BCM-7 peptide as emerging parameters of milk quality*" by Giribaldi et al..

Due to natural genetic variation, beta-casein (up to ∼30% of the total protein) can be present in cows' milk as two distinct forms, A1 or A2 that differ for a single but crucial amino acid substitution. Only in A1 or A1A2 beta-casein containing milk and dairy products, the peptide β-casomorphin-7 (BCM-7) is released upon intestinal digestion. Such BCM-7 release has been associated with inflammatory disturbances of the gastrointestinal tract with alteration of the gut microbiota. The health ramifications of milk containing A2 β-casein subtype are highlighted.

"Evolution of milk consumption and its psychological determinants" by Castellini and Graffigna.

The food industry has developed new products in order to respond to consumer's needs and expectations, in spite of Institutional recommendations. The widespread consumption of lactose-free products (LFP) is therefore unjustified considering either the scientific evidence and the consumers' perspective. The review highlights the research findings related to the motives and psychological factors mainly influencing consumers to prefer LFP.

"*Milk: A scientific model for diet and health research in the twenty-first century*" by German et al..

Milk's glycans highlight the Darwinian pressure on lactation as a complete, nourishing and protective diet. These polysaccharides reach undigested the lower intestine where bacteria compete to release the monosaccharides and ferment them. *B. infantis*, is uniquely equipped with a repertoire of genes encoding enzymes capable of metabolizing the complex glycans of human milk. The intestinal microbiome dominated by *B. infantis*, shields the infant from the growth of enteropathogens and their endotoxins as a clear health benefit. The paper highlights how scientists should guide the future of agriculture and food in response to twenty-first century challenges to produce a food supply at the same time nourishing, safe and sustainable. Lactation provides an inspiring model of what future research strategy could be.

- Sensory cues and taste

"*Influence of sensory properties in moderating eating behaviors and food intake*" by Forde and de Graaf.

An overview of recent findings and opportunities to use foods' sensory properties as a "functional" component that may help promoting healthier eating habits while maintaining eating pleasure. Addressing the serious public health challenges posed by the modern food environment will require changes in food formulation and intake behavior. The utilization of foods sensory properties may support healthier food choices and intakes while suggesting a better management of chronic conditions such as obesity and type-2 diabetes.

"*Extra-oral taste receptors: function, disease, and perspectives*" by Behrens and Lang.

A brief introduction into human taste perception, receptive molecules and signal transduction is highlighted. The five basic taste qualities (i.e., salty, sour, sweet, umami, and bitter) provide important information on the energy content, the concentration of electrolytes and the presence of potentially harmful components in food items. Taste receptors in the gastrointestinal tract, participate in a variety of bioprocesses with meaningful effects on health too. Accordingly, complex selective forces may have contributed to shape taste receptors during evolution.

- Microbiome studies

"*Diet and gut microbiome and the "chicken or egg" problem*" by Daniel.

A concise and provocative scientific argument for a more comprehensive assessment of the individual's intestinal phenotype in microbiome studies to resolve the "chicken or egg" problem that has emerged from observational studies on functional effects is provided. It highlights that quantity and quality of the intestinal and fecal microbiome vary considerably between individuals and are dependent on a wide spectrum of intrinsic and/or environmental factors.

Controversial aspects of the modern food era: Processes, dietary impact, and nutritional recommendations

"*Food innovation in the frame of circular economy by designing ultra-processed foods optimized for sustainable nutrition*" by Capozzi.

Circular economy emerges as a crucial driving force considering the future predicted world population growth. It highlights the necessity for finding the resources essential to produce food in sufficient quantity and quality, looking for sustainable sources, while trying to exploit all the value obtainable from raw materials. Nutritional studies will stimulate the selection of sources richer in nutrients and bioactive molecules. The assessment of the quality and safety of functional foods based on ingredients derived from food waste requires a more robust validation by means of the food-omics approach, which considers not only the composition of the final products but also the structural characterization of the matrix, as the bioaccessibility and the bioavailability of nutrients are strictly dependent on the functional characteristics of the innovative ingredients. This new approach offers a new avenue to assess relationships between circular economy and UPFs. Suitable solutions are proposed, analyzed, and discussed.

"*Integrating dietary impacts in food life cycle assessment*" by Jolliet.

Food production and food consumption have been too long studied separately. The review highlights how nutrition affects human health and states that environmental impacts of the entire food production and consumption can and should be consistently and systematically assessed, on a life cycle-based and a health-based perspective. The review also provides a novel approach to calculate the Health Nutrient Index score expressed in minutes (gained/lost) of healthy life per serving. This integration combined with utilization of Big Data and machine learning methods will help reporting interactions among healthy and sustainable foods.

"*Dietary patterns vs. dietary recommendations*" by De Cosm et al..

The classic views of nutrient-based healthy recommendations should today be replaced by the holistic view of "whole food form" patterns, epidemiologically connected to indices of human health. The Mediterranean, New Nordic and Japanese diets, respectively, offer three possible paradigms of this novel approach.

The program of the Master Degree in "Innovation in Food Science and Technology—Michele Ferrero" focused on innovation, as a key characteristic of food system, sustainable nutrition, and personalized health and nutrition. A multidisciplinary approach and international perspective characterized the teaching activities. This unique collaboration between Academia and Industry should serve as a model highlighting a new mindset. The "old normal" pre COVID-19 has been disrupted, while embracing the "new normal" becoming the only way forward. Facilitating new mindset and leading future innovation processes, strategic considerations, and developing new partnerships are paramount. Program like the one offered by the Ferrero Foundation is paramount and a significant bridge and a platform in pursuing future challenges.

Author contributions

IS, GP, and CA: conceptualization. IS and GP: writing—original draft preparation. IS, GP, CA, and MC: writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The guest editors declare that this Research Topic received limited partial founding from Soremartec Italia Srl. GP, IS, and CA were involved in Master Michele Ferrero academic course and webinars and received limited partial funding from Fondazione Piera, Pietro e Giovanni Ferrero and Soremartec Italia S.r.l. MC is an employee of Soremartec Italia S.r.l.

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Diet and Gut Microbiome and the "Chicken or Egg" Problem

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Quantity and quality of the intestinal and fecal microbiome vary considerably between individuals and are dependent on a very large number of intrinsic and environmental factors. Currently, only around 15% of the variance in microbiome diversity can be explained by these factors. Although diet and individual food items have effects, other individual parameters such as gender, age, body mass index (BMI), but also plasma lipids and blood pressure reveal stronger associations with microbiome diversity. In addition, gastrointestinal functions that translate into changes in stool frequency, stool volume, and stool appearance rank very high as effectors of microbiome signatures. In particular, the intestinal/colonic transit time is a critical factor that alters the substrate load for bacterial growth and metabolism as it alters simultaneously stool volume, water content, bacterial mass, and diversity. Moreover, metabolic and neurological diseases are frequently associated with marked changes in intestinal transit time that may translate into the reported changes in gut microbiota. This review provides scientific arguments for a more comprehensive assessment of the individual's intestinal phenotype in microbiome studies to resolve the "chicken or egg" problem in these observational studies.

Keywords: intestine, microbiome, diet, determinants, treatment, diseases, transit time

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INTRODUCTION

The interplay of the diet with the human gut microbiome has recently gained scientific and public popularity like no other aspect of food and nutrition sciences and there is hardly a disease that has not been linked to the composition of the gut microbiome. Since the diet is generally considered a key determinant of gut microbiome diversity, it is believed that dietary maneuvers easily alter the microbiota and thereby prevent diseases or slow disease progression. Targeted interventions to change the microbiome however that would require that we know what characterizes a "healthy microbiome." But such a definition is still not available (1). Moreover, based on the huge variability in the composition of the microbiome across individuals but even within an individual with changes, day by day or depending on the time of sampling a "normal" microbiome is equally difficult to define and consequently "dysbiosis," as deviation from normal, cannot be defined either (2). Yet, gut "dysbiosis" is often claimed as a critical factor in the susceptibility to and severity of diet-dependent diseases.

It appears as generally accepted that high bacterial diversity is the signature of a "healthy" microbiome although that is only based on observational evidence and is mainly derived from studies in which fecal samples from industrialized and nonindustrialized populations are compared. In addition to bacteria, the intestinal ecosystem harbors thousands of different viruses/bacteriophages (3) but also yeast and nematodes (see below). Although a huge number of variables have already been identified as contributing to microbiome diversity in populations from across the world and from different sociocultural and ecological environments those currently explain all-together only around 15% of the variance (1). It needs to be emphasized that almost all studies published in recent years provide only relative abundance data for the different phyla or genera of species in a sample. Given the fact that quantitative data are of utmost importance in all areas of biomedical and clinical research, the work with relative abundance data seems thus unique to microbiome science. Although various studies have assessed bacterial densities in the stool (4–6), a more recent analysis demonstrates that even a 10-fold difference in bacterial counts is not mirrored in relative abundance profiles (7). In addition, many variables affect the quality of analysis of stool samples (8) and the same sample analyzed by different laboratories can produce quite large differences in microbiome signatures (9). Given these caveats, caution should guide our recommendations to consumers interested in their microbiota. Here it will be critically assessed what influences bacterial density and diversity in stool samples and what diet effects have been observed in intervention studies. In addition, the question of whether the microbiome follows alterations in host physiology when moving into disease states or whether the microbiome is in a causative manner involved in disease initiation or progression will be discussed.

DETERMINANTS OF HUMAN GUT MICROBIOME DIVERSITY

Hundreds of population studies have meanwhile assessed microbiome profiles in stool samples and hundreds of parameters significantly associated with the diversity of microorganisms in the samples have been identified. Most interestingly, host genetics has only small effects with an inheritance of microbiota diversity accounting for around 2–9% (10, 11). As the most consistent finding in studies on host genetics and loci linked to the microbiome has the lactase gene been identified (12). Many other factors such as geographical origin or occupational state of the person rank also high among the key drivers of microbiome diversity.

Since stool samples from nonindustrialized communities but also paleosamples often display a wider range of bacterial species, these more diverse microbiomes are currently considered as a goal by dietary interventions. However, whether the highest diversity is the ultimate measure of a "healthy microbiome" has also been questioned (2). A very recent analysis of prehistoric stool samples (5,000–8,000 years old) from sites in the mid-west of the United States and Mexico (13) concluded that the bacterial diversity of these ancient samples is higher than that of samples representing industrial societies. However, the article reports as well that most paleosamples contained parasites. Another such example is stools of bronze-age miners recovered from salt mines in Austria with an exceptional preservation state and here also almost all samples contained eggs of various species of worms and other parasites (14). But even when modern samples from rural areas are analyzed, these frequently contain parasites and most interestingly, parasite infections associate with higher microbiome diversity (15, 16). Moreover, in animal studies, parasitic infections were shown to increase microbiome diversity which declined again when the infection was over (17). These observations ask whether high hygiene standards are also a critical determinant for less-diverse microbiomes.

Among the factors that have the strongest association with stool microbiome diversity are age, sex, body mass index, and the Bristol Stool Scale (BSS) that classifies color and consistency of stool (18);(Falony, 2018). Although BSS can easily be defined based on a cartoon, it is unfortunately not often recorded. But stool water content has been related to microbiome diversity and the BSS contains the consistency of stool as a key classifier (19, 20). Stool water on the other hand is highly correlated with the gastrointestinal transit time (20) and the underlying motility program of the gut. Mean transit time (MTT) is highly variable and differs between men and women and is also age dependent (21, 22). Any maneuver that increases or decreases the gastrointestinal transit time causes changes in feces (**Figure 1**) with differences in bacterial density in stool samples and microbiome composition (23). Bacterial mass in the stool (g/day) can be altered almost 3-fold by MTT modifying agents and there is a close relationship between mass and the logMTT (24). In humans, colonic transit time measured by radio-opaque markers *via* x-ray correlates with the richness as diversity markers in stool samples (23). In a cohort of > 850 individuals in which transit time was measured, various species revealed a significant increase in relative abundance in stool with longer gut transit time while *Eubacterium rectale* density simultaneously decreased (25). The increased prevalence of the phylum *Bacteroidetes* with longer gut transit times had been observed before and similarly also an increase in *Akkermansia muciniphila* (20). In mice treated with loperamide to slow-down transit the density of *Bacteroidetes* was similarly observed (26). Along with those qualitative changes in stool bacterial signatures there are also changes in the bacterial counts in feces that increase by around 15% (per g dry weight) when transit is delayed or increase by nearly 20% when transit is increased (24). To which extent bacterial diversity is associated with the altered number of bacteria in stool samples is currently unclear.

Furthermore, MTT is a critical determinant for the rate of glucose absorption in the upper small intestine and the postprandial glucose profiles (27). By using a blue dye given in cupcakes for measuring transit time, it was shown to highly correlate with both, microbiome diversity and glycemic response to a carbohydrate load (25). These two read-outs appear to originate from a common intestinal phenotype—connected through motility and transit time with marked intraindividual differences. Interpretation of studies on postprandial glycemia in association with the microbiome should also take into account that high postprandial glucose concentrations (as found in individuals with insulin resistance or type 2 diabetes) can alter gastric, pancreatic, and intestinal responses to diet and change the transit time (28) and that these may well be factors contributing to microbiome changes reported in these disease states. A direct proof of the hypothesis that the MTT of the individual is a critical determinant of both, microbiome mass and diversity, and postprandial glucose

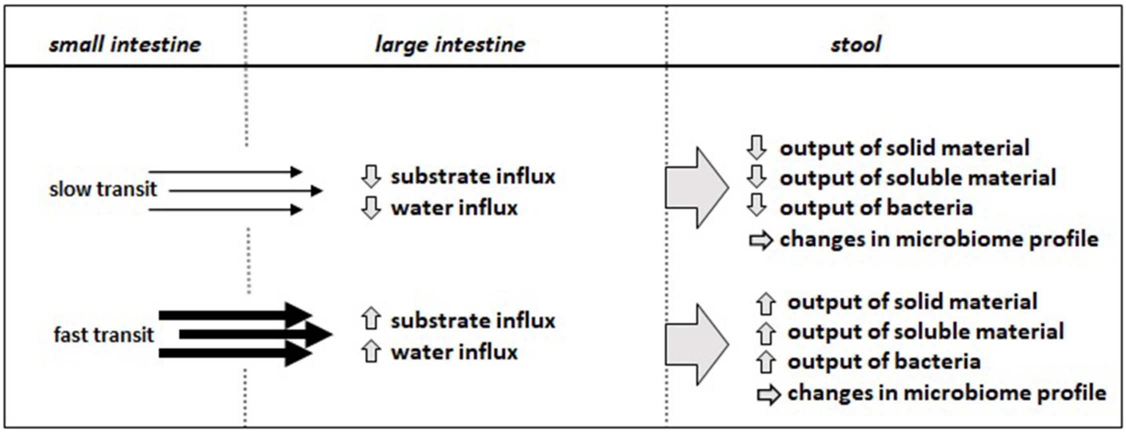

FIGURE 1 | Parameters in fecal samples that change upon alterations of intestinal transit time based on findings derived from observational studies or intervention studies with agents that increase or slow-down transit time.

responses requires further studies with a comprehensive analysis of all related parameters.

DIET AND MICROBIOME COMPOSITION

From population studies with the recording of food intake *via* 24-h recall or food frequency questionnaire, many food items have been identified as significantly contributing to microbiome diversity. That covers in essence almost all food and drink categories with very similar but generally very small effect sizes per item (18, 29). One of the most prominent factors that affect the microbiome in an unexpected manner is alcohol consumption (30) and which is prone to underreporting in observational studies. Yet, it confirms that food and drinks are all relevant factors among the many determinants of microbiome compositional signatures. However, not all studies provide convincing evidence that diet and microbiome diversity associate strongly. For example, volunteers consuming a chemically defined liquid diet as a meal replacement for 17 days did not show any significant difference in microbiome signatures (tested every day) when compared to volunteers consuming ordinary diets (31). Moreover, when volunteers consuming diets with average fiber content (mean fiber intake 22 g/day) were shifted to high fiber diets (mean fiber intake > 45 g/day) neither microbiome composition nor stool short-chain fatty acid (SCFA) concentration showed significant alterations (32). In a study in which volunteers consuming an entirely plant-based as compared to an animal-product based diet for 5 consecutive days with wash-out between the two arms, only in the animal-product-based arm, a significant effect on ß-diversity in stool was found (33). Intervention studies with fermentable fibers (12–15 g/day for 4 or even 12 weeks) as substrates for bacterial metabolism consistently report significant elevations in the abundance of a very few species, mainly of *Bifidobacteria* (8, 34), whereas overall microbiome diversity remained in almost all the studies unchanged [for review see also (35)]. Taken together, diet and many individual food items have been shown to associate with microbiome diversity, but intervention studies based on discrete diets or by providing dietary fibers of different quality and quantity so far provided only very limited evidence for successful steering of microbiota toward increased richness.

DIET, DISEASES, AND MICROBIOME

Many noncommunicable diseases (NCDs) have been associated with sedentary lifestyles and dietary factors. In the Global Burden of Disease Studies, diet quality (intake of fruits, nuts, etc.) usually ranks high next to smoking, high blood pressure, BMI, and lack of physical activity (36). That now the microbiome and its diversity are brought into the health-disease trajectory is not surprising given the fact that microbiomes can easily be profiled these days for reasonable costs. Yet, the key question is of whether the microbiota is a causal factor in initiating or promoting diseases or whether changes in its composition just serve as a "reporter" of a disease state. The evidence that changes in the microbiome can affect disease severity or cause, is currently very limited. The best evidence may be provided by the outcomes of fecal microbiota transplantation (FMT) in which a suspension of feces from a healthy donor(s) is transmitted into a diseased person. This approach is the most successful treatment of recurrent *Clostridium difficile* infections (37) and is the "new gold" standard. Other attempts to alter disease progression or the physical state of the patient *via* FMT delivered less convincing or controversial outcomes (38). There are some trials in which treatment with FMT for people suffering from obesity, metabolic syndrome, or type 2 diabetes mellitus revealed some minor improvements but the more consistent finding was that there were no clinically significant effects (39, 40). Similarly, in patients with metabolic syndrome and elevated plasma trimethylamine-oxide (TMAO) levels, FMT with stool from a vegan donor was without effect on parameters of vascular inflammation (41). Epidemiological studies identified increased TMAO levels as associated with various cardiovascular disease types suggesting it to be a causative agent (42). TMAO is produced in the liver from

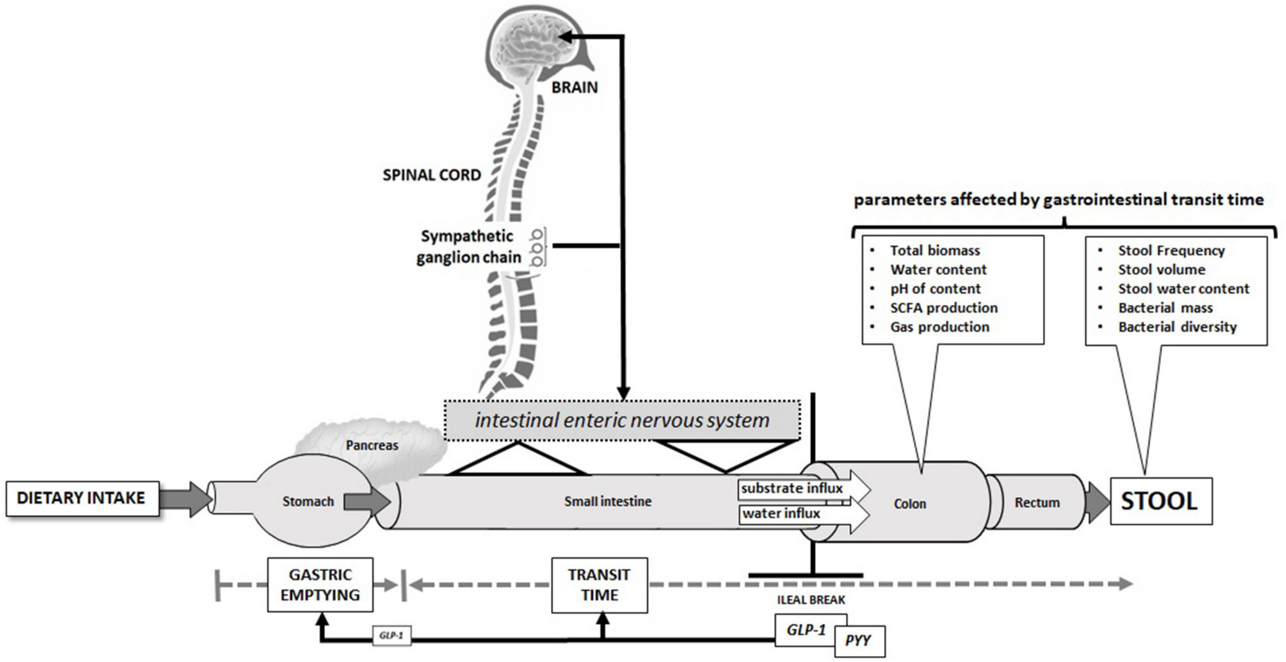

FIGURE 2 | Selected physiological parameters that participate in the regulation of gastrointestinal motility and transit time and how alterations in transit time cause changes in the colonic microbiome and in stool characteristics that all have been demonstrated to alter microbiome diversity and biomass.

trimethylamine produced in the microbiome from carnitine or choline and related compounds provided by the food of animal origin. Meanwhile, studies using *Mendelian Randomization Analysis* suggest that elevated blood TMAO levels may be an indicator of impaired renal clearance in these patients preselected for cardiovascular diseases rather than directly involved in pathogenesis (43). Taken together, changes in gut microbiota *via* stool transplantation have not yet convincingly demonstrated that metabolic health can significantly be improved. Similarly, treatment with antibiotics that caused severe alterations in microbiomes did also not significantly alter any of the markers of metabolic health in volunteers with type 2 diabetes (44). Thus, to establish that changes in microbiomes by any treatment has beneficial effects for metabolic health in NCDs, it needs larger trials with well-phenotyped volunteers or patients.

The intestine is a complex organ with an extensive neuronal network organized in plexi that receives multiple inputs from cells seeded into the mucosa from the stomach to the anus which are equipped with a multitude of sensors (45). The neuronal mesh underlying the mucosa acts in many ways as a mediator and is in contact with the sympathetic ganglion chain in the spinal cord and with the brain by which a bidirectional organ cross-talk of intestine and brain is realized (**Figure 2**). The intestine has in addition a large hormone system that produces numerous peptide hormones and a large number of amines, including the classical neurotransmitters, and those control in essence every process in the gut from digestion to absorption, to secretion and motility (46). Some of the hormones produced in enteroendocrine cells in the gut also reach peripheral organs and the brain and mediate satiety and metabolic control. Given these multidimensional networks connecting brain and gut, it is not surprising that many diseases—including neurological diseases—secondarily affect the gastrointestinal tract and its functionality.

The motility of the intestine translates into the surrogate of transit time and that is a critical determinant of the number of bacteria excreted with stool and of the diversity of the microbiome. Consequently, any alteration in transit time affects bacterial signatures (23, 24). Similarly, stool frequency has a significant effect on microbiome diversity (30, 47, 48) and a first genome-wide association study on stool frequency determinants has recently been published (49). When diseases have a demonstrated association with altered microbiome composition, it is thus important to assess whether intestinal functions are altered as the underlying cause of microbiome changes and that seems to be the case in many of the classical NCDs.

Obesity and metabolic syndrome have associated changes in gastrointestinal physiology with constipation, diarrhea, and fecal incontinence recognized as the most common intestinal complications in diabetes (50). They have their origin in changes in sensory functions with transmission into altered hormone and neuronal responses and changes in motor-neuron activities of the entire intestine (51). Other diseases with demonstrated alterations in microbiome profiles are Parkinson's disease (52) and Alzheimer's (53) disease, but also autism. A very recent meta-analysis of studies in Autism (54) reports that across various cohorts 45–85% of patients with autism have diarrhea or suffer from obstipation while a recent study in children with autism revealed that abnormal diet behaviors may be the prime reason for the changes in the microbiome and that the microbiota is not causing/promoting the disease (55). Thus, these neurological diseases have all associated changes in motility and motor function of the intestine and that is likely a major contributor to differences in bacterial density and diversity in stool samples (56, 57).

How are these changes in intestinal transit time changing the microbiota in stool? Alterations in transit cause changes in substrate flow across the ileocecal valve providing different substrate loads to the microbiota for utilization and growth. This influx of substrates into the colon is controlled *via* the "ileal break" which seems to sense the caloric load reaching the terminal ileum followed by the release of peptide hormones like glucagon-like peptide 1 or peptide YY that can reduce the gastric emptying rate and intestinal motility to allow better digestion/absorption (**Figure 1**). However, as shown by the use of compounds that change transit time in patients with ileostoma, different quantities of starch, for example, reach the colon when 50 g of potato starch are administered (58). Such maneuvers also change substantially the mean stool weight and bacterial mass in stool samples. A very interesting approach combined *in vivo* and *in-vitro* experiments (59) to assess the effects of transit time on fermentation of dietary fiber. It included the monitoring of SCFA levels and production rates and gas released when samples were collected from volunteers on identical diets but taking drugs that increase transit (cisapride) or slow transit (loperamide). Large differences in pH and SCFA concentration in the inoculum (stool) were already seen when transit time was altered, and fermentation *in vitro* also revealed major differences. A significant inverse relationship was found between SCFA production and the log of MTT, in analogy to previous studies that demonstrated such an inverse relationship also for the log MTT and the mean bacterial mass (g/day) excreted in the stool (24). That again demonstrates the close interrelationship of gut motility, colonic fermentation capacity, and the bacterial mass and spectrum in the large intestine and stool.

Taken together, there is convincing evidence that alterations in MTT occur in many diseases, and this alters the substrate load for fermentation in the colon including major effects on pH and SCFA concentrations associated with changes in stool frequency, stool volume/mass, stool water content, and, in turn, the amount and the composition of bacteria excreted. When inspecting all determinants of microbiome diversity identified so far, it appears that MTT is one of the most relevant factors and should therefore be determined in all studies that assess the links between diet, diseases, and microbiomes. There are various methods available to determine MTT with minimal efforts (60) including the use of colorants such as brilliant blue (E133) or spirulina to dye food items (25). Applying those methods would also help to overcome the "chicken or egg problem" in microbiome science.

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Evolution of Milk Consumption and Its Psychological Determinants: A Mini-Review

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The consumption of lactose-free products and in particular lactose-free milk is increasing worldwide. Although many studies claim that this dietary trend is mainly determined by the number of lactose intolerant people that is growing, others state that most of them self-report an intolerance that has not been diagnosed by medical tests. However, many researchers reported that the consumption of lactose-free milk may put the consumers' health at risk especially when the subjects are not intolerant. Consequently, understanding this new dietary trend considering its main determinants it is necessary to generate educational and intervention campaigns useful to guide people toward healthier and more adequate eating styles. For these reasons we conducted a narrative mini review to summarize the factors contributing to the consumption of lactose-free milk as an alternative to cow's milk, exploring intrinsic and extrinsic product characteristics, biological and physiological, as well as psychological, situational and socio-cultural factors. This narrative mini-review shows that there are six categories of factors that affect the consumption of lactose-free milk. In particular, the intrinsic aspects linked to the product and the socio-demographic characteristics of the consumer are the most explored. On the contrary, situational and socio-cultural factors are the least studied. Finally, this study argues that there are too few studies that investigates the emotional, identity and social aspects underlying these food choices, suggesting the development of future research that investigate the implicit consumer subjective levers to decipher lactose-free milk consumptions.

Keywords: milk, consumer psychology, lactose-free, food, determinant

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INTRODUCTION

Milk consumption is definitely declined in the last decades, particularly in developed countries (1). In Italy the consumption of dairy products and milk has been decreasing in a progressive way, from 56.4 L pro capita in 2009 to 50.2 L in 2014 (1). On the other hand, lactose-free dairy market is expected to reach a turnover of 9 billion by 2022 and continues to surpass overall dairy products (7.3 vs. 2.3%) (2). Milk is the dairy category with the highest proportion of lactose-free products, represents two-thirds of the market and determines the growth of the category (2). However, it was demonstrated that this widespread consumption of "lactose-free" products can generate many health problems. In particular, the problematic aspects generated by this eating style are both nutritionally (3) and in terms of quality of life (4), especially when the subjects are not intolerant consumers (5, 6). Given these premises many studies have been carried out to explore this food trend (7, 8) and to understand consumers' attitudes and purchase decisions. Indeed, the identification of consumption determinants is paramount to guide educational and communication interventions to support suitable and health diets. Personal differences, such as knowledge, attitudes habits and socio-demographic factors, are linked to consumers' purchase behaviors increasing the intricacy of decision-making process. These variables are well described and considered by the recent perspective of Köster and Mojet (9). They suggested an interdisciplinary framework to organize and describe the connection among the variables implied in consumer food choice and eating behaviors. This model is particularly innovative and complete in considering the complexity of consumer food choice, and particularly for the case of "free-from" food products (10). Considering the consumption of lactose-free milk, some studies underlined that these changes in milk consumption seem to be more related to the consolidation of new lifestyles and psychosocial variables than simple health reasons such as medical requirement for facing intolerances (11–14). However, there are no studies that try to summarize the main psycho-social factors that lead consumers to prefer consuming lactose-free milk instead of cow's milk. In this narrative mini-review we will contribute to the scientific debate by summarizing the main psycho-social factors contributing to the consumption of lactose free milk as an alternative to cow's milk.

MATERIALS AND METHODS

Search Strategy and Data Analysis

A search for literature investigating the factors that influence the consumption of lactose-free milk was carried out mainly on Scopus and PsycINFO using the keywords "milk", "lactose-free", "determinants" and "consumption". In this narrative mini-review peer-reviewed papers written in English and in Italian related to factors influencing lactose-free milk consumption were considered. A qualitative synthesis of the main determinants of lactose-free milk consumption was conducted, organizing them according to the framework proposed by Köster and Mojet (9). In more details, the model groups the factors that can affect a consumption choice in 6 areas: *psychological factors*, such as cognitive processes, decision making, and personality traits; *situational factors*, such as habits and social signification processes of the context; *sociocultural factors,* like culture, beliefs, and socio-demographic features; *extrinsic product characteristics*, such as brand, labels, and packaging; *intrinsic product characteristics*, such as texture, smell, taste, and nutritional composition; and finally, *biological factors*, such as variables related to consumers' intolerances and immune system functioning.

RESULTS

The Main Determinants of the Consumption of Lactose-Free Milk

There are several variables that have been studied to understand the determinants that influence the consumption of lactose-free products and in particular the consumption of milk. As anticipated, we organized them according to the model of Koster and Mojet (9) considering 6 main areas (**Figure 1**).

The Psychological Factors That Influence the Lactose-Free Milk Consumption

Some researchers have focused on understanding the connection between characteristics linked to cognitive processes, decision making and some personality traits and the consumption of lactose-free milk. It has been shown that *nutrition knowledge* and in particular the knowledge of the different nutritional properties of milk can influence the consumption of lactose-free milk (15, 16) especially if consumers *frequently look for information* regarding food nutritional features on food packages (14). Moreover, another important variable in affecting this type of consumption is the *perception of risk* linked to the product and, in particular, the risk of getting cancer. A study carried out on an Italian sample of consumer (1) noted that the non-consumption of milk (with or without lactose) is mainly determined by the expectation to prevent cancer. In addition, *the positive sensation perceived thinking about lactose-free milk (affect)* increases the intention to buy and pay more for it. Moreover, the *perception of product healthiness* and the *preference for natural products* lead to a greater consumption and an enhanced willingness to pay a premium price for lactose-free milk, in different countries such as UK, Sweden, Poland and France (14). Finally, another important variable that in the last years has been often used to explore consumers' intentions or behaviors is *Food Neophobia* (17, 18). Correlating this variable with the consumption of lactose free milk, it can be noticed that those who have a low level of food neophobia are more willing to buy lactose-free milk (19). Finally, a last variable that was studied to map lactose-free milk consumption is the *general health interest* (20). This variable led to conflicting results because some studies show that the general interest in own health increases the consumption of lactose-free milk (19), whereas others found no significant relationship between them (14).

The Biological Factors That Influence the Lactose-Free Milk Consumption

Past studies noticed that those who consume a high quantity of lactose-free milk have a *medium-low Body Mass Index* (1) and they often have *gastro-intestinal problems* (21) not always certified as intolerances. However, those who have a *certified intolerance* consume lactose-free milk more frequently (22).

The Socio-Cultural and Situational Factors That Influence the Lactose-Free Milk Consumption

If we consider aspects linked to people's socio-demographic characteristics, we notice that *employed women* with a *high educational* qualification and a *high income* consume more lactose-free milk than other targets (1, 13, 15, 16, 21, 22). Moreover, people *without children* and therefore with a family composed by few members are those who consume more frequently lactose-free milk. This study also noticed that *ethnicity* is an aspect that affects the consumption of this product (13). In particular blacks or Asians are those who consume more lactose-free milk. Moreover, there are contrasting results about the role of *age*. Indeed, some researches show that elderly people

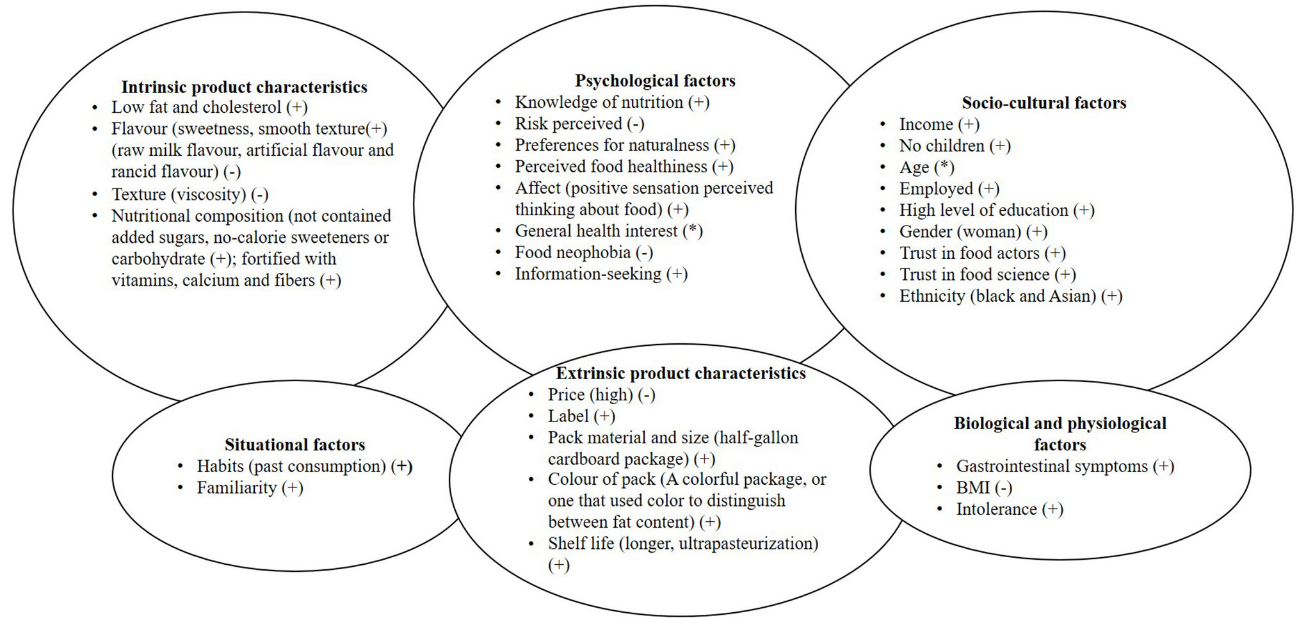

FIGURE 1 | An integrated model of consumer behavior determinants in lactose-free milk consumption. (+), facilitators; (–), barriers; (*), No univocal role.

consume higher quantities of lactose-free milk (16) whereas in other researches elderly people do not consume milk even if without lactose (1) and young people under the age of 30 consume more lactose-free milk (22). The *trust in food actors and in food science* are other variables took into account by past research (14). Some studies show that people with a high level of trust in food science and in food actors are more prone to consume lactose-free milk. Considering situational factors, it is possible to claim that *consumption habits* and *familiarity* with the product affect the consumer behavior, indeed those who are used to consume lactose-free products or plain processed milk are more willing to consume lactose-free milk (19, 20).

The Extrinsic Product Characteristics That Influence the Lactose-Free Milk Consumption

The main extrinsic characteristics of lactose-free milk that can affect its consumption are *the price* and *the labels*. In particular, although people are willing to pay more for this product, the price has a negative correlation with the consumption of lactose-free milk (16, 20, 23). In addition, the presence of a known label that guarantees the absence of lactose in the milk increases the intention to purchase it (14, 22). Finally, also the *color, size of the pack and the shelf life* have an impact on lactose-free milk consumption. Ultra-pasteurized lactose-free milk in a half-gallon cardboard package was the ideal (20).

Intrinsic Product Characteristics That Influence the Lactose-Free Milk Consumption

Many studies have focused on understanding how the intrinsic characteristics of the product can impact on its consumption. In particular, it has been observed that the consumption of lactose-free milk is mainly determined by the belief that it contains *less fat and cholesterol* than milk with lactose (15). Considering the nutritional composition, consumers prefer lactose-free milk that does not contain *added sugars, calorie sweeteners or carbohydrate* and that is *enriched with vitamins, calcium and fibers* (22, 24). Furthermore, the *flavor* and in particular the sweetness and smooth consistency determine higher level of lactose-free milk consumption (1, 19, 20). On the contrary, grassy *odor*, raw milk flavor, artificial flavor and rancid flavor negatively affect the consumption of lactose-free milk. Moreover, the *texture* and in particular the viscosity of milk can affect its consumption (20). In particular lactose-free milk was preferred to milk with lactose because its viscosity is lower.

DISCUSSION

The studies carried out on lactose-free milk consumers have investigated different drivers that influence this type of consumption. However, the aspects related to the intrinsic characteristics of products and socio-demographic features of consumers are the most analyzed while psychological and contextual factors are less explored. In particular, this study shows that lactose-free milk consumers have a high socio-demographic profile given by a high income and educational qualification (13, 15, 22). This profiling is in line with other studies carried out on "free from" consumers (25). Another important factor concerns the socio-cultural and situational characteristics of consumers. Those who are more prone to purchase lactose-free milk are people who have a strong trust toward food actors and food science and have a strong familiarity toward this product since they consumed it in the past (14, 20). In addition, these consumers prefer labels on milk which clearly certify the absence of lactose (14, 22). Moreover, if we consider the psychological variables, the study shows that consumers of lactose-free milk declare to be aware of their consumption choices as they have knowledge about food that allow them to choose quality products (15, 16). They are also particularly attentive about food choices indeed they frequently consult labels in order to understand the nutritional qualities of products (14, 24). However, we note that there are emotional components that influence the consumption of lactose-free milk both as barriers and as facilitators of consumption (1, 14). In particular, research conducted by Hartmann et al. (14) showed that the positive emotional reaction (affect influence), triggered by the label "lactose-free", is an aspect that positively influences the consumption of lactose-free milk. The consumer, in fact, believes that this "free-from" label is synonymous with healthiness, encouraging the purchase of lactose-free milk. Many studies carried out on "free-form" labels (26, 27), have noted that these open up a positive psychological dimension in consumers even in the absence of risk information on the eliminated ingredient. These studies highlight an unconscious psychological mechanism that the "free-from" label generates in consumers: they perceive the removed ingredient as risky just because it has been removed (according to the simplifying mental equation that "if it is removed it is because is dangerous") and the positive emotion given by the avoidance of a possible health risk leads them to a greater willingness to purchase "free-from" products and in particular lactose-free milk. These findings underline that the perception of risk is an important emotional barrier that influence the consumption of milk in general. Indeed, some Italian consumers (1), even though they believe that lactose-free milk is healthier than milk with lactose, it is equally perceived as harmful to health and therefore avoided.

All these findings seem to describe an aware and informed consumer, attentive to his/her food choices with a high socio-demographic profile that gives him/her the economic and cultural power to make accurate and conscious consumer choices. However, by applying a psychological lens to the reading of the data, we can argue that this consumer is strongly affected by emotions that drive the decision-making process. Consumers, in fact, tend to demonize lactose considering it as an ingredient to be avoided and emotionally linked to negative feelings and health risk. Moreover, the awareness and food knowledge declared by lactose-free milk consumers is mainly aspirational since it was scientifically demonstrated that the consumption of this product can determine health risks, especially when the subjects are not intolerant consumers (5, 6). These results show how consumers of lactose-free milk aspire to be aware of their choices and that they have a need to control them, wanting to play a leading role in their food consumption by choosing products that support this identity image such as lactose-free milk. Indeed, as already showed by past studies (7) the purchase of "free from" products is a means that allow consumer to express their affirmation and their control on food choices, showing their active and critical role as consumer. "Free-from" food choices, therefore, are strongly governed by emotional, identity and psychological aspects linked to a need for self-affirmation and self-expression rather than rational and conscious processes. As pointed out by other research, food choices and particular dietary styles are means used by people to establish social connections (28), to express own identity in order to be accepted by others (29, 30). Hence, the subjective meaning given to food plays a key role in the purchase of it. Furthermore, as demonstrated by other researchers, social influence considered as imitation, group belonging, and social identification, can play an important role in determining food choices and especially the "free-from" ones (31). Indeed, as showed by Xhakollari et al. (31), the fact that family members or friends believe that it is right to follow a gluten-free diet increases the likelihood that the person follows this eating style, especially if the choice is voluntary and not determined by certified intolerances. However, there are too few research on the consumption of lactose-free milk that investigates the emotional, identity and social factors underlying these food choices. This highlights the lack of consumer psychology studies on the topic of "free-from" consumption that should be deepen. This unexplored field of research should be covered by carrying out research that investigates the relationship between lactose-free milk consumption and the individual and social dimensions of consumers because only in this way it is possible to understand what are the most important determinants of this consumption, creating communication processes that guide people toward healthier diets.

AUTHOR CONTRIBUTIONS

GC: conceptualization, methodology, and writing—original draft. GG: writing—review and editing and supervision. Both authors have approved the final article.

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Oxysterols as Reliable Markers of Quality and Safety in Cholesterol Containing Food Ingredients and Products

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Cholesterol is a lipid of high nutritional value that easily undergoes oxidation through enzymatic and non-enzymatic pathways, leading to a wide variety of cholesterol oxidation products (COPs), more commonly named oxysterols. The major oxysterols found in animal products are 7α-hydroxycholesterol, 7β-hydroxycholesterol, 7-ketocholesterol, 5α,6α-epoxycholesterol, 5β,6β-epoxycholesterol, cholestan-3β,5α,6β-triol, and 25-hydroxycholesterol. They are all produced by cholesterol autoxidation, thus belonging to the non-enzymatic oxysterol subfamily, even if 7α-hydroxycholesterol and 25-hydroxycholesterol are, in part, generated enzymatically as well. A further oxysterol of the full enzymatic origin has recently been detected for the first time in milk of both human and bovine origin, namely 27-hydroxycholesterol. Nowadays, gas or liquid chromatography combined to mass spectrometry allows to measure all these oxysterols accurately in raw and in industrially processed food. While non-enzymatic oxysterols often exhibited *in vitro* relevant cytotoxicity, above all 7β-hydroxycholesterol and 7-ketocholesterol, 27-hydroxycholesterol, as well as 25-hydroxycholesterol, shows a broad spectrum *in vitro* antiviral activity, inhibition of SARS-CoV-2 included, and might contribute to innate immunity. Quantification of oxysterols was afforded over the years, almost always focused on a few family's compounds. More comprehensive COPs measurements, also including oxysterols of enzymatic origin, are, nowadays, available, which better display the many advantages of systematically adopting this family of compounds as markers of quality, safety, and nutritional value in the selection of ingredients in processing and storage. Regarding foodstuff shelf life, COPs monitoring already provided useful hints for more suitable packaging. The identification of a subset of non-enzymatic and enzymatic oxysterols to be routinely assessed in food production and storage is proposed.

Keywords: cholesterol, oxysterols, COPS, autoxidation, cytotoxicity, food processing, shelf life, markers

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INTRODUCTION

Cholesterol is a lipid of high nutritional value that easily undergoes oxidation, both enzymatically and not enzymatically driven, by this way leading to a wide variety of cholesterol oxidation products (COPs), more commonly named oxysterols. Oxysterols differ from the parental molecule for an epoxy- or hydroxyl- or ketone group in the steroid nucleus or a hydroxy group in the hydrophobic side chain (1, 2). In all animals, humans included, widely distributed specific enzymes represent an important endogenous source of oxysterols, of which those of main physiological interest are 27-hydroxycholesterol [systematic name (25R) 26-hydroxycholesterol] (27OHC), 24-hydroxycholesterol (24OHC), 7α-hydroxycholesterol (7αOHC), 20α-hydroxycholesterol (also 20S-hydroxycholesterol) (20αOHC), 25-hydroxycholesterol (25OHC) (3–5). Of note, the last three oxysterols, namely 7αOHC, 20αOHC, and 25OHC, may be, in part, generated non-enzymatically as well (3, 5).

Indeed, cholesterol autoxidation can be induced in food ingredients and products by heat, light exposure, refrigeration, freeze-drying, and spray-drying, leading to the formation of non-enzymatic oxysterols, namely 7β-hydroxycholesterol (7βOHC), 7-ketocholesterol (7KC), 5α,6α-epoxycholesterol (α-epoxy), 5β,6β-epoxycholesterol (β-epoxy), cholestan-3β,5α,6β-triol (triol) (3, 5, 6). Another important source of the same non-enzymatic cholesterol oxides, in this case an endogenous one, is represented by the reactive oxygen species (ROS) that are generated in a variety of pathophysiological conditions in tissues and cells; indeed, high amounts of oxysterols are produced during the inflammatory process that often sustains and promotes chronic human diseases (7, 8). In **Figure 1**, all main enzymatic and non-enzymatic oxysterols of pathophysiological interest are reported.

With regard to the detection and quantification of oxysterols in biological samples, as well as in food, mass spectrometry either coupled to gas chromatography (GC-MS) or liquid chromatography (LC-MS/MS) has been adopted for many years. However, because of the relatively very low amount of oxysterols as to cholesterol in the various matrices, the difficult chromatographic separation of some of these compounds, and the easy autoxidation of cholesterol during the extraction and purification procedures, often generated data that are lacking in precision and are hardly comparable. Only very recently, consensually standardized GC-MS and LC-MS/MS procedures have finally allowed to obtain accurate, precise, and reliable quantification of oxysterols from different sources (2, 9).

Hereafter, the measurement of oxysterols in food industry will be reviewed and discussed, with some emphasis on the cutting-edge results achieved on milk and milk-derived products. For an adequate and complete analysis of the high translational power of oxysterols quantification in food and other industry fields, see also another recent review by Poli et al. (10).

MEASUREMENT OF OXYSTEROLS IN FOOD INDUSTRY: GENERAL ASPECTS

Many reports have been published over the years, providing quantification of oxysterols of a non-enzymatic origin in chicken, pork or beef meat, fish, egg, butter, whole or skimmed milk powder [for a review see (6, 11)]. Because of the above reported complexity of oxysterols measurement, the collected data were not always comparable to each other. In addition, quite often, only a few oxysterols were analyzed, and, rarely, an actually comprehensive detection was carried out, despite the frequent use of the COPs term. Anyway, even if not all non-enzymatic oxysterols of pathophysiological interest were searched and detected, 7αOHC, 7βOHC, and 7KC consistently appeared as those quantitatively more represented in the different foods examined, their concentration was significantly varying, for example, with the total cholesterol, total polyunsaturated fatty acids, and total antioxidants content of a given food or food product.

Only very recently, the concentration of oxysterols in foodstuff has been analyzed in a more comprehensive way, in particular in milk, milk powder, and related products, including chocolate (12–14). Certainly, such a more complete approach took advantage from the technology, meanwhile much improved and standardized, and, at least, in part, suggested by the previous analyses afforded on human breast milk. Indeed, all major oxysterols of both enzymatic and non-enzymatic generation were detectable in human colostrum, intermediate and mature milk (9). Of particular interest was in this case the novel observation of a high concentration of 27OHC in the colostrum, which, later on, confirmed to occur in bovine colostrum as well (12). 27OHC, named galactosterol since among the different cholesterol-containing foods, which was shown for the first time in the (cow) milk, has recently been shown, along with 25OHC to have strong and wide-spectrum antiviral properties [for a review see (10, 15)].

The antiviral potential of 27OHC, present in mature bovine milk in concentrations of physiological interest (12), as well as that of 25OHC, appears to be an emerging nutritional factor that could be considered in the overall evaluation of the quality of cholesterol-containing foods. Indeed, even if never investigated so far, 27OHC is certainly present in detectable amounts also in meat, fish, egg, and the other foods of animal origin.

POTENTIAL CYTOTOXICITY OF NON-ENZYMATIC OXYSTEROLS IN FOOD

While oxysterols of enzymatic or partially enzymatic generation, like 27OHC and 25OHC, respectively, have shown remarkable broad antiviral effects, only toxicologic effects have been described so far for non-enzymatic oxysterols when present in excess in the human body but also in the ingested food. By far, the two widely most abundant and more cytotoxic oxysterols formed by autoxidation are 7βOHC and 7KC. In a comprehensive review by (16), the toxicity of an excess amount

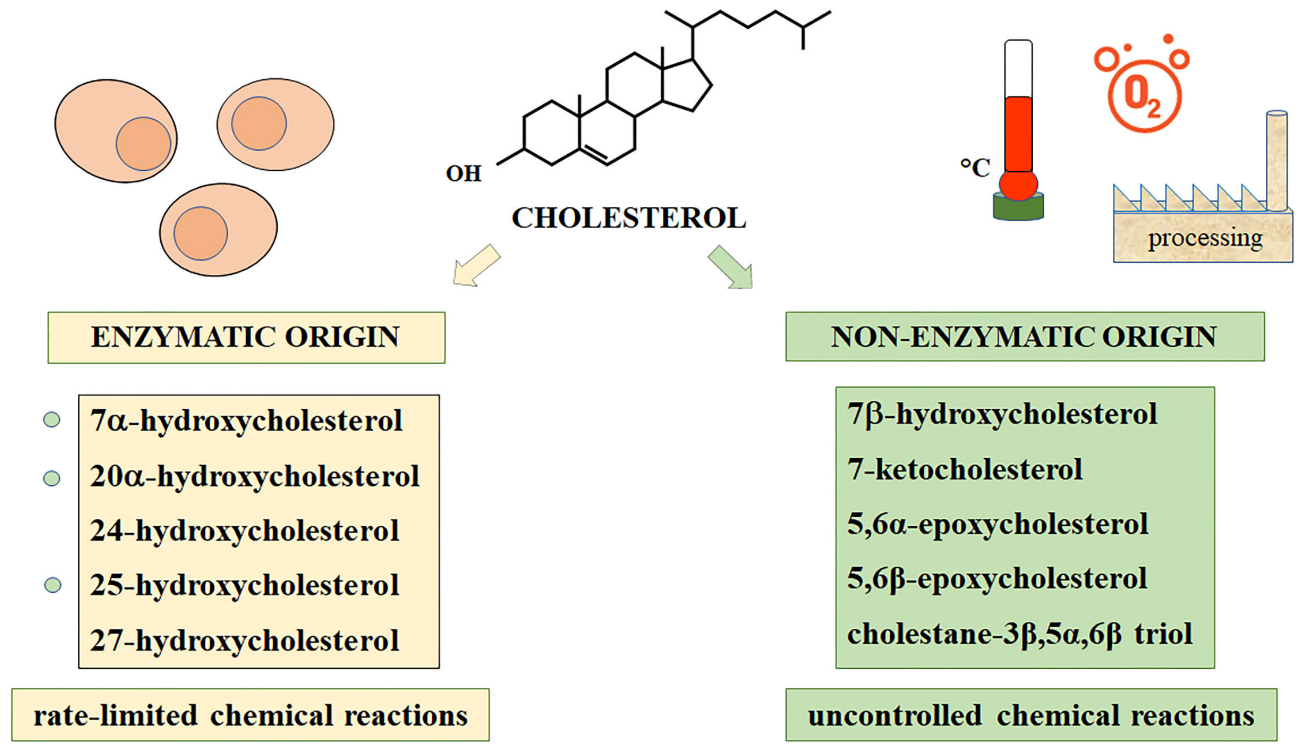

FIGURE 1 | Main oxysterols of enzymatic and non-enzymatic origins.

of these two oxysterols was deeply analyzed with regard to the different body districts, including heart, brain, and gut, as observed both in *in vitro* cell lines and in *in vivo* animal models. These authors provided interesting and informative insights into the signaling mechanisms through which these two cholesterol oxides may induce oxiapoptophagy, a type of cell death associated with oxidative stress, apoptosis, and enhanced autophagy, and promote inflammation. Indeed, these and other oxysterols, when present in the body in excessive amount, could contribute, through the above-described mechanisms, especially through inflammation, to the expression and complication of major chronic diseases, namely cardiovascular, respiratory, intestinal diseases, cancer, diabetes (8, 17, 18). Last but not least, the tissue damage exerted by toxic oxysterols could interfere with healthy aging (19, 20).

Thus, the two oxysterols, 7βOHC and 7KC, this time in a mixture of cholesterol oxides, which are actually that obtainable by heating pure cholesterol for 3 h at 180°C (21), showed to be still the key players in exerting oxidative stress, inflammation, and, eventually, apoptotic death in *in vitro* cultures of differentiated intestinal cells of human origin, namely CaCo-2 cells (22, 23). A similar pathophysiologically relevant mixture of non-enzymatic oxysterols was then employed to challenge *in vitro* differentiated enterocyte-like CaCo-2 cells and its effect on the intestinal barrier permeability evaluated by measuring cell monolayer transepithelial electrical resistance (TEER), as well as the cellular level of the main components of the intercellular tight junctions, namely junctional adhesion molecule-A (JAM), occludin, and zonula occludens-1 (ZO-1). A marked decrease of the protein level of all three tested junction proteins, especially of ZO-1, was observed in such an *in vitro* experimental model (24). Of note, in the latter oxysterol mixture mimicking that occurring in a high cholesterol diet, the percent amount of 7KC was around 40%, and that of 7βOHC was nearly 15%; thus the two oxysterols together appeared likely responsible for at least half of the observed enterocyte tight junctions derangement (24).

Unfortunately, although dietary oxysterols might represent a risk for human health, no toxicity limit for such compounds has been specified yet. Cardenia and colleagues (11) suggested that the threshold of toxicological concern (TTC) (25) for unclassified compounds (.15 µg per single compound/person/day) should be utilized as reference. Probably, this recommendation is too careful. The toxicological studies carried on so far in the *in vitro* model represented by enterocyte-like cell lines suggest that the daily uptake of total oxysterols should not exceed 1-µM concentration (24), which would approximately correspond to 0.4 µg/g of product. Indeed, the amounts of total oxysterols of a non-enzymatic source very recently calculated on fresh whole milk and fresh egg powders, obtained by spray drying, (14) or in prototype milk chocolate tablets up to 120 days of shelf life (13), were confirmed to be within such a potentially acceptable threshold. Certainly, more accurate and reliable warning would be provided by a comprehensive pharmacokinetic analysis of the most dangerous non-enzymatic oxysterols administered to experimental animals individually or in a mixture. The few data presently available would indicate a better intestinal absorption of 7βOHC, 7KC, and α-epoxy in comparison to that of β-epoxy and 25OHC (26), with a relatively more rapid hepatic metabolism of 7KC as to 7βOHC (27).

FURTHER GENERATION OF NON-ENZYMATIC OXYSTEROLS DURING FOOD PROCESSING AND STORAGE

The accurate quantification of oxysterols, especially the autoxidation ones, in the raw food and food ingredients containing cholesterol, as well as in processed and stored foodstuff, definitely appears as a convenient procedure that should be systematically carried out. It would be a further valid tool to assess at the same time quality and safety of both ingredients and food products.

Cholesterol present in food is an essential nutrient for appropriate cell membrane structure, steroid hormones synthesis, numerous tissue functions of its metabolites, but it must be consumed in an adequate daily amount. In addition, its predisposition to undergo oxidation reactions deserves great attention. For these reasons, its concentration in a given food or food ingredient should be fine-tuned, but, afterwards, during processing and storage, its expected partial autoxidation should be monitored and adequately limited.

The spray drying of milk and eggs (14, 28), or the heat processing of meat (29) significantly increases the preexisting amount of potentially harmful cholesterol oxides. Fresh and pasteurized products, milk and eggs, contain lower COPs than the previous ones (30). Hence, the monitoring of at least the most represented and more toxic oxysterols, namely 7βOHC and 7KC, during food processing would allow to improve and better standardize the procedure itself.

The storage of food ingredients is another critical factor that could heavily modify the relative oxysterols concentration. Undoubtedly, the ultimate concentration of oxysterols in food products placed on the market depends very much on the time length and condition of the storage, whether in air or under a vacuum, on the packaging system, on the presence or absence of endogenous or supplemented antioxidants and type of fats (e.g., saturated or unsaturated) (11, 31).

In general terms, the storage/shelf life of food ingredients and final products seems, by far, the most critical phase. Chudy and Makowska (32) monitored by capillary gas chromatography (GC) the content of 7αOHC, 7βOHC, 7KC, α-epoxy, and β-epoxy in milk, egg, and dairy-egg powders, packaged in air atmosphere or under a vacuum, fresh or stored for various periods of time up to 24 months. A shelf life of 3 months already led to a significantly increased production of the five oxysterols in all examined food powders, while their rise almost halved in samples identical but packaged under a vacuum. Notable was the observation of striking quenching of both single and total oxysterols generation, either in air or in a vacuum, when the milk and egg powders were mixed, probably due to a competition for oxygen by the different autoxidation pathways (32). In a subsequent study by Chudy and Teichert, expanding the literature on the quantification of oxysterols in these commodities, reconfirmed the trend found in the previous study (14).

Storages under air or under increased oxygen percentage (32%) were compared in raw beef slices wrapped in a transparent shrink film and refrigerated. Total oxysterols increased with the time, in significant higher percent in the samples stored at 32% oxygen tension, being 7βOHC and 7KC, the quantitatively more represented cholesterol oxides (33). The same group further analyzed the effect of different types of packaging on the storage-induced increase of oxysterols. Frozen horse meat slices were wrapped with either transparent or non-transparent to light films and then stored at 0–4°C and exposed to light for 8 h. The protection against cholesterol photooxidation by wrapping in non-transparent to light film was remarkable indeed, with 7βOHC and 7KC still representing the main non-enzymatic oxysterols (34). Worth noting is the total oxysterols concentration measured at the end of the meat storage in the packaging protecting against light oxidation appeared significantly lower than that measured in identical samples at time-zero storage. The oxysterols that showed much higher reduction were α-epoxy and β-epoxy (34), and one likely explanation would be their faster reaction with protein amino groups, preferably lysine and histidine, in a process known as protein sterylation, actually occurring in food processing (35). One more reason is to prefer 7βOHC and 7KC as quality markers in a cholesterol-containing food industry and, at the same time, an incentive to further investigate in the near future the reactivity of oxysterols with proteins.

The effect of food storage on the concentration of these two oxysterols was also observed in commercial fish meals, with 7βOHC showing to be much more sensitive to autoxidation than 7KC (36). Interestingly, the same evidence was consistently obtained when measuring oxysterols content in milk powders (12) and in prototype milk chocolate tablets made with whole milk powder stored for different periods of time at controlled temperatures (20 ± 2°C) and humidity (<65% relative humidity) in the dark under non-vacuum conditions (13).

ADVANTAGES OF A SYSTEMATIC ADOPTION OF COPS QUANTIFICATION IN CHOLESTEROL-CONTAINING FOOD INGREDIENTS AND FINAL PRODUCTS

According to the literature on oxysterols measurement in food industry available, and on the clear enhancing effect of food processing and storage on their original concentration, it appears plausible and even appropriate to systematically add oxysterols quantification to the main parameters presently used to check and maintain the quality of food of an animal origin during processing and storage (37). In **Table 1**-A, the main advantages of adopting oxysterols as markers of quality but also of nutritional value in the case of cholesterol-containing food are summarized. No doubt that measuring the relative amount of oxysterols in food ingredients from different suppliers would contribute to properly choose the most reliable ones. Moreover, oxysterols monitoring during food processing and packaging would allow to control their correct performance and even to improve them.

However, some oxysterols present in food could also have a relevant nutritional value. In fact, at least, some chain oxysterols of exclusive or partial enzymatic origin, like 27OHC and 25OHC, respectively, showed quite promising antiviral properties with a wide spectrum of action (10, 15). Both cholesterol metabolites could play a role in innate and adaptive immunity by contributing to fight not only viral but also bacterial infections through the depletion/segregation of accessible cholesterol by acting as chemoattractants of different immune cells and modulating macrophage differentiation and activity [for a review see (38)]. Moreover, 20α- or 20S-hydroxycholesterol, an oxysterol of both enzymatic and non-enzymatic sources, very recently detected and quantified in egg and milk powders (14), is considered to be provided with pro-osteogenic and anti-adipogenic properties [see (15)].

Until today, enzymatic oxysterols have not been much considered in food industry, even if their presence in raw material of an animal origin should have been expected, most likely because their nutritional potential has been disclosed just recently. A future development of enzymatic oxysterols monitoring in food industry is thus expected.

TABLE 1 | Oxysterols as quality markers in food industry.

A) Advantages	B) Oxysterols suitable to routinary monitor the quality of food ingredients and products
○ Selection of raw material suppliers	*7βOHC and 7KC*
○ innovative science-based support of food freshness and quality	○ The first two fully non-enzymatic oxysterols stemming from cholesterol autoxidation
○ Improvement of industrial processing	○ Relatively stable compounds
○ Improvement of food product storage (shelf life)	○ Same catabolic route
○ Development of new packaging procedures (e.g., under vacuum or modified atmosphere)	○ Already known in the literature
○ Keeping low the level of oxysterols of toxicological concern	○ Relatively high cytotoxicity in cell cultures (7βOHC being the most toxic non-enzymatic oxysterol)
○ Promotion of emerging nutritional factors (e.g., oxysterols with antiviral or pro-osteogenic properties)	*27OHC*
	○ Enzymatic origin only
	○ Stable compound
	○ The most represented side-chain oxysterol in human and cow milk
	○ Molecule of high nutritional perspective

APPLICATION OF A SELECTED SUBSET OF OXYSTEROLS TO ROUTINE MONITORING OF FOOD QUALITY

There are still numerous gaps to be filled with regard to oxysterols as has been highlighted by Garcia-Llatas et al. and Kilvington et al., starting from their quantification in foodstuff to the one of the most desirable, dietary intakes (37, 39). A comprehensive analysis of COPs is highly recommended but difficult to be applied in a routine way, and not simply for economic reasons. A more applicable solution to routinely check the commercial and nutritional value of food products would appear to be the monitoring of a restricted subset of oxysterols. As reported in **Table 1**-B, such a restricted selection that cannot miss 7βOHC, apparently, the best marker of cholesterol autoxidation and, concurrently, the most harmful among its oxidative metabolites. It is usually tested in combination of 7KC, another pretty harmful oxysterol of a non-enzymatic source. Convenient is to include a side chain oxysterol as well to potentially able to add a nutritional value to a given food product, which is 27OHC or 25OHC, being the first one of an enzymatic origin only and present in human and cow milk in concentrations of biological relevance (9). Of interest, milk processing, but above all, milk powder storage, moderately reduced the original content of 27OHC while significantly increasing that of 25OHC, being prone to autoxidation (12, 13).

OXYSTEROLS TOXICITY AND MEDICAL BIOREMEDIATION

Preventing or at least quenching the formation of oxysterols in food production and cooking is certainly a must to guarantee safe food consumption. The group of Lizard adequately reviewed the most practical approach to quench or even prevent the formation of 7βOHC and 7KC, namely the addition of especially natural molecules provided with marked antioxidant effect, which are numerous, indeed (40) Tocopherols (α- and γ-tocopherols), oleic acid, polyphenols, and theobromine have been demonstrated to be some of the most effective compounds able to prevent the impair damages induced by 7KC. α-tocopherols, for instance, exert the most efficient cytoprotective effect, as well as prevention, in a dose-dependent manner, of 7KC-induced oxiapoptophagy and peroxisomal dysfunctions. Some of these molecules are also cytoprotective against 7βOHC (40). Thus, these data suggest that eating habits and food-industry *ad hoc* formulations rich in functional foods with such beneficial effect can have a role in the prevention of oxysterols-affected diseases.

Recently, another very innovative approach related to medical bioremediation, which could be combined to the food addition with suitable molecules able to reduce oxysterols autoxidation, has been the use of exogenous microbial enzymes for the degradation of oxysterols. In two studies conducted by Ghosh and Khare (41, 42), using two strains, specifically *Rhodococcus erythropolis* MTCC 3951 and *Pseudomonas aeruginosa* PseA, are able to strongly degrade 7KC, counteracting its cytotoxic effect. As mentioned by the authors, these microbial enzymes involved in the bioprocess, such as cholesterol oxidase, lipase, dehydrogenase, and reductase, could be used for protective purposes, in those food products that have undergone heat treatment, resulting in induced oxidative stress, minimizing the risk of possible harmful effects.

CONCLUSIONS

Really comprehensive oxysterols measurements in food ingredients and products have finally become available only recently, allowing to clearly outline the various advantages to systematically adopt their quantification at the different stages of food industry, from the raw material up to the storage of the commercial product. Oxysterols definitely appear as suitable markers of quality, safety, and nutritional value in the selection of food ingredients in the most appropriate food processing and storage.

Still, a few current research gaps can be envisaged, which should be tackled in the near future: (1) reliable knowledge of the actual harmfulness of certain non-enzymatic oxysterols when present in mixture in foodstuffs; (2) the identification of those oxysterols that are actually able to react with aminoacid residues of proteins (protein sterylation) and the entity of such a reaction; (3) the elucidation of the bioavailability of oxysterols (absorption, distribution, metabolism, and disposition); (4) the interaction of food oxysterols with the gut microbiota; (5) the nutritional and/or medical remediation of oxysterols toxicity.

AUTHOR CONTRIBUTIONS

Conceptualization was contributed by DR, GP, and RM. Methodology was contributed by VL. Writing–original draft preparation was contributed by GP. Writing–review and editing were contributed by DR, FC, and GR. Supervision was contributed by VL and RM. All authors contributed to the article and approved the submitted version.

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Food Products and Digital Tools: The Unexpected Interconnections

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This article discusses the current advances and proposes future directions in the use of science-based digital tools in food product design, highlighting some unexpected interconnections among tools science-based and tools thought for other purposes. The article is structured in two main parts: an overview of the literature on the work done to explore food-related apps and social media for understanding consumers' perception and preferences; a discussion on the integration of consumers' perception and preferences in a wider scheme for food product design based on a prediction of product features using advanced multiscale and hybrid methods for the design of food product features associated to consumer perception and preferences. Understanding consumer needs and preferences and linking them to product features will benefit start-uppers and researchers who develop tools for reinventing food product design.

Keywords: food product design, digital tools, food ingredients, food process modeling, food and social networks

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INTRODUCTION

A portion of food is a formulated product, a mix of ingredients (sometimes, many ingredients), undergoing a sequence of manipulation processes (sometimes, many processes). The design of food products involves – on one side – the capability to capture the consumers' needs and preferences, and – on the other side – the capabilities to translate these preferences in product attributes related to the dichotomy of ingredients' choice and manipulation. Thus, the design procedure requires three steps: (1) identification of the consumer needs and preferences; (2) translation of these needs and preferences into chemical/physical properties and features; (3) combination of ingredients in a mix and in several operations (what we call process) to obtain a product that is characterized by these properties and features.

In the design of new food products, an important role is played by the consumers' needs and preferences since they determine the final characteristics that a food product must have so that the consumer will select this product above the others. Consumer needs and preferences can deal with different aspects, some of them being:

- the food product price (yes, price is still one of the most important tenets when choosing food);
- the food product taste (besides any possible health claim, some consumers are just attracted by the sensorial experience a certain food product will bring to them);
- the food product composition (a vegan consumer will not buy a product made with animal-based ingredients; a consumer guided by healthy motivation will avoid consuming food high in salt, fat or sugar).

Certainly, other aspects should be taken into account, such as the supply chain and the logistics, the consumption trends, the sustainability.

Big food companies knew and know how to perform marketing research, they have their experts in understanding the consumers' trends and their experts in food product formulation and food process design. Small and medium food companies (often still run as family companies) own their traditional recipe and can exploit their competence in some market niches. This leads to the question, why should they explore new ways, digitally based, to improve their food design capabilities?

Digital tools, undoubtedly, allow shortening the time-to-market (1). Being based on computation, they can virtually provide answers to complex problems in a short time, exploring scenarios with a very limited cost and – potentially – without any limit. So, in a world running toward personalized nutrition, the possibility to tremendously speed up the time-to-market would open new roads to established food companies but also to start-ups (2).

From an engineering point of view, the design of a food problem is a multi-scale, interdisciplinary problem, its heart being the optimization of different product specifications. As in a classical pooling problem (3), the goal is to find the lowest cost flow rates in the network that satisfy the market demands. Talking about cost, one should also consider sustainability, including environmental and social costs. It is possible to use mathematical methods, software, and any other possible virtual/digital tool to fulfill all the relationships (input-toward-output, so consumers' need and preferences toward final product characteristics, along important intermediate steps related to ingredients' choice and process choice) and thus to design a new product (or to optimize an existing one).

In the following discussion, the logistics and the supply chain are not considered, since there are consolidated methodologies and software instruments to comply with it (4), and the digital tools that can be used for determining the needs and preferences of customers are first introduced and discussed; subsequently, the discussion will deal with the possibility to combine these tools with other methodologies (standardized and not) for predicting the effect of processing on a food product, for optimizing the ingredient choice and the recipe.

For further discussion on selected approaches, best practices, hurdles, and limitations regarding knowledge transfer *via* software and the mathematical models embedded in it, the work recently published by Kansou et al. (5) can establish a reference point for the food community.

NEW WAYS TO IDENTIFY AND TRANSLATE THE CONSUMER NEEDS

As in other industrial sectors, also in the food industry, the design of a product according to the consumers' needs is surely a key target (6). Customers' needs, and desires would determine the willingness of consumers to pay for a particular product. The biggest challenge is then represented by the ability of a food producer to understand the consumers' needs, capture their attention, and transform the consumers' ideas into chemical and physical parameters of the final food product. Of course, market research can help a lot when it is combined with profound physicochemical knowledge of the product. This also will help to develop understanding and models (which could be simply data-based) able to link the properties of the product and the characteristics that the final consumer looks for.

The thing here is: are there innovative ways, based on digital tools, to identify consumer needs? Ideally, social networks can reveal some consumer needs and preferences, but to date, there are no studies showing how data on consumer preferences (taken from social networks, or any other virtual space where consumers commonly upload and share food images but also recipes, cooking images or videos, and food diaries, leading to large-scale food data) can be translated in bounded sensorial preferences about a given class of products or a specific product. An interesting review of computing technology applied to the food virtual/social world has been presented by Min et al. (7). There are also studies on possibilities offered by social media in identifying consumers' preferences, and they are discussed in the following paragraphs.

"Tweet What You Eat"

An interesting example of using social networks to capture some trends about consumers' preferences was provided by Abbar et al. (8). Their starting question was: Can we use social media to get insights into the dietary habits of a community? The authors analyzed the potential of social networks to provide insight into dietary choices of 210K US resident Twitter users by linking the tweeted dining experiences to their interests, demographics, and social networks. It was found out that a correlation exists among the foods mentioned in the daily tweets (of analyzed users), the local obesity and diabetes statistics. Calculating the energy content related to mentioned foods, authors found out how food tweeted energy content is correlated to user interest and demographic indicators, and that users. No doubt that there is a lot to do to develop sensitive and accurate tools for user characterization, with both textual and social network information available. For example, the fact itself that in a place with a high percentage of population suffering from obesity most of the tweets talk about high energy foods does not reveal anything specific on the food preferences of consumers in such a place. The analysis must be crossed with other kinds of information. Or imagine a start-up interested to launch a new plant-based gelato. Before diving into the preferred product characteristics, the start-up maybe wants to target where the ice cream lovers are. Distinguishing foods tweets between rural and urban zones (8) one may conclude that consumers from the rural area are the right target. On the other hand, in large urban areas consumers are more open to adopting a plant-based diet and are more prone to spend some dollars more to buy a healthier product as a plant-based gelato could be.

Apps and Food

Differently than social networks, apps directly related to the food world may help better in this task. Most of the people thinking about app and food think just about an app for food delivery. But these apps are not the only ones. Many apps about nutrition/diet exist as well as apps about food preparation. Also, apps pretending to help reduce food waste are gaining interest.

Some of them cover more than one goal at the same time (9). Let us see if and how they can help with food product design.

Apps on nutrition/diet/ health are sources of data on true food consumption, consumer habits, and dietary requirements: very important data, also going toward possible personalized nutrition.

Franco et al. (10) analyzed the main features of the most popular nutrition apps and compare their strategies and technologies for dietary assessment and user feedback. By exploring stores from main providers of smartphone services, authors found 13 apps using several keywords, such as diet tracker, dietician, eating, fit, fitness, food, food diary, food tracker, health, lose weight, nutrition, nutritionist, weight, weight loss, weight management, weight watcher, and so on. Most of these apps allow to download of the diet diary of active users, thus providing quite detailed information on their daily food intake, in terms of food items, quantity, and – sometimes – preparation. Weber and Achananuparp (11) used the public food diaries of more than 4,000 long-term active users of an app called MyFitnessPal. The heart of their analysis was a classifier able to predict the diet trajectory with respect to a certain self-defined calorie goal, just using the list of foods consumed by a user. Even if the purposes of the above-mentioned pieces of research were other than understanding consumer needs and preferences, there is no doubt that the apps mentioned in these pieces of research are surely a very good source of data to be used to classify consumers' needs and preferences when talking about diet, food products, and their characteristics, at least in terms of calories, composition and nutrition facts.

As an example, it can be interesting to look at the info one can download from the MyFitnessPal database, with daily meals, branded products consumed, also according to the lifestyle of the consumers. Marketing-wise, apps like this are also very useful to push the user to get rewards. And here the healthy characteristics of a branded product (think about a snack) can be used to market that product through the app.

Food Blogs and AI: Comment – Instruction

A very good source about consumer taste preferences is given by apps about food preparation, where also data about consumer habits and leftovers can be mined. On blogs about food preparation, or reviews about specific food products sold online, we can read the reviews from consumers.

These are good sources of info. It is possible to identify what people like most and, also, why people like a particular food product or preparation. Techniques of word to vectors can be used in such cases. Furthermore, there are artificial intelligence techniques, often using expert knowledge, to relate a comment to an action, instruction, or at least to a suggestion (12).

The readers can have a look at a recipe blog (13) where – in the case of chocolate oatmeal cookies – comments like the following can be found:

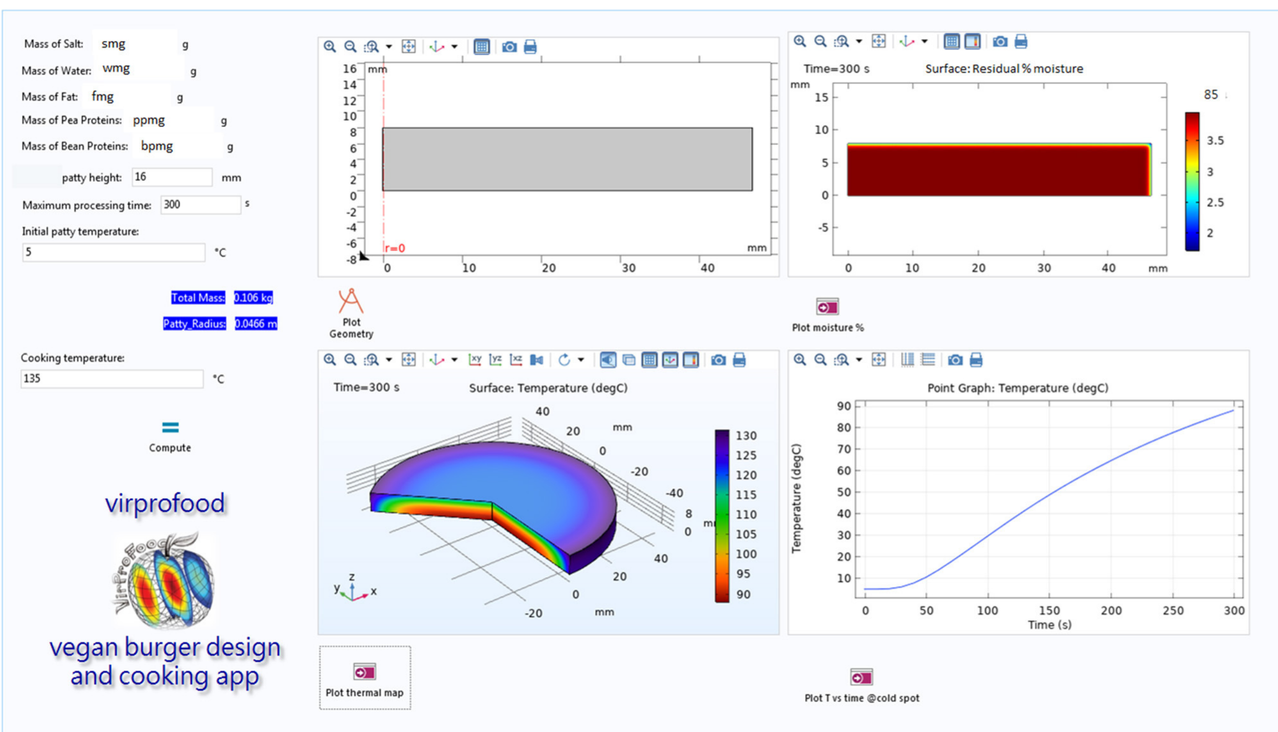

FIGURE 1 | Graphical user interface of an app for the design and the cooking simulation of plant-based burger, developed by VirProFood team at University of Salerno, Italy.

"This recipe did not turn out well. Flat and greasy and inedible."
"We didn't like the combination of chocolate and cinnamon at all....for those that love chocolate and cinnamon together - you'll like this recipe."
"I saw the picture and was excited to try this recipe! However,... They are not as moist or as sweet as I expected them to be."

It is not difficult to translate comments like these into recommendations for better food preparation. Being too greasy, the recipe maybe needs a reduction of the fat content or the selection of another fat ingredient. If the final product (the cookie) is found to be too brown, this can suggest reducing the baking temperature or the baking time. If it is too hard, again the baking time or temperature can be reduced, as well as the flour content, or another flour ingredient must be found.

DIGITAL TOOLS TO PREDICT PROCESSING EFFECTS ON THE FINAL PRODUCT

Some interesting examples discussed how algorithms can help even during domestic cooking sessions (14), but undoubtedly at the industrial level is the mechanistic modeling which would help in simulating the effect of ingredients and processing on the final properties of a certain food product (15). Mathematical modeling of transport phenomena is a consolidated science and there is a good choice of software for dealing with it (1). More complicated is the thermodynamics modeling for the prediction of properties, which often needs a combination of heuristics, models based on experience, whereas available data on properties are still scattered and not unified for immediate usage.

Focusing on the mesoscale process, apps based on mechanistic models can help food scientists to predict the behavior of food products undergoing further process, like in the case of a vegan burger cooking. In **Figure 1**, it is shown the graphical user interface of an app, designed by the VirProFood team at the University of Salerno (Italy) to simulate the heating of a plant-based burger, for which the composition is given as input, predicting the heating behavior and the change in moisture content of the burger, as a function of the burger dimensions, of the cooking temperature and of the heating time. It is the app itself that calculates the thermo-physical properties of the burger based on its compositions. This kind of app will start to be popular, as high computational level software (able to solve quite complicated systems of the partial differential equation describing the evolution of energy, mass, and properties in a food product) can provide the users with a compiler capable to produce easy-to-use apps (as in the case of COMSOL Compiler 5.6).

CONCLUSIONS

There are, of course, challenges to be faced before a completely digital approach can be used for food product design: probably the quality and the quantity of available data are not still enough to capture trends in consumers' needs and preferences. On the other hand, the work already done about vectorization of words related to comments on recipes or commercial food products can quickly bring to hybrid machines able exploit all the capabilities of digital tools. For instance, hybrid machines, because they will be based on approaches when taking into account consolidated modeling techniques and artificial intelligence. Molecular dynamics and thermodynamics can help to discriminate ingredients and predict properties. Mechanistic models can be used for predicting the properties and performances of the product. Artificial Intelligence (machine learning in this case) techniques can be appropriated for relating product features to sensorial attributes preferred by the consumer and also to choose ingredients (12).

No doubt then that the virtual/digital tools can accelerate time to market for new food products. The exploitation of these tools needs a multidisciplinary eco-system, where food engineers, food scientists, and experts in ingredients and nutrition will seat together with computer scientists to find new ways.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Influence of Sensory Properties in Moderating Eating Behaviors and Food Intake

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Sensory properties inform likes and dislikes, but also play an important functional role in guiding food choice and intake behavior. Odors direct food choice and stimulate sensory-specific appetites and taste helps to anticipate calorie and nutrient content of food. Food textures moderate eating rate and the energy consumed to satiation and post-ingestive metabolism. We summarize how sensory cues moderate intake, and highlight opportunities to apply sensory approaches to improve dietary behavior. Salt, sweet and savory taste influence liking, but also influence energy intake to fullness, with higher taste intensity and duration linked to lower intake. Psycho-physical studies show it is relatively easy to rank taste intensities at different concentrations but more challenging to discriminate fat contents, and fat discrimination declines further when combined with high-taste intensity. Fat has low impact on sensory intensity, but makes significant contributions to energy content. Combinations of high taste and fat-content can promote passive energy over-consumption, and adding fat also increases energy intake rate (kcals/min), reducing opportunities to orally meter consumption. Consumers adapt their oral processing behaviors to a foods texture, which can influence the rate and extent of energy intake. Understanding how texture influences eating behaviors and bolus formation, affords new opportunities to impact eating rate, energy intake and metabolic response to food. Food formulation has traditionally focused on composition and sensory appeal. Future research needs to consider the role of sensory properties in moderating consumer interaction with their food environment, and how they influence calorie selection, and shape our eating behaviors and intake.

Keywords: sensory, food choice, energy intake, texture, odor, taste

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INTRODUCTION; SENSORY CUES AS *FUNCTIONAL* FOOD PROPERTIES

A foods sensory appeal is largely determined by the physical and chemical properties that are sensed before and during consumption, which informs initial acceptance and the degree to which a food will be consumed (1). High sensory appeal is proposed as the main reason for excessive energy intakes, yet dietary energy intake patterns are not dominated only by highly palatable foods, and most energy is consumed from staple foods and meals with diverse sensory properties. This suggests that palatability is only one dimension of food intake, and that the sensory properties of food play an important *functional* role in guiding intake behavior, beyond simply promoting "liking". The senses of vision and olfaction are involved in the anticipation of food intake and direct sensory specific appetites and food choice. By contrast, hearing, taste, retro-nasal olfaction, texture perception and trigeminal stimulation are directly involved during consumption, and collectively inform the onset of satiation and the termination of energy intake (2). These sensory signals are integrated to form a dynamic perceptual impression of a food, which determines both our liking and intake behavior to the point of satiation (3). Sensory cues are operational before and during a meal, having a direct effect on satiation, with less of an impact on satiety (4).

This mini-review provides a summary of recent findings on the role of odor, taste and texture on calorie selection and energy intake. We highlight the differential role of smell and taste and texture perception in the initiation and termination of eating, and the sensory impact of fat in promoting higher energy intake rates. Food texture can also influence the oral phase of digestion and subsequent metabolic responses, and we highlight opportunities to apply an empirical understanding of the role of sensory cues to moderate food choice, intake and the eating behaviors associated with the healthiness of the food supply.

IMPACT OF PALATABILITY, ODORS, AND TASTE ON ENERGY SELECTION AND INTAKE

High palatability is a powerful incentive to eat, and the ingestion of "good tasting foods" has been linked to a multitude of positive emotions (5). A higher palatability increases the probability that a particular food will be chosen amongst a set of alternatives (6), and research has also shown that higher palatability leads to an increase in energy intake [i.e., (7)]. However, it is an oversimplification to assume that we only choose and consume foods based on palatability, and food intake decisions are influenced by a complex set of factors that go beyond palatability (1). Food choice and intake are influenced by a multitude of factors and we do not only consume our "most liked" foods (8). Highly palatable foods are often regarded as "treats", and are consumed infrequently and so do not contribute disproportionately to higher energy intakes. For example, treat foods such as ice cream contribute a relatively small proportion (5%) to consumed calories (9). The majority of daily energy intakes comes from "savory-fatty" foods (10, 11) and staple foods (12) which often have relatively low hedonic valence, such as rice, potato or pasta, rather than indulgent "treat" products often characterized as junk foods or empty calories (13). Whereas, liking may predict choice, the effect of higher palatability on intake is not a linear relationship, with research showing the predictive relationship between liking and intake tends to diminish at higher levels of palatability. For example, in a field study with US soldiers, soldiers consumed 100% of served portions when the liking rating on the 9-point hedonic scale was either a "8" or a "9", yet the relationship between liking and intake tended to plateau at ratings above score of 5–6 (6). Beyond their role in liking, research in from numerous controlled sensory-feeding behavior studies has highlighted the role of food sensory properties in calorie selection and intake.

Research has shown that food related ambient odors can increase sensory specific appetites and directly influence food choice (14, 15). For example, when customers at an experimental restaurant were asked to choose their meals from a menu, the proportion selecting a fruit dessert increased when choices were made in the presence of a non-attentively perceived "pear" odor, than when choices were made without an odor (16). The implication is that our response, particularly to unattended odors, are likely to play an important role in food choices. Similarly, when exposed to odors signaling a specific "taste" (i.e., sweet/savory) participants had a greater appetite for congruent sweet/savory food, compared to incongruent products, suggesting odors can induce "sensory specific appetites" that influence choice, independently of liking (17, 18). Although this effect has been reproduced many times, it seems limited to choice and despite early findings to the contrary (19, 20), odors do not seem to have a direct impact of energy intake in realistic consumption conditions (21, 22).

By contrast taste quality and intensity have been shown to moderate energy selection and intake. Consuming foods with higher *umami* intensity has been shown to reduce subsequent energy intake (23, 24), and foods with congruent savory-taste and protein content have been shown to enhance post-meal satiety (25, 26). Taste *quality* and *intensity* reflect the concentration of the taste substrate in the food environment, such that "sweeter" foods tend to contain more mono- and di-saccharides and salty foods contain more NaCl. However, there are also exceptions to this relationship, where fat (which is usually present as triacylglycerol), has a low sensory impact, but a large impact on the energy content of foods. Fat sensation affects mouthfeel, flavor release, and can directly impact the rate of the energy intake (27). In many cases the widespread use of low and no-calorie sweeteners now means there can be a strong taste signal in the absence of any sugar. Humans are largely blind to the primary macronutrients sources of energy we consume including starch, protein and triacylglycerol, which have little or no taste activity (13). As such, the sense of taste is influential in linking what is perceived during consumption with the positive post-ingestive consequences of food intake, and through repeated exposure, taste acquires a predictive capacity where we learn to imprint preferences and habitual eating habits via a reciprocal effect of flavor-consequence learning (28, 29).

Whether one taste quality is more satiating than another has been investigated based on anecdotal reports that "sweet" foods were wrongly believed to be less satiating than savory foods on a kcal for kcal basis, and may therefore promote increased energy intake. Early research on this topic showed no difference in the short term effect of sweet/non-sweet carbohydrates on subsequent satiety (30) and later findings support this showing that energy compensation is no different whether the energy taste quality was sweet or savory (31). This is further supported by research on taste and satiation, which showed that *ad libitum* intakes were equivalent for sweet and salty/savory tasting versions of the same meal (32).

Within a meal, the combined duration and intensity or "magnitude" of a taste may also affect the onset of satiation. Studies have investigated the impact of taste duration on *ad libitum* intakes, while maintaining a constant intake rate using a peristaltic pump. In one study, researchers measured individual concentration-pleasantness curves for salt in tomato soup, and exposed subjects to equally palatable low and high intensity salt during separate *ad libitum* test meals (33, 34). A longer oro-sensory exposure time and higher salt intensity combined to decreased food *ad libitum* intake by ∼9%, though the oro-sensory exposure had a stronger impact than taste intensity. Vickers et al. showed that high yogurt sweetness was liked more than a low sweetness, but consumption showed the opposite effect, indicating that higher sweetness intensity led to earlier satiation (35). Lasschuijt et al. showed that higher taste intensity led to earlier meal termination, but as with previous findings, the effect of oro-sensory duration had a stronger impact than taste intensity (36).

SENSORY CONTRIBUTION OF "FAT"; PERCEPTUALLY BENIGN BUT ENERGETICALLY POTENT

New techniques have been developed in recent years to profile dietary energy-intake behaviors based on the predominant taste properties of the foods consumed. This has produced new insights on consumer sensory-patterns of dietary intake based on the preferred taste quality of energy and nutrients consumed (37). This approach has been described as *"sensory-epidemiology"* and it enables comparison of daily energy intakes by clustering foods by their predominant taste quality, and then comparing the relative contribution of taste clusters to higher or lower energy consumed. Whereas, much attention has been directed to role of sweet foods and added sugar to high energy intakes, findings suggest that the excess energy intakes are mostly associated with greater intakes of "savory–fatty" tasting foods, which are consistently associated with increased energy intakes and higher rates of overweight (11). The implication is that foods high in "savory-fat" combinations make a significant contribution to daily energy intakes. Previous research has shown that our ability to discriminate between fat levels in food is reasonably linear at low taste intensity, but this ability dramatically decreases when fat is presented alongside higher intensity of sweet (38) or salty (39, 40) tastes. The implication is that when we are unable to detect increases in energy density due to higher fat, it becomes more difficult to adjust portion selected or later energy intakes in response to higher energy consumed from fat (41). It is therefore relatively easy to "hide" fats in foods without the fat being sensed, yet it makes a significant contribution to energy intakes. For example, *ad libitum* energy intake was ∼2,100 kcal on a diet with 15–20% energy from fat compared to 2,600 kcal in a diet of equal palatability which derived 45–50% energy from fat (42).

Foods with a higher fat content can also lubricate and agglomerate more rapidly during consumption, which enhances bolus formation and increases eating rate and the extent of energy intake (43–45). As we summarize in the following section, this dual impact of increased eating rate and energy density can also promote excessive energy intakes.

FOOD TEXTURE, EATING RATE, ENERGY INTAKE, AND METABOLISM

Eating behaviors emerge in response to the texture challenges encountered during consumption, where consumers adapts their microstructural patterns of oral processing to prepare the initial structure for safe swallow (46). The effect of texture on satiation/food intake is mainly operational through eating rate, where harder, chunkier, more viscous textures result in lower eating rates (47). Previous research on liquid and semi-solid foods has shown that *ad libitum* intake of a liquid was ∼30% higher than that of a semi-solid food (48). Difference in intake between liquid and semi-solids disappear when eating rates are set equal, with the help of peristaltic pump (49). There is wide natural in the eating rate of foods commonly encountered, with recent comparisons highlighting a range of between 10 and 120 g/min for solid foods, and rates of up to 400–600 g/min for liquids (50). Energy dense liquids pose a double-risk as they can be easily over-consumed, but also deliver poor satiety on a kcal for kcal basis (51).

Significant progress has been made in our understanding of how food texture influences oral processing (47, 52) and the specific influence of food textures on food intake (53). Food texture has been shown to drive eating rate (44, 54, 55) which in turn can influence *ad libitum* energy intake to satiation (56), and several studies have shown that faster eating is associated with the transition to overweight and obesity and poor cardio-metabolic health (55, 57–59). A meta-analysis of the food physical and sensory properties that affect intake concluded that people tend to consume less when solid-foods were harder, chunkier and more viscous (60). Evidence from numerous studies (53, 54, 61) now suggest that with a 20% reduction in eating rate, it is possible to reduce *ad libitum* energy intake by 1–14% without a loss in subsequent feelings of satisfaction (62). Food form and mode of consumption can also influence the rate and extent of intake, and solids have been shown to have a higher satiating efficiency than semi-solids and liquids, unless consumed slowly (as a soup) (63). Similarly, intakes were ∼100 g lower each day when a semi-solid food was consumed with a spoon than a straw, highlighting that slower eating rate can support the onset of satiation for fewer calories (64). Food can influence eating rate but also oral processing and saliva-bolus uptake during the oral phase of digestion. Differences in food oral processing behavior have been shown to contribute to temporal changes in post-prandial glucose and insulin, and post-meal satiety responses (65–67). Slower eating rates result in greater bolus surface area, saliva uptakes and may have an incretin effect as early glucose release stimulates greater early insulin release (36, 65). Taken together, these findings indicate that food texture contributes much more simply "sensory appeal", and can effect satiation and satiety by moderating eating rate, but can also exerts influence on the oral phase of digestion and the subsequent metabolic response to ingested nutrients. Further research is needed to understand how food texture based differences in eating rate can influence food intake control and support healthy metabolic responses to ingested nutrients.

FUTURE OPPORTUNITIES FOR SENSORY NUTRITION

Public health guidelines recommend reductions in sugar, salt and fat but rarely consider the functional role of a foods sensory properties on choice and intake, or opportunities to incorporate an understanding of sensory cues in guiding reformulation or eating behavior changes. This review provides an overview of data that consistently shows how sensory cues have a reproducible influence on how we select, consume and feel satisfied from the foods in our diet. Further research is need to understand whether sensory properties can support sustained changes in eating behavior and promote healthier dietary patterns in the longer-term. Future product development and renovation requires significant reductions in several public sensitive nutrients (i.e., salt, sugar and fat) alongside enhanced nutrient density, to support better health and reduce the risk of diet related chronic disease. Understanding how consumers perceive and consume a food is central to the success of efforts to improve dietary behavior. We outline three potential opportunities for future applications of "sensory-nutrition" approaches to support improved eating behavior, dietary patterns and health.

Using food odors to promote healthy food choice: Research has highlighted the food odors stimulate sensory specific appetites, and are associated with recalled energy content and memory for foods. This may influence "foraging" behavior and is likely to support how we navigate the food environment when making choices on what to consume (68). Limited research to date has focused on the application of odor primes to encourage sensory-appetites and choice for healthier food products, and future research should aim to explore whether odor cues can be applied to stimulate consumer appeal and reinforce positive elements of healthy food choice and consumption.

Application of low-calorie taste compounds to sustain the appeal reduced energy foods: Extensive research has shown the impact of no- and low-calorie sweeteners (non-nutritive sweeteners, NNS) to support sugar reduction, and this has been particularly effective in removing sugar from soft-drinks. Numerous meta-analyses of experimental evidence highlight that applying non-nutritive sweeteners to reduce the sugar content of the diet can both lower dietary energy density and support clinically significant reductions in body weight [i.e., see (69)]. However, as demonstrated earlier, "savory-fatty" foods make a significant contribution to daily energy intakes (11), yet less research has been focused on how to sustain sensory appeal of savory foods with reduced energy density. In addition to the potential application of umami savory enhancers highlighted in the current review, recent findings suggest that *kokumi* may have the potential to enhance sensory appeal, increase calorie estimates, while supporting energy density reduction (70). These *kokumi* compounds are low calorie taste enhancers, often comprising tri-peptides and yeast extracts, that are known to enhance sensations of mouthfulness, continuity and complexity, often mimicking the sensory impact of fat. Preliminary findings demonstrate that addition of *kokumi* compounds can enhance sensory dimensions linked to calorie expectations, and promote higher estimated calories and expected fullness across a series of equi-caloric broths. Future research should further explore the potential of Kokumi compounds to support calorie reduction while maintaining product sensory appeal.

Texture and Energy Density to reduce intake to satiation; Evidence from several controlled feeding studies has demonstrated that energy density (71) and food texture (53) can independently and in combination influence the rate and extent of energy intake within meals. Findings from a recent RCT on ultra-processed foods highlights that higher energy intake rates (kcals/min) support sustained increases in *ad libitum* energy intake (72). These energy intake rates have been shown to vary widely within the food environment (27). Enhancing food texture in combination with energy density reductions combine to produce an 10–14% reduction in energy intakes, with no loss in meal palatability or post-meal satisfaction (53, 62). Further research is now needed to demonstrate the sustained effect of texture-energy density interventions on habitual energy intakes and subsequent energy balance.

CONCLUSIONS

Knowing that the sensory properties of food influence choice and intake behavior is important, but this knowledge will have little impact if we do not apply sensory cues to encourage the consumption of healthier diets. As illustrated above, a number of proof of principle studies have clearly shown that it is possible to change sensory cues in the food environment in such a way that people consume less calories while maintaining the palatability of diets. These approaches require further research to understand the longitudinal impact of sensory properties on energy intake in the food environment and across a wider population of consumers. Controlled "sensory-nutrition" intervention studies are required to further understand how effective these longer term approaches are in producing sensory optimized foods that help to moderate the flow of energy though our diets.

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CF and KG conceived and wrote the manuscript. Both authors revised and approved the submitted version.

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Impact of Dietary Palmitic Acid on Lipid Metabolism

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Palmitic acid (PA) is ubiquitously present in dietary fat guaranteeing an average intake of about 20 g/d. The relative high requirement and relative content in the human body, which accounts for 20–30% of total fatty acids (FAs), is justified by its relevant nutritional role. In particular physiological conditions, such as in the fetal stage or in the developing brain, the respectively inefficient placental and brain blood–barrier transfer of PA strongly induces its endogenous biosynthesis from glucose *via de novo* lipogenesis (DNL) to secure a tight homeostatic control of PA tissue concentration required to exert its multiple physiological activities. However, pathophysiological conditions (insulin resistance) are characterized by a sustained DNL in the liver and aimed at preventing the excess accumulation of glucose, which result in increased tissue content of PA and disrupted homeostatic control of its tissue concentration. This leads to an overaccumulation of tissue PA, which results in dyslipidemia, increased ectopic fat accumulation, and inflammatory tone *via* toll-like receptor 4. Any change in dietary saturated FAs (SFAs) usually reflects a complementary change in polyunsaturated FA (PUFA) intake. Since PUFA particularly n-3 highly PUFA, suppress lipogenic gene expression, their reduction in intake rather than excess of dietary SFA may promote endogenous PA production *via* DNL. Thereby, the increase in tissue PA and its deleterious consequences from dysregulated DNL can be mistakenly attributed to dietary intake of PA.

Keywords: palmitic acid, *de novo* lipogenesis, fatty acid metabolism, dietary fatty acids, saturated/unsaturated ratio

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INTRODUCTION

Palmitic acid (PA) is one of the most abundant saturated fatty acids (SFAs) in nature, which is present in animal and human tissues, plants, algae, fungus, yeast, and bacteria. Its distribution varies both within species and among species, and its content can be influenced by several environmental factors as the variation of soil pH, nutrient–ion interaction, age, water, and climate (1, 2).

The average dietary intake of PA is around 20–30 g/d representing about 8–10%en (3–5) and can be found in different vegetable and animal fat sources (**Table 1**) (6), with levels of 20–30% in animal lipids and 10–45% in vegetable oils. Methods that are used to prepare the food also impact on PA amount; for example, in processed and preserved meats, the content is higher than fresh meat with values up to 7.6/100 g of edible portion in salami and in lard 21/100 g of edible portion. It should be pointed out that due to high within-food variability of PA content, it is very difficult to assess its precise dietary intake. In addition, PA absorption and metabolic fate are strongly influenced by several factors, such as food matrix and pathological or physiological conditions.

TABLE 1 | Palmitic acid content of oils and fats from vegetable and animal sources (expressed as percentage mass fraction of total FAs) (6).

Vegetable sources	% Fraction/total FA	Animal sources	% Fraction/total FA
Palm oil	40.1–47.5	Lard	21.07
Cottonseed oil	21.4–26.4	Goose	7.41
Cocoa butter	25.4	Whole chicken	2.19
Olive oil	7.5–20.0	Pork loin	2.06
Oat bran oil	17.4	Lamb	0.58–1.99
Avocado oil	17.2	Rabbit	1.22–1.95
Wheat germ oil	16.6	Beef meat	0.31–1.14
Corn oil	8.6–16.5	Horse meat	1.65
Peanut oil	8.3–14.0	Sheep meat	0.58
Soya bean oil	8.0–13.3	Goat meat	0.40
Grapeseed oil	5.5–11.0	Deer meat	0.12
Sesame oil	7.9–10.2	Salami	5.73–7.55
Coconut oil	8.2	Mortadella	5.70
Walnut oil	3.9–7.2	Ham	3.93–4.93
Linseed oil	4.0–7.0	Speck	3.71
Almond oil	6.5	Pancetta	5.67–5.99
Safflower oil	4.8–6.2	Butter	20.86
Linola oil	6.0	Parmesan cheese	8.04
Cashew nut oil	4.0–6.0	Fontina cheese	7.31
Rapeseed oil	1.5–6.0	Cream	5.72
Sunflower oil	5.4–5.9	Ricotta cheese (cow)	3.49
Hazelnut oil	5.2	Ricotta cheese (sheep)	2.85
Canola oil	4.0	Cow's whole milk	0.92–1.97
Eggs sources		Sheep's whole milk	1.58
Hen egg (whole)	1.90–5.90	Goat's whole milk	1.34
Duck egg	3.00	Semiskimmed milk	0.45
Turkey egg	2.72	Yogurt	0.92

IMPORTANCE OF THE MATRIX AND PA DISTRIBUTION ON METABOLISM

In evaluating the effects of food on health, the overall macronutrient composition and structure need to be considered, i.e. the "food matrix" (7), meaning that food chemical compounds behave differently in isolated form in comparison to part of food structures (8), as well as the resistance of a food to the mastication and the viscosity of aliments, which may affect the bioavailability and digestibility of dietary lipids (9). Dietary fats comprise cholesterol and fatty acids (FAs), which can be free or components of complex lipids, as triacylglycerols (TAGs), and phospholipids (PLs), organized in structures able to modulate FA final metabolic fate. FA esterification on different positions of the TAG glycerol backbone (central sn-2 position, external sn-1 and sn-3 positions) or on a PL may also impact on their digestibility and metabolism (10–16). PA in foods is mainly present esterified in PL and TAG.

Dietary PL represents 1–10% of total daily fat intake (17). PL is mainly catabolized by pancreatic phospholipase A2 (PLA2) that produces free FA (FFA) and lysophosphatidylcholine (lysoPL), which once absorbed by the intestinal epithelium are reacylated or hydrolyzed to form PL or glycerol-3-phosphorylcholine, respectively. FFAs are instead used for TAG synthesis that are subsequently incorporated into chylomicrons (17).

Over 90% of dietary FAs are esterified to TAG preferentially hydrolyzed by digestive lipases (18) on sn-1,3 positions followed by pancreatic lipase to give 2-monoacylglycerol (2-MAG) and FFA (15), which cross the apical membranes of the enterocytes and are reassembled into TAG for secretion to plasma in chylomicrons. SFA released from positions sn-1 and sn-3 may form insoluble soaps with ions as calcium that are not absorbed, a singularity lost if SFA is in the TAG sn-2 position (19), as confirmed by animal and human infant studies which demonstrate that sn-2 esterified FA is efficiently absorbed as 2-MAG (20, 21). The peculiar sn-2 position of PA in human milk results from the activity of the glycerol-3-phosphate (G-3-P) acyltransferase, present in the mammary gland, which acylates an unsaturated FA at the sn-1 position of G-3-P and subsequently a PA at the sn-2 position (22, 23). Human milk, which contains 20–25% of PA with respect to the total FA whose 70% is in sn-2 of TAG, limits PA malabsorption providing the infant with high PA (19, 23–25). Conversely, 45 and 58% of cow and rodent milk fat (25 and 15% of PA on the total FA, respectively) are esterified at the TAG sn-2 position (23, 26). FA composition of the early diet influences intestinal membrane FA, which affects nutrient transport, permeability, and inflammatory pathways that persist into later life (27, 28). Notably, PA also plays an important role in the developing fetus with the term infant reaching 13–15% of body fat of which 45–50% is PA, mostly derived from endogenous synthesis in the fetus (29).

PA peculiar tissue distribution results in its better incorporation in several tissues, for example, adipose tissues, with a lower deposition of fat in the visceral depots and higher in the subcutaneous fat (30). Interestingly, several studies demonstrated the protective effect of breastfeeding against obesity in childhood (31, 32) and adulthood (33–36). Also, donkey milk contains high concentrations of PA in sn-2 of TAG and is recognized as the best potential substitute for human milk due to its remarkable nutritional value, good palatability, and reduced allergenicity (37, 38). A recent study in rats showed that oral supplementation with human or donkey milk ameliorated metabolism and reduced inflammation potentially mediated by an improved redox status, mitochondrial uncoupling, and dynamics (39). In addition, it has been demonstrated that PA in sn-2 by modifying endocannabinoids and congeners biosynthesis in different tissues may potentially concur in the physiological regulation of energy metabolism, brain function, and body fat distribution (40). In contrast to milk, in animal tissues that include human adipose tissue and also beef tallow and in soybean oil and cocoa butter, PA is mainly at sn-1,3 position, whereas the sn-2 is occupied by an unsaturated FA (41–45). Lard, having high amounts of PA at TAG sn-2, represents an exception (23), and in animal studies, PA from lard was better absorbed with respect to PA from cocoa butter and palm oil (46, 47). This PA peculiar position led food industries to often use interesterification to produce functional infant formula containing TAG with a high amount of sn-2 PA (48, 49). Amounts of PA in the sn-2 position in breast-fed infants (81%) or in infants fed formula prepared with synthesized TAG (39%), plasma chylomicron TAG containing PA in sn-2 position were higher with respect to those fed with standard infant formula with 6% of PA in sn-2 position (50), and it was shown in infants that PA loss in stools was 8-folds less using infant formula with lard TAG with respect to randomized lard (51). Also, an increase in the proportion of sn-2 PA by interesterification of TAG in coconut oil and palm olein improved PA absorption and metabolism in rats (52, 53). Therefore, the matrix/esterified position plays a crucial role in determining the metabolic fate of dietary PA.

ASSESSMENT OF DIETARY PA INTAKE IN HUMANS

Most of the studies aimed at evaluating dietary FA intake rely on food frequency questionnaires (FFQs), and food diaries where even repeated measurements do not necessarily provide valid measures of individual intake. Extreme intakes may reflect under- and overreporting rather than true low or high intakes, and subjects most prone to reporting bias may be repeatedly misclassified in quantiles of the distribution (54). In addition, assessing the precise nutrient intake is quite difficult because of the errors made in recalling or the identification of the amounts of foods eaten, especially in processed foods (55).

Measurement of circulating PA is not also a reliable marker of its dietary intake; in fact, the dietary consumption of PA has low impact on plasma levels compared with its endogenous biosynthesis; data from a controlled human feeding trial showed that variations in SFA intake from 11 to 30%en did not change circulating SFA, including PA (56). Accordingly, cohort studies did not show a solid correlation between the PA dietary intake (evaluated by FFQ) and its plasma levels ($r = -0.02$ to 0.09) (57–60).

Factors other than dietary intake have been suggested to influence FA composition in tissues, first FA metabolism efficiency, genetic variations, and even intrauterine and perinatal program. In fact, considering the relationship between the tissue FA composition and dietary fat, among plasma lipid fractions, only TAGs appear to reflect dietary polyunsaturated FA (PUFA) and SFA, but not monounsaturated FA (MUFA) (61) within the first hours after intake (62). Whereas, FA in serum cholesteryl esters (CEs) and in PL is related to average intake of dietary FA composition during the previous 3–6 weeks, FA of erythrocyte membrane PL and adipose tissue TAG reflect the dietary fat intake of previous months or years, respectively (62).

Noteworthy, it has been demonstrated, by isotope labeling studies in men, that low-fat high-carbohydrate diet stimulates *de novo* lipogenesis (DNL) with the accumulation of VLDL-TAG PA that led to linoleic acid (LA) reduction probably due to dilution effect, whereas with high-fat (40% fat, 45% carbohydrate) DNL is neglectable (63). This suggests that circulating PA levels are largely driven by endogenous synthesis through DNL rather than direct dietary intake. Therefore, the relative strict regulation of PA tissue concentration, with variable amount of the endogenously produced, leads to a high unreliability of the use of PA plasma levels as a tool to determine its dietary intake.

The potential increase of tissue PA by dietary intake is prevented by the contribution of its conversion to palmitoleic (POA), by the insertion of one double-bond through stearoyl-CoA desaturase-1 (SCD1) (62), which reduces PA availability in tissues, but also *via* elongation to stearic acid (SA) and further desaturation *via* SCD1 to form oleic acid (OA). A possible protective capacity of OA to drive PA to be deposited in the neutral form of TAG (64, 65) and POA to improve insulin sensibility has been described (66).

FATE OR METABOLISM OF PA FROM *DNL*

When the energetic sources are in excess, the non-fat surplus, mainly carbohydrates, is converted to FA by DNL, a pathway that begins with the conversion of acetyl-CoA into malonyl-CoA by acetyl-CoA carboxylase (ACC). During fed and insulin-stimulated conditions, ACC increases malonyl-CoA levels whereas AMP-activated protein kinase (AMPK) stops the synthesis, probably by inhibiting sterol regulatory element-binding protein (SREBP) (67).

Further evidence indicates that adipose tissue DNL supports metabolic homoeostasis of distant organs, as in liver and muscle, by producing cytokine-like lipids, lipokines, with antidiabetogenic and antiinflammatory activities, such as POA and branched FA esters of hydroxy FA (FAHFA) (66, 68).

In normal conditions, adipose tissue is the major site for DNL, which significantly contributes to body lipid reserves, energy storage, and to the maintenance of serum TAG homeostasis that derived instead from dietary sources (69–75). Furthermore, adipose tissue DNL is considered as an energy-inefficient source of lipids because it yields fewer lipids per calorie consumed, thus being a promising strategy for the treatment of lipotoxicity-related diseases. In fact, adipose tissue DNL is positively correlated with postprandial energy expenditure (76) subsequently to carbohydrate overfeeding, but not fat overfeeding which failed to significantly increase any component of energy expenditure (77, 78).

On the other hand, under specific conditions in the liver, such as insulin resistance, the impaired glycogen biosynthesis and consequent accumulation of glucose induce DNL that may contribute up to 26% to ectopically intrahepatocellular lipids in the pathogenesis of nonalcoholic fatty liver disease (NAFLD). In fact, hepatic DNL is positively correlated with insulin resistance and fatty liver, whereas the correlation with adipose tissue DNL is the opposite (73, 79–81).

In addition, a high-carbohydrate diet, particularly rich in simple sugars as fructose (82–84), activates a lipogenic response and increases the synthesis and secretion of VLDL in liver (85) contributing to hypertriglyceridemia (74). DNL contributes to 10–35% of the total VLDL-TAG pool, probably increasing the size (~130 nm), but not the number of VLDL secreted (86), and is in general higher in insulin-resistant states, and in overweight subjects compared to lean individuals (87–91).

Regulation of DNL occurs through the regulation of transcriptional factors as SREBP-1c and carbohydrate-responsive element-binding protein (ChREBP), activated by increased insulin signaling and increased glucose concentrations, respectively, and both induced by feeding (85, 92–95).

In liver, PUFA downregulates DNL *via* decreased expression of SREBP-1c (96), and leptin reduced adipogenesis through the inhibition of SREBP-1c expression (97). In addition, insulin and SREBP-1c stimulate peroxisome proliferator-activated receptor-γ (PPAR γ) expression (98, 99), which regulates glucose and lipid metabolism thus having adipogenic and lipogenic effects (100) and promotes FA storage in mature adipocytes by the stimulation of lipoprotein lipase (LPL), CD36, and glucose transporter GLUT-4 (101–103).

Therefore, DNL has a dual function, to supply PA in deficiency conditions, such as in the fetus (29) and developing brain (104) to overcome the difficulties of PA to pass, respectively, the placenta and the brain–blood barrier and to prevent the excess accumulation of glucose in the liver. In the latter case, significant increase of tissue PA is detected eluding the homeostatic control of tissue PA concentration and increased endogenous PA production may enhance inflammatory susceptibility through toll-like receptor (TLR4) activation (105) and insulin resistance by ceramide accumulation (106).

CONSIDERATIONS OVER HIGH SFA DIETS VS. PUFA-DEFICIENT DIETS ON METABOLISM

Dietary guidelines recommend limiting SFA intake to <10% of calories per day. Correlation between dietary SFA intake and cardiovascular disease (CVD) is quite controversial (107). The Cochrane analysis showed an association between reducing SFA intake and a reduction in cardiovascular events and replacing the energy from SFA with PUFA appear to be useful strategies, whereas effects of replacement with MUFA are unclear (108). SFA increases LDL plasma particle concentration but also their size, which is less associated with CVD (109) because more rapidly cleared than small-dense LDL particles from the circulation due to reduced receptor-mediated uptake (110). SFA increases blood total, LDL, and HDL cholesterol concentrations and decreases fasting TAG concentrations not changing the total–HDL cholesterol (TC/HDL) ratio. The capacity of increasing circulating HDL levels decreases with increasing chain length of SFA and for some studies, but not all, myristic acid and PA, and also carbohydrate intake, negatively affect TC/HDL ratio (111).

In vitro cell culture studies showed that PA in the free form in the medium elicits, insulin resistance (112), inflammation *via* TLR4 (105) and prometastatic activities (113), which implies that increased dietary PA may result in higher PA availability to cell tissues in the free form, while as already mentioned, higher intake of SFA results in a decrease of circulating PA in the free form and increase of its monounsaturated metabolites POA and OA. Therefore, *in vitro* models, while may elucidate a limited molecular mechanism, are by far not mimicking pathophysiological conditions. The extremely high concentrations typically used *in vitro* are not achievable *in vivo*, thus the results obtained do not prove any relevant pathophysiological information.

Any change in dietary SFA reflects a complementary change in MUFA and/or PUFA intake. As mentioned above, PUFA (70), particularly n-3 highly PUFA such as EPA and DHA, suppresses lipogenic gene expression by reducing the nuclear abundance and DNA-binding affinity of transcription factors responsible for imparting insulin and carbohydrate control to lipogenic and glycolytic genes (114); thereby, most of the detrimental effects should be ascribed to the lower PUFA intake rather than high dietary SFA.

From, a meta-analysis of randomized controlled trials emerged that replacing 5% energy from carbohydrate with SFA had no significant effect on fasting glucose but lowered insulin, and replacing SFA with PUFA lowered glucose, HbA1c and HOMA. This suggests that consuming more unsaturated FA in place of either carbohydrates or SFA will help to improve blood glucose control while exchanging dietary carbohydrate with SFA does not appreciably influence markers of blood glucose control, and therefore an approach based only on reducing carbohydrates or SFA intake, without considering the source of energy replacement would not be optimal (115).

Data are often contradictory and may be difficult to interpret into dietary advise: some studies suggested that n-6 PUFA would increase CVD risk (116, 117), and therefore the Institute of Medicine recommends a relatively modest range of 5%–10% energy consumption from PUFA, limiting its plausibility as a meaningful replacement for SFA (118). Increasing dietary PUFA may not be desirable as dietary levels of LA are already higher than recommended (119), particularly the n-6/n-3 PUFA ratio (119). The physiological role played by the SREBP-1c, which is inhibited by n-3 FA (114) and in general by PUFA (18), for glycogen biosynthesis and overall glucose homeostasis (120), stresses the point that balance between different dietary FA is strongly recommended and any unbalance may lead or increase the chance to set into motion a disrupted metabolism. In fact, while replacing SFA with LA has an established cholesterol lowering effect, it has not been shown that this lowering reduces mortality (107).

In addition, recently, it has been shown that lower dietary PUFA/MUFA and n-3/n-6, and not SFA, were associated with disturbances in metabolic syndrome-related indices in postmenopausal women, and that polymorphisms of FA desaturase FADS1 (rs174546) and FADS2 (rs3834458) were associated with unfavorable FA profile in red blood cells (121). It has also been demonstrated that the polymorphism rs1761667 of multifunctional CD36 scavenger receptor that facilitates FA uptake and oxidation, leads to a distinct metabolic pattern in normal weight and in obese subjects (122). Thus, changes of tissue FA profile and associated metabolic changes may also be determined by different genetic polymorphisms, which should be considered in developing personalized therapeutic strategies for ameliorating dyslipidemia and other metabolic disorders.

From several studies exploring the molecular mechanism of dietary FA interactions emerged that the reduction of PUFA intake, especially n-3 PUFA, rather than the excess of dietary

SFA, may favor insulin resistance (123), promoting endogenous PA production *via* DNL. Thus, the increase in tissue PA from dysregulated DNL and its deleterious consequences can be mistakenly attributed to dietary intake of PA (**Figure 1**).

Interestingly, it has been proposed that the claimed adverse effect on cholesterol exerted by high dietary SFA/PUFA ratio may represent a physiological mechanism aimed at fulfilling the needs of tissues for cholesterol (126) and the yield of larger LDL makes this increase not to be related to CVD (7).

Many of the purported harmful effects of dietary PA are based on experimental animal studies, mainly on mice on a high-fat diet, which consists of 45–60%en whereas the optimal fat content in the rodents diets ranges from 9 to 16%en (127). Therefore, high-fat diets contain from 3- to 6-folds of the fat content required, with usually an extremely high percentage of PA and low in PUFA and n-3/n-6 PUFA ratio, which makes difficult to pinpoint the effects of a high-fat content, high concentration of PA, or high n-6/n-3 PUFA ratio. These diets were created to induce obesity as quickly as possible (128) and not to assess the nutritional impact of dietary FA. Therefore, whereas they might be suitable as a model of obesity, they cannot be taken into consideration for translational nutritional studies on the effects of dietary FA (128).

CONCLUSIONS

Several pieces of evidence suggest that the nutritional impact of dietary FA is strictly related to the balance among them and with other macronutrients. Most of the studies claiming negative effect of PA rely on *in vitro* cell culture studies,

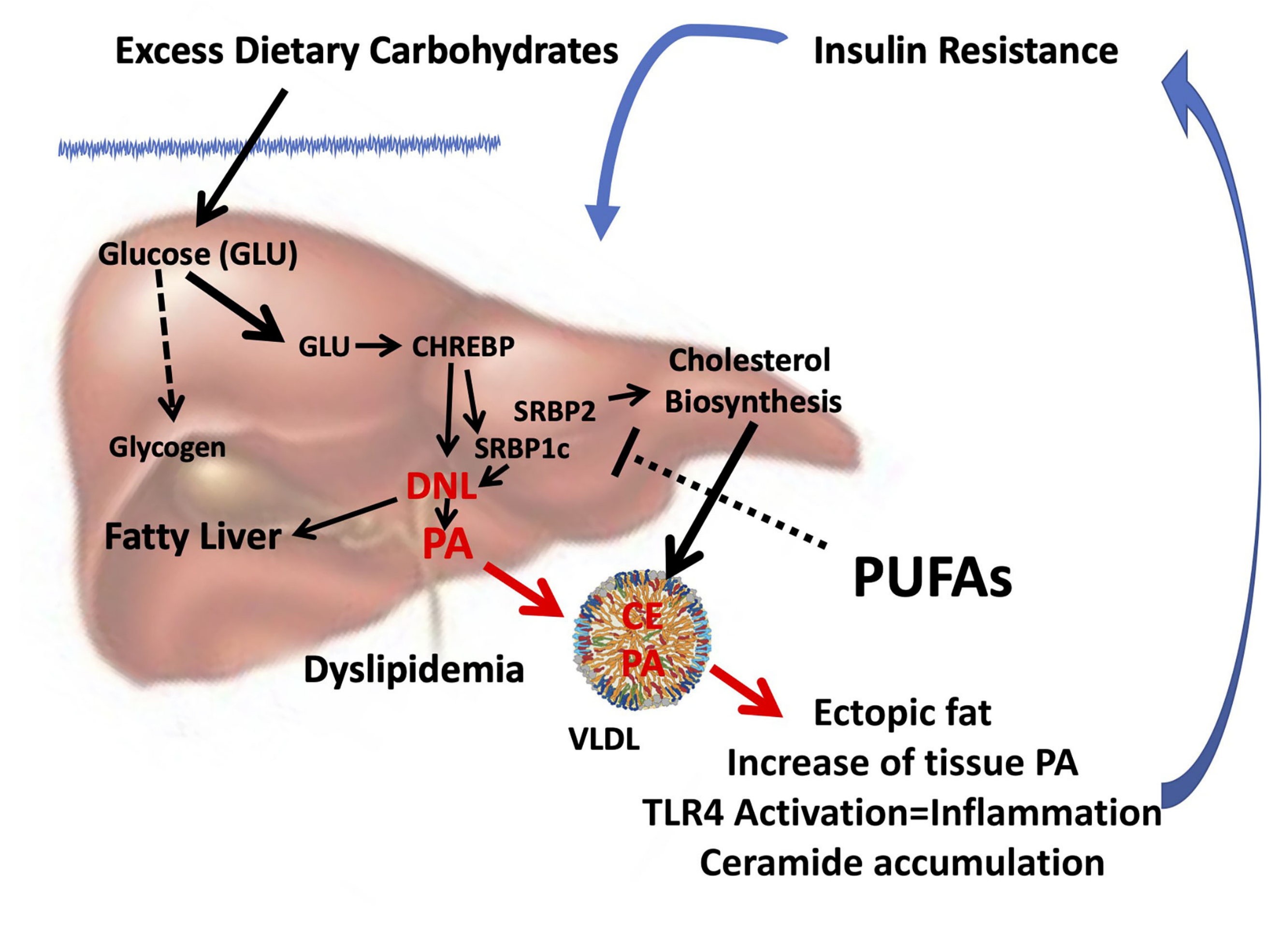

FIGURE 1 | Combined consequences of liver insulin resistance and reduced PUFA intake. Insulin resistance in the liver is characterized by hyperinsulinemia and a reduced ability to store glycogen. In the presence of excess glucose, CHREBP is activated which, in turn, together with hyperinsulinemia, induces SREBP1c, and synergistically induces DNL (124) and thereby the biosynthesis of endogenous PA. Reduced PUFA intake can further promote PA and cholesterol biosynthesis since PUFAs inhibit both SREBP1c (123) and SREBP2 (125). Enhanced DNL can cause fatty liver and formation and release of VLDL enriched with PA and cholesterol esters. As a result, the accumulation of ectopic fat occurs in different tissues, and the increase in tissue PA can sustain insulin resistance by inducing inflammation through the activation of TLR4 (105) and accumulation of ceramides (106), setting in motion a vicious circle. Because reduced PUFA intake is often associated with an unbalanced increase in dietary SFA/PUFA, the rise in tissue PA can be mistakenly attributed to its dietary intake. CHREBP, carbohydrate-responsive element-binding protein; SREBP, sterol regulatory element-binding protein; DNL, *de novo* lipogenesis; PA, palmitic acid; PUFA, polyunsaturated fatty acid; TLR4, toll-like receptor 4; SFA, saturated fatty acid.

incubating cells with extremely high concentrations and as a single FA without considering that dietary PA does not modify its tissue concentration, or with animal models of obesity with an extremely high-fat content not achievable by humans (128) and not specifically designed for studying dietary FA and thereby without any translatability to human conditions. More preclinical and clinical studies are needed to better discern the metabolic fate and interaction between dietary and *de novo* PA particularly in relation to PUFA intake, macronutrient balance, and pathophysiological states.

To blame a single nutrient, such as PA, widely present in our diet from several sources and with several well recognized fundamental physiological properties (129), as detrimental, suggesting that is sufficient to reduce its dietary intake for improving our health and prevent pathological states from CVD to cancer, is rather simplistic but it has a great praise probably because of the human nature to choose less time and energy consuming solutions for complex issues (130).

Thus, guidelines or recommendations to the general population to avoid or increase the intake of single nutrients, without considering the complexity of nutrient-nutrient interactions and the individual-specific nutritional response in relation to age, genetic, environmental, physiological and pathophysiological conditions, do not follow the amount of growing scientific data that suggest we should not be focusing on single nutrients but on increasing diet variability within a personalized nutritional approach.

AUTHOR CONTRIBUTIONS

EM, CM, GC, and SB: conception and design of the review, organized the literature search, wrote the first draft of the manuscript, and contributed to wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Extra-Oral Taste Receptors—Function, Disease, and Perspectives

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Taste perception is crucial for the critical evaluation of food constituents in human and other vertebrates. The five basic taste qualities salty, sour, sweet, umami (in humans mainly the taste of L-glutamic acid) and bitter provide important information on the energy content, the concentration of electrolytes and the presence of potentially harmful components in food items. Detection of the various taste stimuli is facilitated by specialized receptor proteins that are expressed in taste buds distributed on the tongue and the oral cavity. Whereas, salty and sour receptors represent ion channels, the receptors for sweet, umami and bitter belong to the G protein-coupled receptor superfamily. In particular, the G protein-coupled taste receptors have been located in a growing number of tissues outside the oral cavity, where they mediate important processes. This article will provide a brief introduction into the human taste perception, the corresponding receptive molecules and their signal transduction. Then, we will focus on taste receptors in the gastrointestinal tract, which participate in a variety of processes including the regulation of metabolic functions, hunger/satiety regulation as well as in digestion and pathogen defense reactions. These important non-gustatory functions suggest that complex selective forces have contributed to shape taste receptors during evolution.

Keywords: taste receptors, gastrointestinal tract, pathogen defense, nutrient sensing, metabolism and endocrinology

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INTRODUCTION

The concerted action of vision, olfaction, mechanoreception, and gustation enables humans to differentiate nutritionally valuable food items from inedible or even potentially harmful ones. The final gatekeeper is our sense of taste, which provides a rapid analysis of the relevant food-borne chemicals in the oral cavity prior to ingestion. To facilitate the detection of nutritionally relevant molecules among countless food constituents, the oral cavity is equipped with sensors for the five basic taste qualities salty, sour, sweet, umami (in humans mainly the taste of L-glutamic acid) and bitter (1). The sensing of table salt helps to maintain our body's electrolyte balance, sourness hints at the presence of unripe or spoiled food, sweet and umami tastes assess the energy content of food, and bitter sensing helps to avoid potentially harmful compounds (1). While taste sensing is limited to the sensory cells in the oral cavity, the detection of tastants by taste receptors continues throughout the alimentary canal as well as in other non-gustatory tissues. Among the extra-oral tissues expressing taste receptors, the airways have received considerable attention, because numerous cell types have been shown to respond to stimulation with tastants and the activation of these cells results in a wide range of profound physiological responses. The stimulation of solitary chemosensory cells in the respiratory epithelium of rodents with bitter compounds leads to respiratory depression (2–4) and elicits the discharge of antimicrobial peptides (5), the contact of ciliated lung cells increases their beat frequency (6) and bitter compound treatment of airway smooth muscle cells induces relaxation (7) making bitter compounds a relevant target for the treatment of asthma. These effects have been associated with the expression of the corresponding taste receptors in the various cell types. Other tissues shown to express taste receptors are the reproductive tract (8), urethra (9), skin (10–12), brain (13), heart (14, 15), pancreas (16, 17) and blood cells (18–22). For the sake of space, we will focus in this mini-review on the gastrointestinal (GI) tract and refer the interested reader to a number of comprehensive recent review articles for further reading (23–25). Before discussing the function of taste receptors in the GI tract, we will briefly introduce the receptors, their signaling elements and cells in their "original" environment, the taste system.

Taste Cells and Receptors

The cells devoted to detect food constituents occur combined into taste buds, which consist of about 100 cells, on the tongue, the soft palate and the throat (26). The taste information gathered in the oral cavity are transmitted to the brain, where complex percepts are formed and innate as well as learned behaviors are evoked that regulate food intake. On the molecular level, tastants interact with taste receptors expressed in the taste receptor cells of the taste buds. The ionic taste stimuli are detected by ion channels, with the proton-gating channel otop-1 serving as sour taste receptor (27–29) and the epithelial sodium channel ENaC acting as salt taste receptor (30, 31). While the identity of otop-1 is meanwhile firmly established, the exact composition of the salt sensor is still a matter of debate (32–34). The receptors for sweet, umami and bitter taste belong to the large superfamily of G protein-coupled receptors (GPCR). The 3 *TAS1R* (taste 1 receptor) genes code for heteromers that assemble the predominant umami taste receptor, TAS1R1/TAS1R3 (35, 36), the sweet taste receptor, TAS1R2/TAS1R3 (37–42), and exert long extracellular so-called venus flytrap domains typical for class C GPCRs. In contrast, the 25 putatively functional bitter taste receptors belong to the TAS2R (taste 2 receptor) gene family with short amino termini (43–45).

Upon activation of one of the taste-GPCRs a signaling cascade centered around the IP_3/Ca^{2+} second messenger system is initiated [for a review see (46)]. Briefly, depending on whether a sweet, umami, or bitter taste receptor cell is activated, a heterotrimeric G protein complex is recruited and, after GDP to GTP exchange, dissociates into the α-subunit and the βγ-heterodimer. The βγ-subunits in turn activate phospholipase Cβ2 resulting in the generation of IP_3 from the membrane-associated precursor PIP_2. Subsequently, the release of calcium ions from the lumen of the endoplasmatic reticulum via the receptor IP_3R3 is triggered. Next, the elevated level of cytosolic calcium ions opens the cation-channels TRPM4 and TRPM5, which allow the influx of sodium ions into the cell causing depolarization. Finally, voltage-gated sodium channels open and the neurotransmitter ATP is released through the voltage-gated channel calcium homeostasis modulator 1 and 3 complex resulting in the activation of puringergic afferent nerve fibers and signal propagation toward the central nervous system.

Tastant Reception in the GI Tract

Apart from its role in nutrient absorption, the GI tract is a site where nutrient sensing occurs and complex biological responses involving humoral and neural signals are triggered. The first hints that some of these responses may involve components of the taste transduction system came from the detection of α-gustducin, a Gα-subunit first identified in the rodent gustatory system (47), in brush cells of the stomach and small intestine (48). Nowadays, sweet, umami and bitter taste receptors and all canonical taste signaling components have been detected in GI tissues from stomach to colon (23–25). Moreover, a variety of GI cell types expressing the taste signaling molecules including enteroendocrine cells, brush cells, goblet cells, and Paneth cells have been discovered and nutrient sensing mechanisms involving taste-like signaling molecules were proposed (23–25).

Sweet, Umami and Bitter Sensing in the GI Tract

Already the observation that the taste-related signaling molecule α-gustducin is expressed in brush cells of the GI tract raised the question if also other components involved in taste sensation might play a role in nutrient sensing in the alimentary canal. Indeed, over the past two decades all canonical taste signaling elements including the G protein-coupled receptors for sweet, umami and bitter detection have been identified in the GI tract of vertebrates. Moreover, a number of physiological functions of taste GPCR-mediated signaling have emerged. Here, we will point out only some key aspects of GI taste signaling, the interested reader is referred to one of the recent full-length review articles (24, 25).

Taste Receptor-Expressing Cell Types

Although a larger number of cell types have been implicated in taste receptor-mediated signaling, two types of cells stand out because of their central role(s) and frequent implications in taste-related signaling events (**Figure 1**). The first cell type are the brush cells, which are frequently also named tuft cells or solitary chemosensory cells. These cells occur throughout the alimentary tract as individual cells, which are equipped with an apical tuft of microvilli [for a review see (50)]. They were shown to express sweet, umami and bitter taste receptors [but cf. (51)] as well as canonical taste signaling elements such as α-gustducin, PLCβ2, TRPM5 (52). It is believed that brush cells are capable to signal their activation via the transmitter acetylcholine in a paracrine fashion (53). The second cell type are so-called enteroendocrine cells, which can be further subdivided depending on the peptide hormones they secrete upon activation. Also the enteroendocrine cells were identified to express the already mentioned taste-GPCRs for sweet, umami and bitter sensing and the canonical taste-signaling elements. Stimulation of enteroendocrine cells results in the release of important peptide hormones involved in metabolic regulation, such as GLP-1 from enteroendocrine

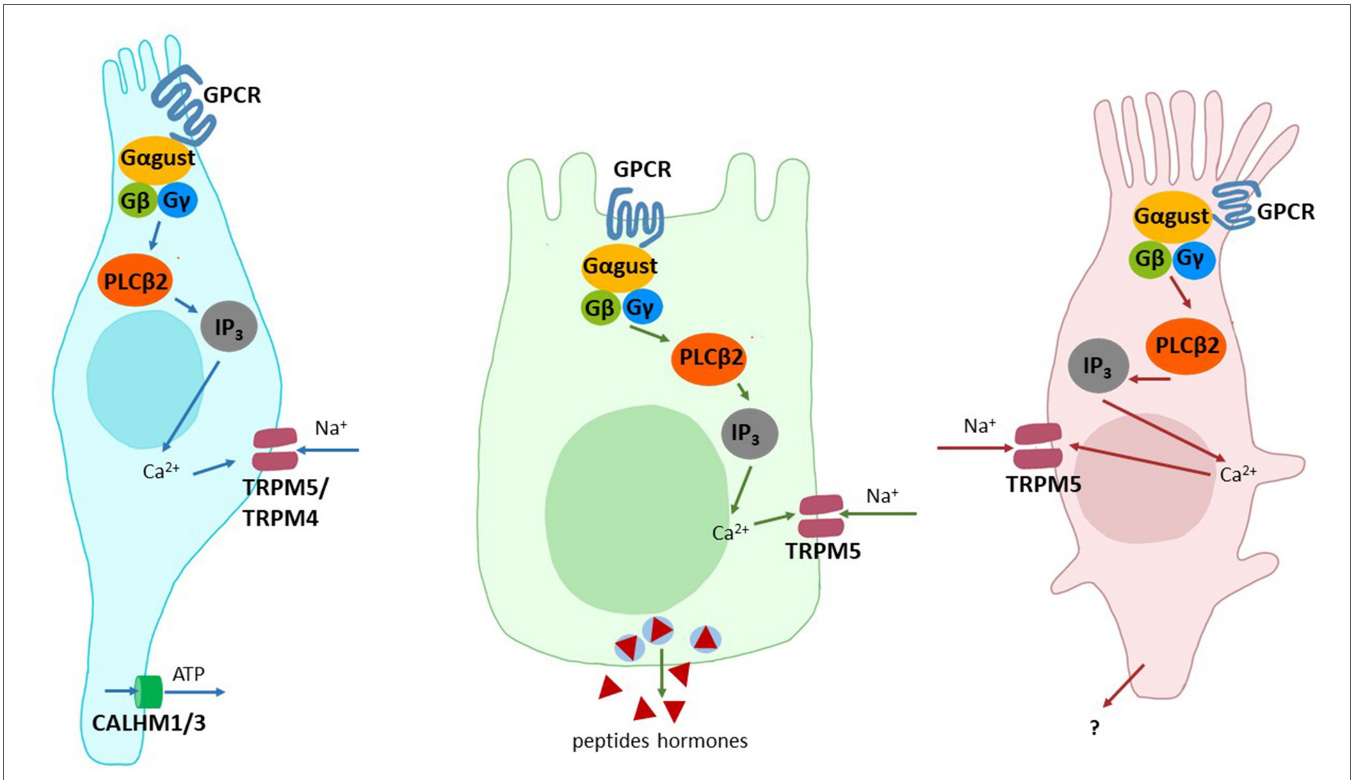

FIGURE 1 | Cell types involved in the detection of taste stimuli. Shown are schematic drawings of type II taste receptor cells (left), enteroendocrine cells of the GI tract (middle) and brush cells (right). The signal components involved/implied in signal transduction are depicted: Adenosine triphosphate (ATP), calcium ions (Ca^{2+}), Calcium homeostasis modulator 1 and 3 (CALHM1/3), G protein-coupled receptor (GPCR), G protein alpha subunit α-gustducin (Gαgust), G protein beta subunit (Gβ), G protein gamma subunit (Gγ), Inositol 1,4,5-trisphosphate (IP_3), Phospholipase C beta 2 (PLCβ2), sodium ions (Na^+), transient receptor potential cation channel subfamily M members 4 and 5 (TRPM5/4).

L cells, GIP from K cells, hunger-satiety regulation, such as ghrelin from P or X cells to name just a few [for a review see (54)]. Other, less well investigated cell types implicated in tastant-induced signaling in the GI tract include enterocytes (55), Paneth (56) and goblet cells (20). It is important to emphasize that the expression of sweet, umami and bitter taste receptors in a given cell type does not imply that individual cells actually house all three taste receptor types. While some cell lines of enteroendocrine origin may indeed contain taste receptors for multiple taste modalities, *in vivo* data on the co-expression does not exist to date.

Tastant-Induced Functions in the GI Tract

Quite a number of physiological roles have been assigned to taste receptor-mediated signaling in the GI tract. However, not all physiological responses triggered by tastants must occur via the activation of taste receptors, in fact, in many cases where taste receptors are implicated in GI tastant sensing additional research is warranted. Among the best investigated processes elicited by tastants in the GI tract are peptide hormone secretions from various enteroendocrine cell types. One of these hormones is the incretin hormone GLP-1 (glucagon-like peptide-1) which is produced by enteroendocrine L cells. The cells express both TAS1R subunits, namely TAS1R2 and TAS1R3, constituting the functional sweet taste receptor as well as the canonical taste signaling elements. Challenging the cells with sweet compounds results in the acute release of GLP-1 and the subsequent insulin secretion from pancreatic beta-cells leading to a reduction of blood sugar levels and, in case of chronic stimulation, an elevated absorptive capacity of intestinal enterocytes via the upregulation of the transport molecule SGLT-1 (57, 58). Also bitter compounds, such as KDT-501, a synthetic derivative of hop bitter compounds, have been shown to result in elevated GLP-1 levels in the blood of mice (59). Whether this implies co-expression of sweet and bitter taste receptors in L cells or suggests the existence of specialized subpopulations of sweet and bitter responsive L cells is unknown. Further effects of GI bitter stimulation on hormone secretions are the release of CCK (cholecystokinin) from I cells and a subsequent delayed gastric emptying and conditioned taste aversion (60, 61). Interestingly, bitter tastant-responsive X/A-like cells in the stomach also facilitate the release of the hunger-inducing peptide hormone ghrelin (62), a fact which appears counterintuitive on the first glance with the above reported CCK-effects. Not all presumably taste receptor-mediated GI effects involve necessary hormonal signaling events. It was shown that the bitter compound caffeine regulates via bitter taste receptors acid secretion in the human stomach (63) and in the colon of rodents an increased fluid

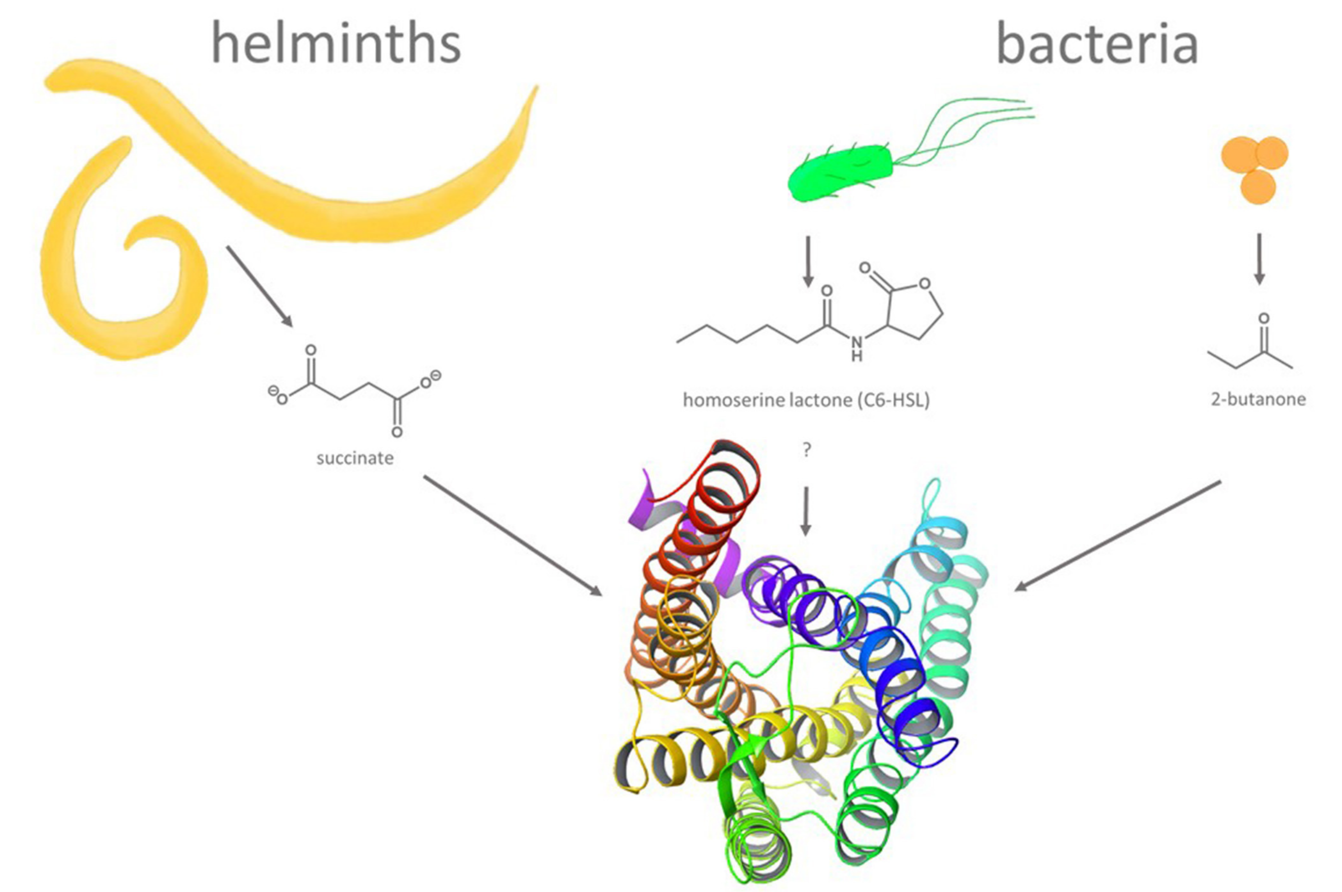

FIGURE 2 | Molecules and organisms implicated in triggering GPCR-mediated defense reactions in non-gustatory epithelia. Gastrointestinal infections with succinate secreting helminths and bacteria secreting quorum-sensing molecules (homoserine lactones, e.g., C6-HSL) or metabolites (e.g., 2-butanone) are believed to result in the activation of GPCRs including bitter taste receptors. A ribbon structure (seen from the top) of a homology model of human bitter taste receptor TAS2R14 [derived from (49), modified with Maestro 12.9 software (Schrodinger)], one of the TAS2Rs implicated in innate immune responses, is depicted at the bottom.

secretion into the lumen (64). Moreover, the modulation of the intestinal motility via the interaction of selective bitter substances with bitter taste receptors in intestinal smooth muscle cells has been reported (65).

Compared to enteroendocrine cells, intestinal brush cells seems to play a very different role, the defense of pathogenic organisms (66–68) (**Figure 2**). In fact, even though brush cells have been demonstrated to express all elements required for taste-GPCR signal transduction, albeit with some deviations from the canonical type II taste cell pathway (52), the taste receptors themselves were not detected in all studies [cf. (51)]. Nevertheless, brush cells respond to helminth and protist infections as well as to bacterial dysbiosis [for a review see (69)] and may indeed rely on the activation of bitter taste receptors (70). A central role in the pathogen response against these intestinal intruders was demonstrated for SUCNR1 (71, 72), a succinate-sensing GPCR (also known as GPR91) (73). Indeed, succinate is released by various pathogens [e.g., protozoa (72)] triggering IL-25 discharge from brush cells (72) in an α-gustducin- and TRPM5-dependent fashion (71) and a subsequent activation of group 2 innate lymphoid cells to promote pathogen removal (74). As succinic acid has been associated with a umami-like orosensory perception (75, 76), this process could be judged to represent an activity by a tastant-like substance. Although the majority of tastant or tastant-like molecules triggering important physiological responses in the GI tract have been associated with enteroendocrine or brush cells, other bitter taste receptor expressing cell types such as Paneth cells (56) or goblet cells (20) were shown recently to play critical roles in innate immune responses as well (77).

DISCUSSION

After the discovery of taste receptors outside the oral cavity, the research field of extra-oral taste receptors practically exploded. Taste receptors were found in an increasing number of tissues and were associated with numerous roles. Whereas, some of the most optimistic appraisals had to be corrected, other proposed opportunities solidified over the years resulting in realistic research goals such as the use of bitter compounds as asthma medication or compounds to improve metabolic functions.

One research gap that exists since the discovery of non-gustatory taste receptors and the subsequent investigations of their physiological roles is the firm association of taste stimuli with specific cellular functions and the unambiguous involvement of the corresponding taste receptors in this process. Moreover, many observations of physiological effects in tastant-responsive GI cells were rather broadly assigned to specific cell types, which may underestimate diversity with regard to taste receptor expression and function. Another gap comes from the observation that a large number of animals exhibit taste receptor pseudogenizations, which usually correlates well with their nutrition, however, it has so far not been investigated how these animals compensate for the loss of those receptors and their function in extra-oral tissues.

In summary, research on taste receptor functions outside the gustatory system has become a topic of great interest with future prospects ranging from more healthy nutrition to even using tastants and/or their derivatives for medicinal treatments.

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PERSPECTIVE
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A Need for a Paradigm Shift in Healthy Nutrition Research

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Research in the field of sustainable and healthy nutrition is calling for the application of the latest advances in seemingly unrelated domains such as complex systems and network sciences on the one hand and big data and artificial intelligence on the other. This is because the confluence of these fields, whose methodologies have experienced explosive growth in the last few years, promises to solve some of the more challenging problems in sustainable and healthy nutrition, i.e., integrating food and behavioral-based dietary guidelines. Focusing here primarily on nutrition and health, we discuss what kind of methodological shift is needed to open current disciplinary borders to the methods, languages, and knowledge of the digital era and a system thinking approach. Specifically, we advocate for the adoption of interdisciplinary, complex-systems-based research to tackle the huge challenge of dealing with an evolving interdependent system in which there are multiple scales—from the metabolome to the population level—, heterogeneous and—more often than not— incomplete data, and population changes subject to many behavioral and environmental pressures. To illustrate the importance of this methodological innovation we focus on the consumption aspects of nutrition rather than production, but we recognize the importance of system-wide studies that involve both these components of nutrition. We round off the paper by outlining some specific research directions that would make it possible to find new correlations and, possibly, causal relationships across scales and to answer pressing questions in the area of sustainable and healthy nutrition.

Keywords: nutrition, complex systems, digitalization, data science, health

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COMPLEX INTERACTIONS AND CONFOUNDING FACTORS

Nutritional science is largely based on observational evidence that is often subject to many confounding factors. Traditionally, analytical epidemiology, and especially cohort studies, have relied on exploring multiple time- and exposure-related associations, while having fundamental shortcomings when it comes to proving causation. This approach seeks to link nutrients and other substances in food with individuals' health and disease. Methodologically, subjects are selected at random from a population, categorized according to their exposure (for instance, dietary habits, known confounding factors, etc.), and their health status monitored over time. This "follow the individual" approach presents many known methodological problems associated with time, cost, the internal and external validity of the sample, uncertainty of exposure, and individual variability in physiological response. On top of these problems, nutrition research needs to tackle the challenge of combining with diets and health entirely new sets of highly variable biological and non-biological covariates, such as intestinal microbiota at the molecular scale and behavioral contagion at the population level. The large concomitant uncertainties affect how scientists and health authorities define and interpret recommendations and guidelines and how the industry is consequently pushed toward innovation and reformulation. This, in turn, influences the food system in terms of food quality, availability and preferences, possibly resulting in further biological and behavioral changes. It also affects the entire food production systems, whose economic and environmental impacts have been largely considered in separate disciplines. As an historical example of loss function (the cost of being wrong), we should remember how the cholesterol-saturated fat hypothesis, endorsed by health authorities worldwide during the mid-1990s, led to the widespread introduction from the 1960s through the 1980s of hydrogenated fats as a healthy vegetable substitute for butter, and compare it to the current efforts to remove trans fats from the food system (1, 2).

MAKING SENSE OF BIG DATA

We believe that the aforementioned methodological shortcomings and challenges represent an opportunity for a paradigm shift of increased application of techniques borrowed from other fields of science, particularly, from complexity science and artificial intelligence (AI). Certainly, unraveling causal relationships between nutrients, food ingredients, human health and disease implies the study of the "emergent" features generated by the complex, non-linear, multi-scale, and multi-level interactions and correlations among the several agents that make up such an interdependent system. A complexity-based approach places the focus on the connections among the components of the system, rather than on the single elements and looks for properties emerging from such associations. **Figure 1** illustrates the proposed methodology. It schematically represents three scales of interactions: nutrients and chemicals, food raw materials, and finally the socio-cultural component of populations exemplified by diets, daily intake, and recipes. The mathematical tool that encodes and describes the interlinked relationships is a graph, which captures pairwise and other higher-order interactions, including situations in which the connections among the system components are best represented by a network of networks, namely, a multilayer network like the one depicted in **Figure 1** (3). With these tools, it is possible to capture some of the non-trivial health impacts that food pairings might have, such as the pairing of red meat and garlic in the Mediterranean diet (4). Other higher-order systems, such as simplicial complexes, might be also used to capture further properties of these pairings as the changes produced during cooking, the non-trivial interactions among chemical compounds or their bioavailability. The proposed approach is also particularly suited to capture social covariates. Admittedly, at variance with communicable diseases, non-communicable diseases can spread by social influence, that is, there is mounting evidence that the prevalence of food-related diseases like obesity correlates with social habits, physical activity, behavioral factors, and the composition of an individual social circle (5–7). This needs to be incorporated in more traditional longitudinal analyses, where social factors are either disregarded or not methodologically formalized, with the result of inconsistencies across studies.

The advent of the digital era has revolutionized almost all fields of science, currently providing in a single year more data than what has been generated up to that moment by humankind. Nutrition is no exception, and the genomic era is uncovering an increasingly large number of metabolic networks of nutritional interest as well as an unprecedented quantity of data concerning the impact of nutrition on human health. Data on agriculture, food production and environmental impacts are also increasingly becoming available at global and local levels, providing unique opportunities to explore the complex interactions between a global production system, land use and deforestation, climate change, and local to global environmental impacts on humans and ecosystems. However, access to data is only the tip of the iceberg. There are many new challenges as we now need to be able to understand, interpret, and use this huge amount of data, both already available and to come. This is a task that can be successfully completed only by developing systems-based methodologies and artificial intelligence methods that fully enable cross-disciplinary integrative approaches and transform data into information and knowledge. A primary example of this systems-based approach is the creation of ontologies that connect knowledge across different disciplines related to nutrition research such as the Ontology for Nutritional Studies (ONS) (8). Additionally, big data analysis and artificial intelligence techniques can contribute to trace back behavioral traits in chemical consumption, including cross-comparison among geographical zones, inequality, income, historical, and other social determinants (9).

The combination of the methods and techniques from complex systems and artificial intelligence will enable the analysis of groups and clusters built across a large number of independent sets of data related to a large number of individuals—treated as a single multi-component ecological niche—to draw a picture able to explain the most likely interactions occurring in a country or continent-wide population. In other words, the possibility of linking nutrients to food to diet to health would allow for an "ecological" approach that could identify multiple relationships given by different aspects of the biological and social human environment out of the boundaries set for individual associations (10). These approaches also offer the possibilities to relate the nutritional effects of food consumption with the food production system, to also apprehend the socio-economic and environmental impacts of nutritional choices. This is key to understanding synergies and trade-offs, to then select or promote

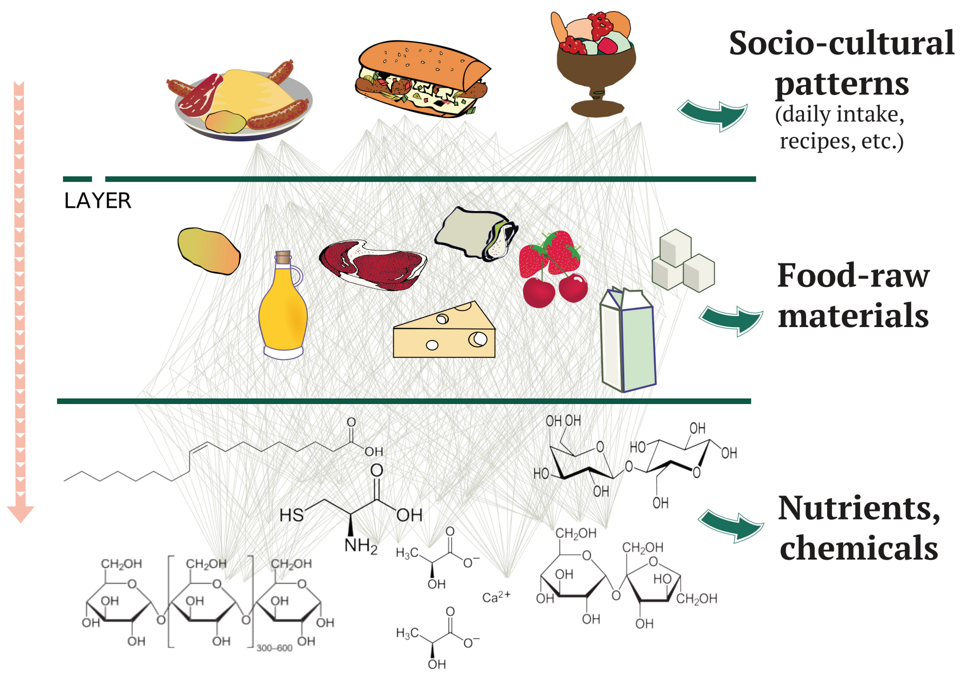

FIGURE 1 | Multilayer schematic representation of the interactions that are involved at three different complexity levels. These interactions link together food composition and socio-cultural covariates. Each layer is represented as a network of interactions among the components at that scale.

dietary changes and adapt the production system in ways that are beneficial for both human health and the environment. However, there are many difficulties inherent to following the proposed research methodology, ranging from the very existence of the data needed, to technical difficulties when it comes to glue together the different networks of interactions and their interdependencies. In what follows, we briefly describe in more detail two of these challenges.

NEED FOR A DATA STANDARD

One key step is to characterize the exposure to the food system. To this end, the first and most pressing challenge is to obtain compositional data, which provide the building blocks of the interactions-based approach. In an ideal world, we should know in detail the chemical (nutrient and bioactive) composition of all foods and beverages that are available to consumers. The ingredients used for food preparation, additional characteristics such as energy density, sensorial attributes, type of processing, modes of production, trade patterns, and their socio-economic and environmental impacts (e.g., 247 indicators across 17 sustainable development goals), must also be known to draw a comprehensive picture of the existing food system. This might be explored through a detailed collection of data related to the existing food supply over a given space and time, taking advantage as much as possible of actual records provided by food producers, processors, and retailers. Nonetheless, one must be aware of the potential problems of the existing data. Classical, targeted analyses that look for a single or few compounds can be fooled and provide biased estimates of food composition (such as the substitution of protein by melamine in adulterated foods) or miss important chemical compounds that were not screened. Non-targeted analyses can alleviate some of these problems and have shown promising results in the detection of food fraud, but still cannot provide reliable enough quantitative estimates (11, 12). Furthermore, the analysis of real data availability reveals a situation that is far from the ideal scenario. Indeed, despite many efforts to gather, mine, and curate data, it is not homogeneous and often, it is noisy and incomplete. Several EU and US initiatives have tried to remedy this, such as EuroFIR, USDA or INFOODS, so far with a diverse degree of success (13, 14).

To exemplify the current problems associated with the quantity and quality of data for nutritional studies, we use as a typical case a common ingredient of the European—and particularly, Mediterranean—diet, namely, olive oil. The advantages of olive oil used to be attributed to its high oleic content, but nowadays it has been established that the small molecules composing the unsaponifiable fraction (representing 1–2% of the total oil weight) are also associated with beneficial health effects (15–17). However, olive oil composition is highly variable and depends on many genetic, environmental, and technological factors (18–21). This impacts both the fatty acid and unsaponifiable fraction compositions. For instance, in the case of fatty acids, cooler regions yield higher oleic acid than warmer climates. As such, the international olive oil council (IOOC) establishes wide ranges for its purity guidelines, with pure olive oil being composed of 55%−83% oleic acid (22).

Data incompleteness is also hampering progress in at least two ways, e.g., by yielding misleading results or unsubstantiated correlations (23, 24). A traditional nutritional approach would first reduce foodstuff to its main nutritional components using food composition databases. This is followed by monitoring nutrient intake by individuals, which is eventually linked statistically to outcomes, i.e., actual disease or, more often, markers of disease. This procedure however disregards non-trivial interactions that might arise between different food elements and neglects the effects of any chemical component not contained in the database. For instance, meta-analyses on the effect of monounsaturated fatty acids (MUFA) on coronary heart disease can yield inconsistent results if the source of the fat is not considered (25). Yet, if the source of MUFA is properly accounted for, it is observed that when it is of vegetable origin, the benefits are larger. As such, rather than promoting a low-fat intake, healthier sources of fat should be encouraged (26, 27). This implies that, either the specific chemical composition of those fatty acids, or other components that are contained in those products, can be partially responsible for the observed health effects. In other words, the whole complexity of food composition should be considered. This is nonetheless hardly achievable using currently available food composition databases. A review of the food composition tables of 74 countries looking for olive oil composition revealed that the information reported is usually scarce and inconsistent (**Figure 2**). Besides, several countries do not provide any information on olive oil, especially in countries in which this ingredient is uncommon. Interestingly, several databases report the presence of trans-unsaturated fatty acids, which should not be present in pure olive oil and can be associated with fraud and adulteration of the oil (22, 28). Furthermore, compounds not directly linked to nutrition are not reported. In addition, and of particular relevance is the fact that more general databases such as FooDB [one of the largest and most comprehensive resource on food constituents (29)] also show deep knowledge gaps in relation to the chemical composition of vegetable oils. For instance, of almost 6,000 chemical compounds associated with each oil crop from which oil is commonly extracted, roughly 100 are quantified, while the rest are "expected but not quantified" —which some authors refer to as nutritional dark-matter (4). Of those, <50 are tagged as associated with the oil. The others are associated with the raw element. This characterization is even worse in the case of palm and rapeseed oils, see **Figure 3**. The reason is that these products are mainly consumed in oil form and, thus, there are not many chemical compounds associated with their raw form in the database.

The preceding analysis clearly shows the need of increasing the quality and availability of food chemical composition data. Otherwise, the serious lack of data about the chemical composition of food raw material—here shown for vegetable oils—would make it hard to arrive to meaningful causal associations between such food and individuals' health and disease or to even compare benefits and inconveniences of different kinds of a given food material (e.g., vegetable oils). And, even if the composition was perfectly known, it would still be challenging to properly determine the effects of non-trivial interactions among chemical compounds, since as in any complex system the total is not just the addition of its parts. Another sensitive part of the data needed for nutritional studies is the variability associated with intake estimations. This is an area in which improving the techniques used to analyze nutrient intake is pressing and challenging but could capitalize on the proposed roadmap. The exposure assessment includes the amount of food eaten, but also meal occasions, hours of the day when meals are consumed, and other meal-related characteristics. This is a multidimensional problem as the actual human exposure to the food system strongly depends on exogenous factors such as individual economic capacity—workload and ability for accessing food stores and shops, food cost, etc.—, market share of different products, socio-cultural and geographical factors—local gastronomic habits linked to tradition and heritage—and, increasingly important, behavioral contagion and social pressure to adopt dietary habits—including traditional and social media, food labeling rules, ethical or religious constraints, etc. It is worth mentioning at this point that the same sort of difficulties arises when defining relations among nutrition and health status. Indeed, health is a multifactorial derivative that varies among individuals, time and location according to many metabolic, environmental and behavioral characteristics. Similarly, the production system, and its economic and environmental impacts over the entire local to global production supply chain would need to be much better characterized, with standardized data collection including food losses and combined with nutritional composition (30, 31). Therefore, providing recommendations to a global population about healthy diets from food systems regardless of cultural and behavioral covariates is a pressing issue whose satisfactory solution can only be obtained using a system-wide analysis. This is the second challenge that we discuss in more detail next.

REVEALING INTERDEPENDENCIES AND CORRELATIONS IN FOOD CONSUMPTION

To illustrate the hardships to be faced in the field of healthy nutrition, let us discuss one of the conclusions of the EAT-Lancet commission (32), namely, to have legumes as the main source of proteins, while red meat consumption should be minimal. Whereas data on risk of low intakes of red meat are imprecise, a diet low in legumes has been associated with a higher mortality rate (33). However, dietary recommendations for individual food items are often based on individual studies, without being supported by a comprehensive understanding of the interaction between foods and without fully accounting for the effects of substituted foods. It is therefore risky to translate independent observations into recommendations without further analysis. A complex system-wide perspective would reveal hidden correlations which in turn depend on multiple confounding factors such as cultural habits and tradition. Take as an example

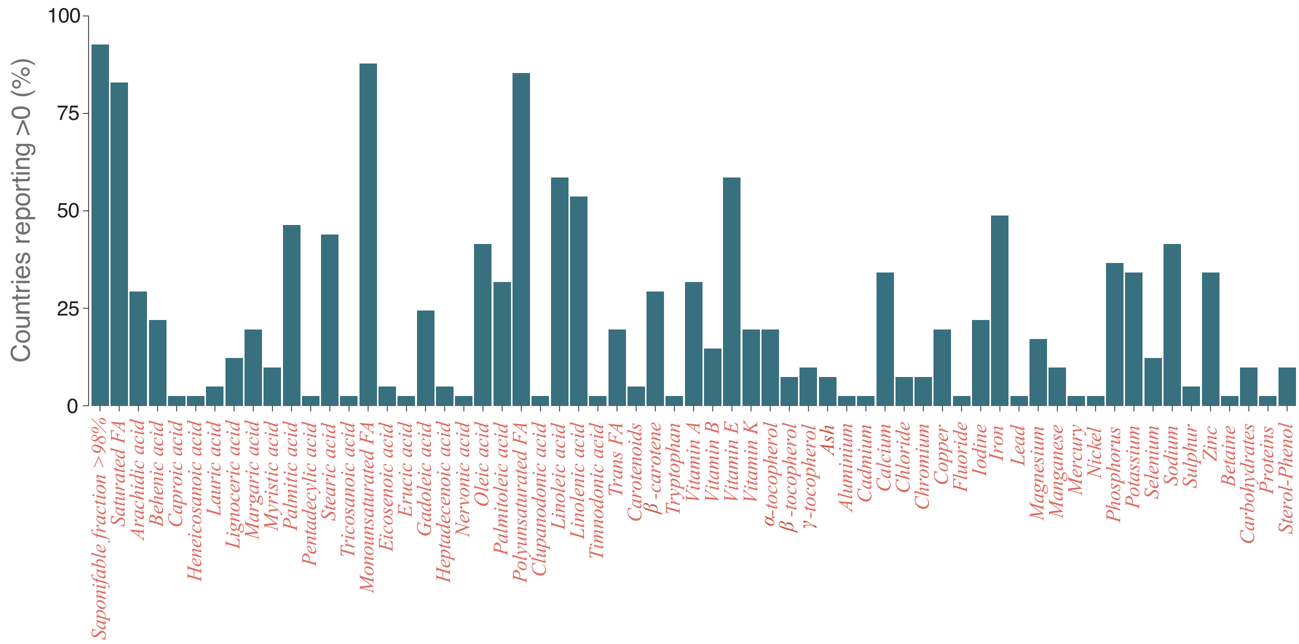

FIGURE 2 | Percentage of countries whose food composition table quantifies each chemical compound for olive oil. We include as a quantified chemical those with an estimated quantity larger than 0, regardless of the specific amount or units shown in the database.

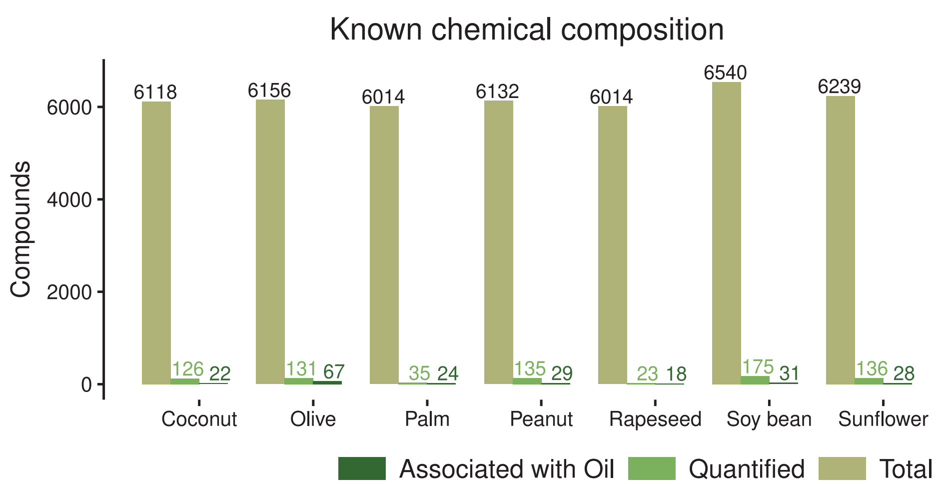

FIGURE 3 | The number of chemical compounds associated with each source of vegetable oil in FooDB as of April 2020. From the total number of chemicals associated with each crop, the large majority are "expected [to be present] but not quantified". The others can be associated with the ingredient in its raw form or in its oil. Most quantified compounds are associated with the raw product, and only a tiny fraction is explicitly associated with the oil. Note that for palm and rapeseed the amount of chemicals associated with the oil is almost the same as the quantified fraction, likely because these products are mostly consumed in their oil form.

the consumption of beans, chickpeas and lentils in Western and Northern Europe in comparison to other regions of the continent with data from 2018 (34), see **Figure 4A**. This simple analysis already reveals important sociocultural differences that could undermine the success of the aforementioned recommendation by the EAT-Lancet commission. On the other hand, food raw materials are usually paired together (see **Figure 1**), therefore, the proposed solution might not be as simple as it appears. Although intake questionnaires have the potential to consider the pairing of multiple food products, these are rarely considered comprehensively when analyzing their relation to health.

For illustrative purposes, we have chosen a longitudinal set of recipe sources that, even though they cannot be directly employed as proxies of the actual recipes used by the population, at least they might let us uncover some patterns. In particular, we have first selected four recipe books containing traditional

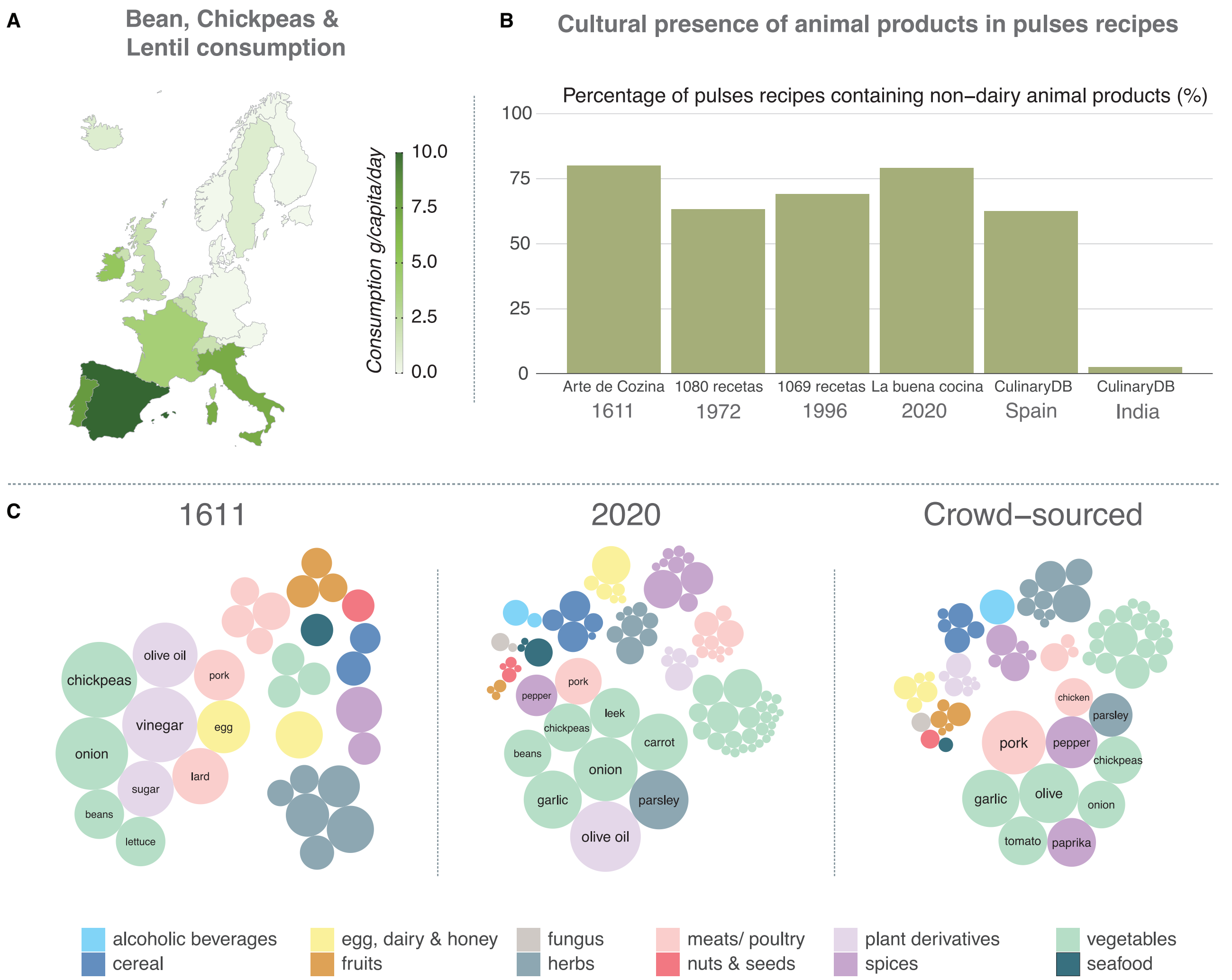

FIGURE 4 | A complex systems view of food consumption. **(A)** shows a comparison of the intake of legumes in Southern, Western and Northern Europe, which reveals the role of sociocultural factors. Looking at the ingredients that are commonly paired with these legumes in Spanish cuisine, one finds that this consumption is heavily related to the consumption of non-dairy animal products, although this is not true for the Indian cuisine sample **(B)**. In **(C)**, each circle represents a single ingredient used in at least one recipe containing beans, chickpeas or lentils. The size of the circle is proportional to the number of recipes containing the ingredient and the color the group they belong to. In all cases only the top 10 ingredients are labeled.

Spanish food. The first one is "Arte de Cozina," a book published in 1611, which stands out by not having any references to (nowadays) common foodstuffs coming from America, such as tomatoes or potatoes. The second is "1080 recetas", published in 1972 by Simone Ortega, whose French origin influenced many recipes in the book. Nonetheless, her book is still being reedited today and has sold over 3 million copies, and thus its influence on the recipes commonly cooked in Spanish households might be important. Lastly, we have selected two books written by Karlos Arguiñano, a famous Spanish chef who has hosted a cooking show on TV for more than 30 years and published more than 40 recipe books. As we can see in **Figure 4B**, in all these cases the percentage of pulses recipes containing non-dairy animal products is larger than 60%, reaching even 75% in the last book considered. Interestingly, the distribution is fairly constant throughout the books, signaling that, indeed, pairing animal products with legumes can be considered part of Spanish food culture. We have further explored an online database of parsed recipes extracted from several websites, CulinaryDB (35). Even though crowd-sourced recipes, such as the ones found online, can have many biases, we once again find a strong association between legumes and animal products in Spanish cuisine. On the other hand, if we look at recipes from India obtained in the same database, we find that this association is not present at all (**Figure 4B**).

Lastly, we explore the composition of recipes containing the aforementioned legumes in the recipes appearing in the book published in 1611, the one published in 2020 and online (**Figure 4C**). The first observation is that the number of ingredients increases significantly over time. It is also interesting to note how vinegar and lard disappear from modern cuisine. In particular, lard can only be found in one recipe over the whole set of recipes in the book from 2020, while it played a relevant role in 1611. This contrasts with central European countries in which animal fat is still one of the main sources of fat (36). On the other extreme, and related to the problems that we described previously in regard to quality and heterogeneity of data sources, we can see that recipes obtained from crowd-sourced data also differ from the ones found in printed sources. Olive oil, which is central to Spanish cuisine, does not appear in the online database and is substituted by the ingredient olive (**Figure 4C**). This reflects another challenge of analyzing large amounts of information, namely, disambiguating the terminology. Raw olives have many different properties, for example as a source of bioactives or as a ratio bioactive/fat, and are consumed in completely different recipes than their oil, and yet during the data cleaning process one might decide to consider them to be the same. A similar problem might appear in other foodstuffs, especially when they are regional or just a seemingly slight variation of the raw product.

The previous analyses, though simple, demonstrate the complexity behind cultural habits and their relation to nutrition. Given the emerging overall picture coming out from the above examples, it becomes clear that shifting from traditional diets to new, more sustainable diets is not straightforward. Finding and handling the proper data on food pairing and consumption in the population is key, but it does not represent the only open challenge. Accessing health data at a population level is relatively simple for diseases that are uniformly classified and registered. However, it remains difficult to identify disease risk factors, especially the metabolic ones, based on freely accessible data, even more when the evidence of causal associations between food consumption and health markers is not conclusive. The linkage between health, food consumption and other databases (e.g., personal care product consumption) at the individual level is also crucial for developing precision nutrition (37), studying multiple interactions and establishing causation, but are rarely available or allowed due to data protection. Finally, it is worth mentioning that an ecological approach could also be beneficial in terms of exploiting heterogeneities and differences of the populations, which might help expand the ability to identify associations. We hope that adopting a holistic perspective will increase our chances to move toward more healthy diets.

CHARACTERIZING CAUSATION

Before concluding, we also stress that an important issue and a crucial ingredient for the paradigm shift described here is to characterize causation, which should be of fundamental priority. Even intuitively, causation requires not just correlation, but counterfactual dependence. Therefore, it can only be inferred with some probability, never exactly known. However, a large part of the literature on data analytics, including that related to nutrition, is based on the principle that one can legitimately deduce a cause-effect relationship between two events solely based on an observed mutual correlation between them. In most cases, the latter does not hold. Thus, a paradigm shift on policy regarding the way we draw conclusions that lead to recommendations on healthy nutrition is also required. To this end, one can capitalize on statistical methods for data experiments that approximate at best the counterfactual state of the system. In particular, Bayesian statistics, based as it is on the Bayesian interpretation/expression of probability as a "degree of belief" in the happening of an event, may come to the rescue. The Bayesian method is grounded in Bayes' theorem, which describes the probability of an event based on prior knowledge in terms of conditional probabilities, so as to be able to compute and update probabilities after acquiring new data. This is not an easy task, as the formulation of mathematical models in terms of Bayesian statistics requires the specification a priori of probability distributions for the model parameters. Moreover, as the parameters of prior distributions may themselves have prior distributions, one has indeed a hierarchy, a network of Bayesian models. On the other hand, finding correlations does not make forecasting easier. Indeed, when forecasts are at stake, it is the Granger approach that enters the game. Granger's causality test aims at determining whether a given time series is useful in forecasting another. While ordinarily regressions reflect mere correlations, Granger's method assumes that causality may be tested for by measuring the ensuing ability to predict the future values of a dataset from the prior. Of course, what Granger test finds—and efficiently—is predictive causality, not true causality, as it identifies the cause-effect relations only as conserved co-occurrence. Furthermore, it can lead to wrong conclusions if confounding factors are uncontrolled, something that is especially hard to do—or even impossible—in any observational study. Rigorously, inference is instead essentially inductive reasoning, and a priori we should accept our inability to legitimately deduce a complete cause-effect relationship: that's why assuming that correlation implies causation is a logical fallacy. All of this is a severe collection of constraints on the quality, homogeneity and reliability of the datasets utilized. Notwithstanding, these statistical techniques can be complemented, or even superseded in some cases, by omics approaches and more direct, experimental techniques such as the ones based on biomarkers (38).

In summary, we believe that it is becoming apparent that existing guidelines and parameters defining healthy nutrition are not producing the desired results given the ever-increasing prevalence of food-related non-communicable diseases such as diabetes and obesity. There could be many reasons for this failure, including that recommendations are not backed up by data and the limitations inherent to the traditional approaches. This calls for the need to change the prevalent methodological approach. Here, we have discussed through a few examples, what new insights can be gained with such a toolbox. Our analyses suggest a roadmap that should include at least two areas of work: (i) the need to gather, mine and curate better food composition data, because with the current data we cannot go from specific to general recommendations—as of now, it is even impossible to have unique chemical composition of common foodstuff—, and (ii) the need of adopting radically new points of view and methodologies that account for many existing interdependencies in chemicals, nutrients and foods and their total and relative intake so as to advance in our quest to find new correlations and causation and in the redefinition of the parameters of healthy and sustainable nutrition. While we focused here on the consumption aspects of nutrition, we recognize that the sustainability of production is an additional societal concern, analysis of which ultimately needs to be incorporated in complete food chains. We believe that the foundations of such a roadmap is at the crossroad of Big Data, Artificial Intelligence and Complex Systems sciences.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

YM and AA wrote the first draft of the manuscript. FB, OJ, EM, RS, and MR wrote sections of the manuscript. All authors contributed to conception and design of the study. All authors contributed to manuscript revision, read, and approved the submitted version.

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Dietary Fats, Human Nutrition and the Environment: Balance and Sustainability

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Dietary fats are essential ingredients of a healthy diet. Their production, however, impacts the environment and its capacity to sustain us. Growing knowledge across multiple disciplines improves our understanding of links between food, health and sustainability, but increases apparent complexity. Whereas past dietary guidelines placed limits on total fat intake especially saturated fats, recent studies indicate more complex links with health. Guidelines differ between regions of general poverty and malnutrition and those where obesity is a growing problem. Optimization of production to benefit health and environmental outcomes is hindered by limited data and shared societal goals. We lack a detailed overview of where fats are being produced, and their environmental impacts. Furthermore, the yields of different crops, for producing oils or feeding animals, and the associated land needs for meeting oil demands, differ greatly. To illuminate these matters, we review current discourse about the nutritional aspects of edible fats, summarize the inferred environmental implications of their production and identify knowledge gaps.

Keywords: nutrition, dietary fat, environment – agriculture, sustainable development goals, planetary boundaries, undernourishment

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INTRODUCTION

Our ancestors have been dubbed "fat hunters" (1), indicating our needs for dietary fats. Oils and fats (further referred to as "fats") are an important component of our diets and, while in parts of the world there is overconsumption (2), an estimated 720 to 811 million people were undernourished worldwide in 2020 (3). About 25–30% of daily energy needs in a normal modern healthy diet comes from fats (4), and facilitating access of undernourished people to fats is important. Currently, an estimated 45 million tons (Mt) of dietary fat per year are required to reach recommended levels of fat consumption (5). This includes both a reduction of fat consumption in regions of overconsumption of especially animal fats, and an increase in areas of underconsumption. If this "fat gap" is projected to 2050, an additional 88–139 Mt are required. This will mostly come from soybean oil, which in 2019, globally contributed 9.88 g of fat per capita per day, palm oil 7.17, sunflower oil 4.35, butter and ghee 3.62, and rapeseed and mustard oil 3.51 (6). Combined these five sources contribute an estimated 62% of the global consumption. Nearly 80% of the fats produced for human consumption are derived from oil crops, for which global production is currently around

208 Mt of oil (7). The remaining fat production derives from animal fats ("dairy" which includes butter, ghee, cheese, milk etc.), which was 46 Mt in 2019 (8) with additional animal fats produced in lard (6 Mt) and tallow (7.3 Mt) (6).

The health aspects of fats as well as the environmental impacts of their production receive significant media attention. How to best produce oils from plants, and fats from animals feeding on plants, is therefore not only of nutritional and human health importance but also relates to planetary health. For example, different oil crops have different yields and land requirements to produce the same amount of oil (9, 10). These crops are also grown in different parts of the world, with oil palm a typical crop of the tropics, and soybean of the subtropics and temperate climate zones. For many uses, oils are interchangeable (11), so a reduction in the production of one type of vegetable oil will result in an increase in another, and thus affect where land is allocated to oil production.

Here we review current knowledge of the nutritional and health aspects of dietary fats, and how this affects people in different parts of the world. We also review how the demand for dietary fats could be met and what the possible environmental consequences will be.

AFFORDABLE FATS OF SATISFACTORY NUTRITIONAL VALUE

Fats (or lipids) are the primary structural components of cellular membranes and are also sources of energy (12). Furthermore, fats provide essential fatty acids and facilitate the absorption of fat-soluble vitamins (A, D, E, and K) (13). Fats include various food oils—with "oils" being colloquially used for fats that remain liquid at room temperature. Dietary fats fall into three categories based on the number of chemical double bonds: monounsaturated fats, polyunsaturated fats, and saturated fats. A fourth category, trans fats, forms during partial hydrogenation of vegetable oils produced industrially (e.g., margarines), or naturally in beef, lamb, and dairy products (5). Monounsaturated fats are mostly found in fish, many plant-derived oils, nuts, and seeds. Saturated fats primarily occur in animal products and in palm oil (12). In practice, such general terms can seldom be used with precision though. Most fats are complex chemical mixtures of all major saturated fatty acids in differing proportions, along with many other fatty and non-fatty acids (14). All these different types of fats have different impacts on health, sometimes negative, or sometimes positive, such as in the case of polyunsaturated essential fatty acids. The science around the complex interactions between hundreds of thousands of food components, how these interact among each other, and how they interact in turn with different components of human health, is still developing (15).

While fats are one of the potential sources of energy in humans, some fats are essential. One of these is alpha-linolenic acid, an omega-3 fatty acid, that is particularly abundant in walnuts, rapeseed, some legumes, flaxseed, and green leafy vegetables (16). Another essential fat is linoleic acid, an omega-6 fatty acid, which plays an important role in functions such as cell physiology, immunity, and reproduction. Linoleic acid is an important component of breast milk, and, in many vegetable oils, it represents more than 50% of the lipid content. High amounts of linoleic acid are also present in nuts, cereals, legumes, some meats, eggs, and dairy products (17). Fats also influence bioavailability of fat-soluble vitamins, with a Western diet high in fat causing alterations of gut microbiota and potentially reducing the bioavailability and function, and possibly introducing potential toxicities, of these vitamins (18). Finally, pentadecanoic acid and heptadecanoic acid, found mainly in milk and other dairy products, are trace saturated fatty acids which cannot be synthesized by the human body in sufficient amounts and have therefore been proposed as essential in small doses (19).

Dietary guidance around the world has evolved into desirable dietary patterns. Recommendations now support food practices, such as the Mediterranean diet, which are often high in dietary fat, but include other recommended foods, such as vegetables, fruits, legumes, and whole grains (20). These dietary patterns have implications beyond cardiovascular disease with new emphasis on brain health, gut health, and weight management. Additionally, a diet's fat quality is recognized as more important than the saturated fat content (14, 21). A meta-analysis by Astrup et al. (14) indicated that replacement of fat with carbohydrate was not associated with lower risk of coronary heart disease, and may even be associated with increased total mortality. Also, systematic studies find no significant association between saturated fat intake and coronary artery disease or mortality, and some even suggested a lower risk of stroke with higher consumption of saturated fat (14). High fat diets, even those high in saturated fat, may be protective in cardiometabolic disease as when fats are removed from the diet they are replaced by carbohydrates which are linked to health risks (22). In the context of contemporary diets, therefore, these observations would suggest there is little need to further limit the intakes of total or saturated fat for most populations (14). Similar changes surround past concerns around cholesterol and heart disease. Cholesterol – mostly found in animal fats – is essential for human life but also not a required nutrient as, if it isn't ingested, the human body can make what it needs. It is a component of the cell membrane, a precursor molecule in the synthesis of vitamin D, steroid hormones, and sex hormones, and also plays a role in the absorption of fat-soluble vitamins (23). The effects of dietary fats on cardio-vascular disease risk have traditionally been estimated from their effects on serum cholesterol, although the thinking about health implications of these measures are changing (14, 24). Also, there is ongoing debate about the optimal intake ratios of various omega-3, 6, and 9 fatty acids (25–27).

Most of the nutritional and health studies have evaluated the role of different fats on people in the global North, often in relation to the 1.9 billion adults worldwide that are overweight (28). Fat limitation in early dietary guidance primarily applied to obese societies because fats contain 9 kcal/g vs. 4 kcal/g for carbohydrates and protein, but for people who are underweight energy-dense food is important. Geographically undernourishment and food insecurity are concentrated in sub-Saharan Africa, parts of Asia and the Caribbean (**Figure 1**). The "depth of the food deficit," i.e., a measure providing an estimate of the number of additional calories the average

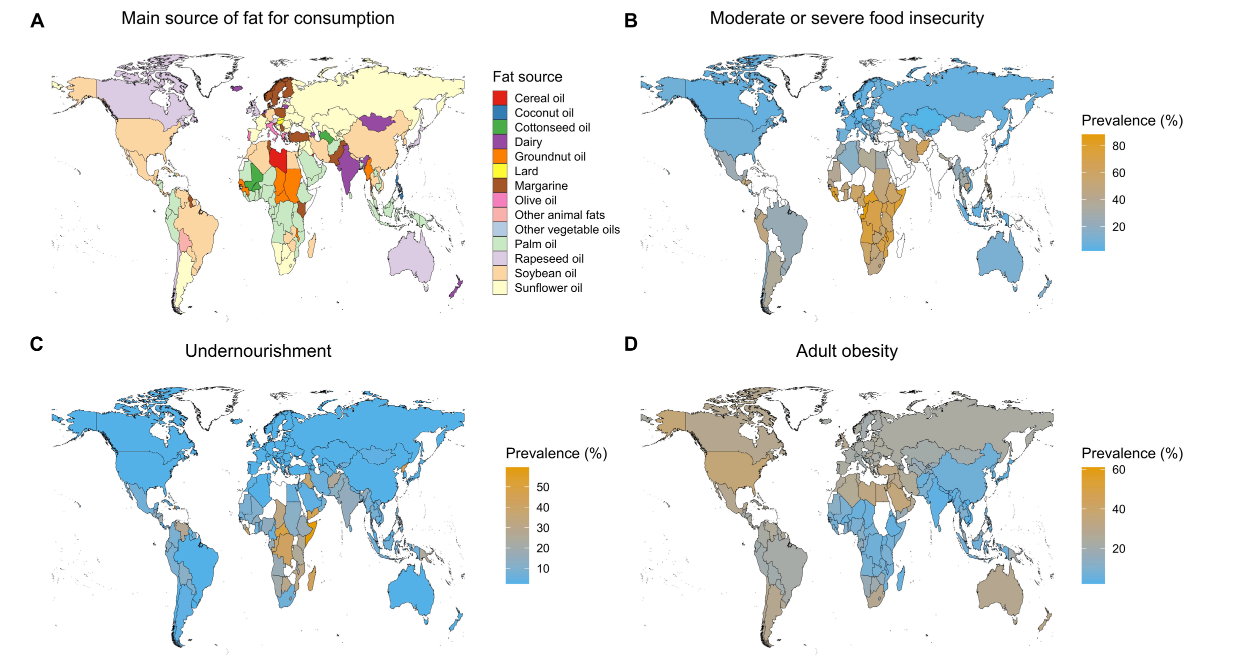

FIGURE 1 | The dominant sources of fat consumption **(A)**, and the prevalence of severe food insecurity **(B)**, undernourishment **(C)**, and adult obesity **(D)** per country. For details on data and methods used for maps refer to **Supplementary Materials**.

individual needs is especially high in countries such as Haiti (530 kcal/person/day), or the Central African Republic (380 kcal kcal/person/day) (29). Countries with high food deficits coincide with parts of the world with large fat gaps: Eastern, Northern, Middle and Western Africa; East, Southeast and South Asia, and the Caribbean (5). Understanding fats in diets of undernourished people is important, and may also impact infants through quality of breast milk related to fat intake by mothers (30). Regional studies in South America note, however, that feeding energy-rich micronutrient-poor foods to undernourished people can promote obesity (31). The extent to which fats can contribute to closing the food deficit without resulting in obesity (32, 33) remains therefore unclear, although dietary fats will likely play some role in increase energy intake among undernourished people.

Addressing the food deficit requires affordability and availability (34). Compared to other food groups, fats are cheap. With a cost per person per day of less than USD 0.20, fats contribute about 4% to the average global cost of a healthy diet. In comparison, the cost is ca. USD 0.40 for starch staples, USD 0.60-1.00 for protein-rich foods, and around USD 0.70 for dairy, fruits and vegetables (34). Compare these costs to the international poverty line for low-income countries of USD 1.90/day (35). Fat prices vary with type and origin (36), but generally affordability favors local productions. Transport and logistics costs in tropical America and the Caribbean, for example, made up 20% of the cost of food products (37). **Figure 1** shows that crops such as peanut in central Africa and palm oil central Africa and in South-East Asia could play important roles in the local supply of affordable fats.

COMPARING OILS AND FATS IN AN ENVIRONMENTAL CONTEXT

Environmental Impacts of Fat Production

Expanding agriculture is the principal cause of biodiversity decline (38), a major contributor to nitrogen and phosphorus pollution (39), to land degradation (40) and to freshwater depletion (41). From 2003 to 2019, global cropland areas increased by 9%, with a near doubling of the annual expansion rate, primarily due to agricultural expansion in Africa and South America (42). Half of the new cropland area (49%) replaced natural vegetation and tree cover, indicating a conflict between the goals of producing food and protecting terrestrial ecosystems (42). Such expansion risks lasting damage to the habitability of the planet (43). With 331 million ha, oil crops make up about 23% of the total land area allocated to crop production, but at 41% the oil crops area expanded even more than overall croplands between 2003 and 2019 (6).

In relation to the production of fats, excessive nitrogen flows are focused on areas favoring production of soybean and dairy (**Figures 2A–C**). Concerns about biosphere integrity coincide with areas producing soybean, sunflower, dairy, olive oil, and groundnut (**Figures 2A,B,D**). Concerns about land-system change dominate the wet tropics where oil palm and soybean are grown and parts of the palearctic where sunflower and tallow are produced (**Figures 2B,E**). Concerns around freshwater focus on drier areas in the western United States, Mediterranean, and South Asia where olive, sunflower, dairy and soybean predominate (**Figures 2A,B,F**).

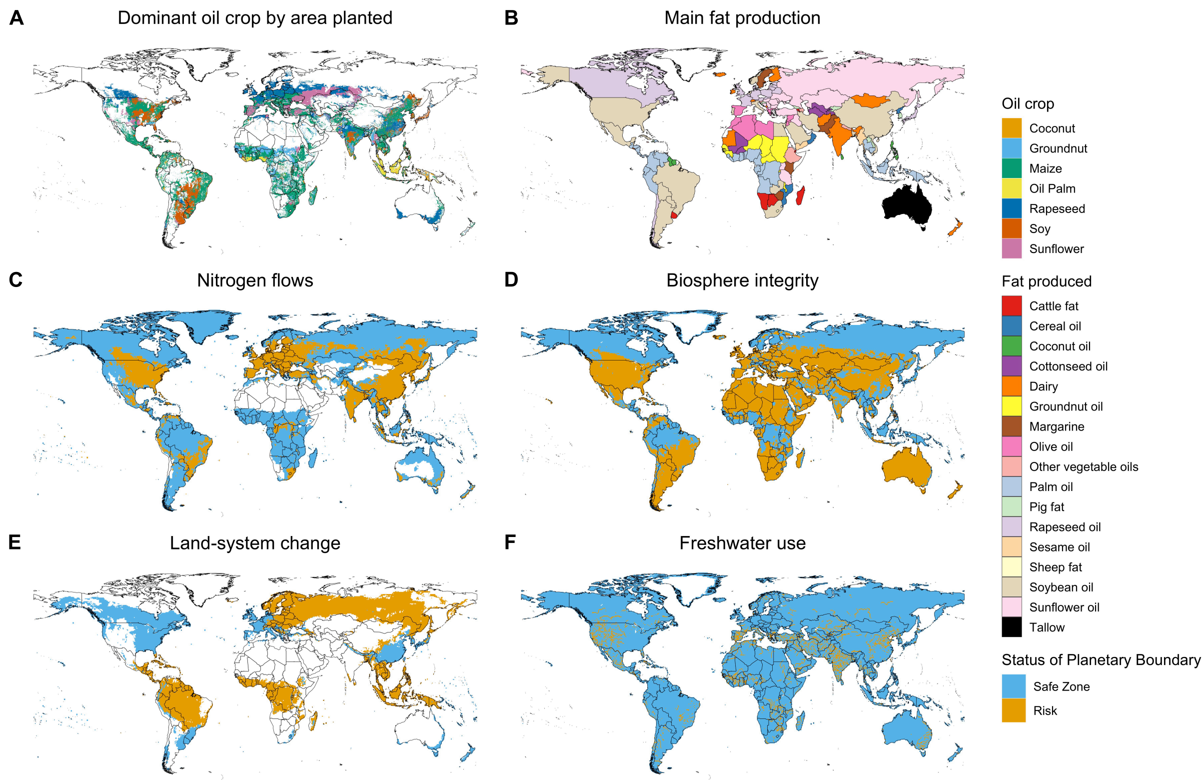

FIGURE 2 | (A–F) The status of planetary boundaries for nitrogen flows, biosphere integrity, land-system change and freshwater use compared to the main oil crop and fat production areas. For details on data and methods used for maps refer to **Supplementary Materials**.

Meeting Future Fat Demands

With an increasing global population, demand for fat will increase and this will mostly be met through oil crops. Because of the energetic costs of transforming plant material into animal material, more land is needed to produce a certain amount of animal fat than directly from plants. Animals do not only eat oil crops, but also consume plants such as grasses not normally eaten by people. There is debate surrounding the extent and conditions under which production of animal fats and vegetable oils compete, with much depending on the particular production systems compared (44).

An increase in fat production through oil crops can be achieved in two ways: (1) by increasing the yield of existing crops, thus producing more oil on the same amount of land, or (2) by allocating new land for the production of oil (9). Currently just four crops—oil palm, soybean, sunflower and rapeseed—provide most vegetable oil. Though values can vary considerably with context, typical yields differ among crops. For example, oil palm typically yields 2.84 tons of oil per ha, while soybean produces 0.45 tons, and groundnut 0.18 tons (10). As a result oil palm supplies 36% of global vegetable oil volumes on just 8.6% of the land allocated to oil production (10). Comparable figures for soybean are 25.5% of production on 39% of land, for rapeseed and mustard 11.3% on 12%, and for sunflower 9% on 8.3% (10).

The impacts of oil crop expansion on natural ecosystems is extensive in, for example, South-East Asia, where oil palm and coconut replaced tropical forest (45, 46), South America, where soybean has replaced tropical forest and savannahs (47), and equatorial Africa where maize, groundnut and cotton are expanding into tropical forest and savannah (48). Expansion of oil crops also impacts Australia where the area of rapeseed has increased 100-fold over the past 40 years (6), including in areas of threatened natural ecosystems (49), and the United States, where soybean and maize has expanded into large areas of relatively biodiverse natural grass and scrublands in recent decades (50). Similar processes have occurred with rapeseed and sunflower cultivation in Russia, Kazakhstan and Ukraine. Quantifying such impacts remains imprecise, because, except for oil palm (51), none of these crops have been globally mapped at sufficient resolution.

DISCUSSION

Our review of the impact of fat production and consumption on human and planetary health indicates potential tradeoffs and synergies from different fat choices. Fat demand is likely to increase to feed an increasing number of people. In parts of the world with widespread overweight, reduced fat intake and more balanced consumption of different and essential fats is needed. In parts of the world with high incidence of undernourishment, increased production of local, affordable fats seems important, although global recommendations still call for avoidance of fat and especially saturated fat (3). The availability of products such as Plumpy'Nut, a peanut-based paste that consists for one-third of fat and is used for treatment of severe acute malnutrition, indicates the importance of fats in regions of undernourishment. Better guidance is needed regarding which fats might help address undernourishment, without adverse health impacts, and costs.

While the health impacts from consumption of saturated fats may have been overstated, dairy has a high environmental footprint, and use should be reduced. Increased consumption of lard and tallow proportionally to pork and beef production, on the other hand, would allow more optimal use of edible fat (5). Nevertheless, in terms of planetary health, the production of plant-based fats has lower negative impacts than the production of animal fats, and growing crops with high oil yields is recommended as this spares land. We must moderate the impacts from crop expansion on biodiversity and natural ecosystems and depletion of groundwater (39). How to best seek a balance between these different objectives is difficult to determine because ultimately many choices are value driven – e.g., saving orangutans from oil palm expansion versus the need to provide poor people with affordable fats. Nevertheless, some general patterns can guide decision-making on future fat production choices.

Palm oil is an important oil for cultural and price reasons in large parts of South-East Asia and central Africa, and its alleged negative health impacts because of high saturated fat content is increasingly questioned (52, 53). Among the oil crops it is the most land-efficient fat and efficiency could be further improved, especially through mechanized harvesting and better chemical management, but deforestation must be avoided to protect biodiversity and carbon stocks (9). Peanut provides a healthy and cheap source of oil, and improved peanut production could reduce fat gaps in key regions of human population growth (i.e., Africa and south Asia). Because both palm oil and peanut oil are relatively cheap, they will remain important oils for many people. Coconut, another oil crop of tropical regions is an important source of fat to many people. Impacts on health remain debated (54), and differ for different types of coconut oil (55). Furthermore, there are concerns about coconut's environmental impacts, especially on tropical islands with high species endemism where loss of natural ecosystems because of coconut expansion threatens biodiversity (46).

Soybean oil, as the largest oil crop in area, will likely remain a leading source of oil, and it is also a key component of animal feed. Reducing pork and poultry production can lead to reduction in soybean oil production and spare land in regions of high deforestation such as South America. There are concerns about negative health impacts related to the lipid profile of sunflower oil, especially its very high omega-6 to omega-3 ratio (5), but it is difficult to generalize about this, also because there are different types of sunflower oil that vary significantly in their oleic, linoleic (omega-6) and stearic acid content.

Finally, further research is needed in the opportunities to produce fats at scale from microbial and insect sources. Algal, yeast and other microbial oils have major potential for the production of design oils that meet human health requirements, but remain relatively expensive to produce (56). The environmental impacts of such oils depend on the need for a feedstock, with especially carbon-based feedstocks (often sugars) requiring crop land for their production (57). Edible insects are an alternative fat and protein source with low greenhouse gas emissions and low land use, and with at least 2000 edible species of insects (58) there is much to choose from. Given these developments, it is likely that dietary guidance on fats will continue to emerge and change with developments in science, technology and future challenges and opportunities.

AUTHOR CONTRIBUTIONS

EM conceived the initial study, conducted literature review, wrote the initial manuscript, and coordinated the study. JA implemented the mapping for this study and contributed to the manuscript revisions. JS provided input on the text on nutrition. DS provided input into the original study design and edited the manuscript on several occasions. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.878644/full#supplementary-material

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Plant-Based: A Perspective on Nutritional and Technological Issues. Are We Ready for "Precision Processing"?

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The rapid evolution of consumers' preference despite being still rooted in taste is rapidly combining with an exponential growth of environmental awareness. Both are forcing innovation into the food industry sector. Today, it is common in the scientific literature to find awareness of nutrition and sustainability, functionality and freshness, taste, and pollution; the most relevant and recognized trends are evolving with unprecedent speed toward a new paradigm. The perfect storm of fast-growing population, together with an exploding level of environmental pollution, is combining with the request for functional foods with more defined health properties and is strongly pushing the food sector to new defined innovation objectives to keep and develop the economic role of most loved brands around the world. The most debated conundrum is how to provide healthy food for all human beings, without further affecting our Mother Earth. Innovation in food raw materials as well as innovation in food processing seems to be the magic solution to provide *twice with half*, that is, to double the food production combined with declining resources. One of the fastest growing segments in the food industry is the plant-based segment. The status of the available options in food processing applied to plant-based food will be discussed, with a special focus on novel physical processing technologies and atomic force microscopy as possible complementary weapons in science-based definition of a sustainable nutrition approach. A call for a new paradigm such as "precision processing" should be adopted to drive the evolution of the whole food system.

Keywords: plant-based, sustainability, nutrition, novel physical processing technologies, protein, precision processing

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INTRODUCTION

Nutrition science is expanding its core competence from the simple profiling of nutrients to a more holistic approach that includes the sustainability of nutrition based on sustainable development goals (1). As the EAT Lancet committee firmly indicated, diet, health, and environmental sustainability are closely intertwined, with food being the lever to optimize human and environmental health (2). Following a plant-based diet, according to what has been demonstrated in the ever-growing literature on the subject, would seem to represent a winning approach for both people and the planet, and, driven by this concept, the growing demand of plant-based food was the primer of incredible number of scientific and related publication during the last 5 years, when 23,383 articles were published (3). In this context, protein takes on a critical role, both from nutritional and environmental perspectives. In fact, in view of the growth of the global population in the near future, which is expected to be 10 billion in 2050, it becomes of primary importance to ensure an adequate protein intake for all the world's population, in addition to meeting the global caloric needs. Considering the intense amount of land and resources required for animal proteins' production, it, once again, becomes necessary to shift the focus to alternative sources of protein, such as plant-based proteins, representing a promising solution to our nutritional needs due to their long history of crop use and cultivation, lower cost of production, and easy access in many parts of the world (4). Such proteins could be found in pulses (e.g., peas, beans, chickpeas, lentils, and lupines), oilseeds (soybeans, peanut, flaxseed, and rapeseed/canola), cereals (wheat, corn, rice, oats, barley, and sorghum), and pseudocereals (quinoa, amaranth, chia, and buckwheat) (5). However, plant proteins present some challenges, given the lower protein quality and technological functionality; therefore, it is of primary importance in the production of this new generation of plant-based foods to have a thorough understanding of the characteristics of the plant-derived ingredients that comprise it to identify desirable physicochemical and sensory attributes in the finished product (6). Research in recent years is consolidating a certain know-how aimed at improving the technological profile of vegetable proteins, starting from their manipulation in the production phase, such as during extraction, fractionation, and modification that can considerably enhance their functionality (7–9). The literature is, indeed, showing how modifying the structural arrangements of plant proteins toward forms that give physicochemical and functional properties comparable to those provided by animal proteins is the core challenge in this research field (4). The increasing demand for better performing proteins has led to the implementation of various thermal and non-thermal treatments to modify plant proteins. In particular, novel physical processing technologies (NPPT) claimed to be *emerging high-potential treatments for tomorrow* are needed in this context and will be further explored in the next chapter (5, 10).

CLASSIFICATION OF THERMAL AND NON-THERMAL TECHNOLOGIES AND THEIR CONCRETE APPLICATIONS: FOCUS ON NPPT

Global food markets demand for plant-based ingredients and food that are, first of all, safe, preferably with a natural halo, and with good nutritional value. The sustainability of processes as well seems to be a parameter recognized and requested by consumers and the market for this type of product (11). Conventional heat-dependent technologies, such as pasteurization and sterilization, however, can have a strong impact on sensory and nutritional characteristics that adversely affect the overall quality of the food product (11); therefore, alternative techniques have gained much attention, with the development of so called "novel" and "emerging" technologies.

Over the years, two main options are subject of intensive research and are emerging in food systems: non-thermal technologies and novel thermal processing technologies (11). Non-thermal technologies, such as high pressure, pulsed electric field (PEF), carbon dioxide processing, and membrane processing, are recognized as value-added processes and sustainable alternatives to conventional treatments, mainly due to the reduction of energy and water consumption (12). These non-thermal techniques are based on the inactivation of microorganisms and spoilage enzymes by means of physical hurdles, such as pressure, electromagnetic fields, and sound waves. They can result in sterilization at room temperature or lower than thermal analogs and are more and more adopted because of the efficient inhibitory effects on microbes, with the promise that taste and texture features are consistent with the chemical properties of ingredients. On the other side, we have the novel thermal technologies that mainly use energy generated by microwave and radio frequency, such as ohmic heating, microwave heating, dielectric heating, or radio frequency heating (13).

As mentioned at the beginning, in addition to food safety aspects also considering the sustainability of the process used, it is of fundamental importance in the context of plant-based foods not to forget the challenges imposed by these new ingredients both from nutritional, sensorial, and technological points of view. Plant-based proteins have, in fact, limits in their applications because of their poor techno-functionality, digestibility, bioactivities, and presence of anti-nutritional compounds with certain off taste (10). Conventional heat treatments, such as drying, extrusion, roasting, boiling, and steaming, are among the most common methods applied for physically modifying the structure of proteins in order to enhance their functionality. However, these techniques, given the heavy conditions intrinsic in the process, could induce denaturation and damages on the secondary and tertiary structures, causing alteration in the nutritional and sensory profile of proteins (4, 14).

In this context, NPPTs, such as high pressure, ultrasound, microwave, radiofrequency, ozone, ultraviolet-C, cold plasma, ionizing radiation, and the pulsed electric field, are emerging as promising new technologies able to overcome the limit expressed above – see **Figure 1**. These NPPTs are able to modify the protein structure by disrupting various interactions among protein molecules, leading to techno-functionality changes (10). When we are talking about techno-functionality related to plant-based proteins, four are the main aspects we should consider: water/fat absorption capacities, protein solubility, emulsifying and foaming properties, and gelation and rheological properties (5, 10).

To explore one of the most studied techniques in this context, high pressure processing (HPP) has gained much attention in the food industry with the purpose of inactivate spoilage microorganisms and dangerous pathogens (5). In HPP, the heat is substituted by pressure (ranging from 100 to 800 MPa) (5), resulting in cold pasteurization, therefore avoiding the damage caused by high temperatures. Furthermore, over years, this technique has been shown to positively affect protein structure and related functionalities, such as the capacity to stabilize

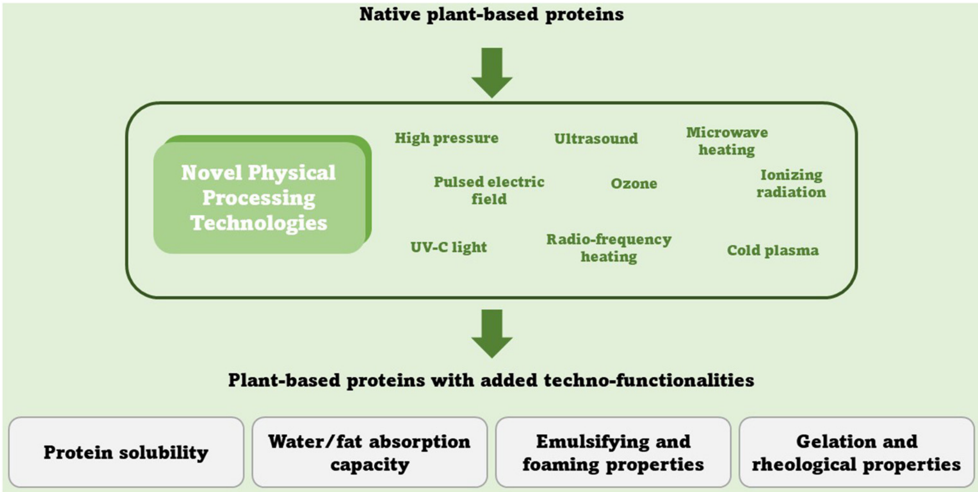

FIGURE 1 | A summary of NPPT able to impact plant-based protein functionalities.

emulsions and foams, and to form aggregates and gels, mainly impacting the secondary, tertiary, and quaternary structures of proteins, considering the HPP effect on noncovalent bonds (15). The level of improvement of HPP-induced modifications and its commercial applications depend on several factors, such as pH, the pressure level, treatment time and temperature, as well as protein type (15). In addition, it is worth mentioning that the application of HPP has been shown to be effective as a pre-treatment of legumes followed by enzymatic hydrolysis in increasing protein digestibility (16).

Another technique that should be mentioned is ultrasound, which is a promising sustainable novel technology for plant protein treatment, mostly for its ability to enhance green chemistry by using nontoxic, clean, and green solvents (17). Furthermore, in comparison with other eco-innovative technologies, it requires lower investment and shorter times. As with HPP, the right combination of processing conditions has been shown to increase solubility, oil absorption, water-holding capacity, emulsifying, and gelling properties (13), and also proves to be an efficient method for protein extraction (14).

These are some examples that highlight the potential of these innovative techniques to address the need for greater use of plant proteins in the food industry, increasing their functionality and potential. In fact, we are witnessing a paradigm shift in which food safety, a fundamental requirement of the food industry, is being joined by new concepts, such as sustainability and functionality of the process and ingredients. The change in perspective forces us to ask ourselves how traditional processes can adapt to these new requirements, and we may find the answer in *precision processing*. This means the search for processes capable of adapting to the available raw materials, enhancing their natural characteristics but, at the same time, strengthening their functions in order to be suitable for tomorrow's food system, which will have to rely on alternative sources of nutrients, especially proteins, mostly of vegetable origin.

PRECISION FOOD CHARACTERIZATION

The momentum for change in food processing is fostered by a general concern about continuing with thermal technology. Growing evidence suggests that non-thermal technology is providing substantial benefits in energy needs, while combination of thermal and non-thermal technology is in place (18). Moreover, the merging of public health nutrition and sustainability is the major challenge in the XXI century, with the protein transition diet (less animal protein, more plant protein) being central to our species' chance of survival (19) as well as the codification of a global diet (2). Based on this perspective, it will be necessary to initiate in-depth research aimed at precision characterization of foods. To deal with this ambitious aspect, a first attempt in precisely characterized foods could be the application of atomic force microscopy (AFM), a very high-resolution type of scanning probe microscopy, which has been extensively reviewed in a recent special issue (20). There are several applications of this technique in food science as reported in **Table 1**.

DISCUSSION

As briefly described, we are facing a new era in which food(s) will be more and more integral to our way of life, not based only, as in the past, on tradition or on consolidated features but also on addressing broader the scientific horizon of human beings. What we expect from the food of future is to continue to enjoy tasteful food, with the intrinsic property of safety at the maximum level, but more respectful of the environment and with an egalitarian principle as founding elements. We, therefore, need to develop the food of the future according to "precision processing," using innovative processes able to adapt to the raw materials available, enhancing their quality and

TABLE 1 | Applications of atomic force microscopy (AFM) in food science research.

AFM applications	References
Asses nanomechanical properties of food materials.	(20)
Proteins	
Topography characterization of protein.	(21)
Processing and preservation effects on food proteins.	(21)
Interaction research between food proteins and other substances.	(21)
Food packaging	
Characterization of different chemicals and physical properties.	(22)
Bacterial adhesion on food packaging surfaces.	(22)
Food safety	
Food toxins detection.	(23)
Quantify the dimension alterations and surface features of food borne pathogens and spoilage microbes to elucidate bactericidal mechanisms and cellular responses under adverse environments.	(24)
Analyses of the adhesion capacity of food borne pathogens, contribute to the biocontrol of biofilm in food-processing surfaces, the elimination of disease transmission, and the prolongation of product shelf life.	(24)
Polysaccharides	
Morphology characterization of pectin, xanthan, carrageenan, β-glucan, hemicellulose, starch and others.	(25)
Investigation of structure-function properties of polysaccharides in various conditions and complex systems.	(25)
Opportunities to control and improve the quality of food product during processing and preservation.	(25)

functionality. That is why we suggest a re-examination of raw materials from vegetable sources based on an intrinsic assessment of environmental costs, processing costs without forgetting the growing demand for more functional foods. Previous experience has documented that, without focusing on taste, it is difficult to gain consumer support without the vast majority of consumers' final choice being focused on conscious evaluation and preferred consumed items. Only if we face the problem with holistic and non-biased eyes can we look for the definition of a set of principles that will allow the scientists to rank possible suitable options for a healthy, egalitarian diet that is available for all and will not further affect our Mother Earth. It is also clear that, now, even the most innovative processes are far from being perfect, but, in any case, we know that *business as usual* is no longer a choice or even an option. Therefore, any kind of prejudices should be avoided; new unexplored ideas must enter in the scientific arena. Our perspective cannot be exhaustive of such a very complex matter, and we decided that the simple way of listing the findings showing the distance between what is possible and what is not is the only way to start together a new era and face new paradigms. We know that new technologies are having huge potential; they impact the structure, the organization, the facility cost, and the day-to-day operations, but, moreover, they can really promote a better nutrition for all. We must acknowledge the time in which we can try to solve the problems of food supply for humanity is getting shorter and shorter; the approach that is proposed as *precision processing* is at the end, only a way to call for a common effort and to focus on realistic solution.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

Conceptualization and writing—original draft preparation was contributed by RM. Writing—review and editing and visualization were contributed by GR and FC. All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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A2 Milk and BCM-7 Peptide as Emerging Parameters of Milk Quality

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Beta-casein makes up about 30% of the total protein contained in milk and can be present in cows' milk in two distinct forms (A1 or A2) or as a combination of the two. The only difference between these two variants of β-casein (β-CN) is a single amino acid substitution. This results in a different behavior of the protein upon enzymatic cleavage, following human consumption or due to microbial action. In most of the commercially available milk containing A1 or A1/A2 β-CN variants, the β-casomorphin-7 peptide (BCM-7) is released upon digestion and during cheese manufacturing/ripening, while this does not happen with A2 milk. BCM-7 is a known μ-opioid receptor agonist that may influence the gastro-intestinal physiology directly and may also exert effects elsewhere in the body, such as on the cardiovascular, neurological and endocrine systems. The present article is aimed at a revision of prior review papers on the topic, with a focus on the impact of ingestion of A1 β-CN milk and A2 β-CN milk on any health-related outcomes and on the impact of A1 or A2 β-CN variant on technological properties of cows' milk. When systematic reviews were considered, it was possible to conclude that A2 β-CN exerts beneficial effects at the gastrointestinal level compared with A1 β-CN, but that there is no evidence of A1 β-CN having negative effects on human health. Physicochemical differences among cows' milk containing either β-CN A2 or β-CN A1 and their effects on technological properties are discussed.

Keywords: beta-caseins, health effect, opioid peptides, technological traits, cows' milk

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INTRODUCTION

Caseins constitute almost 80% of the proteins present in cows' milk. The casein class includes four different subtypes, α-s1-casein, α-s2-casein, κ-casein and β-casein (β-CN), which is one of the most abundant subtypes, accounting for about the 30% of the total caseins in cows' milk (1). The genetic characterization of dairy cows has highlighted that 13 genetic variants of β-CN exist: A1, A2, A3, B, C, D, E, F, G, H1, H2, I and J, among which the variants A1 and A2 are the most common in dairy cattle worldwide (2).

The difference in the two genetic forms concerns a single amino acid mutation, at position 67 of the polypeptide chain, which results in a histidine (His67) in A1 β-CN milk and a proline (Pro67) in A2 β-CN milk. The presence of His67 in A1 β-CN milk allows the human gastrointestinal enzymes, or the microbial proteolytic system, to perform a proteolytic cleavage of β-CN, which in turn causes the release of β-casomorphin-7 (BCM-7) during digestion and cheese ripening. On the other hand, proteolytic cleavage appears to be hampered in A2 β-CN, where Pro67 is present (2). β-casomorphins (BCMs) have been demonstrated to be able to bind the μ-opioid receptors that are located in the central nervous system and in the gastrointestinal tracts of humans (3). In the last few decades, the scientific community has shown increasing interest in the potential impact of BCM-7 and the related peptides on human health. In 2009, an EFSA scientific report concluded that the available data were insufficient to suggest a cause-effect relationship between BCMs and non-communicable disorders, such as cardiovascular disease, autism and insulin dependent diabetes mellitus (4). Four systematic reviews on A1 and A2 β-CN consumption and health-related outcomes have been conducted so far (1, 5–7). All of them concluded that the consumption of A2 β-CN milk may benefit the gastrointestinal status when compared to A1 β-CN milk, however the evidence about other health benefits was inconclusive (1, 5–7).

The possible effect of the differences in the structural and physicochemical properties of the main β-CN milk variants on specific technological aspects, and on cheese-making in particular, is a much less explored topic. The substitution of Pro/His at position 67 seems to affect the structure and conformation of the hydrophobic part of the β-CN sequence, and seems to ultimately affect the emulsifying and stabilizing properties of the two isoforms, as well as its coagulating capacity (8, 9).

The aim of the present review is to provide a critical concise overview of the available evidence: (i) on the health effects of consuming milk containing either A1 or A2 β-CN, and (ii) on the differences in the technological traits of milk containing A1 or A2 β-CN.

METHODOLOGY

The present mini-review was conducted by resorting on different electronic databases (Scopus, Medline, WoS, PubMed and PMC), which were systematically searched on January 14th 2022 (**Supplementary Figure 1**). The search terms used in the Title/Abstract/Keywords (Scopus), or in the MeSH and Title/Abstract, or in the Topic (Medline and WoS), or in "All Fields" (PubMed and PMC), were: (casein AND "A2 milk" OR "A2A2 milk" OR "A2/A2 milk" OR "A2 beta casein" OR "A2 BCN" OR "A2 CASB" OR "A2 variant" OR "BCM7" OR "BCM-7"). The Document type was set as "Review". The search results were first screened for relevance by considering the title and abstract by one of the authors (MG). In the case of ambiguity, the paper underwent a full-text analysis and was checked for final inclusion. The obtained results were then screened by another author (CL) to recognize studies included in the meta-review analysis of health-related outcomes associated with A2 milk and/or BCM-7 avoidance from the diet. The bibliographies of the studies included in the systematic review were also examined to find any additional pertinent studies. The adopted exclusion criteria were: the study design was a letter to the editor or a conference paper, or a study that had not been peer-reviewed; the review investigated non-bovine milk; the article merely described methods used for the detection of A2 β-CN or BCM-7; the review focused only on the prevalence of specific β-CN genotypes in different breeds.

The data extracted from each relevant review on clinical studies/ health-related aspects, reported in **Table 1**, included: the type of review considered (narrative or systematic), the type of study considered (human clinical or epidemiological studies, animal-based studies and *in vitro* studies), a summary of the main finding and the outcomes with a qualitative evaluation.

The data extracted from each relevant review on qualitative/technological aspect, reported in **Table 2**, included: observed food product(s), investigated quality/ technological characteristic(s), and a summary of the main findings/evidences.

A1 vs. A2 Cows' Milk β-Casein and Health

The review papers that reported evidence on the health effects of milk containing A1 and A2 β-CN, and which were selected using the meta review approach described above, are listed in **Table 1**.

The majority of the papers are reviews conducted without using a systematic approach, the so-called narrative reviews. They report several possible health effects linked to the consumption of milk containing A1 β-CN, ranging from non-communicable diseases to neurological and gastrointestinal disorders. The earlier revisions in the literature, which focused on the possible correlation between the cows' milk β-CN variant and an increased risk of developing specific diseases in humans, showed contradictory results. In 2005, Truswell (10) claimed that no association between A1 β-CN consumption and type I diabetes or coronary heart diseases could be demonstrated. On the other hand, in the same period, the reviews by Bell et al. (11) and Kamiński et al. (2), reported that the consumption of milk containing A1 β-CN seemed to be correlated with a higher incidence of cardiovascular disease and type 1 diabetes and high level of BCM-7 in urine might be associated with sudden infant death syndrome and neurological disorders, such as autism and schizophrenia. On the basis of the available evidence at that time, in 2009 EFSA concluded that "cause-effect relationship between the oral intake of BCM7 or related peptides and etiology or course of any suggested non-communicable diseases cannot be established" (4). Later on, in 2014, the review by Raikos and Dassios (12) concluded that BCM7 is released from infant formulas after simulated gastrointestinal digestion (SGID), but that the *in vivo* effects of these peptides on the human physiology cannot be fully described. In 2015, Pal et al. (13), reported that, in rodents, milk containing A1 β-CN significantly increases gastrointestinal transit time and the inflammatory marker myeloperoxidase. They also concluded that, despite the fact that clinical trials in humans were limited at that time, preliminary evidence from two human studies suggested proinflammatory factors alongside effects on gastrointestinal transit time. In 2017, Chia et al. (14) reviewed animal-based and *in vitro* evidence, concluding that A1 β-CN and BCM-7 were the dominant triggers of type 1 diabetes in individuals with genetic risk factors (14). This was in accordance to the observation of Kalra and Dhingra (15), who reported the hypothesis that exposure to A1/A1 β-CN milk of exotic breeds, such as those from India, might be linked with the rising incidence of type 1 diabetes. On the same topic, Kohil et al. (25) concluded that specific dietary patterns can exert a direct impact on pathogenesis of type 1 diabetes through epigenetic modifications and that BCM-7 could act as an epigenetic modulator, differentially methylating genes involved in type 1

TABLE 1 | List of the selected review papers reporting the association between of A1 or A2 β-casein consumption and health status.

	Type of review	Type of studies considered	Main conclusion	Outcome qualitative evaluation	Outcomes
Truswell (10)	Narrative	H, A	No association between A1 β-CN consumption and T1DM or CHD		
Bell et al. (11)	Narrative	H, A	A relationship between A1 milk and the risk of chronic condition such as T1DM and CVD has been shown. Moreover, A2 milk may be associated with less severe symptoms of autism and schizophrenia	⊖	CVD + T1DM + ND
Kamiński et al. (2)	Narrative	H, A	Consumption of milk containing A2 β-CN associated with lower incidence of CVD and T1DM. SID, autism and schizophrenia possibly associated with high urine level of BCM-7	⊖	CVD + T1DM + SID+ ND
Raikos and Dassios (12)	Narrative	H, A, V	The formation of BCMs in infant formulas after simulated gastrointestinal digestion has been demonstrated. The *in vivo* effects of these peptides on the human physiology have not yet been fully described		
Pal et al. (13)	Narrative	H, A	In rodents, A1 milk increases GI transit time, inflammatory myeloperoxidase and dipeptidyl peptidase. In double-blind, randomized cross-over study, participants consuming A1 milk showed higher Bristol stool values compared with those receiving A2 milk	⊖	GI and T1DM
Chia et al. (14)	Narrative	H, A	In subjects with genetic risk factors, A1 β-CN and BCM-7 are causal triggers of T1DM.	⊖	T1DM
Kalra and Dhingra (15)	Narrative	H	Exposure to A1/A1 milk may be linked with the rising incidence of T1DM in India.	⊖	T1DM
Ledesma-Martínez et al. (16)	Narrative	A, V	Caseins and their fragments: (i) enhance lymphocytes proliferation and generation of antibodies; (ii) regulate normal hematopoiesis *in vitro* and *in vivo via* cytokine secretion, (iii) may induce apoptosis	⊕	P on lymphocyte+ AP on neoplastic cells
Aslam et al. (17)	Narrative	H, A	BCM-7 might have multiple functions correlated to human health, but, the evidence is limited and mainly derived from either epidemiology, which cannot establish causality, or animal experiments, which may not be generalizable to humans	⊖	GI and obesity
Hegde (18)	Narrative	H, A	There was no clear evidence to link BCM-7 intake with T1DM, CVD or SID. Further clinical studies are needed to evaluate A1 milk effects in a broad range of population groups and dietary conditions		
Wong et al. (19)	Narrative	H, A, V	BCM-7: (i) may affect nervous, digestive and immune functions by altering the gene expression of μ-opioid receptors; (ii) seems to be associated with childhood mental disorders, T1DM, SID, AD.	⊖	GI + ND + T1DM + SID +AD
Tulipano (20)	Narrative	H, A	BCM-7: (i) slows down GI transit time, (ii) induces a pro-inflammatory effect in the colon by opioid-receptor mediated mechanism	⊖	GI
Thiruvengadam et al. (21)	Narrative	H, A, V	A1 milk (i) consumption is a risk factor CVD, (ii) play a role in the onset of T1DM, iii) BCM-7 is present at high levels in blood, urine and CSF of children affected by autism, iv) depending on BCM-7 concentration, either suppression or stimulation of lymphocyte proliferation may occur, v) BCM-7 interaction with cancer cells seems to exhibit anti-cancerous activity *in vitro*	⊖⊕	All

(Continued)

TABLE 1 | Continued

	Type of review	Type of studies considered	Main conclusion	Outcome qualitative evaluation	Outcomes
Kay et al. (22)	Narrative	H, A, V	Pro-inflammatory role of A1 β-CN on GI, endocrinological, neurological, and CV systems	⊖	GI+ND+EC+CVD
Leischner et al. (23)	Narrative	H, A, V	BCM-7 seems to be able to induce apoptosis of pro-myeloic leukemia cells	⊕	AP on neoplastic cells
Woodford (24)	Narrative	H, A, V	Food-derived opioids induce delayed GI transit, intestinal inflammation and permeability, altered microbiome	⊖	GI
Kohil et al. (25)	Narrative	H, A, V	Specific dietary patterns can exert a direct impact on pathogenesis of T1DM through epigenetic modifications. Among these, BCM-7 could act as an epigenetic modulator differentially methylate genes involved in T1DM development	⊖	T1DM
Brooke-Taylor et al. (5)	Systematic	H, A, V	In rodents, A1 milk consumption causes delayed GI transit and increased inflammatory response. In humans, A1 milk consumption is associated with delayed GI transit, looser stool consistency and digestive discomfort (paper searching updated through April 2017)	⊖	GI
Kuellenberg de Gaudry et al. (6)	Systematic	H	In humans, moderate certainty for adverse digestive health effects of A1 β-CN compared with A2 β-CN. Very low certainty for other health benefits (paper searching updated through October 2017)	⊖	GI
Kuellenberg de Gaudry et al. (7)	Systematic	A	Considering animal studies, A2 milk might have beneficial effect on GI tract, whereas outcomes related to CVD and T1DM seem inconclusive (paper searching updated through March 2020)	⊖	GI
Daniloski et al. (1)	Systematic	H, A	A2 β-CN can have some beneficial effects on the gastrointestinal system (paper searching updated through July 2020)	⊖	GI

β-CN, β-casein; H, human clinical or epidemiological studies; A, animal-based studies; V, in vitro studies; T1DM, type 1 diabetes mellitus; CHD, coronary heart diseases; CV, cardiovascular; CVD, cardiovascular disorder; SID, sudden infant death syndrome; ND, neurological disorders; GI, gastrointestinal; BCM, β-casomorphin; AP/P, anti-proliferative/proliferative effect; EC, endocrinological effect; AD, atopic dermatitis. ⊖ Negative health effect of A1 β-casein/ BCM-7 containing milk; ⊕ Positive health effect of A1 β-casein/ BCM-7 containing milk.

TABLE 2 | List of the retrieved papers concerning physicochemical properties and protein functionality of A1 and A2 β-CN containing milk.

Review	Matrix	Investigated quality/ technological characteristic(s)	Main findings
Kamiński et al. (2)	Milk and dairy	Release BCM-7 during digestion	Release of BCM-7 following β-CN digestion requires a multi-enzyme system BCM precursors are detected in cheese; BCM-7 is largely detected in infant formulas A1 and A2 variants may present different physical properties in micelles
Raikos and Dassios (12)	Infant foods	Presence of BCM-7 in IF	BCM-7 and derivatives are released from commercial milk-based infant formulas following SGID
Nguyen et al. (9)	Milk and dairy	Presence of BCM-7 in dairy	BCM-7 is detected in raw milk and cheeses, but not in commercial yogurt, nor in pasteurized milk BCM precursors are detected in several cheeses BCM-7 in cheese does not originate from that originally present in milk, because peptides would be removed from the curd during the drainage of whey BCM-7 is higher in mold cheeses (Brie and Rokpol) than in semihard cheeses (Edamski, Gouda and Kasztelan) Proteolysis by enzymes from cheese starter cultures may reduce the amount of BCM-7
Pal et al. (13)	Milk and dairy	Presence of BCM-7 in dairy	BCM-7 is released from milk, yogurt and cheese following SGID Modest release of BCM-7 in cheese- and yogurt-making processes Certain yogurt bacteria may hydrolyze BCM-7
Brooke – Taylor et al. (5)	Milk	Release of BCM-7 during digestion	Release of BCM-7 following β-CN digestion requires a multi-enzyme system Presence of BCM-7 in fresh milk could be due to extended acidic hydrolysis *In vivo* studies indicate the release of BCM other than BCM-7
Gai et al. (8)	Milk and dairy	Effect of β-CN variants on milk yield, composition, protein structure, coagulation, foaming, emulsifying capacity	A2 variant has better chaperone capacity than A1, due to more proline helix formation Milk yield, protein yield, fat percentage and fat yield are significantly affected by β-CN variant, and the effect is enhanced by association with specific κ-CN variants A2 variant shows poorer coagulation properties than A1 (longer rennet coagulation time and looser curd), but may result in more easily digestible yogurt A2 variant shows a more acidic pI than A1, is more soluble, reaches the oil droplet surface more rapidly, but does not result in better emulsion stability. Results of the foaming properties of different β-CN variants are controversial
Summer et al. (26)	Milk and dairy	Presence of BCM-7 in dairy and effect on its release during digestion	Small amounts of BCM-7 could be released from A2 β-CN due to acidic hydrolysis in gastric environment BCM-7 is detected in a number of dairy products before and after SGID (pasteurized milk, cheese, laboratory-made yogurt, and other dairy products) Manufacturing and ripening in matured cheeses, and proteolysis by lactic acid bacteria and probiotics, exert a pivotal role in modulating the release BCM-7 before and after SGID The release of BCM-7 during SGID of sterilized infant formulas was hindered by protein glycation
Thiruvengadam et al. (21)	Milk and dairy	BCM-7 structure and metabolism	BCM-7 sequence is more hydrophobic, bitter to taste and its further digestion of is difficult because of the large percentage of proline BCM-7 and derivatives are released during the food processing (pasteurization, cheese- and yogurt-making, and other dairy products)

IF, Infant Formula; BCM, β-casomorphin; β/κ-CN, Casein β/κ; SGID, Simulated GastroIntestinal Digestion.

diabetes development. However, more recently, both Aslam et al. (17) and Hegde (18) concluded that there was no clear evidence linking BCM-7 intake with type 1 diabetes, cardiovascular disease and neurological disorders. Aslam et al. (17), even considering the implications on obesity and gastrointestinal discomfort, stated that evidence was limited, and mainly derived from either epidemiology, which cannot establish causality, or animal experiments, which may not be generalizable to humans. When studies regarding the effect of purified/synthetized BCM peptides were reviewed, it was reported that they may improve the proliferation of lymphocytes and the generation of antibodies, while negatively regulate the proliferation of leukemia cells (16, 21). The anti-proliferative effect of BCM-7 has also been reported in a series of studies on prostatic cancer cells, breast cancer T47D cells and HL-60 promyeloic leukemia cells (23).

The ability of BCM-7 to pass through human intestinal barriers, and the consequent effects on immune functionalities have also been assessed (19). This is the mechanism potentially underlying the association of BCM-7 with several negative health outcomes, including type I diabetes, childhood mental disorders such as autism, the sudden infant death syndrome, and atopic dermatitis. One revision (20) has recently proposed a correlation between BCM-7 and digestive discomfort induced by a pro-inflammatory effect due to the same molecular mechanism in rodents. The suggested path is that of the activation of the opioid receptors in the gut, which could alter its microbial composition, with a subsequent impairment of the gut barrier integrity and bile acid metabolism. Woodford (24) suggested that the diverse presence of opioid receptors across all major human organs provides insights as to why the effects of A1 β-CN and BCM7 have also been identified in relation to such diversity of organs. This hypothesis has also been supported by a different series of studies (22, 26), in which the pro-inflammatory role of the A1 β-CN and its effect have been confirmed, not only at the gastrointestinal level, but also on the endocrinological, neurological and cardiovascular systems. Despite the large range of evidence on the effects of food- derived opioids on delayed intestinal transit, intestinal inflammation, intestinal permeability and an altered microbiome, it is clear that, when analyzing the conclusions of the narrative reviews, considerable variability in evidence exists regarding the effect on non-communicable diseases. The four systematic reviews published between 2017 and 2021 (1, 5–7) constitute a tool for interpreting such variability. These reviews were all conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, with the aim of critically analyzing the existing data from well-controlled human clinical trials and animal studies on the impact of ingestion of A1 β-CN milk and A2 β-CN milk on health-related outcomes. The four systematic reviews concluded that consumption of A1 β-CN milk is associated with increased gastrointestinal transit times. As far as other health outcomes (CVD, diabetes, neurological diseases) are concerned, according to Kuellenberg de Gaudry and colleagues (6), the certainty of the evidence, according to the GRADE assessment, was judged as very low for most health outcomes considered in clinical trials and epidemiological studies published prior to October 2017. Using the same methodological approach, this was confirmed by Danilowsky and colleagues (1), for clinical trials and animal studies published prior to 2021 and for animal –based studies published prior to 2020 (7).

It can be, thus, concluded that, in order to unravel the possible role of particular β-CN variants and BCM forms in the development of non-communicable diseases, further longstanding clinical trials are needed with more participants from different geographical regions, gender, and age.

The Physicochemical, Technological, and Functional Properties of A2 Variant of Cows' Milk β-CN

The bibliographic search highlighted that the majority of the published reviews scarcely considered the quality-related aspects associated with the A2/A2 genotype in milk and dairy products, or specific technological aspects, including cheese-making. When considered, the majority of the reviews (**Table 2**) reported the effect of processing/manufacturing techniques on the amount of BCM-7 released by food products containing either A1 or A2 β-CN. The only exception is represented by the very recent article by Gai et al. (8), that described in details most of the studies conducted until 2017 that were not addressing health-related aspects of A2 β-CN variant.

The amount and the generation of BCM-7 and related peptides during the manufacturing of different dairy products were revised multiple times in the past. BCM-7 was reported as detectable in a number of dairy products before and after SGID (milk, cheese, laboratory-made yogurt, and other dairy products) (9, 12, 13, 21, 26). BCM-7 in cheese was reported as not originating from that originally present in milk, since peptides would be removed from the curd during the drainage of whey (9). Also, manufacturing and ripening in matured cheeses, and proteolysis by lactic acid bacteria and probiotics, are thought to exert a pivotal role in modulating the release BCM-7 before and after SGID (26). For instance, BCM-7 was reported to be higher in mold cheeses (Brie and Rokpol) than in semi-hard cheeses, although proteolytic enzymes from cheese starter cultures were reported to reduce its amount during ripening (9). On the contrary, the occurrence of BCM-7 in yogurt has been rather controversial, and mainly reported for non-commercial, laboratory-scale yogurt manufacturing (9, 26), probably because of hydrolysis by specific yogurt bacteria (13). BCM-7 was largely detected in infant formulas (2), including some formulas produced by A2/A2 β-CN milk, thus indicating a possible problem of purity, in particular because of the presence of added proteins in the formulation (mainly whey protein concentrates and isolates), rather than being generated by processing itself. The release of BCM-7 during SGID of sterilized infant formulas was hindered by protein glycation (26).

The qualitative parameters revised by Gai et al. (8) included productive traits (milk yield and composition, coagulation attitude), as well as physical properties, of different variants of β-CN, including foaming, emulsifying and heat stability. The structural and conformational changes brought by the substitution of Pro/His in the β-CN sequence in A2 vs. A1 variant, indeed, occur in the hydrophobic part of the sequence, and may affect some technological aspects of the different isoforms, as emulsifying and stabilizing properties. For instance, the higher Pro content of A2 variant, increasing the formation of polyproline helices, seems to ultimately improve its chaperone ability.

Early reports on the milk quality traits in A2/A2 genotyped bovine breeds were mostly focused on productive traits, such as milk yield, protein and fat yields, and on the overall casein concentration. The β-CN A2 variant has been positively associated with higher milk yield and protein yield when compared to A1, while the contrary has been reported for fat percentage and yield (8). These characteristics may be enhanced by association of β-CN variants with specific κ-CN genotypes, such as for the composites A2A2-AB, A2A2-AA and A1A2-AE of β-κ-CN, positively correlated with milk and protein production, while variants A1A1-BB, A1A1-AB and A1A1-BE were associated with high fat percentage. More studies are required to better elucidate the effect of composite phenotypes or haplotypes on these aspects, and on the technological properties of milk, in order to possibly disclaim the overwhelming role of associated κ-CN variants.

One of the most frequently investigated aspect of A2/A2 milk was its poorer coagulating capacity than that of A1/A1 and A1/A2 β-CN milk (8). Several authors reported a higher occurrence of the A2 variant in non-coagulating milk, a longer coagulation time, looser curd formation, and a lower cheese yield. The reasons for this lower attitude toward rennet coagulation were mainly related to a lower exposed hydrophobicity, which results in more soluble isoforms, or in larger micelle size (2, 8). Indeed, the casein micelles in A2 milk were characterized by a larger particle size and lower negative ζ-potential, more random structures, and fewer α-helical structures than in A1 β-CN milk. The tendency to form looser curds may ultimately result in softer gels, characterized by larger pores, and a less dense protein network, also at the end of yogurt fermentation with A2/A2 β-CN milk. The resulting yogurt may therefore be more delicate and prone to deformation, but probably also more rapidly digested in the human stomach (8). For coagulation, the association of A2 β-CN variant in specific haplotypes with κ-CN also seems to result in higher occurrence of poorly or non-coagulating milk, as for A2A2-AA, A1A2-BE and A1A2-AE composite genotypes. Other technological aspects that were reported to be modified by specific β-CN variants were related to milk emulsifying and foaming properties. A2 variant has a more acidic pI than A1, and is therefore more soluble, reaching the oil droplet surface more rapidly. The presence of an additional proline in A2, as mentioned above, increases the content of polyproline-II helix, leading to a less ordered structure, that may influence the emulsifying properties and the foaming properties. Gai et al. (8) reported that the influence of β-CN A2 variant on foam formation and stability has been controversially reported in different studies, with poorer foaming capacity, or better foaming properties compared to A1, probably due to the different methods used in the formation of the foam.

CONCLUSIONS

When analyzing the available evidence by means of a systematic approach, it is possible to conclude that consuming cows' milk containing A2 β-CN, instead of A1 β-CN, results in an overall improved gastrointestinal status and reduced milk related gut discomfort. As far as the technological traits are concerned, some differences have been observed among cows' milk containing either A2 β-CN or A1 β-CN, with A2 β-CN milk usually associated with poorer technological properties. The presence of an additional proline in A2 was reported to have a major impact on the hydrophobicity of the protein, thus leading to less ordered structures, that ultimately impact both casein micelle size, emulsifying and foaming properties, as well as the formation of rennet and acidic curd.

AUTHOR CONTRIBUTIONS

MGB: conceptualization, writing original draft, and formal analysis. CL: writing original draft and formal analysis. SC: writing original draft. MGF: writing review and editing. LC: conceptualization, writing review and editing, and supervision. All authors have contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.842375/full#supplementary-material

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MINI REVIEW
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Dietary Patterns vs. Dietary Recommendations

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Dietary Reference Values (DRVs) are important for developing labeling laws, identifying populations at risk of over- or under-consumption, and promoting public health interventions. However, the process of developing DRVs is quite complex, and they should not be viewed as recommendations ready to use or goals for individuals. Rather, they require interpretation by professionals and can form the basis of dietary advice. On the other hand, focusing on foods rather than macronutrients can assist individuals in understanding a healthy diet by taking into consideration many variables that may help compliance with a healthy dietary style. Evolution, tradition within specific geographical and historical contexts, taste, economic affordability, season-associated local dietary resources, and lifestyle may all explain the increasing popularity of dietary patterns that are highly successful today. Three models (the Mediterranean, New Nordic, and Japanese) have been recently characterized for geographical setting and food composition, as well as the associated lifestyle. Of note, all these three models rely on pyramids sharing a large basis made up of local vegetal resources and a top of red meats (allowed in many cases, but in limited amounts), thus allowing for the urgent demand of sustainability for the planet's health. This mini-review aimed to summarize the meaning of DRVs and to describe the dietary patterns that better contemplate health, diet diversity, and sustainability.

Keywords: dietary recommendations, dietary patterns, sustainability, food preferences, complementary feeding

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INTRODUCTION

Dietary Reference Values

Dietary reference values (DRVs) are an umbrella term for a set of nutrient reference values. DRVs are the instruments for nutrition and health professionals to evaluate dietary habits and plan diets at the population level. On the one hand, these instruments allow for the identification of populations at risk of over- or under-consumption. On the other hand, they mainly refer to healthy individuals' needs since people who suffer from diseases usually have different requirements. Overall, DRVs provide the scientific basis to build nutrition recommendations and establish dietary guidelines. They are also useful for scientists involved in nutrition research and for the food industry and as they form the basis for food labeling (1).

The term "DRVs" includes the average requirement (AR), the population reference intake (PRI), the adequate intake (AI), and the reference intake range for macronutrients (RI). The AR and PRI describe the distribution of requirements in a population. These give the intake of a nutrient that meets the physiological daily needs of, respectively, half or most (97.5%) of the people in the population. Assuming normality for the distribution of the individual requirements for a nutrient, the PRI is calculated as the AR plus two times its standard deviation (SD). The AI and RI are calculated when there is insufficient scientific evidence to determine the AR and the PRI. The AI is the level of intake that is assumed to be sufficient based on observations from groups of apparently healthy people and it is interpreted as the PRI. RI indicates the range of intakes of an energy source that is adequate for maintaining health and is proposed for fat and carbohydrates based on their relative contribution to total energy intake. In the end, DRVs include a tolerable upper intake level (UL): the maximum quantity of a nutrient that can be consumed without generating adverse events over a long period of time (1). This article is a narrative mini-review that aims to summarize the meaning of DRVs, their translation into recommendations, and to characterize the dietary patterns that better contemplate health, diet diversity, and sustainability.

Translating DRVs to Population-Based Recommendations

A healthy diet has a significant impact on health and ensuring that the population eats a healthy diet remains a public health challenge (2). As a general principle, achieving a healthy diet is possible by basing a diet on a variety of whole foods, such as fruits, vegetables, legumes, whole grains, nuts, seeds, and fish, in place of poorer quality highly processed foods. The diets that better comprehend these models are the Mediterranean, the New Nordic, and the Japanese. Each model encapsulates the culture of a population, its identity, and traditions. All of these are healthy patterns that, even with differences between each other's, since they are based on the respective local foods, share some important aspects. These patterns have in common: a great consumption of fresh fruits and nuts, vegetables, legumes (source of fiber, polyphenols, and plant proteins), cereals, and fish, and a low consumption of meats. Pyramids are visual and easy-to-understand tools for dietary guidance and nutrition education.

The Mediterranean Diet

The Mediterranean diet (MD) is based on the traditional foods that people used to eat in countries bordering the Mediterranean Sea. It is a dietary pattern based on the high consumption of plant-based foods, such as vegetables, whole grains, nuts, fish, and extra virgin olive oil, allowing moderate consumption of wine. It has been associated with a variety of benefits, since the 1960s, when the Seven Countries Study showed that mortality due to coronary heart diseases in the Mediterranean area was 2–3 times lower than in North Europe and the United States (3). According to different meta-analyses and large cohort studies, a two-unit increase in adherence to the MD has been associated with a reduced risk of mortality by 8, 17, and 6%. Higher levels of adherence seems associated with higher values of risk reduction (3, 4).

The Japanese Diet

The traditional Japanese diet (JD) has been widely considered as healthy, contributing to longevity and protecting against several non-communicable diseases (NCD) (5). A JD pyramid has been proposed by Kanauchui et al. (6). It is characterized by the moderate consumption of green tea (≥2 cups/day), at the base of the pyramid, followed by rice, miso soup, vegetables, and fruits that should be eaten every day; followed by a high consumption of fish (≥7 times/week), soy products and pickles (≥6 times/week), seaweeds, mushrooms, and Japanese-style confectionery (i.e., wagashi). At the top of the pyramid, there are meats and meat products as foods to limit.

The New Nordic Diet

The New Nordic diet (NND) is a dietary pattern conceived starting in 2004 and characterized by foods that are traditionally consumed and locally available in the Nordic countries. It wants to emphasize the values of potential health-promoting and gastronomic properties, sustainability, and identity of that region (7). Because of the Nordic climate, the typical foods are represented by native berries, legumes, apples, pears, root vegetables, cabbage, cauliflower, curly kale, onions, and mushrooms, as well as barley, wheat, spelt, oats, buckwheat, and rye thrive. It also implies regular fish consumption, seaweed, free-range animals and wild game (8).

Dietary Patterns as Cultural Models

Besides the importance of these dietary patterns in terms of health, it is worth to be highlighted their role as comprehensive cultural models that underline the importance of traditional cuisine as a means of sustainable development. In the United Nations Educational, Scientific, and Cultural Organization (UNESCO) Representative List of the Intangible Cultural Heritage of Humanity, three dietary traditions have been inscribed: the MD, the Mexican traditional cuisine, and the Washoku, traditional of the Japanese, notably for the celebration of New Year (9).

The MD, as seen in the above paragraph, is associated with health benefits, and it involves skills and traditions concerning crops, harvesting, fishing, animal husbandry, conservation, processing, and cooking. Sociality has an important role in the MD diet: eating together is the foundation of the cultural identity of communities throughout the Mediterranean basin. Shared meals represent a moment of social exchange and intercultural dialog (10).

Traditional Mexican cuisine comprehends farming, ritual practices, age-old skills, culinary techniques, and ancestral community customs and manners. The basis of traditional Mexican cuisine is the collective participation in the food chain, from planting the seeds to harvesting, to cooking and eating. The diet is founded on corn, beans, and chili and on native ingredients, such as tomatoes, squashes, avocados, cocoa, and vanilla (11).

Washoku is a Japanese social practice built on a set of skills and knowledge, strictly connected to the production, processing, preparation, and consumption of food. Respect of nature is central to this practice, and it is closely related to the sustainable use of natural resources. The Washoku characteristics are typically seen during New Year celebrations, when Japanese people make special meals that have a symbolic meaning, using beautifully decorated dishes and tableware to welcome the deities

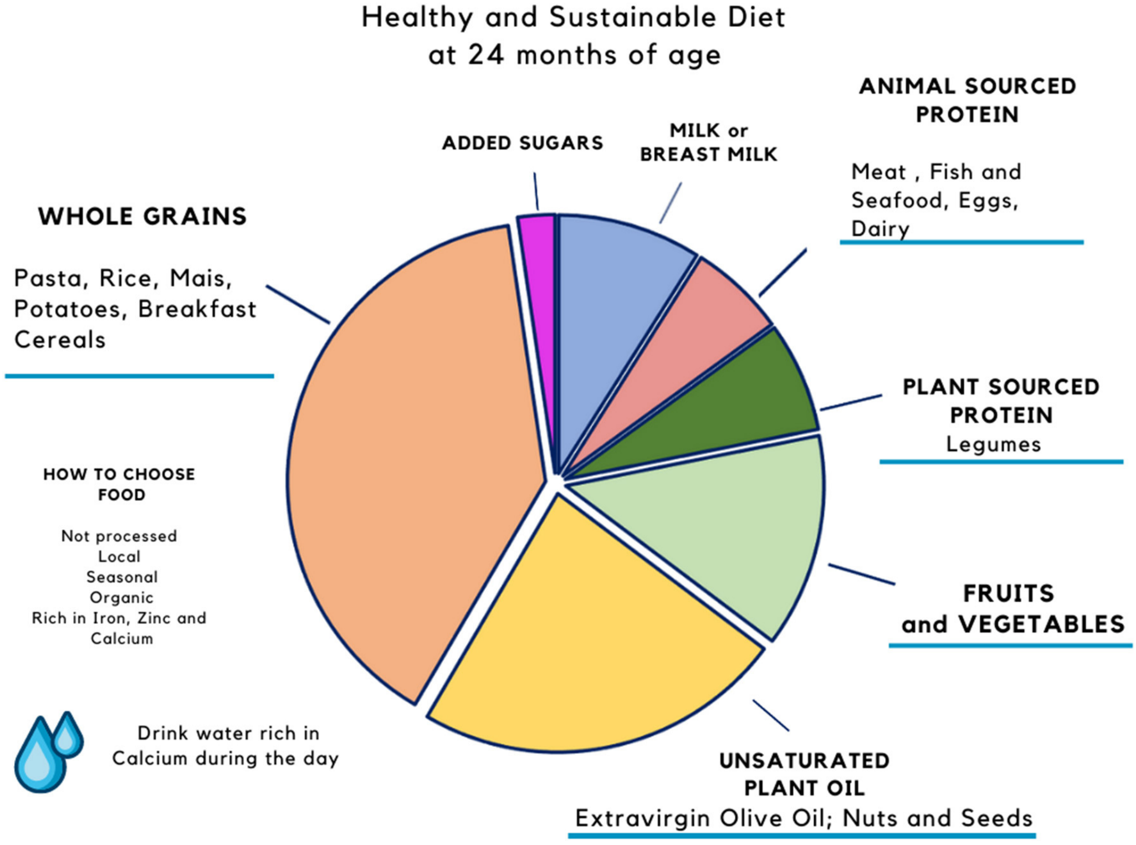

FIGURE 1 | Healthy and sustainable diet at 6 months of age. Proposal of diet at 6 months of age. Percentages refer to the total amount of calories required per day by each food group for a 6-months old baby. From Mazzocchi et al. (15).

of the incoming year. Washoku favors the consumption of various natural, locally sourced ingredients, such as rice, fish, vegetables, and edible wild plants (12).

DIET DIVERSITY AND SUSTAINABILITY

An additional measure to consider when describing the value of a certain nutritional pattern is diet sustainability and diversity. Nowadays, the challenge is to prefer and follow the so-called "win-win diets," which are dietary models built to preserve both human health and planet sustainability (13). This means nutritional patterns with evidence in the prevention and contrast of diet-related non-communicable diseases and with a positive influence on the stability of the earth's system reducing greenhouse-gas emissions, pollution, climate change, freshwater and land consumption, and biodiversity loss (14). Achieving a healthy and sustainable diet relies on preferring vegetable, organic, and minimally processed foods, as well as regional, seasonal, and fair-trade products (15). There is not a single valid green model of the food system in the world, but, in the European scenario, the MD and the NND reflect the principles of sustainable nutrition. As seen above, these nutritional patterns recommend a daily consumption of plant-based foods with a low ecological footprint. In terms of human health, the choice of this kind of products guarantees a greater supply of vitamins and minerals and other "non-nutrient" compounds, such as the fiber, which, in turn, promotes better general well-being (e.g., higher antioxidant activity, cholesterol control, and weight-body maintenance) (16). In terms of planet health, the shift from animal to plant-based foods, such as vegetables, fruits, legumes, and cereals, could reduce the environmental impact in all the different phases of the food supply chain (production, transformation, distribution, preparation, consumption, and waste management) (17). Empathizing local and seasonable products aids the regional economy as well. Considering a projected population growing to about 10 billion by 2050, the transformation of nutritional habits toward more green models is a challenging goal for the single individual, the whole population, and the next generations.

CHILDREN'S FOOD PREFERENCES, TASTE EXPERIENCES, AND PARENTS' DIET

Sustainability goes hand in hand with diet diversity. The definition of diet diversity is "the number of different foods or

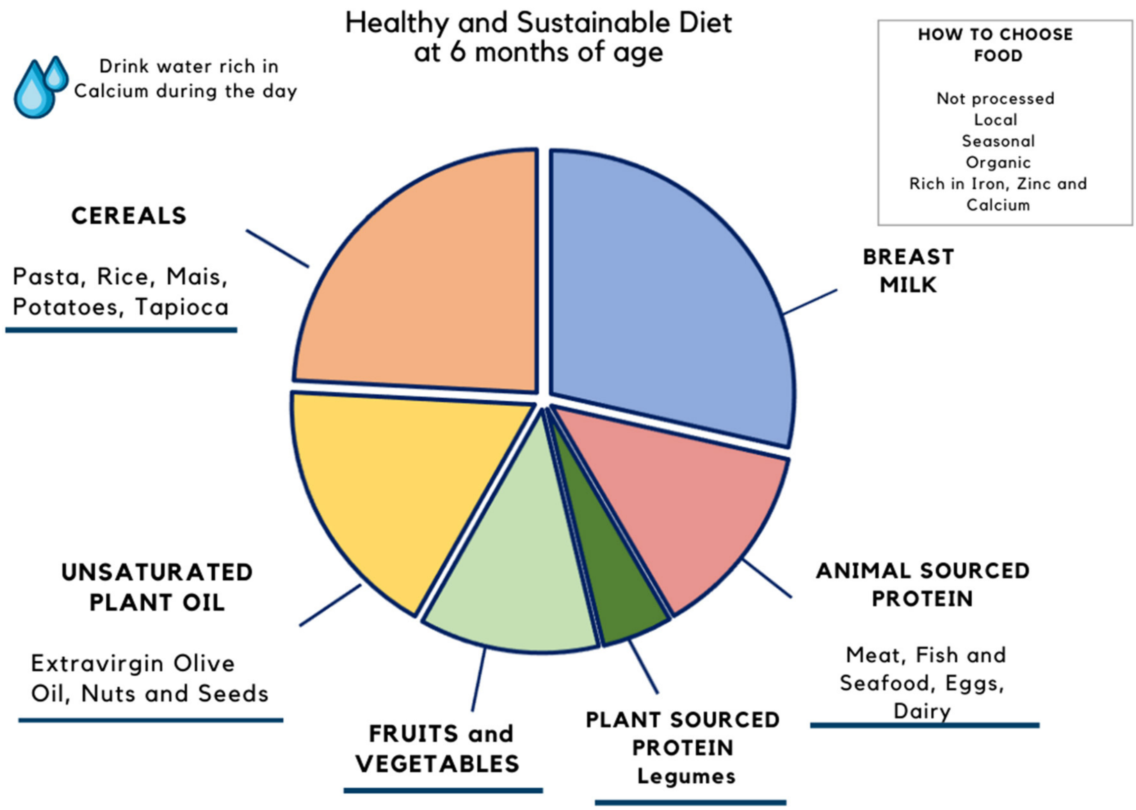

FIGURE 2 | Healthy and sustainable diet at 24 months of age. Proposal of diet at 24 months of age. Percentages refer to the total amount of calories required per day by each food group for a 24-months old baby. From Mazzocchi et al. (15).

food groups consumed over a given reference time period." As a matter of fact, diet diversity means: seasonability, predominant vegetal over animal sources, lower emissions of greenhouse gases, and nutrition positive for the human microbiome. The predilection for plant-based, local, seasonable (and organic) foods helps to preserve the biodiversity of products, the landscapes, and the sea, and maintains the local economy (16).

Early dietary styles may be adopted from the beginning of complementary feeding (CF), a precious period in which essential nutrients must be provided to the infant and healthy dietary patterns should be established. Offering infants seasonal and local foods is a strategy to favor their acceptance and to create a habit of consumption that will last through adolescence and adult life. The recommendations from the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) state that a varied diet since the initial stages of CF should be offered to infants. Exposing infants to foods with different tastes and textures, such as bitter-tasting green vegetables, is preferred (18). Infants have an innate refusal of bitter tastes and a preference for sugar and salty foods. Families may modify these preferences doing the right choices of foods to offer. Parents' attitudes regarding the nutrition of their infants have an important role, too. It is demonstrated that responsive parenting intervention, oriented to promote the self-regulation of children, initiated in early infancy, when compared with a control intervention, results in a reduction in BMI *z*-scores at an age of 3 years (19).

Complementary feeding is important not only for the child's growth, attitudes, and preferences but also for reorganizing the dietary choices of the whole family. It is the *window* in which new eating habits may be established, shifting the choices toward more sustainable and diverse foods, avoiding food waste. In the previous article from our group, we proposed two models of a sustainable diet that respects EFSA nutritional recommendations for an infant between 6 and 24 months of age fed breast milk on demand and 2 complimentary feeding meals (15). These models are reported in **Figures 1**, **2**. Besides the macro- and micronutrients composition of plates, the practical advice to develop a sustainable behavior are: (1) prefer foods produced close to home, especially fruits, vegetables, and legumes; (2) choose non-processed foods, without added ingredients; (3) prefer non-packaged meals (15).

For a better understanding of the child's dietary pattern, the role of the parents' dietary pattern has been recently studied in a few reports. A study involving more than 2,500 mother–child pairs in the United States found that total fat intake was similar between maternal and child's diets (20). A survey conducted among 1,640 children identified a strong association between maternal and 3-year-old children's diet (21). Finally, a very recent study conducted in Iran observed inverse associations between mother–child dyad protein dietary intake and the risk of being underweight and wasting in children (22). These data highlight the importance of shared family dietary patterns that should be better explored in the context of the Japanese, the Mediterranean, the New Nordic, and the Mexican traditional cuisine diet models.

DISCUSSION

In our epoch, the two extremes of malnutrition coexist. Undernutrition and overweight, or obesity, represent both an actual burden to contrast. These two conditions can sometimes affect the same person in life: an individual who is overweight today may have had a nutritional deficit earlier in life, even in the intrauterine life. To provide healthy and sustainable dietary models, as those discussed in this article, an adequate nutritional intake, both regarding quality and quantity, especially when we consider essential nutrients important to preserve health during the life course, should be concurrently considered. This concept must be accounted for, especially in critical *windows* of life (such *windows* as infancy or the reproductive age), which are more sensitive to an optimal dietary intake (23).

Dietary patterns include sustainability (for the planet) and health (for the individual). Some dietary patterns coming around the world, particularly, we described the JD, the MD, the NND, and the Mexican Traditional cuisine as effective ways to promote a diverse and sustainable diet. From an evolutionary perspective, we may understand that "evolution-drivers" among dietary patterns exist, since nutrition evolved in different settings (23). Accordingly, foods locally selected through evolution should be the most indicated for local populations, following the season's cycles. On the other hand, the increasing availability of processed or ultra-processed food should not be ignored, and its potential effects both on health and the circular economy in the context of these models deserve new approaches and investigations (24).

This review has the strength to be a summary of dietary patterns that have both health and cultural implications. It highlights the importance of learning how to make conscious choices since infancy. By narrowing all these aspects to the complex system of personalized nutrition and sustainability, we may expect to personalize the same dietary patterns in turn. Food diversity represents the perfect connection between sustainable and personalized nutrition (25). As an example, a study aimed to challenge personalized nutrition within children following the pattern of MD, with a collaboration between Italian groups in Naples and Israel is currently ongoing. Nevertheless, some of the first researchers in the field of personalized nutrition have underlined, that even prediction models are not able to achieve a full prediction (e.g., of the glycemic response) (26) and that many confounders still need to be accounted for (27). Very few nutritional intervention trials have been planned to get long-term observations to derive useful indications. These factors have been recognized as possibly limiting the effects of personalized nutrition. Therefore, genetic heredity comes first, then the epigenetic changes through an evolutionary perspective (with the derived local lifestyle and dietary patterns), and third, the acute responses to acute changes, whose duration is highly debatable.

From a social epidemiological perspective, preserving these cultural inheritances is a way to achieve planetary health for our and future generations. In line with the present and prospective applications of personalized nutrition, future research in social interventions aimed to improve socioeconomic conditions and spread the knowledge regarding how to preserve the planetary health, at a population level, may be a target point in primary prevention.

CONCLUSIONS

A healthy and sustainable diet is possible from infancy, but only if all aspects of the individual are concurrently considered. DRVs are important for supporting public health. Healthcare providers should help and encourage families to follow a sustainable diet from the start of CF in their children. The role of shared dietary patterns should be considered within these interventions.

We proposed two models of an ideal diet at 6 and 24 months that take into consideration both the nutritional needs of the child and the ecological footprints (15). Future studies should investigate the reliability and effectiveness of such models in the real life.

AUTHOR CONTRIBUTIONS

VD, AM, and GM drafted the manuscript. VD arranged the references. CA proofread the manuscript. All authors contributed significantly to the article, agreed on the manuscript in its current form, read, and agreed on the published version of the manuscript.

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MINI REVIEW
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Food Innovation in the Frame of Circular Economy by Designing Ultra-Processed Foods Optimized for Sustainable Nutrition

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Despite the large debate about the relationship between ultra-processed foods and the prevalence of some diet-related diseases, the innovative potential of various processing technologies has been evidenced in pathways that could lead to modifications of the food matrix with beneficial health effects. Many efforts have been directed toward the conjugation of a healthy diet and sustainable exploitation of natural resources for the preparation of accessible foods. This minireview highlights the possible links between processing, sustainability, and circular economy through the valorization of by-products that could be exploited to prepare nutrient-rich ingredients at lower economic and environmental costs. The assessment of the quality and safety of functional foods based on ingredients derived from food waste requires a more robust validation by means of the food-omics approach, which considers not only the composition of the final products but also the structural characterization of the matrix, as the bioaccessibility and the bioavailability of nutrients are strictly dependent on the functional characteristics of the innovative ingredients.

Keywords: by-products, food processing, food-omics, functional food, sustainability

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INTRODUCTION

Six classification systems have been identified to classify foods and beverages based on processing levels, including the International Food Information Council, the International Agency for Research on Cancer, and NOVA classifications (1). In particular, the NOVA classification system introduced the term "ultra-processed" food (UPF) as a new class that adds to the previous triad of unprocessed (NPF), minimally processed (MPF), and processed foods (PF). As processing changes the physical, chemical, and biological properties of foods, the level (intensity, duration, and number of processes) and type of technology used in the processing operations are relevant for determining shelf life, food safety and quality, and the bioavailability of nutrients (2). UPFs are formulations of ingredients, most of exclusive industrial use, that result from a series of industrial processes, including the fractioning of whole foods into substances, chemical modifications of these substances, assembly of unmodified and modified food substances, frequent use of cosmetic additives and sophisticated packaging (3). This way, food classification moves away from traditional food groupings (e.g., "grains and grain products" and "meat and meat products"), and not necessarily consider established methods based on nutrients (e.g., sodium, dietary fibers, saturated fat, and added sugars) (4).

As consumers find a wide variety of affordable, palatable, accessible, and stable UPFs, they now account for a substantial share of overall food intake, with significant heterogeneity across countries and socioeconomic strata. For example, the lowest intake was observed in Italy with around 10% of total kcal from UPFs and the highest in the United States and the United Kingdom with over 50% of total kcal from (5). It was recently observed that UPFs consumption is associated with a deterioration in diet quality, with UPFs intake being negatively correlated with fibers and protein and positively correlated with sugar, fat, and saturated fat intake (6). From a nutrient point of view, UPFs have on average a higher energy density (2.3 vs. 1.1 kcal/g) and a lower nutrient density than minimally processed foods (7). Moreover, changes in the food matrix can also alter nutrient bioavailability and UPFs tend to be more hyperglycemic than MPFs (8). Moreover, the high palatability of UPFs has the potential to promote a faster eating rate and energy overconsumption, as they are consumed more quickly, also due to a reduced oro-sensory exposure time, delaying the onset of satiation (9).

Although epidemiologic evidence has been postulated for the association between UPFs and health, most of the observations linking UPFs to diet-related diseases derived from studies conducted with food questionnaires that are not specifically validated for UPFs, although some efforts have been made in this direction [e.g., (10, 11)]. Descriptions of UPFs within the NOVA system vary with distinguishing features including single vs. 2–3 vs. $\geq$5 more ingredients, natural/fresh vs. imitation or industrial, and whole foods vs. fractioned substances. This means that different studies may have classified the same food as UPFs or not based on the distinguishing feature used for classifying foods (5). Even for the only intervention study so far conducted to investigate the impact of UPF on human health, the choice of UPFs was arbitrary and not representative of the whole range of available items, notably spanning different nutrient/energy densities (12). Thus, further efforts are essential to confirm the results previously obtained and to investigate further the association between UPFs consumption and health status, also considering the actual contribution within different dietary patterns, which has been less investigated to date (5). Moreover, the series of inconsistencies originated from the lack of a shared definition of food categories associated with UPFs, and a common language among nutritionists, food scientists, and technologists, have led to a semantic debate, rather than a scientific one, on the motivations for adopting strategies that reduce the consumption of UPFs, as a whole (13). Indeed, the drastic reduction or elimination of the availability of all categories of UPFs without simultaneous consideration and efforts to replace them with better, affordable, and practical alternatives is not a winning strategy. Nevertheless, eliminating UPFs that provide many desirable properties (economic, microbiological safety, nutrient fortification, extended shelf life, and affordability) can only worsen existing disparities in food insecurity (14). Moreover, ingredients and processing should not be considered independently, as the nutritional content largely depends on the recipe (ingredients) and not exclusively on the preparation procedure. Avoiding foods considered UPFs, such as whole/enriched bread and grains or flavored milk, may not address obesity but may reduce the intake of folate, calcium, and dietary fibers (15).

Rather than eliminating ready-to-eat (RTE) or ready-to-heat (RTH) UPFs, their usefulness in food use and the household should be recognized, considering that their reformulation, rather than elimination, could have a more significant impact on improving nutritional quality and health at the population level (14). For this purpose, some nutrient-based quality descriptors should be selected, such as the nutrient-rich food index (NRFI) based on the content of protein, fibers, vitamins, minerals, saturated fat, and added sugar and sodium (16). Studies comparing UPFs with respect to their NRFI show that most UPFs have low nutritional quality, but some are high, thus evidencing that the inclusion of an item in the category of UPFs is not a synonym for bad quality. According to the same index, most MPFs have high nutritional quality, but some are still low quality, and the consumption of the latter should be minimized as well (7). Taking for granted that the simple NOVA classification cannot be adopted alone, and a better definition of food quality must include the actual molecular composition, new formulations for UPFs could be achieved, improving their nutritional quality.

ADDING NUTRITIONAL VALUE TO ULTRA-PROCESSED FOODS

While the dilemma on the link between ultra-processing and the onset of food-related diseases cannot yet be definitively resolved, the idea that the composition of UPFs can be improved through reformulations richer in noble nutrients remains valid. Thus, reformulation strategies tend to enrich largely consumed foods with proteins, vitamins, or dietary fibers, while reducing, if not eliminating, nutrients that in prevalent diets normally exceed the recommended doses, such as saturated fats, sodium chloride, or simple sugars. Such a strategy is driving the development of "Healthy" UPFs, often plant-based alternatives, carrying nutrition claims such as "fat-free," "reduced salt," "low sugar" or "added fibers" according to the nutritional guidelines and the CE Regulation n. 1924/2006. Other "healthy" UPFs, such as fortified bread, have been suggested to be important sources of vitamins and minerals, and the avoidance of such UPFs may lead to micronutrient deficiencies (17). It is worth noting that foods are not simple homogeneous mixtures and formulations must also consider the nature of the substituting ingredients, as the structure of the food matrix, and consequently the bioavailability of the nutrients, is deeply affected by the tight coupling of chosen sources and applied technologies. To this end, food technologists, inspired by nutritional goals, can take advantage of ultra-processing technology to design healthier foods, making them more appreciated, therefore more frequently consumed (**Figure 1**). While food fortification would be a solution, any strategy based on it would have to consider the actual exposures of different population groups. Conversely, the transition to the

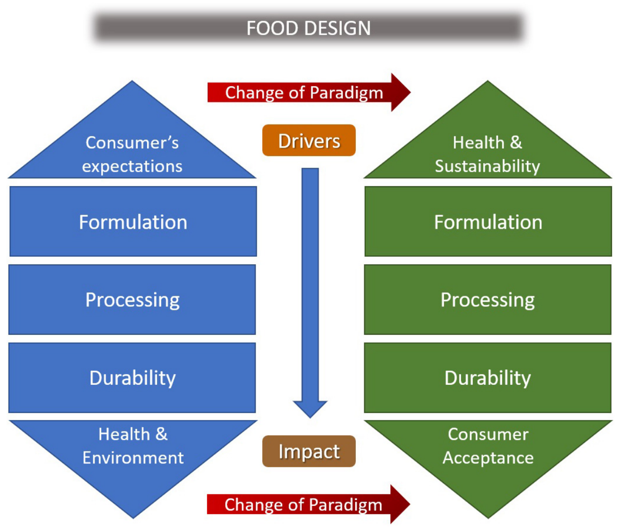

FIGURE 1 | A new paradigm in the development of innovative products should be considered by the industrial food value chain, where the healthiness is no more a tentative consequence of the intended result. Current efforts are mainly directed to fulfill the consumers' compliance, based on tangible attributes like sensorial acceptance and economic affordability. In a new food system, the main driver for food design must be the healthiness attribute, while selecting sustainable ingredients and technologies, to get the best market acceptance.

reduced content of some ingredients, e.g., salts or other additives, cannot be pursued by simply eliminating them, so as not to expose consumers to pathogenic risks. Thus, reformulating does not mean a simple elimination or substitution but can involve a complete redesign of the food in its entirety. In this regard, the interconnection between different types of experts is mandatory to promote solid food design for healthy and necessary products tailored to the right target group.

In addition to the mandatory safety requirement, another factor must be considered when designing a tailor-made food, namely consumer acceptability. Even if the elimination of an ingredient does not involve safety risks, the very existence of a product in the form that consumers do expect can be compromised. In bakery products, such as cookies and cakes, sugar is one of the main components, contributing up to 30–40% of the total recipe, and intense scientific research is performed regarding the replacement of sugars with more healthy alternatives. However, the reformulation of confectionery and bakery products with a substantial reduction in sugars has proven difficult due to the multiple functionalities that sugars exert in bakery products, next from simply providing sweetness. Sucrose cannot just be replaced by a single compound, but a mixture of compounds, assuming that sweetness and color can be decoupled from structural and textural attributes like firmness, crispiness, and dryness. Rather than proceeding empirically, by trial and error, to find an optimal formulation, considerable progress has been made in building digital tools to predict the outcome of a substitution. Recently, van der Sman and Renzetti (18) made much progress in developing a numerical model, incorporating predictive thermodynamic theories, for optimization of sugar-reduced formulations in an effective and efficient manner, also providing guidance for replacement strategies (e.g., by the inclusion of dietary fibers). The technological operations underlying the production of UPFs are often accused of being destructuring the natural matrix that constitutes food, a fact considered deleterious for the quality of food, as the matrix is seen as an intrinsically positive constituent of the raw food, which is lost in its transformation into edible food. It has been suggested that the presence of acellular nutrients, food additives, non-energetic artificial sweeteners, and possibly advanced glycation end products, as well as the lack of fermentable fibers and phytochemicals, could be responsible for the altered composition and metabolism of gut microbes (19).

As mentioned before, the destruction of the barriers exerted by the compartmentalization of animal tissues and, even more, of plant tissues, makes nutrients immediately available for absorption, creating glucose peaks in hematic concentrations that can overload normal physiological functions, thus generating a low-grade systemic inflammation (20). For this reason, considering the disintegrating capacity, the most offending practices for food processing include the fractionation, which transforms raw ingredients or whole foods into simple molecules such as sugars, oils and fats, proteins, starches, and fibers. Some of these substances are then subjected to hydrolysis hydrogenation, or other chemical modifications to make them even more suitable for their incorporation in formulations, using industrial techniques such as extrusion or molding. It is worth mentioning here that some population groups (e.g., the elderly, infants, or pregnant women) can benefit from readily available crucial nutrients. Likewise, nutrient deficiency associated with poor bioavailability is also relevant for malnourished populations who consume only raw or whole foods. Certainly, it is not only the number of nutrients that counts but also, and above all their quality. Therefore, it is necessary to ensure that the nutrients made available best meet nutritional needs.

A further criticism of the artificial nature of the UPFs assembly is the use of cosmetic additives, which include substances selected to improve aroma, enhance flavor, give attractive color, stabilize emulsions or gels, sweeten, thicken or, conversely, increase the volume of food preparation. These classes of additives can also be used to hide undesirable sensory properties created by ingredients or processes. For this reason, their use is seen as a camouflage of poor quality, and consumers are pushing for "clean label" food, i.e., with low or no artificial additives while attributing a nutritional detriment to their use.

THE CONSUMER'S CHOICE FOR "CLEAN LABEL" FOODS AND NEW NATURAL IMPROVERS FOR ULTRA-PROCESSED FOODS

The "clean label" choice, initially associated with the absence of E-numbers in the list of ingredients, has driven the food industry to communicate whether a certain artificial ingredient or additive is not present in the food product (21). Additives are not optional as they are necessary for food stability and consumer acceptance. Even more so, when some excess ingredients are replaced by others, e.g., in "vegetable meat" or "gluten-free pasta," additives are mandatory. The challenge is to find natural ingredients instead of refined artificial ones, with optimal properties and suitable for use in food processing. Therefore, replacing a list of additives with a few natural ingredients that collect all the properties necessary to stabilize foods, would move UPFs away from the term "ultra" and wash them to be "clean." Thus, there is a significant trend toward the consumption of products with a clean label which is driving food researchers and technologists to explore new "natural" ingredients and processes for the preparation of novel foods. This new way of conceiving healthy and "green" foods must be demonstrated by scientific evidence with a measure of impacts on the human metabolome, looking at the food topic with a new perspective offered by the "foodomics approach" (22).

The food industry is constantly looking for new ingredients able to replace sugar's technological functionality while satisfying the consumer's request for a clean label. For instance, based on corn (*Zea mays*) and chickpeas (*Cicer arietinum*), a fiber syrup was tested as a bulking agent in cookies to reach up to 50% sugar reduction, allowing to obtain sugar-reduced cookies qualified for "reduced in sugar" and "high in fiber" nutritional claims (23). Regarding grain-based foods, it is noted that the world consumption of whole grains and legumes is significantly below what is recommended. The focus is being placed on new raw materials from little-used ancient cereals, pseudo-cereals, or legumes, but the main challenge remains to improve their technological and sensorial properties while avoiding the use of additives that would deviate them from the clean label. For this reason, non-thermal technologies have been explored as an alternative to additives (24).

As most additives are used to stabilize foods, more and more solutions are sought to replace them with treatments that adequately modify the structure of the ingredients to make them stable naturally. Among these, non-thermal treatments are emerging, such as high hydrostatic pressure (HPP), cold gas plasma, ultrasound, ozonation, ultraviolet and pulsed light, aimed at stabilizing food avoiding the use of chemical additives. They were originally developed to inactivate microorganisms and enzymes in foods, in alternative to conventional processing methods (e.g., boiling and steaming) that destroy nutritional components. Several studies have shown that such novel processing techniques generally perform better in maintaining the original characteristics of foods (25). In the case of cereal products, these technologies can be used at low temperatures to modify the most important component of wheat flour, i.e., gluten and starch, which are responsible for the rheological properties of wheat flour dough. Non-thermal technologies can be responsible for the denaturation of gluten or the debranching of starch. These changes can result in increased numbers of protein aggregates that can directly affect the elasticity and strength of the dough. Studies have shown that HHP can produce partially gelatinized starch that can improve water retention and rheological characteristics of the dough. In bread making, the damaged-starch content is important for dough hydration; however, the damaged-starch content greater than 10% and the presence of pre-gelatinized starch can overhydrate the flour and make it sticky, making the dough difficult to handle (24). For this reason, in the development of each specific formulation, the appropriate parameters should be finely optimized for each ingredient-technology pair. At the same time, the impact on the bioaccessibility and bioavailability of the nutrients together with the sensorial properties of the new final product should be evaluated.

By combining new sources of nutrients and natural additives with the use of improving technologies, to make these ingredients more effective in their function, the exploitation of food industry by-products is an almost automatic consequence. This strategy, called circular economy, is successful when new nutritional sources, of equal or better quality than those used conventionally, are exploited because it has the merit of linking the demand for healthier foods with the sustainability of their production. Still remaining in the field of cereal-based products, the use of bread' leftovers that are withdrawn from the market due to texture issues, but that has not experienced microbial deterioration, is being considered. In this regard, research has shown that these materials could be incorporated to produce bread, cakes, or cookies (26). However, these additions can have negative implications on the quality of final products, especially on their organoleptic acceptability, which makes necessary focused research to minimize these negative problems, mainly by optimizing the percentages that can be incorporated to achieve final products with acceptable organoleptic properties.

Thus, the incorporation of ingredients derived from valorized agro-industrial by-products in "clean label" foods may be seen as a possible solution for replacing "artificial foods" with natural recipes. Interestingly, not only by-products obtained during the processing of cereals, such as bran and germs, are incorporated in grain-based food but also by-products from the fruit and vegetable industry (27). Martins et al. (28) collected, in a comprehensive review, a large collection of data on fruit by-products, including not only their content of nutrients and bioactive compounds but also their respective rheological and functional properties, in the optic of possible exploitation as natural ingredients in the bakery industry, with stabilizing and enhancing sensorial properties. However, using whole-wheat flour or the addition of dietary fibers, seeds, fruits, or flours from different sources is not a trivial practice, as they disrupt the starch–gluten matrix by affecting the viscoelasticity of the dough, resulting in lower-quality bread (24). The processing technologies, in particular those with a lower impact on the nutrient content, are increasingly explored to conjugate the content of sustainable and minimally fractionated ingredients with good taste. The great challenge is to collect ingredients, containing healthy nutrients that are deficient in a large part of the population, valorizing by-products and leftovers to exert a lower impact on the natural resources. The final goal of such a valorization route is a comprehensive scoring system that summarizes the quality of the food product in a way that sustainability and healthiness should be correctly emphasized together with the other quality

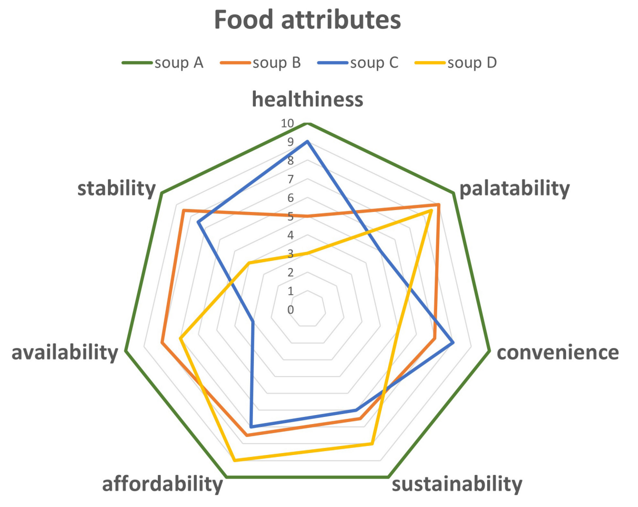

FIGURE 2 | The spider plot allows the consumer a rapid appreciation of all the attributes of food quality. Each colored line represents a food with different quality attributes. For instance, soup A is "healthier" than soup C, which conversely is more appreciated for its sustainability. The main challenge in this kind of representation is the arbitrary rationale behind the assignment of relative scores to each attribute, that must be normalized in an appropriate ponderal scale so that healthiness has the proper weight compared to the other quality attributes.

attributes conventionally addressed by the food industry to meet the consumers' acceptance (**Figure 2**).

INGREDIENTS FROM WASTE TO FOOD

In the previous sections, it has been highlighted how important, and at the same time difficult, is to design new foods using new natural sources to obtain ingredients and applying technologies capable of making these new ingredients suitable for the production of palatable food. The next step, addressed in this section, is to make this process also sustainable from the point of view of the impacts on natural resources. This need has become an absolute priority on the agendas of all policymakers. In fact, the EU prioritizes the sustainability of food systems and circular economy to reduce the environmental impact. It recommends the reuse of all waste suitable for human consumption to be reintroduced into the food chain (29).

The circular bioeconomy strategy starts from the premise that 30% of the world's food production is wasted and the whole current agrifood system consumes about 70% of the world's freshwater. Thus, recovering ingredients from wastes means a partial recovery of water, as well as other natural resources, for purposes, i.e., the human feeding, that was originally intended as the target destination of such exploitation. The adoption of advanced technologies, such as biotechnology, can procure novel foods and feed ingredients, to privilege pathways where functional properties are safeguarded and directly valorized into ingredients. A very recent review by Javourez et al. (30) classified 150 different biomass residues from ten categories of raw materials: (i) wood-related, (ii) primary crop, (iii) manure, (iv) food waste (from households or the service sector such as restaurants, etc.), (v) sludge and wastewater, (vi) green residual biomass, (vii) slaughterhouse by-products, (viii) agrifood co-products, (ix) C1 gases, and (x) others. They were further logically analyzed according to four ideal building blocks for conversion pathways transforming waste into ingredients for food or animal feed:

(i) Enhancement, i.e., increase of quantity, preservation, or accessibility of nutrients, without removal of any components.
(ii) Cracking, i.e., deconstruction of extremely recalcitrant structures to facilitate the release of nutritional compounds.
(iii) Extraction, i.e., selective solubilization and/or separation of a target fraction from a matrix
(iv) Bioconversion, i.e., conversion of feedstocks into nutritional ingredients using the metabolic processes of living organisms.

A resource is considered a food or feed grade ingredient when the nutrients contained within the ingested ingredients are released and assimilated without adverse effects. Besides composition and structural characteristics, safety is determined by the inherent features of the digestive tract. For this reason, what is considered safe for ruminants, could not be the same for humans. The nutritional quality of an ingredient is characterized by three main factors: (i) the absence of anti-nutritional compounds, (ii) the degree of structural complexity, and (iii) the concentration of macro- and micronutrients. Most residual biomasses cannot be considered food grade. Anti-nutritional factors often arise because of large heterogeneity and/or biological activity found in most of the leftovers (e.g., in food waste). Moreover, they include recalcitrant matrices that are incompatible with direct edibility. Accordingly, to transform waste into ingredients, a sequence of operations is required that breakdown structural barriers, remove harmful compounds, and possibly, enriches the assimilable nutrients.

One example of enhancement is represented by whole apple pomace (containing pulp, peel, seeds, and stems) collected from juice factories, immediately after pressing. Then, they are dehydrated at the industrial level and ground into flour used to fortify cookies, enriched with dietary fibers and flavonoids, produced by replacing 25% of wheat flour (31). Also, brewers' spent grains milled into bakery flour is another example of an enhancement pathway: the bitter taste and unpleasant mouthfeel, is eliminated by cleaning, drying, and milling the spent grains, and the ingredient is used to enrich dry pasta (up to 135% fiber, 57% resistant starch, 85% β-glucan), involving minimal effects on sensory properties of cooked pasta (32).

As far as the extraction pathway is concerned, proteins from defatted rice bran represent a valuable nutrient that is easily recovered by alkaline extraction, to obtain concentrate ingredients useful for preparing protein-enriched flour substitute in biscuits. A two-fold increase in the protein content of biscuits has been reported with the incorporation of 15% rice bran protein concentrate (33). Grass and vegetable leaves were also exploited as a source of a beneficial protein isolate that resulted in good gluten substitution in the bakery. A sequence of industrial operations, including mechanical disruption to extract green juice, removal of chloroplast membrane through heat treatment coagulation, ultrafiltration, hydrophobic column adsorption, and spray drying, was optimized to extract the rubisco protein from the cellulosic structure rich in phenol compounds (34).

From lignocellulosic feedstocks, by means of a cracking pathway, a detoxified hemicellulose hydrolyzate, has been manufactured. The hemicellulose hydrolyzate has been obtained through dilute acid hydrolysis and further bio-converted by fermentation with *Candida athensensis* to produce xylitol as an alternative sweetener (35). Feather is another interesting source of free amino acids and functional short-chain peptides, obtained by enzymatic conversion of keratin (yield of 50-60%). Although keratin constitutes <80% of dry matter of feathers, its resistance to digestibility makes such a protein useless as a nutrient (36).

The last pathway for the transformation of wastes in food ingredients is bioconversion: insects farming on food waste and microalgae cultured on aquaculture wastewater are emerging as sustainable practices for the exploitation of sources, coupling very high conversion efficiency of natural resources with low environmental impact and high nutrient density. Fractionation of insect biomass is currently the best option for broader adoption in western countries, as consumers may be reluctant to accept whole insects for cultural reasons. This suggests that the preferable approach would be to transform insects in meals, using protein and other fractions as food/feed ingredients. Processing of larvae into separate fractions may also address microbiological safety issues by killing bacteria during drying and extraction steps (37).

CONCLUSION

The definition of UPF for nutritional assessment is controversial, as it is mainly based, according to the NOVA classification, on the number of ingredients, which are refined and mostly artificial additives. However, since foods are not simple homogeneous mixtures, additives are not optional to obtain products that are also acceptable to consumers and appreciation is one of the most important drivers for consumption. Artificial additives are currently used to achieve the stability and good sensory attribute of foods, but these ingredients are viewed negatively by UPF detractors, describing these chemicals as man-made, non-natural, and possibly harmful to human health. For this reason, the reduction or elimination of these artificial additives is considered a further improvement also by nutritionists. Replacing a list of additives with a few structured ingredients that collect all the properties necessary to stabilize food, would move UPFs away from the term "ultra" and make them "clean label". The challenge is to find optimal natural ingredients instead of refined artificial ones, satisfying another emerging need dictated by society: zero impact on the environment.

The ecological transition, defined as the "Green Deal" by the European Union, must be applied in every production sector, especially in the agri-food sector where great exploitation of natural resources takes place. Greater efficiency of the production system, through more precise agronomic and breeding practices, is certainly the main pathway. However, considering that one-third of food production becomes waste, it is necessary to develop strategies that minimize waste, for example by increasing the stability of products over time. In addition, it must also recover value from any form of a by-product that contains non-negligible quantities of nutrients. Food technologies can help exploit ingredients derived from by-products through inclusion in foods with high functional and sensory qualities. However, this use of alternative ingredients and innovative technologies cannot ignore the healthiness of the final product. For this reason, the ever-closer collaboration between food technologists and nutritionists is necessary for the development of foods that will be part of the future diet in the name of environmental sustainability.

AUTHOR CONTRIBUTIONS

FC: accountable for the whole content of the work.

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Milk: A Scientific Model for Diet and Health Research in the 21st Century

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The origin of lactation and the composition, structures and functions of milk's biopolymers highlight the Darwinian pressure on lactation as a complete, nourishing and protective diet. Lactation, under the driving pressure to be a sustainable bioreactor, was under selection pressure of its biopolymers with diverse functions acting from the mammary gland through the digestive system of the infant. For example, milk is extensively glycosylated and the glycan structures and their functions are now emerging. Milk contains free oligosaccharides; complex polymers of sugars whose stereospecific linkages are not matched by glycosidic enzymes within the mammalian infant gut. These glycan polymers reach the lower intestine undigested. In this microbe-rich environment, bacteria compete to release and ferment the sugars *via* different hydrolytic strategies. One specific type of bacteria, *Bifidobacterium longum* subsp. *infantis*, (*B. infantis*) is uniquely equipped with a repertoire of genes encoding enzymes capable of taking up, hydrolyzing and metabolizing the complex glycans of human milk. This combination of a distinct food supply and unique genetic capability shapes the composition and metabolic products of the entire microbial community within the lower intestine of breast fed infants. The intestinal microbiome dominated by *B. infantis*, shields the infant from the growth of gram negative enteropathogens and their endotoxins as a clear health benefit. The world is facing unprecedented challenges to produce a food supply that is both nourishing, safe and sustainable. Scientists need to guide the future of agriculture and food in response to these 21st century challenges. Lactation provides an inspiring model of what that future research strategy could be.

Keywords: milk, lactation, genomics, oligosaccharides, bifidobacteria

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INTRODUCTION

The world is facing an urgent challenge: transform the existing agriculture and food enterprise into a sustainable, nourishing and health-promoting system. A daunting problem is the lack of knowledge of what we should eat. While necessary, obtaining all of the essential nutrients is not sufficient to health. The tools are emerging to measure diet as a complex ensemble of biomolecules at specific concentrations (1, 2). What is needed, in addition to compositional data, is to determine which and how much of those hundreds of thousands of components should each individual human eat, according to their genotypic variations, phenotypic diversity, life stage and lifestyle? Databases of food composition (Periodic Table of Foods), annotated for bioactivities are emerging as the knowledge resources needed to take advantage of computational biology (3).

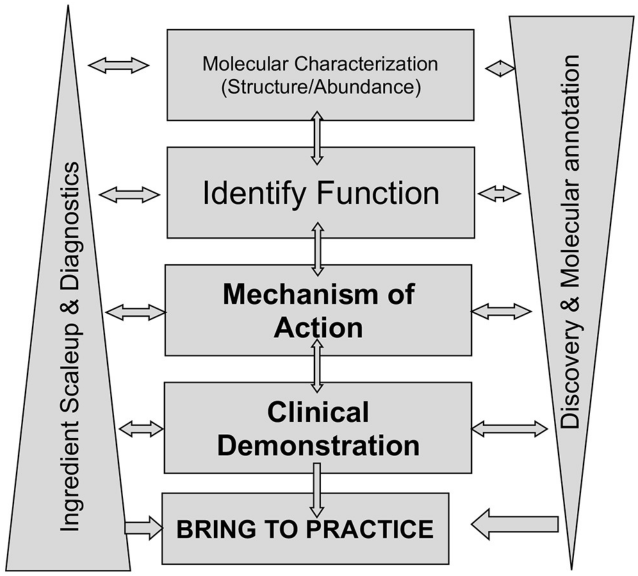

FIGURE 1 | Strategic model for research and development of lactation and its biological product milk.

As the life sciences advance with powerful new tools of biology and genomics, of big data and artificial intelligence, we are faced with many challenges, from demographics to emerging pathogens. Ideally, a goal of health is prevention. The aim is to understand biology: how to intervene pro-actively, build individual defenses and protections that prevent the development of disease. Prevention is challenging. Interventions must act on healthy individuals. There is not the simplifying focus of disease diagnostics, there is no disease to diagnose. What targets improve performance, while protecting and preventing diseases in healthy individuals? The cost-benefit ratio is different. If one is suffering from a disease, then the costs of reversing that disease are tangible, quantifiable and specific. The risk of side effects of disease therapeutics can be evaluated within a context. What costs are justified to prevent a disease that one is never going to get? Even more profoundly, an intervention that lowers the risk of one disease but increases the risk of another is a hollow prevention. What scientific strategy would allow investigators to understand how to improve the health of healthy individuals, to act on preventing all diseases and to do so without putting any individuals at risk?

The biological history of mammalian lactation is a process of evolutionary selection of the output of that tissue: milk, sculpted by infant survival and long term genetic success. Mammalian mothers literally dissolve themselves to make a complete and comprehensive diet for their infants. From the earliest pre-mammals, secreting fluids from a hyperactive sweat gland (4), generation after generation, selective pressure rewarded mothers whose lactation secretions gave their offspring a competitive advantage *via* diet, milk. The combination of cost to the mother and advantage to the infant has yielded the rosetta stone for scientific discovery of nourishment, and of the entire principle of diet. Milk nourishes healthy infants, guides their development, protects them from biological and chemical threats and equips them for the complex environments that they will face, life long. This article describes the implementation of a research strategy based around lactation as a scientific focus.

A basic strategy to study milk is summarized in **Figure 1**. The goals are to build a map, molecule by molecule, target by target, of how milk achieves its benefits to health. A range of disciplines must work in open collaboration of parallel discovery and innovation. One aim is to identify the components of milk, their structures, abundances and variation within and across mammalian lactation. Another aim is to develop methodologies to isolate these components in purity to enable detailed mechanistic investigations. Another aim is to use a range of biological models in the presence and absence of those isolated components. Once mechanisms of action are discovered, they must move into clinical tests of efficacy. This aim requires insights into the utility of discovered mechanisms: what is the breadth of efficacy across lifespan and lifestage; what diagnostics identify need among the population and what diagnostics provide absolute markers of efficacy. The final imperative is to bring the discoveries to practice as innovations for human benefits.

TOOLSETS

Lactation Genomics

The tools to understand lactation are from genomics to physiology. Whole genome sequencing provides the basic knowledge set. The challenge is to identify and annotate genes associated with lactation. The goals for lactation genomics were propelled by a diverse group of scientists participating with the International Milk Genomics Consortium (5). The diversity of lactation across mammalia is an important asset, so the goal of the IMGC was to assemble a variety of entire genomes from marsupials to humans (6). Comparing these genomes formed the basis for interpreting the evolution of mammalian lactation (7), the expression of genes during lactation (8), the sequences (9) and digestibility of proteins (10), the sequences of peptides (11) and their formation (12), the biosynthetic pathways of glycans (13), the variation among women due to genetic diversity (14), timing of lactation (15), diet (16) and the biosynthesis of lipids (17).

Lactation Analytics

Milk is a challenge for analytical chemistry. From small molecules to entire cells, milk is a cornucopia of biomolecules varying in size and concentration by orders of magnitude. All the essential nutrients are in milk, each present within a matrix that enhances their bioavailability and controls their chemical reactivity. These matrices that enhance bioavailability impede the characterization of the molecules analytically. Every class of biopolymer is present in milk, all the substrates and intermediates in their synthesis. Milk oligosaccharides were typical. Entire methodological platforms had to be developed for this one biopolymer class alone (18). Oligosaccharide method development required innovative approaches to initial separation, liquid chromatography on novel stationary matrices, mass spectrometry techniques including highly sensitive time of flight and triple quadropole mass spectrometry. The construction of structurally annotated databases of mass spectra was necessary to automate high throughput (19).

Lactation Bioseparations

The scientific investigations to discover biological actions of milk require that the components be available as purified research materials in quantities and purities maintained in their native conformations for the multiple assays by which investigators address their hypotheses. Also, human milk is a rare and valuable material and simply accessing milk as research material is and should be a process of regulatory, safety and ethical formalities. Combinations of traditional separation technologies and bioguided separations were needed (20). Strategies such as physical separation of milk components by size achieved enrichment in oligosaccharides but retained contamination by peptides and lactose (21). Peptides are an important biological resource in milk but vary widely in abundances and structures depending on the stages of lactation, treatment of milk etc. (22).

TARGETS OF BIOLOGICAL FUNCTION

The evolutionary history of mammalian lactation is remarkable across all of biology. Once begun, the complex interplay between the composition of epithelial secretions and the success of offspring set in motion a Darwinian engine of diet for protection and nourishment of the mother-infant dyad (23). The challenge of annotating lactation is in identifying their mechanisms of function. The challenge of milk research is to understand their role within infants (24). Yet, what are possible actions that would lead to a selective advantage in the mother-infant dyad? Complex oligosaccharides provide an example.

Milk Oligosaccharides and the Perplexing Lack of Digestion

Glycans are abundant across the tree of life and the most abundant biopolymer in the biosphere (25). Despite their importance they are not sequence encoded but products of enzymatic metabolism. The enzyme specificity to produce glycan structures limits the number of biological structures that are found relative to the enormous number of structures that are mathematically possible. This difference between biologically feasible and mathematically possible has led to the concept of bio-defined analytics (C. Lebrilla, 2000, unpublished). Combining biology with chemical analysis has guided analytical strategies to catalog the glycan structures present in milk and a variety of organisms (26). Structures of glycans include monosaccharide composition, branching, the stereospecific linkages of those sugars all leading to multiple isomers even for a single net atomic mass. Glycan structures are both free and bonded to proteins, peptides or lipids again by enzymatic synthesis. Every glycan, in each sample, must be explicitly analyzed to be identified (14).

The oligosaccharides of human milk have been attractive to scientists because they are free, abundant (1-2% w/v) and yet indigestible by the neonate. They are perplexing to annotate: why would mothers "dissolve themselves" to produce these biopolymers in such abundance? The scientific challenges posed by this apparent paradox propelled laboratories to pursue the analytical platforms to identify and annotate them (27).

The Bacterial Support Functions of Human Milk Glycans

The structures of milk oligosaccharides have been selected, in part, for an unusual biological value: NOT to be consumed by infants. Research on oligosaccharides in human milk has established as one function, that they support the growth of specific bacteria notably strains of the genus *Bifidobacterium* (28). While the mechanisms and extent of microbial diversity in breastfed infants are still being actively documented, the basic observation that bifidobacterial species dominate the microbiota of breastfed infants around the world compared with formula-fed infants has been well-established (29). How an intestinal microbial ecosystem maintains a dominant and consistent bacterial population in the face of repeated and diverse inoculations with environmental microorganisms has been largely speculative until recently. The idea launched by Gyorgi that oligosaccharides were a Bifidus factor (30) was unfortunately insufficiently specific. Oligosaccharides do not stimulate the growth of the entire genus of *Bifidobacterium* in general. *Bifidobacterium* represent a broad genera of bacteria whose members occupy a wide range of ecological niches. Though first identified microscopicslly by Tissier in the 19th century in breast fed infants only recently has research recognized the unusual specificity of the strains of *Bifidobacterium* that dominate the intestinal microbiome of breast fed infants (31–33). Intensive studies revealed the remarkable interaction between the stereospecific linkages of milk oligosaccharides and the genetic repertoire of glycosidases and solute binding proteins that provide these bacteria a distinct competitive growth advantage within the intestine of the breast fed infant (34).

Bifidobacteria and the Colonization of the Infant Microbiome

The colonization of the infant by microorganisms begins at birth (35). The consensus of microbiome research argues that the infant gut is ostensibly sterile at birth and those organisms that may have arrived into the amniotic compartment prior to delivery are not competitive once the "flood" of exogenous microorganisms (bacteria, yeast, fungi, viruses) that accompany a normal human birth. These initial inocula are the first of a continuous wave of inoculations of the infant from the environment (36). The mode of delivery, vaginal or by C-section has been noted to alter the gut microbiota of term infants in early life (37), however, these observations are mainly of infants within a restricted microbial environment, the modern hospital delivery room. Infants delivered vaginally acquire bacterial communities resembling those of maternal vagina and fecal microbiomes, while C section babies initially reflect a microbiota resembling that of maternal skin. Infants delivered vaginally exhibited higher abundances of Bacteroidaceae and lower abundances of Enterococcaceae, Pasteurellaceae, Carnobacteriaceae, and Gemellaceae compared to C section delivered infants (38).

Knowing that each infant is inoculated with a diverse array of organisms, a goal was to understand the role of that environment and milk components simultaneously in guiding the distinct microbiological community in the breast fed infant. Which microorganisms utilize and grow on specific components of milk (39)? Many components from milk, in isolation, can support microbial growth. Thus, enabling technologies were needed: isolating potential growth substrates in pure form from milk and media for bacterial culture assays that include all of the nutrient requirements for growth, but lack a carbon fuel source. Into these media can then be added the components of milk that are expected to arrive at different sections of the intestine (39). The complex oligosaccharides from milk were isolated to assess bacterial growth on those undigestible components of milk that arrive at the lower intestine. Surprisingly, initial growth experiments did not observe significant growth of bacteria when human milk oligosaccharides were the sole source of carbon in the otherwise supportive medium (40). Among gut-related bacteria tested (including *Lactobacillus, Clostridium, Eubacterium, E. coli, Veillonella, Enterococcus* isolates) only *Bifidobacterium* and *Bacteriodes* species grew to high cell densities yet, growth was strain specific (41). Robust growth on HMO was found just in a select group of *B. bifidum* and *B. longum* subsp. *infantis* (*B. infantis*) strains. In these same growth conditions even isolates of *B. longum* subsp. *longum* and *B. breve* showed poor growth and strains of *B. adolescentis*, and *B. animales* were unable to grow on HMO (41).

Any ecosystem is driven by accessible food. The lower intestine of the breast fed infant is supplied by those components of milk that are not digested nor absorbed by the infant in the upper intestine. Thus, those bacteria capable of accessing oligosaccharides are provided a competitive advantage by the infant's mother's milk. Nonetheless, only the combination of microorganisms growing on the oligosaccharides coded by lactation genes from each infant's mother that confer a selective advantage to infant success would be rewarded through evolution. The outcomes of that Darwinian engine, pathogen protection to immune education are continuing to emerge as novel mechanisms of *Bifidobacterium* dominated microbiome actions (42).

One defining set of traits for colonic bacteria is their ability to degrade biopolymers and access the monomeric sugars, amino acids etc., in that environment. How they do that is important. Most intestinal bacteria secrete extracellular glycosidase enzymes into the luminal environment and these enzymes catalyze the hydrolysis of complex glycans and liberate free sugars extracellularly. Free sugars are taken up by bacteria and metabolized. Select strains of bifidobacteria use extracellular lacto-N-biosidase activity to break down oligosaccharides (43). Some bacterial strains, notably *B. infantis*, pursue a different strategy of transporting oligomeric structures into the interior of the cell and breakdown reactions occur internally. This internal feeding strategy confers an advantage to the host by blocking the liberation of simple sugars into the lumen that other organisms can utilize. Cross feeding liberated sugars to other organisms is a known mechanism to promote the growth of undesirable, opportunistic pathogens (44).

The discovery that growth of bacteria on milk oligosaccharides was a strain specific, gene driven process and that *B. infantis* ATCC15697 was uniquely capable phenotypically, prompted the goal to sequence its genome and begin the process of annotating its unique capabilities. One of the joys of being a scientist is those occasions when you are witness to the sheer elegance of biology. The genetic repertoire of *B. infantis*, was one of those rare moments in which scientific discovery revealed that elegance (31). This specific strain provides the field of microbiome research with insights into the traits associated with capabilities to thrive within the anaerobic intestine including genes providing the strain its phenotype (31). Breast fed infants that are exposed to such HMO consuming strains are colonized by them and in turn achieve direct and indirect benefits. Those benefits even include the protection from the horizontal transfer of virulence and antibiotic resistance traits (45). These benefits are consistent with the concept that the oligosaccharides produced by the mammary gland and the emergence of oligosaccharide consumption gene clusters in specific strains of bifidobacterial strains are an example of symbiotic co-evolution.

The principle of nourishment as the center of cross-kingdom partnerships is not unique to lactation. Glycan based nourishment appears to be at the center of most cross-kingdom symbioses from plants feeding pollinating insects with sugar rich nectar (46) to roots feeding nitrogen fixing bacteria (47). This same strategy emerging from evolution of milk feeding a metabolically distinct and mutually beneficial bacterial population (mutualism) in infants is another example. The challenge is what do we learn by understanding it?

Evidence from epidemiology, mechanistic insights and increasingly prospective interventions shows that the mutualism between human breast milk and the *B. infantis* commensal is important, yet fragile. The importance was first suggested by premature infants. Infants born premature, by Cesarian section, are placed in an incubator. At that point the immediate hospital environment serves as the inoculating reservoir of seeding microorganisms. In such an environment, the explicit steps taken to prevent cross-patient pathogen transfer, (scrupulous hygiene, sanitation, etc.) have the unintended consequence of preventing the transfer of commensal organisms as well. The first indications of the outcomes of that environment emerged in studies comparing the explicit inoculation of candidate organisms. Studies used *in-vivo* administration of *B. infantis* to premature infants fed either formula or breast milk. Breast milk-fed infants, when supplemented with *B. infantis* saw increases in fecal bifidobacteria and decreases in γ*-Proteobacteria* compared with a formula-fed group (48).

Following on those initial studies, *B. infantis*, used clinically, has already been demonstrated to significantly impact the development of inflammation (49), autoimmunity (50) and necrotizing enterocolitis and mortality of premature infants (51). Thus, understanding how mothers are shaping the protective milk-oriented microbiota (MOM) of their infants through breast milk is an urgent model for guiding microbial communities at all ages.

CONCLUSIONS

The deconstruction of human milk through a highly interactive and multi-disciplinary program of research has illuminated the profound interactions between mammals and their resident bacteria. The traditional view of bacteria on and in humans is that they are potentially pathogenic and deleterious. While some bacteria are unquestionably deleterious to animal health, this simple concept that all bacteria are deleterious is incompatible with the realization that human breast milk contains abundant undigestible matter that explicitly feeds a specific strain of *B. infantis*. Research must now pursue studies that illuminate all the reasons why selective pressures through evolution have favored this remarkable partnership.

AUTHOR CONTRIBUTIONS

The authors jointly wrote and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Integrating Dietary Impacts in Food Life Cycle Assessment

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Food production and food consumption have been too long studied separately. This paper therefore reviews progresses in assessment methods and identifies how nutrition effects on human health and environmental impacts of the entire food production and consumption can and should be consistently and systematically assessed, on a life cycle-based and a health-based perspective. Main observations include: (a) The strong activity in the Life Cycle Assessment (LCA) of a large range of agriculture production, covering beyond carbon footprint the biodiversity and health impacts of land, water, fertilizers, and pesticide use. (b) The multi-functionality of all foods and the need to compare a wide range of possible alternative including comparing serving size, meal alternatives and diets. (c) The availability of epidemiological dietary risk factors expressed in DALYs, enabling the creation of an additional LCA nutritional impact category and providing much broader flexibility in the choice of the functional unit and the kind of valid comparison LCA can address. (d) The need to use Big Data and machine learning method to better understand interactions and propose healthy and sustainable food baskets. As illustrated by the fruit yogurt example, dietary impacts on human health often dominate the life cycle impacts on human health and it is strongly recommended to consider them in the life cycle inventory and impact assessment of all commodities and foods that will eventually be consumed.

Keywords: food, life cycle assessment, sustainable, nutrition, health nutrient index, human health

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INTRODUCTION

Food production and consumption are key factors both for our environment and for our health (1). Sustainable production and processing of food is a crucial question in a time where eutrophication, particulate matter, water, and land use from food production exceeds planetary boundaries, set high pressure on our climate, and is a high factor responsible for the threat on hundred thousands of endangered species. What "offerings of food" can be produced and how the entire world population can be fed, while limiting environmental impact and maintaining these within the limits of the planetary boundary are key challenges for our societies (2).

Food and diet are also key determinants of health. Most of the dominant risk factors identified by the Global Burden of Disease (GBD)–(3) are directly associated with dietary risks, or indirectly related to nutrition (e.g., high systolic blood pressure, low-density cholesterol, plasma glucose, and body mass index), and are responsible for tens of millions of death annually (4).[1] A main challenge is the multidimensional nature of diet-health interactions, in term of the multiplicity of foods, health outcomes and their possible combinations which makes it difficult for the consumer to identify what really matters.

Major scientific progress have been achieved in the last three decades in assessing agriculture and food production over life cycle showing the importance of direct emission on field, as well as the high burden associated with food waste. Thoma et al. (5) provide a very informative overview of how Life Cycle Assessment (LCA) can be applied to agriculture and food production, for each of the four main LCA phases, i.e., (1) the goal and scope definition that determine the functional unit retained as the basis for the comparison as well as the food system boundaries, (2) an inventory of flows coming from the environment or released to the environment per defined functional unit, (3) the associated impact on human health, ecosystem biodiversity and resource use, determined using so called "midpoint category" (e.g., fine particulate, human toxicity, or land use and eutrophication) that provide specific characterization to each pathway, and (4) the interpretation phase that interprets the different results of each phase and assesses uncertainties. However, food production and food consumption have been too long studied separately (6), and both nutrition and environmental fields have often drawn conclusions without accounting for the complex interactions between these dimensions. It is especially strange that food LCAs, aiming to cover holistically the whole life cycle of food systems, have in practice mostly neglected the dominant dietary impacts of food on human health during use stage. Also LCA usually compares foods based on a single functional unit, which might fail to fully reflect the natural multi-functionality of foods and diets (7, 8).

This paper therefore reviews progresses in the environmental life cycle assessment of agriculture and food products. It then identifies how nutrition effects on human health and environmental impacts of the entire food production and consumption during use stage can be consistently assessed, both on a life cycle-based and a health-based perspective. It also illustrates how this opens new possibilities to compare a broader range of food alternatives and account for the multiple nutrients and functionalities of food.

STATE OF THE ART AND PROGRESS IN LIFE CYCLE ASSESSMENT OF AGRICULTURE AND FOOD SYSTEMS

Major progresses have been achieved in assessing the environmental performances of agriculture production and food systems over life cycle. Food is one of the domain with most LCA activity since the early 1990s, and has contributed to pioneer LCA methodological approaches, with several milestones and unique developments. From 1993 to 1996 a European concerted action on harmonization of environmental LCA for agriculture determined and compared six evaluations of impacts of wheat production, also setting the basis for the ISO hierarchy on allocation (9). Intensive developments of Process-oriented life cycle inventory databases have led to the creation of several food oriented databases covering the entire supply chain of agriculture production, including the World Food LCA Database and its integration in ecoinvent (10), the Agribalyse Database (11), or the Agri-footprint database (12). The emergence of Multi-Regional Input-Output databases and their combination with always more comprehensive global Life Cycle Impact Assessment method enable us to account for the global nature of food production (13) and the trade-off between local production [Poore and Nemecek (14) for country specific production inventories] and transported food produced in best suited climatic condition and location (15).

Food losses have been modeled in further details and identified as a major driver of environmental impacts of foods, with high potential for improvement (16, 17). Food processing has been included in several LCA studies [e.g., Kim et al. (18) for cheese], but this is certainly a domain together with the cooking mode that would deserve additional attention, data collection, and further development. This is in particular true for pre-processed mixed dishes and meals that become increasingly popular.

Major advances have also been achieved for the Life Cycle Impact Assessment (LCIA) of food-related impacts on human health and on ecosystem quality. Eutrophication fate and effect factors have been developed (19) and further refined in the frame of the UN project for developing a consensus-based Global Impact Assessment Method (GLAM)–(20, 21). Impacts of pesticides on ecosystem quality and human health are increasingly characterized (22, 23), also accounting for the pesticide residues consumed in multiple crop types (24, 25). Main impacts on human health associated with the creation of secondary fine particulate smaller than 2.5 μm diameter ($PM_{2.5}$) have been modeled in detail, with agriculture specific characterization factors expressed in e.g., $DALY/kg_{precursor}$ in particular for ammonia emissions (26). For land use and land use change impacts on biodiversity, major progress have been reached by Chaudhary et al. (27) and Chaudhary and Brooks (28) to assess ecoregion specific impacts for five different types of land use. Kuipers et al. (29) provided additional information on habitat fragmentation and global extinction probabilities. For water footprint, the impact of agriculture as the dominant consumptive user of water can now be assessed using the AWARE method (30) enabling to better assess the depletion of water use for both ecosystems and humans. In a study of the water footprint of US dairy milk in 50 states and 18 water basins, Henderson et al. (31) demonstrate the very localized character of water impacts for feed and dairy production. For assessing the carbon footprint, LCIA methods such as Impact World+ (32) enable to calculate impacts for different time periods (both for the first 100 years and for longer term), avoiding the arbitrary choice of a fixed time horizon, which could strongly influence the impacts of methane relative to CO2.

The LCA food conference (33), hold every other years, has provided since the nineties a forum for intensive exchange

[1] https://vizhub.healthdata.org/gbd-compare/

FIGURE 1 | Word cloud of most frequent words in the titles of 4,131 papers containing life cycle assessment together with agriculture or food in their title, abstract or keywords. Created with WordArt and Scopus on 1 March 2022.

on data, methods and the assessment of multiple crops and diets. This intense activity in agriculture and food LCAs is reflected in the more than 4,000 papers that have Life Cycle Assessment together with Agriculture or Food in their title, abstract or keywords. **Figure 1** presents the most frequent words in the titles of these papers. Interestingly for fields of study, Waste is as prominent as Food, Agriculture or Crop. In terms of environmental impacts as expected Carbon Footprint, Greenhouse Gases are often mentioned together with Water issues. Dairy and Milk are the most prominent commodities, followed by Beef, Rice, Pig, Tomato with also strong occurrence of Energy related production with Oil, Bioethanol, Biodiesel, or Biogas. For regions, studies on China are most frequent, followed by Brazil, United Kingdom, Iran, Europe/EU, and Switzerland.

THE MULTI-FUNCTIONAL NATURE OF FOODS—BEYOND FUNCTIONAL UNIT

In LCA an important choice is the selection of the functional unit (FU), i.e., the basis for comparing different scenarios, all emissions and impacts across alternatives being calculated per functional unit. For agriculture of food, a wide range of functional units have been used, including per kg or 100 g, per kcal, per serving, per meal or per person per day for an entire diet (**Figure 2**, left column). LCA studies only use a single metric at a time as functional unit, whereas multi functionality is intrinsic to food. This becomes a problem if it is assumed unrealistically that all functions and benefits of food can be reduced to a single variable, that accounts for the entire nutritional function for all compared alternatives. In contrast, a unique functional unit is not a problem if the environmental or health aspects that are not covered by the functional unit are included in the impact assessment. Rather than debating whether nutrition should be considered within the functional unit of a LCA or within the impact assessment (8), we propose to use both approaches, applying the following recommendations, first for the functional unit:

a) It is useful to systematically reporting of mass-based results and mass is a main reference flow, but mass is very rarely a good functional unit, and is most of the time misleading, since substitution and alternatives is not primarily mass related.
b) The serving size has been created by food agencies and is used worldwide as a default basis for comparison, and could be one interesting functional unit, but needs to be complemented by a health/nutritional impact assessment. Other functional units could also be legitimately considered such as kcal if the function is to provide energy, etc.
c) The functionality of food is very rarely mono-dimensional or mono-functional. To believe that we can force the multi-functionality of foods into a common functional unit that fully reflects health performances and nutrition and the function of nutrition [more than 10,000 different nutrients in one food—(34)] is an illusion. It is trying to force reality to fit a too simplified LCA framework.
d) Since most nutrient index include detrimental nutrients (e.g., sodium), the use of nutrient index score as a functional unit is debatable, since it indirectly qualifies detrimental components as part of the food function. It becomes even impossible to compare alternatives if some of the net nutrient scores are negative (more detrimental than beneficial nutrients). These

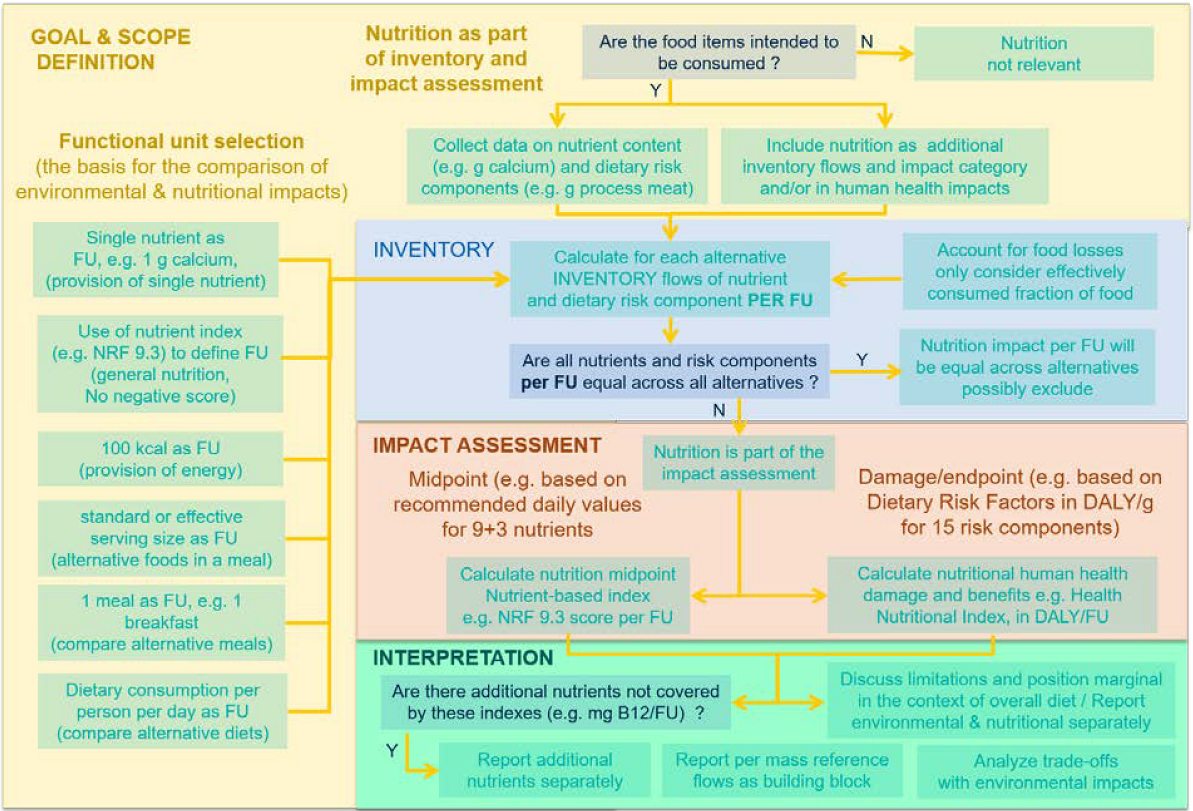

FIGURE 2 | Integration of the nutrition impact associated with food consumption during use stage, in the life cycle assessment of foods or food ingredients.

detrimental impacts rather belong in LCA to the impact assessment phase.

e) The nutritional and human health impacts performances per functional unit of two food items, two breakfasts, two meals, or two diets, are in general different (even very different sometimes). These differences in human health impacts or benefits can and should be accounted for separately in the impact assessment, considering both impacts and benefits. The assessment of human health impacts (with uncertainty) of nutrition needs therefore to be considered in food LCAs, unless they are exactly equal per FU.

f) In the rare cases where compared alternatives have exactly equal human health impacts related to the food nutritional value, this is not a problem and there is no double counting since the human health impacts are equal and do not bias the comparison between these alternatives. In addition, it is still always useful to put in perspective and compare the human health impacts of food production with the often dominant human health impacts of their consumption.

Best practice recommendations were further developed under the FAO umbrella to address the intended purpose of an LCA study and related modeling approach, choice of an appropriate functional unit, assessment of nutritional value, and reporting nutritional LCA results (35). Main recommendations included: (a) When nutrients are and/or nutrition is relevant to the decision-maker and decision context, nutrient and nutrition related impacts should be considered in the LCA; (b) as many essential nutrients as possible should be reported in the inventory; (c) though research on the potential human health impacts of food items is at an early stage, it is recommended using in the life cycle impact assessment phase a nutrition impact category to account for the benefits or impacts of nutrition on human health. In this line of thought, having a human health dietary impact category in LCIA, provides much more flexibility for comparing a wide variety of foods in a consistent way. The next section will review how this can be achieved.

CONSISTENTLY ACCOUNTING FOR DIETARY IMPACTS ON HUMAN HEALTH IN LIFE CYCLE ASSESSMENT

How can dietary impacts during use stage be assessed in LCA, ensuring consistency with other types of human health impacts considered during production stage (such as the health impacts associated with the generation of fine particulate)?

Epidemiologically-determined risk ratios from e.g., the GBD have become available for various nutrients and food groups (3, 4). According to the GBD, beneficial risk components include fluid milk, nuts and seeds, fruits, calcium (excluded for fluid

TABLE 1 | Calculation of the health nutrient index for a three ingredients strawberry yogurt [adapted from Thoma et al. (5)].

Yogurt composition	Mass	Energy	Fibers fruits	Calcium	PUFA	Fruit	Sodium	Transfat	
	[g/serving]	[kcal/serving]	[g/serving]	[g/serving]	[g/serving]	[g/serving]	[g/serving]	[g/serving]	
Corn syrup	10.0	28.4					0.006	0.003	
Strawberries	6.0	1.9	0.12	0.00	0.01	5.95			
Yogurt plain low fat milk	154.0	97.1		0.28	0.07		0.108	0.027	
Total d_r strawberry yogurt	**170.0**	**127.4**	**0.12**	**0.28**	**0.08**	**5.95**	**0.114**	**0.030**	
Dietary risk factor DRF_r	[μDALY/g]		–0.18	–5.15	–0.61	–0.19	13.90	4.44	**Total**
Health nutrient index, HENI	[min gained/serving]		–0.01	–0.77	–0.02	–0.59	0.83	0.07	**–0.48**

Bold are totals.

milk to avoid double counting), omega-3 fatty acids from seafood, fibers (fibers from fruits, vegetables, legumes, and whole grains differentiated from other sources), and polyunsaturated fatty acids (PUFAs). GBD detrimental factors include health damages associated with processed meat, red meat, trans fatty acids (TFAs), sugar-sweetened beverages (SSBs, mediated through body mass index) and sodium (mediated through blood pressure). For LCA, depending on the LCA scope definition, there is a need to look both at overall diet changes, and analyze marginal changes in the context of an overall diet.

Figure 2 summarizes how these relative risks, burden rates and exposures from the GBD can be used within LCA for marginal effects of individual food items. We collect data on the nutrient content and food group components of each of the food ingredient (e.g., g calcium or g fruits per 100 g of milk, strawberries and corn syrup for a strawberry yogurt). Based on the food composition, we first determine the content levels to each risk factors by quantifying as inventory flows the amount of dietary risk component r per functional unit [d_r, in e.g., g calcium or g fruits per serving of yogurt, **Table 1**; also see Fulgoni et al. (36)]. These amounts are then multiplied by the impact assessment characterization factor, the so-called Dietary Risk Factor expressed in μDALY per g of each risk components (DRF_r, in e.g., μDALY/$g_{calcium}$ or g_{fruit}) and summed up across all relevant risk factors to yield the impact per functional unit (e.g., in μDALY/serving of yogurt), or the Health Nutrient Index (HENI) score expressed in minutes of healthy life gained per serving, considering that there are 0.526 million seconds in a year (37):

$$HENI = -0.526 \times \sum_{r=1}^{n} \left(d_r \times DRF_r\right)$$

Stylianou et al. (37, Supplementary Table S3) determined DRF values for the US for the 16 GBD dietary risk factors, accounting for 400 risk-outcome associations, stratified by 15 age groups and gender. Combining these with food composition and food consumption data enabled them to determine the minutes of healthy life lost or gained per 100 g, per kcal and per serving for more than 5,800 foods items consumed in the United States. Since some essential nutrients are not specifically covered by the GBD (e.g., anti-oxidants, Vitamin B12, or other essential vitamins), complementary nutrient might be considered at midpoint level, to complement the HENI score.

For 170 g serving of the strawberry yogurt given as example in **Table 1**, this calculation of the HENI score results in a reduction of –0.92 μDALY/serving, i.e., 0.5 min of healthy life gained per serving, considering that there are 0.526 million seconds in a year. This is the difference between 1.5 min gained mostly via calcium (since yogurt is not considered as milk) and fruit, minus 0.9 min mainly associated with sodium. As further discussed by Thoma et al. (5), these dietary impacts of 0.5 min per serving yogurt are restricted compared to other foods such as hot dogs (36 min lost per hot dog), but are still an order of magnitude higher than the estimate of climate change and fine particulate, thus the importance to account for them.

The marginal human health impacts of individual food items should be considered in the context of an overall diet. This is accounted for by the GBD maximum theoretical limits (TMRELs) above or below which there is no benefit or impact as defined by the Global Burden of Disease [see, for example, Supplementary Table S3 of Stylianou et al. (37)], whereas the majority of the population is in the active range of consumption for which marginal changes leads to effective changes. For more substantial dietary changes, a multiplicative approach should be used according to the GBD, as applied for entire diets by Walker et al. (38).

DISCUSSION, CONCLUSION, AND PERSPECTIVES

The proposed approach enables us to consistently account for dietary impacts, in parallel to environmental impacts, a major progress in determining the life cycle impacts of foods on human health, with the possibility to consider country specific mortality and morbidity rates. As illustrated in **Figure 2**, as soon as an LCA of agriculture and food systems address commodities that are intended to be consumed, or are ingredients of foods to be consumed, it is strongly recommended to consider their nutritional impacts in the life cycle inventory and impact assessment. Since these dietary impacts on health are expressed in DALYs (detrimental effects) or avoided DALYS (beneficial effects), they can directly be compared and summed up at damage level with the other impacts such as human toxicity, impacts of pesticides residues (24) and fine particulate damages on human health, while keeping track of the respective contributions.

Several limitations need to be further addressed: The present resolution of epidemiological data is still course, with e.g., all fruits considered as equally beneficial per g. The underlying data are usually analyzed for one or two risk factors at a time and do not fully reflect the combined interactions and confounding factors between substitutions, since increasing a serving size of a food group also results in decreasing the consumption of other food items. There is still ongoing debate for multiple items [see e.g., Stylianou et al. (39) for milk that could have additional detrimental effects on prostate cancer or and beneficial effects for stoke according to various meta studies] and regular revisions in the expert judgment of the GBD author. So far the HENI index has strictly followed the GBD risk estimates, but there is also a need to further stabilize the GBD data that have been changing substantially with time. For example, between the 2016 GBD data used in Stylianou et al. (37) and the 2019 GBD data (3) relative risks for red meat have been multiplied by a factor 5, and reduced by a factor 10 for the benefits of omega-3 acids in seafood.

The rapidly growing realm of data and of machine learning techniques made available offers interesting perspectives to address these limitations. Beyond the GBD data, the merging of different databases offers very interesting perspectives on health analysis. A good example is the combination of the NHANES effort that includes data on nutrition, physical activity, occupation, metabolism, and measured chemical biomarkers and biomarkers of physiological indicators, with mortality data on each of the participants. Zhao et al. (40) used applied survival random forest (41) to 47,000 individuals of this cohort to analyze the combined effect and respective importance of physiological indicators on all-cause mortality. This will enable us in the near future to identify more advanced dose-responses and quantify multi-stressor risks in an exposome-based approach that can look at the combined effects of e.g., nutrition, pesticide residues and physical activity on mortality.

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The author confirms being the sole contributor of this work and has approved it for publication.

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