European Journal of Nutrition (2022) 61:2239–2253
https://doi.org/10.1007/s00394-021-02786-8

REVIEW

Chronic diseases are first associated with the degradation and artificialization of food matrices rather than with food composition: calorie quality matters more than calorie quantity

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Received: 8 September 2021 / Accepted: 13 December 2021 / Published online: 24 January 2022

Abstract

Purpose For decades, it has been customary to relate human health to the nutritional composition of foods, and from there was born food composition databases, composition labelling scores and the recommendation to eat varied foods. However, individuals can fully address their nutritional needs and become chronically ill. The nutrient balance of a food is only a small part of its overall health potential. In this paper, we discussed the proof of concept that the increased risk of chronic diseases worldwide is primarily associated with the degradation and artificialization of food matrices, rather than only their nutrient contents, based on the assumption that "food matrices govern the metabolic fate of nutrients".

Methods An empirico-inductive proof of concept research design has been used, based on scientific data linking the degree of food processing, food matrices and human health, notably on the glycaemic index, nutrient bioavailability, satiety potential, and synergistic effects.

Results We postulate that if the nutrient content is insufficient to fully characterize the diet-global health relationship, one other dimensions is necessary, i.e., the food matrix through the degree of processing. Both matrix and nutrient composition dimensions have been included under the new concept of the 3V index for Real (Vrai), Vegetal (Végétal), and Varied (Varié) foods. The Real metric, reflecting the integrity of the initial food matrix, is the most important, followed by the Vegetal (nutrient origin) and the Varied ("composition" effect) metrics.

Conclusion Concerning their effects on health, food matrix comes first, and then nutrient composition, and calorie quality matters more than calorie quantity.

Keywords Food matrix · Chronic diseases · Ultra-processed foods · The 3 V index · Food synergy · Nutrient contents

Introduction

For decades, the diet–health relationship has been based on and explained almost exclusively by food composition (i.e. calorie, macro- and micronutrient contents) [1], leading to recommendations of reducing sugar, salt and fat [2] and indirectly suggesting that fully addressing the recommended dietary intakes would be sufficient to stay healthy. To date, the dominant tendency in nutrition research has therefore been to analyse food through the perspective of the "nutrient gate". However, in view of the accumulating scientific evidence during the last decades, i.e. mainly that linking food processing and human health [3–6], and the food matrix effect with human metabolism—especially for cereal- [7], fruit- [8] and dairy-based products [9]—this priority given to nutrients must be strongly questioned. Notably, education in dietetics, medical, and agro-food engineering schools is still largely based on the nutrient paradigm, as are the numerous recently developed nutrient-based food composition scores worldwide, as the primary health policy tool to help consumers buy healthy foods [10].

However, as recently reported by Aguilera [11], "*The concept of food matrix is extensively used by food and nutrition scientists to try to explain why a component or nutrient behaves differently in a food than in isolated form*". To say it differently, two foods with identical compositions but differing structures (i.e. food matrices) may have different

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metabolic and physiological effects in the short term and health effects in the long term [10]. For example, type 2 diabetes, which may be initially triggered by consumption of high glycaemic index diets or high levels of added free sugars (i.e. without matrix) [12–15], is therefore primarily an issue of high sugar bioaccessibility and bioavailability, rather than only that of the sugar content of real foods, and, in the end, is thus strongly related to the matrix effect [16]. Indeed, a high level of processing that drastically deconstructed food matrices (e.g. refining, extrusion cooking and puffing), associated with excessive addition of free sugar without matrix, renders starch, mono- and di-saccharides easily digestible and bioavailable within the bloodstream, leading first to insulin resistance, then prediabetes and finally type 2 diabetes [17]. Therefore, beyond the example of type 2 diabetes, among the complex nutrient interactions within the structured natural matrix, food composition databases do not say so much about food health potential [18].

Recently, we inductively redefined food health potential based on a holistico-reductionist paradigm combining the food matrix (the "holistic food fraction") and composition (the "reductionist food fraction") (Fig. 1) [10]. The quantitative 'composition fraction' is useful to define food composition and nutritional needs, to prevent deficiencies, to help choose varied raw and mildly processed food sources to address nutritional needs. Notably, the foods we eat supply more than 26,000 different bioactive compounds to our bodies [19]. The more qualitative 'matrix fraction' plays different roles, such as in the degree of chewing, digestive transit time and satiety [20], nutrient bioaccessibility/bioavailability [8, 9, 21], hormonal secretions [22], and the synergy of the actions of the different bioactive nutrients [23]. Finally, humans first consume complex food matrices, not isolated nutrients, and the primary action on human organisms is associated with the food matrix, interconnecting the mouth–digestive tract–brain network and chewing as a signal for satiety [22]. More generally, the first function of the human digestive tract is dedicated to deconstruct food matrices via chewing, peristalsis, and enzymatic actions (to break the links between nutrients), then to allow nutrients entering human bloodstream; this is why people unable to digest foods are feed through direct supply of nutrients without matrices, e.g. parenteral nutrition.

Therefore, food processing is a crucial factor since it modifies both food matrix and composition, which have effects on the healthfulness of foods; and the real issue is "to what extent matrix and composition may be modified without altering human health?" For example, food processing may improve the bioavailability of many nutrients, e.g. starch from raw grain-based foods [24], lycopene in tomatoes [25], reduce the content in anti-nutrient factors, e.g. phytic acid and tannins in legumes [26], and even increase the antioxidant and vitamin contents, e.g. fermentative processes applied to pseudo-cereals [27].

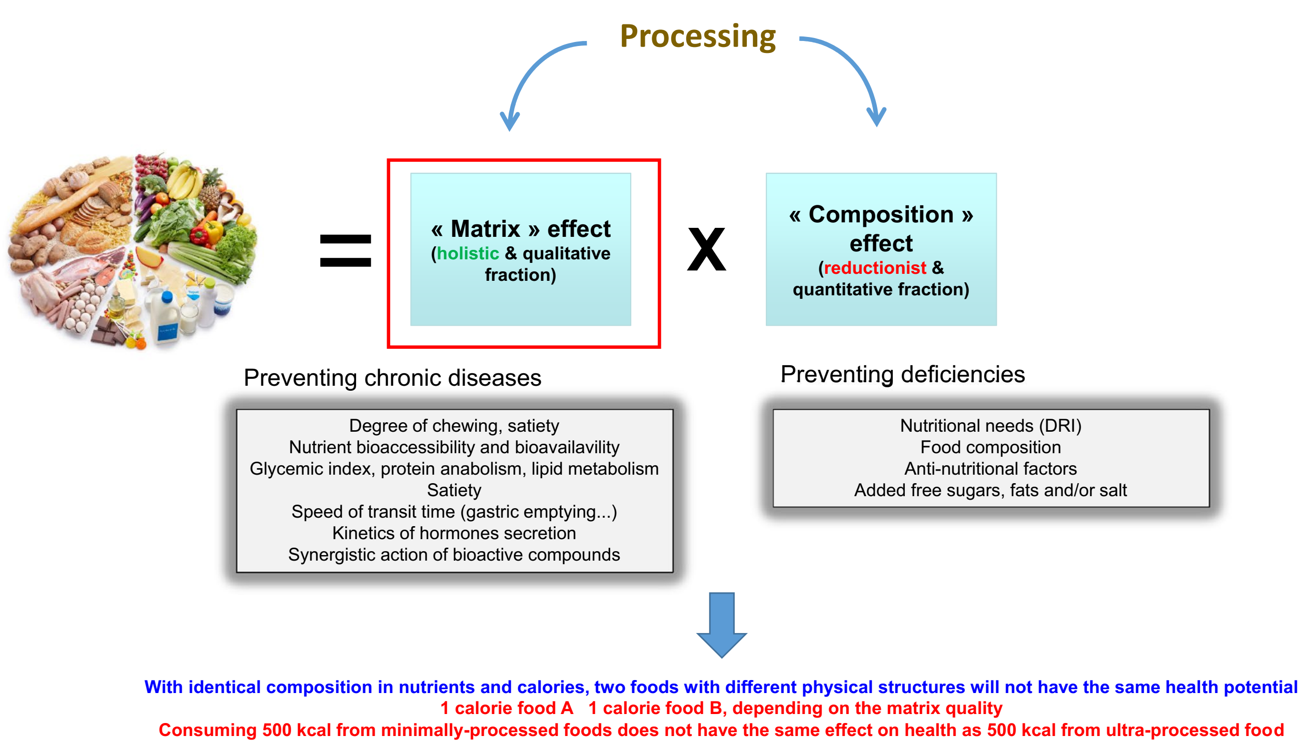

Fig. 1 The holistico-reductionist conception of the food health potential (adapted with permission of Oxford University Press©)

Otherwise, during this last decade, emphasis has been placed on the new proposed concept of ultra-processed foods, moving from the nutrient to the processing paradigm [28] to explain the increased risks of several chronic diseases worldwide [3, 4, 29]. Indeed, if processing has already been well demonstrated to modify food nutrient contents, it also modifies the food matrix [5]; the impact of the latter has not been studied as much. Notably, a lot of ultra-processed foods are characterized by deteriorated matrices due to new and highly denaturing technological treatments, e.g. extreme fractionation of foods into extracted and isolated purified compounds, puffing, extrusion-cooking, and/or chemical and enzymatic modifications [30, 31].

In this paper, we will further investigate the concept that "the increased chronic disease prevalence worldwide is primarily associated with the degradation and artificialization of food matrices rather than food composition". What is meant by "artificialization" in this paper is the addition of cosmetic agents to real foods (colouring and texturizing agents, taste enhancers, aromas…) or the creation of new unnatural food matrices from purified isolated ingredients. An empirico-inductive proof of concept research design will be used to conduct the investigation [32]. It is based on scientific data linking the degree of food processing, food matrices and human health. The defence of this proof of concept takes into account both food matrices and food composition to characterize the diet–human health relationship (Fig. 1), not only through the nutrient contents, but also the new paradigm of primarily the food matrix and then secondarily its composition, notably for preventing chronic disease development. In other words, we propose to change our perspective of the food by first exploring its matrix to reach more robust and efficient diet recommendations and to characterize more strongly the associations between diet and global health issues. For this, we will notably discuss that a healthy food is not a food that scores high with nutrient-based composition scores, but rather a food with the most and best preserved matrix, and, through the newly developed 3 V index, that such foods with a high matrix quality are in the end more sustainable.

Evaluation of the empirico-inductive proof of concept

Below is a discussion on how the effects of a degraded food matrix, beyond only excess calorie, salt, sugar and/or fat intake, may be associated with an increased risk of chronic diseases.

Evidence (apparently) against the proof of concept

It is true that, today, accumulating scientific evidence seems to associate excess calorie, salt, sugar and/or fat intake with an increased prevalence of some chronic diseases, hence the development of nutrient-based composition scores worldwide [32]. Thus, excess salt intake is robustly associated with hypertension and a subsequent increased risk of some cardiovascular diseases [33]; excess free sugar intake is also associated with increased risks of chronic disease [34, 35], especially those in sugar-sweetened beverages [36]; and excess fat, especially saturated fatty acid, intake is also associated with an increased risk of cardiovascular diseases [37]. Therefore, ostensibly, it appears logical to reduce food salt, sugar and/or saturated fatty acid contents; hence, the implementation of the sugar tax for reducing sugar-sweetened beverage purchases and dietary intake [38, 39]. Yet, this is not because there is a positive association between an isolated nutrient and risk of one chronic disease that this relation is true for the complex food that contains it [10].

Thus, scientific evidence about the role of only one nutrient in the development of chronic diseases has also been disputed, as this role might be dependent on food sources and therefore on the nature of food matrices [40, 41]. Indeed, excess salt, sugar and fat intake appears to be the effect of degraded food matrices [42] and, reasonably, could not be the primary cause of chronic diseases or the main focus of their prevention (Fig. 1). This is why we postulate that the excess consumption of these "a-matrix" or "non-cellular" nutrients, i.e. not integrated within a complex food, is primarily due to altered food matrices.

Altered food matrices and their impact on human health

Glycaemic responses are associated with "a-matrix" free sugars and degraded food matrices

At equal carbohydrate contents, different glycaemic indices are due to different matrices, as demonstrated with fruit- [8] and starch- [7] based foods. This is due to starch being more easily bioaccessible to α-amylase within the digestive tract by matrix deconstruction, or to added free sugars that have no more links within the matrix (i.e. "a-matrix" sugars), and are finally more rapidly absorbed into the bloodstream. Obviously, beyond the only altered food matrix, differences in glycaemic indices can be also due to extrinsic factors, such as the other foods or nutrients within the diet, e.g. the presence of fat or protein that decreases the glycaemic response [43, 44] through delayed gastric emptying [45] or the level of physical activity/exercise [46, 47].

Therefore, type 2 diabetes would not be primarily a "disease of excess carbohydrate" intake, but instead is associated with a degraded "matrix effect", leading to hyperglycaemia and hyper-insulinaemia, upstream of insulin resistance, and finally type 2 diabetes [16, 48]. Ultimately, type 2 diabetes might be considered a disease of ultra-processing [49–52], rendering carbohydrates readily available, notably in ultra-processed fruit-based products and starchy foods, and possibly others. This has important implications for dietary recommendations because instead of advising diabetic patients to consume fewer sugars (effect), they should be advised to consume fewer ultra-processed foods and more minimally processed foods (cause), regardless of the carbohydrate contents of the initial foods. Indeed, before the worldwide advent of ultra-processed foods after the Second World War (notably through food fractionation into purified and ultra-processed ingredients, e.g. glucose–fructose syrup was the first ingredient issued from such a food destructuring or cracking added with enzymatic treatment) [1], main civilizations were used to consuming many starchy foods (e.g. maize in Latin America, rice in Asia, wheat in Western countries and millet in Africa), and diabetes was not as prevalent to such an extent; notably, this can still be observed today in some traditional cultures (e.g. hunter-gatherers, simple agriculturists, rudimentary horticulturists, and pastoralists) [53], and/or less developed countries where the prevalence of food ultra-processing is still rare (even if the prevalence of type 2 diabetes appears to parallel the level of food industrialization) [54]. Beyond the role of food (ultra) processing on the matrix structure, other factors are obviously involved in the increased prevalence of type 2 diabetes during the last decades, notably lifestyle factors such as a lower level of physical activity or higher level of sedentary lifestyle due to urbanization [55–57] or deregulated eating frequency [58, 59]; this latter can also be associated with ultra-processed foods, e.g. binge eating [60] or inappropriate eating contexts [61].

On the other hand, if pasta generally has moderate glycaemic indices, this is due to the interaction of the gluten network with moderately gelatinized starch [62, 63]. Conversely, bread made of similar durum semolina has a higher glycaemic index due to looser ties between proteins and starch [64]. The health potential of pasta therefore appears to be primarily associated with the food "matrix effect" [62].

If food matrices govern nutrient health effects (Figs. 1 and 2a, b), then it is important to focus on the preservation of the matrices of foods with natural low glycaemic indices. This can be seen in the consumption of whole fruits versus 100% fruit juices versus sweetened fruit juices. In most studies, sweetened/soft fruit juices are associated with an increased risk of type 2 diabetes [65], whereas 100% pure fruit juices are generally not associated with a risk of type 2 diabetes [66–69] and whole fruits may even be protective [70]. With a priori equal sugar content in whole fruits and 100% fruit juices, the latter are less satiating and contain highly bioavailable sugars—as shown for example several decades ago with apples in the form of the whole food, purée or juice [71]—i.e. with the elimination of such strong interactions with other nutrients in juices and a more degraded food matrix [8].

Therefore, concerning added sugars, the issue does not appear *sensu stricto* sugars by themselves but the fact that they are added, which means that they are not linked to other nutrients and are fully bioavailable (i.e. "a-matrix" or "non-cellular" sugars). Nutrient interactions therefore appear to be the key point for glycaemic indices.

Satiety is associated with the food "matrix effect"

Another parameter of a healthy diet is its satiety potential since satiety has been shown to be regulator of food intake, especially on a day [72]—although it may obviously happen that people eat when they are not hungry (in this case the pleasure to eat surpasses the feeling of satiety, e.g. with hyper-palatable foods) and do not eat when they are hungry for a very large number of practical reasons. For example, the higher the glycaemic index for cereal-based foods is, the lower the satiety responses, and both indicators are closely correlated [73–75].

Thus, satiety is primarily associated with the oral processing behaviour and sensory properties of foods [20, 76], notably the degree of chewing [22]. Since the degree of chewing is associated with the food matrix, either solid, semisolid/viscous or liquid, the more we consume solid foods instead of their semisolid, viscous or liquid counterparts, the more we are satiated, the more we consume slow carbohydrates, and the more our food intake is regulated [20]. In this case, we will naturally limit excess intake of added sugar, fat, additives, and other xenobiotics (these can be also potential endocrine disruptors—such as notably some additives and compounds migrating from packaging, and potentially found in ultra-processed foods [77]—associated with chronic diseases [78]) (Fig. 3). In addition, as discussed above with ultra-processed foods whose food matrices seem to prompt the consumption of more calories per minute [42, 79], the artificialization of foods with aroma, texturizing agents, colouring agents and taste enhancers (Fig. 3) may disconnect the consumer from its real satiety, notably by creating deregulated nutrient sensing [80]. Thus, through artificially modifying and exacerbating the oro-sensorial properties of foods (colour, aroma, taste and texture), we may hypothesize that the pleasure of eating outweighs satiety, leading to questions about the addictive nature of these foods [81–84].

Besides, satiety also seems to be modified by micronutrients, non-nutrients, and some bioactive food constituents, notably the protein fraction, which elevates serum amino acid concentrations, and reduced hunger sensations and food intake [85]. The fibre fraction also plays a role in the satiety

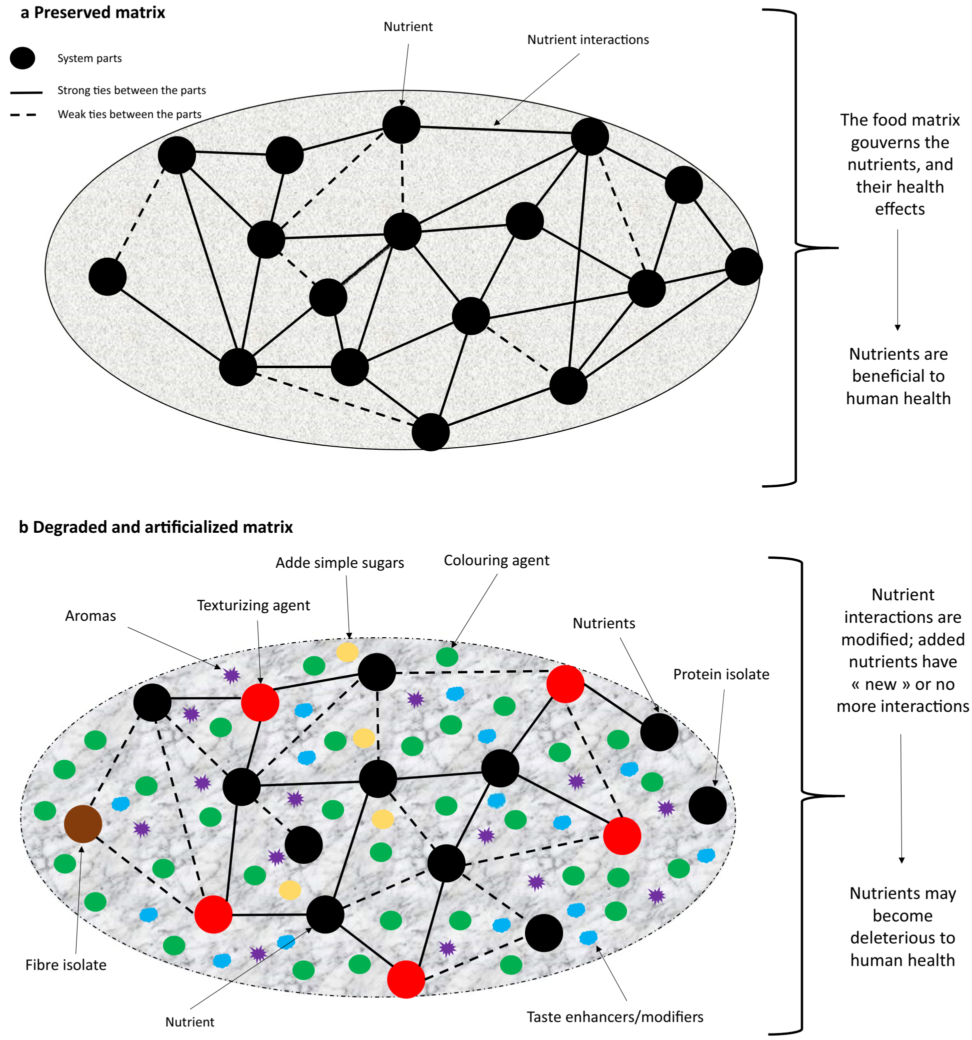

Fig. 2 Conceptualization of a **a** preserved/minimally processed and **b** degraded/artificialized food matrix related to the ultimate health potential of nutrients

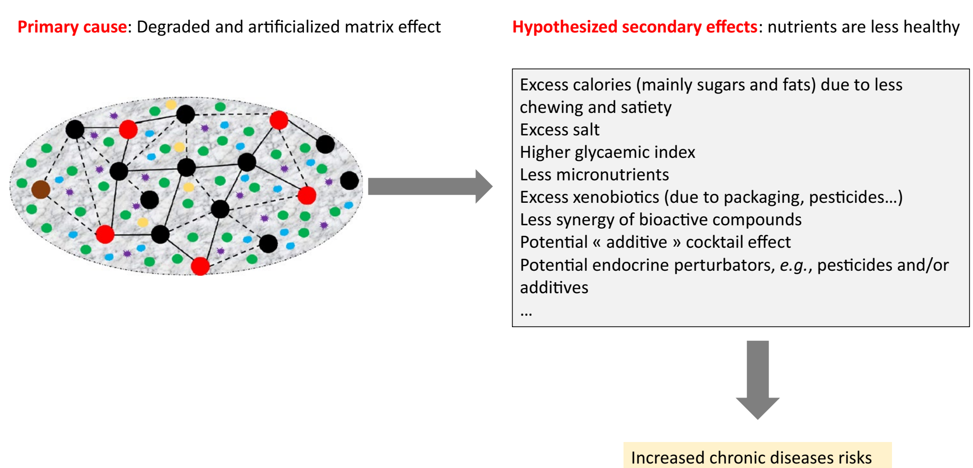

Fig. 3 The link between degraded and artificialized matrix effects (cause) and deregulated impacts of nutrients (effects) leading to chronic diseases

potential of foods [86, 87]. However, the effects of nutrients occurs after oral processing, suggesting that both solid and fibre/protein-rich foods are among the most satiating, as notably previously reported [88]. Indeed, the protein and fibre fractions confer food matrix to plant-based and animal-based foods, respectively.

Synergy is associated with the food "matrix effect"

Synergy is another crucial point to address with regard to food health potential [23, 89] and is associated with the "food matrix" effect. Indeed, the physiological and/or metabolic effect of a given food compound is closely related to the action of the other bioactive compounds in a food. There are several examples to illustrate this.

Natural fibre has a natural matrix involving a tangle of several types of fibres, such as soluble and insoluble fibre, cellulose with pectins and arabinoxylans [90, 91], and fibre co-passengers (e.g. linked antioxidant phenolic compounds) [92]. This complexity is necessary to supply organisms with maximum health benefits, contrary to the addition of purified fibre with less healthy properties (e.g. lower swelling or water-holding capacities) [93, 94]. At the colonic level during fermentation by bacteria, complex fibrous matrices first stimulate a trophic chain involving several bacterial species that act in synergy to deconstruct the fibre matrix (as observed in fibre-rich diets versus Western diets [95]), while isolated purified added fibre does not stimulate to such an extent (only a few bacterial species) the trophic chain, notably because there are fewer linkages to hydrolyse. In addition, natural fibres are richer in attached antioxidants that can be supplied to the blood to prevent LDL oxidation and/or to the colon to fight against free radicals generated by microbiota [92], which is not so much the case, again, with purified added fibre. Otherwise, it must be underlined that natural complex fibres, and therefore their associated matrix effect, may also bind and chelate minerals, rendering them less bioavailable to human organism, i.e. antagonism; but colonic fermentation of dietary fibres may offset this negative effect by liberating bound minerals and promoting colonic absorption [96].

Antioxidants also act in synergy. Therefore, an isolated added antioxidant is less well regenerated by other complementary or synergistic antioxidants once it becomes a pro-oxidant through the oxidation–reduction reaction [97]. Thus, theoretically, vitamin C becomes the ascorbyl radical that is regenerated by vitamin E, which becomes the tocopheryl radical that is regenerated ultimately by glutathione, ending the oxidoreduction chain by combining two oxidized glutathiones into a neutral molecule [97]. For example, in cereals, there are more than 35 different antioxidant compounds with different modes of antioxidative action, but these actions are complementary or synergistic [98]. Minimally processed micronutrient-rich food matrices are ultimately more prone to supply such a synergy of action of bioactive compounds, which in humans is not the same for artificial micronutrient-enriched foods and/or nutritional supplements. More studies about micronutrient synergism are warranted [99].

Nutrient bioavailability is associated with the food "matrix effect"

Numerous studies have shown that, depending on the food matrix, the same nutrient is not equally bioavailable [7–9, 100]. Thus, the kinetics of nutrient release notably impact the secretion of hormones, e.g. insulin, as shown with slow versus rapid carbohydrates from apples [71] or the degree of chewing with almonds [101]. Beyond the above-mentioned reviews on the "food matrix effect" and nutrient bioaccessibility/bioavailability, some recent studies again support the "matrix" effect:

For example, it was recently reported with choline that, depending on matrix sources (hard-boiled eggs, choline bitartrate supplements, hard-boiled eggs + choline bitartrate supplements, egg whites + choline bitartrate supplements, or phosphatidylcholine supplements), the impact on trimethylamine-*N*-oxide (TMAO) and platelet function in healthy human subjects was significantly different, with participants consuming four eggs daily showing no significant increase in TMAO or platelet reactivity, while those consuming choline bitartrate supplements providing comparable total choline showing a significant increase in TMAO and platelet reactivity [99].

Concerning lipids, the resistance of the cheddar matrix to degradation and the large fat droplets in cheddar have been reported to be responsible for its slower fat digestion in vitro than homogenized cheddar cheese, micellar casein and cream drink or micellar casein and cream gel (all of identical protein:fat and calcium:fat ratios) [102]. In the same way, with various beverages (fruit juices and water, milk or soymilk), the treatment modulated the food matrix and the bioaccessibility of carotenoids as well as their lipophilic antioxidant potential [103].

Concerning polyphenols, it was recently shown that the apple food matrix and its processing may influence the postprandial nutrigenomic response of flavan-3-ol monomers to dietary inflammatory stress in minipigs challenged with a high-fat meal supplemented with raw fruit, puree, or apple phenolic extract with a matched content of flavan-3-ol monomers [104]. Concerning vitamins, in 12 healthy male volunteers, the highest folate bioavailability was observed for pudding and, to a lesser extent, sponge cake; the lowest bioavailability was observed for custard (liquid texture) and, to a lesser extent, biscuits (hard solid texture), with these latter two matrices presenting very different rheological properties [105]. Similarly, calcium bioavailability in humans from dairy products may importantly vary, i.e. between approximately 17 and 55% depending on the food form and matrix, with the majority of studies giving values between 20 and 30% [9].

Finally, it can be hypothesized that rendering many nutrients more bioavailable, e.g. through micronutrient-enriched ultra-processed foods or supplements, does not guarantee the occurrence of the biological activities of these nutrients, and the resulting health impacts, as observed in studies using purified components, and often studied at the supra-nutritional level, e.g. with β-carotene and vitamin A [106] and antioxidants [107] or more generally with nutritional supplements [97]. Therefore, increasing the nutrient bioavailability through food processing is not always a guarantee of a better health on the long term.

How the proof of concept might be tested?

The empirico-inductive proof of concept that "chronic diseases are more associated with the degradation and artificialization of food matrices than with food composition" is indirectly supported by the studies on ultra-processed foods and increased risks of chronic diseases [3, 4, 29], by those showing increased calorie intake in the form of sugar and fats when consuming these foods [42, 79], and more generally by other studies in humans as described above. However, beyond the only epidemiological studies on ultra-processed foods, to directly obtain a causality it would not be ethically possible to carry out an interventional study in thousands of healthy humans over several years with diets of identical composition but different food matrices and to assess the occurrence or absence of chronic diseases. Only short-term interventional studies could be performed, such as that of Hall et al. [42], notably, to measure the variations in some prognostic metabolic biomarkers that are indicative of chronic disease to occur later [108].

From the scientific evidence associating the "food matrix effect" with human health, we therefore develop a new empirico-inductive paradigm to try to better reflect the overall health potential of a diet, including the degree of food processing, because it impacts both the food matrix and food composition,

The 3 V index to conceptualize and include the "matrix effect" for global health

Definition of the 3 V index: a fundamental question of hierarchy

Recently, we created the 3 V index, where 3 V is for Vrai, Végétal, Varié (if possible, organic, local and seasonal) in French, or Real (i.e. not ultra-processed foods), Vegetal and Varied foods in English [109] (Fig. 4). The 3 V index was created to combine both the food matrix and composition but with a hierarchical application (Fig. 4).

These three metrics are those that we have observed as potentially governing the diet–global health relationship [110]. Through their holistic essence, these metrics encompass all nutritional needs when following the 15% maximum and optimum daily ultra-processed (metric 1) and animal (metric 2) food calories recommendation and

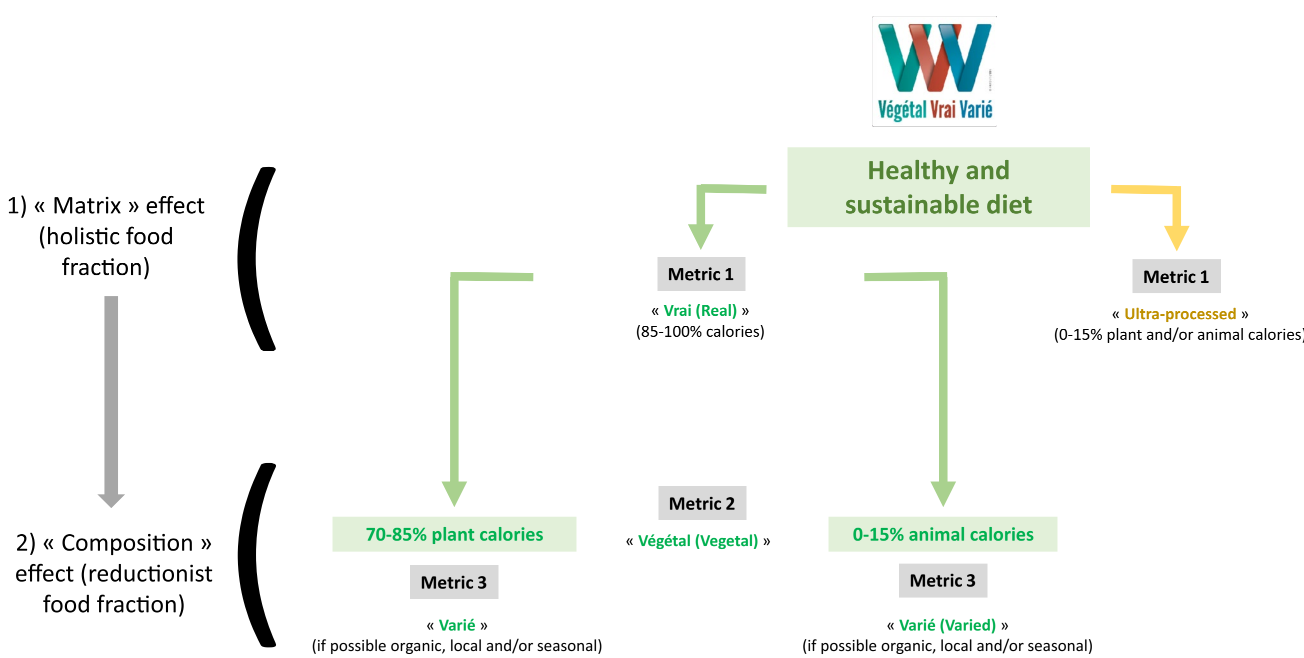

Fig. 4 The hierarchy of the three metrics of the 3 V index: the food matrix "governs" the metabolic fate of nutrients

varying both food groups and foods among them (metric 3) [109]. If a dimension is not fully addressed, then the diet is no longer protective of global health. Indeed, a Real/*Animal*/Varied-based diet is related to an increase in greenhouse gas emissions and some chronic diseases [111, 112], an *Ultra-processed*/Vegetal/Varied-based diet is also related to unsustainable food systems and an increased risk of numerous chronic diseases [3, 4, 29, 113], and a Real/Vegetal/*Monotonous-based* diet is related to a lack of environmental biodiversity and some potential nutritional deficiencies [114, 115]. These three dimensions suggest that if the Vegetal and Varied metrics address the quantitative nutritional needs, the third dimension addresses the quality of the calories and nutrient interactions, i.e. their matrix environment modified by the degree of processing applied (Fig. 4).

To date, the Vegetal and Varied metrics have been privileged through recommendations for reduced animal-based food consumption [116–118] and viewing foods as only the sum of nutrients [119], respectively. However, there was a missing link, food processing, consequently addressing the "matrix" effect [2]. Therefore, it does not seem sufficient to recommend the revegetation of the diet; the addition of "minimally processed plant-based foods" should also be recommended. Ultimately, while agricultural production addresses the Vegetal and Varied metrics, food processing (at the interface of agricultural production and food retail/consumption) addresses the Real metric.

The consumption of Vegetal/Animal and Varied foods to address nutritional needs

Why is it recommended to consume varied foods? Because no food supplied by our environment is fully nutritionally balanced. If this were not the case, it would be sufficient to consume the same food throughout our entire life span, even in the form of a capsule or nutritional supplements, and ultimately there would be no need to chew. However, a primary important point to emphasize is that an individual can become chronically ill, especially diabetic and/or obese, while fully meeting their nutritional needs. For example, the consumption of many micronutrient/fibre-enriched ultra-processed foods and/or "empty calories" along with nutritional supplements is not a guarantee to stay healthy since excess ultra-processed food consumption is associated with many chronic diseases [3, 4, 29, 120, 121]. In addition, as discussed above, food composition says nothing about chewing and satiety, nutrient bioaccessibility/bioavailability, and the synergistic effects of bioactive compounds.

Thus, it has been observed in several ecological studies that, despite decreased calorie consumption over several decades at the level of the overall populations, chronic disease risk continues to increase, e.g. in China [122] and France [123]. Although ecological studies remain approximate for evaluating calorie intake, and that they do not take into account the differences in consumption at the level of an individual or a group of individuals, this increase can be nevertheless partially attributed to the parallel important increases in the consumption of animal-based and highly industrially processed foods, the latter often being less satiating and more hyperglycaemic foods [79, 124–126]. This means that beyond nutrient composition alone, the quality of calories matters; we expressed this in the Real dimension of the 3 V index (Fig. 4) [109]. Notably, in whole complex and minimally processed foods, there are also synergistic and balanced effects of bioactive compounds [89] that can be lost in micronutrient-enriched ultra-processed foods and/or nutritional supplements [97, 127]. For example, added isolated antioxidants will not have the same physiological effects as those embedded in a whole food matrix in synergy with other antioxidants [97, 127].

Fibre and proteins confer food matrices and a three-dimensional architecture in plant- and animal-based foods, respectively. These matrices thereafter require a certain degree of chewing and then confer satiety and the regulation of food intake [72]. However, excess animal-based food consumption may supply excess saturated fatty acids and iron, which are involved in the impairment of some metabolic mechanisms, either at the cardiovascular level [37, 128] or the colon level [129, 130], respectively. Excess haemic iron may become, for example, a pro-oxidant through Fenton's reaction [131]. Apparently, concerning plant-based foods, there were no reported important deleterious health impacts when consumed in excess, except for potential digestive discomfort with excess fibre [132], lower mineral bioavailability with phytic acid and other anti-nutritional factors [133], and potential nutritional deficiencies in vegans, e.g. vitamins D [134] and B12 deficiencies [135–137].

However, too highly processed plant-based foods may become deleterious and lead to the same coronary heart disease risk as excess animal-based food consumption for each supplemental serving [138], and the revegetation of our diet today appears to be associated with an increased consumption of ultra-processed plant-based foods as meat substitutes [139], with ultra-processed foods being associated with increased risks of chronic diseases [3, 4, 29]. This strongly suggests that the degree of food processing appears to be the missing dimension to fully characterize the food health potential, leading to an underestimation of—or even ignoring—the fundamental "matrix" effect.

Real foods (i.e. non-ultra-processed foods) to address the "matrix" effect

Food processing appears to be the possible missing link to fully characterize the diet-human health relationship and to achieve non-contradictory scientific results, especially for nutritional recommendations [2]. This new dimension emerged at the beginning of the 2010s with the NOVA classification [140], although the potential impact of food processing on health had already been studied but not with a so generic approach, e.g. whole versus refined cereals, red versus processed meat, whole versus fruit juice, and whole versus semi-skimmed versus skimmed milk, among others [5] or the Western diet, generally rich in ultra-processed foods or "empty calories" [141–146], notably compared, e.g. with a Mediterranean diet [147]. Ultra-processed foods have been shown to lead consumers in the short term to consume up to + 20% calories and to eat between 56 and 100% more calories per minute [42, 79], probably due to their particular artificialized matrices, which demand less chewing with more friable, viscous and liquid textures [30, 42, 124]. Therefore, the paradigm underlying the newly developed concept of ultra-processed foods is not primarily altered nutritional composition—even if these foods overall have a lower nutritional density [148]—but the degradation of the "matrix effect" (Figs. 2a, b and 3) [10, 30], which leads us to postulate that the increase in chronic disease prevalence worldwide is associated with the "lost" or degraded "matrix effect" through ultra-processed, artificialized and hyperpalatable food matrices. Consequently, the consumption of excess sugars, salt, fats, additives and other xenobiotics is an effect, not the root primary cause, of chronic diseases (Fig. 3) [10]. Obviously, beyond the factors linked to food matrix and unbalanced diets, the trigger of chronic diseases is multifactorial, and notably also involve a low level of physical activity, smoking, alcoholism and increased environmental pollution, among the other leading factors [149].

For example, concerning cereal-based products based on the NOVA classification, while muesli, pasta and cooked oat flakes are classified as minimally processed (NOVA 1), traditional breads as processed (NOVA 3), and industrial soft white breads or extruded cooked breakfast cereals for children as mainly ultra-processed (NOVA 4), in all groups food matrices are modified, but to different extents. Thus, in NOVA 1 and 3, food matrices are modified by thermal (e.g. steam cooking), mechanical (e.g. grinding, simple extrusion) and/or fermentative (e.g. leavening or yeast) treatments, or the addition of traditional culinary ingredients (e.g. table sugar, salt and/or fat in traditional biscuits or pastries), but in ultra-processed cereals, the presence of markers of ultra-processing (MUPs) linked to food cracking or extrusion cooking can be found, in which food matrices are much more degraded or fully deconstructed up to isolating the nutrients and modifying them with enzymatic or chemical treatments, e.g. hydrogenation. Therefore, isolated purified and synthetic MUPs are compounds without matrix [150]. Therefore, in NOVA 1–3 enough of the food matrix is retained, e.g. after grinding, to benefit from the myriad molecules present in combination in these foods. However, special attention must be paid to non-ultra-processed refined cereals with regard to the reported increased risks of type 2 diabetes with refined rice compared to brown rice [151, 152], and more generally with refined cereals compared to whole grain cereals [153]. In this case, refining the food matrix appears sufficient to generate chronic diseases, both through an important loss of protective micronutrients [98] and an altered matrix that can be less satiating and more hyperglycaemic [126].

Finally, in view of the role of food matrix on the health potential of cereal products, a natural and minimally processed whole grain cereal product would not be the same as a reconstituted whole grain cereal product by adding a posteriori the initially removed cereal fractions during refining. Actually, in reconstituted whole grain cereal products, which for tolerance limits should be something equivalent to about 97% extraction, one tends to eliminate most part of the germ. This "close enough" reconstitution opens the door for industry to increase shelf life at the expense of keeping the initial whole and complex food.

Conclusions

Ultimately, a food's health potential is not primarily and only associated with its nutritional composition. Without a preserved food matrix, the expected nutrient-based health impacts may be misinterpreted and even be unhealthy, notably through modified kinetics of release within the digestive tract and altered bioaccessibility and bioavailability. Thus, it appears that "the matrix governs the metabolic fate of nutrients", and their health effects depend primarily on the quality of the matrix in which they are embedded. If not, it would be sufficient to consume capsules containing all the nutrients necessary for the human body without chewing. Therefore, without the matrix, nutrients may even deregulate metabolism, leading to chronic diseases. This is notably suggested through the more than seventy epidemiological studies associating excess ultra-processed food consumption with increased risks of chronic diseases, with ultra-processed foods being primarily characterized by degraded and artificialized food matrices, and, yet, many of them are enriched with fibre and micronutrients.

However, food matrices are always modified by processing to some extent, and a food product may remain healthy, even if not optimal for health. Otherwise, in most cases, food matrix processing is essential for rendering the food edible, safe and healthy. Therefore, the main issue is not processing as such, but rather the "degree" of processing, i.e. "to what extent a food matrix can be processed without altering human health?" As of today, the scientific evidence about food processing and health strongly suggests that a high level of food refining, food cracking, extrusion cooking and processing solid foods into their liquid form should be limited, and be the exception, not the rule, for human consumption.

In addition, this empirico-inductive proof of concept about the degraded food "matrix effect" being associated with chronic disease risk may lead to another postulate: "no food supplied by our environment is 'good' or 'bad' in essence, but it is the quantity consumed and the degree of processing that render it healthy or unhealthy for human health", meaning that any food becomes deleterious if consumed in excessive quantity and if its matrix is ultra-processed/artificialized. Therefore, human intervention on foods appears to be the key parameter to consider for defining a healthy food or not.

Consequently, today, the strong focus on food nutrients, as exemplified with food composition databases [18] and compositional food scoring [10], is insufficient to put forth strong nutritional recommendations for the majority of the public, mainly because it ignores the "matrix" effect. It appears now crucial to include both the origin of calories (vegetal versus animal) and the degree of processing (real versus ultra-processed) in analyses of food health potential to preserve both human health and food system sustainability in the long term, i.e. global health.

In conclusion, including the matrix effect in analyses of food health potential has very important potential implications in terms of public health, notably, to abandon nutrient-based composition scores as the main tools for helping consumers to choose potentially healthy foods (because a healthy food is a food for which its matrix is the most preserved, not a food balanced in only a few nutrients), to encourage the agro-food industry to develop less processed foods rather than only reformulating ultra-processed foods, and not relating environmental issues and global health to food nutrient contents.

Acknowledgements Not applicable.

Author contributions AF and ER are equally responsible for the design, writing, and final content. All authors have read and approved the final version of the manuscript.

Funding The authors did not receive support from any organization for the submitted work.

Availability of data and material Not applicable.

Code availability Not applicable.

Declarations

Conflict of interest Since 2017, A. Fardet has been a consultant and member of the Siga and Wuji & Co. society scientific committee. He is also a member of the scientific committee of the French MiamNutrition and ComplexusCare associations. Edmond Rock: none.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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