UNIVERSITÁ DEGLI STUDI DI PADOVA

CORSO DI LAUREA MAGISTRALE IN MEDICINA E CHIRURGIA

DIPARTIMENTO DI MEDICINA - DIMED

Direttore: Chiar.mo Prof. Roberto Vettor

TESI DI LAUREA

Animal- and plant-based proteins: human health outcomes and environmental impact

RELATORE: Prof. Francesco Visioli

CORRELATORE: Dott. Stefan-Alexandru Panaite

LAUREANDO: Luca Ferrari

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ABSTRACT

Background

The fact that dietary proteins play a fundamental role in human nutrition is indisputable; among their functions, the one certainly best known and studied is the tissue-building one. However, the beneficial effects of ingested proteins also affect body composition, regulation of various metabolic pathways, satiety and immune system activity, therefore these energy and regulatory functions are equally important.

Over the last 60/70 years, in high income countries there has been an exponential increase of animal protein sources intake and a complementary decrease of plant-based protein sources consumption: these dietary changes have been identified as one of the elements with greatest role in the chronic diseases rise and, at the same time, has led to significant environmental impacts.

Study's aim

The main aim of the study was to evaluate the effects of the two protein sources categories (animal and plant-based) on human health; more specifically, we wanted to investigate the relationship between their intake and the most prevalent chronic diseases globally. At the same time, we also considered the environmental impacts of these foods in a planetary health perspective: human health, in fact, cannot be separated from planet's health.

By integrating these two aspects, the intention is to propose a first draft of a multidisciplinary approach in the field of nutrition, which can also be used in the clinical-health field to also consider the environmental aspect in patient care.

Materials and methods

The article has been divided into four parts that deepen various aspects of this topic: protein quality, vegetarian dietary patterns, the Mediterranean diet double pyramid and finally the study of individual protein sources through the creation of ad hoc tables.

For each section we searched various types of papers according to needs (narrative reviews, consensus papers, systematic reviews, meta-analyses of prospective cohort studies, umbrella reviews, and even some interventional studies) from the most important databases (PubMed, Google Scholar, WebScience, Cochrane Library and Scopus).

Results

The data discussed in this thesis allow us to conclude that plant-based protein sources consumption is associated with better health outcomes (namely, on the cardiovascular system) than animal-based product use. As far as mechanisms of action are concerned, there are currently no data to explain these effects and much more research is needed. However, the irrefutable healthier activities of plant-based protein sources dovetails with their lower environmental impact, which must be taken into account when we design optimal diets. The health of the planet cannot be disjointed from the health of the human being.

Conclusions

Future research will clarify the putative health effects of plant-based protein sources when compared with animal ones and will foster better agronomic practice and influence public health in a direction that will benefit both the planet and its inhabitants.

RIASSUNTO

Premesse

Il fatto che le proteine alimentari svolgano un ruolo fondamentale nel campo della nutrizione umana è indiscutibile; tra tutte le loro funzioni, quella certamente più conosciuta e studiata è quella plastica. Tuttavia, tra gli effetti benefici dell'assunzione di proteine vi è anche l'influenza sulla composizione corporea, la regolazione di vie metaboliche endogene, il senso di sazietà e l'attività del sistema immunitario.

Nel corso degli ultimi 60/70 anni, nei Paesi ad elevato reddito si è verificato un incremento esponenziale dell'assunzione di fonti proteiche animali e contemporaneamente una riduzione di quelle vegetali: questo cambiamento è stato identificato come uno degli elementi che ha contribuito maggiormente all'aumento delle malattie croniche; allo stesso tempo, ciò ha determinato anche notevoli impatti sull'ambiente.

Scopo

L'obiettivo di questo studio è stato quindi quello di valutare gli effetti delle due principali categorie di fonti proteiche (quelle animali e quelle plant-based) sulla salute umana approfondendo, in particolare, la relazione tra il loro consumo e le patologie croniche più diffuse. Contemporaneamente si è considerato anche l'impatto ambientale di tali alimenti in un'ottica di salute planetaria: la salute umana, infatti, non può essere scissa da quella del pianeta. L'integrazione di questi due elementi vuole porre le basi per un approccio multidisciplinare nell'ambito della nutrizione che possa essere fruibile in ambito clinico-sanitario per tener conto anche dell'aspetto ambientale nella cura del paziente.

Materiali e metodi

L'articolo è stato diviso in quattro parti che approfondiscono vari aspetti di questo tema: la qualità proteica, i pattern dietetici vegetariani, la doppia piramide della dieta mediterranea e infine lo studio delle singole fonti proteiche mediante la creazione di tabelle ad hoc.

Per la stesura di queste quattro sezioni ci si è serviti di varie tipologie di papers in base alle esigenze (narrative reviews, consensus papers,

systematic reviews, metanalisi di studi prospettici di coorte, umbrella reviews, e anche alcuni trials clinici) estrapolati dai database più importanti (PubMed, Google Scholar, WebScience, Cochrane Library e Scopus).

Risultati

Dallo studio emerge che il consumo di fonti proteiche vegetali determina migliori risultati per la salute (ossia, sul sistema cardiovascolare) rispetto all'uso di prodotti a base animale. Per quanto riguarda i meccanismi d'azione, attualmente non ci sono dati che spieghino questi effetti ed è necessaria molta più ricerca. Oltre a questo, è da tenere in considerazione, in ottica di planetary health, che le fonti proteiche vegetali hanno un impatto ambientale notevolmente minore, fattore che deve essere valutato quando si progettano diete ottimali. La salute del pianeta non può essere disgiunta dalla salute dell'essere umano.

Conclusioni

La ricerca futura chiarirà i presunti effetti sulla salute delle fonti proteiche vegetali rispetto a quelle animali e promuoverà una migliore pratica agronomica che influenzerà la salute pubblica in una direzione che andrà a beneficio sia del pianeta che dei suoi abitanti.

1. INTRODUCTION

The fact that dietary proteins play a fundamental role in human nutrition is indisputable. Although complex, their most well-known, best studied and at the same time essential function is certainly the tissue-building one: in fact, they provide amino acids for the maintenance of an adequate level of protein synthesis within the body. However, the effects of ingested proteins also affect body composition, regulation of various metabolic pathways, satiety and immune system activity, therefore these energy and regulatory functions are equally important to take into account in specific research studies [1,2].

In the field of nutrition, protein consumption can be examined from a quantitative or a qualitative point of view.
On the first aspect have been concentrated many studies already in the last century and over the years it was defined a specific Recommended Dietary Allowance (RDA) for this macronutrient, that is "the average dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97.5%) healthy individuals in a particular life stage and sex group" [3]. The current value is **0.8 g per kg of body weight** for healthy adults and in normal conditions [4], but it varies depending on some factors (age. physiological need of the extremes of the population, pregnancy, etc.); on the value of this parameter there are conflicting positions and there are those who propose to increase it by identifying the optimal range between 1.2 and 1.6 g/kg [4].
As for the qualitative evaluation, it is important to analyze the so-called **protein quality** that distinguishes proteins into two groups on the basis of the amino acid composition: high-quality and low-quality proteins, commonly understood as animal and vegetable proteins respectively.

Another important factor is the total composition of protein foods: if in the AMDR is considered as optimal a range of protein intake between 10 and 35% (however variable according to the individual, sex, age, general health and specific pathological conditions)[5], this does not mean that protein foods should cover this percentage of daily intake; this is because their nutritional composition is multiple and varies from each food. Excluding dried edible insects - which can contain up to 60 g of protein on 100 g of product, range 35% - 61% [6,7] - and some other little consumed foods (such as soy protein isolate, stockfish, scraps of swine fat and roe), the most commonly consumed protein foods reach a maximum protein content of between 33% and 37% per 100g of product: some of the best examples are dried soya and the flour derived from it, grana cheese and caciocavallo cheese, bresaola and guinea fowl [8]. For this reason, in the nutritional field it is more appropriate to talk about **"protein sources"** rather than "proteins".

Nowadays in high income countries there is an imbalance in the consumption of the two macro-categories of protein sources, precisely those animals and plant-based; more generally, the excessive consumption of animal source products is now identified as one of the elements that contribute to the risk of developing chronic diseases.
For this reason today’s nutritional guidelines emphasize the relevance of assuming a more plant-based diet, which is not necessarily equivalent to vegetarian patterns.
In this context, the importance of an adequate nutritional prescription, both clinically and at the level of territorial medicine: diet therapy and a healthy diet as a primary and secondary prevention play an important role in the fight against "Global burden of chronic diseases".

However, as clearly visible in Figure 1 taken from the paper by Afshin et al. [9], the «determinants of food choices and dietary behaviors» are multiple and difficult to evaluate; but to contribute also through adequate nutrition to the achievement of an important long-term goal of public health, such as to decrease mortality and morbidity in non-communicable diseases, it is necessary to take into account several determinants and certainly the environmental pressure of the food system is among the main ones. The syndemic relationship between chronic diseases and climate change is well known and the planetary health approach proposed by the report of the Rockefeller Foundation [10] is crucial to understand the overall effects of the consumption of protein sources on human health and the environment.

In this thesis the main protein food groups were analyzed (based on the classification proposed by EUROCODE 2 System [11]) and were divided into the two macro-categories **"animal protein sources"** and **"plant-based protein sources"**.

This analysis was carried out with priority given to the assessment of the direct effects of such foods on human health; consequently, correlations between their consumption and main chronic diseases and certain clinical conditions requiring a specific protein sources prescription were evaluated. In addition, their environmental impacts have also been investigated with the aim of returning a more complete picture of the implications of different protein sources.

In evaluating this intricate picture, a brief but punctual description of some topics related to protein sources, such as protein quality, vegetarian and plant-based dietary patterns and the double food pyramid of the Mediterranean Diet, was also necessary.

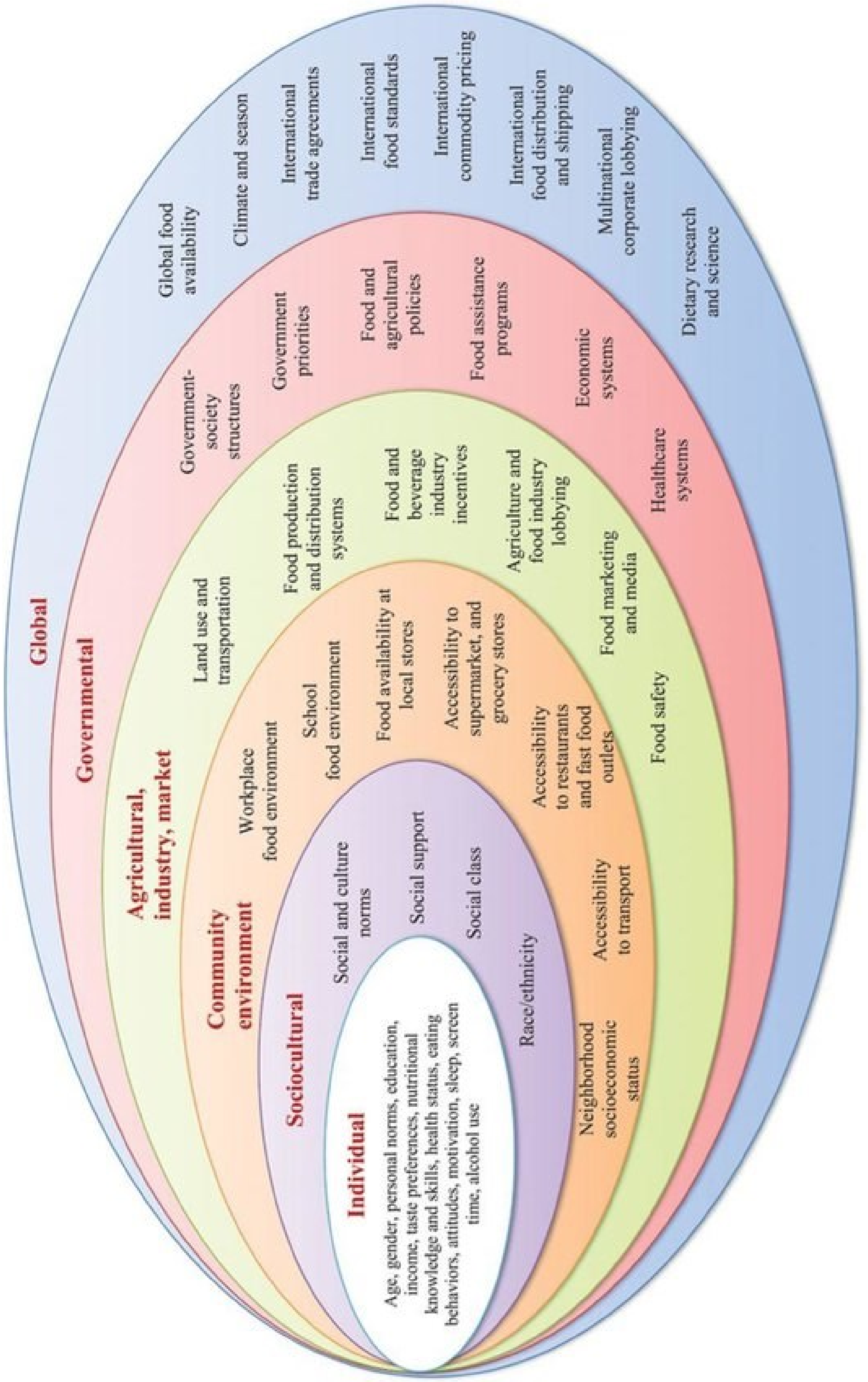


Figure 1 – Barriers and opportunities for healthy-eating.

2. AIMS

The main aim of the study was to evaluate the effects of the two categories of protein sources, animal and plant-based, on human health; more specifically, we wanted to investigate the relationship between their consumption and the most prevalent chronic diseases globally. Furthermore, we wanted to investigate these associations by evaluating both the two macro-categories and the individual protein sources in order to highlight any different trends and to give, as far as possible, an overview.

The analysis of the different forms of environmental impact related to each protein source was another objective of the work, from a planetary health perspective.

By integrating these two aspects, the intention is to propose a first draft of a multidisciplinary approach in the field of nutrition, which can also be used in the clinical-health field.

3. MATERIALS and METHODS

In the first part of the paper we went into detail on a number of topics which were functional for the analysis of the main topic: for the part on protein quality and the double food pyramid we relied on various narrative reviews, some consensus papers and systematic reviews; for the analysis of the vegetarian and Mediterranean dietary patterns we used studies similar to the previous ones, as well as systematic reviews, meta-analyses of prospective cohort studies and umbrella reviews to assess the association between these two dietary patterns and chronic diseases. The latter types of paper also served us for the inclusion of data in the tables on individual protein sources, whereas interventional studies (i.e. RCTs) were not taken into account; for the last part we searched for some reviews or guidelines for certain disease conditions.
We searched the most popular databases (PubMed, Google Scholar, WebScience, Cochrane Library and Scopus) for the most recent publications and reviews on this topic; these were read, interpreted, discussed and commented on, and the main data and conclusions were extracted.
Various forms for the description of plant-based protein sources (“plant-based protein” or “plant-based protein sources”, “vegetable protein” or “vegetable protein sources”) have been found in the scientific literature, but these were always referred to using the first two terms.
The analysis of these different types of studies results in a narrative review with the objectives as outlined above.

To make the consultation of tables on individual protein sources more usable, here we will follow a brief legend: the orange color indicates an absence of significance of the data; yellow indicates an association (inverse or positive) "almost significant"; all other data on a green background have statistically significant associations (inverse or positive).

4. RESULTS and DISCUSSION

4.1. DIETARY PROTEIN QUALITY

In order to make a comparison between animal and plant-based protein sources from both a nutritional and a sustainable point of view, it is useful to start from the **concept of "protein quality"**.
There is currently a debate in this specific field of scientific literature about the need to revise and broaden this concept: in common language the term "quality" is almost always associated with the idea of "desirability" and therefore its use in this context may be inappropriate and lead to misinterpretations [12].

In describing protein quality, one may take different approaches:

- The most traditional: to consider the positive biochemical impact of dietary proteins on protein synthesis and nitrogen balance [13].
- An alternative approach: to consider the impact of dietary proteins on the function and metabolism of specific organs and/or hormones (e.g., evaluating the regulation of body composition and bone health, gastrointestinal function and bacterial flora, glucose homeostasis, cell signaling, satiety) [14].
- The most recent and far-reaching: to consider the net effects on human health and environment [12].

4.1.1. Traditional Approach

In the traditional approach, the quality of a given protein source can be defined as its ability to efficiently meet the requirements of both nitrogen and essential amino acids, and depends on two factors:

a) the specific amino acid composition (the **intrinsic** quality of proteins);
b) digestibility (the **extrinsic** quality of proteins) [15].

a) As for the first component, Essential Amino Acids (EAAs) are a key factor in determining the **intrinsic** quality of proteins, which is, as a matter of fact, represented by the combination of the 9 EAAs' content. Before getting into the details, it's useful to list them: **lysine (Lys), threonine (Thr), methionine (Met)**, **tryptophan (Trp),** phenylalanine (Phe), histidine (His), isoleucine (Ile), leucine (Leu) and valine (Val).
If the dietary content of a single EAA is lower than the individual's reference requirement, this specific deficiency limits the use of any other amino acid: therefore, even if the total nitrogen intake level is adequate, the **"limiting amino acid"** prevents normal rates of protein synthesis and determines the nutritional value of the total protein (or nitrogen) content in the diet [15]. This is however a theoretical and didactic simplification, given that the evaluation in the daily diet is more complex because of the mixture of different protein sources ingested: as seen later, it is possible to circumvent the "limiting amino acid" problem through the precise **complementation** of protein sources [16].

The concept of "limiting amino acid" has led to the development of the amino acid scoring, and consequently to a **reference amino acid scoring pattern;** although there are currently some uncertainties in establishing it, it's surely useful for comparing the quality of different protein sources [13,15].

The Table I [13] summarizes the reference amino acid scoring pattern for adults, which differs from that of other age groups; the life-course of amino acid requirements is represented by an inverse J-curve: newborns and infants need high amounts of them for growth, children

Amino acid protein[b]	Present estimates		1985 FAO/WHO/UNU[a]	
	mg/kg per day	mg/g protein[b]	mg/kg per day	mg/g protein[b]
Histidine	10	15	8–12	15
Isoleucine	20	30	10	15
Leucine	39	59	14	21
Lysine	30	45	12	18
Methionine + cysteine	15	22	13	20
Methionine	*10*	*16*	–	–
Cysteine	*4*	*6*	–	–
Phenylalanine + tyrosine	25	38	14	21
Threonine	15	23	7	11
Tryptophan	4	6	3.5	5
Valine	26	39	10	15
Total indispensable amino acids	**184**	**277**	**93.5**	**141**

[a] From reference *1*.
[b] Mean nitrogen requirement of 105 mg nitrogen/kg per day (0.66 g protein/kg per day).

Table I - Summary of the adult indispensable amino acid requirements

and adolescents need higher intakes than adults and the same thing for the elderly that should increase their consumption in order to counteract some aging processes [13].

b) For **extrinsic** protein quality, there are two processes to consider:

- the first one, the digestion of proteins and absorption of the constituent amino acids (so called **digestibility**); «digestibility is defined as the difference between the amount of N ingested and excreted, expressed as a proportion of N ingested». Due to the processes of protein metabolization of the intestinal microbiota, it is more appropriate to consider the **ileal digestibility** than the fecal one. [17] More precisely it is necessary to measure the True Ileal Digestibility (TID) which also takes into account the endogenous protein losses (both basal and specific ones) [17].
- And the second one, the utilization of the absorbed amino acids to support whole body protein synthesis (so called **availability**).

These two different processes constitute what can be defined as **bioavailability** (or metabolic availability) of nutrients, in this specific case of amino acids from dietary protein sources.

In 1991 the “joint FAO/WHO Expert Consultation on Protein Quality Evaluation” [18] proposed a first score to merge these two components and then to evaluate quantitatively the protein quality: it is the PDCAAS (Protein Digestibility Corrected Amino Acid Score), whose formula is:

$$PDCAAS\ (\%) = \frac{[mg\ of\ limiting\ amino\ acid\ in\ 1\ g\ test\ protein]}{mg\ of\ same\ amino\ acid\ in\ 1\ g\ reference\ protein} \times [true\ digestibility\ (D_F)\ (\%)]$$

The subsequent research has led to highlight some limits of this score; the main ones are:

- the truncation of the score to the value of 100%, not allowing the comparison between very high value’s proteins [19];
- the use of fecal digestibility (instead of true ileal digestibility, TID)[19];
- the restriction to only the first limiting amino acid [19];
- the lack of consideration of the bioavailability of every single EAA [14,20].

The latter one is particularly important since the relevance of considering amino acids as individual nutrients has recently been understood [21].

In order to replace PDCAAS and exceed its limits, in 2011 “FAO Expert Consultation on Protein Quality Evaluation in Human Nutrition” introduced another score, **DIAAS (Digestible Indispensable Amino Acid Score)**; DIAAS is calculated as shown in Figure 2 [20]:

$$\text{DIAAS}\ (\%) = 100 \times [(\text{mg of digestible dietary IAA in 1 g of the dietary test protein}) / (\text{mg of the same amino acid in 1 g of the reference protein})]$$

Figure 2 - DIAAS Formula

According to this new score, protein sources are classified into 3 categories:

- "excellent" source (DIAAS $\geq$ 100%);
- "good" source (75% $\leq$ DIAAS < 100%);
- "no claim" source (DIAAS < 75%) [20].

In order to compare the quality of **animal** and **plant-based** protein sources, it's useful to refer to Table II [22], which shows the values for each EAA and the resulting DIAAS.

Since they generally contain reduced amounts of 1 or more EAAs, the **plant-based protein sources** have lower values of DIAAS (as it was with PDCAAS) and are therefore defined **"low-quality protein sources"** [23]**.**
The term "**incomplete** protein sources" "is no longer commonly used as all proteins contain all 20 amino acids" and to change are precisely their degrees and their combinations [24].
The most frequently limiting EAAs for plant-based protein sources have long been known and are the following 4: **lysine, methionine** (more generally Sulfur Amino Acids [SAA]), **threonine** and **tryptophan**.

However, plant-based protein sources are complementary to each other; the classic example of **protein complementation** is the combination of cereals and legumes (for simplicity think of the Italian recipe of pasta and beans): legumes typically have low/limiting levels of methionine (sulfur-containing amino acid) and high levels of lysine. Cereals have exactly the opposite characteristics [23].
In addition to this well-known example, it is possible to consider multiple combinations: the recent reviews by Huppertz et al. [16] and Herreman et al. [22] analyze many possibilities of complementation and between animal- and plant-based proteins.

Even if the score and its components are conceptually solid and the values of EAAs' requirements used in the calculation are the best currently available, the score and its ability to quantitatively evaluate the quality of different protein sources might be improved [19].
Progress has certainly been made in the methodologies that establish the digestibility of individual EAA, particularly in stable isotope-based methods [25,26], but it is necessary to promote research in this field with the future aim of implementing the DIAAS into regulatory standards for therapeutic foods.

Protein source	Histidine	Isoleucine	Leucine	Lysine	Met + Cys	Phe + Tyr	Threonine	Tryptophan	Valine	DIAAS	Limiting AA[a]
Corn	110 ± 29.7	90 ± 14.6	162 ± 58.2	36 ± 14.9	126 ± 22.2	140 ± 42.8	86 ± 10.2	52 ± 35.4	90 ± 14.4	36	Lys
Rice	93 ± 7.0	89 ± 17.4	80 ± 12.4	47 ± 2.3	104 ± 11.0	119 ± 29.6	75 ± 4.1	114 ± 28.6	95 ± 18.0	47	Lys
Wheat	118 ± 21.7	91 ± 10.5	87 ± 11.1	48 ± 10.6	127 ± 19.4	109 ± 16.9	78 ± 7.1	127 ± 17.8	92 ± 9.8	48	Lys
Hemp[b]	124 ± NA	106 ± NA	85 ± NA	54 ± NA	121 ± NA	131 ± NA	87 ± NA	-	99 ± NA	54	Lys
Fava bean	108 ± 4.1	106 ± 2.2	95 ± 5.4	95 ± 4.3	55 ± 5.1	119 ± 3.4	91 ± 6.2	68 ± 7.8	83 ± 2.2	55	Met + Cys
Oat	91 ± 11.4	100 ± 4.2	94 ± 4.9	57 ± 5.8	151 ± 52.9	135 ± 9.2	85 ± 5.9	110 ± 17.2	102 ± 3.4	57	Lys
Rapeseed	107 ± 8.0	90 ± 4.9	78 ± 5.0	67 ± 10.3	125 ± 14.3	92 ± 12.3	97 ± 6.5	106 ± 9.4	92 ± 4.6	67	Lys
Lupin	121 ± 16.1	104 ± 27.2	89 ± 19.3	75 ± 12.3	68 ± 12.7	121 ± 35.6	97 ± 22.7	72 ± 22.5	78 ± 14.6	68	Met + Cys
Pea	99 ± 9.7	101 ± 13.1	87 ± 11.5	110 ± 10.8	70 ± 12.3	116 ± 16.3	94 ± 7.9	77 ± 7.1	83 ± 9.8	70	Met + Cys
Canola	105 ± 6.9	93 ± 9.9	79 ± 7.8	72 ± 9.2	121 ± 10.4	97 ± 6.1	97 ± 12.2	112 ± 19.5	87 ± 9.1	72	Lys
Soy	119 ± 9.4	124 ± 8.3	102 ± 6.1	96 ± 9.0	91 ± 11.5	147 ± 8.3	105 ± 6.0	132 ± 21.1	95 ± 7.3	91	Met + Cys
Potato	100 ± 7.3	156 ± 9.2	143 ± 11.2	122 ± 4.6	115 ± 6.0	210 ± 18.2	165 ± 12.0	128 ± 13.7	138 ± 5.1	100	NA
Gelatin	34 ± 9.5	34 ± 10.6	35 ± 8.7	60 ± 11.5	27 ± 10.3	36 ± 13.0	46 ± 4.9	2 ± 3.0	46 ± 8.6	2	Trp
Whey	85 ± 10.8	166 ± 23.2	138 ± 22.9	131 ± 25.2	132 ± 21.6	101 ± 14.0	174 ± 22.8	180 ± 47.0	116 ± 14.3	85	His
Egg	101 ± 11.7	129 ± 25.5	103 ± 16.2	133 ± 58.4	123 ± 53.2	144 ± 18.9	106 ± 14.1	129 ± 49.7	105 ± 32.3	101	NA
Casein	147 ± 9.4	153 ± 4.3	141 ± 6.6	134 ± 4.3	117 ± 5.0	201 ± 8.0	130 ± 4.3	159 ± 13.4	148 ± 2.7	117	NA
Pork	197 ± 13.6	153 ± 11.1	122 ± 9.2	157 ± 10.7	128 ± 10.7	148 ± 10.4	145 ± 10.1	144 ± 17.1	117 ± 9.0	117	NA

Note: Data expressed as mean of individual DIAA values ± standard deviation.

[a]Limiting AA when DIAAS <100, NA not applicable when DIAAS ≥100.

[b]Dataset does not include tryptophan measurements. This is however the only publication reporting the ileal digestibility of hemp in pig studies. These data were therefore included for comparison.

Table II - Digestible indispensable amino acid scores of various protein sources according to the 0.5-to 3-year-old reference pattern score

For a more complete and accurate evaluation of the “traditionally conceived” protein quality, an accurate analysis of the role of antinutritional factors (ANFs) contained in the various protein sources, the food matrix and the processing processes of different protein foods could be integrated.

4.1.2. Recent Approaches

As the functions of dietary proteins have expanded in recent years compared to merely maintaining body protein mass, the concept of protein quality has to be broadened in order to include these new elements in a quantitative evaluation; to achieve this new "protein quality metric" it is also necessary to consider as normal, at least in high income countries, intakes higher than the Recommended Dietary Allowances (RDAs)[14], since these levels were established based only on the maintenance of the nitrogen balance in nearly all - precisely 97.5% - healthy individuals [27].

At the same time, it is also necessary to consider environmental impact in all its facets; of all the various factors that can be measured through the footprints methodology [28], the main ones related to food systems that will be evaluated are listed below:

- **GHG emissions** (carbon footprint);
- **freshwater (or bluewater) use** (water footprint);
- **(crop)land use** (land footprint or the wider ecological footprint);
- **cumulative energy demand** (CED, carbon component of the ecological footprint);
- **loss of biodiversity** (biodiversity footprint);
- **use of chemicals**, such as **fertilizers, pesticides**, antibiotics and other drugs (specific component of material footprint for fertilizers and specific component chemical footprint for others).

A first attempt at such a measurement was proposed by Katz et al. [12] through the definition of two different sample metrics, as shown in Table III; these ordinal scales to assess health outcomes and environmental impacts are just an example of how these elements can be integrated quantitatively.

Given the enormous complexity of the topic in terms of both nutrition and sustainability, multiple aspects must be evaluated [12,16]. At present there are still differing opinions on how the different factors should be considered, trivially even on the measurement units to be used; an example is provided by the paper by Tessari et al. [29] which questions how the cropland use and GHG emissions of various protein sources should be measured. The urgency of developing an evidence-based tool in this specific area is perfectly expressed by Berardy et al. in their recent article [30]: the basic requirement is certainly the use of Life Cycle Assessment (LCA) as a method of analysis [31–33].

Criterion	Maximum score	Beef, most cuts[2]	Beef, extra lean[2]	Dark meat chicken, with skin[3]	Skinless chicken breast[3]	Low-fat milk[2]	Soy[2]	Chickpeas[4]	Almonds[3]	Pistachios[3]	Whole-grain wheat[2]	Brown rice[3]
Sample metric 1: stand-alone rating system												
PDCAAS (>80: 2; 50 to <80: 1; 30 to <50: 0; <30: −1)	2	2	2	2	2	2	2	1	0	1	0	1
Recommended for health (recommended: 2; no mention: 0; discouraged: −1)	2	−1	2	−1	2	2	2	2	2	2	2	2
Environmental impact (low: 2; medium: 0; high: −1)	2	−1	−1	2	2	0	2	2	2	2	2	2
Total	6	0	3	3	6	4	6	5	4	5	4	5
Sample metric 2: metric used as an adjustment factor												
PDCAAS (range: 0.0–1.0)	1	0.92	0.92	0.94	0.94	1.0	0.92	0.52	0.43	0.73	0.42	0.69
Recommended for health (recommended or no mention: 1; discouraged: 0)	1	0	1	0	1	1	1	1	1	1	1	1
Environmental impact (low: 1; medium: 0.5; high: 0)	1	0	0	1	1	0.5	1	1	1	1	1	1
Average score	1	0.31	0.64	0.65	0.98	0.83	0.97	0.84	0.81	0.91	0.81	0.90

Table III - Sample Modernized Protein Rating Metrics

4.2. VEGETARIAN DIETARY PATTERNS

The various dietary patterns can be differentiated between them according to various methods [31,34]:

- the former uses an *a priori* index derived from a series of dietary recommendations for a healthy and high-quality dietary model;
- the second method of dietary pattern assessment consists of "data-driven" approaches, such as cluster analysis and factor analysis, that are outcome-independent and derive *a posteriori* patterns;
- the third one is based on individual preferences in food and beverage intake.

Vegetarian dietary patterns are an emblematic example of the third assessment method, but they can also be characterized by the first *a priori* method through the more generic distinction in "plant-based diets.

There are various categories and different subtypes of **vegetarian dietary patterns**, which differ from each other for specific absences of certain animal protein sources: from the semi-vegetarian diet (flexitarian) to the vegan one, animal meat (red meat, poultry and seafood) and animal derivatives (eggs and dairy products) are progressively eliminated [35,36]. The schematic Figure 3 is very clear and helps to keep differences in mind [37].

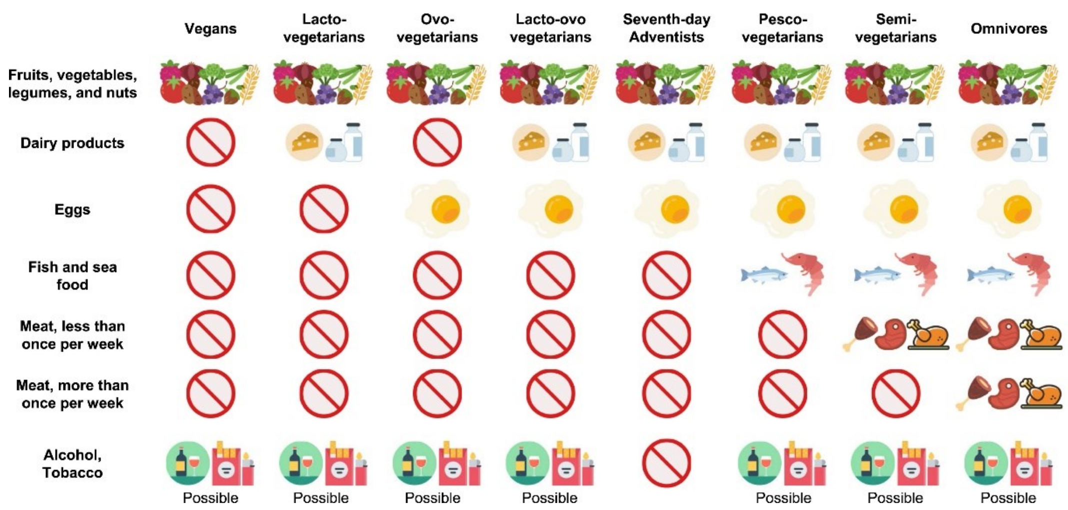


Figure 3 - Differences in various vegetarian dietary patterns

Another slightly different definition of vegetarian patterns is given by Orlich et al. [38]: the frequency greater or less than 1 time per month is used to classify the dietary intake of different animal protein sources.

However, several studies have shown that the differences in the intake of the various foods between the omnivorous diet and the various subtypes of vegetarian diets do not only concern animal protein sources.
In the cohorts of Adventist Health Study 2 (AHS-2)[39,40], European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford)[41] - the largest two of known ongoing prospective studies that include high proportions of vegetarians - and National Health and Nutrition Examination Surveys (NHANES) 2013-2016 [42] vegetarian dietary patterns are characterized by:

- a greater intake of certain major food categories [clearly plant-based protein sources (legumes, seeds and nuts) but also fruits, vegetables, whole grains and tubers] and of some micronutrients [fibers, minerals (magnesium on all) and vitamins (A, C and E types)];
- a lower intake of other categories (refined cereals, trans saturated fats of animal origin, added fats, sweets, snack foods and non-water beverages) and of other micronutrients (cholesterol, sodium, vitamin B12 and zinc).

Therefore, the discrepancies in terms of health outcomes - in more detail here below - cannot be **directly linked only** to the different consumption of **protein sources**.

4.2.1. Health Outcomes

First of all, to link also to the previous paragraph, the US National Academy Press with «Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids», published in 2006 [43], stated that «a varied vegetarian diet can get the same quality of protein and similar amounts of nitrogen as yielded by animal protein or a mixed diet»; moreover the 2015-2020 DCAG also defined that "Healthy Vegetarian Pattern" is associated with health benefits [31]. In addition the Italian Society of Human Nutrition declared through a position paper that «well-planned vegetarian diets […] provide adequate nutrient intake» [36]. A recent review has definitively dispelled the myth of the inadequacy of various vegetarian diets for protein and amino acids requirements [44].

To better understand the differences about health outcomes between omnivorous diet and vegetarian diets many studies have been carried out; among those selected there are some systematic reviews and meta-analysis [37][37,45–54], a position paper of the US Academy of Nutrition and Dietetics [35], the US National Guidelines report (2020 US DGAC Report)[3] and some relevant cross-sectional analysis of the AHS-2 cohort [38,55–63], of the EPIC-Oxford one [63–70] and also of other cohorts [70–75].

Some of the chosen papers distinguish only between vegetarians and non-vegetarians, while most subdivide the population taken into account in the 4 subtypes of vegetarian dietary patterns considered above and differently defined according to the article: "semi-vegetarian diet" or "low-occasional meat-eaters" (flexitarian), "pesco-vegetarian diet" or "fish-eaters" (pescetarian), "lacto-ovo vegetarian diet" or more generically "vegetarians", and "vegan diet" or "vegans".

In some of the papers considered, **all-causes mortality of vegetarian diets** is **comparable to or lower than** that of the omnivorous diet considering a population group with similar lifestyles and adjusting the results for age, sex, smoking status and alcohol consumption.

Among the various analyses of prospective studies, a paper of 1999 already identified that the total risk of mortality was **5% lower** in vegetarians than non-vegetarians; although the result wasn't statistically significant, the data were quite reliable because only staggered by the results of the vegan pattern, the less represented group: the other 3 patterns, "occasional meat-eaters", "fish eaters" and "vegetarians", had a statistically significant reduced risk by 16%, 18% and 16% respectively [71].

Subsequent analyses have confirmed this trend among vegetarians and non-vegetarians:

- comparable values in all-causes mortality were found by Key et al. [64] analyzing the results from the EPIC-Oxford cohort;
- while a meta-analysis of 2012 found, although not statistically significant, a decreased mortality of 9% [45] and a relevant study of 2013 (and its update of the following year) based on the results of AHS-2 cohort set it at **12%** (statistically significant) [38,56]. Regarding these studies, the data divided by the different patterns have been reported in Table IV.

Therefore at the moment the data on all-causes mortality drawn from the two large cohorts are contrasting. The difference between the results of the British (EPIC-Oxford) and US (AHS-2) cohort studies' analysis might be explained by the fact that «British vegetarians and US Adventist vegetarians eat somewhat differently» [38].
To clarify this aspect, and thus to obtain wide statistical significance, other well-designed prospective studies will certainly be necessary; they should provide for the distinction into the five subgroups of vegetarian patterns and not only for the simple "vegetarian and non-vegetarian" binarity.

STUDIES SELECTED	VEGETARIAN DIETARY PATTERNS				
	VEGETARIANS (total)	FLEXITARIAN	PESCETARIAN	LACTO-OVO VEGETARIAN	VEGAN
Key et al. (1999) [71]	0.95 (0.82 - 1.11)	0.84 (0.77 - 0.90)	0.82 (0.77 - 0.96)	0.84 (0.74 - 0.96)	**1.00 (0.70 - 1.44)**
Key et al. (2009) [64]	1.05 (0.93 - 1.19)	/	0.89 (0.75 - 1.05)	**1.03 (0.90 - 1.16)**	
Huang et al. (2012) [45]	0.91 (0.66 - 1.16)	/	/	/	/
Orlich et al. (2013)[38] (2014) [56]	0.88 (0.80 - 0.97)	0.92 (0.75 - 1.13)	0.81 (0.69 - 0.94)	0.91 (0.82 - 1.00)	**0.85 (0.73 - 1.01)**

Table IV – All-cause mortality of vegetarian patterns compared to the omnivorous reference diet

Legend: black → inverse statistically significant association; **yellow** → inverse statistically nearly significant; **red** → absence of association; / → missing value

In any case, even nowadays, specific studies on **longevity** identify the pescetarian diet as the best option for an extended lifespan and health span [76]. In addition, two other analysis of prospective studies that used the first method of dietary patterns assessment (that is by defining *a priori* indices for diets) and that were conducted in larger populations than those previously mentioned (not only Seventh-Day Adventists, vegetarians and more generally healthy-conscious individuals) have highlighted how **plant-based diets** are associated with a **statistically significant decrease in all-cause mortality** compared to more animal-based ones; the two values found were 24% [75] and 5% [74].

The non-vegetarian pattern and vegetarian ones were also compared for other health outcomes and not only for all-causes mortality:

- **mortality** and **morbidity (incidence or prevalence)** from specific groups of diseases, like cardiovascular or metabolic diseases and cancers;
- **mortality** and **morbidity (incidence or prevalence)** from a single disease, like CHD, stroke, type 2 diabetes (T2D) and a specific cancer.

Recently this field of research has expanded enormously and among many studies and many health outcomes considered, here have been highlighted those considered most relevant taking as principal reference the umbrella review by Oussalah et al. [37].

➢ CARDIOVASCULAR and METABOLIC DISEASES

In the field of cardiovascular diseases **(CVDs)**, the sharpest considerations can be made for **coronary heart disease (CHD)**: several studies have shown a reduction in both mortality and incidence associated with vegetarian diets compared to the non-vegetarian diet.

It has been demonstrated a statistically significant **reduced mortality** ranging between 24% and 29% [45,46,71] (accompanied by similar values not statistically significant of other studies [38,64]) and a **reduced incidence** between 25% and 32%, which is also statistically significant [46,66]. An even higher value of this specific decreased mortality was

found in the cohort of AHS-2, more precisely associated with the Pescetarian diet, with a reduction of 35% [38].
On the other hand, to date, a statistical significance between vegetarian diets (both total and subtypes) and a reduction in mortality and morbidity in **cerebrovascular diseases** has not been found: indeed, some results point to a trend with a positive outcome in the mortality associated (reduction between 7% and 12% [45,46,71]); other studies instead come to the opposite conclusion (increase in mortality by 10% or greater [64,72]).
This is why at the moment vegetarian diets can't be associated with a reduction in mortality and morbidity of CVDs more generally; in addition to the reduced values not statistically significant of the studies already seen [38][45][46][64], only a paper that define *a priori* a healthy plant-based diet have evidenced positive results in terms of reduction of incidence and mortality of CVDs in adults [75].

As for **cardiovascular risk factors**, vegetarian dietary patterns have been demonstrated to have overall considerable advantages over an omnivorous diet: the following list shows the main results.
Blood pressure of subjects who follow a vegetarian diet is reduced compared to those of non-vegetarian subjects; a meta-analysis that analyzed 7 clinical trials and 32 observational studies reported a statistically significant **drop** in both systolic pressure (about 5 mmHg) and diastolic pressure (about 2 mmHg) in the first type of studies and statistically significant **lower values** both systolic pressure (about 7 mmHg) and diastolic pressure (about 5 mmHg) also in the second type [48]. The analysis of AHS-2 cohort also found that lacto-ovo vegetarian and vegan diets are associated with a significant **reduction in the prevalence of hypertension** by 43% and 63% respectively (in non-black subjects)[57] and for the two diets together by 44% (in black subjects)[58].

Vegetarians have generally a significant **reduction in total blood cholesterol** and also **LDL cholesterol**: for <u>the first factor</u> the reduction is between 28 and 29 mg/dl in two meta-analyses of observational studies

[46,49], whereas LDL cholesterol is reduced by a value between 21 and 23 mg/dl in the same two studies [46,49] and by about 0.45 mmol/l in an analysis of the EPIC-Oxford cohort [66].

Another cross-sectional analysis of the same cohort showed that LDL cholesterol values are progressively reduced in the different subtypes of vegetarian patterns starting from non-vegetarians to vegans: [4,11 non veget, X Flexit, 3,85 Pescet, 3,71 Veget, 3,26 Vegan] [68].

Against vegetarian diets should be reported **HDL cholesterol values**: the results of three meta-analyses report significantly lower values among cross-sectional studies (between 2.7 and 3.6 mg/dl)[46][49] and a significant reduction in the analysis of controlled clinical trials [3,4 mg/dl [49] and 0,10 mmol/l [50]].

In current studies, data on **triglyceride levels** associated to different types of diets are conflicting [46,49,50].

As regards **obesity and overweight** there are significant differences between vegetarians and omnivores in both prevalence and incidence.

Already in the past, EPIC-Oxford cohort analysis found significant discrepancies between various dietary patterns in terms of **average value of BMI** adjusted for lifestyle factors (24.39 kg/m^2 Meat-eaters, 23.35 kg/m^2 Pescetarians, 23.38 kg/m^2 Vegetarians, 22.53 kg/m^2 Vegans; these are male data but similar differences are also present in female data)[69]; different but equally progressively lower values from the omnivorous diet to the vegan diet have been found in the cohort AHS-2 (28.3 kg/m^2 Non Veget, 27.3 kg/m^2 Flexit, 26.0 kg/m^2 Pescet, 26.1 kg/m^2 Veget, 24.1 kg/m^2 Vegan; sex-adjusted data)[38]. These data have been confirmed by the recent meta-analysis of Dinu et al. [46]: the average BMI of vegetarians is significantly lower than that of omnivores, with a WMD of -1.49 kg/m^2.

A 2005 cross-sectional study of the Swedish Mammography Cohort highlighted a different prevalence of overweight and obesity among various patterns (40% Non Veget, 29% Flexit, X Pescet, 25% Veget, 29% Vegan); flexitarian, vegetarian and vegan women present a significantly lower risk than non-vegetarian women also in terms of incidence of these two conditions, by 48%, 46% and 65% respectively [73].

Significant differences in prevalence and incidence of **T2D** were highlighted in the two cohort AHS-2 analyses: the first focused on different prevalence in various dietary patterns (7.6% Non Vegetarian, 6,1% Flexitarian, 4,8% Pescetarian, 3,2% Vegetarian and 2,9% Vegan) with a reduced risk for vegetarian patterns of 24%, 30%, 46%, 49% respectively [59]; the second also found a lower incidence for them of 51% (Flexit), 21% (Pescet NSS), 38% (Veget) and 62% (Vegan)[60]. Data from a recent meta-analysis confirm this trend, fix the significant reduction in incidence to 28.4% overall for vegetarian diets [51] and are consistent with the significantly lower blood glucose level among vegetarians reported by the paper of Dinu et al. [46]. The main analysis of the AHS-2 cohort study also suggests the association between vegetarian diets and reduced diabetes-related mortality [38].

As regards metabolic syndrome (MetS), a reduced prevalence (39.6% Non Veget, 37,6% Flexit and Pescet considered together, 25,2% Veget and Vegan together as well) and a decreased incidence (-56% for Vegetarian and Vegan diet) of this clinical condition has been highlighted [61]. This comes to no surprise, given each above-mentioned positive correlation between vegetarian diets and metabolic risk factors.

➢ <u>CANCERS</u>

Many studies focus on the link between cancer and different vegetarian dietary patterns. Nonetheless, results were not decisive and thus clinically useful conclusions cannot be drawn.

The major differences are visible for **global cancer incidence** since two relevant distinct studies have identified a significant reduction in vegetarian patterns considered overall: <u>8%</u> in the analysis of the AHS-2 cohort [55] and <u>18%</u> in the meta-analysis by Huang et al. [45]. The recent meta-analysis taken as a reference [46] confirms these data, fixing as well at <u>8%</u> the reduction for incidence.

In the analysis of the cohort EPIC-Oxford this outcome was investigated only considering separately the various patterns and the results are as follows: there is a significant reduction for pescetarian (12%), for vegetarians (11%) and also for vegans (19%)[70].

Up to now, however, any study has shown a decreased **cancer-related mortality** associated with vegetarian dietary patterns and there are inconclusive or contrasting data in **cancer-specific morbidity**.

4.2.2. Environmental Impact

In the analysis of vegetarian and non-vegetarian dietary patterns a fundamental element to be evaluated is definitely the **environmental impact**: adopting a vision of planetary health and considering the trilemma "diet-environment-health" [77,78] is necessary in a historical phase of demographic increase and given the remarkable influence of food systems on the current climate crisis and the environmental degradation (globally responsible for 21-37% of GHG Emissions and 70% of the freshwater use) [79–83].

The study by Springmann et al. [84] highlighted the significant role of dietary change in reducing the impact of all 4 considered elements of “environmental pressure” - carbon, water and land footprints and fertilizer use - especially in the predictions made for 2050, in which it is stated that the impact of the food systems could increase between 50% and 90% over the next 30 years.

In this study, compared to the starting condition (current dietary habits), were considered the actual implementation of the nutritional guidelines and the shift towards the flexitarian diet ("more plant-based" diet); it was seen how the latter element is particularly relevant in reducing GHG emissions (carbon footprint) and is necessary to remain with certainty below the specific planetary boundaries, despite simultaneously achieving maximum improvements in technologies and maximum management and reductions in food loss and waste.

Although to a lesser extent than this factor, the transition to a flexitarian diet also plays an important role in the other three environmental impact factors considered (water footprint, cropland use and fertilizer use, divided into nitrogen and phosphorus application), as shown in Figure 4 [84].

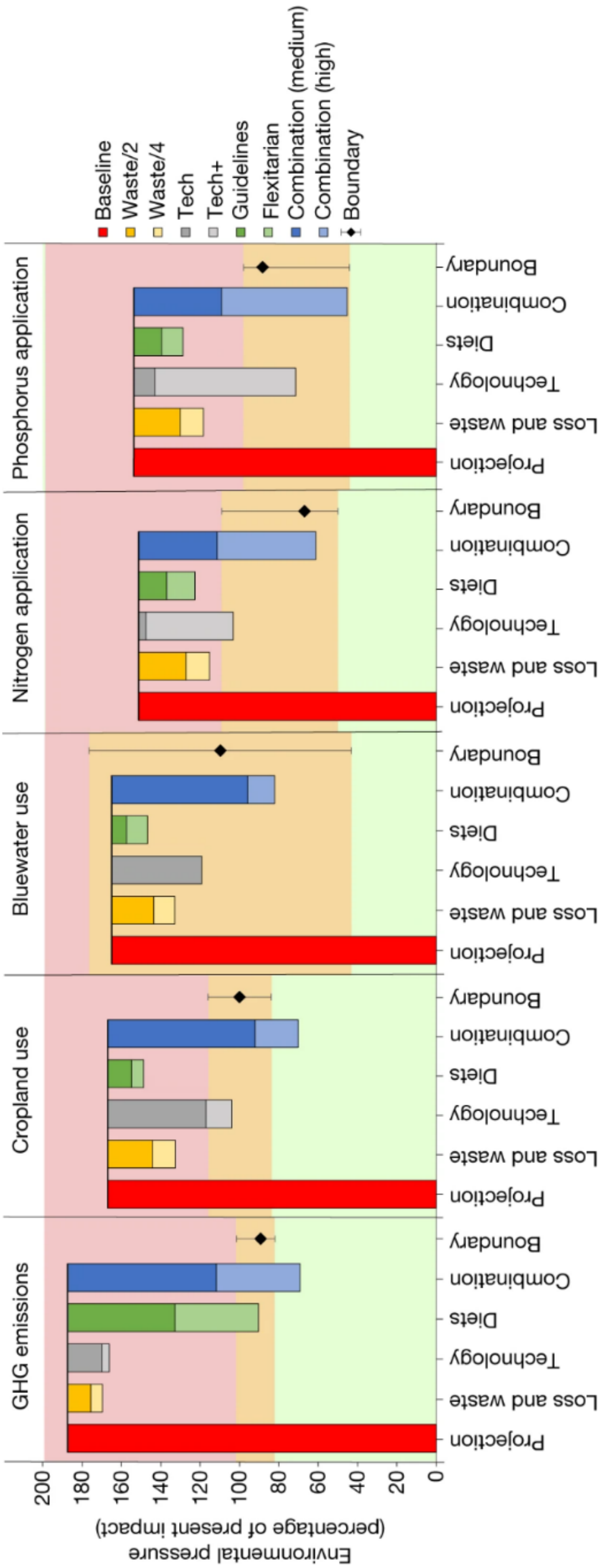


Figure 4 - Impacts of reductions in food loss and waste, technological change, and dietary changes on global environmental pressures in 2050

Another paper by Springmann et al. [85], parallel to the previous one, analyzed at the same time the reduction of premature mortality and of the same environmental impact factors seen before by considering not only the flexitarian diet, but **different dietary patterns** - called diet scenarios for the research method used - that were subdivided in 3 different groups:

a. the first included plant-based diets based on environmental objectives that progressively replace [from 25% (ani-25) to 100% (ani-100)] animal-source foods with some isocaloric plant-based ones (fixed mix of 75% legumes and 25% fruit-vegetables);
b. in the second there were patterns not relevant to this research (based on food security objectives and which improved energy imbalances by 25-50-75-100% and simultaneously reduced levels of underweight, overweight and obesity);
c. the third consisted in **vegetarian dietary patterns** “based on public health objectives” (**vegan**, **vegetarian**, **pescetarian** and precisely **flexitarian**).

a. With the diets of the first group, excellent results were obtained in the reduction of premature mortality (12% as mean value) and GHG emissions (up to 84%), discrete results in cropland use and fertilizer use only in high-income countries, but negative global results in freshwater use (increase of up to 16%) (Figure 5 and Figure 6) [85].

c. On the other hand with **vegetarian patterns**, while in low-income countries the decrease occurred only with the premature mortality and carbon footprint, in high- and medium-income countries positive results were registered for all factors; as shown in Figures 5 and 6 the drop in mortality was significant and between 19% (flexitarian diet) and 22% (vegan diet), while the reduction of the environmental impact was progressively greater from the flexitarian diet to the vegan diet for all factors except the water footprint, which had an inverse trend. The reduction in values ranged between 54-87%, 2-11%, 8-11% and 41-46% respectively for GHG emissions, freshwater use, cropland use and fertilizer use (summing the application of nitrogen and phosphorus).

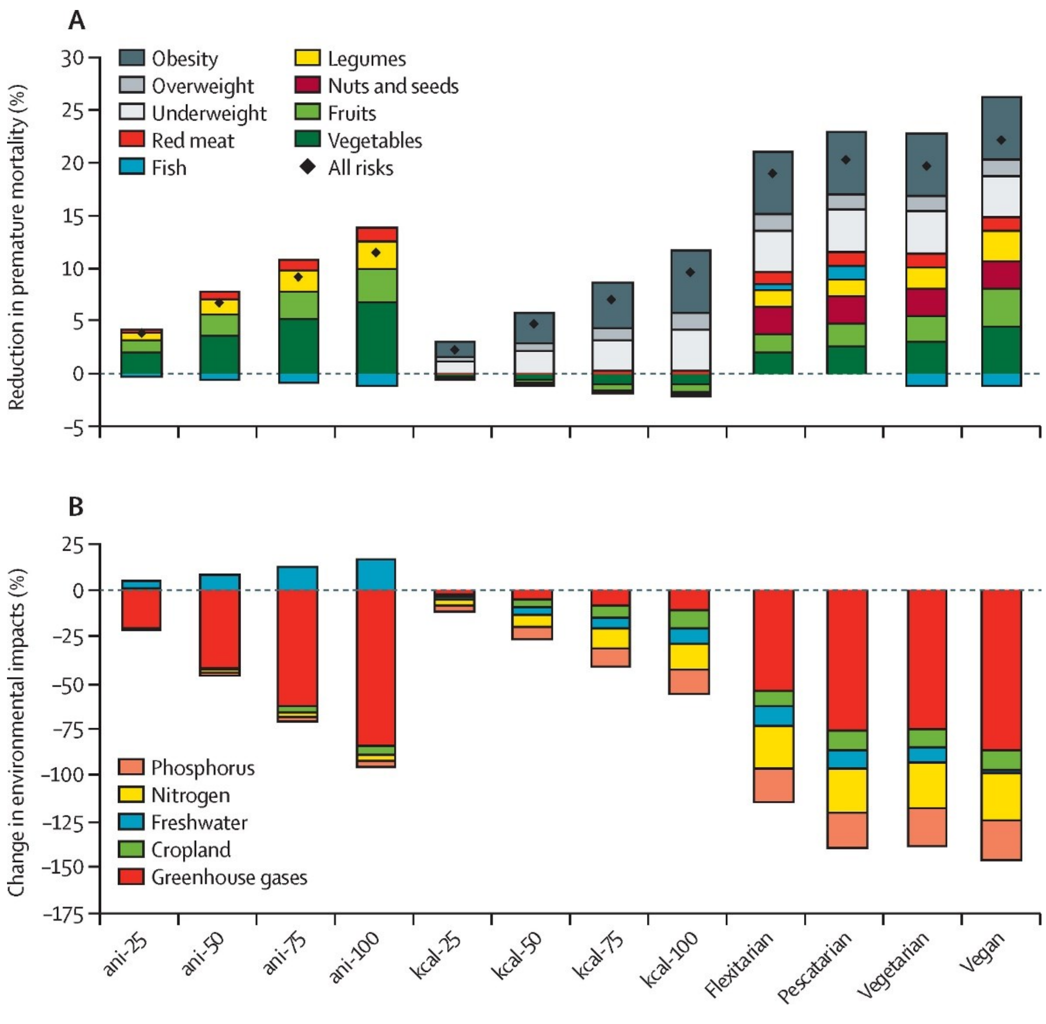


Figure 5 - Premature Mortality and Environmental Impacts of Diet Scenarios in 2030

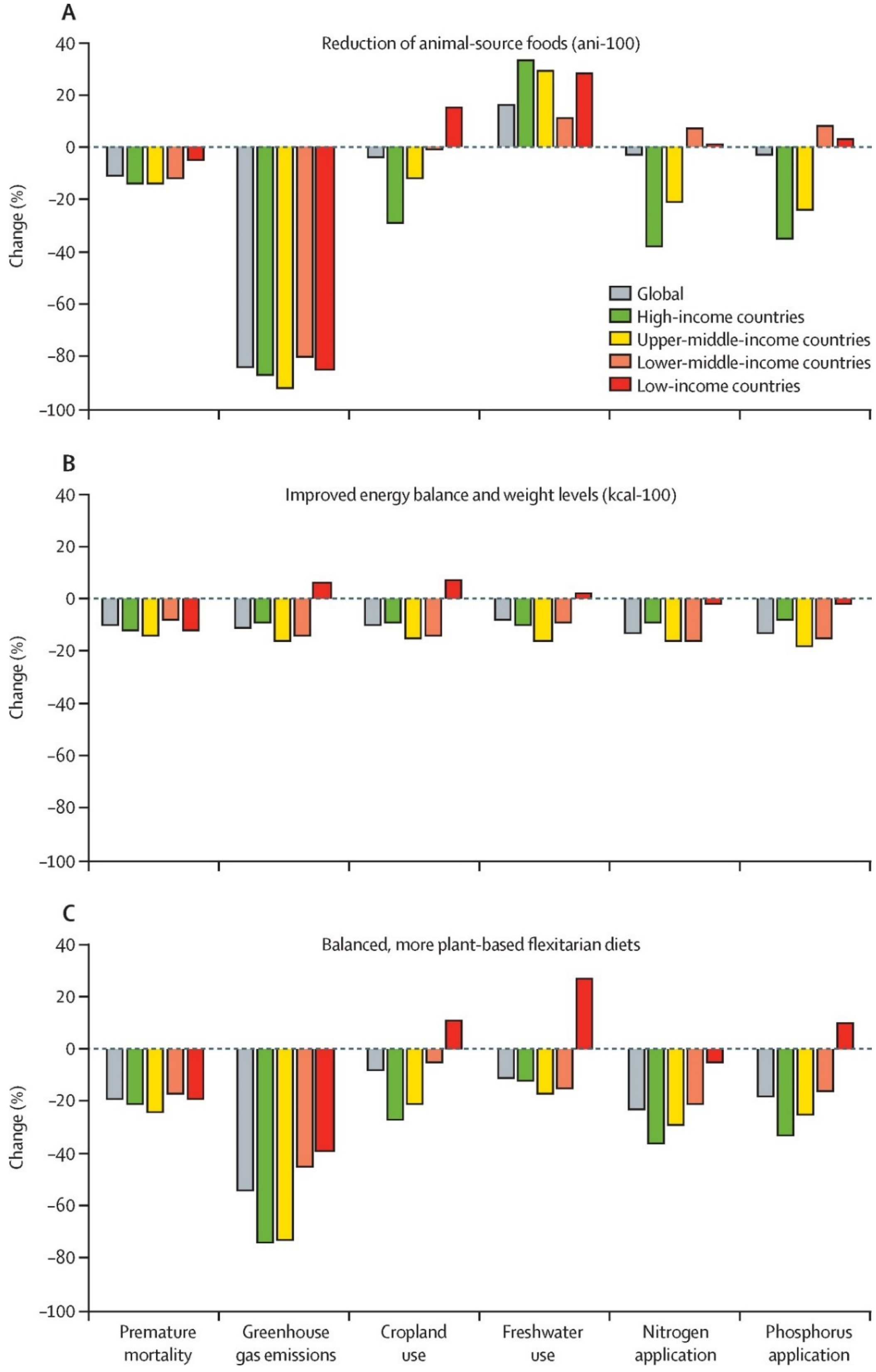


Figure 6 - Regional Changes in Premature Mortality and Environmental Impacts of Dietary Change

The strengths of this "global modelling analysis" are the simultaneous assessment of both environmental impact and health outcomes (the premature mortality from chronic diseases) related to dietary patterns - adding significant evidence to the results reported in the previous paragraph - and the consideration of different socio-economic contexts (150 different countries), thus broadening the view of the subject beyond national borders. It follows that:

- both sustainability and nutritional appropriateness of diets are **context-related** and this additional level of complexity must always be kept in mind;
- it would always be preferable to carry out investigations that assess health outcomes and environmental impacts together, as was already done through the Life Cycle Assessment (LCA) by a major Italian study [86].

Further data of this type, excluding the use of fertilizers, have been summarized in Table V taken from the recent review by Fresán and Sabatè [87], which is currently the most up-to-date source: compared to the previous paper, here were considered only vegan and ovolactovegetarian (vegetarian) diets and the analyses showed lower

	GHG emissions		**Land use**		**Water use**	
	Median (min, max)	***n***	**Median (min, max)**	***n***	**Median (min, max)**	***n***
Current review						
Ovolactovegetarian	−35 (−13, −85)	29	−42 (−27, −74)	10	−28 (−7, −52[2])	11
Vegan	−49 (−23, −89)	20	−49.5 (−29, −80)	10	+17 (−22, +107)	4
Aleksandrowicz L et al. 2016 (65)						
Ovolactovegetarian	−31 (−15, −58)	20	−51 (−28, −67)	7	−37 (−16, −52[2])	9
Vegan	−45 (−23, −72)	14	−55 (−40, −80)	6	+107	1
Hallström E et al. 2015 (22)						
Ovolactovegetarian	−24 (−18, −32)	7	−39.5 (−27, −52)	2	—	—
Vegan	−33 (−23, −53)	6	−51 (−50, −59)	3	—	—

Table V - Relative difference (percentage) in GHG emissions, land use, and water use shifting from current dietary patterns to vegetarian reductions in GHG emissions (24-49%), but greater decreases in (fresh)water use and (crop)land use [28-37% (only vegetarian diet) and 42-55% respectively]. Another difference is represented by the increase - although not significant - of the water footprint associated with the vegan diet compared to that of the omnivorous one.

Each of the above GHG emissions data shows the same trend as the analysis of the two main vegetarian cohorts, AHS-2 and EPIC-Oxford [88,89]; Figure 7 taken from the mini-review by Segovia-Siapco and Sabatè [63] shows the various data collected in absolute values of kg CO2 equivalents (adjusted to a normocaloric diet); the relative reductions expressed in percentage are:

a. 22% and 29% in the AHS-2 cohort, respectively for flexitarians and vegetarians;
b. 22% to 60% in the EPIC-Oxford cohort progressively from an omnivorous medium-meat intake diet to a vegan diet, via flexitarian, pescetarian and vegetarian diets.

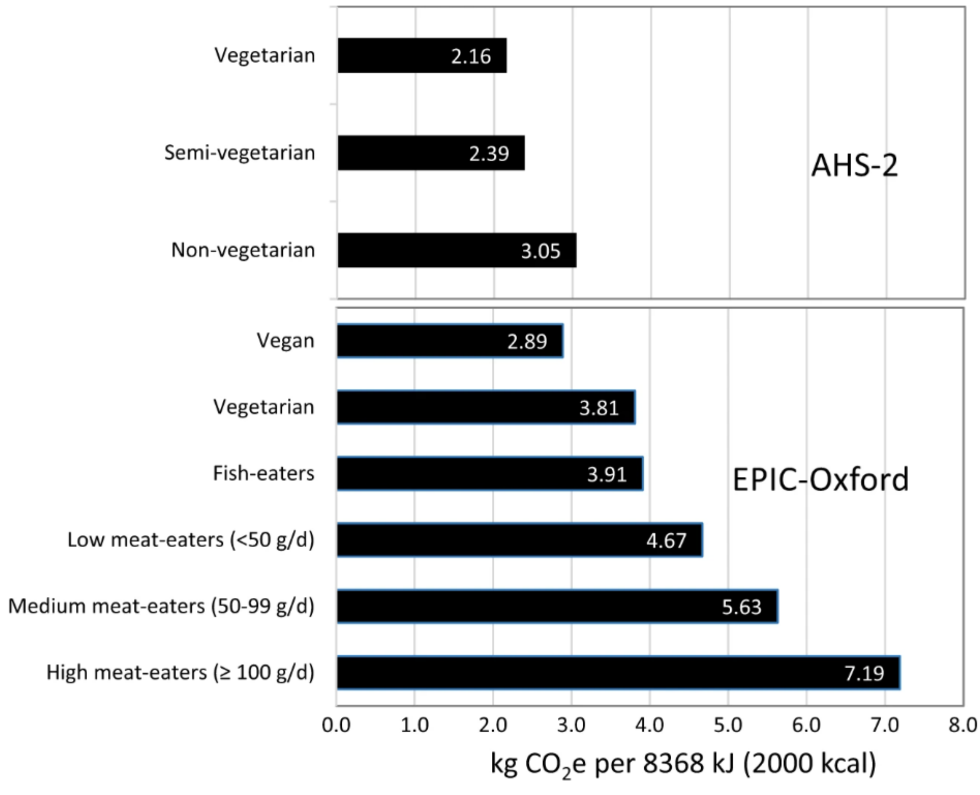


Figure 7 - Mean greenhouse gas emissions in kg CO2 equivalents adjusted to 8368 kJ (2000 kcals) by type of diet in the AHS-2 and EPIC-Oxford cohorts

Therefore it has been largely demonstrated that vegetarian patterns have, to a different extent, a lesser negative impact than omnivorous diets; in this perspective they could be a valid solution to the aforementioned trilemma [90] whether there will be a population-level dietary change.

The last necessary consideration regards the high interindividual variability among vegetarians' diets: in order not to make false considerations one should not always rely on average nominal diets (diet scenarios) but it would be necessary to evaluate the foods actually consumed within the individual vegetarian diet since in some cases it is possible that these patterns have a greater total environmental impact than those of some omnivores [91]. This is why such dietary patterns are not the only solution to this huge public health problem, and other healthy dietary patterns (such as an effective Mediterranean diet and the DASH diet) are certainly other arrows to our bow to counteract the environmental impact overall. The impact of Mediterranean diet will be analyzed in the following paragraph.

4.3. DOUBLE PYRAMID AND MEDITERRANEAN DIET

It is understood as the set of eating habits rooted within the 16 states bordering the Mediterranean basin; although there are differences between the various "Mediterranean diets" for socio-cultural, religious and agri-food reasons, they present some widely known elements in common, synthetically presented below [92,93]:

- high consumption of fruits and vegetables;
- cereals as the main source of energy, therefore prevalence of carbohydrates in the AMDR (50%) compared to proteins and fats;
- higher consumption of proteins of plant origin than from animal sources, and among them fish is preferred over meat (also based on territorial location);
- use of olive oil as the main seasoning and source of fat;
- moderate consumption of wine.

In addition to its well-known nutritional benefits, it stands out for its environmental, economic and social values, which is why it was listed as part of the intangible cultural heritage of humanity by UNESCO in 2013 [94,95].

The concept of the food pyramid has been associated with the Mediterranean diet since the first “International Conference on the Diets of the Mediterranean” held in Boston in 1993; the paper by Willett, Trichopoulos et al. [96] published two years later reported an early version of the Mediterranean diet pyramid, visible in Figure 8.
This specific structure was used with the intentions of conveying an overview of healthy food choices and the relative consumption frequencies of the various food groups and of creating a reference and user-friendly tool for the average adult population [96].

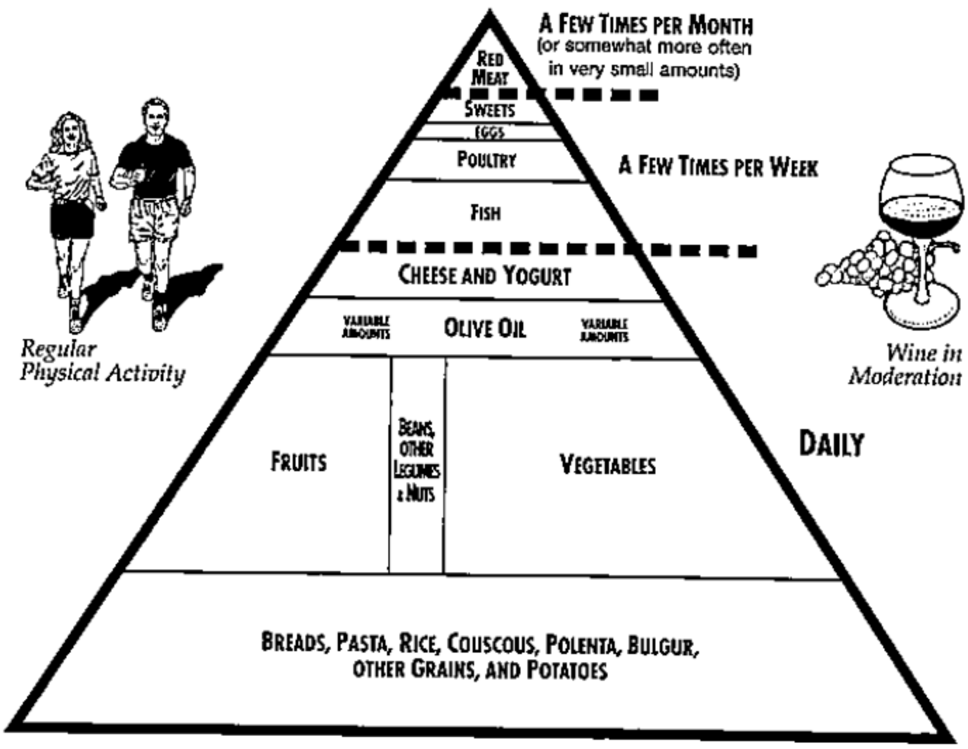


Figure 8 - The Mediterranean diet pyramid: a cultural model of healthy eating 1994

But as early as the 1950s/60s, at the apex of the economic boom, the phenomenon of the **"nutrition transition"** - term coined by Popkin in 1993 [97] - also gradually took hold in the countries of the Mediterranean basin, despite the presence of a strong food and therefore also cultural tradition.

The real Mediterranean diet consumed by the generations before the "baby boomers" (born between 1946 and 1964) has been lost over time; an emblematic example is that provided by the Italian region "Campania": in the past the area of reference for the first studies on the Mediterranean diet by Ancel Keys [98,99], today it has the highest national rate of childhood obesity (37.8%) and among the highest rates of obesity in adulthood (11.7%)[100].

This phenomenon of "nutrition transition", represented more specifically by <u>pattern 4 (degenerative disease)</u> in the developed Western World [101], has led to significant changes in dietary habits, converging towards a sweeter, energy-dense diet, characterized by:

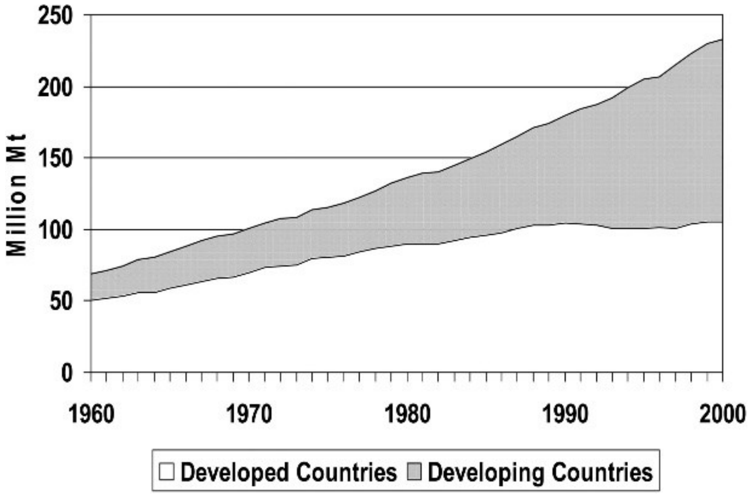
- an increased consumption of sugar, saturated fats (especially from animal products) and refined foods;
- a progressive transition from plant-based foods to those of animal origin (the so-called “substitution effect” mentioned by Kearney [102]).

In recent decades the same path has become visible in developing countries due to the "Livestock revolution", term coined by Delgado et al. in 2001 [103].

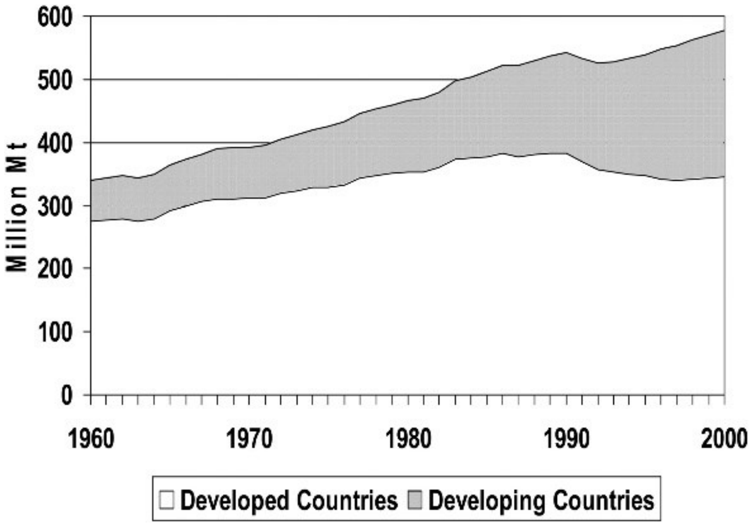
Overall, these processes have led to a considerable global increase in the consumption, and therefore in the production, of animal protein sources (mainly meat, milk and dairy products, but also eggs): the trend is clearly visible in Figure 9 (9a., 9b. and 9c.), taken from the study by Speedy [104] and produced with data collected by FAO.

Also because of these social phenomena have been proposed various scores with the aim of evaluating the real adherence to the Mediterranean diet; the first tool - or "adhesion index" as it has collectively named by Bach et al. [105] - was called Mediterranean Diet Score 1 (MDS-1) and was proposed in 1995 by Trichopoulou et al. [106]; a few years later it was updated with the Mediterranean Diet Score 2 (MDS-2) which became the most widely used tool [107].

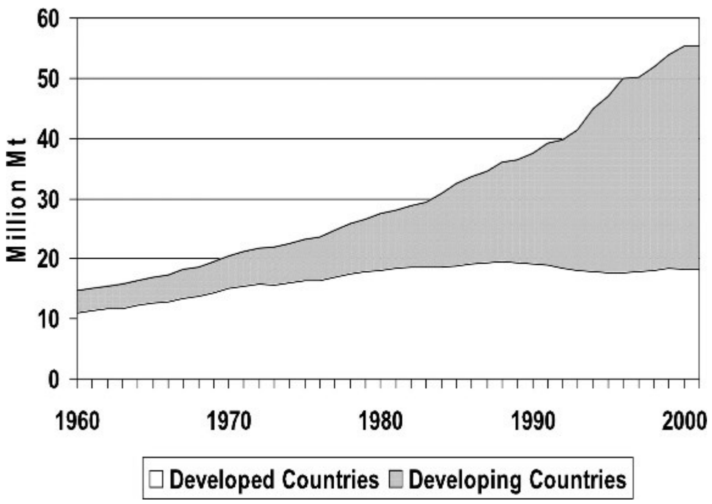
In the last two decades these scores have been regularly used to attest the health benefits of the Mediterranean diet and more recently also to evaluate its sustainability and environmental impact.



9a. Meat Changes



9b. Milk Changes



9c. Eggs Changes

Figure 9a.- 9b.- 9c. - Changes in meat/milk/eggs production in developed and developing countries, 1960–2000.

4.3.1. Health Benefits

As for the health benefits, **many observational studies** have been carried out, which have shown that the Mediterranean diet is probably the healthiest diet at a global level. A series of systematic reviews have been written over time and the three chosen as reference for data are:

- two meta-analyses (the first of 2010 and the second of 2013, update of the first) published by Sofi et al [108,109], an important research group on this subject based in Florence;
- a more recent review of August 2021 by Willett and Guasch-Ferrè [110].

Based on data found in prospective studies analyzed by these three systematic reviews, Table VI has been created to summarize the main positive health outcomes associated with the Mediterranean diet.

Health Outcomes	Mortality	Incidence
All-cause	0.92 (0.91 - 0.93)[109][a] 0.90 (0.89 - 0.91)[111][a]	/
CVDs	0.79 (0.77 - 0.82)[112][b]	0.90 (0.87 - 0.92)[109][ac]
CHD	0.83 (0.75 - 0.92)[112][b]	0.73 (0.62 - 0.86)[112][b]
Stroke	0.87 (0.80 - 0.96)[112][b]	0.80 (0.71 - 0.90)[112][b]
T2D	/	0.87 (0.82 - 0.93)[113][b]
MetS	/	0.74 (0.63 - 0.88)[114][b]
Neurodegenerative diseases (NDDs)	/	0.87 (0.81 - 0.94)[108][a] 0.74 (0.65 - 0.84)[110][bd]
Total Cancer	0.87 (0.82 - 0.92)[115][b]	0.96 (0.95 - 0.97)[109][ac]
Breast cancer[e]	/	0.94 (0.90 - 0.97)[115][b]
Colorectal Cancer (CRC)[e]	/	0.83 (0.76 - 0.90)[115][b]
Respiratory tract cancers[e]	/	0.84 (0.76 - 0.94)[115][bf]

Gastric cancer[e]	/	0.70 (0.61 - 0.80)[115][bf]

Table VI - The most relevant health benefits from a good adherence to the Mediterranean diet found in some of the main prospective studies of the last decade. Each data inserted refers to a fixed-effects model.

a. when was reported a 2-point increase in adherence score to the Mediterranean diet;
b. when comparing the highest versus the lowest categories of MedDiet adherence;
c. combination of mortality and incidence;
d. in this case the risk of cognitive impairment, all types of dementia and Alzheimer's specifically were considered at the same time;
e. for most of the site-specific cancers, as well as for inflammatory and metabolic parameters, the evidence was interpreted as only suggestive and weak, and further research is needed for these outcomes [104];
f. compared to breast and colorectal cancers, the number of observational studies considered is lower.

The Mediterranean diet has not only been considered as one of the main elements of a good lifestyle and therefore as a primary prevention tool; several interventional studies have shown that this dietary pattern is an effective therapeutic option even in secondary prevention.
One of the most important works is certainly the PREDIMED Study [116] [117]: given the greater effect in reducing the risk of cardiovascular events obtained with a high content of olive oil and **nuts** in the dietary pattern, it has been shown that a diet rich in highly unsaturated fatty acids (UFAs) from plant-based sources is better than a diet with a reduced fat intake for CV health.

In Figure 10, taken from the recent meta-analysis of Willett and Guash-Ferrè [110], are briefly summarized the main beneficial effects.
These data are practically similar to those of an important umbrella review by Dinu et al. [118]: the relevance in terms of evidence-based medicine is very high for this type of study.

In some cases, a comparison has also been made between the Mediterranean diet and a vegetarian diet; the PREDIMED study [119] and the CARDIVEG study [120,121] showed that there are no differences between the two diets for CV diseases and for CV risk factors respectively. Further extensive, robust and well-constructed studies are required to effectively compare health benefits by the two different diets.

Mediterranean diet and Chronic Diseases

Outcome	Relative Risk (95% CI)	NStudies	NMedDiet	NControl	Reference
Overall mortality	1.00 (0.86, 1.16)	5	6630	4041	Liyanage 2016
CVD mortality	0.59 (0.39, 0.90)	4	7418	4875	Grosso 2015
CHD incidence	0.48 (0.33, 0.70)	1	499	501	Becerra-Tomas 2019
Stroke incidence	0.64 (0.47, 0.87)	2	6617	4071	Grosso 2015
Myocardial infarction incidence	0.66 (0.48, 0.90)	3	7116	4572	Grosso 2015
Composite CVD	0.55 (0.39, 0.77)	4	7418	4875	Grosso 2015
Type 2 diabetes	0.70 (0.54, 0.91)	1	2394	1147	Salas-Salvado 2014
Metabolic Syndrome	0.45 (0.32, 0.64)	2	902	482	Kastorini 2017
Breast cancer	0.41 (0.19, 0.88)	1	2761	1391	Toledo 2015

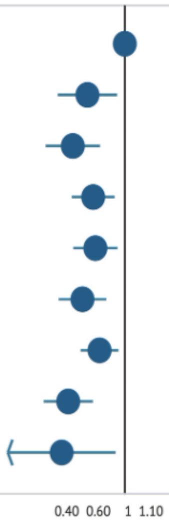


Figure 10 - Mediterranean diet and chronic diseases: health benefits found in some interventional studies

4.3.2. Environmental sustainability

Some papers have also been carried out on environmental sustainability, comparing the effects of these two diets: the previous cited relevant review by Fresán and Sabatè [87] stated that healthy Mediterranean diet - and also some national dietary guidelines-related diets - contribute significantly less to a reduction in GHG emissions than vegetarian patterns (10% against 22-87% range seen in the previous paragraph), contrary to the 2015 US DGAC Report [31] and its subsequent review [122] that placed them on the same level.

The role of the Mediterranean diet in the challenge against climate change is however noteworthy, given the reduced effect on a number of factors of "environmental pressure". As early as 2008 FAO defined it as “rich in biodiversity and nutritionally healthy” [123] and three years later it was referred to as an example of a sustainable diet [124].

Regarding GHG emissions, in 2017 an Italian study proposed the **hourglass environmental approach** as a useful tool «to help translate health-promoting dietary recommendations that consider regional circumstances and cultural diversity into practical eating habits, to promote sustainable and environmentally friendly consumption» [125]. Figure 11 shows the comparison between weekly GHG emissions of a canonical Mediterranean diet and the new Nordic diet (NND) made using this tool [125]: foods are divided into food categories, the arrangement of which follows the position inside the food pyramid (also that of the Mediterranean

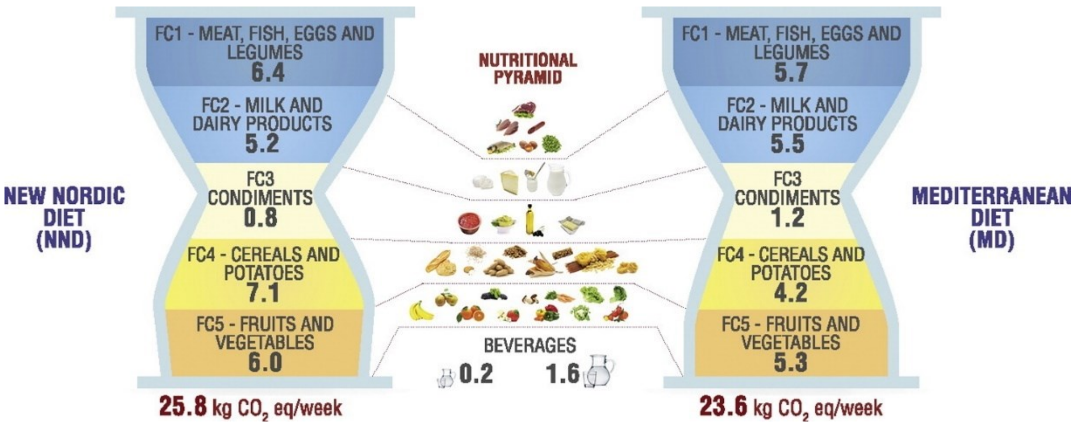


Figure 11 - Environmental Hourglass of Mediterranean Diet (MD) and New Nordic Diet (NND)

diet seen above) and allows the hourglass to be shaped according to the emissions of related GHG. As can be seen from the image, the study in question, based on data from the Barilla Center for Food and Nutrition technical database (BCFN)[126], reported a weekly total of emissions of GHG comparable between the two diets considered.

To extend the discussion to the other environmental impact factors listed in the first paragraph (the various environmental footprints), it is useful to mention a Spanish cohort study by Fresán et al. [127] of 2018. More precisely, together with GHG emissions, land use, water use and energy demand were also included: the objective was to evaluate the effect of greater adherence to the Mediterranean diet (using the MDS-2 Score [107]) on the “environmental pressure” factors considered both separately and as a whole. It is evident from Figure 12 [127] that the greater the adherence to the Mediterranean diet (divided into 4 categories according to the MDS-2 Score, "≤2", "3-4", "5-6" and "≥7") the lower the environmental impact for all the elements considered, except for the water footprint of the two intermediate categories. This result makes it possible to affirm that a "well-executed" Mediterranean diet (the highest category "≥7") is really a sustainable diet also considering the overall reduction of the environmental footprint by 24% compared to the lowest one ("≤2").

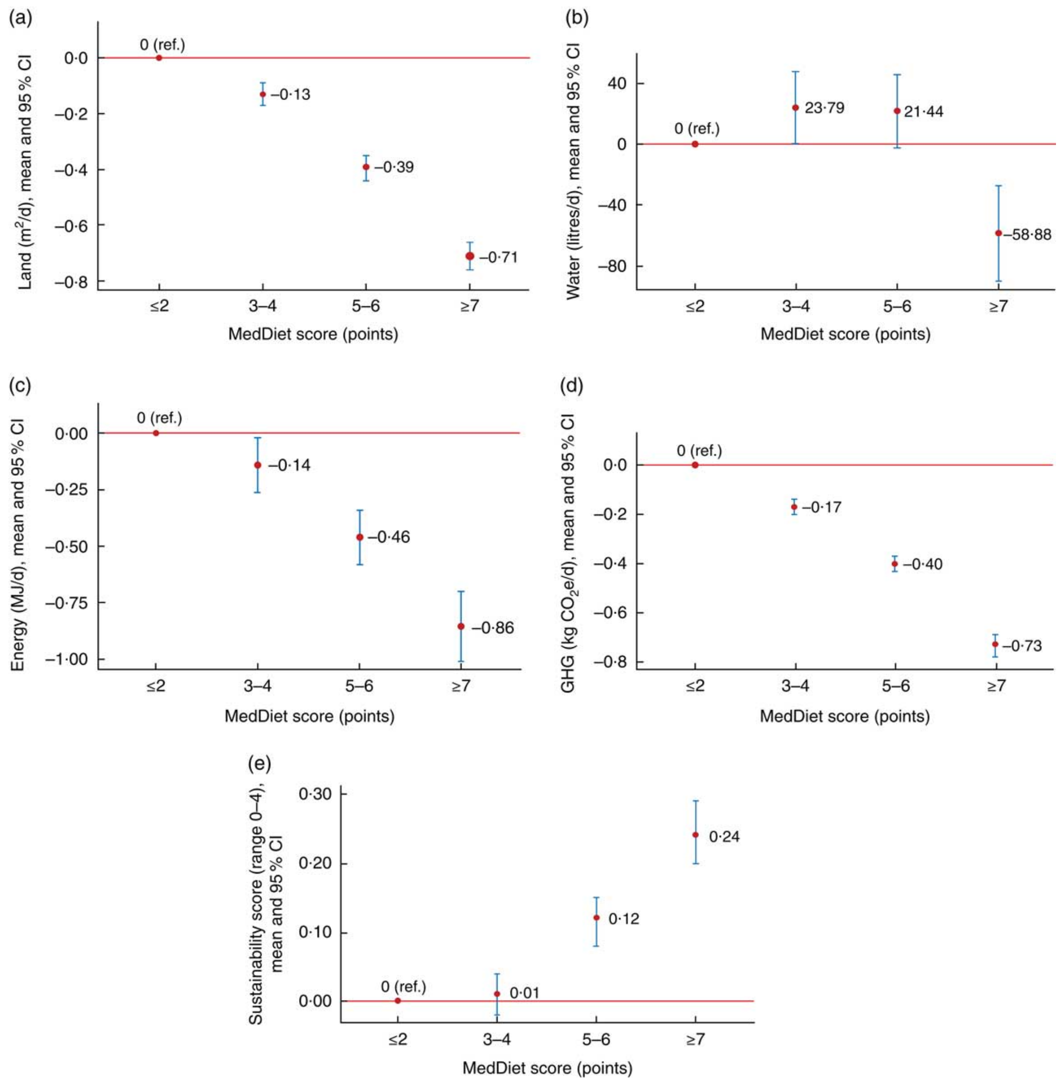


Figure 12 - Land use (a), water consumption (b), energy consumption (c), greenhouse gas (GHG) emission (d) and sustainability score (e) according to adherence to the Mediterranean diet (MedDiet) among 20363 participants in the SUN cohort

4.3.3. Double Pyramid

Considering the overall results of the Mediterranean diet in terms of health benefits and environmental impact just proposed, it is clear how it is essential to consider both elements simultaneously during the studies on this topic, exactly how it was said for vegetarian patterns. The new version of the pyramid of the Mediterranean diet (reported in Figure 13) proposed in 2011 by Serra-Majem et al. [128] was already in the perspective of planetary health; later other papers have stressed the importance of performing multi- and cross-disciplinary studies [129,130].

While for more than 3 years there has been a huge report by the EAT-Lancet Commission [131], which is a useful tool for synthesizing such a complex subject, on the other hand studies are needed to analyze the specific dietary patterns of the various regions of the world, having regard to the enormous diversity of habits and customs linked to food. An example of study that deepens at the same time health benefits and environmental impact and that is more easily ascribable to a specific context is the review of Aboussaleh et al. [132]; in the next few years will serve many studies of this type in an attempt to make more accessible and "insertable" in people’s daily lives such a complex and delicate subject.

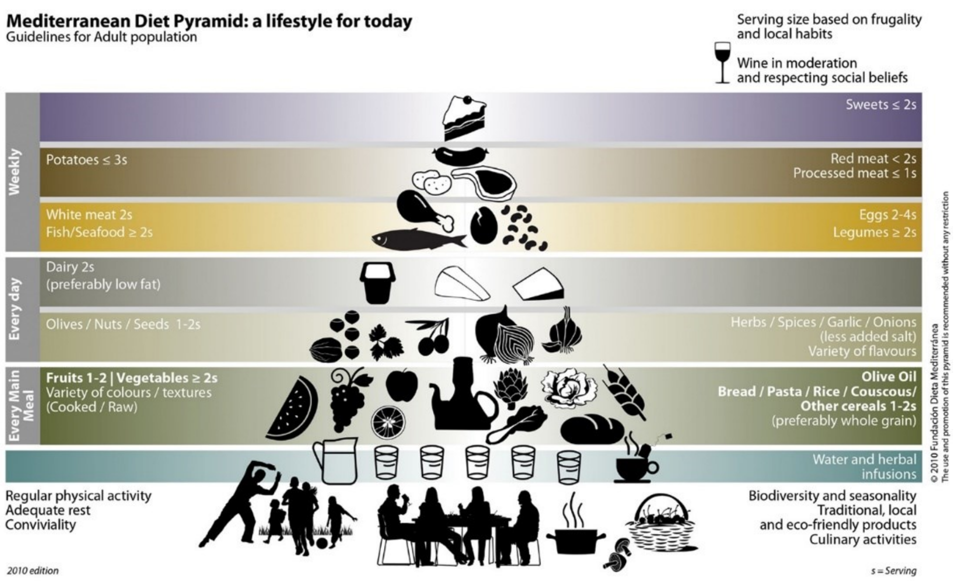


Figure 13 – Updated version of Mediterranean diet pyramid (2010)

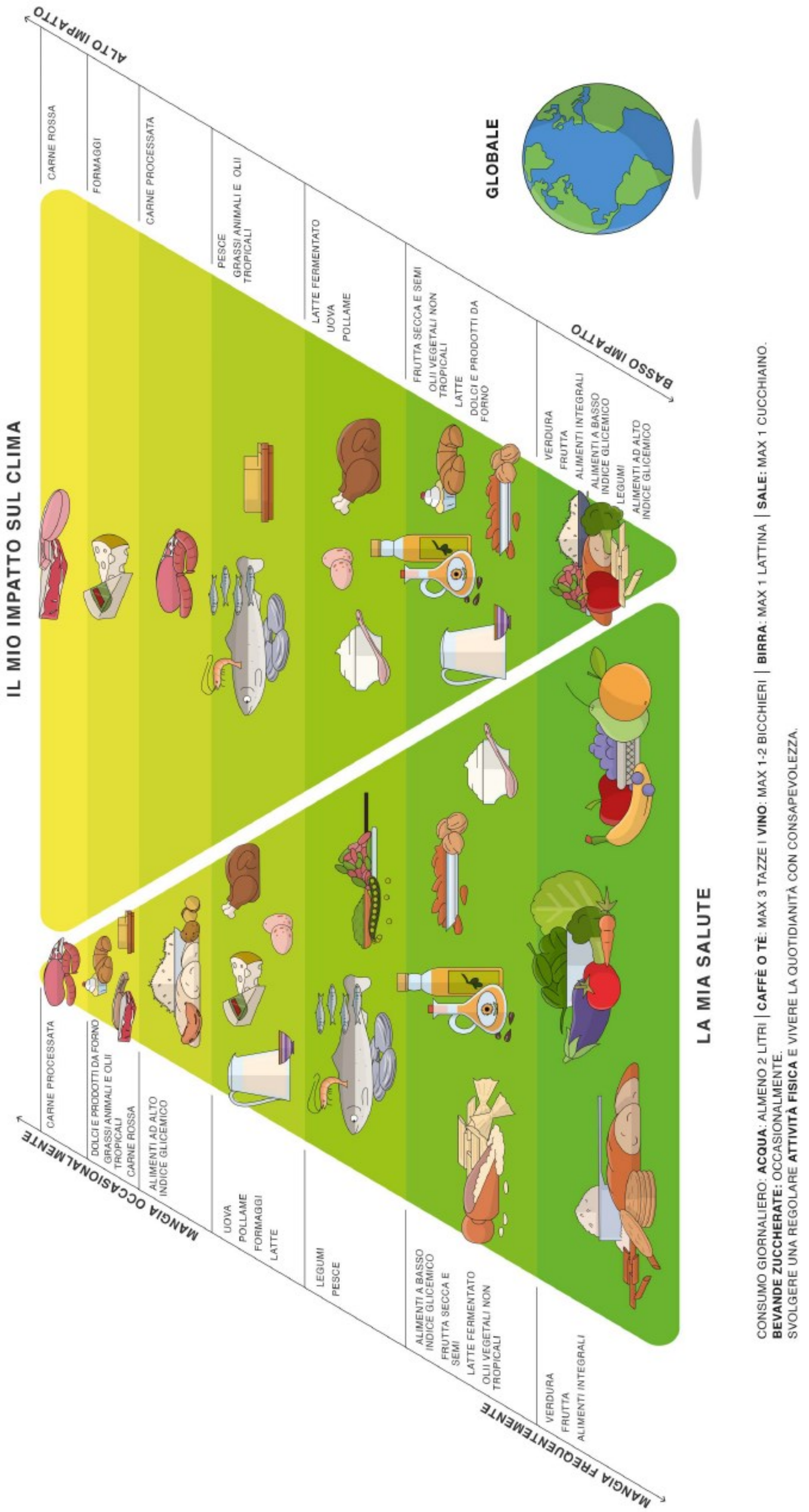


Figure 14 - Updated version of Double Pyramid; Font: Barilla Foundation 2021

Surely a very useful tool for this purpose is the **"Double Pyramid"** proposed for the first time in 2010 by the Barilla Center for Food and Nutrition (BCFN)[133]; over the years this coupling between the classic nutritional pyramid and the inverted environmental food pyramid has been updated and improved, made context-specific to each continent of the planet (plus the one for the Mediterranean basin) and supported by more and more material [134].

The 2021 updated "global" version has been reported in Figure 14 [133]: it can be easily observed that most foods (except legumes, milk and foods with a high glycemic content) are more or less at the same level in the two pyramids side by side. This, quite simply, aims to convey the message that the **food groups to be consumed most frequently** (according to the nutritional indications of the Mediterranean diet) **are also those with the least environmental footprint, and vice versa**: "in practice, two different but equally relevant goals - people's health and environmental protection - fit into one single food model" [135].

All three environmental impact indicators considered (carbon footprint, water footprint and ecological footprint) have been estimated using the Life Cycle Assessment (LCA) previously seen [136][137]. The environmental pyramid was initially constructed based on the pyramidal pattern of the

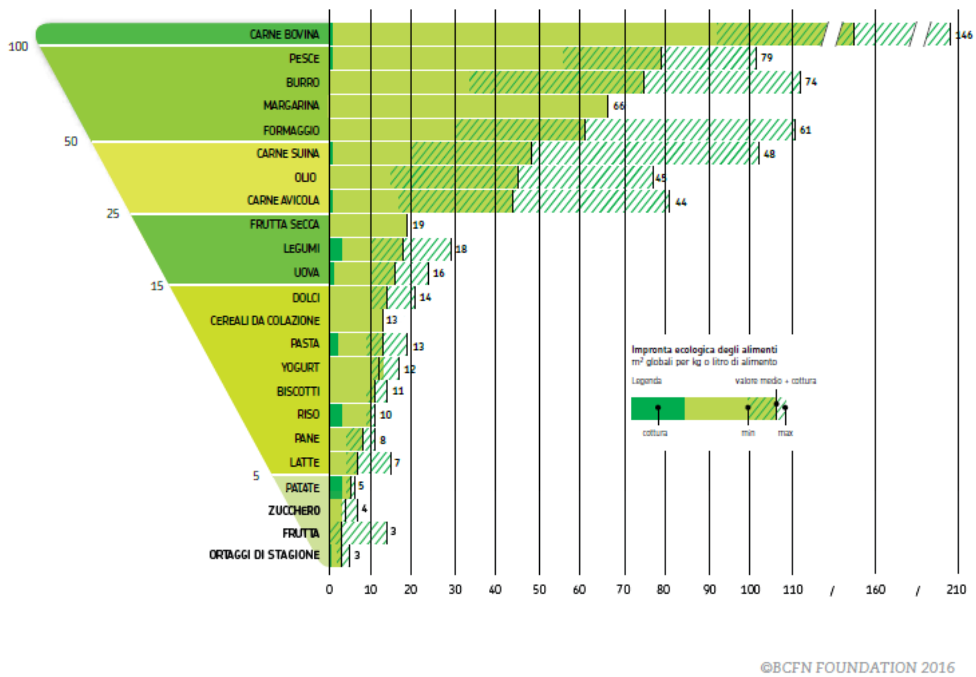


Figure 15 - Ecological Footprint Double Pyramid BCFN 2016

ecological footprint values of the main foods, shown in Figure 15 [138]; to measure the total environmental impact of food, which will be used in the next chapter for the evaluation of various protein sources, were also used the other two indicators (water and carbon footprints).

Through these studies the BCFN has shown that a menu based on meat has a total environmental impact (2.5) two and a half times greater than a vegetarian menu [139][140]: Table VII shows the data of the three footprints on a daily basis of the two menus divided by the various meals, Table VIII compares the environmental impact data of the two menus on a daily and weekly basis.

. Vegetarian menu impact

	Breakfast	Mid-morning snack	Lunch	Snack	Dinner	TOTAL
Ecological Footprint [global sq m2]	1	2	5	1	10	19
Carbon Footprint [g CO2-eq]	150	242	914	108	763	2,177
Water Footprint [liters]	230	242	499	164	1,089	2,225

. Meat-based menu impact

	Breakfast	Mid-morning snack	Lunch	Snack	Dinner	TOTAL
Ecological Footprint [global sq m2]	3	1	17	2	21	42
Carbon Footprint [g CO2-eq]	270	96	2,963	194	3,535	7,058
Water Footprint [liters]	230	186	1,915	149	2,552	5,031

Table VII - Environmental impacts of menu

	Weekly Impact			Average daily impact		
	Carbon Footprint [g CO2-eq]	Water Footprint [liters]	Ecological Footprint [global sq m2]	Carbon Footprint [g CO2-eq]	Water Footprint [liters]	Ecological Footprint [global sq m2]
7 Times Meat Menu	49,406	35,217	294	7,058	5,031	42
5 Times Vegetarian Menu + 2 Time Meat Menu	25,001	21,187	179	3,572	3,027	26
7 Times Vegetarian Menu	15,239	15,575	133	2,177	2,225	19

Table VIII - Variations in the environmental impact depending on eating choices

4.4. HEALTH OUTCOMES AND ENVIRONMENTAL IMPACT OF PROTEIN SOURCES

The objective of this chapter is to investigate the different health outcomes and environmental impacts related to the various protein sources: in the nutritional field it is important to deepen the different food macro-groups and their subcategories due to the great inter-individual variability of dietary patterns. In fact, as previously seen for vegetarian patterns [91], using hypothetical or predefined diets on the average population pattern (diet scenarios) is not always adequate and sometimes leads to evaluations that are incorrect; the use of the recent versions of the Principal Component Analysis (PCA) method allows the best evaluation of these dietary differences within the population considered in the studies [91].

Similarly but in the opposite direction, the methodology used in the first decades of modern nutritional studies that consists in an exclusive analysis of the effects of micro- and macronutrients considered separately from foods, is inadequate because reductive and simplistic [141]. Foods should not be considered as a "vector of single beneficial micro- and macronutrients", but as a complex mix of them in multiple combinations and with a fair variability even between foods of the same category. Obviously in the short term evaluating food by food on all possible health outcomes and environmental impacts would be very difficult as well as a potential waste of time and resources; but carrying out some analyses on principal food macrogroups - which straddle between nutrients and preset dietary patterns - can be a useful approach in the definition of increasingly valid and multidisciplinary nutritional guidelines [142].

Since they are the main suppliers of proteins and amino acids, **protein sources** are among these main food macrogroups and a thorough analysis of them is certainly useful to better understand both health benefits and the environmental impact related to their intake.

As previously seen from the 50s-60s of the last century there was the phenomenon of “nutrition transition” that among other effects also caused a shift towards animal-source foods (pattern 4, “degenerative disease”)[101]; therefore this has also led to a high consumption of animal protein sources favoring them over plant-based ones, an element strongly associated with economic and income growth [143].

The results of the systematic analysis of the Global Burden of Disease (GBD) Study 2017 on the health effects of dietary risks can be used to prove this: it reports for all the world’s high-income regions (including Western Europe, and therefore Italy) a consumption of **animal protein sources** (considered only meat and dairy products) higher than the optimal level, identified «as the level of risk exposure that minimizes the risk from all causes of death» [144]; in detail the global intake of **red meat** is 18% higher than the optimal amount, but if you consider only high-income regions the value is on average double that amount. At the same time in these regions the consumption of **plant-based protein sources** (legumes, nuts, seeds and whole grains) is on average below optimal intake, only with some exceptions for nuts and seeds [144].

Nowadays a huge amount of specific studies in the literature, but also many nutritional guidelines emphasize the importance of a nutrition transition in the opposite direction (**pattern 5, “behavioral change”** as shown in Table IX [101]) referring more generally to plant-based foods, but **also specifically to plant-based protein sources**; although this area of research is really complicated, it has been widely shown that this dietary change would lead to positive effects on human health, deepened gradually throughout the chapter. Nonetheless there would also be significant positive consequences in terms of environmental sustainability, as demonstrated by Springmann et al. [84] in the formerly reported study; once again the importance of a multidisciplinary approach is manifested, which in this case is guaranteed by a newborn field of studies - **planetary health** - proposed for the first time by the study conducted by the special "The Lancet - Rockefeller Foundation commission” [10].

	Transition profile				
	Pattern 1: collecting food	Pattern 2: famine	Pattern 3: receding famine	Pattern 4: degenerative disease	Pattern 5: behavioral change
Nutrition profile					
Diet	Plants, low-fat wild animals, varied diet	Cereals predominant, diet less varied	Fewer starchy staples; more fruit, vegetables, animal protein; low variety continues	More fat (especially from animal products), sugar, processed foods; less fiber	Higher-quality fats, reduced refined carbohydrates, more whole grains, fruit, vegetables
Nutritional status	Robust, lean population; few nutritional deficiencies	Children and women suffer most from low fat intake, nutritional-deficiency diseases emerge, stature declines	Continued MCH[1] nutrition problems, many deficiencies disappear, weaning diseases emerge, stature grows	Obesity, problems for elderly (bone health, etc), many disabling conditions	Reduction in body fat and obesity, improvement in bone health
Economy	Hunter-gatherers	Agriculture, animal husbandry, homemaking begin; shift to monocultures	Second agricultural revolution (crop rotation, fertilizer), Industrial Revolution, women join labor force	Fewer jobs with heavy physical activity, service sector and mechanization, household technology revolution	Service sector mechanization and industrial robotization dominate, increase in leisure exercise offsets sedentary jobs
Household production	Primitive, onset of fire	Labor-intensive, primitive technology begins (clay cooking vessels)	Primitive water systems, clay stoves, cooking technology advances	Household technology mechanizes and proliferates	Significant reduction in food preparation costs as a result of technologic change
Income and assets	Subsistence, primitive stone tools	Subsistence, few tools	Increases in income disparity and agricultural tools industrialization	Rapid growth in income and income disparities, technology proliferation	Decrease in income growth, increase in home and leisure technologies
Demographic profile					
Mortality and fertility	Low fertility, high mortality, low life expectancy	Age of Malthus; high natural fertility, short life expectancy, high infant and maternal mortality	Mortality declines slowly, then rapidly; fertility static, then declines; small, cumulative population growth, which later explodes	Life expectancy hits unique levels (ages 60–70), huge decline and fluctuations in fertility (eg, postwar baby boom)	Life expectancy extends to ages 70 and 80 y, disability-free period increases
Morbidity	Much infectious disease, no epidemics	Epidemics, endemic disease (plague, smallpox, polio, tuberculosis), deficiency disease begins, starving common	Tuberculosis, smallpox infection, parasitic disease, polio, weaning disease (diarrhea, retarded growth) expand, later decline	Chronic disease related to diet and pollution (heart disease, cancer), decline in infectious disease	Increases in health promotion (preventive and therapeutic), rapid decline in cardiovascular disease, slower change in age-specific cancer profile
Age structure	Young population	Young, very few elderly	Chiefly young, shift to older population begins	Rapid decline in fertility, rapid increase in proportion of elderly person	Increases in the proportion of elderly >75 y of age
Residency patterns	Rural, low density	Rural, a few small, crowded cities	Chiefly rural, move to cities increases, international migration begins, megacities develop	Dispersal of urban population decrease in rural green space	Lower-density cities rejuvenate, increase in urbanization of rural areas encircling cities
Food processing	Nonexistent	Food storage begins	Storage processes (drying, salting) begin, canning and processing technologies emerge, increases in food refining and milling	Numerous food-transforming technologies	Technologies create foods and food constituent substitutes (eg, macronutrient substitutes)

Table IX - Characteristics of the 5 pattern of the nutrition transition

Within this section at first has been deepened various protein sources both animal and plant-based, highlighting **positive and negative effects on human health** by focusing and on the most significant correlations and on the most relevant chronic diseases; the following chronic diseases (risk of incidence) and the following groups of diseases (risk of mortality) were used for the analysis in terms of health outcomes:

- incidence of coronary heart disease (CHD), stroke, high blood pressure (HBP), chronic heart failure (CHF), type 2 diabetes (T2D), overweight/obesity, metabolic syndrome (MetS), colorectal cancer (CRC), breast cancer and gastric cancer;
- all-cause mortality, cardiovascular diseases (CVDs) mortality and cancer mortality.

In addition, the main scientific data currently known also on **insects** (as regards animal protein sources) and on the various **"plant-based milks"** (for plant-based ones) have been provided.

Then a more generic comparison was made on the main health outcomes between animal and plant-based protein sources, reporting some risks of morbidity and mortality associated with a higher intake of some chronic diseases, or groups of them.

On the other hand the **environmental impact of protein sources** through both the construction of a dedicated table (Table XX) at the end of the section, taking into account the six footprints already mentioned in this thesis, and a brief analysis of source-specific positive/negative elements.
Finally some figures from the literature have been reported that allow to have an overview on the impact of the main subgroups of protein sources on the same environmental problem.

For the health outcomes' evaluation Italian data, where available, have been privileged; otherwise, in order of priority, reference have been made to data from neighboring countries (such as those in the European Mediterranean basin) and then to high quality data, often coming from the USA.

Contrarily, in the environmental field, references were selected only on the basis of quality, given the global nature of the climate crisis and some environmental impacts.

A fundamental premise concerns the **selection of functional units** to be used for the analysis of health outcomes and environmental impact associated with the consumption of certain food groups [145]; if the use of functional nutritional units in the assessment of the life cycle at the level of individual foods (LCA) is increasingly widespread for the area of food sustainability [146], in the health field there is not the same homogeneity in the use of fixed quantities of a certain food (dietary serving sizes) for the evaluation of nutritional benefits in "dose-response" analyses.
Although it is certainly complex to promote the use of the same approach globally, also given the great differences in terms of dietary patterns and eating habits, it would be appropriate to support its use to obtain reliable and evidence-based scientific data of ever-increasing quality.
In this analysis, an attempt has been made to compensate for this lack of homogeneity by taking as a reference for each protein source evaluated the amount in grams constituting a serving most widely used in the literature; the various amounts have been reported in each caption of Tables.

For the composition of Tables X-XVII and Table XIX on the main health outcomes, priority was given to meta-analyses of prospective cohort studies or umbrella reviews of such meta-analyses; only in the absence of these types of papers individual prospective cohort studies have been taken into account, evaluating the quality and reliability of data and always choosing whenever possible the most recent ones.
Only in the text in support of the Tables have been reported the results of some relevant RCTs or their systematic reviews or meta-analyses.

4.4.1. Animal protein sources

As seen in Chapter 1, protein quality can be evaluated in various ways: according to the traditional method linked to the amino acid composition alone, and therefore to the ability of protein sources to provide protein synthesis while maintaining nitrogen balance, animal protein sources have **higher values** than plant-based ones **with the DIAAS score** currently used (for more details see Table II) and are therefore defined as "**high-quality proteins"**.
In this regard, the report of the EAT-Lancet Commission, based on the conclusions of a major study on cancer pathophysiology [147], states that an excessive contribution of high-quality proteins in adults could "maximally stimulate cell replication and growth" thus increasing the risk of cancer [82]. Even with this last consideration, the choice of high-quality proteins is not the only element to give priority in the definition of the consumption of protein sources.

Among the examined sources, there are two animal meats (**fish**, or more generally seafood, and **meat** commonly understood) and two products of animal origin (**eggs** and **dairy products**).

4.4.1.1. Meat

The first protein source analyzed is certainly the most studied in the literature: about meat have been made multiple researches in different fields of medicine to highlight possible associations between different levels of intakes and some diseases.

Meat can be classified using two different main criteria: the first is based on the origin of the product (red meat, poultry and bush-meat); the second considers the processing (processed and unprocessed meat).

So, there are a lot of different types of meat due to the various combinations deriving from these two classifications; thus, studying all of them is expensive from many points of view.

This study has only deepened total meat, red meat and processed meat. As you can see in Table X, "total meat" has more often less significant data compared to the other two groups chosen.

Red meat or processed meat has shown a lot of positive associations with chronic diseases, more than any other food group analyzed; this can be explained by higher contents of trans saturated fatty acids (SFAs)[148]. These components have been associated with a series of molecular mechanisms harmful to the main groups of chronic diseases, such as CVDs, metabolic diseases and some cancers.

Meat processing and some cooking methods play a role in increasing cancer risk: processed meat, due to higher concentrations of nitrates and nitrites, lead to higher risks of GI tract cancers through the formation of N-nitroso-compounds [149]; as regards the second one, exposure to high temperature during cooking processes is very harmful because of the formation heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs), recognized as carcinogenic to humans and associated with increased CRC risk [149].

As regards breast cancer, it was reported a significant positive association with meat intake (considering total, red and processed meat) also within the umbrella review by Buja et al. [150]; the risk seems to be stronger in postmenopausal women.

In addition, to underlining the increased risk of developing T2D associated with the consumption of an extra serving/day of meat, and especially of red meat and processed meat, the umbrella review of Neuenschwander et al. [151] reports a further increase in risk (41%) in the consumption of processed red meat, combining the results of 8 previous meta-analyses. The 4 meta-analyses considered [152–155] are the same mentioned by a review prior to this [156] which however has not further processed the data thus becoming an umbrella review, but focused on a thorough analysis of the complex physio pathological mechanisms underlying the increased risk of T2D associated with the high/moderate intake of red and processed meat.

Among the various risk factors for T2D analyzed by another umbrella review [157], the **consumption of processed meat** (considered as a dichotomous variable) is the worst one among dietary risk factors, with a 41% increase in the incidence rate.

<u>Health Outcomes</u>	Unit of Intake	Red meat	Processed meat
ALL-CAUSE MORTALITY	Highest vs Lowest	[158][w] 1.10 (1.00 - 1.22) [159][c]	1.21 (1.16 - 1.26) [159][k]
	Dose-Response	1.10 (1.04 - 1.18) [159][c] 1.12 (1.05 – 1.21) [160]	1.23 (1.12 - 1.36) [159][k] 1.41 (1.21 - 1.67) [160]
TOTAL CVDs MORTALITY	Highest vs Lowest	<u>0.79 (0.70 - 0.90)</u> [161][s] 1.16 (1.03 - 1.32) [162][t]	<u>0.81 (0.75 - 0.87)</u> [161][s] 1.18 (1.05 - 1.32) [162][t]
	Dose-Response	1.15 (1.05 - 1.26) [162][u]	1.24 (1.09 - 1.40) [162][u] 1.15 (1.07 - 1.24) [158][w]
CHD	Highest vs Lowest	1.16 (1.08 - 1.24) [163][g] 1.15 (1.08 - 1.23) [160]	1.15 (0.99 - 1.33) [163][i]
	Dose-Response	1.15 (1.08 - 1.23) [163][h]	1.42 (1.07 - 1.89) [164][k] 1.27(1.09 - 1.49) [163][j][160]
STROKE	Highest vs Lowest	1.16 (1.08 - 1.25) [163][g] 1.11 (1.03 - 1.20) [165][v]	1.16 (1.07 - 1.26) [163][i] 1.17 (1.08 - 1.25) [165][v]
	Dose-Response	1.12 (1.06 - 1.17) [163][h][160]	1.17 (1.02 - 1.34) [163][j][160]
HBP	Highest vs Lowest	1.15 (1.02 - 1.28) [166][b]	1.12 (1.02 - 1.23) [166][b]
	Dose-Response	1.14 (1.02 - 1.28) [166][b]	1.12 (1.00 - 1.26) [166][b]
CHF	Highest vs Lowest	1.12 (1.04 - 1.21) [163][g]	1.27 (1.14 - 1.41) [163][i]
	Dose-Response	1.08 (1.02 - 1.14) [163][h]	1.12 (1.05 - 1.19) [163][j]
T2D	Highest vs Lowest	1.22 (1.09 - 1.36) [167]	1.39 (1.29 - 1.49) [167]
	Dose-Response	**1.17 (1.08 - 1.26)** [151][d] 1.13 (1.03 - 1.23) [160]	1.57 (1.28 - 1.93) [164][k] **1.37 (1.22 - 1.54)** [151][d] 1.32 (1.19 - 1.48) [160]
OVERWEIGHT / OBESITY	Highest vs Lowest	<u>*1.23 (1.07 - 1.41)*</u> [168][x]	/
	Dose-Response	/	/
MetS	Highest vs Lowest	/	/
	Dose-Response	/	/

TOTAL CANCER MORTALITY	Highest vs Lowest	[158][w]	/
	Dose-Response	/	1.08 (1.06 - 1.11) [158][w]
TOTAL CANCER INCIDENCE	Highest vs Lowest	/	/
	Dose-Response	/	/
CRC	Highest vs Lowest	1.12 (1.06 - 1.18) [169][a]	1.14 (1.06 - 1.21) [169][a]
	Dose-Response	1.12 (1.06 - 1.19) [169][a][160] 1.12 (1.00 - 1.25) [170][p]	1.17 (1.10 - 1.23) [169][a][160] 1.18 (1.10 - 1.28) [170][p]
BREAST CANCER	Highest vs Lowest	[171][l] 1.09 (0.99 - 1.21) [150][n]	1.07 (1.01 - 1.14) [171][m] 1.09 (1.03 - 1.13) [150][n]
	Dose-Response	1.07 (1.01 - 1.14) [171][l]	1.09 (1.02 - 1.17) [171][m]
GASTRIC CANCER	Highest vs Lowest	[172][q] [173][r]	1.15 (1.03 - 1.29) [173][r] 1.24 (1.04 - 1.47) [172][q]
	Dose-Response	[172][q]	1.21 (1.04 - 1.41) [172][q]

HEALTH OUTCOMES	**Unit of Intake**	**Total meat**	**Poultry**
ALL-CAUSE MORTALITY	Highest vs Lowest	/	/
	Dose-Response	/	[160][o]
TOTAL CVDs MORTALITY	Highest vs Lowest	[162][t]	[162][t]
	Dose-Response	[162][u]	[162][u]
CHD	Highest vs Lowest	1.23 (0.98 - 1.49) [174][y]	/
	Dose-Response	/	[160][o]

STROKE	Highest vs Lowest	1.18 (1.09 - 1.28) [165][v]	0.87 (0.78 - 0.96) [165][v]
	Dose-Response	/	/
HTN/HBP	Highest vs Lowest	/	/
	Dose-Response	/	/
CHF	Highest vs Lowest	/	/
	Dose-Response	/	/
T2D	Highest vs Lowest	/	/
	Dose-Response	1.12 (1.01 - 1.24) [151][e]	[151][f] [160][o]
OVERWEIGHT / OBESITY	Highest vs Lowest	/	/
	Dose-Response	/	/
MetS	Highest vs Lowest	/	/
	Dose-Response	/	/
TOTAL CANCER MORTALITY	Highest vs Lowest	/	/
	Dose-Response	/	/
TOTAL CANCER INCIDENCE	Highest vs Lowest	[175]	/
	Dose-Response	/	/
CRC	Highest vs Lowest	/	/
	Dose-Response	/	[170][p] 0.78 (0.62 - 0.94) [160][o]
BREAST CANCER	Highest vs Lowest	/	[171][m]
	Dose-Response	/	[171][m]

GASTRIC CANCER	Highest vs Lowest	[173][r]	[172][q] [173][r]
	Dose-Response	/	[172][q]

Table X - Association between red meat, processed meat, total meat and poultry meat intake and some major chronic diseases incidence / major diseases groups mortality (RR, 95% C.I.). The dose-response meta-analysis refers always to an additional serving of a food per day relative to the average intake of that food observed in a cohort study (100 g for total meat, red meat and poultry, 50 g for processed meat).

a. data obtained from meta-analysis of 25/18/21/16 prospective cohort studies respectively;
b. data obtained from 7/7/5/4 prospective cohort studies respectively;
c. data obtained from meta-analysis of 12/10/6/6 prospective cohort studies respectively;
d. data obtained from 14 primary meta-analysis of prospective cohort studies;
e. data obtained from 8 primary meta-analysis of prospective cohort studies;
f. data obtained from 3 primary meta-analysis of prospective cohort studies;
g. data obtained from meta-analysis of 3/7/5 prospective cohort studies respectively;
h. data obtained from meta-analysis of 3/7/4 prospective cohort studies respectively;
i. data obtained from meta-analysis of 5/6/3 prospective cohort studies respectively;
j. data obtained from meta-analysis of 3/6/2 prospective cohort studies respectively;
k. data obtained from meta-analysis of 12/6 prospective cohort studies respectively;
l. data obtained from meta-analysis of 8/6 prospective cohort studies respectively;
m. data obtained from meta-analysis of 14/12/11/10 prospective cohort studies respectively;
n. data obtained from meta-analysis of 7/15 prospective cohort studies respectively;
o. data to be related to chicken consumption only, and not to white meat in general;
p. data obtained from meta-analysis of 8/10/6 prospective cohort studies respectively;
q. data obtained from meta-analysis of 6/4/10/7/5/4 prospective cohort studies respectively;
r. data obtained from meta-analysis of 13/8/13/7 prospective cohort studies respectively;
s. data obtained on lowest consumption taking the highest one as a reference, therefore in contrast to all the others ("lowest vs highest");
t. data obtained from meta-analysis of 5/7/6/6 prospective cohort studies respectively;
u. data obtained from meta-analysis of 3/6/6/5 prospective cohort studies respectively;
v. data obtained from meta-analysis of 3/4/4/2 prospective cohort studies respectively;
w. data obtained from meta-analysis of 2/6/2/5 prospective cohort studies respectively;
x. data obtained from meta-analysis of 1 prospective cohort studies;
y. data obtained from meta-analysis of 7 prospective cohort studies.

4.4.1.2. Fish

For this second category of animal protein source, the term “seafood” has not been intentionally used, since marine foods of vegetable origin, such as algae and seaweeds, also fall within this term with wider meaning.
Therefore we have chosen a generic "fish" that is reflected in a "total fish" in Table XI; this group should be properly divided into “shellfish” and “finfish” with analyses that evaluate separately these two food subgroups; if for the first one the data are strongly lacking, the second can be in turn diversified into “oily fish (high-fat)” and “lean fish” (low-fat) and where specific data have been reported.

The reason for this further subdivision is to be found mainly in the difference in content of **specific polyunsaturated fatty acids (PUFAs), "marine ω-3" ones**: eicosapentaenoic acid (**EPA**) and docosahexaenoic acid (**DHA**); some species of fish - precisely every "oily fish" - have high levels of them unlike “lean fish”.
Omega-3 fatty acids are one of the most crucial elements in the nutritional field and the recent international summit is evidence of the multidisciplinary interest around them [176].
The molecular mechanisms through which they act are multiple and varied; some are well known and others still to be confirmed. The review of Mozaffarian and Wu [177] and that of Adkins and Kelley [178] present a clear picture of the action exerted within the human organism by these specific macronutrient: a reduction in inflammation (via the eicosanoid synthesis pathway) and LDL cholesterol are two of the main mechanisms demonstrated.

The main beneficial effects concern cardiometabolic health, cancer and brain health and the paper of Shadidi and Ambigaipalan [179] is a complete synthesis of them. The positive outcomes related to high or increased consumption of fish on cardiovascular health outcomes, except for high blood pressure, are visible in Table XI.

Within the area of metabolic diseases, the beneficial effect of high plasma-level of omega-3 fatty acids on reducing the risk of overweight/obesity is widely proven [180], but this does not automatically lead to similar improvements even with fish consumption; also in this specific case there is a discrepancy between the level of macronutrients and that of food.
In fact, within the Table XI have been inserted the data of a single meta-analysis and the results are not statistically significant, indeed they are almost significant for an increase in the risk of overweight/obesity in dose-response analysis [168]; similarly, from the meta-analyses of prospective cohort studies, there is also no evidence on the risk of incidence of T2D and MetS associated with the consumption of this protein source [151,160,167,181], also due to the lack of such studies at European level.
The only valid data in this field concerns the <u>reduction of the risk of abdominal obesity</u>, one of the diagnostic elements of MetS: it was found a significant decrease both in “highest vs lowest” (RR 0.75, 95% C.I. 0.62 - 0.89) and “dose-response” (RR 0.83, 95% C.I. 0.71 - 0.97) analyses [168].
Among the RCTs the results are more promising: a meta-analysis by Bender et al. [182] has shown positive effects also related to oily fish intake (in addition to that of "marine omega-3") both on the body weight and waist circumference.
However, it has not yet been clearly demonstrated that the increase in total fish consumption and its replacement instead of meat are associated with a reduction of the risk of obesity, MetS and T2D incidence and the development of insulin resistance [183].

In addition it is important to add some data on the association with breast cancer: although two recent meta-analyses of prospective cohort studies have not shown a positive association between total fish intake and such cancer [171,184], the study by Zheng et al. [184] and previous complete review [179] reported the positive effect of **"marine" omega-3 fatty acids (EPA and DHA)** against this specific cancer. The reduction in incidence shown in meta-analysis was significant in the "highest vs lowest intake" analysis (RR 0.86, 95% C.I. 0.78 - 0.94) and nearly significant in "dose-response" one (RR 0.86, 95% C.I. 0.78 - 0.94) (11 and 8 prospective cohort studies were evaluated respectively).

Finally a relevant paper of 2006 by Mozaffarian and Rimm [185] stated that the nutritional benefits of fish consumption are far greater than the related risks: the important role in cardiovascular health and neurodevelopment makes it an important food within the diet. The negative consequences related to the content in contaminants (such as mercury, other heavy metals and dioxins and polychlorinated biphenyls) are currently considered less relevant than the health benefits.

At this point, however, some considerations on the insights just made in a planetary health perspective are necessary.

- In view of the dynamic trend of natural phenomena and the imminent climate crisis, it is important to carry out increasingly thorough and appropriate research to monitor the concentration in marine waters of the main heavy metals and in particular mercury, having regard to the proven or even currently assumed/probable adverse health effects [186]. This is because in the last two decades the levels of mercury in the atmosphere and in oceanic waters have increased, also due to natural processes, but above all because of the greater impact of human activities that also affect the former [187].
- Although cardioprotective effect and improvement of metabolic parameters related to the intake of omega-3 supplements LC-PUFAs (fish oil) are widely proven [188], It is equally true that there is a large gap between supply and demand of these macronutrients due to the progressive depletion of wild fish stocks [189]. It is therefore important to compare the effects of fish consumption and this supplementation both from a clinical-nutritional point of view and from an environmental point of view with the aim to achieve greater sustainability and overall long-term health benefits.

A possible alternative is offered by nuts and seeds: their high content in alpha-linolenic acid (the only vegetable omega-3) has proven positive effects on health and for a more complete treatment we refer to the specific paragraph.

Health Outcomes	Unit of Intake	Total Fish
ALL-CAUSE MORTALITY	Highest vs Lowest	0.94 (0.90 - 0.98) [190][m] 0.95 (0.92 - 0.98) [159][f]
	Dose-Response	0.89 (0.84 - 0.94) [190][m] 0.93 (0.88 - 0.98) [159][f][160]
TOTAL CVDs MORTALITY	Highest vs Lowest	/
	Dose-Response	/
CHD	Highest vs Lowest	0.81 (0.70 - 0.92) [174][l] 0.94 (0.88 - 1.02) [163][d] 0.91 (0.84 - 0.97) [191][r]
	Dose-Response	0.88 (0.79 - 0.99) [163][e][160]
STROKE	Highest vs Lowest	0.95 (0.89 - 1.01) [163][d] 0.90 (0.85 - 0-96) [192]
	Dose-Response	0.94 (0.89 - 0.99) [193][gh] 0.86 (0.75 - 0.99) [163][e][160]
HTN/HBP	Highest vs Lowest	[166][c]
	Dose-Response	1.07 (0.98 – 1.16) [166][c]
CHF	Highest vs Lowest	0.89 (0.80 - 0.99) [163][d]
	Dose-Response	0.80 (0.67 - 0.95) [163][e]
T2D	Highest vs Lowest	[151][b] [167]
	Dose-Response	[160]
OVERWEIGHT / OBESITY	Highest vs Lowest	[168][t]
	Dose-Response	*1.06 (0.99 - 1.14)* [168][a]
MetS	Highest vs Lowest	/
	Dose-Response	*0.80 (0.66 - 0.96)* [181][n]

TOTAL CANCER MORTALITY	Highest vs Lowest	/
	Dose-Response	/
TOTAL CANCER INCIDENCE	Highest vs Lowest	0.98 (0.96 - 1.00) [175]
	Dose-Response	/
CRC	Highest vs Lowest	0.93 (0.86 - 1.01) [194][p] 0.96 (0.90 - 1.01) [169][s]
	Dose-Response	0.93 (0.85 - 1.01) [169][s] [160] 0.89 (0.80 - 0.99) [170][k]
BREAST CANCER	Highest vs Lowest	[184][o] [171][j]
	Dose-Response	[171][j]
GASTRIC CANCER	Highest vs Lowest	[173][l]
	Dose-Response	/

Health Outcomes	Unit of Intake	Oily Fish (fatty)	Lean Fish
STROKE	Highest vs Lowest	0.88 (0.74 - 1.04) [195][h]	0.81 (0.67 - 0.99) [195][h]
	Dose-Response	/	/
T2D	Highest vs Lowest	0.89 (0.82 - 0.96) [151][b]	[151][b]
	Dose-Response	/	/

Table XI - Association between total fish, oily fish and lean fish intake and some major chronic diseases incidence / major diseases groups mortality (RR, 95% C.I.). The dose-response meta-analysis refers always to an additional serving of a food per day relative to the average intake of that food observed in a cohort study (100 g for total fish, oily fish and lean fish).

a. obtained from meta-analysis of 1/1 prospective cohort studies respectively;
b. obtained from meta-analysis of 7/4/4/3 prospective studies respectively;
c. obtained from meta-analysis of 8/7 prospective cohort studies respectively;
d. obtained from meta-analysis of 22/20/8 prospective cohort studies respectively;
e. obtained from meta-analysis of 15/15/7 prospective cohort studies respectively;
f. obtained from meta-analysis of 38/19 prospective cohort studies respectively;
g. per 3 servings/week vs no intake;
h. obtained from meta-analysis of 11 prospective cohort studies respectively;
i. obtained from meta-analysis of 29 prospective cohort studies respectively;
j. obtained from meta-analysis of 18/13 prospective cohort studies respectively;
k. obtained from meta-analysis of 11 prospective cohort studies;
l. obtained from meta-analysis of 10 prospective cohort studies;
m. obtained from meta-analysis of 12/7 prospective cohort studies respectively;
n. obtained from meta-analysis of 6 prospective cohort studies, but any of this in Europe;
o. obtained from meta-analysis of 11 prospective cohort studies;
p. obtained from meta-analysis of 22 prospective cohort studies;
q. obtained from meta-analysis of 31 prospective cohort studies;
r. obtained from meta-analysis of 22 prospective cohort studies;
s. obtained from meta-analysis of 21/16 prospective cohort studies respectively.

4.4.1.3. Eggs

Eggs are a protein source different from the others, consisting of two parts well distinct from each other and with equally different nutritional properties: in fact, the egg white consists mainly of water and albumin; while the yolk is rich in nutrients relevant for human nutrition such as cholesterol (main dietary source), vitamins (each of those fat-soluble and many of the B series), choline (also called vitamin J) and various minerals (calcium, phosphorus, zinc and selenium on all, in relation to other sources).
In relation to the consumption of eggs, omega-3 and choline are the most evaluated and studied in relation to health benefit among the micronutrients just listed.

The amino acid composition of the egg has been taken as a **reference for the evaluation of protein quality** with the most classic approach, given the great balance in the content of essential amino acids.

As for the association between their intake and the main health outcomes, the trend is peculiar and the data presented here in Table XII give a clear idea about that; to best clarify this overview it was exceptionally added to the evaluation the outcome "total CVDs incidence". From the literature considered, it is reported:

- a nearly significant increase in all-cause mortality [159];
- as regards the CV field, a non-significant reduction of total CVDs mortality and stroke (in the most recent meta-analysis), significant one of total CVDs incidence, but at the same time absence of association with CHD and stroke (previous studies) and increased risk of CHF. Data related to HBP indicate a strong significant reduction, but they are not very reliable given the low quality of evidence related to the fact that the large and important meta-analysis of reference reported only one study for this outcome (unlike the others).
- a not significant or conflicting result with both T2D and CRC risks).

The molecular mechanisms underlying these ambivalent outcomes are not yet fully understood and certainly need further specific both prospective studies and clinical trials; it has also to be better investigated potential confounding effects of some variables such as sex, geographic area, general dietary habits [196].

In addition, it should be stressed that eggs are not only a source of cholesterol and therefore directly associated with a high CV risk; it is a myth as much trumpeted as potentially misleading. A recent systematic review highlights that the effects of dietary cholesterol are not yet fully clarified and concludes by highlighting the importance of further “carefully adjusted and well-conducted cohort studies” [197].

Health Outcomes	**Unit of Intake**	**Total Eggs**
ALL-CAUSE MORTALITY	Highest vs Lowest	1.06 (1.00 - 1.12) [159][c]
	Dose-Response	1.15 (0.99 - 1.34) [159][c] [160]
TOTAL CVDs MORTALITY	Highest vs Lowest	/
	Dose-Response	0.95 (0.88 - 1.03) [196][a]
TOTAL CVDs INCIDENCE	Highest vs Lowest	/
	Dose-Response	0.94 (0.89 - 0.99) [196][a]
CHD	Highest vs Lowest	[163][e] [174][g]
	Dose-Response	[160] [163][f] [196][a] [198]
STROKE	Highest vs Lowest	[163][e]
	Dose-Response	[160] [163][f] [198] 0.97 (0.93 - 1.02) [196][a]
HTN/HBP	Highest vs Lowest	*0.54 (0.32 - 0.91)* [166][b]
	Dose-Response	*0.25 (0.08 - 0.74)* [166][b]
CHF	Highest vs Lowest	1.25 (1.12 - 1.39) [163][e]
	Dose-Response	1.16 (1.03 - 1.31) [163][f] 1.11 (0.99 - 1.25) [196][a]
T2D	Highest vs Lowest	[167][a]
	Dose-Response	[151][d] [160] 1.16 (1.09 - 1.23) [199]
OVERWEIGHT	Highest vs Lowest	/

Table XII - Association between eggs intake and some major chronic diseases incidence / major diseases groups mortality (RR, 95% C.I.). The dose-response meta-analysis refers always to an additional serving of a food per day relative to the average intake of that food observed in a cohort study (50 g for eggs).

a. obtained from meta-analysis of 8/9/12/6/4 prospective cohort studies respectively;
b. obtained from only 1 prospective cohort study;
c. obtained from meta-analysis of 8/5 prospective cohort studies respectively;
d. obtained from meta-analysis of 13 prospective cohort studies;
e. obtained from meta-analysis of 11/10/4 prospective cohort studies respectively;
f. obtained from meta-analysis of 9/10/4 prospective cohort studies respectively;
g. obtained from meta-analysis of 6 prospective cohort studies;
h. obtained from meta-analysis of 9/8 prospective cohort studies respectively;
i. obtained from meta-analysis of 9 prospective cohort studies;
j. obtained from meta-analysis of 4/3 prospective cohort studies respectively.

/ OBESITY	Dose-Response	/
MetS	Highest vs Lowest	/
	Dose-Response	/
TOTAL CANCER MORTALITY	Highest vs Lowest	/
	Dose-Response	/
TOTAL CANCER INCIDENCE	Highest vs Lowest	/
	Dose-Response	/
CRC	Highest vs Lowest	1.35 (1.11 - 1.36) [169][j]
	Dose-Response	[160] [169][j]
BREAST CANCER	Highest vs Lowest	[171][h]
	Dose-Response	[171][h]
GASTRIC CANCER	Highest vs Lowest	[173][i]
	Dose-Response	/

4.4.1.4. Dairy products

As clearly visible in Table XIII, the consumption of total dairy products (Dp), but also of total milk and yogurt is associated with a sharp reduction in the **MetS incidence** both in "highest vs lowest" and “dose-response” analyses [200]; every single component of the MetS evaluated in the study (5 in total, hyperglycaemia, low HDL-cholesterol, hypertriacylglycerolaemia, abdominal obesity and high blood pressure) is reduced following the consumption of each of these 3 subgroups of Dp, also here in both types of analysis. Thus this meta-analysis shows a significant decrease in abdominal obesity due to a higher consumption of total Dp, total milk and yogurt, respectively of 24%, 17% and 26%, making up for the low significance (for total Dp) or a lack of data (for other two subgroups) on overweight/obesity [200].

Health Outcomes	Unit of Intake	Total Dp	Total milk
ALL-CAUSE MORTALITY	Highest vs Lowest	1.03 (0.98 - 1.07) [159][c] [201][q]	[201][a]
	Dose-Response	0.98 (0.93 - 1.03)[159][c][160] 0.99 (0.97 - 1.01) [201][q]	1.03 (0.99 - 1.06) [201][a]
TOTAL CVDs MORTALITY	Highest vs Lowest	0.93 (0.88 - 0.98) [201][q]	[201][a]
	Dose-Response	0.98 (0.96 - 1.00) [201][q]	[201][a]
CHD	Highest vs Lowest	[163][f] 0.91 (0.82 - 1.00) [164][h]	/
	Dose-Response	[163][g] [160]	/
STROKE	Highest vs Lowest	0.79 (0.75 - 0.82) [164][h] 0.96 (0.90 - 1.01) [163][f]	/
	Dose-Response	0.98 (0.96 - 1.00) [163][g][160]	/
HTN/HBP	Highest vs Lowest	0.89 (0.86 - 0.93) [166][b]	/
	Dose-Response	0.95 (0.94 - 0.97) [166][b]	/
CHF	Highest vs Lowest	[163][f]	/
	Dose-Response	*1.08 (1.01 - 1.15)* [163][g]	/
T2D	Highest vs Lowest	0.92 (0.86 - 0.97) [164][h] 0.89 (0.84 - 0.89) [167]	/
	Dose-Response	0.96 (0.94 - 0.99) [151][d][160]	[151][e]
OVERWEIGHT / OBESITY	Highest vs Lowest	[168][s]	/
	Dose-Response	0.97 (0.93 - 1.01) [168][s]	/
MetS	Highest vs Lowest	0.75 (0.66 - 0.84) [200][t]	0.78 (0.69 - 0.87) [200][t]
	Dose-Response	0.91 (0.85 - 0.96) [200][u]	0.87 (0.79 - 0.95) [200][u]

TOTAL CANCER MORTALITY	Highest vs Lowest	1.03 (0.98 - 1.07) [201][q]	[201][a]
	Dose-Response	[201][q]	1.03 (0.99 - 1.06) [201][a]
TOTAL CANCER INCIDENCE	Highest vs Lowest	0.95 (0.90 - 1.00) [175]	/
	Dose-Response	/	/
CRC	Highest vs Lowest	0.83 (0.76 - 0.89) [169][r]	/
	Dose-Response	0.93 (0.91 - 0.94) [169][r][160] 0.87 (0.83 - 0.90) [170][m]	0.94 (0.92 - 0.96) [170][m]
BREAST CANCER	Highest vs Lowest	0.90 (0.83 - 0.98) [202][l]	0.92 (0.84 - 1.02) [171][i] 0.94 (0.86 - 1.03) [202]
	Dose-Response	0.97 (0.95 - 0.99) [202][o]	0.97 (0.93 - 1.01) [171][i]
GASTRIC CANCER	Highest vs Lowest	[173][n]	/
	Dose-Response	/	/

Health Outcomes	**Unit of Intake**	**Whole Milk (W) or Skim Milk (S)**	**Yogurt**
ALL-CAUSE MORTALITY	Highest vs Lowest	1.15 (1.09 - 1.20)[201][p](W) [201][p] (S)	/
	Dose-Response	1.10 (1.00 - 1.21)[201][p](W) [201][p] (S)	/
TOTAL CVDs MORTALITY	Highest vs Lowest	1.09 (1.02 - 1.16)[201][p](W) [201][p] (S)	/
	Dose-Response	[201][p] (W) [201][p] (S)	/
CHD	Highest vs Lowest	/	/
	Dose-	/	/

	Response		
STROKE	Highest vs Lowest	/	[203]
	Dose-Response	/	/
HTN/HBP	Highest vs Lowest	/	/
	Dose-Response	/	/
CHF	Highest vs Lowest	/	/
	Dose-Response	/	/
T2D	Highest vs Lowest	0.87 (0.78 - 0.96) [167] (W) / (S)	0.83 (0.70 - 0.98) [167]
	Dose-Response	[151][e] (W and S)	0.94 (0.91 - 0.98) [151][d]
OVERWEIGHT / OBESITY	Highest vs Lowest	/	/
	Dose-Response	/	/
MetS	Highest vs Lowest	/	0.77 (0.66 - 0.88) [200][t]
	Dose-Response	/	0.82 (0.73 - 0.91) [200][u]
TOTAL CANCER MORTALITY	Highest vs Lowest	1.17 (1.08 - 1.28)[201][p](W) [201][p] (S)	/
	Dose-Response	1.13 (1.01 - 1.28)[201][p](W) [201][p] (S)	/
TOTAL CANCER INCIDENCE	Highest vs Lowest	/	/
	Dose-Response	/	/
CRC	Highest vs Lowest	/	/
	Dose-Response	/	/

BREAST CANCER	Highest vs Lowest	[171][j] [202][l] (W) 0.93 (0.85 - 1.00) [171][j] (S) 0.93 (0.84 - 1.02) [202][l] (S)	0.90 (0.82 - 1.00) [171][k] 0.91 (0.83 – 0.99) [202][l]
	Dose-Response	[171][j] (W) 0.96 (0.92 - 1.00) [171][j](S)	[171][k]
GASTRIC CANCER	Highest vs Lowest	/	/
	Dose-Response	/	/

Table XIII - Association between total dairy products (Dp), total milk, whole or skim milk and yogurt intake and incidence of some major chronic diseases/mortality of major diseases groups (RR, 95% C.I.). The dose-response meta-analysis refers always to an additional serving of a food per day relative to the average intake of that food observed in a cohort study (200 g for total Dp and yogurt, 200 ml for total milk, whole milk and skim milk).

a. obtained from meta-analysis of 27/16/15/9/13/8 prospective cohort studies respectively;
b. obtained from meta-analysis of 9 prospective cohort studies;
c. obtained from meta-analysis of 27/16 prospective cohort studies respectively;
d. obtained from meta-analysis of 21/11 prospective cohort studies respectively;
e. obtained from meta-analysis of 10/9/7 prospective cohort studies respectively;
f. obtained from meta-analysis of 13/12/3 prospective cohort studies respectively;
g. obtained from meta-analysis of 10/11/*1* prospective cohort studies respectively;
h. obtained from meta-analysis of 11/7/4 prospective cohort studies respectively;
i. obtained from meta-analysis of 18/11 prospective cohort studies respectively;
j. obtained from meta-analysis of 9/8/5/5 prospective cohort studies respectively;
k. obtained from meta-analysis of 5/3 prospective cohort studies respectively;
l. obtained from meta-analysis of 16/7/6/7 prospective cohort studies respectively;
m. obtained from meta-analysis of 10/9 prospective cohort studies respectively;
n. obtained from meta-analysis of 3 prospective cohort studies;
o. 1 serving/day compared with no Dp consumption;
p. obtained from meta-analysis of 9/8/6/6/5/4/4/4/7/7/6/6 prospective cohort studies respectively;
q. obtained from meta-analysis of 33/20/16/13/19/9 prospective cohort studies respectively;
r. obtained from meta-analysis of 18/15 prospective cohort studies respectively;
s. obtained from meta-analysis of 6/5 prospective cohort studies respectively;
t. obtained from meta-analysis of 12/7/3 prospective cohort studies respectively;
u. obtained from meta-analysis of 9/6/3 prospective cohort studies respectively.

4.4.2. Plant-based protein sources

While plant-based proteins sometimes contain lesser concentrations of certain indispensable amino acids having some limiting amino acids, people who consume a varied vegetarian diet can get the same quality of protein and similar amounts of nitrogen as yielded by animal protein or a mixed diet [204].

Among the examined sources here, there are legumes, nuts and seeds and cereal grains.

4.4.2.1. Legumes

Health Outcomes	Unit of Intake	Total Legumes	Soybean
ALL-CAUSE MORTALITY	Highest vs Lowest	0.96 (0.94 - 1.00) [159][b]	/
	Dose-Response	0.96 (0.90 - 1.01) [159][b] 0.88 (0.73 - 1.03) [160]	/
TOTAL CVDs MORTALITY	Highest vs Lowest	/	/
	Dose-Response	/	/
CHD	Highest vs Lowest	0.91 (0.84 - 0.99) [163][e]	[205]
	Dose-Response	0.96 (0.92 - 1.01) [163][f] 0.88 (0.78 - 1.03)[160] 0.86 (0.78 - 0.94) [206][l]	/
STROKE	Highest vs Lowest	[163][e]	[205]
	Dose-Response	[163][f] [160] [206][l]	/
HTN/HBP	Highest vs Lowest	0.92 (0.86 - 0.98) [166][c]	/
	Dose-Response	0.98 (0.95 - 1.01) [166][c]	/
CHF	Highest vs Lowest	/	/
	Dose-Response	/	/
T2D	Highest vs Lowest	/	0.87 (0.74 - 1.01) [167]
	Dose-Response	[151][d] [160] [206][l]	/
OVERWEIGHT / OBESITY	Highest vs Lowest	*0.87 (0.81 - 0.94)* [168][n]	/
	Dose-Response	*0.88 (0.84 - 0.93)* [168][n]	/
MetS	Highest vs Lowest	/	/

	Dose-Response	/	/
TOTAL CANCER MORTALITY	Highest vs Lowest	/	[207][a]
	Dose-Response	/	/
TOTAL CANCER INCIDENCE	Highest vs Lowest	0.97 (0.93 - 1.01) [175]	0.90 (0.83 - 0.96) [207][a]
	Dose-Response	/	/
CRC	Highest vs Lowest	[169][m]	0.88 (0.76 - 1.02) [207][a]
	Dose-Response	[169][m] [160] [170][h]	/
BREAST CANCER	Highest vs Lowest	/	0.92 (0.84 - 1.00) [171][g] 0.96 (0.90 - 1.02) [207][a]
	Dose-Response	/	0.91 (0.84 - 1.00) [171][g] 0.89 (0.79 - 0.99) [208][jk]
GASTRIC CANCER	Highest vs Lowest	[173][i]	/
	Dose-Response	/	/

Table XIV - Association between total legumes and soybean intake and some major chronic diseases incidence / major diseases groups mortality (RR, 95% C.I.). The dose-response meta-analysis refers always to an additional serving of a food per day relative to the average intake of that food observed in a cohort study (50 g both for total legumes and soybean).

a. obtained from meta-analysis of 10/35/4/10 prospective cohort studies respectively;
b. obtained from meta-analysis of 17/6 prospective cohort studies respectively;
c. obtained from meta-analysis of 6/5 prospective cohort studies respectively;
d. obtained from meta-analysis of 12 prospective cohort studies;
e. obtained from meta-analysis of 10/6 prospective cohort studies respectively;
f. obtained from meta-analysis of 8/6 prospective cohort studies respectively;
g. obtained from meta-analysis of 10/7 prospective cohort studies respectively;
h. obtained from meta-analysis of 4 prospective cohort studies;
i. obtained from meta-analysis of 9 prospective cohort studies;
j. to be referred only to soy isoflavones;
k. obtained from meta-analysis of 14 prospective cohort studies;
l. obtained from meta-analysis of 5/5/2 prospective cohort studies respectively;
m. obtained from meta-analysis of 11/10 prospective cohort studies respectively;
n. obtained from meta-analysis of 1/1 prospective cohort studies respectively.

4.4.2.2. Nuts and Seeds

In this section nuts and seeds have been inserted together since they are two food sub-groups with similar nutritional properties, but if for nuts a good number of studies in line with the selection made for this thesis have been found, for seeds only any prospective cohort studies (and therefore also meta-analysis) have been found in the literature; instead, there are:

- studies that consider nuts and seeds as a single class; among them a prospective study on cohort AHS-2 showed how their high consumption (highest-lowest analysis) reduces by 40% the risk of CVDs mortality (C.I. 95% 0.42 - 0.86) [209].
- meta-analyses and systematic reviews of both observational and interventional studies that highlights a potential reduction in breast cancer risk associated with flaxseeds intake, mainly due to lignans, phenolic plant compounds highly contained in them [210–212].

Although Table XV with meta-analyses of prospective cohort studies data shows incomplete results or only nearly significant of a positive correlation compared to other protein sources and between the consumption of nuts and the risk of major chronic diseases considered, this protein source has known benefits on some of the major health outcomes.
Nuts contain many healthful components including unsaturated fatty acids (UFAs), dietary fiber, folate, antioxidant and vitamins (vitamin E and tocopherols), minerals (like magnesium and potassium), and phytochemicals (eg, flavonoids), which, «in isolation or as part of enriched foods, improve cardiometabolic risk factors» [206].
Many controlled trials (CTs) showed positive effects on CVDs risk factors [164] and the previously mentioned PREDIMED study showed the importance of nuts consumption in reducing the risk of cardiovascular events [117].

The recent meta-analysis of 5 prospective cohort studies of Nishi et al. [213] shows that adequate consumption of nuts has been positively associated with both primary and secondary endpoints; in addition to the significant **decrease in the risk of overweight/obesity incidence** (primary), they also reduce the risk of weight gain and increased waist circumference. The same study carried out a meta-analysis of many RCTs, showing that there is no weight gain associated with the not excessive consumption of nuts (below the maximum limit identified by the main nutritional guidelines). These data confirm some results previously published [214,215] and confirm how unfounded is the perception that the intake of this protein source is related to weight gain. This is probably due to their high content of fatty acids, but instead this element is one of their strengths: nuts are high density foods and this associates them with greater satiety; in addition one of their main components are the MUFAs - and in some cases the PUFAs, especially in walnuts - which through various mechanisms have an important role in improving CV health [216]. Concerning that, this paper showed that the intake of MUFAs and PUFAs of plant origin (especially the only omega-3 PUFA, ALA) has clear advantages over the consumption of SFAs of animal origin [216].

A specific analysis on alpha linolenic acid has been proposed by Visioli and Panaite [217] and the prospects of its role in the prevention of cardiovascular and metabolic diseases are really good. Future specific researchs will have to be focused on the conversion efficiency of ALA in EPA and DHA, the two omega-3 fatty acids that our body uses for various functions.

From the quantitative point of view the content of ALA in nuts, flax seeds and chia seeds is greater than that contained in all species of oily fish [218].

Health Outcomes	Unit of Intake	Nuts	Seeds
ALL-CAUSE MORTALITY	Highest vs Lowest	0.80 (0.74 - 0.86) [159][b]	/
	Dose-Response	0.76 (0.69 - 0.84) [159][b][160]	/
TOTAL CVDs MORTALITY	Highest vs Lowest	/	/
	Dose-Response	/	/
CHD	Highest vs Lowest	0.70 (0.57 - 0.82) [174][g] 0.80 (0.62 - 1.03) [163][e]	/
	Dose-Response	0.67 (0.43 - 1.05) [163][f][160] 0.76 (0.69 - 0.84) [206][i]	/
STROKE	Highest vs Lowest	0.94 (0.85 - 1.05) [163][e]	/
	Dose-Response	[163][f] [160] [206][i]	/
HBP	Highest vs Lowest	0.85 (0.78 - 0.92) [166][d]	/
	Dose-Response	[166][d]	/
CHF	Highest vs Lowest	[163][e]	/
	Dose-Response	1.09 (0.97 - 1.22) [163][f]	/
T2D	Highest vs Lowest	/	/
	Dose-Response	[151][c] 0.79 (0.70 - 0.90) [160] 0.87 (0.81 - 0.94) [206][i]	/
OVERWEIGHT / OBESITY	Highest vs Lowest	0.91 (0.80 - 1.03) [168][a]	/
	Dose-Response	0.93 (0.88 - 0.98) [213] [168][a]	/
MetS	Highest vs Lowest	/	/
	Dose-Response	/	/

TOTAL CANCER MORTALITY	Highest vs Lowest	/	/
	Dose-Response	/	/
TOTAL CANCER INCIDENCE	Highest vs Lowest	0.97 (0.94 - 1.00) [175]	/
	Dose-Response	/	/
CRC	Highest vs Lowest	0.96 (0.90 - 1.02) [169][j]	/
	Dose-Response	[169][j] [160]	/
BREAST CANCER	Highest vs Lowest	[171][g]	/
	Dose-Response	[171][g]	/
GASTRIC CANCER	Highest vs Lowest	/	/
	Dose-Response	/	/

Table XV - Association between nuts and seeds intake and some major chronic diseases incidence / major diseases groups mortality (RR, 95% C.I.). The dose-response meta-analysis refers always to an additional serving of a food per day relative to the average intake of that food observed in a cohort study (28 g for nuts and seeds).

a. obtained from meta-analysis of 3/3 prospective cohort studies respectively;
b. obtained from meta-analysis of 16 prospective cohort studies;
c. obtained from meta-analysis of 7 prospective cohort studies;
d. obtained from meta-analysis of 4 prospective cohort studies;
e. obtained from meta-analysis of 4/6/3 prospective cohort studies respectively;
f. obtained from meta-analysis of 4/6/2 prospective cohort studies respectively;
g. obtained from meta-analysis of 3 prospective cohort studies;
h. obtained from meta-analysis of 5 prospective cohort studies;
i. obtained from meta-analysis of 4/6/2 prospective cohort studies respectively and based on intake on 4 servings/week of nuts;
j. obtained from meta-analysis of 6/4 prospective cohort studies respectively.

4.4.2.3. Cereal grains

Cereal grains, despite being the one with the mean lowest protein content among those selected, were also considered among plant-based protein sources; this choice has been done because it is the main source of proteins in some low- and middle-income countries and mainly because whole grains are the source that shows the best results regarding health outcomes chosen. This last element is a further demonstration of the fact that the beneficial effects of protein sources are not only related to their protein content but to all the nutrients contained in them.

One of the most noteworthy inverse associations in Table XVI is the reduction of T2D risk: two recent umbrella reviews confirmed the results of 12 and 2 previous meta-analyses respectively [151][157] and showed (the first one with high quality evidence) a significant reduction in the risk of T2D (13%) associated with a serving per day increase of whole grains.

Health Outcomes	Unit of Intake	Whole grains	Refined grains
ALL-CAUSE MORTALITY	Highest vs Lowest	0.88 (0.84 - 0.92) [159][b]	[159][i]
	Dose-Response	0.92 (0.89 - 0.95) [159][b][160]	0.99 (0.97 - 1.01) [159][i][160]
TOTAL CVDs MORTALITY	Highest vs Lowest	0.79 (0.73 - 0.85) [164][jk]	/
	Dose-Response	/	/
CHD	Highest vs Lowest	0.81 (0.75 - 0.86) [174][k] 0.85 (0.81 - 0.90) [163][c]	1.11 (0.99 - 1.25) [163][g]
	Dose-Response	0.95 (0.92 - 0.98) [163][f][160]	1.01 (0.99 - 1.04) [163][h][160]
STROKE	Highest vs Lowest	0.83 (0.68 - 1.02) [164][jk] 0.91 (0.82 - 1.02) [163][c]	[163][g]
	Dose-Response	0.99 (0.95 - 1.03) [163][f][160]	[163][h][160]
HTN/HBP	Highest vs Lowest	0.86 (0.79 - 0.93) [166][d]	0.95 (0.88 - 1.03) [166][e]
	Dose-Response	0.92 (0.87 - 0.98) [166][d]	[166][e]
CHF	Highest vs Lowest	0.91 (0.85 - 0.97) [163][c]	[163][g]
	Dose-Response	0.96 (0.95 - 0.97) [163][f]	[163][h]
T2D	Highest vs Lowest	/	/
	Dose-Response	0.79 (0.72 - 0.87) [164][kl] 0.87 (0.82 - 0.93) [151] 0.88 (0.83 - 0.93) [160]	0.98 (0.96 - 1.01) [160]
OVERWEIGHT / OBESITY	Highest vs Lowest	0.85 (0.79 - 0.91) [168][a]	[168][a]
	Dose-Response	0.93 (0.89 - 0.96) [168][a]	1.05 (1.00 - 1.10) [168][a]
MetS	Highest vs Lowest	/	/
	Dose-Response	/	/

TOTAL CANCER MORTALITY	Highest vs Lowest	/	/
	Dose-Response	/	/
TOTAL CANCER INCIDENCE	Highest vs Lowest	0.93 (0.88 - 0.98) [175]	/
	Dose-Response	/	/
CRC	Highest vs Lowest	0.88 (0.83 - 0.94) [169][p]	[169][p]
	Dose-Response	0.95 (0.93 - 0.97) [169][p][160] 0.83 (0.79 - 0.89) [170][m]	/
BREAST CANCER	Highest vs Lowest	/	/
	Dose-Response	/	/
GASTRIC CANCER	Highest vs Lowest	/	/
	Dose-Response	0.83 (0.78 - 0.89) [219][no]	/

Table XVI - Association between whole and refined grains (cereal grains) intake and some major chronic diseases incidence / major diseases groups mortality (RR, 95% C.I.). The dose-response meta-analysis refers always to an additional serving of a food per day relative to the average intake of that food observed in a cohort study (30 g for whole and refined grains).

a. obtained from meta-analysis of 5/3/3/3 prospective cohort studies respectively;
b. obtained from meta-analysis of 19/11 prospective cohort studies respectively;
c. obtained from meta-analysis of 7/7/5 prospective cohort studies respectively;
d. obtained from meta-analysis of 4 prospective cohort studies;
e. obtained from meta-analysis of 3 prospective cohort studies;
f. obtained from meta-analysis of 5/4/2 prospective cohort studies respectively;
g. obtained from meta-analysis of 5/6/1 prospective cohort studies respectively;
h. obtained from meta-analysis of 4/4/1 prospective cohort studies respectively;
i. obtained from meta-analysis of 4/4 prospective cohort studies respectively;
j. 2.5 vs 0.2 servings/day;
k. obtained from meta-analysis of 11/7/4/6 prospective cohort studies respectively;
l. each 2 servings/day;
m. obtained from meta-analysis of 5/6/1 prospective cohort studies respectively;
n. obtained from meta-analysis of 6 prospective cohort studies;
o. for an increment of three servings daily;
p. obtained from meta-analysis of 10/2/9 prospective cohort studies respectively.

4.4.3. PROTEIN SOURCES COMPARISON

Comparing the two macrocategories of protein sources has a different effectiveness depending on whether we talk about health outcomes or environmental impact:

- data on main chronic diseases' mortality and incidence risks associated with the consumption of one or the other category of protein sources are less significant than the data reported for individual protein sources; «generalizing the health benefits of plant protein over animal protein is difficult due to trial inconsistencies and limited control of variables» [220]. Therefore the protein sources dichotomization in animal and plant-based ones leads to less valid results, which is not in contrast to the widely demonstrated benefits associated with the consumption of plant-based protein sources [221]; simply, it suggests that studies and analyses must be carried out primarily by focusing research on individual protein sources and not on the whole category.
- For the environmental impact assessment, however, this dichotomy is not associated with a lesser results significance because there is a big difference between two categories in terms of total environmental pressure.

4.4.3.1. Health outcomes

➢ Mortality

Data on all causes mortality and CVDs mortality related to the different consumption of the two protein sources categories - reported in Table XVII from the wide analysis of two of the largest US cohorts ("Nurses Health Study" and "Health Professionals Follow-up Study") by Song et al. [222] - were split into two groups of participants. The data were statistically significant (inverse association) for plant-based sources and nearly significant for animal ones only among those with at least one unhealthy lifestyle factor (smoking, alcohol consumption, physical inactivity and overweight/obesity were considered):

- increased mortality due to larger intake of animal protein sources, 1.03 (C.I. 95% 0.99 - 1.07) for all-causes and 1.08 (C.I. 95% 1.00 - 1.17) for CVDs;
- reduction of mortality related to higher consumption of plant-based ones, 0.90 (0.85 - 0.95) for all-causes and 0.88 (0.79 - 0.98) for CVDs.

The same study confirmed, with evidence of higher quality and greater completeness, the results of a previous paper on the reduction of CVDs mortality associated with the substitution of various animal protein sources with plant-based ones [223]; moreover the HRs of other causes of death related to this protein source **replacement for a 3% total energy** were highlighted. An overview of the results is visible in Figure n [222].

A subsequent 2019 systematic review by Naghshi et al. [224] confirmed almost entirely the data obtained from the previous study, both those related to the three mortality groups for the two different categories of protein sources (Table XVIII) and those for the **substitution** of animal protein sources with plant based ones for 3% of the total energy ingested.

The **substitution of animal protein sources with plant-based protein sources** is another method by which associations between dietary protein intakes and health outcomes can be evaluated; the use of "highest vs lowest" and "dose-response" analyses is not so effective when comparing two macrogroups that contain foods with different characteristics to each other. There are few studies in scientific literature that carry out such analyses and for this reason Tables XVII and XIX present fewer data than those on individual protein sources.

Health Outcomes	ANIMAL protein sources[a]	PLANT-BASED protein sources[b]
ALL-CAUSE MORTALITY	[222][ab] [224][d]	0.90 (0.86 - 0.95)[222][ac] 0.92 (0.87 - 0.97)[224][e]
TOTAL CVDs MORTALITY	1.08 (1.01 - 1.16)[222][ab] [224][d]	0.88 (0.80 - 0.97)[222][ac] 0.88 (0.80 - 0.96)[224][e]
TOTAL CANCER MORTALITY	[222][ab] [224][d]	[222][ac] [224][e]

Table XVII - Association between animal and plant-based protein intake and all-cause, CVDs and cancer-related mortality risks.

a. Multivariable-adjusted HR (95% C.I.);
b. Highest vs lowest intake category of animal protein sources measured as % of total diet energy (thus "per 10% energy increment");
c. Highest vs lowest intake category of plant-based protein sources measured as % of total diet energy (thus "per 3% energy increment");
d. Highest vs lowest intake of animal protein sources through the computation of estimates by using the fixed effects model and Orsini method; examined in 11/8/9 prospective cohort studies for all cause, CVDs and cancer mortality respectively;
e. Highest vs lowest intake of plant-based protein sources through the computation of estimates by using the fixed effects model and Orsini method; examined in 13/10/9 prospective cohort studies for all cause, CVDs and cancer mortality respectively.

Within the systematic analysis of the GBD Study 2017 cited above [144], mortality and days related to dietary risks have been extensively analyzed: as regards Western Europe (the area in which Italy is included), it emerged that about 40-45% of both mortality and DALYs is related to imbalances in the intake of protein sources (considering whole grains as a plant-based protein source). One consideration to be made in the light of the results of this analysis is that negative health outcomes (considered mortality and DALYs) linked to a too **low consumption of plant-based protein sources** are much greater than that of excessive animal protein sources intake; this should be an important public health message to encourage the transition to increased consumption of plant-based protein sources.

Animal Protein Source by Cause of Death	HR (95% CI)
All cause	
Processed red meat	0.66 (0.59-0.75)
Unprocessed red meat	0.88 (0.84-0.92)
Poultry	0.94 (0.90-0.99)
Fish	0.94 (0.89-0.99)
Egg	0.81 (0.75-0.88)
Dairy	0.92 (0.87-0.96)
CVD	
Processed red meat	0.61 (0.48-0.78)
Unprocessed red meat	0.83 (0.76-0.91)
Poultry	0.91 (0.83-1.00)
Fish	0.88 (0.80- 0.97)
Egg	0.88 (0.75-1.04)
Dairy	0.89 (0.80-0.98)
Cancer	
Processed red meat	0.86 (0.71-1.04)
Unprocessed red meat	0.96 (0.89-1.03)
Poultry	0.99 (0.91-1.06)
Fish	0.98 (0.91-1.06)
Egg	0.83 (0.73-0.93)
Dairy	1.00 (0.93-1.09)
Other	
Processed red meat	0.55 (0.46-0.67)
Unprocessed red meat	0.84 (0.78-0.90)
Poultry	0.93 (0.86-1.00)
Fish	0.94 (0.87-1.01)
Egg	0.76 (0.67-0.86)
Dairy	0.86 (0.80-0.93)

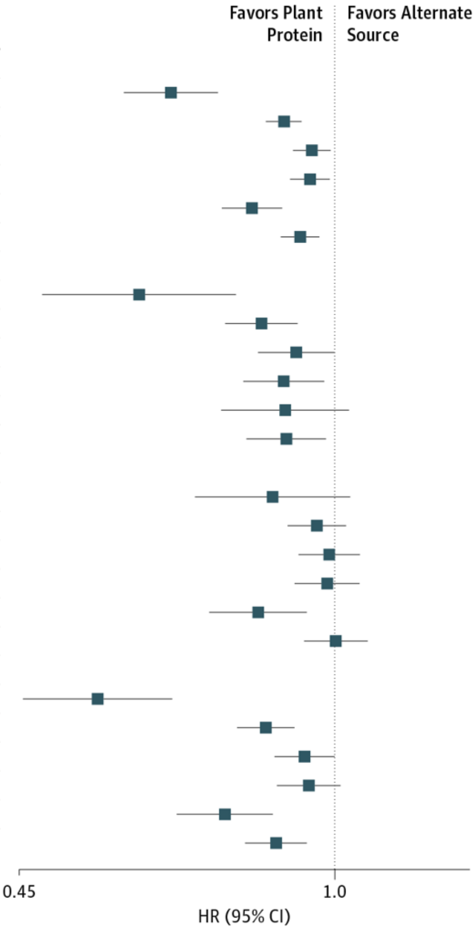


Table XVIII - Association between different forms of mortality and the replacement of various animal protein sources with plant-based protein sources

- <u>Incidence:</u>

HEALTH OUTCOMES		ANIMAL protein sources[a]	PLANT-BASED protein sources[b]
CHD	Highest vs Lowest	[225][b]	0.91 (0.80 - 1.02)[225][b]
	Dose-Response[a]	/	/
STROKE	Highest vs Lowest	/	/
	Dose-Response[a]	/	/
HBP	Highest vs Lowest	[225][c]	0.87 (0.74 - 1.01)[225][c]
	Dose-Response[a]	/	/
T2D	Highest vs Lowest	1.14 (1.09 - 1.19)[167] 1.13 (1.06 - 1.21)[226]	[167] 0.91 (0.84 - 0.98)[226]
	Dose-Response[a]	1.12 (1.08 - 1.17)[151]	0.87 (0.74 - 1.01)[151]
OVERWEIGHT / OBESITY	Highest vs Lowest	/	/
	Dose-Response[a]	/	/
TOTAL CANCER INCIDENCE	Highest vs Lowest	/	/
	Dose-Response[a]	/	/
CRC	Highest vs Lowest	/	/
	Dose-Response	EPIC ITALY [227]	EPIC ITALY [227]

Table XIX - Association between animal and plant-based protein intake and some major chronic diseases incidence / major diseases groups mortality (RR, 95% C.I.)

[a.] intake increment per 5% energy/day;
[b.] data obtained from meta-analysis of 5/4 prospective cohort studies respectively;
[c.] data obtained from meta-analysis of 5 prospective cohort studies.

The report by Mozaffarian, Appel and Van Horn [164] collects a series of prospective cohort and RCTs on clinical CV endpoints (CHD, stroke or T2D) and the main CV risk factors associated with the intake of specific food groups. Considering only the evaluated protein sources, it can be shown that the consumption of nuts and whole grains, among the plant-based ones, and of fish and dairy products, among the animal sources, are associated with a reduction in CV risks and in the incidence of these above-mentioned clinical conditions, including with substantial evidence; on the contrary, the consumption of unprocessed red meat and processed meat increases the risk of cardiovascular disease in almost all studies, other than the zero effect of unprocessed red meat found with low evidence in prospective cohort studies. Further studies have been carried out over the last decade, but more are needed to obtain cleaner and more reliable data.

Within the analysis for each protein source, no specific data were reported on the association with **neurodegenerative diseases**, which was instead included in the previous evaluation of health benefits for the Mediterranean diet. Referring precisely to dietary patterns, a major study in 2015 showed that there is a reduction in the incidence of Alzheimer's associated with all 3 patterns considered in the paper: if for Mediterranean and DASH diets the reduction is significant only by comparing "highest vs lowest" adherence diet scores (in tertiles), for the MIND diet it is also significant for the intermediate tertile (moderate adherence) [228,229].
This dietary pattern, as well as for a greater intake of plant-based foods and of «phytonutrient-rich foods, such as berries and green leafy vegetables, which have been demonstrated to have neuroprotective benefits» [230], is also characterized by a high consumption of fish as an important source of omega-3 fatty acids.

Seen and considered their demonstrated neuroprotective effects [179], it is plausible to propose a role of fish as a suitable protein source for the prevention of neurodegenerative diseases, in addition to the protective effect for the main cardiovascular diseases (CHD, stroke and CHF of all) already highlighted in the dedicated section.

Already in 2002, the final paper of a French cohort study showed a significant inverse association between dementia (classified at the time with the obsolete DSM-III-R) and the consumption of at least one serving per week of fish; the identified risk reduction was 34% (HR 0.64, 95% C.I. 0.47 - 0.93)[231]. This data, although limited to a single court, dated and not of high quality, has been included in a more recent review that associates various nutritional elements to the risk of cognitive impairment [232]; among protein sources, fish is the one with the largest number of observational studies that demonstrates a protective effect (5 out of 7).

Another protein source evaluated in the same review that may have a potential role in this clinical area is nuts since it contains another omega-3 PUFA previously named, alpha linolenic acid (ALA); although the studies reported here that showed a protective effect were only two small trials in which the consumption of olive oil was not evaluated separately, in the scientific literature there are several papers that show the beneficial effects of this omega-3 fatty acid [233,234] .

4.4.3.2. Environmental impact

As previously mentioned, it is also important to consider the environmental impact that protein sources have, in a planetary health perspective. In addition to the GHG emissions along the entire Life Cycle of the products (carbon footprint), the environmental impact in the food sector also refers to the consumption of natural or artificial resources and the consequences on the ecosystem: therefore, the measurements of water and soil consumed and that of the amount of fertilizers and energy needed for production, associated with the estimation of the use of potentially harmful substances (such as pesticides and drugs) and the loss of biodiversity as an index of damage to the natural environment, can return a fairly clear idea of the "environmental cost" of a food or group of foods. For a more detailed description of the various types of footprint, see the paper by Vanham et al. [28].

As for the strictly health field, also in this case it is possible to carry out quantitative analysis through multiple units of measurement; thus the data can also slightly change depending on the functional reference. Taking the example of the carbon footprint, in the table were inserted data only in kg CO_2-eq/kg food (or food group); but in the literature there are studies that refer to the standard units of food (g or kg CO_2-eq/serving), the caloric intake (g or kg CO_2-eq/kcal) or only at the amount of protein (g or kg CO_2-eq/g prot)[77]. The lack of uniformity certainly complicates the assessment of these various environmental impacts; relying on the consideration already mentioned that protein sources are not only made up of proteins and maintaining a linearity with the analyses presented in the previous section, the first two units of measurement were chosen for reference, thus referring to the food weight (net or in preselected servings).

In any case, Table XX clearly shows a more dichotomous trend between animal protein sources and plant-based protein sources than the previous analysis of health outcomes.

ENVIRONMENTAL FOOTPRINTS		Units of measurement	RED MEAT	POULTRY	FISH	EGGS
CARBON FOOTPRINT[a]		kg CO_2-eq/kg (food)	25.58 / 26.61 [235] [a] 5.77[b] [235]	3.65 [235]	3.49 [235]	3.46 [235]
WATER FOOTPRINT (TOTAL)		m^3/ton (food)	8761 / 15415 [236] [a] 5988 [236] [b]	4325 [236]	1974 [240]	3265 [236]
LAND FOOTPRINT		m^2/kg (food)	308.58 / 542.82 [237][a] 19.53 [237] [b]	19.22 [237]	0 - 10 [241]	17.83 [237]
CUMULATIVE ENERGY DEMAND [f]		MJ/kg (food)	37 - 82 [238] [a] 25 - 31 [238] [b]	18 - 33 [238]	/ [c]	12 - 17 [238]
USE OF CHEMICALS	FERTILIZERS (N Footprint and P Footprint)	10 g N/serving	30.01 / 30.27[a] [82] 56.68[b] [82] [b]	55.22 [82]	18.46 [82]	25.61 [82]
		10 g P/serving	5.43 / 5.89[a] [82] 9.75 [82] [b]	9.92 [82]	3.98 [82]	4.40 [82]
	PESTICIDES	/	/	/	/	/
BIODIVERSITY FOOTPRINT (Biodiversity Loss)		/ [h]	[242]	[242]	[239]	[239]

ENVIRONMENTAL FOOTPRINTS		Units of measurement	DAIRY PRODUCTS	LEGUMES	NUTS	CEREAL GRAINS
CARBON FOOTPRINT[a]		kg CO2-eq/ kg food	8.55 / 9.25 [235] [d] 1.29 [235] / 2.59 [244] [e]	1.20 [235]	0.51 [235]	0.50 [235]
WATER FOOTPRINT		m^3/ton	5553 / 6760 [236] [d] 1020 [236] / 1485 [244][e]	9063 [236]	4055 [236]	1644 [236]
LAND FOOTPRINT		m^2/kg	60.27 / 65.20 [237] [d] 9.09 [237] / 12 [244] [e]	6.96 [237]	11.19 [237]	2.81 [237]
CUMULATIVE ENERGY DEMAND [f]		MJ/kg (food)	38 [238] [d] 3.0 - 3.1 [238] [e]	2.9 - 7.4 [238]	/	1.7 - 9.6 [238]
USE OF CHEMICALS	FERTILIZERS (N Footprint and P Footprint)	10 g N/serving	15.18 [82]	0 [82]	4.28 [82]	/
		10 g P/serving	3.79 [82]	0 [82]	0.63 [82]	/
	PESTICIDES	/	/	/	/	/
BIODIVERSITY FOOTPRINT (Biodiversity Loss)		/ [h]	[239]	[239]	[239]	[243] [i]

Table XX – Environmental footprints of various protein sources

a. referred to beaf;
b. referred to pork;
c. not reported due to absence of total fish data
d. referred to cheese/butter (dairy products with higher fat content);
e. referred to milk/yogurt (dairy products with lower fat content);
f. ranges of data have been included for this footprint because in the study from which they were extrapolated (study among the most recent and authoritative) were considered only specific foods and not the food groups mentioned in this Table;
g. For this category a sum of the data reported on the specific foods was made;
h. Red: strong negative impact; Orange: moderate negative impact; Yellow: neutral; Green: positive impact. Scale made taking as reference specific table of the HCWH report "Redefning protein: adjusting diets to impact public health and conserve resources" [239];
i. must be differentiated whole grains from refined ones: the impact of the former is decidedly less.

It has been demonstrated that protein efficiency is much higher for foods of plant-based origin than those of animal origin [245]; the two groups of protein sources with the greatest overall environmental impact are meat and dairy products, mainly because of livestock production [246,247].
To give an example of how much the "environmental pressure" of animal protein sources is greater than plant-based ones, a quote with some data from a paper by Sabatè et al. [248] has been reported here comparing different environmental footprints associated with kidney beans and various animal sources: «to produce 1 kg of protein from kidney beans required approximately eighteen times less land, ten times less water, nine times less fuel, twelve times less fertilizer and ten times less pesticide in comparison to producing 1 kg of protein from beef. Compared with producing 1 kg of protein from chicken and eggs, beef generated five to six times more waste (manure) to produce 1 kg of protein. » [248].

An element that stands out is that legumes have a zero impact on footprints related to the use of fertilizers (N footprint and P footprint); moreover, this is the only protein source that has a positive impact on the biodiversity loss since it leads to an increase in so-called agrobiodiversity. These two features are linked to their ability to fix nitrogen and stimulate microbial activity in soil respectively.

As for the pesiticids, although a factor of fundamental importance, we have not found studies that could be included in this type of table [239]. Another relevant element for planetary health that could be included in “use of chemicals” factor is the use of antibiotics associated with the production of these protein sources; one of the main public health issues in the coming decades will be Antimicrobial Resistance (AMR) [249].

Finally, it is necessary to stress how these different environmental impacts also - directly or indirectly - cause multiple health consequences with mechanisms and processes that will not be explored here, given the high complexity of the subject.

5. CONCLUSIONS

The data discussed in this thesis show that - in the field of nutrition - it is always essential to distinguish the level of analysis considered.
The evaluation of dietary patterns, which includes various foods and their effects at molecular level on macro- and micronutrients cannot directly compared food items with each other, but must be instead integrated: for example, to say that vegetarian diets have better average health outcomes than omnivorous diets, is not the same as stating that the consumption of a given plant-based food is more associated with a considered clinical endpoint or a greater number of beneficial effects than a food of animal source. The complexity and the inter-individual variability of human nutrition does not allow this kind of generalizations.

As for dietary patterns, several prospective cohort studies, some of their meta-analyses and also an umbrella review of various meta-analyses, have shown that vegetarian patterns are better than omnivorous diets in terms some major metabolic diseases and CVDs. At the same time, no differences have been demonstrated between the two types of diets in terms of muscle and bone health, and there are some clinical conditions to which one is exposed with greater risk following a vegetarian diet (Vitamin B12 deficiency and related reduced functioning of one-carbon metabolism, zinc deficiency and hypoferritinemia).
It has also been seen that a well-executed Mediterranean diet (with a good level good level of adherence measured with a proper score) is comparable to a healthy vegetarian diet in terms of health outcomes. The real Mediterranean diet, used as a reference by practically all international guidelines, could be defined as a *de facto* flexitarian (or semi-vegetarian) diet and therefore it is easier to understand how the benefits are comparable. On the contrary, current omnivorous diets, especially in high-income countries, deviate from this model and are thus associated with greater risks. As a result of this scientific evidence, most international nutritional guidelines reaffirm the importance of a transition to a more plant-based diet.

But if at the level of dietary patterns there are differences, the comparison between the two macrocategories of protein sources does not return such a clear picture. The most significant differences are noted in the comparison between all-cause, CVDs and cancer-related mortality risks and protein sources intake; if both groups of protein sources have non-significant values for cancer mortality, plant-based protein sources have shown an inverse association with all-cause and CVDs mortality, for which animal ones have a non-significant association and a positive association respectively. More generally, it has been shown that plant-based protein sources are associated with longevity.

On the other hand, comparing the association between the consumption of a protein source and the risk of morbidity/mortality of the main chronic diseases, emerges that whole grains, within the category of cereal grains, are the food source with the greatest number of published inverse associations: their intake can be defined as protective, especially for CVDs for which numerous data have been reported.

Compared to the latter, however, refined cereals have a significant lack of association and this would seem to be due to their processing, since the composition in terms of macronutrients and protein quality are practically identical to those of whole grains.

In addition to this food category, other protein sources with a similar trend are dairy products and fish as a whole ("total dairy products" and "total fish") and nuts. The number of published inverse associations for the dairy group is mainly due to products with a lower content of saturated fatty acids of animal origin: although the data we report in Table XIII are scant, it is noted that yogurt and skin milk have a better performance than whole milk and this could be extended to other foods of this macrogroup not considered in this analysis.

Although they are an animal protein source and a plant-based one, respectively, fish and nuts show a similar trend, decreasing the risk especially for CVDs: this reinforces the important role of omega-3 PUFAs

since they are the main food sources (EPA and DHA in fish and ALA in nuts).
The other foods reviewed so far have no clear positive association with the health risks analyzed, but only some conflicting data emerge; on the contrary, the intake of certain types of meat, especially red and processed meat, are often associated with increases in the risk of mortality and incidence of major chronic diseases. Also in this case, as for cereals, the differences between red meat and processed meat are to be attributed to the increased processing of food.
The two remaining protein sources - eggs and legumes - show more ambivalent data, although they are not significantly associated with any increased risk of incidence or mortality. This may be due to the reduced presence of prospective cohort studies that consider these two sources and therefore further research becomes even more necessary.

While the overall picture is not entirely clear, it can be inferred that every clinical condition potentially requires an *ad hoc* prescription of some protein sources compared to others, as well as for other food macrocategories.

What emerged from this thesis does not claim to be neither a complete and exhaustive analysis, nor a tool already usable in the clinical field in its current form; the study can be considered as an attempt to give an overview of the effects of the main protein sources present in the Mediterranean diet.
It should be noted, however, that the considerable difference between different geographical areas in terms of dietary habits can affect the quality of these conclusions, which is why it is always good to keep this potential bias in mind in order to carry out quality studies.

With a view to planetary health, it is necessary to take into account the overall "environmental pressure" of food production also in nutrition claims; for this reason, a synthesis of the main environmental impact factors of the various protein sources has been carried out. It can be noted that generally animal protein sources have a greater impact than plant-based ones and therefore a comparison between the two macrocategories is more appropriate than the strictly nutritional field. While several multidisciplinary studies have extensively analyzed the issue of sustainable nutrition, there is lack of tools in the medical-health field that allow us to apply this vision of global health also in the nutritional prescription for patients.

Along the attempt to define protein quality with a new approach that also includes environmental effects, this work ends by showing in Figures 16 and 17 the two tools proposed by Clark et al. [160], designed to simultaneously have a vision of both the medical-nutritional and environmental impact of the various food groups.

In conclusion, the data discussed in this thesis allow us to conclude that vegetable protein consumption is associated with better health outcomes (namely, on the cardiovascular system) than animal-based product use. As far as mechanisms of action are concerned, there are currently no data to explain these effects and much more research is needed. However, the irrefutable healthier activities of vegetable protein dovetails with their lower environmental impact, which must be taken into account when we design optimal diets. The health of the planet cannot be disjointed from the health of the human being.

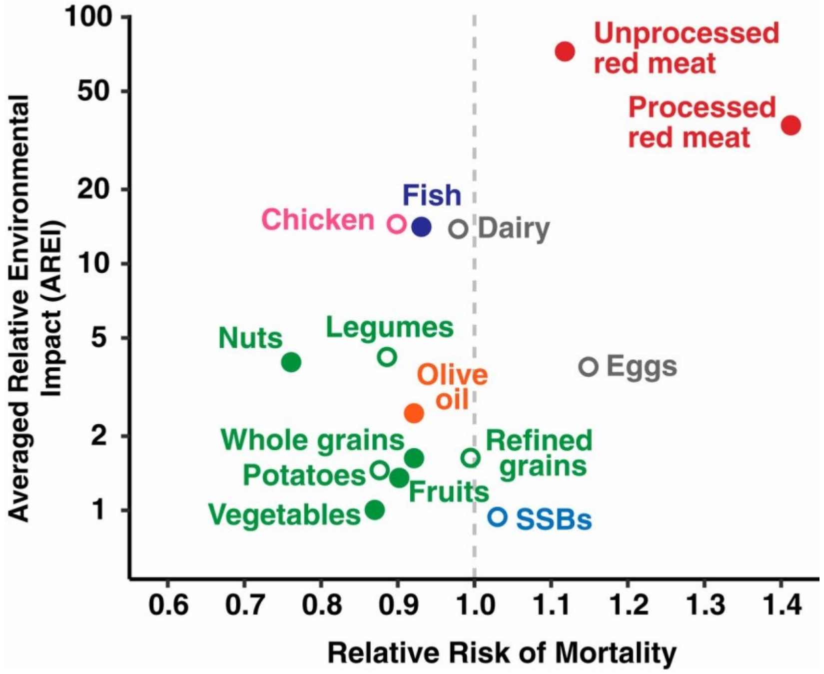


Figure 16 - Association between a food group’s impact on mortality and its AREI

Future research will clarify the putative health effects of vegetable proteins when compared with animal ones and will foster better agronomic practice and influence public health in a direction that will benefit both the planet and its inhabitants.

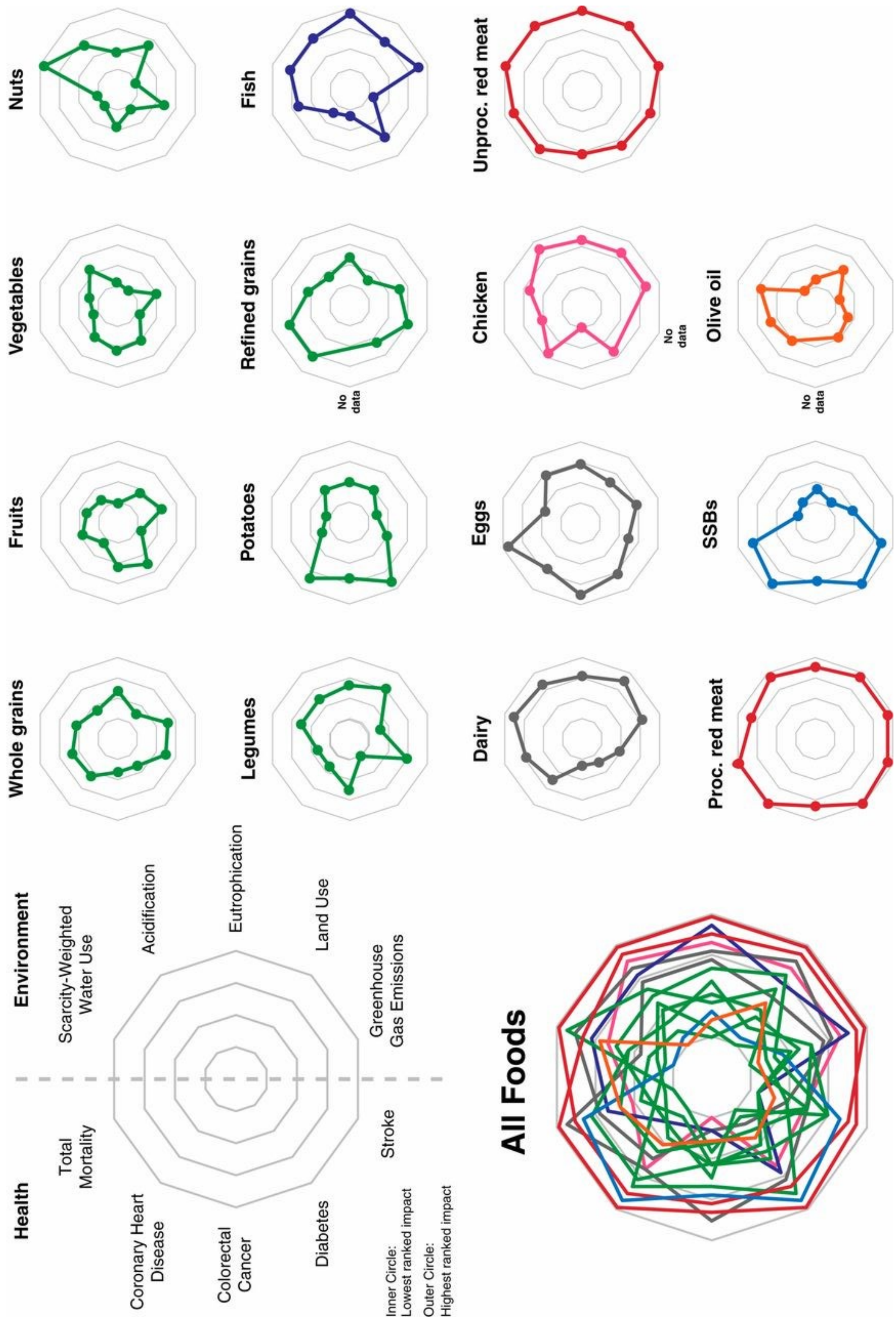


Figure 17 - Radar plots of rank-ordered health and environmental impacts per serving of food consumed per day

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