# PUBLIC HEALTH NUTRITION: ASSESSING EVIDENCE TO DETERMINE POLICY AND PRACTICE

EDITED BY: Alessandra Lafranconi, Sumantra Ray and Giuseppe Grosso
PUBLISHED IN: Frontiers in Public Health and Frontiers in Nutrition

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88945-856-1
DOI 10.3389/978-2-88945-856-1

## About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

## Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

## Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

## What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

# PUBLIC HEALTH NUTRITION: ASSESSING EVIDENCE TO DETERMINE POLICY AND PRACTICE

Topic Editors:
**Alessandra Lafranconi,** Department of International Health, FHML, CAPHRI, Maastricht University, Netherlands
**Sumantra Ray,** NNEdPro Global Centre for Nutrition and Health, United Kingdom
**Giuseppe Grosso,** NNEdPro Global Centre for Nutrition and Health, United Kingdom

**Citation:** Lafranconi, A., Ray, S., Grosso, G., eds. (2019). Public Health Nutrition: Assessing Evidence to Determine Policy and Practice. Lausanne: Frontiers Media. doi: 10.3389/978-2-88945-856-1

# Table of Contents


04 ***Editorial: Public Health Nutrition: Assessing Evidence to Determine Policy and Practice***
Alessandra Lafranconi, Sumantra Ray and Giuseppe Grosso

06 ***A Review of the Mycotoxin Enniatin B***
Alessandra Prosperini, Houda Berrada, María José Ruiz, Francesca Caloni, Teresa Coccini, Leon J. Spicer, Maria Chiara Perego and Alessandra Lafranconi

17 ***Dietary Practice and Nutritional Status of Tuberculosis Patients in Pokhara: A Cross Sectional Study***
Lal M. Gurung, Laxman D. Bhatt, Isha Karmacharya and Dipendra K. Yadav

23 ***Environmental Impacts of Plant-Based Diets: How Does Organic Food Consumption Contribute to Environmental Sustainability?***
Camille Lacour, Louise Seconda, Benjamin Allès, Serge Hercberg, Brigitte Langevin, Philippe Pointereau, Denis Lairon, Julia Baudry and Emmanuelle Kesse-Guyot

36 ***Perspectives From the Third International Summit on Medical Nutrition Education and Research***
Jennifer Jean Crowley, Celia Laur, Harrison David Edward Carter, Glenys Jones and Sumantra Ray

44 ***Hypertension in Children: Role of Obesity, Simple Carbohydrates, and Uric Acid***
Antonina Orlando, Emanuela Cazzaniga, Marco Giussani, Paola Palestini and Simonetta Genovesi

51 ***Survival Mediterranean Style: Lifestyle Changes to Improve the Health of the US Fire Service***
Maria Korre, Mercedes Sotos-Prieto and Stefanos N. Kales

58 ***The Cambridge Intensive Weight Management Programme Appears to Promote Weight Loss and Reduce the Need for Bariatric Surgery in Obese Adults***
Rajna Golubic, Celia Laur, Megan Kelsey, Alana Livesy, Joanna Hoensch, Adrian Park and Sumantra Ray

frontiers in Public Health

EDITORIAL
published: 14 February 2019
doi: 10.3389/fpubh.2019.00021

# Editorial: Public Health Nutrition: Assessing Evidence to Determine Policy and Practice

*Alessandra Lafranconi*[1,2]*, *Sumantra Ray*[3] and *Giuseppe Grosso*[3]

[1] School of Medicine, Università degli Studi di Milano Bicocca, Milan, Italy, [2] Department of International Health, Care and Public Health Research Institute (CAPHRI), Faculty of Health, Medicine and Life Sciences (FHML), Maastricht University, Maastricht, Netherlands, [3] NNEdPro Global Centre for Nutrition and Health, Cambridge, United Kingdom

**Keywords: food safety, food security, environmental factors, human nutrition and health, education tools, children, weight loss intervention, workplace health promotion**

## Editorial on the Research Topic

## Public Health Nutrition: Assessing Evidence to Determine Policy and Practice

The concept of public health nutrition embraces many diverse areas, spanning from food safety, and food security, to environmental sustainability as well as human nutrition and health.

The present collection includes papers that touch upon all the aforementioned areas, providing a fascinating and variegated scenario of what public health nutrition stands for and how it may at times be overlooked in the twenty-first century.

With regards to **food safety**, Prosperini et al. present a review on a mycotoxin, Enniatin, and its specific profile of toxicology. The need of such review lies at the interface between science and policy, and attempts to respond to a specific mandate, whereby the European Commission asked the European Food Safety Authority (EFSA) for a scientific opinion, to quantify the risks related to acute and chronic exposure to Enniatin. Whilst the answer was unambiguous for acute toxicity (i.e., such toxins do not represent concerns for human health), there were no conclusions about chronic toxicity, mainly because of the complexity of performing a complete risk assessment for dietary exposure to the toxin itself. Moreover, the authors touch on some recent findings on carcinogenesis: Enniatin has been found to have anti-cancer actions, both *in vitro* and *in vivo*, at multiple cellular levels.

**Food security issues**, which are often dealt with at the national level, have different distributions in developing and developed countries (1); nevertheless, food insecurity constantly affects the most vulnerable classes of any given population, typically the children and the elderly. Gurung et al. focus on children affected by tuberculosis (TB) in Nepal, thus analyzing the conditions of an extremely vulnerable population segment. The authors performed a cross-sectional descriptive study to assess the dietary intake and nutritional status of children affected by TB, and found that about one-fifth of them did not consume a sufficient amount of calories, compared to the recommended daily average. Acting in a vicious circle, undernutrition increases the risk of TB progression into active disease, thus leading to further weight loss. Such data call for dietary assessments and nutritional treatments in children affected by TB.

According to the concept of planetary health (2), food security and **environmental factors**, such as greenhouse gas emissions (GHGEs), water depletion, land use, food waste, and ecosystem exploitation are highly entangled (3). Lacour et al. carried out a life-cycle assessment (LCA) study to compare GHGEs, energy demand and land occupation in a plant-based diet versus an animal-based diet, using a French cohort as baseline for the simulation. They found that those diets with a higher pro-vegetarian score (i.e., those diets with a preference for plant-based food) were significantly associated with lower GHGEs, lower energy demand and lower land occupation. Moreover,



***Edited and reviewed by:***
*Ross Bailie,*
*University of Sydney, Australia*

***Correspondence:**
*Alessandra Lafranconi*
*alessandra.lafranconi@unimib.it*

***Specialty section:***
*This article was submitted to Public Health Policy, a section of the journal Frontiers in Public Health*

***Received:*** *12 December 2018*
***Accepted:*** *24 January 2019*
***Published:*** *14 February 2019*

***Citation:***
*Lafranconi A, Ray S and Grosso G (2019) Editorial: Public Health Nutrition: Assessing Evidence to Determine Policy and Practice. Front. Public Health 7:21. doi: 10.3389/fpubh.2019.00021*

they investigated the modulation of such relationship, between type of diet and environmental impacts, by organic consumption; the authors found that organic food consumption modified the association between pro-vegetarian score and environmental impacts for plant-based diets, but not for animal-based diets.

Last, but not least, we included a number of papers on **human nutrition and health**. Nutrition has received significant attention in the last few years due to the increase in research done on its impact on non-communicable chronic and degenerative diseases. **Education tools** for healthcare professionals and for the general public are highly requested, as described by Crowley et al. massive open online courses might meet such needs, to counteract bad science and to provide practical help, especially in countries with low resources.

Progress in global, national, and local nutrition policies has been made, for instance with regards to specific population subgroups such as children and workers, where interventions to change the current food environment and, consequently, food habits, have been proposed.

Orlando et al. reviewed the link between obesity and hypertension in **children**, highlighting the role of fructose intake and the consequent rise in uric acid, which is a well-known independent risk factor for hypertension in children and adults. The authors then focused on nutritional policies aimed at decreasing the intake of fructose through actions on sweet drinks and carbonate beverages; effective actions appeared to be mainly carried out in school settings. Nevertheless, no data on cost-effectiveness of such policies have been presented.

Similarly, **workplace health promotion interventions** have been deemed effective. Korre et al. sketched their findings from their previous research on firefighters (a population at high risk of cardiovascular diseases, and often characterized by poor diet) and proposed a prospective intervention to modify their food environment through the adoption of Mediterranean diet, which has been shown to be palatable to them.

Another prospective intervention has been undertaken by Golubic et al. severely obese patients have been enrolled in a **multidisciplinary weight loss intervention**, prior to bariatric surgery. Interestingly, changes in weight were not-significantly modified by smoking or employment status: the intervention seemed to work homogeneously, despite the presence of social inequalities among the participants.

Taken together, the papers of our collection show research gaps in the following areas: measurement of actual costs of interventions, projection of impacts derived from nutrition policy implementations, and cost-effectiveness analysis of such interventions.

It is therefore unclear which evidence could be used to develop programmes and policy interventions that aim to improve health. This depends upon the different perspectives of researchers and decision-makers: the former, who are focused on knowledge generation, and the latter who are focused on assessing the disease burden that could be prevented or reduced by an intervention, and how feasible those interventions might be.

Especially in the European context, where a multitude of different legislation impacts our food environment and nutritional settings produce a variable science and policy lab, it is highly desirable to reach a consensus on minimum requirements that should apply to scientific evidence on nutrition interventions and policies. Only a solid assessment of costs and expected impacts can guide the design and implementation of a public health nutrition agenda which represents an interplay between heath and economic outcomes determined by food availability, dietary choices, and nutritional status of the population as well as how this can be modulated at each stage through effective risk assessment as well as risk management.

## AUTHOR CONTRIBUTIONS

This Editorial has been written by AL, SR, and GG in order to summarize the articles (with their main findings) included in the Research Topic. All authors contributed to the Editorial, and they agree to the submitted version.

## REFERENCES

1. Pereira RA, Hodge A. Food insecurity: a critical public health nutrition concern. *Public Health Nutr*. (2015) 18:2893–4. doi: 10.1017/S136898001500292X
2. Whitmee S, Haines A, Beyrer C, Boltz F, Capon AG, Dias BF, et al. Safeguarding human health in the Anthropocene epoch: report of The Rockefeller Foundation–Lancet Commission on planetary health. *Lancet* (2015) 386:1973–2028. doi: 10.1016/S0140-6736(15)60901-1
3. Berry EM, Dernini S, Burlingame B, Meybeck A, Conforti P. Food security and sustainability: can one exist without the other? *Public Health Nutr*. (2015) 18:2293–302. doi: 10.1017/S136898001500021X

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Public Health

REVIEW
published: 16 November 2017
doi: 10.3389/fpubh.2017.00304

# A Review of the Mycotoxin Enniatin B

*Alessandra Prosperini[1]*, Houda Berrada[1], María José Ruiz[1], Francesca Caloni[2], Teresa Coccini[3], Leon J. Spicer[4], Maria Chiara Perego[4] and Alessandra Lafranconi[5,6]*

*[1] Laboratory of Toxicology, Faculty of Pharmacy, University of Valencia, Valencia, Spain, [2] Department of Veterinary Medicine (DIMEVET), Università degli Studi di Milano, Milan, Italy, [3] Laboratory of Clinical and Experimental Toxicology, Toxicology Unit, Maugeri Clinical Scientific Institutes SpA-BS, IRCCS Pavia, Pavia, Italy, [4] Department of Animal Science, Oklahoma State University, Stillwater, OK, United States, [5] Centro di Studio e Ricerca sulla Sanità Pubblica (CESP), Università Milano Bicocca, Milan, Italy, [6] Department of International Health, FHML, CAPHRI, Maastricht University, Maastricht, Netherlands*

Mycotoxin enniatin B (ENN B) is a secondary metabolism product by *Fusarium* fungi. It is a well-known antibacterial, antihelmintic, antifungal, herbicidal, and insecticidal compound. It has been found as a contaminant in several food commodities, particularly in cereal grains, co-occurring also with other mycotoxins. The primary mechanism of action of ENN B is mainly due to its ionophoric characteristics, but the exact mechanism is still unclear. In the last two decades, it has been a topic of great interest since its potent mammalian cytotoxic activity was demonstrated in several mammalian cell lines. Moreover, the co-exposure *in vitro* with other mycotoxins enhances its toxic potential through synergic effects, depending on the concentrations tested. Despite its clear cytotoxic effect, European Food Safety Authority stated that acute exposure to ENNs, such as ENN B, does not indicate concern for human health, but a concern might be the chronic exposure. However, given the lack of relevant toxicity data, no firm conclusion could be drawn and a risk assessment was not possible. In fact, very few studies have been carried out *in vivo* and, in these studies, no adverse effects were observed. So, research on toxicological effects induced by ENN B is still on-going. Recently, some studies are dealing with new advances regarding ENN B. This review summarizes the information on biochemical and biological activity of ENN B, focusing on toxicological aspects and on the latest advances in research on ENN B.

**Keywords: enniatin B, toxic effects, biological properties, biochemical activities, emerging findings**

OPEN ACCESS

***Edited by:***
*Amelia Kekeletso Ranotsi, Maluti Adventist College, Lesotho*

***Reviewed by:***
*Maria Korre, Harvard University, United States*
*Fabio Galvano, Università degli Studi di Catania, Italy*

****Correspondence:***
*Alessandra Prosperini*
*alessandra.s83@gmail.com*

***Specialty section:***
*This article was submitted to Public Health Policy, a section of the journal Frontiers in Public Health*

***Received:*** *03 August 2017*
***Accepted:*** *02 November 2017*
***Published:*** *16 November 2017*

***Citation:***
*Prosperini A, Berrada H, Ruiz MJ, Caloni F, Coccini T, Spicer LJ, Perego MC and Lafranconi A (2017) A Review of the Mycotoxin Enniatin B. Front. Public Health 5:304. doi: 10.3389/fpubh.2017.00304*

## INTRODUCTION

*Fusarium* species[1] are common pathogens of cereal grains, animal feeds, and food commodities worldwide (1). Under favorable conditions, their secondary metabolism can produce hexadepsipeptidic mycotoxins,[2] such as enniatins (ENNs). ENNs are commonly found in several grains and their derived products, in fish, dried fruits, nuts, spices, cocoa, coffee products, etc. (2–7).

[1] *Fusarium* is a large and diverse genus of filamentous fungi of great agricultural and economic importance, containing many plant pathogens and mycotoxin producers.

[2] Mycotoxins are secondary metabolites produced by microfungi that are capable of causing disease and death in humans and other animals.

Moreover, some food processes including cooking, baking, frying, roasting, etc. do not affect their chemical structure; so, detoxification strategies to mitigate the risks of ENNs presence in foods and feed may be difficult (8, 9).

Structurally, ENNs are cyclohexadepsipeptides composed of alternating residues of three N-methyl amino acids, commonly valine, leucine, and isoleucine, and three hydroxy acids, typically hydroxyisovaleric acid. Several ENNs analogs (A, A1, B, B1, B2, B3, B4, D, E, F, and G) have been identified. Among them, the most prevalent ENNs reported as natural contaminants in cereals in Europe are ENN A, A1, B, and B1 (10). Their chemical structure is reported in **Figure 1**.

The lipophilic nature of ENNs allows them to be incorporated into lipid bilayers of cell membranes and creates cation selective pores that cause an increase in the permeability for cations, resulting in disturbances of the physiological cation level in the cell (11). Their ionophoric[3] behavior seems to be related to their wide range of biological activity. ENNs are known to be insecticidal, antifungal, antibacterial, and antihelmintic (12). Moreover, they exerted a potent cytotoxic effect in several human and animal cell lines at very low micromolar range (10, 13–18). Despite the strong cytotoxicity *in vitro*, a few studies carried out *in vivo* did not show relevant toxicity (19–23).

Unlike other *Fusarium* mycotoxins, such as deoxynivalenol (DON), T-2, HT-2, fumonisins (FB), and zearalenone (ZEA), whose presence in food and feed has been regulated by authorities, no limits have been set for ENNs, up to now. However, an increasing number of studies are proving their presence in several food and feed commodities and also their toxicity (2). This fact may constitute a great concern for human and animal health, since their toxicity could be also enhanced by the presence of other mycotoxins at the same time. The European Commission asked the European Food Safety Authority (EFSA) for a scientific opinion on the risks to human and animal health related to the presence of ENNs in food and feed. EFSA concluded that acute exposure to ENNs does not indicate concern for human health. There might be a concern with respect to chronic exposure, but no firm conclusion could be drawn and a risk assessment was not possible for dietary exposure to ENNs, due to the overall lack of toxicity data (24). At the moment, EFSA is still collecting occurrence data for a future risk assessment.

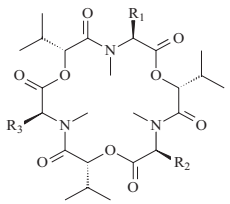
Among the four ENNs above-mentioned, ENN B is currently the most studied since it has been the most-often detected in unprocessed and processed grains from European countries. Concentrations of ENN B in grains range from a few μg/kg to over mg/kg (12). In a multi-mycotoxins analysis of maize silage in NW Spain, Dagnac et al. (25) found that ENN B was the most prevalent mycotoxin detected in 51% of the samples (average concentration: 157 μg/kg). Similar ENN B concentrations (195.5 ± 47.0 μg/kg) were observed in cereal samples collected from European and African countries (26). Svingen et al. (27) demonstrated the ENN B presence in all of the samples of Danish grain collected during the 2010 and 2011 harvests, with the highest value of 3,900 μg/kg detected in rye sample. A survey in Finland showed that ENNs were frequently detected in unprocessed grains including wheat, barley, rye, and oats, and that the maximum concentration was found for ENN B (10,280 μg/kg) in a barley sample (28).

Regarding grain-based products, in pasta samples bought from Dutch shops, de Nijs et al. (8) found the highest incidence for ENN B with concentrations ranging from 7.0 to 175 μg/kg. Higher concentrations of ENN B (up to 1,100 μg/kg) was detected in pasta and baby food from Italian supermarkets by Juan et al. (2). Zinedine et al. (7) demonstrated that wheat couscous semolina has a higher ENN B incidence and concentration (592 ng/g) than barley (50 ng/g) or corn (57 ng/g) semolina couscous. In beer samples from Germany, ENN B was the only ENN detected (0.9 μg/L) showing increased incidence than other mycotoxins (29).

Therefore, the attention on ENN B toxicological aspect is still highly concerning, considering that its potential toxicity may be enhanced by co-occurrence with other ENNs or other mycotoxins (15, 30, 31).

Besides its ionophoric property, ENN B toxicity involves the inhibition of acyl-CoA: cholesterol acyl transferase (ACAT) activity[4] (32) and oxidative stress[5] (16). ENN B also exerts cytotoxic activities by inducing mitochondrial modifications and cell cycle disruption, finally resulting in apoptotic cell death (16, 33–35). Moreover, it produces adrenal endocrine toxicity (36). A recent study reports a potential anticancer activity (37).

The objective of this review is to compile the effects produced by the *Fusarium* mycotoxin ENN B, focusing on its biological properties, biochemical activity and *in vitro* toxicological effects including the latest research on ENN B, in terms of biological properties, biochemical activity, and toxicity.



| ENN | R1 | R2 | R3 |
|---|---|---|---|
| **A** | $CH(CH_3)CH_2CH_3$ | $CH(CH_3)CH_2CH_3$ | $CH(CH_3)CH_2CH_3$ |
| **$A_1$** | $CH(CH_3)CH_2CH_3$ | $CH(CH_3)CH_2CH_3$ | $CH(CH_3)_2$ |
| **B** | $CH(CH_3)_2$ | $CH(CH_3)_2$ | $CH(CH_3)_2$ |
| **$B_1$** | $CH(CH_3)_2$ | $CH(CH_3)_2$ | $CH(CH_3)CH_2CH_3$ |

**FIGURE 1** | Chemical structure of enniatins (ENNs).

## BIOLOGICAL PROPERTIES OF ENN B

Enniatin B exhibits a wide array of biological activities. Several studies investigated the insecticidal activity of ENN B individually

[3] Ionophores are molecules that facilitate ion passage in or out of cell membranes.

[4] ACAT is an intracellular enzyme located in the endoplasmic reticulum that transfer fatty acyl groups from one molecule to another.

[5] Oxidative stress is defined as a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses.

and in complex with other ENNs (38–42). This activity has been confirmed in the blowfly *Calliphora erythrocephala*, in the mosquito larvae (*Aedes aegypti*), in the spruce budworm (*Choristoneura fumiferana*) and against the plant-parasitic nematode *Meloidogyne javanica* (38–40). Moreover, ENN B partially inhibited spore germination of *B. cinerea* (42). However, no insecticidal activity of ENN B was found by Mulè et al. (43) against larvae of *Galleria mellonella*.

Enniatin B exhibits antibacterial activity against some pathogens of humans, such as *Escherichia coli* (CECT 4782), *Enterococcus faecium* (CECT 410), *Salmonella enterica* (CECT 554), *Shigella dysenteriae* (CECT 584), *Listeria monocytogenes* (CECT935), *Yersinia enterocolitica* (CECT 4054), *Clostridium perfringens* (CECT 4647), *Pseudomonas aeruginosa* (CECT 4628), and two strains of *Staphylococcus aureus* (CECT 240 and CECT 976) (44). Moreover, antibacterial effect of ENN B has been demonstrated against *Mycobacterium phlei* and *M. paratuberculosis* (45–47).

On the other hand, ENN B acts also as antifungal agent for *Beauveria bassiana* (CECT 20499, CECT 20191, CECT 20412) and *Trichoderma harzianum* T22 (48). A mixture of ENNs (ENN A, A1, B, and B1 in ratio 5:15:35:45) caused necrotic lesions in potato tuber tissue (49) and ENN B on knapweed leaves (*Centaurea maculosa*) when exposed with acetamido-butenolide (50). Combination of ENN A + ENN B showed decreased leaf and root development, wilting of shoots, necrosis of leaves, and loss of turgor (51, 52).

## BIOCHEMICAL ACTIVITY OF ENN B

### Ionophoric Properties

The ionophoric property of ENNs allows them to be capable of promoting the transport of mono- and divalent cations through membranes leading to toxic actions via disturbances in their normal physiological concentrations (1). The primary action is the ionophoric property, which enables ENNs to form stable complexes with cations, and transport them into the lipophilic phase (1) evoking changes in intracellular ion concentration, disrupting cell functions (**Figure 2**) (53).

The ability of the ENNs to form complexes with alkali metal ions and increase the cationic permeability of membranes has been previously documented (54, 55). In particular, cations transported by ENNs in liposome seems to involve a mobile carrier mechanism which is selective for $K^+$ versus $Na^+$, requiring two ENN molecules, and it is realized by a "sandwich" model (56). ENNs form both 1:1 and 2:1 ENN:cation complexes with alkali, alkaline earth, and various transition metal ions. The probability of the 3:2 conformations is much less than the two other conformations (57). It has been suggested that

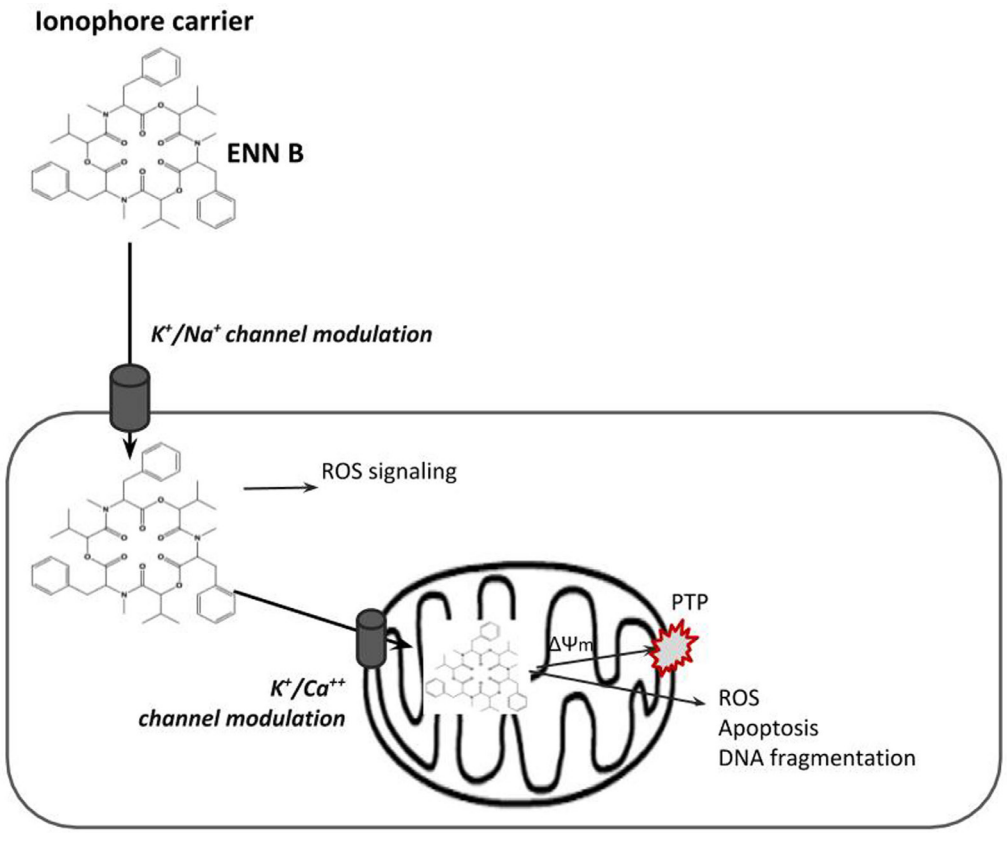



**FIGURE 2** | Scheme of the ionophore enniatin (ENN) B carrying ions by diffusing through membrane lipids.

electronic, inductive, or steric effects could indirectly stabilize the 2:1 complex. Cation selectivity was ranked as follows: $K^+ > Ca^{2+} \geq Na^+ > Mg^{2+} > Li^+$ (56). In addition, the transport efficiency appears to be related to the hydrophobic trait of the ENN molecules. The largest conductivity was shown for ENN B, followed by ENN A1 and B1 (56).

The mitochondriotoxic properties of ENNs have been demonstrated in isolated rat mitochondria (11). The mitochondrial effects were strongly connected with the $K^+$ ionophoric activity with ENNs inducing $K^+$ uptake by mitochondria. Moreover, they decreased the calcium retention capacity of the mitochondrion matrix leading to the mitochondrial membrane potential (MMP) collapse via permeability transition pore (PTP) opening (11, 58).

## Enzyme Inhibitor

The inhibition of the activity of ACAT by ENN B has been demonstrated (32). Such inhibition could be significant in the treatment and prevention of atherosclerosis and hypercholesterolemia. Trenin et al. (59) showed strong hypolipidemic activity of ENN B in human hepatoma HepG2 cells as a result of the inhibition of ACAT activity, triglyceride biosynthesis, and diminished pool of free fatty acids in the cells.

## Other Biochemical Properties

Enniatin B was the most effective inhibitor of one of the major multidrug efflux pumps such as Pdr5p[6] in *Saccharomyces cerevisiae* at non-toxic concentrations (60). The inhibition mechanism is clearly different from its function as an ionophore (60). This ENN B property may be important for the clinical use in combination with chemotherapeutic drugs.

Enniatins interact with membrane-located ATP-binding cassette (ABC) transporters[7], especially with ABCB1 and ABCG2 transporters, suggesting potential influences on bioavailability of xenobiotics and pharmaceuticals (61).

# TOXICITY OF ENN B

Few toxicological studies of ENN B have been performed *in vivo*. **Table 1** illustrates *in vivo* studies carried out with ENN B alone and in combination with other ENNs. *In vivo* toxicokinetic trials using pigs demonstrated a higher bioavailability of 91% for ENN B (62). Interestingly, Rodríguez-Carrasco et al. (22) found no acute toxicity in mice after intraperitoneal administration, although ENN B bioaccumulation in the lipophilic tissues was observed. According to Fraeyman et al. (63), ENN B was readily distributed to broiler chicken tissues, with mean volumes of distribution of 33.91 L/kg.

Comparing to *in vitro* studies, the number of studies *in vivo* is very low. *In vitro* cytotoxicity studies have been carried out for individual ENN B as well as for mixtures of ENNs, since mycotoxins, either from the same or from different fungal species, occur simultaneously in plant and food products (12). A scheme of *in vitro* studies on ENN B is shown in **Figure 3**.

## *In Vitro* Cytotoxicity

### Cytotoxicity Studies of Individual ENN B

Different cell lines and assays have been chosen to determine ENN B cytotoxicity. **Table 2** collects the cytotoxic activity studies performed in several cell lines exposed to ENN B tested individually and in complex with other ENNs (ENN A, A1, and B1) according to the type of cells, the toxicity endpoint, and the time of exposure. Data from literature show that human colon intestinal Caco-2 cells have been the most studied cell line when ENN B is applied alone (not in complex mixture), followed by HepG2 and CHO-K1 cells (**Table 2**). Exposure time goes from 3 to 72 h and the ENN B $IC_{50}$ values ranged in: (i) Caco-2 cells from 1.4 to >30 μM; (ii) HepG2 cells, from 0.9 to 435.9 μM; and (iii) CHO-K1 cells from 2.80 ± 0.16 to 11 μM. The lowest value

[6] Yeast multidrug resistance protein that belongs to the family of ABC transporters. Pdr5p has been shown to confer resistance to a wide range of compounds and metal ions.

[7] The ABC transporter superfamily is the largest transporter gene family. These proteins translocate a wide variety of substrates including sugars, amino acids, metal ions, peptides, and proteins, and a large number of hydrophobic compounds and metabolites across extra- and intracellular membranes.

**TABLE 1** | *In vivo* toxicity studies of enniatin B (ENN B).

| Animal | Dosage/route | Effects | Reference |
|---|---|---|---|
| Broiler chicken | 0.2 mg/kg b.w.<br>Bolus | Tissue bioaccumulation | Fraeyman et al. (63) |
| Mice | 5 mg/kg b.w.of ENN B<br>Intraperitoneal on two consecutive days | No acute damage<br>Tissue bioaccumulation | Rodríguez-Carrasco et al. (22) |
| Mice | 1.25–40 mg/kg b.w. (every 8 h)<br>Intraperitoneal | Mice died in 2–5 days (10–40 mg/kg b.w.)<br>Reduction of weight<br>No anti-HIV activity | McKee et al. (19) |
| Pigs | 0.05 mg/kg b.w.<br>Oral bolus | Absorption<br>ENN B > B1 > A1 > A | Devreese et al. (62) |
| Wistar rats | Mixture of ENNs containing 1.19, 2.16, 1.03 and 1.41 mg/kg b.w.of ENN A, A1, B, and B1<br>Oral | No adverse effect | Escrivá et al. (23) |

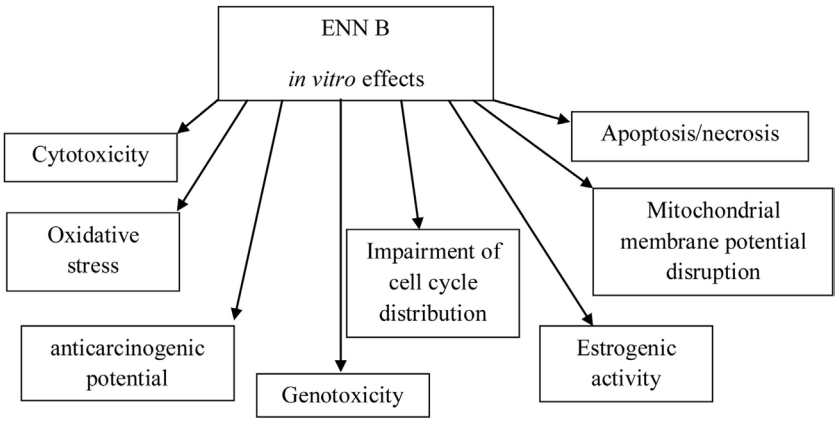



**FIGURE 3** | Schema showing *in vitro* effects of enniatin B (ENN B).

obtained was 0.50 of $ED_{50}$ in HepG2 cells, suggesting higher sensitivity of this type of cells to ENN B. HT-29, MRC-5, and V7 cell lines were also studied with different ENNs individually and $IC_{50}$ concentrations ranged from 1.4 to 16.8 μM for HT-29, from 0.6 to 9.8 μM for MRC-5, and from 2.5 ± 0.4 to 43 ± 20 μM for V7 cells, respectively.

### Cytotoxicity Studies of Combined Mycotoxins Including ENN B

There are several studies involving mixtures of ENNs including ENN B, as shown in **Table 2**; some of these ENNs mixtures do not indicate exactly the percentage of each ENN. Review of the literature showed that the lowest $IC_{50}$ value obtained with mixture of ENNs was for MVP-overexpressing subline cells (GLC-4/adr) with 1.41 ± 0.20 μM at 72 h and, the highest was obtained in porcine kidney cells (PK-15) with 41 μM at 72 h, followed by $IC_{50} > 10$ μM at 72 h for human lung cancer cells (VL8), embryonic fibroblast cells (WI-38), and human glioblastoma cells (T98-G).

Studies about cytotoxicity effects of ENN B in combination with other ENNs, and ENN B in combination with other mycotoxins, are collected in **Table 3**. ENN B was tested in combination with ENN A, A1, and B1 by Prosperini et al. (31) in Caco-2 cells and by Lu et al. (30) in CHO-K1 cells. Both studies aimed to investigate the type of interaction that occurs when ENNs appear in combination such as: synergism, antagonism, or additive effect by using isobologram method (70). The analysis was performed by testing binary and ternary combination in CHO-K1 and binary, ternary, and quaternary combination in Caco-2 cells. Prosperini et al. (31) reported a reduction of Caco-2 cell viability (%) in a dose-dependent manner for binary mixture tested in the following increasing order: ENN A + ENN A1 (48%) = ENN A1 + ENN B1 (47%) > ENN A1 + ENN B (35%) = ENN A + ENN B (33%) = ENN A + ENN B1 (32%) > ENN B + ENN B1 (26%). Similarly, tertiary and quaternary mixtures reduced cell viability in a dose-dependent manner with a reduction in viability of approximately 40%. Generally, additive cytotoxic effect was observed for all combinations; however, synergistic effects were observed for the following mixtures: ENN B + ENN A1, ENN B1 + ENN A1, and ENN A + ENN A1 + ENN B and, a moderate antagonism was produced by ENN B + ENN B1 combination.

Lu et al. (30) found that the binary combinations ENNs A + B1, ENNs A1 + B, and ENNs B + B1 showed additive effects with all concentrations tested in CHO-K1 cells. Synergistic effect of combined ENNs A + A1, A + B, A1 + B1, A + A1 + B, A + A1 + B1, A + B + B1, and A1 + B + B1 at higher concentrations occurred. Synergism effect was observed at higher concentrations with binary and tertiary combinations of ENN A, while antagonism effects were obtained at lower concentrations for ENNs A + A1 + B1 and ENNs A1 + B + B1.

In addition, studies about the combination of ENNs with other mycotoxins have been carried out (15, 65, 71). Briefly, ENN B, tested with beauvericin, had additive cytotoxic effect on Human hematopoietic progenitors (71). Binary mixtures of ENN B with ZEA, DON, and nivalenol showed antagonistic and strong antagonistic effects on Caco-2 cell viability (65). As Fernandez-Blanco et al. (15) reported, mixtures of ENN B + DON and ENN B + Alternariol (AOH) were found to be synergic, depending on the concentrations tested.

## Oxidative Stress

One of the key players in the production of oxidative stress is reactive oxygen species (ROS). Moreover, intracellular ROS generation in the hydrophobic compartment of a cell can induce lipid peroxidation (LPO).[8] ROS generation and LPO have been observed in mammalian cells exposed to ENN B (10, 16). In addition, Ivanova et al. (10) found that ENN B-induced ROS production after 3 h exposure to ENN B in Caco-2 cells that were generated downstream the ENN B-induced cytotoxic events by the mitochondria. On the contrary, Dornetshuber (68) demonstrated that genotoxic potential and cytotoxicity of ENNs is independent of ROS generation. Further research is needed in this area.

[8]Lipid peroxidation can be described generally as a process under which oxidants such as free radicals attack lipids containing carbon-carbon double bond(s), especially polyunsaturated fatty acids.

**TABLE 2** | *In vitro* cytotoxicity studies on enniatin B determined by different toxicity endpoint, time of exposure and cell types.

| Cell lines | Cell types | Parameter | Exposure time (h) | $IC_{50}$ (μM) | Reference |
|---|---|---|---|---|---|
| A427<br>A549 | Human lung cancer | MTT | 72 | $ENN_{mix}$: 1.61 ± 0.14<br>$ENN_{mix}$: 4.08 ± 1.04 | Dornetshuber et al. (33) |
| Balb 3T3 | Mouse embryo fibroblast | ATP production<br>BrdU ELISA<br>Apoptosis induction | 24 | $ED_{50}$: 8.4 ± 0.76<br>$ED_{50}$: 4.24 ± 0.06<br>$ED_{50}$: 11 | Jonsson et al. (13) |
| Caco-2 | Human colon adenocarcinoma | NR | 3, 24<br>24, 48, 72<br>24, 48<br>24, 48<br>72<br>24, 48, 72 | 10.0 ± 3.8–2.1 ± 0.4<br>>15–1.4 ± 0.2<br>>30<br>No $IC_{50}$ value obtained<br>$ENN_{mix}$: 1.99 ± 0.09<br>>15–11.7 ± 2.4 | Ivanova et al. (10)<br>Prosperini et al. (16)<br>Meca et al. (44)<br>Meca et al. (64)<br>Dornetshuber et al. (33)<br>Prosperini et al. (31) |
| | | WST-1 | 24 | 6.3 | Vejdovszky et al. (65) |
| CHO-K1 | Chinese hamster ovary | MTT | 24, 48, 72<br>24 | 11.0 ± 2.65–2.80 ± 0.16<br>11.0 ± 2.65 | Lu et al. (30)<br>Lombardi et al. (66) |
| C6 | Rat glioma | MTT | 3, 24 | $ENN_{mix}$: 2.5–10 | Wätjen et al. (34) |
| GLC-4 | Breast adenocarcinoma | MTT | 72 | $ENN_{mix}$: 2.40 ± 1.53 | Dornetshuber et al. (33, 61) |
| GLC-4/adr | MVP-overexpressing subline | MTT | 72 | $ENN_{mix}$: 1.41 ± 0.83 | Dornetshuber et al. (61) |
| GBL1<br>GBL2<br>GBL3<br>GBL4 | Human Glioblastoma | MTT | 72 | $ENN_{mix}$: 2.65 ± 0.30<br>$ENN_{mix}$: 2.29 ± 0.05<br>$ENN_{mix}$: 2.55 ± 0.14<br>$ENN_{mix}$: 2.33 ± 0.30 | Dornetshuber et al. (33) |
| H-4IIE | Rat hepatocarcinoma | MTT | 3, 24 | ENN A1, B and B1: 1–1.5 | Wätjen et al. (34) |
| Hep G2 | Human hepatocarcinoma | MTT | 24, 48<br>3, 24 | No $IC_{50}$ value obtained<br>ENN A1, B and B1: 10 | Meca et al. (64)<br>Wätjen et al. (34) |
| | | Alamar Blue BrdU | 24 | 206.7–435.9<br>0.9–1.1 | Ivanova et al. (18) |
| | | ATP production<br>BrdU ELISA | 24 | $ED_{50}$: 2.9 ± 0.7<br>$ED_{50}$: 0.50 ± 0.09 | Jonsson et al. (13) |
| | | Qaudroprobe multiparametric liver toxicity assay[a] | 24, 72 | 0.9[b] | Svingen et al. (27) |
| HL60 | Promyelocityc leukemia carcinoma | MTT | 72 | $ENN_{mix}$: 1.74 ± 0.20 | Dornetshuber et al. (33, 61) |
| HL60/vinc | ABCB1-overexpressing subline | MTT | 72 | $ENN_{mix}$: 2.40 ± 0.14 | Dornetshuber et al. (61) |
| HL60/adr | ABCC1-overexpressing subline | MTT | 72 | $ENN_{mix}$: 2.1 ± 0.12 | Dornetshuber et al. (61) |
| HT-29 | Human colon adenocarcinoma | MTT | 24, 48 | 2.8 ± 0.9 | Meca et al. (64) |
| HUVEC | Human endothelial | MTT | 72 | $ENN_{mix}$: 7.89 ± 0.21 | Dornetshuber et al. (33) |
| KB-3-1 | Epidermal carcinoma | MTT | 72 | $ENN_{mix}$: 1.95–0.12 | Dornetshuber et al. (33, 61) |
| KBC-1 | ABCB1-overexpressing subline | MTT | 72 | $ENN_{mix}$: 1.77 ± 0.04 | Dornetshuber et al. (61) |
| MDA-MB-231 | Alveolar epithelial | MTT | 72 | $ENN_{mix}$: 2.36 ± 1.57 | Dornetshuber et al. (33, 61) |
| MDA-MB-231/adr | ABCG2-overexpressing subline | MTT | 72 | $ENN_{mix}$: 3.18 ± 1.70 | Dornetshuber et al. (61) |
| MGC | Human glioblastoma | MTT | 72 | $ENN_{mix}$: 3.04 ± 0.58 | Dornetshuber et al. (33) |
| MRC-5 | Fibroblast-like fetal lung | Alamar Blue BrdU | 24 | 1.9–9.8<br>1.9–3.6 | Ivanova et al. (18) |
| OS 9<br>OS 10 | Human osteosarcoma | MTT | 72 | $ENN_{mix}$: 3.55 ± 0.77<br>$ENN_{mix}$: 2.10 ± 0.15 | Dornetshuber et al. (33) |
| Porcine kidney cells-15 | Porcine Kidney | MTT | 72 | $ENN_{mix}$: 41 | Uhlig et al. (67) |
| RAW 264.7 | Murine macrophage | Alamar blue<br>NR | 24 | 2.6<br>4.7 | Gammelsrud et al. (35) |
| SAOS | Human osteosarcoma | MTT | 72 | $ENN_{mix}$: 2.13 ± 0.07 | Dornetshuber et al. (33) |

(*Continued*)

**TABLE 2** | Continued

| Cell lines | Cell types | Parameter | Exposure time (h) | $IC_{50}$ (μM) | Reference |
|---|---|---|---|---|---|
| SW1537 | Small cell lung carcinoma | MTT | 72 | $ENN_{mix}$: 2.16 ± 0.12 | Dornetshuber et al. (61) |
| SW1537/2R160 | ABCB1-overexpressing subline | MTT | 72 | $ENN_{mix}$: 2.69 ± 0.60 | Dornetshuber et al. (61) |
| SW480 | Small cell lung carcinoma | MTT | 72 | $ENN_{mix}$: 4.00 ± 1.12 | Dornetshuber et al. (33) |
| T98-G | Human glioblastoma | MTT | 72 | $ENN_{mix}$: >10 | Dornetshuber et al. (33) |
| U373 | Human glioblastoma | MTT | 72 | $ENN_{mix}$: 4.88 ± 0.09 | Dornetshuber et al. (33) |
| U2-OS | Osteosarcoma | MTT | 72 | $ENN_{mix}$: 1.77 ± 0.24 | Dornetshuber et al. (33) |
| V79 | Chinese hamster fibroblast | NR | 48 | 4.4 | Dornetshuber et al. (68) |
| | | Alamar blue<br>NR<br>Protein content (BCA) | 24–48 | 34 ± 20–2.5 ± 0.4<br>36 ± 16–4 ± 1.5<br>43 ± 20–3.9 ± 3.9 | Föllmann et al. (69) |
| VM8<br>VM18<br>VM22<br>VM33<br>VM25 | Melanoma | MTT | 72 | $ENN_{mix}$: 3.19 ± 0.85<br>$ENN_{mix}$: 2.67 ± 0.08<br>$ENN_{mix}$: 1.75 ± 0.15<br>$ENN_{mix}$: 9.65 ± 0.13<br>$ENN_{mix}$: 2.72 ± 0.11 | Dornetshuber et al. (33) |
| VL8 | Human lung cancer | MTT | 72 | $ENN_{mix}$: >10 | Dornetshuber et al. (33) |
| WI-38 | Embryonic fibroblast | MTT | 72 | $ENN_{mix}$: >10 | Dornetshuber et al. (33) |

*$IC_{50}$ = inhibitory concentration at which 50% of enzyme activity is inhibited; $ED_{50}$ = effective dose at which 50% of cells are affected.*

*[a]Usingfour fluorophore probes, six cytotoxicity-associated parameters were analyzed simultaneously: nuclear count and size, plasma membrane integrity, lysosomal activity, mitochondrial membrane potential, and mitochondrial area.*

*[b]The concentration that deviated significantly from the control cell responses.*

**TABLE 3** | Combinedeffect of ENN B tested in combination with other mycotoxins by *in vitro* methods.

| Cell line | Mycotoxin combination | Effect | Interaction (in the combination) | Reference |
|---|---|---|---|---|
| Caco-2 | ENN A + A1<br>ENN A + B<br>ENN A + B1<br>ENN B + B1<br>ENN A + A1 + B1<br>ENN A + B + B1<br>ENN A1 + B + B1<br>ENN A + A1 + B + B1 | Cytotoxicity | Add | Prosperini et al. (31) |
| | ENN A1 + B1<br>ENN A1 + B<br>ENN A + A1 + B | | Syn | |
| | ENN B + B1 | | Ant | |
| | ENN B + ZEA<br>ENN B + DON | Cytotoxicity | Ant | Vejdovszky et al. (65) |
| | ENN B + NIV | | Strong Antagonism | |
| | ENN B + AOH<br>ENN B + DON<br>ENN B + AOH + DON | | Syn<br>Add/Syn<br>Add/Syn | Fernandez-Blanco et al. (15) |
| CHO-K1 | ENN A + B1<br>ENN A1 + B<br>ENN B + B1 | Cytotoxicity | Add | Lu et al. (30) |
| | ENN A + A1<br>ENN A + B<br>ENN A1 + B1<br>ENN A + A1 + B<br>ENN A + B + B1 | | Syn | |
| | ENN A + A1 + B1<br>ENN A1 + B + B1 | | Ant | |
| Human hematopoietic progenitors | BEA + ENN B | Myelotoxicity | Add | Ficheux et al. (71) |

*AOH, alternariol; DON, deoxynivalenol; ZEA, zearalenone; NIV, nivalenol; ENN, Enniatin.*

## Impairment of Cell Cycle Distribution

Cell cycle is the entire process by which a cell undergoes cell division. Cell cycle phases are: the G1 phase, where cells are preparing for DNA, RNA, and protein synthesis, the S phase where DNA is synthesized, the G2 phase, where cells are preparing for mitosis, and finally the M phase (mitosis) where two daughter cells are generated. Cells can remain in a quiescent phase (G0 phase) and they need growth factors to enter the G1 phase.

It has been demonstrated that mycotoxins can disturb the normal cell cycle distribution due to their anti-proliferative effects on several cell types, with an accumulation of cells in one or more phases of the cell cycle (14)[9]. Juan-García et al. (72) observed that in HepG2, ENN B provoked a higher percentage of cells arrested at G0/G1 at 48 h than ENN A. A similar behavior was reported by Gammelsrud et al. (35) on murine monocytes macrophage RAW 267.4 cells: an increase in percentage of cells in G0/G1 phase when treated during 24 h with ENN B (from 1.25 to 10 μM). In general, cell accumulation during cell cycle in any phase after a treatment indicates an anti-proliferative activity of the compound or compounds used. The same behavior was observed in several human cancer cell lines by Dornetshuber et al. (33).

In Caco-2 cells, as described by Prosperini et al. (16), ENN B (3 μM) induced an arrest of the cell cycle in G2/M phase after 72 h of exposure with a significant increase in G2/M cell number compared to the control. A decrease of the S phase cell population and an increase in SubG0/G1 were also observed.

A noticeable increase of cells in the G2/M phase in Caco-2 cells after ENN B treatment was also observed by Ivanova et al. (10) confirming the impairment of mitosis. This type of arrest has been described as a possible consequence of external stimuli leading to apoptosis by activation of the caspase pathway or to non-apoptotic mitotic death.

## Apoptosis/Necrosis

Enniatin B alone and in mixture with other ENNs induced apoptosis in several cell lines with nuclear fragmentation and apoptotic body formation (13, 14, 16, 33–35, 68, 69, 72). Moreover, the necrotic cell death has been also reported (10, 16, 35). Apoptotic effect and necrotic[10] pathway was observed in Caco-2 cells after 48 h of exposure to ENN B (10, 16).

Juan-García et al. (72) found that both ENN B and ENN A (1.5 and 3.0 μM) caused apoptosis in HepG2 cells, after 48 h of exposure, identifying ENN B more toxic than ENN A. Necrotic pathway was not observed. Similar results were obtained in mouse embryo fibroblast (Balb 3T3) cells (from 11 to 45 μM) (13), in murine monocyte (RAW 267.4) macrophages (35) and in human adrenocortical carcinoma cell line H295R (36).

## MMP Disruption

Mitochondria have been recognized for their role in mediating physiological processes and their involvement in signal transduction and regulation of cell proliferation and differentiation. They are involved also in cell death regulation, i.e., necrosis and apoptosis. Due to this role, mitochondria are vulnerable to the toxic effects of xenobiotics that interfere in cellular energy production. Apoptosis and necrosis induced cell death by cytotoxic agents involve similar metabolic disturbances and above all, mitochondrial permeability transition (MPT). Mitochondrial events of apoptosis and necrosis involve opening of a pore in the inner mitochondrial membrane, referred as mitochondrial PTP (MPTP) and the consequent dissipation of membrane potential (73). The dissipation of the MMP results from the unequal distribution of ions (mainly protons) on the inner mitochondrial membrane. The MMP disruption suggests that the proton-moving force and/or the inner membrane permeability has been affected during cell damage. The dissipation of MMP is a general feature of both cell death types (16).

Measurements of MMP are carried out by using lipophylic dyes, which pass through cell membranes and accumulate according to their charge. The alteration of fluorescent intensity can be determined by flow cytometry. Among these dyes, the tetramethylrhodamine methyl ester (TMRM), coupled with the carbocyanine monomer nucleic acid (To-Pro-3), has been used to determine the mitochondrial starting depolarization and cells progressing to death through apoptosis (72).

The disruption of MMP has been demonstrated in KB-3-1 cells exposed to ENNs mixture (33), and to ENN B in Caco-2 and HepG2 cells (10, 16, 72). The exact mechanism by which pro-oxidant mycotoxins induced pore opening is still not fully understood. At least two molecular sites of the complex contribute to this effect. The first site is a redox sensitive membrane dithiol group that can be oxidized by ROS (produced by mycotoxins), the second one remains undetermined.

Mitochondrial membrane potential was measured also by Svingen et al. (27) by the Hep-G2 quadroprobe multi-parametric liver toxicity assay. The strongest effect was seen for plasma membrane integrity, with concomitant effects on mitochondrial area/mass and mitochondrial potential, confirming the involvement of mitochondria in ENNs toxicity (11).

## Estrogenic Activity

Recently, an investigation to evaluate possible endocrine disruptor effects[11] of ENN B was conducted by Kalayou et al. (36) demonstrating that in the human adrenocortical carcinoma cell line H295R, ENN B (10 μM) was able to reduce progesterone, testosterone, and cortisol production at a non-cytotoxic concentration. Higher concentrations (>10 μM) reduced both estradiol and testosterone levels in Leydig cells (36). Additional research

[9] The natural cell cycle includes a number of checkpoints that allow the cell to determine whether to proceed with division or stop. These halts can also be induced by external factors like chemicals. Research on cell cycle arrest provides important information about how cells regulate themselves and what happens when these processes go wrong.

[10] Two different ways of cells can die are apoptosis or necrosis. Apoptosis is described as an active, programmed process of autonomous cellular dismantling that avoids eliciting inflammation. Necrosis has been characterized as passive, accidental cell death resulting from environmental perturbations with uncontrolled release of inflammatory cellular contents.

[11] Chemicals that mimic or antagonize the *in vitro* and/or *in vivo* actions of naturally occurring estrogens are typically defined as having estrogenic activity or anti-estrogenic activity. Effects on estrogen signaling represent the most common and best studied endocrine disruptor activity.

should be conducted using ovarian steroid producing cells such as granulosa cells.

### Genotoxicity

Genotoxicity[12] seems to be not involved in ENN B induction of cell death. As reported by Follmann et al. (69), ENN B, despite its high cytotoxic potential, did not induce any DNA damage by the alkaline Comet Assay in V79 cells after concentrations ranging from 1 to 100 μM. Results are in accordance with those obtained by Gammelsrud et al. (35) and Prosperini et al. (16) in Caco-2 cells.

## EMERGING FINDINGS OF ENN B

Some researchers are underlying the anticancer potential of ENN B (33, 34, 61, 68). Apoptosis with the involvement of p53 and p21 genes was found by Dornetshuber et al. (33), which tested a mixture of ENNs against several human cancer cells, promoting ENNs as anticancer drugs, according also to Wätjen et al. (34) and Dornetshuber-Fleiss et al. (37). In these surveys, ENNs caused caspase 3/7 activation in hepatoma H4IIE cells and caspase-7 activation in the KB-3-1 cell line, respectively, as well as nuclear fragmentation.

Enniatin B is capable of resisting expulsion by the ABC transporters, and also naturally targets tumor cells more specifically than other chemotherapeutic agents. The action is synergic with the clinically approved multi-kinase inhibitor sorafenib (Sora) showing profound synergistic *in vitro* and *in vivo* anticancer effects against cervical cancer (37).

## CONCLUDING REMARKS

Mycotoxins constitute a serious health concern both for animals and for humans, besides economic problems. Productive and nutritive values of food and feed can be compromised by mold and mycotoxin contamination, and toxicological risk derived by ingestion is constantly under Authorities control. Regarding ENNs, a risk assessment is still not available, despite its clear toxicity *in vitro* and its presence in food and feed.

Indeed, several *in vitro* and *in vivo* studies have revealed that ENN B interacts with primary target molecules, induce signaling pathways and effector mechanisms, affects the biological response of cell defenses, promotes cell damage, produces potential interactions between food contaminants (particularly other mycotoxins) leading to abnormally high response, and other molecular events underlying ENN B toxicity. Nevertheless, regulatory limits have not yet been defined, due to a lack of complete toxicity data.

However, in the last decade, novel findings about a potential therapeutic action of ENNB have been proven. These promising findings introduce a new aspect of this toxic compound. Future research focused on elucidating the toxic mechanism of ENN B as well as its anticancer activity could better clarify the real potential of ENN B. These research findings could contribute to establish emerging therapeutic strategy to chronic health problems.

This review wanted to collect all available data regarding toxicological aspect and emerging findings on ENN B in order to underlying the need to continue to study toxic/emerging effects of this compound to finally protect and improve both animal and human well-being.

## AUTHOR CONTRIBUTIONS

AP is the first author (40%). HB (5%), M-JL (10%), FC (10%), TC (5%), LS (10%), MP (10%), and AL (10%).

## FUNDING

This research has been supported by the Spanish Ministry of Economy and Competitiveness (AGL2016-77610-R), and the work of AL is partially supported by a Jean Monnet Erasmus+ grant (574376-EPP-1-2016-1-IT-EPPJMO-MODULE).

[12]Genotoxicity is defined as the destructive effect on a cell's genetic material (DNA and RNA) affecting its integrity.

## REFERENCES

1. Logrieco A, Moretti A, Mule G, Paciolla C, Ritieni A, et al. Advances on the toxicity of the cereal contaminant *Fusarium* esadepsipeptides. *Cereal Res Commun* (2008) 36:303–13. doi:10.1556/CRC.36.2008.Suppl.B.28
2. Juan C, Mañes J, Raiola A, Ritieni A. Evaluation of beauvericin and enniatins in Italian cereal products and multicereal food by liquid chromatography coupled to triple quadrupole mass spectrometry. *Food Chem* (2013) 140(4):755–62. doi:10.1016/j.foodchem.2012.08.021
3. Covarelli L, Beccari G, Prodi A, Generotti S, Etruschi F, Juan C, et al. *Fusarium* species, chemotype characterisation and trichothecene contamination of durum and soft wheat in an area of central Italy. *J Sci Food Agric* (2015) 95(3): 540–51. doi:10.1002/jsfa.6772
4. García-Moraleja A, Font G, Mañes J, Ferrer E. Analysis of mycotoxins in coffee and risk assessment in Spanish adolescents and adults. *Food Chem Toxicol* (2015) 86:225–33. doi:10.1016/j.fct.2015.10.014
5. Quiles JM, Saladino F, Mañes J, Fernández-Franzón M, Meca G. Occurrence of mycotoxins in refrigerated pizza dough and risk assessment of exposure for the Spanish population. *Food Chem Toxicol* (2016) 94:19–24. doi:10.1016/j.fct.2016.05.011
6. Tolosa J, Font G, Mañes J, Ferrer E. Mitigation of enniatins in edible fish tissues by thermal processes and identification of degradation products. *Food Chem Toxicol* (2017) 101:67–74. doi:10.1016/j.fct.2016.12.039
7. Zinedine A, Fernández-Franzón M, Mañes J, Manyes L. Multi-mycotoxin contamination of couscous semolina commercialized in Morocco. *Food Chem* (2017) 214:440–6. doi:10.1016/j.foodchem.2016.07.098
8. de Nijs M, van den Top H, de Stoppelaar J, Lopez P, Mol H. Fate of enniatins and deoxynivalenol during pasta cooking. *Food Chem* (2016) 213:763–7. doi:10.1016/j.foodchem.2016.07.024
9. Luz C, Saladino F, Luciano FB, Mañes J, Meca G. Occurrence, toxicity, bioaccessibility and mitigation strategies of beauvericin, a minor *Fusarium* mycotoxin. *Food Chem Toxicol* (2017) 107(Pt A):430–9. doi:10.1016/j.fct.2017.07.032
10. Ivanova L, Egge-Jacobsen WM, Solhaug A, Thoen E, Faeste CK. Lysosomes as a possible target of enniatin B-induced toxicity in Caco-2 cells. *Chem Res Toxicol* (2012) 25(8):1662–74. doi:10.1021/tx300114x
11. Tonshin AA, Teplova VV, Andersson MA, Salkinoja-Salonen MS. The *Fusarium* mycotoxins enniatins and beauvericin cause mitochondrial dysfunction by affecting the mitochondrial volume regulation, oxidative phosphorylation and ion homeostasis. *Toxicology* (2010) 276(1):49–57. doi:10.1016/j.tox.2010.07.001

12. Jestoi M. Emerging *Fusarium*-mycotoxins fusaproliferin, beauvericin, enniatins, and moniliformin: a review. *Crit Rev Food Sci Nutr* (2008) 48(1):21–49. doi:10.1080/10408390601062021
13. Jonsson M, Jestoi M, Anthoni M, Welling A, Loivamaa I, Hallikainen V, et al. *Fusarium* mycotoxin enniatin B: cytotoxic effects and changes in gene expression profile. *Toxicol In Vitro* (2016) 34:309–20. doi:10.1016/j.tiv.2016.04.017
14. Juan-García A, Manyes L, Ruiz MJ, Font G. Involvement of enniatins-induced cytotoxicity in human HepG2 cells. *Toxicol Lett* (2013) 218(2):166–73. doi:10.1016/j.toxlet.2013.01.014
15. Fernandez-Blanco C, Font G, Ruiz MJ. Interaction effects of enniatin B, deoxinivalenol and alternariol in Caco-2 cells. *Toxicol Lett* (2016) 241:38–48. doi:10.1016/j.toxlet.2015.11.005
16. Prosperini A, Juan-García A, Font G, Ruiz MJ. Reactive oxygen species involvement in apoptosis and mitochondrial damage in Caco-2 cells induced by enniatins A, $A_1$, B and $B_1$. *Toxicol Lett* (2013) 222(1):36–44. doi:10.1016/j.toxlet.2013.07.009
17. Behm C, Degen GH, Föllmann W. The *Fusarium* toxin enniatin B exerts no genotoxic activity, but pronounced cytotoxicity in vitro. *Mol Nutr Food Res* (2009) 53(4):423–30. doi:10.1002/mnfr.200800183
18. Ivanova L, Skjerve E, Eriksen GS, Uhlig S. Cytotoxicity of enniatins A, A1, B, B1, B2 and B3 from *Fusarium avenaceum*. *Toxicon* (2006) 47(8):868–76. doi:10.1016/j.toxicon.2006.02.012
19. McKee TC, Bokesch HR, McCormick JL, Rashid MA, Spielvogel D, Gustafson KR, et al. Isolation and characterization of new anti-HIV and cytotoxic leads from plants, marine, and microbial organisms. *J Nat Prod* (1997) 60(5):431–8. doi:10.1021/np970031g
20. Juan C, Manyes L, Font G, Juan-García A. Evaluation of immunologic effect of enniatin A and quantitative determination in feces, urine and serum on treated Wistar rats. *Toxicon* (2014) 87:45–53. doi:10.1016/j.toxicon.2014.05.005
21. Manyes L, Escrivá L, Serrano AB, Rodríguez-Carrasco Y, Tolosa J, Meca G, et al. A preliminary study in Wistar rats with enniatin A contaminated feed. *Toxicol Mech Methods* (2014) 24(3):179–90. doi:10.3109/15376516.2013.876135
22. Rodríguez-Carrasco Y, Heilos D, Richter L, Süssmuth RD, Heffeter P, Sulyok M, et al. Mouse tissue distribution and persistence of the food-born fusariotoxins enniatin B and beauvericin. *Toxicol Lett* (2016) 247:35–44. doi:10.1016/j.toxlet.2016.02.008
23. Escrivá L, Font G, Manyes L. Quantitation of enniatins in biological samples of Wistar rats after oral administration by LC-MS/MS. *Toxicol Mech Methods* (2015) 25(7):552–8. doi:10.3109/15376516.2015.1061083
24. Benford D, Ceccatelli S, Cottrill B, Dinovi M, Dogliotti E, Edler L, et al. Scientific opinion on the risks to human and animal health related to the presence of beauvericin and enniatins in food and feed. *EFSA J* (2014) 12(8):3802. doi:10.2903/j.efsa.2014.3802
25. Dagnac T, Latorre A, Fernández Lorenzo B, Llompart M. Validation and application of a liquid chromatography-tandem mass spectrometry based method for the assessment of the co-occurrence of mycotoxins in maize silages from dairy farms in NW Spain. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* (2016) 33(12):1850–63. doi:10.1080/19440049.2016.1243806
26. Decleer M, Rajkovic A, Sas B, Madder A, De Saeger S. Development and validation of ultra-high-performance liquid chromatography-tandem mass spectrometry methods for the simultaneous determination of beauvericin, enniatins (A, A1, B, B1) and cereulide in maize, wheat, pasta and rice. *J Chromatogr A* (2016) 1472:35–43. doi:10.1016/j.chroma.2016.10.003
27. Svingen T, Lund Hansen N, Taxvig C, Vinggaard AM, Jensen U, Have Rasmussen P. Enniatin B and beauvericin are common in Danish cereals and show high hepatotoxicity on a high-content imaging platform. *Environ Toxicol* (2017) 32(5):1658–64. doi:10.1002/tox.22367
28. Uhlig S, Jestoi M, Parikka P. *Fusarium avenaceum* – the North European situation. *Int J Food Microbiol* (2007) 119(1–2):17–24. doi:10.1016/j.ijfoodmicro.2007.07.021
29. Habler K, Gotthardt M, Schüler J, Rychlik M. Multi-mycotoxin stable isotope dilution LC–MS/MS method for *Fusarium* toxins in beer. *Food Chem* (2017) 218:447–54. doi:10.1016/j.foodchem.2016.09.100
30. Lu H, Fernández-Franzón M, Font G, Ruiz MJ. Toxicity evaluation of individual and mixed enniatins using an in vitro method with CHO-K1 cells. *Toxicol In Vitro* (2013) 27(2):672–80. doi:10.1016/j.tiv.2012.11.009
31. Prosperini A, Font G, Ruiz MJ. Interaction effects of *Fusarium* enniatins (A, A1, B and B1) combinations on in vitro cytotoxicity of Caco-2 cells. *Toxicol In Vitro* (2014) 28(1):88–94. doi:10.1016/j.tiv.2013.06.021
32. Tomoda H, Huang XH, Cao J, Nishida H, Nagao R, Okuda S, et al. Inhibition of acyl-CoA: cholesterol acyltransferase activity by cyclodepsipeptide antibiotics. *J Antibiot (Tokyo)* (1992) 45(10):1626–32. doi:10.7164/antibiotics.45.1626
33. Dornetshuber R, Heffeter P, Kamyar MR, Peterbauer T, Berger W, Lemmens-Gruber R. Enniatin exerts p53-dependent cytostatic and p53-independent cytotoxic activities against human cancer cells. *Chem Res Toxicol* (2007) 20(3):465–73. doi:10.1021/tx600259t
34. Wätjen W, Debbab A, Hohlfeld A, Chovolou Y, Kampkötter A, Edrada RA, et al. Enniatins A1, B and B1 from an endophytic strain of *Fusarium tricinctum* induce apoptotic cell death in H4IIE hepatoma cells accompanied by inhibition of ERK phosphorylation. *Mol Nutr Food Res* (2009) 53(4):431–40. doi:10.1002/mnfr.200700428
35. Gammelsrud A, Solhaug A, Dendele B, Sandberg WJ, Ivanova L, Kocbach Bolling A, et al. Enniatin B-induced cell death and inflammatory responses in RAW 267.4 murine macrophages. *Toxicol Appl Pharmacol* (2012) 261(1):74–87. doi:10.1016/j.taap.2012.03.014
36. Kalayou S, Ndossi D, Frizzell C, Groseth PK, Connolly L, Sørlie M, et al. An investigation of the endocrine disrupting potential of enniatin B using in vitro bioassays. *Toxicol Lett* (2015) 233(2):84–94. doi:10.1016/j.toxlet.2015.01.014
37. Dornetshuber-Fleiss R, Heilos D, Mohr T, Richter L, Süssmuth RD, Zlesak M, et al. The naturally born fusariotoxin enniatin B and sorafenib exert synergistic activity against cervical cancer in vitro and in vivo. *Biochem Pharmacol* (2015) 93(3):318–31. doi:10.1016/j.bcp.2014.12.013
38. Grove JF, Pople M. The insecticidal activity of beauvericin and the enniatin complex. *Mycopathologia* (1980) 70(2):103–5. doi:10.1007/BF00443075
39. Strongman DB, Strunz GM, Giguère P, Yu C-M, Calhoun L. Enniatins from *Fusarium avenaceum* isolated from balsam fir foliage and their toxicity to spruce budworm larvae, *Choristoneura fumiferana* (Clem.) (Lepidoptera: Tortricidae). *J Chem Ecol* (1988) 14(3):753–64. doi:10.1007/BF01018770
40. Ciancio A. Observations on the nematicidal properties of some mycotoxins. *Fundam Appl Nematol* (1995) 18(5):451–4.
41. Pleiss U, Turberg A, Harder A, Londershausen M, Jeschke P, Boheim G. Synthesis of a radiolabeled enniatin cyclodepsipeptide [3H-methyl]JES 1798. *J Labelled Comp Radiopharm* (1996) 38(7):651–9. doi:10.1002/(SICI)1099-1344(199607)38:7<651::AID-JLCR881>3.0.CO;2-S
42. Pohanka A, Capieau K, Broberg A, Stenlid J, Stenström E, Kenne L. Enniatins of *Fusarium* sp. strain F31 and their inhibition of *Botrytis cinerea* spore germination. *J Nat Prod* (2004) 67(5):851–7. doi:10.1021/np0340448
43. Mulè G, D'Ambrosio A, Logrieco A, Bottalico A. Toxicity of mycotoxins of *Fusarium sambucinum* for feeding in *Galleria mellonella*. *Entomol Exp Appl* (1992) 62(1):17–22. doi:10.1111/j.1570-7458.1992.tb00636.x
44. Meca G, Sospedra I, Valero MA, Mañes J, Font G, Ruiz MJ. Antibacterial activity of the enniatin B, produced by *Fusarium tricinctum* in liquid culture, and cytotoxic effects on Caco-2 cells. *Toxicol Mech Methods* (2011) 21(7):503–12. doi:10.3109/15376516.2011.556202
45. Vesonder RF, Golinski P. Metabolites of *Fusarium*. In: Chelkowski J, editor. *Fusarium: Mycotoxins, Taxonomy and Pathogenicity*. Amsterdam, The Netherlands: Elsevier (1989). p. 1–39.
46. Nilanonta C, Isaka M, Chanphen R, Thong-orn N, Tanticharoen M, Thebtaranonth Y. Unusual enniatins produced by the insect pathogenic fungus *Verticillium hemipterigenum*: isolation and studies on precursor-directed biosynthesis. *Tetrahedron* (2003) 59(7):1015–20. doi:10.1016/S0040-4020(02)01631-9
47. Supothina S, Isaka M, Kirtikara K, Tanticharoen M, Thebtaranonth Y. Enniatin production by the entomopathogenic fungus *Verticillium hemipterigenum* BCC 1449. *J Antibiot (Tokyo)* (2004) 57(11):732–8. doi:10.7164/antibiotics.57.732
48. Meca G, Soriano JM, Gaspari A, Ritieni A, Moretti A, Mañes J. Antifungal effects of the bioactive compounds enniatins A, A(1), B, B(1). *Toxicon* (2010) 56(3):480–5. doi:10.1016/j.toxicon.2010.04.013
49. Herrmann M, Zocher R, Haese A. Enniatin production by *Fusarium* strains and its effect on potato tuber tissue. *Appl Environ Microbiol* (1996) 62(2):393–8.

50. Hershenhorn J, Park SH, Stierle A, Strobel GA. *Fusarium avenaceum* as a novel pathogen of spotted knapweed and its phytotoxins, acetamidobutenolide and enniatin B. *Plant Sci* (1992) 86(2):155–60. doi:10.1016/0168-9452(92)90161-E
51. Gäumann E, Naef-Roth S, Kern H. Zur phytotoxischen Wirksamkeit der Enniatine. *J Phytopathol* (1960) 40(1):45–51. doi:10.1111/j.1439-0434.1960.tb01916.x
52. Burmeister HR, Plattner RD. Enniatin production by *Fusarium tricinctum* and its effect on germinating wheat seeds. *Phytopathology* (1987) 77(10):1483–7. doi:10.1094/Phyto-77-1483
53. Sy-Cordero AA, Pearce CJ, Oberlies NH. Revisiting the enniatins: a review of their isolation, biosynthesis, structure determination and biological activities. *J Antibiot (Tokyo)* (2012) 65(11):541–9. doi:10.1038/ja.2012.71
54. Benz R. Alkali ion transport through lipid bilayer membranes mediated by enniatin A and B and beauvericin. *J Membr Biol* (1978) 43(4):367–94. doi:10.1007/BF01871697
55. Ivanov VT, Evstratov AV, Sumskaya LV, Melnik EI, Chumburidze TS, Portnova SL, et al. Sandwich complexes as a functional form of the enniatin ionophores. *FEBS Lett* (1973) 36(1):65–71. doi:10.1016/0014-5793(73)80338-2
56. Kamyar M, Rawnduzi P, Studenik CR, Kouri K, Lemmens-Gruber R. Investigation of the electrophysiological properties of enniatins. *Arch Biochem Biophys* (2004) 429(2):215–23. doi:10.1016/j.abb.2004.06.013
57. Ovchinnikov YA, Ivanov VT, Evstratov AV, Mikhaleva II, Bystrov VF, Portnova SL, et al. The enniatin ionophores. Conformation and ion binding properties. *Int J Pept Protein Res* (1974) 6(6):465–98. doi:10.1111/j.1399-3011.1974.tb02407.x
58. Hoornstra D, Andersson MA, Mikkola R, Salkinoja-Salonen MS. A new method for in vitro detection of microbially produced mitochondrial toxins. *Toxicol In Vitro* (2003) 17(5–6):745–51. doi:10.1016/S0887-2333(03)00097-3
59. Trenin AS, Tolstykh IV, Terekhova LP, Zenkova VA, Makarova MO, Gladkikh EG, et al. [The hypolipidemic action of antibiotic 86/88 (enniatin B) in a hepatoblastoma G2 cell culture]. *Antibiot Khimioter* (2000) 45(4):6–9.
60. Hiraga K, Yamamoto S, Fukuda H, Hamanaka N, Oda K. Enniatin has a new function as an inhibitor of Pdr5p, one of the ABC transporters in *Saccharomyces cerevisiae*. *Biochem Biophys Res Commun* (2005) 328(4):1119–25. doi:10.1016/j.bbrc.2005.01.075
61. Dornetshuber R, Heffeter P, Sulyok M, Schumacher R, Chiba P, Kopp S, et al. Interactions between ABC-transport proteins and the secondary *Fusarium* metabolites enniatin and beauvericin. *Mol Nutr Food Res* (2009) 53(7):904–20. doi:10.1002/mnfr.200800384
62. Devreese M, De Baere S, De Backer P, Croubels S. Quantitative determination of the *Fusarium* mycotoxins beauvericin, enniatin A, A1, B and B1 in pig plasma using high performance liquid chromatography-tandem mass spectrometry. *Talanta* (2013) 106:212–9. doi:10.1016/j.talanta.2012.11.068
63. Fraeyman S, Devreese M, Antonissen G, De Baere S, Rychlik M, Croubels S. Comparative oral bioavailability, toxicokinetics, and biotransformation of enniatin B1 and enniatin B in broiler chickens. *J Agric Food Chem* (2016) 64(38):7259–64. doi:10.1021/acs.jafc.6b02913
64. Meca G, Font G, Ruiz MJ. Comparative cytotoxicity study of enniatins A, A1, A2, B, B1, B4 and J3 on Caco-2 cells, Hep-G2 and HT-29. *Food Chem Toxicol* (2011) 49:2464–9. doi:10.1016/j.fct.2011.05.020
65. Vejdovszky K, Warth B, Sulyok M, Marko D. Non-synergistic cytotoxic effects of *Fusarium* and *Alternaria* toxin combinations in Caco-2 cells. *Toxicol Lett* (2016) 241:1–8. doi:10.1016/j.toxlet.2015.10.024
66. Lombardi G, Prosperini A, Font G, Ruiz MJ. Effect of polyphenols on enniatins-induced cytotoxic effects in mammalian cells. *Toxicol Mech Methods* (2012) 22(9):687–95. doi:10.3109/15376516.2012.717120
67. Uhlig S, Gutleb AC, Thrane U, Flåøyen A. Identification of cytotoxic principles from *Fusarium avenaceum* using bioassay-guided fractionation. *Toxicon* (2005) 46:150–9. doi:10.1016/j.toxicon.2005.03.005
68. Dornetshuber R, Heffeter P, Lemmens-Gruber R, Elbling L, Marko D, Micksche M, et al. Oxidative stress and DNA interactions are not involved in enniatin- and beauvericin-mediated apoptosis induction. *Mol Nutr Food Res* (2009) 53(9):1112–22. doi:10.1002/mnfr.200800571
69. Föllmann W, Behm C, Degen GH. The emerging *Fusarium* toxin enniatin B: in-vitro studies on its genotoxic potential and cytotoxicity in V79 cells in relation to other mycotoxins. *Mycotoxin Res* (2009) 25(1):11–9. doi:10.1007/s12550-008-0002-y
70. Chou TC, Talalay P. Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors. *Adv Enzyme Regul* (1984) 22:27–55. doi:10.1016/0065-2571(84)90007-4
71. Ficheux AS, Sibiril Y, Parent-Massin D. Co-exposure of *Fusarium* mycotoxins: in vitro myelotoxicity assessment on human hematopoietic progenitors. *Toxicon* (2012) 60(6):1171–9. doi:10.1016/j.toxicon.2012.08.001
72. Juan-García A, Manyes L, Ruiz MJ, Font G. Applications of flow cytometry to toxicological mycotoxin effects in cultured mammalian cells: a review. *Food Chem Toxicol* (2013) 56:40–59. doi:10.1016/j.fct.2013.02.005
73. Kroemer G, Dallaporta B, Resche-Rigon M. The mitochondrial death/life regulator in apoptosis and necrosis. *Annu Rev Physiol* (1998) 60:619–42. doi:10.1146/annurev.physiol.60.1.619


**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Nutrition

ORIGINAL RESEARCH
published: 16 August 2018
doi: 10.3389/fnut.2018.00063

# Dietary Practice and Nutritional Status of Tuberculosis Patients in Pokhara: A Cross Sectional Study

*Lal M. Gurung, Laxman D. Bhatt, Isha Karmacharya and Dipendra K. Yadav**

*Pokhara University, School of Health and Allied Sciences, Lekhnath, Nepal*

**Background:** Undernutrition increases the risk of progression from Tuberculosis (TB) infection to active TB disease and further leads to weight loss. Proper diet and nutrition play significant roles in treating TB patients. Active TB needs high energy requirement. The main aim of this study is to assess the dietary intake and nutritional status of TB patients in Pokhara city of Nepal.

**Methods:** A cross-sectional descriptive study was carried out among 133 TB patients taking anti-tubercular drug. Data were collected using sequential sampling method. Data were collected from 4th October to 7th November, 2016.

**Results:** This study revealed that about one-fifth of TB patients did not consume sufficient amount of calories as per RDA. More than one-third of patients were underweight during the time of registration and this is reduced to 21.8 percent in the present situation. Mean BMI was 20.99 kg/m$^2$ (SD $\pm$ 5.81). Similarly, the mean BMI among Pulmonary TB (PTB) is 19.82 and 22.52 kg/m$^2$ in Extra PTB. Working conditions and food intake frequency were significantly associated with calorie intake. This study found that the amount of calories, food frequency per day, types of TB, and nutritional status during registration were found to be associated with recent nutritional status. The statistical difference between mean BMI at registration and recent BMI and mean weight at registration and recent weight.

**Conclusion:** Nutritional status has improved comparatively from the time of registration to the time of study. Proper nutritional counseling should be given to TB patients along with nutritional support to severely malnourished patients, and nutritional assessment of TB patients should be done periodically.

**Keywords: tuberculosis, nutrition, diet, TB patients, Nepal**

OPEN ACCESS

***Edited by:***
*Giuseppe Grosso, NNEdPro Global Centre for Nutrition and Health, United Kingdom*

***Reviewed by:***
*Justyna Godos, Jagiellonian University, Poland*
*Stefano Marventano, Ospedale Infermi di Rimini, Italy*

****Correspondence:***
*Dipendra K. Yadav*
*dipendrayadavph@gmail.com*

***Specialty section:***
*This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition*

***Received:*** *21 February 2018*
***Accepted:*** *22 June 2018*
***Published:*** *16 August 2018*

***Citation:***
*Gurung LM, Bhatt LD, Karmacharya I and Yadav DK (2018) Dietary Practice and Nutritional Status of Tuberculosis Patients in Pokhara: A Cross Sectional Study. Front. Nutr. 5:63. doi: 10.3389/fnut.2018.00063*

## INTRODUCTION

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* which often affect the lungs, although it can spread to other organs in the body (1). TB is the second deadliest disease worldwide caused by a single infectious agent (1). Globally, in 2014, 9.6 million people were estimated to have fallen ill with TB; among them, 3.2 million were women, 5.4 million were men, and 1.0 million were children. Of the 9.6 million TB cases, in 2014, 12% of them were HIV positive. Now, TB ranks along with HIV as a leading cause of death worldwide (2). However, TB is completely curable through a short course of chemotherapy (DOTS), which has been recognized as a highly cost-efficient and effective strategy (3).

TB spreads from person to person through the air (4). There are two kinds of TB infections: latent and active. In latent TB, the bacteria remain inactive and do not show any typical signs and symptoms of TB. While they are not contagious, they can become active at any time. In active TB, the bacteria show signs and symptoms of TB and are contagious to others (1). Symptoms of active pulmonary TB are coughing, chest pain, fever, night sweats, weight loss, fatigue, and sometimes, the coughing up of blood (5). Active TB, like other infectious diseases, requires high energy consumption i.e., 20–30% extra energy of recommended daily allowance (RDA). Undernutrition increases the risk of progression from TB infection to an active TB disease. Food insecurity and poor nutritional status in the population are important contributors to the global burden of the TB disease (6).

Both malnutrition and TB are of considerable magnitude in most of the underdeveloped regions of the world. Nutritional status is significantly lower in patients having active TB than others (7). Therefore, the present study focused on the dietary intake and nutritional status of TB patients in Pokhara, Nepal.

**TABLE 1 |** Socio-demographic characteristics of TB patients ($n = 133$).

| | Characteristics | *n* | % |
|---|---|---|---|
| Age group | 10–20 | 18 | 13.5 |
| | 20–30 | 44 | 33.1 |
| | 30–40 | 27 | 20.3 |
| | 40–50 | 26 | 19.5 |
| | 50–60 | 7 | 5.3 |
| | more than 60 | 11 | 8.3 |
| Mean = 35.23 years, SD = 15.05, $Min^m = 14$, $Max^m = 82$ | | | |
| Sex | Male | 81 | 60.9 |
| | Female | 52 | 39.1 |
| Family Type | Single | 73 | 54.9 |
| | Joint | 60 | 45.1 |
| Family Size | ≤5 members | 95 | 71.4 |
| | >5 members | 38 | 28.6 |
| Mean = 4.92, SD = 2.27, $Min^m = 1$, $Max^m = 14$ | | | |
| Marital status | Unmarried | 45 | 33.9 |
| | Married | 78 | 58.6 |
| | Separated | 2 | 1.5 |
| | Widow | 8 | 6.0 |
| Ethnicity | Dalit Caste | 20 | 15.0 |
| | Disadvantaged Janajati Caste | 21 | 15.8 |
| | Disadvantaged Non Dalit Terai Caste | 3 | 2.3 |
| | Advantaged Janajati Caste | 44 | 33.1 |
| | Upper Caste | 45 | 33.8 |
| Religion | Hindu | 115 | 86.4 |
| | Buddhist | 13 | 9.8 |
| | Muslim | 1 | 0.8 |
| | Christian | 1 | 0.8 |
| | Others | 3 | 2.2 |
| Occupation | Agriculture | 37 | 27.9 |
| | Employment | 25 | 18.8 |
| | Household activity | 24 | 18.0 |
| | Business | 16 | 12.0 |
| | Student | 16 | 12.0 |
| | Labor | 12 | 9.0 |
| | Others(Trekking) | 3 | 2.3 |
| Education | Illiterate | 15 | 11.3 |
| | No-formal education | 22 | 16.5 |
| | Lower secondary | 28 | 21.0 |
| | Secondary | 32 | 24.1 |
| | Higher secondary | 36 | 27.1 |

**TABLE 2 |** Disease and health services utilization related information.

| Characteristics | *n* | % |
|---|---|---|
| Types TB ($n = 133$) | | |
| Pulmonary TB | 73 | 54.9 |
| Extra PTB | 60 | 45.1 |
| Disease duration ($n = 133$) | | |
| <6 months | 101 | 75.9 |
| ≥6 months | 32 | 24.1 |
| Median = 4, IQR = 3, $Min^m = 0$, $Max^m = 13$ | | |
| Occurrence of complication ($n = 133$) | | |
| Yes | 43 | 32.3 |
| No | 90 | 67.7 |
| Co-morbid diseases ($n = 29$) | | |
| Diabetes | 9 | 31 |
| Arthritis | 4 | 13.9 |
| Hypo-tension | 4 | 13.9 |
| Kidney disease | 3 | 10.3 |
| Hypertension | 2 | 6.9 |
| Gastritis | 2 | 6.9 |
| Thyroid | 1 | 3.4 |
| HIV/AIDs | 1 | 3.4 |
| Others | 3 | 10.3 |
| Treatment CAT ($n = 133$) | | |
| CAT I | 119 | 89.5 |
| CAT II | 14 | 10.5 |
| Start to take medicine after illness ($n = 133$) | | |
| ≤1 month | 77 | 57.9 |
| >1 month | 56 | 42.1 |
| Mean = 0.97, SD = 1.67 | | |
| Phase of medication ($n = 133$) | | |
| Intensive phase | 37 | 27.8 |
| Continuous phase | 96 | 72.2 |
| Duration of missing medication ($n = 15$) | | |
| Not defaulted | 14 | 93.3 |
| Defaulted | 1 | 6.7 |
| Median = 6 days, IQR = 11, $Min^m = 1$, $Max^m = 99$ | | |

**TABLE 3 |** Food related information.

| Characteristics | | *n* | % |
|---|---|---|---|
| Frequency of food intake in a day ($n = 133$) | ≤4 times | 47 | 35.3 |
| | >4 times | 86 | 64.7 |
| | Median = 4, IQR = 1, $Min^m = 2$, $Max^m = 6$ | | |
| Meal not prepared at house consumption per week ($n = 66$) | ≤2 days | 26 | 39.4 |
| | >2 days | 40 | 60.6 |
| | Median = 2, IQR = 4 | | |
| Protein rich food* | Pulses | 123 | 92.5 |
| | Meat | 121 | 91.0 |
| | Egg | 107 | 80.4 |
| | Milk and milk product | 104 | 78.2 |
| | Fish | 57 | 42.9 |
| Protective food* | Vegetables | 130 | 97.7 |
| | Fruits | 125 | 93.9 |
| Calorie intake per day ($n = 133$) | Not sufficient | 29 | 21.8 |
| | Sufficient | 104 | 78.2 |
| | Mean = 3239.39 Kcal, SD = 1352.47, $Min^m = 339$Kcal, $Max^m = 7626.75$ Kcal | | |

*based on multiple response analysis.

**TABLE 4 |** Nutritional Status of TB patients.

| Characteristics | | *n* | % |
|---|---|---|---|
| Recent nutritional status ($n = 133$) | Underweight | 29 | 21.8 |
| | Normal | 81 | 60.9 |
| | Over weight | 23 | 17.3 |
| | Mean BMI = 20.99 k.g/$m^2$, SD = 5.81, $Min^m = 13.699$ kg/$m^2$, $Max^m = 32.8999$ kg/$m^2$ | | |
| **FURTHER CLASSIFICATION OF NUTRITIONAL STATUS** | | | |
| Undernutrition ($n = 29$) | Severe thinness | 6 | 20.7 |
| | Moderate thinness | 4 | 13.8 |
| | Mild thinness | 19 | 65.5 |
| Over weight ($n = 23$) | Pre-obese | 19 | 82.6 |
| | Obese class I | 4 | 17.4 |
| **BASIS OF CALORIE INTAKE** | | | |
| Not sufficient calorie intake ($n = 29$) | Malnutrition | 9 | 31 |
| | Normal | 13 | 44.9 |
| | Over weight | 7 | 24.1 |
| Sufficient calorie intake ($n = 104$) | Malnutrition | 20 | 19.2 |
| | Normal | 68 | 65.4 |
| | Over weight | 16 | 15.4 |

## METHODS

This was a cross-sectional descriptive study conducted among TB patients taking anti-tubercular drug in Pokhara, Nepal, from 4th October to 7th November, 2016. The total number of TB patients in Pokhara were 203 in FY 2072/73. The sample size was determined by assuming the prevalence of malnutrition in TB patients to be 51% (8), 95% confidence limit, and 5% marginal error, and the sample size was 133.

List of total 12 Directly Observed Treatment Short Course (DOTS) centers in Pokhara was obtained from District Public Health Office (DPHO), Kaski, and arranged from numbers one to twelve. A sequential sampling technique was used. Of them, the required sample size was met at the 11th DOTS center. Patients who visited the DOTS center during the data collection period were included in the study.

The structured questionnaire was developed referencing STEP wise approach to Surveillance (STEPS) survey, Nepal (9, 10), and was translated into the Nepali language. The questionnaire was pre-tested on 10% of the total sample in Tanahun, Nepal. Primary data collection was performed through face-to-face interviews. Tools for the data collection were a structured questionnaire, checklist (patient treatment card), bathroom scale weighing machine for weight measurement, stature meter for height measurement, and locally available cups, plates, and glasses for measuring the amount of food consumed.

Data were entered into EpiData software and analyzed by using SPSS 20 version software. Univariate and bivariate analyses were performed for data analysis. The size of dishes used to measure the amount of food was of 250 ml, which was equivalent to a standard cup size. Through this reference, the amount of food was converted into a standard serving size, and the daily energy intake was calculated by Nutrition facts 0.9.5.0 version and Food tables (11).

The study protocol was reviewed and approved by the Ethical Review Committee of Pokhara University Research Centre and permission was taken from DPHO Kaski. Informed verbal consent was obtained from all the participants prior to data collection, and data confidentiality was maintained.

## RESULTS

Out of 133 participants, the majority (33.1%) of them were between 20 and 30 years of age, with the mean age being 35.23 years (SD ± 15.05). More than half (60.9%) of them were males. Most were predominantly upper caste by ethnicity and Hindu by religion (**Table 1**).

Information related to diseases and health service utilization among TB patients is given in **Table 2**. More than half of the patients have Pulmonary TB. 57.9% TB patients started medication in less than 1 month after diagnosis.

Information related to food and its consumption is given in **Table 3**. The majority (78.2%) of the participants consumed a sufficient amount of calories, whereas 21.8% did not. The mean was 3239.39 (SD ± 1352.47).

The nutritional status among TB patients is given in **Table 4**. Mean weight and height were 51.98 kg and 1.57 m, respectively. Relatively, a higher percent were underweight (21.8%) than overweight (17.3%).

Factors which are associated with calorie intake are shown in **Table 5**. Working conditions and food intake frequency were significantly associated with calorie intake. Socio-demographic factors and disease-related factors were not found to be associated with calorie intake.

**TABLE 5 |** Factors associated with calorie intake.

| Characteristics | | Not sufficient | Sufficient | *p*-value | UOR (95% CI) |
|---|---|---|---|---|---|
| **CALORIE INTAKE** | | | | | |
| Sex | Male | 19 (23.5%) | 62 (76.5%) | 0.565 | 1.29 (0.54–3.04) |
| | Female | 10 (19.2% ) | 42 (80.8%) | | |
| Age | ≤30 | 13 (21.7%) | 47(78.3%) | 0.97 | 0.98 (0.43–2.25) |
| | >30 | 16 (21.9%) | 57 (78.1%) | | |
| Ethnicity | Dalit/Disadvantaged group | 12 (27.3%) | 32 (72.7%) | 0.28 | 1.58 (0.68–3.7) |
| | Upper/Advantaged group | 17 (19.1%) | 71 (80.9%) | | |
| Religion | Hindu | 28 (23.7%) | 90 (76.3%) | 0.24# | 4.35 (0.54–34.6) |
| | Other than Hindu | 1 (6.7%) | 14 (93.3%) | | |
| Working condition | Working | 33 (35.5%) | 60 (64.5%) | 0.007* | 3.85 (1.36–10.7) |
| | Not working | 5 (12.5%) | 35 (87.5%) | | |
| Education | Illiterate | 4 (26.7%) | 11 (73.3%) | 0.88# | – |
| | Primary level | 7 (20.6%) | 27 (79.4%) | | |
| | Higher than primary | 18 (21.4%) | 66 (78.6%) | | |
| Food frequency per day | ≤4 times | 15 (31.9%) | 32 (68.1%) | 0.037* | 2.40 (1.04–5.57) |
| | >4 times | 14 (16.3%) | 72 (83.7%) | | |
| Types of TB | Pulmonary TB | 15 (20.5%) | 58 (79.5%) | 0.699 | 0.85 (0.37–1.93) |
| | Extra PTB | 14 (23.3%) | 46 (76.7%) | | |
| Treatment category | CAT I | 24 (20.2%) | 95 (79.8%) | 0.18 | 0.45 (0.14–1.48) |
| | CAT II | 5 (35.7%) | 9 (64.3%) | | |
| Duration of start medication after illness | ≤1 month | 17 (22.1%) | 60 (77.9%) | 0.929 | 1.03 (0.45–2.39) |
| | >1 month | 12 (21.4%) | 14 (78.6%) | | |
| Co-morbid condition | Yes | 8 (27.6%) | 21 (72.4%) | 0.39 | 1.50 (0.58–3.87) |
| | No | 21 (20.2%) | 83 (79.8%) | | |

**Statistically significant p-value from bivariate analysis, #p-value from likelihood ratio.*

**TABLE 6 |** Factors associated with recent nutritional status.

| Characteristics | | Normal | Malnutrition | *p*-value | UOR (95% CI) |
|---|---|---|---|---|---|
| **RECENT NUTRITIONAL STATUS** | | | | | |
| Sex | Male | 49 (60.5%) | 32 (39.5%) | 0.904 | 0.96 (0.46–1.95) |
| | Female | 32 (61.5%) | 20 (38.5%) | | |
| Family size | ≤5 members | 57 (60.0%) | 38 (40.0%) | 0.73 | 0.87 (0.43–1.9) |
| | >5 members | 24 (63.2%) | 14 (36.8%) | | |
| Food frequency per day | ≤4 times | 21 (44.7%) | 26 (53.3%) | 0.005* | 0.34 (0.16–0.73) |
| | > 4 times | 60 (69.8%) | 26 (30.2%) | | |
| Types of TB | Pulmonary TB | 32 (43.8%) | 41 (56.2%) | 0.025* | 0.45 (0.22–0.91) |
| | Extra PTB | 38 (63.3%) | 22 (36.7%) | | |
| Calorie intake | Not sufficient | 13 (44.8%) | 16 (55.2%) | 0.045* | 0.43 (0.186–0.992) |
| | Sufficient | 68 (65.4%) | 36 (34.6%) | | |
| Nutrition at registration | Normal | 61 (87.1%) | 9 (12.9%) | <0.001* | 14.57 (6.05–35.06) |
| | Malnutrition | 20 (31.7%) | 43 (68.3%) | | |

**Statistically significant p-value from bivariate analysis.*

Factors that are associated with recent nutritional status of TB patients are given in **Table 6**. Food frequency, TB types, calorie intake, and nutritional status at the time of registration were significantly associated with the recent nutritional status of the participants.

Statistical differences between mean BMI at registration and recent BMI (MD −1.04; 95% CI −1.05 to −1.39; $p < 0.001$) and mean weight at registration and recent weight (MD −1.52; 95% CI −1.004 to −1.003; $p < 0.001$) are shown in **Table 7**.

## DISCUSSION

This study revealed that about one-fifth of TB patients did not consume sufficient amounts of calories as per the RDA. The study

**TABLE 7 |** Mean difference between BMI and Weight at registration and recent BMI and Weight.

| | *p*-value | Mean difference | 95% CI |
|---|---|---|---|
| BMI | <0.001* | −1.04 | −1.05 to −1.39 |
| Weight | <0.001* | −1.52 | −1.004 to −1.003 |

*Statistically significant p-value based on t-test*

found that 36.1% were underweight and 11.35% were overweight during the time of registration. In contrast, studies conducted in other countries found that 51% in Ghana (8), more than 85% in India (12), 70.6% in Brazil (13), 57% in Malawi (14), and more than 58% in Tanzania (15) were underweight during the time of registration. It might be due to the difference in sampling size and study setting. This study found that male patients were more underweight than females. In contrast, a study conducted in India found that females were more underweight than males during the time of registration (12). However, nutritional status improved by 15.3% in patients who had completed two months of medication. Other studies showed that nutritional status was improved by 11% (8) and 13.5% (12) at the end of the treatment.

The prevalence of co-morbidity was 21.85%, where diabetes was the most prevalent (31%) followed by hypotension and arthritis. A study done in Tanzania showed that prevalence of diabetes among PTB was 6.7% (16). In India, annual cases of TB increased to 46% among people with diabetes (17).

This study found that the amount of calorie, food frequency per day, types of TB, and nutritional status during registration was found to be associated with recent nutritional status. However, socio-demographic factors were not associated with nutritional status, whereas a study in Tanzania found that sex was significantly associated with nutritional status (18). In this study, the majority (86.5%) of patients belonged to the Hindu religion. A study conducted in immigrant Asians from South London revealed Hindu Asians were found to have a significantly increased risk for TB compared with Muslims (19).

## CONCLUSIONS

This study revealed that about one-fifth of TB patients did not consume the sufficient amount of calories as per the RDA. The Mean calorie intake was 3239.39 (SD ± 1352.47). More than one-third of the patients were underweight at the time of registration, but this is reduced to 21.6% in the present situation. The mean BMI was 20.99 kg/m$^2$ (SD ± 5.81): 20.56 kg/m$^2$ in males and 21.67 kg/m$^2$ in females. Similarly, mean BMI among PTB was 19.82 and 22.52 kg/m$^2$ in Extra PTB. The prevalence of co-morbidity was 21.85%, where diabetes was the most prevalent (31%). Working conditions and food intake frequency were significantly associated with calorie intake. This study found that the amount of calories, food frequency per day, types of TB, and nutritional status during registration were found to be associated with the recent nutritional status. There was statistical differences between mean BMI at registration and after treatment and mean weight at registration and after treatment. It was increased after treatment. The nutritional status has improved comparatively from the time of registration to the present situation. Proper nutritional counseling along with nutritional support should be given to severely malnourished TB patients, and nutritional assessment of TB patients should be done periodically.

## ETHICS STATEMENT

Ethical clearance was obtained from the institutional review committee of Pokhara University at the beginning of the study. Detailed information was available in Nepali to all participants. Confidentiality was maintained and the information was used for research purposes only. Each participants participated voluntarily in this study. Written consent was taken from all the participants before the data collection. Participants were informed about their BMI status. In case of an abnormal range, educational counseling was given regarding a balanced diet and they were referred to a nutritionist for the further services.

## AUTHOR CONTRIBUTIONS

LG was the principle investigator for the study. She compiled all contributor tasks, generated the topic and reviewed the related literature. LG and LB facilitated data collection. DY designed the study methodology and overall analysis and helped write the results section. LG, LB, and IK drafted the manuscript. DY reviewed the manuscript.

## FUNDING

DY received a Faculty Research Grant from the University Grant Commission of Nepal and the research was titled Prevalence of Diabetes Mellitus among TB Patients and their Quality of Life in Western Region of Nepal in 2016 (Nepalese fiscal year 2072-2073). DY was required to supervise the dissertation of students researching in a similar area.

## REFERENCES

1. McIntosh J. Tuberculosis: causes, symptoms and treatments. *Medical News Today* (2015).
2. WHO. *Global Tuberculosis Report 2015*.
3. WHO. *What is DOTS (Directly Observed Chemotherapy, Short Course)*. SEARO (2016).
4. WHO. *Tuberculosis*. Geneva: World Health Organization (2015).
5. Sinclair D, Abba K, Grobler L, Sudarsanam TD. Nutritional supplements for people being treated for active tuberculosis. *Cochrane Database Syst Rev*. (2011) 9:CD006086. doi: 10.1002/14651858.CD006086
6. WHO. *Guideline: Nutritional Care and Support for Patients With Tuberculosis*. Geneva: World Health Organization (2013).
7. Gupta KB, Gupta R, Atreja A, Verma M, Vishvkarma S. Tuberculosis and nutrition. *Lung India* (2009) 26:9. doi: 10.4103/0970-2113.45198

8. Dodor E. Evaluation of nutritional status of new tuberculosis patients at the effia-nkwanta regional hospital. *Ghana Med. J.* (2008) 42:22–28.
9. Kumar Aryal K, Neupane S, Mehata S, Vaidya A, Singh S, Paulin F, et al. *Non Communicable Diseases Risk Factors: STEPS Survey Nepal 2013*. (2013).
10. Lamsal A. *Assessment of Food Intake by Children Attending Montessori School of Pokhara Valley Faculty of Health Science*. Lekhnath: Pokhara University (2015).
11. Park K. *Park's Textbook of Preventive and Social Medicine, 19th Edn.* Jabalpur: Banarsidas Bhanot Publishers (2007).
12. Bhargava A, Chatterjee M, Jain Y, Chatterjee B, Kataria A, Bhargava M, et al. Nutritional status of adult patients with pulmonary tuberculosis in rural central India and its association with mortality. *PLoS ONE* (2013) 8:e77979. doi: 10.1371/journal.pone.0077979
13. Bacelo AC, Ramalho A, Brasil PE, Cople-Rodrigues Cdos S, Georg I, Paiva E, et al. Nutritional supplementation is a necessary complement to dietary counseling among tuberculosis and tuberculosis-HIV patients. *PLoS ONE* (2015) 10:e0134785. doi: 10.1371/journal.pone.0134785
14. Zachariah R, Spielmann M, Harries A, Salaniponi F. Moderate to severe malnutrition in patients with tuberculosis is a risk factor associated with early death. *Trans R Soc Trop Med Hyg.* (2002) 96:291–4.
15. Kennedy N, Ramsay A, Uiso L, Gutmann J, Ngowi F, Gillespie S. Nutritional status and weight gain in patients with pulmonary tuberculosis in Tanzania. *Trans R Soc Trop Med Hyg.* (1996) 90:162–6.
16. Mugusi F, Swai A, Alberti K, McLarty D. Increased prevalence of diabetes mellitus in patients with pulmonary tuberculosis in Tanzania. *Tubercle* (1990) 71:271–6.
17. Dye C, Bourdin Trunz B, Lonnroth K, Roglic G, Williams BG. Nutrition, diabetes and tuberculosis in the epidemiological transition. *PLoS ONE* (2011) 6:e21161. doi: 10.1371/journal.pone.0021161
18. PrayGod G, Range N, Faurholt-Jepsen D, Jeremiah K, Faurholt-Jepsen M, Aabye MG, et al. Sex, smoking, and socioeconomic status are associated with body composition among tuberculosis patients in a deuterium dilution cross-sectional study in Mwanza, Tanzania. *J Nutr*. (2013) 143:735–41. doi: 10.3945/jn.112.168997
19. Strachan DP, Powell KJ, Thaker A, Millard FJ, Maxwell JD. Vegetarian diet as a risk factor for tuberculosis in immigrant south London Asians. *Thorax* (1995) 50:175–80.


**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Nutrition

ORIGINAL RESEARCH
published: 09 February 2018
doi: 10.3389/fnut.2018.00008

# Environmental Impacts of Plant-Based Diets: How Does Organic Food Consumption Contribute to Environmental Sustainability?

*Camille Lacour[1], Louise Seconda[1,2]*, Benjamin Allès[1], Serge Hercberg[1,3], Brigitte Langevin[4], Philippe Pointereau[4], Denis Lairon[5], Julia Baudry[1] and Emmanuelle Kesse-Guyot[1]*

[1] Equipe de Recherche en Epidémiologie Nutritionnelle (EREN), Centre d'Epidémiologie et Statistiques Sorbonne Paris Cité, INSERM (U1153), INRA (U1125), CNAM, Université Paris 13, COMUE Sorbonne Paris Cité, Bobigny, France, [2] Agence de l'Environnement et de la maîtrise de l'Energie, Angers, France, [3] Département de Santé Publique, Hôpital Avicenne, Bobigny, France, [4] Solagro, Toulouse, France, [5] Nutrition Obésité et Risque Thrombotique (NORT), Aix Marseille Université, INRA 1260, INSERM UMR S 1062, Marseille, France

OPEN ACCESS

**Edited by:**
Giuseppe Grosso,
NNEdPro Global Centre for Nutrition and Health, United Kingdom

**Reviewed by:**
Alessandra Lafranconi,
Università degli studi di Milano Bicocca, Italy
Eda Bozkır,
Università Politecnica delle Marche, Italy
Alice Rosi,
Università degli Studi di Parma, Italy

***Correspondence:**
Louise Seconda
l.seconda@eren.smbh.univ-paris13.fr

**Specialty section:**
This article was submitted to Nutrition and Environmental Sustainability, a section of the journal Frontiers in Nutrition

**Received:** 31 August 2017
**Accepted:** 22 January 2018
**Published:** 09 February 2018

**Citation:**
Lacour C, Seconda L, Allès B, Hercberg S, Langevin B, Pointereau P, Lairon D, Baudry J and Kesse-Guyot E (2018) Environmental Impacts of Plant-Based Diets: How Does Organic Food Consumption Contribute to Environmental Sustainability? Front. Nutr. 5:8. doi: 10.3389/fnut.2018.00008

**Background:** Studies investigating diet-related environmental impacts have rarely considered the production method of the foods consumed. The objective of the present study, based on the NutriNet-Santé cohort, was to investigate the relationship between a provegetarian score and diet-related environmental impacts. We also evaluated potential effect modifications on the association between a provegetarian score and the environmental impacts of organic food consumption.

**Methods:** Food intake and organic food consumption ratios were obtained from 34,442 French adults using a food frequency questionnaire, which included information on organic food consumption for each group. To characterize the overall structure of the diets, a provegetarian score was used to identify preferences for plant-based products as opposed to animal-based products. Moreover, three environmental indicators were used to assess diet-related environmental impacts: greenhouse gas (GHG) emissions, cumulative energy demand (CED), and land occupation. Environmental impacts were assessed using production life cycle assessment (LCA) at the farm level. Associations between provegetarian score quintiles, the level of organic food consumption, and environmental indicators were analyzed using ANCOVAs adjusted for energy, sex, and age.

**Results:** Participants with diets rich in plant-based foods (fifth quintile) were more likely to be older urban dwellers, to hold a higher degree in education, and to be characterized by an overall healthier lifestyle and diet. A higher provegetarian score was associated with lower environmental impacts (GHG emissions$_{Q5vsQ1}$ = 838/1,664 kg $CO_{2eq}$/year, −49.6%, $P < 0.0001$; CED$_{Q5vsQ1}$ = 4,853/6,775 MJ/year, −26.9%, $P < 0.0001$; land

**Abbreviations:** GHG, greenhouse gas; CED, cumulative energy demand; LCA, life cycle analysis; Q, quintile; PUFA, polyunsaturated acid; MUFA, monounsaturated acid; SFA, saturated fatty acid.

occupation$_{Q5vsQ1}$ = 2,420/4,138 m$^2$/year, −41.5%, $P < 0.0001$). Organic food consumption was also an important modulator of the relationship between provegetarian dietary patterns and environmental impacts but only among participants with diets rich in plant-based products.

**Conclusion:** Future field studies should endeavor to integrate all the components of a sustainable diet, i.e., both diet composition and production methods.

**Keywords: provegetarian dietary pattern, organic food consumption, eco-friendly farming, diet-related environmental impact, sustainability**

## INTRODUCTION

According to the Food and Agricultural Organization (FAO), adopting sustainable diets at a global level is urgently needed (1). Sustainable diets should include a large share of ecologically based, local and minimally processed products and limited consumption of animal products. Sustainable diets are also healthy in terms of both nutrition and sanitary quality (1). Regarding the environmental aspects of a sustainable diet, a shift from current dietary patterns toward more environmentally friendly habits appears necessary. Environmentally friendly habits include reducing the consumption of animal products and increasing the consumption of plant products (2). Indeed, livestock is considered to be responsible for 18% of the greenhouse gas (GHG) emissions from anthropogenic sources at the global level, and this pattern is comparable at the country level in France (3). More specifically, beef and milk production represent 41 and 20% of the emissions from livestock, respectively (3). Livestock requires substantial energy for multiple activities such as the production of feed, breeding activities, production and spread of fertilizers, electricity use, and operating costs of farm buildings (4). Intensive livestock production is also responsible for a large part of the loss in biodiversity due to important land use for grass and feed crops (5). Conversely, extensive livestock farming is suggested to have positive effects on biodiversity. Studies investigating these issues have consistently reported that decreasing the consumption of animal products would have a considerable beneficial impact on the environment (6, 7).

The FAO also mentions that alternative modes of production may be important to the promotion and development of sustainable diets. Organic agriculture is defined as a system that relies on ecosystem services rather than external agricultural inputs (8). It is generally considered a more environmentally friendly production model that enhances the quality of soil leading to higher plant and fauna diversity and lower nitrate leaching. Nevertheless, disparities in agro-ecological practices still remain (9–12). The sustainability of organic food systems and their ability to feed the global population have often been questioned mostly due to their usually lower crop yields (13, 14). It is now largely recognized that organic production requires less energy inputs than conventional systems (15–17), although benefits in terms of GHG reduction are not straightforward (18). Moreover, firm conclusions about conventional and organic systems are moderated by the functional unit (18–20).

Despite ample literature on environmentally sustainable diets, few studies have considered both dietary patterns and production modes. It is, therefore, of interest to study both parameters simultaneously to be able to estimate the extent to which organic food consumption affects diet-related environmental impacts. It is of considerable interest to consider both plant-based and organic foods, which are consumed by vegetarians in Western countries (21).

A review of Aleksandrowicz et al. revealed that the change from a traditional western diet to alternative dietary patterns (e.g., Mediterranean, vegetarian, or vegan) normally provides benefits for both individual health and the environment (22). The reductions in environmental footprints should generally be proportional to the magnitude of the restriction of animal-based products (22). Despite lower environmental impacts when compared to omnivorous diets (23), vegan or vegetarian diets are still not culturally accepted, particularly in France, where meat-based meals and cheese are an integral part of the traditional diet (24). In this context, the provegetarian score (25), which characterizes diets by the level of plant and animal product consumption, and not directly by animal product exclusion, is highly relevant in the French environment.

Thus, the first objective of this study is to estimate diet-related environmental effects according to the provegetarian score. Second, we focused on studying the moderating effects of organic food consumption according to the level of plant-based food consumption. Data are based on a large sample from the NutriNet-Santé study within the framework of the BioNutriNet project, which enabled us to collect food consumption data and environmental data on both organic and conventional products.

## MATERIALS AND METHODS

### Study Population

The subjects are adult volunteer participants from the prospective NutriNet-Santé cohort, which was launched in May 2009 in France. The NutriNet-Santé study has been previously described in detail in another study (26). At inclusion in the cohort and yearly thereafter, the participants completed three 24-h randomly distributed accounts that were provided over a period of 15 days. They were also asked to complete a set of questionnaires about their sociodemographics, anthropometrics, health status, and lifestyle characteristics. Participants were also regularly invited to complete complementary questionnaires. In 2014, participants were asked to provide information on their organic

food consumption as well as their motives and attitudes toward organic foods.

## Data Collection

### Sociodemographic and Lifestyle Characteristics

The yearly updated inclusion questionnaire provided data on sociodemographic characteristics including age, sex, highest achieved degree (lower than high school, high school, or post-secondary graduate), location (rural community, urban unit with a population smaller than 20,000 inhabitants, between 20,000 and 200,000 inhabitants, or higher than 200,000 inhabitants), and monthly income per household unit (lower than 900 euros, between 900 and 1,200 euros, between 1,200 and 1,800 euros, between 1,800 and 2,700 euros, and higher than 2,700 euros). The monthly income per household unit was obtained by dividing monthly income by consumption units (CU); the first adult in the household represents 1 CU, other persons older than 14 represent 0.5 CU, and other persons younger than 14 years represent 0.3 CU (27).

This set of data also provided lifestyle characteristics such as physical activity (measured by the IPAQ–International Physical Activity Questionnaire) (28–30), smoking status (never, former, and current smoker), and alcohol intake (never, moderate, or frequent drinker). Moderate alcohol consumption was defined as an intake lower than 20 g/day for women and lower than 30 g/day for men (31).

### Dietary Data and Organic Food Consumption

Between June and December 2014, participants were asked to complete an optional organic food semi-quantitative frequency questionnaire (Org-FFQ) based on the original validated Nutrinet FFQ (32). The Org-FFQ collected information on consumption frequencies (yearly, monthly, weekly, and daily units) and portion sizes for 264 food and beverage items over a year. The total food intake was estimated by multiplying the consumption frequency and portion size for each item. To estimate the share of organic food consumption in the diet, for each item in the Org-FFQ, participants indicated how often they consumed that item in an organic form. Organic food frequency was assessed using a 5-point ordinal scale, "never," "rarely," "half of the time," "often," and "always," which were weighted as 0, 0.25, 0.5, 0.75, and 1, respectively, and yielded an estimate of the proportion of organic food consumed in an individual diet. The contribution of organic food consumption to the diet was calculated by dividing the total organic food intake (g/day) by the total food intake (g/day) excluding water. This ratio was multiplied by 100 to obtain the contribution of organic food as a percentage of weight.

The development of the Org-FFQ and sensitivity analyses for the allocation of arbitrary weightings has been described in another study (21).

The NutriNet-Santé food composition database (33) was used to estimate daily nutrient intake independently of the production method. To assess the nutritional quality of dietary patterns, two indicators were assessed at the individual level: the PANDiet (based on the probability of adequate nutrient intake for 24 nutrients) (34) and the mPNNS-GS (modified French national nutrition and health programme (Programme National Nutrition Santé), with the PNNS-guidelines score based on the adherence to the PNNS recommendations excluding physical activity) (35).

### Environmental Data

The methodology for the environmental evaluation of individual diets is described in detail in the Presentation S1 in Supplementary Material. Data were collected *via* the French diagnostic tool DIALECTE (36) using the life cycle assessment method (LCA) (37, 38) at the farm level (from agricultural inputs and animal feed production to harvest). To date, DIALECTE is the only French database that covers such a large panel of data for both organic and conventional agricultural products. This study considers the three environmental indicators available: (1) GHG emissions were estimated including carbon dioxide, methane and nitrous oxide emissions and were expressed in kilogram $CO_2$ equivalent per day. (2) The cumulative energy demand (CED) indicator was defined as the consumption of renewable and unrenewable energy in megajoules per day according to the CED method (39). (3) Finally, land occupation was defined as the area in square meters needed per day. The environmental database includes information on 62 raw agricultural products based on measurements from 2,086 farms in France and on 30 raw agricultural products based on information from the literature. Among these farms, 46% follow certified organic agricultural practices (as defined by European regulations).

For each participant, organic and conventional food consumption was multiplied by the environmental impact of each product to estimate the impact of the overall diet for each participant.

## Construction of the Provegetarian Score

The provegetarian score was developed to reflect the proportion of plant-based food consumed in a diet (25). Components of the provegetarian score include seven vegetable food groups and five animal food groups (25) (Table S1 in Supplementary Material). Sex-specific adjustment for total energy intake was made for the consumption of each food group using the residual method (40). Energy-adjusted, sex-specific quintile values for each plant component were calculated by allocating 1 to 5 points. For animal food groups, the quintile values were reversed (from 5 for the first quintile to 1 for the fifth quintile). Finally, the provegetarian score was obtained by summing the quintile value of each vegetable food group and the reverse quintile value of each animal food group. The score ranges from 12 (low consumption of plant food) to 60 (high consumption of plant food).

## Data Treatment and Statistical Analysis

Among the 37,685 participants who completed the Org-FFQ, participants with missing sociodemographic data or aberrant data were excluded ($N = 1{,}390$). To detect under reporting and over reporting, energy requirements were calculated for each individual using physical activity level (IPAQ) and basal metabolic rate, estimated by Schofield's equation (41) and taking into account age, sex, and BMI. The ratio of energy intake to energy requirement was calculated, and participants with a ratio below 0.35 or above 1.93 were excluded ($N = 1{,}099$). Finally, only participants living in mainland France and having complete data to calculate

the nutritional quality scores were included. The final sample included 34,442 participants, with 22,813 women and 7,569 men.

Sociodemographic and lifestyle characteristics along with food and nutrient intakes were presented across the provegetarian score quintiles. For descriptive purposes, nutrient and food data were adjusted for total energy intake by sex using the residual method (40). Means, SDs and percentages were provided as appropriate. *P* values referred to the Mantel–Haenzel chi-square trend test for categorical variables and to the linear contrast test (ANCOVA) for continuous variables.

The contributions (as percentages) of different food groups to diet-related GHG emissions and CED across provegetarian score quintiles are presented. All *P*-trends were obtained with linear contrast tests (ANCOVA).

As an interaction between the provegetarian score and organic food consumption was observed ($P \leq 0.0001$), data were stratified by the level of organic food consumption. Associations between the provegetarian score and environmental impacts for the overall sample and the stratified tertiles of the contribution of organic consumption to the whole diet were estimated using ANCOVA adjusted with Dunett's test. All models were adjusted for sex, age, and energy intake. In addition, the ratio of organic food consumption as a continuous variable was included in the stratified analyses to account for residual confounding. The ordinal margins option was used. In all the analyses, the environmental indicators were log-transformed to improve the normality of the distributions. The data are presented as adjusted means with their 95% confidence intervals. Unadjusted models are provided in the Table S2 in Supplementary Material. Two-sided tests and a *P*-value <0.05 were used for statistical significance.

All analyses were performed using SAS software (SAS Institute Inc., Cary, NC, USA).

# RESULTS

## Individual Characteristics

**Table 1** presents sociodemographic and lifestyle characteristics of the participants across provegetarian score quintiles. No difference in the sex distribution of participants across the quintiles was observed. Participants with higher provegetarian scores were more likely to be highly educated, physically active, non-smokers, and moderate or non-drinkers. The Q5 of the provegetarian score (reflecting high consumption of plant food) included the highest proportion of participants with the lowest monthly income per household unit (<900 euros), while Q4 included the highest proportion of participants with the highest monthly income (>2,700 euros). The highest proportion of participants living in population-dense urban units was found in the Q4. Finally, the largest share of vegetarians was included in the Q5 of the provegetarian diet (8.3% in Q5 versus 0.2% in Q1).

## Food and Nutrients Intake by Provegetarian Score Quintile

**Tables 2** and **3** present food groups and nutrient intake across provegetarian score quintiles. By construction, the consumption of animal-based products decreased while the consumption of plant-based products increased across quintiles. Participants in the highest quintile also consumed less fast food products (hamburgers, pizzas, and sandwiches), sweets, and alcohol and had a higher intake of salad dressings, popcorn, or nuts. Overall, considering nutrient intake, a higher provegetarian score was associated with a lower overall protein intake but a higher proportion of plant protein (50.5% in Q5 versus 22.2% in Q1) and a higher polyunsaturated fatty acid (PUFA) and monounsaturated fatty acid (MUFA) intake as well as a lower saturated fatty acid intake and higher n-6/n-3 PUFA ratio. The intake of carbohydrates and fiber increased across provegetarian score quintiles. Participants in the Q5 of the provegetarian score also displayed the highest level of organic food consumption, as organic food represented a 50% share of their total food consumption.

Considering vitamins and minerals, iron intake increased across the quintiles of the provegetarian score while haem iron decreased. As expected, participants in the Q5 of the provegetarian score also exhibited a higher intake of most micronutrients (β-carotene, B1, B6, B9, C, E, K vitamins, and minerals Mg, K, and Mn). According to both the mPNNS-GS and PANDiet scores, participants in the last quintile showed the highest adherence to the French dietary guidelines.

## Environmental Impacts by Provegetarian Score Quintile

After the adjustment for energy intake, age, and sex, diet-related GHG emissions, CED, and land occupation decreased across the provegetarian score quintiles by −49.6, −26.9, and −41.5%, respectively, between Q5 and Q1 (**Table 4**). For all indicators, a linear association was observed ($P < 0.0001$). This reflects that the richer a diet is in plant products, the lower the environmental impacts are. For informational purposes, crude means and SDs of environmental indicators across the quintiles of the provegetarian score are presented in Figure S1 in Supplementary Material.

## Contribution of Food Groups to Diet-Related GHG Emissions, CED, and Land Occupation by Provegetarian Score Quintile

**Figure 1** indicates that the main contributor to diet-related GHG emissions across the different provegetarian score categories was animal-based products, particularly ruminant meat consumption. Animal products were responsible for approximately 80% of the dietary GHG emissions for diets rich in animal products (Q1 of the provegetarian score), between 70 and 80% for diets moderate in animal products and approximately 60% for diets rich in plant products (Q5 of the provegetarian score). Specifically, ruminant meat represented approximately half of the diet-related GHG emissions, regardless of the type of diet considered.

Concerning the CED (**Figure 2**), consumption of fruits, and vegetables was the major contributor (except for Q1 and Q2). Estimates of the contribution of monogastric meat and ruminant meat to diet-related CED were similar.

Finally, **Figure 3** presents land occupation by food group and by quintile. The results were closer than those for GHG emissions,

**TABLE 1** | Sociodemographic and lifestyle characteristics by provegetarian score quintile, *N* = 34,442, BioNutriNet study, 2014.[a]

| | Q1 | Q2 | Q3 | Q4 | Q5 | *P*-trend[b] |
|---|---|---|---|---|---|---|
| *N* (%) | (17.8) | (23.6) | (20.2) | (16.8) | (21.6) | |
| **Provegetarian score** | | | | | | |
| Mean | 27.4 (2.5) | 32.6 (1.1) | 36.0 (0.8) | 38.9 (0.8) | 44.5 (3.5) | <0.0001 |
| Median (IQR) | 28 (3) | 33 (2) | 36 (2) | 39 (2) | 44 (2) | |
| **Sex (%)** | | | | | | |
| Female | 75.8 | 75.5 | 75.2 | 75.3 | 76.0 | 0.81 |
| Male | 24.2 | 24.5 | 24.8 | 24.7 | 24.0 | |
| **Age (years)** | 52.0 (14.0) | 53.0 (14.1) | 53.5 (14.0) | 54.5 (13.6) | 53.4 (14.1) | <0.0001 |
| **Education level (%)** | | | | | | |
| <High-school diploma | 21.6 | 21.5 | 21.5 | 21.0 | 19.1 | <0.0001 |
| High-school diploma | 15.9 | 15.4 | 14.3 | 13.8 | 14.1 | |
| Post-secondary graduate | 62.5 | 63.1 | 64.1 | 65.2 | 66.8 | |
| **Monthly income per household unit (%)** | | | | | | |
| Refuse to declare | 5.8 | 6.2 | 6.3 | 5.7 | 7.1 | 0.01 |
| <900 euros | 7.4 | 6.6 | 6.0 | 6.3 | 8.7 | |
| 900–1,200 euros | 5.2 | 4.4 | 4.6 | 4.4 | 4.7 | |
| 1,200–1,800 euros | 24.2 | 23.1 | 23.6 | 22.1 | 22.4 | |
| 1,800–2,700 euros | 27.3 | 27.7 | 26.7 | 27.7 | 26.9 | |
| >2,700 euros | 30.1 | 31.9 | 32.9 | 33.7 | 30.3 | |
| **Location (%)** | | | | | | |
| Rural community | 22.9 | 23.2 | 22.3 | 20.7 | 22.3 | 0.11 |
| Urban unit with a population of <20,000 inhabitants | 16.1 | 15.4 | 15.7 | 15.0 | 15.2 | |
| Urban unit with a population of 20,000–200,000 inhabitants | 17.8 | 18.5 | 18.4 | 18.8 | 19.0 | |
| Urban unit with a population of >200,000 inhabitants | 43.2 | 42.9 | 43.6 | 45.6 | 43.5 | |
| **Physical activity (%)** | | | | | | |
| Missing value | 11.6 | 11.5 | 10.9 | 10.3 | 9.9 | <0.0001 |
| Low | 22.9 | 21.7 | 19.5 | 17.4 | 15.2 | |
| Medium | 35.3 | 36.3 | 37.2 | 37.2 | 37.2 | |
| High | 30.2 | 30.5 | 32.4 | 35.1 | 37.6 | |
| **Smoking status (%)** | | | | | | |
| Non-smoker | 48.6 | 48.5 | 48.4 | 48.6 | 49.3 | 0.04 |
| Former smoker | 13.3 | 11.6 | 11.2 | 9.7 | 9.0 | |
| Smoker | 38.0 | 39.8 | 40.5 | 41.7 | 41.7 | |
| **Alcohol intake (%)** | | | | | | |
| Non-drinker | 4.9 | 4.8 | 5.2 | 4.6 | 7.9 | <0.0001 |
| Moderate drinker (<20 g/day for women and <30 g/day for men) | 83.5 | 86.0 | 86.1 | 88.0 | 85.8 | |
| High drinker (>20 g/day for women and >30 g/day for men) | 11.6 | 9.2 | 8.7 | 7.4 | 6.4 | |
| **Diet (%)** | | | | | | |
| Vegetarians | 0.18 | 0.39 | 0.83 | 1.46 | 8.27 | <0.0001 |
| Vegans | 0.00 | 0.01 | 0.04 | 0.12 | 5.28 | |

*IQR, interquartile range; Q, quintile of provegetarian score.*

[a]*Values are presented as the mean (SD) or as a percentage.*

[b]*Values based on linear contrast test or* $\chi^2$.

showing a high contribution of animal products specifically ruminant meat to land occupation.

Moreover, the contribution of carbohydrates and oil to GHG emissions and CED increased across the provegetarian score quintiles. Of note, the contribution from cheese consumption was more important than from the contribution from dairy products and milk across quintiles.

## Diet-Related Environmental Impacts Considering both the Provegetarian Score and the Level of Organic Food Consumption

**Table 4** presents the association between the provegetarian score and the environmental impacts stratified by the level of organic food consumption. Similar linear trends were observed between the provegetarian score and environmental impacts across the different levels of organic food consumption. Considering diet-related environmental impacts in diets that contained low or moderate (Q1, Q2, and Q3) amounts of plant products (i.e., ≥70% animal protein for protein intake and ≥45% animal lipid for lipid intake), the level of organic food consumption did not significantly modify the association between the provegetarian score and the environmental impacts (GHG: $P_{Q2vsQ1} = 0.97$ and $P_{Q3vsQ1} = 0.28$; CED: $P_{Q2vsQ1} = 0.94$ and $P_{Q3vsQ1} = 0.10$; land occupation $P_{Q2vsQ1} = 0.78$ and $P_{Q3vsQ1} = 0.97$). However, for diets rich in plant foods (Q4 and Q5), the differences in the environmental impacts across the provegetarian score quintiles increased across the organic food ratio tertiles ($P < 0.0001$ except for land occupation $P_{Q4vsQ1} = 0.01$).

**TABLE 2** | Food and nutrient intake by provegetarian score quintile, *N* = 34,442, BioNutriNet study, 2014.[a]

| | Q1 | Q2 | Q3 | Q4 | Q5 | *P*-trend[b] |
|---|---|---|---|---|---|---|
| **Nutrients intake** | | | | | | |
| Energy intake without alcohol (kcal/day) | 2,218.8 (638.5) | 1,969.9 (597.1) | 1,885.6 (614.0) | 1,868.2 (599.6) | 1,982.9 (613.6) | <0.0001 |
| Proteins (%)[c] | 20.7 (3.6) | 19.5 (3.3) | 18.5 (3.2) | 17.5 (2.9) | 15.6 (2.9) | <0.0001 |
| Plant proteins (% protein)[c] | 22.2 (6.3) | 27.0 (7.3) | 31.3 (8.3) | 36.1 (9.3) | 50.5 (17.9) | <0.0001 |
| Animal proteins (% protein)[c] | 77.8 (6.3) | 73.0 (7.3) | 68.8 (8.3) | 63.9 (9.3) | 49.5 (17.9) | <0.0001 |
| Lipids (%)[c] | 41.2 (6.4) | 40.2 (6.7) | 39.8 (7.1) | 39.9 (7.2) | 40.2 (7.5) | <0.0001 |
| Plant lipid (% of lipid)[c] | 34.4 (10.4) | 40.7 (10.8) | 46.1 (11.5) | 51.2 (12.0) | 63.3 (15.0) | <0.0001 |
| Animal lipid (% of lipid)[c] | 65.6 (10.4) | 59.3 (10.8) | 53.9 (11.5) | 48.8 (12.0) | 36.7 (15.0) | <0.0001 |
| PUFA (%)[c] | 5.6 (1.7) | 6.1 (2.0) | 6.4 (2.3) | 6.9 (2.4) | 8.3 (3.0) | <0.0001 |
| MUFA (%)[c] | 15.4 (3.2) | 15.5 (3.6) | 15.8 (4.0) | 16.2 (4.2) | 17.1 (4.6) | <0.0001 |
| SFA (%)[c] | 17.0 (3.5) | 15.6 (3.1) | 14.6 (3.1) | 13.8 (3.0) | 12.0 (3.1) | <0.0001 |
| Omega 3 (%)[c] | 2.0 (0.9) | 2.2 (1.0) | 2.3 (1.1) | 2.5 (1.2) | 3.0 (1.6) | <0.0001 |
| Omega 6 (%)[c] | 10.9 (3.0) | 12.1 (3.5) | 13.0 (3.9) | 14.0 (4.0) | 16.8 (5.1) | <0.0001 |
| Ratio n-6/n-3 | 6.3 (2.7) | 6.5 (3.0) | 6.6 (3.1) | 6.5 (3.1) | 6.7 (3.3) | <0.0001 |
| Carbohydrates (%)[c] | 35.3 (7.1) | 37.5 (7.2) | 39.0 (7.2) | 40.0 (7.3) | 41.9 (7.6) | <0.0001 |
| Fibers (%)[c] | 1.7 (0.5) | 2.0 (0.6) | 2.2 (0.6) | 2.5 (0.7) | 3.0 (0.8) | <0.0001 |
| Alcohol (g/day) | 9.9 (14.8) | 8.9 (12.6) | 8.5 (13.2) | 7.95 (10.7) | 7.17 (10.3) | <0.0001 |
| **Food consumption (g or ml/day)[d]** | | | | | | |
| Vegetables and fruits | 424.4 (301.7) | 564.3 (314.9) | 660.6 (346.0) | 734.8 (354.1) | 881.7 (420.0) | <0.0001 |
| Meat | 165.3 (85.4) | 139.4 (65.8) | 123.3 (60.2) | 109.2 (54.2) | 71.9 (54.8) | <0.0001 |
| Ruminant (%) | 36.0 (15.7) | 35.4 (16.0) | 35.3 (15.9) | 34.2 (16.4) | 32.1 (18.1) | <0.0001 |
| Pork (%) | 42.1 (15.9) | 41.8 (16.2) | 41.1 (16.6) | 41.4 (17.4) | 40.8 (19.9) | <0.0001 |
| Poultry (%) | 20.7 (13.9) | 21.4 (14.5) | 22.1 (15.5) | 22.9 (16.1) | 25.5 (19.3) | <0.0001 |
| Rabbit (%) | 1.2 (2.4) | 1.4 (2.7) | 1.5 (2.7) | 1.5 (2.6) | 1.6 (3.7) | <0.0001 |
| Eggs | 13.5 (15.2) | 11.2 (11.7) | 10.1 (10.8) | 9.4 (9.8) | 8.4 (11.0) | <0.0001 |
| Fish | 53.6 (56.3) | 49.3 (39.1) | 47.1 (39.8) | 45.4 (34.3) | 37.4 (38.0) | <0.0001 |
| Dairy products | 320.6 (248.1) | 265.7 (209.3) | 227.6 (184.4) | 185.5 (161.0) | 112.1 (145.0) | <0.0001 |
| Starchy food | 159.9 (82.4) | 179.1 (86.7) | 189.8 (89.1) | 194.6 (91.4) | 213.1 (110.6) | <0.0001 |
| Whole cereal products | 33.3 (54.2) | 47.0 (62.0) | 54.0 (62.4) | 63.7 (68.0) | 84.1 (81.7) | <0.0001 |
| Soy products | 1.1 (54.2) | 8.5 (61.7) | 16.2 (76.8) | 27.2 (97.7) | 70.6 (140.7) | <0.0001 |
| Fast food | 38.7 (48.1) | 36.1 (31.6) | 33.9 (33.1) | 32.7 (29.0) | 27.3 (24.2) | <0.0001 |
| Nuts | 2.00 (8.63) | 4.03 (8.93) | 5.39 (10.79) | 7.14 (13.19) | 11.36 (15.25) | <0.0001 |
| Extra food (excluding nuts) | 9.55 (9.26) | 9.84 (9.80) | 9.93 (9.51) | 9.59 (9.99) | 8.50 (9.07) | <0.0001 |
| Sweet products | 80.6 (60.6) | 77.3 (52.6) | 74.0 (46.3) | 69.7 (41.2) | 61.9 (39.1) | <0.0001 |
| Oil | 8.9 (12.2) | 13.0 (12.5) | 15.8 (13.3) | 18.3 (14.1) | 22.7 (15.5) | <0.0001 |
| Butter | 8.6 (7.9) | 7.4 (6.7) | 6.7 (6.2) | 6.2 (6.1) | 4.5 (5.6) | <0.0001 |
| Other fats | 2.4 (4.6) | 2.3 (4.7) | 2.4 (4.8) | 2.1 (3.9) | 2.1 (4.6) | 0.1 |
| Non-alcoholic drink | 1571 (769) | 1600 (763) | 1590 (739) | 1607 (731) | 1591 (755) | 0.1 |
| Alcoholic drink | 180.7 (162.6) | 177.7 (142.6) | 174.0 (144.4) | 170.5 (118.5) | 158.1 (114.8) | <0.0001 |
| **Level of organic food consumption (in % of weight)** | 18.2 (19.8) | 22.5 (22.2) | 26.3 (24.2) | 32.1 (26.4) | 48.2 (30.7) | <0.0001 |
| Median of organic food consumption | 12 | 17 | 21 | 26 | 48 | |
| IQR | 26 | 32 | 36 | 41 | 53 | |
| **mPNNS score (/13.5)** | 7.6 (1.87) | 8.3 (1.73) | 8.6 (1.67) | 8.8 (1.66) | 8.8 (1.68) | <0.0001 |

*PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid; IQR, interquartile range; Q, quintile of provegetarian score.*

[a]*Values are presented as the mean (SD).*

[b]*Values based on a linear contrast test.*

[c]*As percent of energy intake.*

[d]*Values adjusted on the energy intake.*

## DISCUSSION

In our study, participants with a high provegetarian score were characterized by an overall healthier lifestyle, including healthier diets, as reflected by higher PANDiet and mPNNS-GS scores. Diets rich in plant products displayed lower environmental impacts (GHG emissions, CED and land occupation). Moreover, the consumption level of organic products was shown to have a positive moderating effect on diet-related environmental impacts only in diets rich in plant-based food.

Overall, a higher provegetarian score was associated with lower environmental impacts, particularly GHG emissions, across all levels of organic food consumption. These results at the individual diet level were expected since livestock is the most substantial agricultural contributor to GHG emissions, demands high energy inputs, and requires important land resources (42–44).

Similar results for GHG emissions were documented in the EPIC-Oxford observational study. However, the estimations were not adjusted for energy intake, and the LCA did not consider the production mode even though it included all stages of production, transformation, and distribution. The authors showed that a diet rich in animal products emitted 2.5 times as much GHG than a vegan diet. For women and men, GHG emissions from the diets of meat-eaters were 46 and 51% higher, respectively, than those of fish-eaters (or pesco-vegetarians), and 50 and 54% higher, respectively, than those of vegetarians (45). Other studies

**TABLE 3** | Consumption of micronutrients by provegetarian score quintile, *N* = 34,442, BioNutriNet study, 2014.[a]

| | Q1 | Q2 | Q3 | Q4 | Q5 | *P*-trend[b] |
|---|---|---|---|---|---|---|
| **Vitamins**[c] | | | | | | |
| Retinol (µg/day) | 769.42 (1,530.30) | 667.23 (1,052.50) | 590.84 (420.54) | 558.82 (362.70) | 432.86 (353.49) | <0.0001 |
| β-carotene (µg/day) | 2,685.90 (2,025.9) | 3,579.01 (3,040.9) | 4,175.05 (2,459.7) | 4,677.09 (2,956.2) | 5,872.50 (3,443.6) | <0.0001 |
| Vitamin B1 (mg/day) | 1.33 (0.40) | 1.35 (0.40) | 1.35 (0.38) | 1.37 (0.38) | 1.48 (0.52) | <0.0001 |
| Vitamin B2 (mg/day) | 2.47 (0.70) | 2.31 (0.61) | 2.20 (0.55) | 2.13 (0.52) | 1.99 (0.51) | <0.0001 |
| Vitamin B3 (mg/day) | 26.61 (8.44) | 26.21 (7.29) | 25.70 (6.68) | 25.64 (6.41) | 24.23 (6.30) | <0.0001 |
| Vitamin B5 (mg/day) | 6.76 (1.65) | 6.54 (1.44) | 6.39 (1.33) | 6.26 (1.23) | 6.06 (1.19) | <0.0001 |
| Vitamin B6 (mg/day) | 1.91 (0.50) | 1.96 (0.47) | 1.99 (0.46) | 2.04 (0.46) | 2.17 (0.56) | <0.0001 |
| Vitamin B9 (µg/day) | 317.56 (122.44) | 359.11 (123.69) | 385.77 (116.52) | 410.20 (123.12) | 482.06 (157.47) | <0.0001 |
| Vitamin B12 (µg/day) | 8.69 (9.07) | 7.67 (6.41) | 6.96 (3.14) | 6.57 (2.77) | 5.23 (2.93) | <0.0001 |
| Vitamin C (mg/day) | 104.49 (70.41) | 126.24 (70.54) | 141.66 (81.21) | 151.66 (78.85) | 174.60 (90.83) | <0.0001 |
| Vitamin D (µg/day) | 3.55 (2.22) | 3.24 (1.63) | 3.08 (1.70) | 2.97 (1.47) | 2.54 (1.63) | <0.0001 |
| Vitamin E (mg/day) | 9.66 (4.36) | 11.59 (4.37) | 12.74 (4.63) | 13.76 (4.63) | 16.44 (5.67) | <0.0001 |
| Vitamin K (µg/day) | 142.59 (122.15) | 187.11 (143.88) | 217.57 (140.31) | 244.35 (205.46) | 310.09 (201.96) | <0.0001 |
| **Minerals**[c] | | | | | | |
| Ca (mg/day) | 1,172 (391) | 1,094 (329) | 1,044 (304) | 998 (282) | 915 (261) | <0.0001 |
| Fe (mg/day) | 14.23 (3.78) | 14.92 (3.44) | 15.25 (3.25) | 15.83 (3.40) | 17.36 (4.00) | <0.0001 |
| Haem Fe (mg/day) | 1.97 (1.62) | 1.68 (0.85) | 1.50 (0.75) | 1.36 (0.67) | 0.94 (0.65) | <0.0001 |
| I (µg/day) | 160.20 (280.37) | 177.08 (211.47) | 193.07 (275.48) | 203.11 (309.02) | 329.66 (710.17) | <0.0001 |
| Mg (mg/day) | 444.43 (138.26) | 470.93 (134.19) | 482.83 (130.29) | 502.58 (132.78) | 540.85 (140.23) | <0.0001 |
| P (mg/day) | 1,550.19 (315.86) | 1,471.20 (270.59) | 1,420.12 (255.63) | 1,379.49 (238.06) | 1,322.24 (234.55) | <0.0001 |
| K (mg/day) | 3,508.30 (840.07) | 3,645.63 (825.93) | 3,726.91 (831.23) | 3,802.52 (835.48) | 3,961.31 (904.80) | <0.0001 |
| Na (mg/day) | 2,739.20 (592.86) | 2,641.56 (492.86) | 2,570.26 (491.03) | 2,515.43 (475.96) | 2,290.61 (550.78) | <0.0001 |
| Cu (mg/day) | 1.74 (1.48) | 1.90 (1.09) | 1.98 (0.58) | 2.10 (0.54) | 2.38 (0.62) | <0.0001 |
| Zn (mg/day) | 13.98 (3.13) | 13.30 (2.60) | 12.81 (2.31) | 12.52 (2.19) | 11.85 (2.23) | <0.0001 |
| Mn (mg/day) | 3.65 (1.93) | 4.40 (1.95) | 4.84 (1.91) | 5.32 (2.01) | 6.53 (2.47) | <0.0001 |
| Se (µg/day) | 83.19 (26.28) | 80.68 (20.30) | 78.94 (20.02) | 78.04 (18.69) | 75.43 (19.51) | <0.0001 |
| **PANDiet score (/100)** | 62.43 (5.13) | 64.90 (5.99) | 66.37 (6.72) | 67.99 (7.07) | 71.12 (7.13) | <0.0001 |

[a]*Values are presented as the mean (SD).*

[b]*Values based on a linear contrast test.*

[c]*Energy-adjusted mean (SD).*

documented similar trends in regards to environmental impacts of modeled substitutions for meat (46–48). For instance, the modeled substitution in the EPIC-Netherlands cohort demonstrated that substituting meat with 35 g/d of different combinations of plant products including potatoes, pasta, vegetables, nuts, and milky desserts could reduce GHG emissions up to 12% (49). In a recent review, authors concluded that the isocaloric substitution of meat by starchy food, fruits, nuts, and vegetables was more sustainable in terms of GHG emissions. However, in that same review, production modes (more or less agro-ecological modes) were not distinguished (43).

Livestock results in GHG emissions such as nitrous oxide, carbon dioxide, and methane due to high-energy feed production, concentrating production and enteric fermentation of ruminants (3). However, impacts related to ruminant meat are higher when compared to monogastric animals because of methane emissions and the need for substantial livestock feed production needed (43, 50, 51). As consumers in the Q5 of the provegetarian score ate less meat, especially ruminant meat, compared to participants in the other quintiles, the difference in GHG emissions is further increased. A previous study showed that a diet in which ruminant meat is replaced by monogastric meat (pork or poultry) reduced GHG emissions from 20 to 35% and land-use impacts from 30 to 50% (50).

In another study, the CED was computed at the farm level using the LCA method, and it was shown that a 60% decrease in daily meat consumption that is replaced by planted-based products led to an up to 38% decrease in CED, according to various scenarios of self-sufficiency in Austria (48). The review by Perignon et al., which covers 10 cohort studies on the environmental impact of observed individual diets, demonstrates that low-meat diets are more environmentally friendly (43).

Livestock farming requires a substantial input of fossil energy due to farm facilities and production of feed (3). Moreover, plant products have higher energy efficiency when considering the ratio of outputs/inputs for each calorie (52). Regarding the CED by food group and by quintile, there is no clear difference in the CED contribution between ruminant meat and monogastric meat. Considering the level of consumption, food group contribution to CED is probably driven more by the difference in intake than energy use for the different types of meat since the differences they are less noticeable than for GHG emissions (53).

Finally, similar results on land use were found when the average Danish diet was replaced by the new Nordic diet containing 35% less meat with a 24% decrease in diet-related land use. In the model performed for the EPIC-Netherlands cohort, the substitution of meat with 35 g/d of plant products led to an up to 12% decrease in land use (49). Moreover, the review of Hallström et al., which included 14 original studies (mainly based on modeling methods), showed that vegan diets reduced land use up to 60 and 50% for men and women, respectively (50). In fact, livestock farming is the largest user of land due to the total area need for grazing and feed crop production (5).

**TABLE 4** | Association between provegetarian score tertile and environmental impacts according to the level of organic food consumption, BioNutriNet study, 2014.

| | Overall | | Level of contribution of organic food to the diet | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Low (0.03) | | Medium (0.23) | | High (0.63) | | |
| | Mean[a] | 95% CL | Mean[a] | 95% CL | Mean[a] | 95% CL | Mean[a] | 95% CL | |
| **Greenhouse gas emissions (CO2eq/day)** | | | | | | | | | |
| Q1 provegetarian score | 4.56 | (4.51–4.60) | 4.59 | (4.53–4.65) | 4.56 | (4.48–4.63) | 4.10 | (3.99–4.22) | |
| Q2 provegetarian score | 4.05 | (4.01–4.08) | 4.13 | (4.08–4.18) | 4.05 | (4.00–4.10) | 3.74 | (3.66–3.81) | |
| Q3 provegetarian score | 3.62 | (3.62–3.66) | 3.73 | (3.68–3.78) | 3.68 | (3.63–3.74) | 3.34 | (3.28–3.41) | |
| Q4 provegetarian score | 3.23 | (3.20–3.27) | 3.45 | (3.39–3.51) | 3.38 | (3.33–3.43) | 2.94 | (2.89–2.99) | |
| Q5 provegetarian score | 2.27 | (1.33–2.29) | 2.93 | (2.87–2.99) | 2.72 | (2.67–2.76) | 2.12 | (2.09–2.14) | |
| P[b] interaction | | | | | | | | | <0.0001 |
| P[c] Q1 vs Q2 | | | | | | | | | 0.9711 |
| P[c] Q1 vs Q3 | | | | | | | | | 0.2764 |
| P[c] Q1 vs Q4 | | | | | | | | | <0.0001 |
| P[c] Q1 vs Q5 | | | | | | | | | <0.0001 |
| **Cumulative energy demand (MJ/day)** | | | | | | | | | |
| Q1 provegetarian score | 18.55 | (18.43–18.67) | 18.58 | (18.40–18.75) | 18.58 | (18.39–18.78) | 17.33 | (17.05–17.63) | |
| Q2 provegetarian score | 17.43 | (17.33–17.53) | 17.62 | (17.47–17.77) | 17.47 | (17.32–17.63) | 16.53 | (16.32–16.73) | |
| Q3 provegetarian score | 16.48 | (15.52–16.58) | 16.87 | (16.70–17.04) | 16.62 | (16.47–16.78) | 15.59 | (15.41–15.77) | |
| Q4 provegetarian score | 15.62 | (15.52–15.73) | 16.42 | (16.21–16.63) | 16.10 | (15.93–16.27) | 14.62 | (14.45–14.78) | |
| Q5 provegetarian score | 13.29 | (13.21–13.37) | 15.56 | (15.33–15.79) | 14.72 | (14.56–14.89) | 12.66 | (12.56–12.76) | |
| P[b] interaction | | | | | | | | | <0.0001 |
| P[c] Q1 vs Q2 | | | | | | | | | 0.9417 |
| P[c] Q1 vs Q3 | | | | | | | | | 0.1044 |
| P[c] Q1 vs Q4 | | | | | | | | | <0.0001 |
| P[c] Q1 vs Q5 | | | | | | | | | <0.0001 |
| **Land occupation ($m^2$/day)** | | | | | | | | | |
| Q1 provegetarian score | 11.33 | (11.14–11.41) | 10.94 | (10.78–11.10) | 11.58 | (11.39–11.78) | 11.66 | (11.36–11.96) | |
| Q2 provegetarian score | 10.26 | (10.17–10.35) | 9.89 | (9.76–10.03) | 10.31 | (10.17–10.45) | 10.64 | (10.45–10.85) | |
| Q3 provegetarian score | 9.34 | (9.26–9.43) | 8.95 | (8.81–9.09) | 9.43 | (9.29–9.57) | 9.61 | (9.44–9.79) | |
| Q4 provegetarian score | 8.51 | (8.42–8.60) | 8.26 | (8.10–8.43) | 8.68 | (8.54–8.83) | 8.50 | (8.35–8.65) | |
| Q5 provegetarian score | 6.63 | (6.57–6.69) | 7.03 | (6.87–7.19) | 7.09 | (6.97–7.21) | 6.49 | (6.41–6.57) | |
| P[b] interaction | | | | | | | | | <0.0001 |
| P[c] Q1 vs Q2 | | | | | | | | | 0.7782 |
| P[c] Q1 vs Q3 | | | | | | | | | 0.9696 |
| P[c] Q1 vs Q4 | | | | | | | | | 0.0111 |
| P[c] Q1 vs Q5 | | | | | | | | | <0.0001 |

*Models are adjusted on sex, age, and energy intake.*

[a]*Adjusted means were obtained with ANOVA models by the level of organic food contribution in the diet. P-trends across the provegetarian score quintile are all <0.0001 and were obtained with a linear contrast test by the level of organic food contribution in the diet.*

[b]*P for interaction between provegetarian score quintiles and the level contribution of organic food to the diet.*

[c]*P-linear trend of Q*v.Q1 of provegetarian score. It reflects the linearity of the difference between the first and the other quintiles of the provegetarian score across the levels of organic consumption.*

It is worth noting that beyond the benefits to the environment, diets rich in plant products also provide important nutritional and health benefits (54, 55).

We showed that introducing organic food to one's diet had a significant positive environmental effect on GHG emissions in only diets rich in plant products. However, when considering a diet with a moderate amount of plant products, this effect was not substantial.

The weak moderating effect of the organic consumption in a diet with a moderate amount of plant products can be explained by several hypotheses. First, no difference in GHG emissions was reported for both conventional and organic beef and milk production systems (20). In addition, GHG emissions from chicken and pork organic farming practices are higher because feed production is more substantial due to a longer cycle of production and a lower growth rate (in relation to a lower feed-efficiency conversion) (20). Moreover, GHG emissions from organic pork farming practices can be higher because of the high level of nitrous oxide emissions from straw litter (19). However, the differences between chicken and pork production systems have not yet been consistently measured, and further research is needed to improve the reliability of calculating GHG emissions for different farming practices. Second, organic farming results in lower GHG emissions when emissions are expressed by units of area, and no clear trends emerge when they are expressed by units of product weight (18). Finally, organic practices have obvious beneficial effects on GHG emissions in terms of plant production because of the exclusion of synthetic fertilizers that result in high $N_2O$ and $CO_2$ emissions (19, 56). Finally, the proportion of organic food consumption in the diet may be too low in the first provegetarian score quintiles to detect differences in GHG emissions. Considering the CED indicator, the ratio of organic food in the diet positively affects diet-related environmental impacts with increasing effects across provegetarian score quintiles. Organic practices prohibit the use

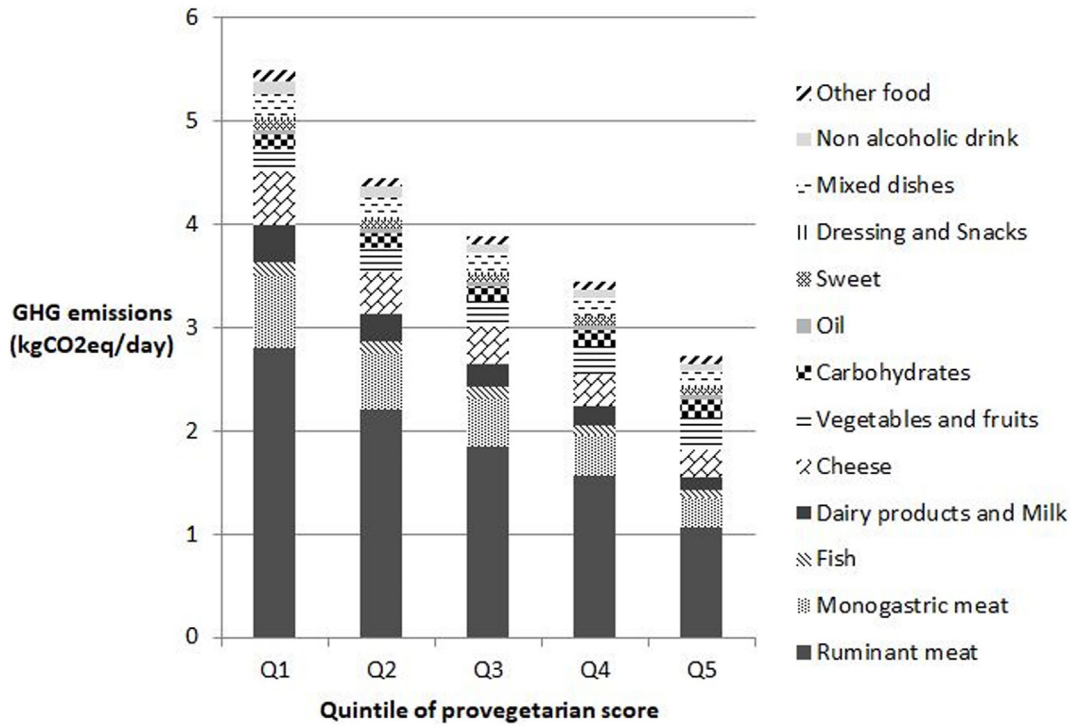



**FIGURE 1** | Greenhouse gas (GHG) emissions by food group and by quintile of provegetarian score. Other food group includes whole products, soy products, eggs, butter, other fats, and alcohol. Food group impacts are all significant (*P*-trend < 0.05).

of synthetic fertilizers which induce high costs in energy for their production and require the use of less mineral fertilizers and feed concentrates (56). However, some studies have determined that CED can be up to 40% higher in organic farming than in conventional systems (19). Another explanation relies on the fact that among the high consumers of organic foods, plant-based food consumption was higher overall. However, the correlation coefficient between the provegetarian score and the level of organic food consumption was estimated to be 0.4.

Regarding land occupation, the level of organic food consumption had a positive impact on diets rich in plant products and had no impact on diets with moderate level of plant product intake. These findings are noteworthy since organic systems require relatively more land (20, 56, 57) than conventional production systems. These lower crop yields are due to lower total nitrogen inputs per hectare (20). Our results may be explained by the fact that in the Q5 of the provegetarian score, consumers that eat a substantial amount of organic food exhibited higher plant-based consumption than their conventional counterparts and thus may have exhibited a lower consumption of meat. Moreover, according to Pimentel and Pimentel, grains and some legumes, which were highly consumed by participants in the Q5 of the provegetarian score, are produced more efficiently than fruits and vegetables (42). This may have led to a reduction in the negative impact of organic production on plant production yields. The absence of a differential effect of organic food consumption on land use for a diet with a moderate amount of plant products may be related to the fact that the ratio of organic foods in the diet is too low to detect any association, which is the same for GHG emissions. These findings regarding land occupation need further investigation since future improvements of management techniques and crop varieties may reduce the difference in crop yields between organic and conventional systems (9). Although this was not evaluated in our study, organic systems generally offer environmental services, do not use pesticides, increase resilience of agriculture and can mitigate the future effects of climate change on yields (58).

The limitations of this study should be noted. An extrapolation of these results to the general population should be done with caution as the participants who completed the BioNutriNet questionnaires were probably more concerned with nutrition and health-related issues. It should be noted that the percentage of participants with a very high consumption of organic foods, as observed in our study, is likely to be minimal in France. The use of a food frequency questionnaire may be prone to incorrectly estimating habitual diets, which is similar to other self-reported food consumption tools (59). Moreover, the effects of the systems of production on the environment should be considered with caution. Indeed, among similar systems of production, effects can be largely different due to climate conditions, soil types and farm management (18, 56). Other indicators such as pesticide use, leaching, and soil quality would have been relevant to addressing the environmental impacts of production systems (60, 61). In addition, our data included neither the origin nor the seasonality of food products, which may impact environmental assessments. Furthermore,

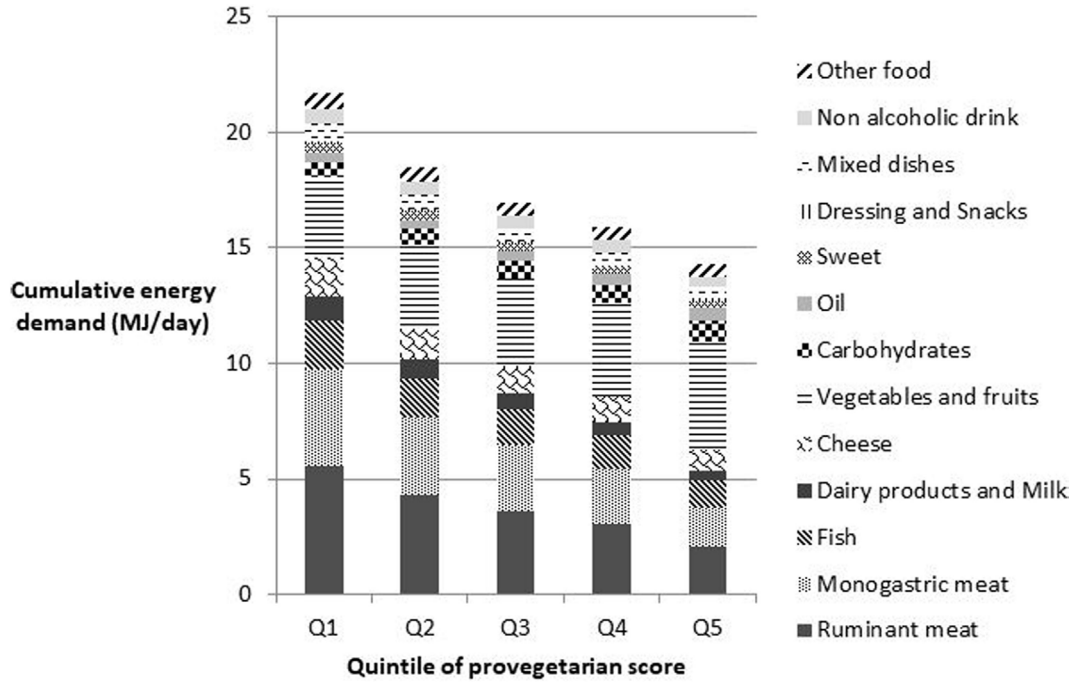



**FIGURE 2** | Cumulative energy demand by food group and by quintile of provegetarian score. Other food group includes whole products, soy products, eggs, butter, other fats, and alcohol. Food group impacts are all significant (*P*-trend < 0.05).

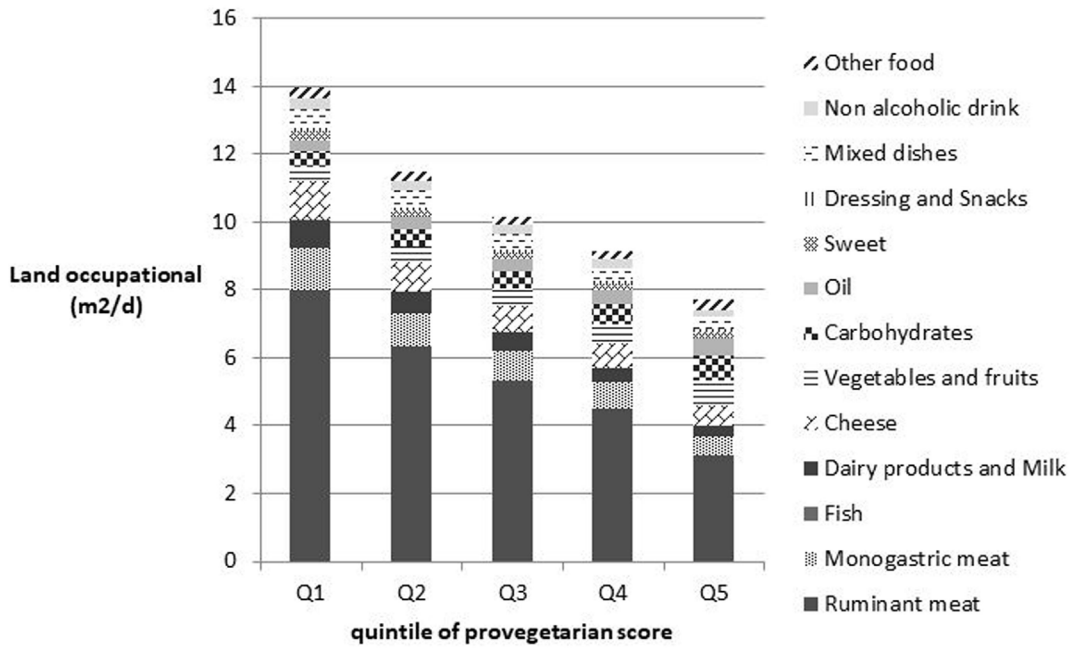



**FIGURE 3** | Land occupation by food group and by quintile of provegetarian score. Other food group includes whole products, soy products, eggs, butter, other fats, and alcohol. Food group impacts are all significant (*P*-trend < 0.05).

environmental impacts were assessed at the farm level and did not consider all of the production, transformation and distribution stages.

However, our study also presents notable strengths. First, to the best of our knowledge, this is the first study to distinguish production modes in the assessment of food consumption

and several subsequent environmental impacts. This is also the first study to investigate moderating effects of organic food consumption on the environmental impact of observed diets. Modeling studies do not necessarily consider isocaloric or representative substitutions. For example, replacing meat with fruit and legumes may not appear entirely realistic. Meat would probably be replaced by energy-dense products such as cereals, potatoes, and legumes. Moreover, these modeling studies rely on small cohorts. Therefore, it was crucial to focus on actual diets assessed in a large cohort to confirm or refute the results from modeling studies. Concerning the strengths of this study, our study is based on a large sample, which allows a wide diversity of dietary behaviors to be considered and in particular eco-friendly behaviors, using accurate environmental and consumption data. The provegetarian score also presents several advantages when compared to other dietary indexes commonly used in the literature such as the Mediterranean diet score (62). Indeed, while the Mediterranean diet recommends limiting milk and red meat, it also recommends consuming fish even though a major part of the fishing industry is not sustainable (63) and degrades maritime ecosystem functions by altering the food chain and fish habitats (64). Finally, the provegetarian score reflects different emerging dietary patterns (e.g., flexitarian diets) that tend to reduce consumption of animal products.

In conclusion, diet-related GHG emissions, CED, and land occupation indicators are negatively associated with a plant-based diet, regardless of the level of organic food consumption. Furthermore, the consumption of organic food showed additional beneficial impacts only in diets rich in plant products. This study demonstrates that the environmental impacts of diets should not only be evaluated in terms of dietary patterns but also should integrate production systems.

## ETHICS STATEMENT

The design was conducted according to the guidelines laid down in the Declaration of Helsinki and was approved by the Institutional Review Board of the French Institute for Health and Medical Research (IRB INSERM no. 0000388FWA00005831) and the "Commission Nationale de l'Informatique et des Libertés" (CNIL no. 908450 and no. 909216). All participants signed an electronic informed consent.

## AUTHOR CONTRIBUTIONS

EK-G, SH, PP, and DL designed the research; CL, LS, BA, BL, PP, DL, JB, and EK-G conducted the research; CL, LS, BA, JB, and EK analyzed the data; and CL and EK wrote the paper. CL, LS, BA, BL, PP, DL, JB, and EK were involved in interpreting the results and editing the manuscript. CL, LS, and EK had primary responsibility for the final content. All authors read and approved the final manuscript.

## ACKNOWLEDGMENTS

We especially thank Younes Esseddik, Paul Flanzy, and Thi Hong Van Duong, computer scientists; Veronique Gourlet, Fabien Szabo, Nathalie Arnault, Laurent Bourhis, and Stephen Besseau, statisticians; and Cédric Agaësse and Claudia Chahine, dieticians. We warmly thank all of the dedicated and conscientious volunteers involved in the Nutrinet-Santé cohort.

## FUNDING

The BioNutriNet project was supported by the French National Research Agency (Agence Nationale de la Recherche) in the context of the 2013 Programme de Recherche Systèmes Alimentaires Durables (ANR-13-ALID-0001). The NutriNet-Santé cohort study is funded by the following public institutions: Ministère de la Santé, Santé Publique France, Institut National de la Santé et de la Recherche Médicale (INSERM), Institut National de la Recherche Agronomique (INRA), Conservatoire National des Arts et Métiers (CNAM) and Paris 13 University. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/articles/10.3389/fnut.2018.00008/full#supplementary-material.

## REFERENCES

1. Fischer CG, Garnett T. *Plates, Pyramids and Planets Developments in National Healthy and Sustainable Dietary Guidelines: A State of Plays Assessment*. Oxford, UK: Food and Agriculture Organization of the United Nations and Food Climate Research Network (2016).
2. Birt C, Buzeti T, Grosso G, Justesen L, Lachat C, Lafranconi A, et al. *Healthy and Sustainable Diets for European Countries*. Utrecht: European Public Health Association (EUPHA) (2017).
3. *Tackling Climate Change through Livestock: A Global Assessment of Emissions and Mitigation Opportunities – i3437e.pdf*. (2017). Available from: http://www.fao.org/docrep/018/i3437e/i3437e.pdf
4. *World Agriculture: Towards 2015/2030 A FAO PERSPECTIVE*. (2017). Available from: http://www.fao.org/3/a-y4252e.pdf
5. *Livestock's Long Shadow Environmental Issues and Options*. (2017). Available from: ftp://ftp.fao.org/docrep/fao/010/a0701e/a0701e.pdf
6. Garnett T. Where are the best opportunities for reducing greenhouse gas emissions in the food system (including the food chain)? *Food Policy* (2011) 36(Suppl 1):S23–32. doi:10.1016/j.foodpol.2010.10.010
7. Westhoek H, Lesschen JP, Rood T, Wagner S, De Marco A, Murphy-Bokern D, et al. Food choices, health and environment: effects of cutting Europe's meat and dairy intake. *Glob Environ Change* (2014) 26:196–205. doi:10.1016/j.gloenvcha.2014.02.004
8. *Organic Agriculture: What Is Organic Agriculture?* (2017). Available from: http://www.fao.org/organicag/oa-faq/oa-faq1/en/
9. Reganold JP, Wachter JM. Organic agriculture in the twenty-first century. *Nat Plants* (2016) 2:15221. doi:10.1038/nplants.2015.221
10. Scialabba N, Hattam C. Organic agriculture, environment and food security. *Food Agric Org* (2002):264.
11. Lotter DW. Organic agriculture. *J Sustain Agric* (2003) 21(4):59–128. doi:10.1300/J064v21n04_06
12. Tuck SL, Winqvist C, Mota F, Ahnström J, Turnbull LA, Bengtsson J. Land-use intensity and the effects of organic farming on biodiversity:

a hierarchical meta-analysis. *J Appl Ecol* (2014) 51(3):746–55. doi:10.1111/1365-2664.12219
13. Connor DJ, Mínguez MI. Evolution not revolution of farming systems will best feed and green the world. *Glob Food Secur* (2012) 1:106–13.
14. Kirchmann H, Thorvaldsson G. Challenging targets for future agriculture. *Eur J Agron* (2000) 12(3–4):145–61. doi:10.1016/S1161-0301(99)00053-2
15. Dalgaard T, Halberg N, Porter JR. A model for fossil energy use in Danish agriculture used to compare organic and conventional farming. *Agric Ecosyst Environ* (2001) 87(1):51–65. doi:10.1016/S0167-8809(00)00297-8
16. Lynch DH, Halberg N, Bhatta GD. Environmental impact of organic agriculture in temperate regions. *CAB Rev*. (2012). Available from: http://orgprints.org/20725/
17. Lee KS, Choe YC, Park SH. Measuring the environmental effects of organic farming: a meta-analysis of structural variables in empirical research. *J Environ Manage* (2015) 162:263–74. doi:10.1016/j.jenvman.2015.07.021
18. Koen M, Aertsens J, Van Huylenbroeck G. A meta-analysis of the differences in environmental impacts between organic and conventional farming. *Br Food J* (2009) 111(10):1098–119. doi:10.1108/00070700910992925
19. Tuomisto HL, Hodge ID, Riordan P, Macdonald DW. Does organic farming reduce environmental impacts? A meta-analysis of European research. *J Environ Manage* (2012) 112:309–20. doi:10.1016/j.jenvman.2012.08.018
20. Treu H, Nordborg M, Cederberg C, Heuer T, Claupein E, Hoffmann H, et al. Carbon footprints and land use of conventional and organic diets in Germany. *J Clean Prod* (2017) 161:127–42. doi:10.1016/j.jclepro.2017.05.041
21. Baudry J, Méjean C, Allès B, Péneau S, Touvier M, Hercberg S, et al. Contribution of organic food to the diet in a large sample of French adults (the NutriNet-Santé Cohort Study). *Nutrients* (2015) 7(10):8615–32. doi:10.3390/nu7105417
22. Aleksandrowicz L, Green R, Joy EJM, Smith P, Haines A. The impacts of dietary change on greenhouse gas emissions, land use, water use, and health: a systematic review. Wiley AS, editor. *PLoS One* (2016) 11(11):e0165797. doi:10.1371/journal.pone.0165797
23. Rosi A, Mena P, Pellegrini N, Turroni S, Neviani E, Ferrocino I, et al. Environmental impact of omnivorous, ovo-lacto-vegetarian, and vegan diet. *Sci Rep* (2017) 7(1):6105. doi:10.1038/s41598-017-06466-8
24. Fiddes N. *Meat: A Natural Symbol*. London: Routledge (1991). 260 p.
25. Martínez-González MA, Sánchez-Tainta A, Corella D, Salas-Salvadó J, Ros E, Arós F, et al. A provegetarian food pattern and reduction in total mortality in the Prevención con Dieta Mediterránea (PREDIMED) study. *Am J Clin Nutr* (2014) 100(Suppl 1):320S–8S. doi:10.3945/ajcn.113.071431
26. Hercberg S, Castetbon K, Czernichow S, Malon A, Mejean C, Kesse E, et al. The Nutrinet-Santé Study: a web-based prospective study on the relationship between nutrition and health and determinants of dietary patterns and nutritional status. *BMC Public Health* (2010) 10:242. doi:10.1186/1471-2458-10-242
27. INSEE. *Définition – Unité de consummation*. Insee (2017). Available from: https://www.insee.fr/fr/metadonnees/definition/c1802
28. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* (2003) 35(8):1381–95. doi:10.1249/01.MSS.0000078924.61453.FB
29. Hallal PC, Victora CG. Reliability and validity of the International Physical Activity Questionnaire (IPAQ). *Med Sci Sports Exerc* (2004) 36(3):556. doi:10.1249/01.MSS.0000117161.66394.07
30. Hagströmer M, Oja P, Sjöström M. The International Physical Activity Questionnaire (IPAQ): a study of concurrent and construct validity. *Public Health Nutr* (2006) 9(6):755–62. doi:10.1079/PHN2005898
31. *Alcohol Guidelines Review – Report from the Guidelines Development Group to the UK Chief Medical Officers*. (2017). Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/545739/GDG_report-Jan2016.pdf
32. Kesse-Guyot E, Castetbon K, Touvier M, Hercberg S, Galan P. Relative validity and reproducibility of a food frequency questionnaire designed for French adults. *Ann Nutr Metab* (2010) 57(3–4):153–62. doi:10.1159/000321680
33. *Table de composition des aliments – NutriNet-Santé,Serge Hercberg*. (2017). Available from: https://www.decitre.fr/livres/table-de-composition-des-aliments-9782717865370.html
34. Verger EO, Mariotti F, Holmes BA, Paineau D, Huneau J-F. Evaluation of a diet quality index based on the probability of adequate nutrient intake (PANDiet) using National French and US Dietary Surveys. *PLoS One* (2012) 7(8):e42155. doi:10.1371/journal.pone.0042155
35. Chauliac M, Razanamahefa L, Choma C, Boudot J, Houssin D. [National health and nutrition program: challenges of a global action plan]. *Rev Prat* (2009) 59(1):10–2.
36. Solagro. *Dialecte*. Solagro (2017). Available from: https://solagro.org/nos-travaux-et-productions
37. Basset-Mens C, Small B, Paragahawewa UH, Langevin B, Paula B. Life cycle thinking and sustainable food production. *Int J Prod Lifecycle Manage* (2009) 4(1–3):252–69. doi:10.1504/IJPLM.2009.031675
38. Owens JW. Life-cycle assessment in relation to risk assessment: an evolving perspective. *Risk Anal* (1997) 17(3):359–65. doi:10.1111/j.1539-6924.1997.tb00874.x
39. *Implementation of Life Cycle Impact Assessment Methods*. (2017). Available from: http://www.proyectaryproducir.com.ar/public_html/Seminarios_Posgrado/Material_de_referencia/EcoInvent%2003_LCIA-Implementation-v2.2.pdf
40. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr* (1997) 65(4):1220S–8S. doi:10.1093/ajcn/65.4.1220S
41. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr* (1985) 39(Suppl 1):5–41.
42. Pimentel D, Pimentel M. Sustainability of meat-based and plant-based diets and the environment. *Am J Clin Nutr* (2003) 78(3):660S–3S.
43. Perignon M, Vieux F, Soler L-G, Masset G, Darmon N. Improving diet sustainability through evolution of food choices: review of epidemiological studies on the environmental impact of diets. *Nutr Rev* (2017) 75(1):2–17. doi:10.1093/nutrit/nuw043
44. Auestad N, Fulgoni VL. What current literature tells us about sustainable diets: emerging research linking dietary patterns, environmental sustainability, and economics. *Adv Nutr* (2015) 6(1):19–36. doi:10.3945/an.114.005694
45. Scarborough P, Appleby PN, Mizdrak A, Briggs ADM, Travis RC, Bradbury KE, et al. Dietary greenhouse gas emissions of meat-eaters, fish-eaters, vegetarians and vegans in the UK. *Clim Change* (2014) 125(2):179–92. doi:10.1007/s10584-014-1169-1
46. Tilman D, Clark M. Global diets link environmental sustainability and human health. *Nature* (2014) 515(7528):518–22. doi:10.1038/nature13959
47. Macdiarmid JI, Kyle J, Horgan GW, Loe J, Fyfe C, Johnstone A, et al. Sustainable diets for the future: can we contribute to reducing greenhouse gas emissions by eating a healthy diet? *Am J Clin Nutr* (2012) 96(3):632–9. doi:10.3945/ajcn.112.038729
48. Fazeni K, Steinmüller H. Impact of changes in diet on the availability of land, energy demand, and greenhouse gas emissions of agriculture. *Energy Sustain Soc* (2011) 1(1):6. doi:10.1186/2192-0567-1-6
49. Biesbroek S, Bueno-de-Mesquita HB, Peeters PHM, Verschuren WM, van der Schouw YT, Kramer GFH, et al. Reducing our environmental footprint and improving our health: greenhouse gas emission and land use of usual diet and mortality in EPIC-NL: a prospective cohort study. *Environ Health* (2014) 13(1):27. doi:10.1186/1476-069X-13-27
50. Hallström E, Carlsson-Kanyama A, Börjesson P. Environmental impact of dietary change: a systematic review. *J Clean Prod* (2015) 91:1–11. doi:10.1016/j.jclepro.2014.12.008
51. Bryngelsson D, Hedenus F, Johansson DJA, Azar C, Wirsenius S. How do dietary choices influence the energy-system cost of stabilizing the climate? *Energies* (2017) 10(2):182. doi:10.3390/en10020182
52. Eshel G, Martin PA. Diet, energy, and global warming. *Earth Interact* (2006) 10(9):1–17. doi:10.1175/EI167.1
53. de Vries M, de Boer IJM. Comparing environmental impacts for livestock products: a review of life cycle assessments. *Livest Sci* (2010) 128(1–3):1–11. doi:10.1016/j.livsci.2009.11.007
54. Schwingshackl L, Schwedhelm C, Hoffmann G, Lampousi A-M, Knüppel S, Iqbal K, et al. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr* (2017) 105(6):1462–73. doi:10.3945/ajcn.117.153148
55. Springmann M, Godfray HCJ, Rayner M, Scarborough P. Analysis and valuation of the health and climate change cobenefits of dietary change. *Proc Natl Acad Sci U S A* (2016) 113(15):4146–51. doi:10.1073/pnas.1523119113
56. Gomiero T, Pimentel D, Paoletti MG. Environmental impact of different agricultural management practices: conventional vs. organic agriculture.

*Crit Rev Plant Sci* (2011) 30(1–2):95–124. doi:10.1080/07352689.2011.554355

57. Baroni L, Cenci L, Tettamanti M, Berati M. Evaluating the environmental impact of various dietary patterns combined with different food production systems. *Eur J Clin Nutr* (2006) 61(2):279–86. doi:10.1038/sj.ejcn.1602522
58. *Building Resilience for an Unpredictable Future: How Organic Agriculture Can Help Farmers Adapt to Climate Change*. (2017). Available from: http://www.fao.org/3/a-ah617e.pdf
59. Cade J, Thompson R, Burley V, Warm D. Development, validation and utilisation of food-frequency questionnaires – a review. *Public Health Nutr* (2002) 5(4):567–87. doi:10.1079/PHN2001318
60. Gattinger A, Muller A, Haeni M, Skinner C, Fliessbach A, Buchmann N, et al. Enhanced top soil carbon stocks under organic farming. *Proc Natl Acad Sci U S A* (2012) 109(44):18226–31. doi:10.1073/pnas.1209429109
61. Skinner C, Gattinger A, Muller A, Mäder P, Flieβbach A, Stolze M, et al. Greenhouse gas fluxes from agricultural soils under organic and non-organic management – a global meta-analysis. *Sci Total Environ* (2014) 468–469:553–63. doi:10.1016/j.scitotenv.2013.08.098
62. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* (2003) 348(26):2599–608. doi:10.1056/NEJMoa025039
63. Pauly D, Christensen V, Guénette S, Pitcher TJ, Sumaila UR, Walters CJ, et al. Towards sustainability in world fisheries. *Nature* (2002) 418(6898):689–95. doi:10.1038/nature01017
64. Dayton PK, Thrush SF, Agardy MT, Hofman RJ. Environmental effects of marine fishing. *Aquat Conserv* (1995) 5(3):205–32. doi:10.1002/aqc.3270050305

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Public Health

PERSPECTIVE
published: 23 March 2018
doi: 10.3389/fpubh.2018.00093

# Perspectives from the Third International Summit on Medical Nutrition Education and Research

*Jennifer Jean Crowley[1,2]*, Celia Laur[2,3], Harrison David Edward Carter[2,4], Glenys Jones[2] and Sumantra Ray[2]**

[1] Discipline of Nutrition, Faculty of Medical Health Sciences, University of Auckland, Auckland, New Zealand, [2] NNEdPro Global Centre for Nutrition and Health, St John's Innovation Centre, Cambridge, United Kingdom, [3] Faculty of Applied Health Sciences, School of Public Health and Health Systems, University of Waterloo, Waterloo, ON, Canada, [4] Department of Public Health and Primary Care, School of Clinical Medicine, Institute of Public Health, University of Cambridge, Cambridge, United Kingdom

Nutrition is an important component of public health and health care, including in education and research, and in the areas of policy and practice. This statement was the overarching message during the third annual International Summit on Medical Nutrition Education and Research, held at Wolfson College, University of Cambridge, United Kingdom, in August 2017. This summit encouraged attendees to think more broadly about the impact of nutrition policy on health and communities, including the need to visualize the complete food system from "pre-farm to post-fork." Evidence of health issues related to food and nutrition were presented, including the need for translation of knowledge into policy and practice. Methods for this translation included the use of implementation and behavior change techniques, recognizing the needs of health-care professionals, policy makers, and the public. In all areas of nutrition and health, clear and effective messages, supported by open data, information, and actionable knowledge, are also needed along with strong measures of impact centered on an ultimate goal: to improve nutritional health and wellbeing for patients and the public.

**Keywords: nutrition, public health, health care, policy, global food systems, implementation**

OPEN ACCESS

***Edited by:***
*Carmencita David Padilla, University of the Philippines Manila, Philippines*

***Reviewed by:***
*Georgi Iskrov, Plovdiv Medical University, Bulgaria*
*Melanie Natascha Tomintz, University of Canterbury, New Zealand*

****Correspondence:***
*Jennifer Jean Crowley*
*jennifercrowley099@gmail.com;*
*Sumantra Ray*
*sr506@cam.ac.uk*

***Specialty section:***
*This article was submitted to Public Health Policy, a section of the journal Frontiers in Public Health*

***Received:*** *21 November 2017*
***Accepted:*** *12 March 2018*
***Published:*** *23 March 2018*

***Citation:***
*Crowley JJ, Laur C, Carter HDE, Jones G and Ray S (2018) Perspectives from the Third International Summit on Medical Nutrition Education and Research. Front. Public Health 6:93. doi: 10.3389/fpubh.2018.00093*

## INTRODUCTION

Nutrition has a vital role in maintaining health and preventing disease. As such, a chain of events from food production, through the food environment to dietary choices, advice and interventions, summatively impact nutritional status, thus modulating health or disease. With an increasing recognition of the preventative role of nutrition in health-related policy and practice, effective strategies are needed to bridge current divides between nutrition research and professional education, as well as between the agricultural and human health-related knowledge bases in nutrition. This was the main message of the third annual International Summit on Medical Nutrition Education and Research event hosted by the Need for Nutrition Education/Innovation Programme (NNEdPro) Global Centre for Nutrition and Health, and the Global Open Data for Agriculture and Nutrition (GODAN) at Wolfson College, University of Cambridge, United Kingdom (UK) on August 1–2, 2017. The Summit brought together international organizations and individuals involved in nutrition education and research. This year, the focus was on how to work together to build a strong evidence base and translate that evidence into policy and practice, looking at the whole system of food, nutrition, and health. A schematic representation

of the conference theme, as outlined by Sumantra Ray (SR) and André Laperrière (AL) is provided in **Figure 1**, and a list of speakers and key messages is in **Table 1**. The aim of this perspective is to outline key messages from the Summit and present ideas for future consideration.

## IMPACTING NUTRITION WITH A FOOD SYSTEMS APPROACH

While nutritional issues can be approached from different perspectives when considering individual United Nations (UN) Sustainable Development Goals (SDG), the UN Decade of Action on Nutrition aims to bring together a matrix of SDG-relevant actions with Nutrition as a common denominator (1, 2). Considering a food systems approach, it is recognized that well-designed policy can impact "pre-farm" by influencing food production from the very beginning of the food-cycle. Determining what crops farmers grow can impact on the farming methods needed to tend and nurture the crop, as well as influence resultant yields. Farming practices also impact food production, which impacts on food environment and nutrient quality, thus subsequently influencing dietary choices, leading to the "post-fork" impact on nutritional and health status. Examining this whole systems approach demonstrated the need for strong evidence and ways to translate that evidence into policy and practice at all levels within the system, including clear communication, and public health messaging.

## ENGAGING POLICY MAKERS AND COMMISSIONERS TO IMPROVE HEALTH

Engaging with policy makers and commissioners is essential, particularly when looking at improving health outcomes of individuals by taking a systems approach of "pre-farm to post-fork." In line with this approach, Franceso Branca from the World Health Organization (WHO) outlined priorities for global nutrition policy in the context of the SDG—agenda 2030, particularly Goal 2: *End hunger, achieve food security, and improved nutrition and promote sustainable agriculture* (1). Policy makers should be addressing the double burden of malnutrition, as undernutrition or overweight/obesity, combined with nutrition-related non-communicable diseases (NCD), can all play a role at individual, household, and population levels, and across the lifespan. Policy coherence is needed across food systems and agriculture, and the UN Decade of Action on Nutrition (2) demonstrates that nutrition is a key concern for the WHO commission.

Policy makers should also recognize that access to open data can support policy decisions in agriculture. For example, Chris Baker presented a search tool that provides a user-friendly graphical interface, for complex *ad hoc* query composition suitable for policy makers or programme managers. This tool will have a query engine that is able to discover online data resources from multiple organizations (e.g., the European Food Safety Authority), retrieve, and integrate the data on a per query basis. This tool could help determine the type of crops and quantities to be grown that would contribute to a healthier diet for a specific population demographic.

John Ingram discussed how policy makers should know the potential for food systems to bridge food production and nutrition. As part of this, they should recognize the differences between the Food and Agriculture Organization of the United Nations definition of "*food security,*" and the Committee on World Food Security (CFS) definition of "*nutrition security*." Overall, "*nutrients are seen as a crucial component of security, and food security is seen as a crucial component of nutrition security*" (3, 4). A food system perspective is needed to structure the necessary dialog between researchers along the whole food chain (plant breeders,

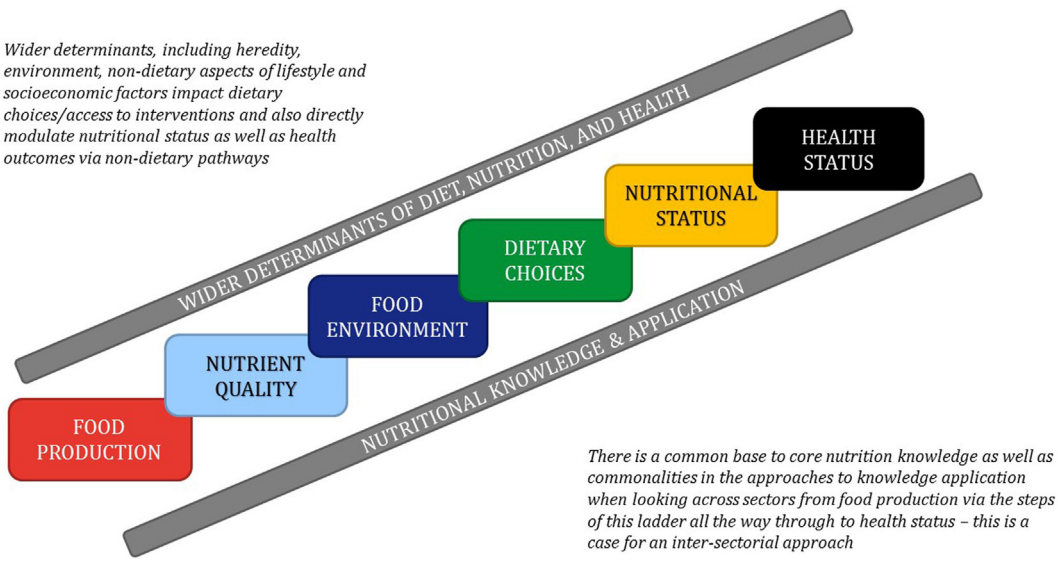



**FIGURE 1** | A schematic representation of the conference themes.

**TABLE 1** | Speakers and key messages from the Third International Summit on Medical Nutrition Education and Research.

| Speaker name | Organization | Country | Key message |
|---|---|---|---|
| **Day 1 (AM): engagement with policy makers and commissioners** | | | |
| **Moderators: Dr. Jennifer Crowley[a] and André Laperrière[a]** | | | |
| Dr. Francesco Branca | World Health Organization (WHO) | Switzerland | Policy coherence across food systems and agriculture is required to address the double burden of disease that exists throughout the world to enable the United Nations to achieve the Sustainable Development Goals-agenda-2030 |
| Boshko Stankovski[a] | Trinity College, University of Cambridge | Republic of Macedonia | The evolving nature of the international right to food has relevance to nutrition research and education |
| Professor Chris Baker | IPSNP Computing Inc. (Canada, UK), University of New Brunswick, Canada | Canada | Real world decision-support (as outlined by the Food and Agriculture Organization of the United Nations "Use Cases") requires rapid access to numerous distributed sources and analysis of data. Queries to these diverse and heterogeneous data sources are typically *ad hoc* in nature. A unique advanced search engine, HYDRA, is able to discover and retrieve relevant sources of data online and integrate it such that the data can provide comprehensive answers. Examples of queries requiring the federation and integration of data were in support of decisions on: which varieties of eggplant to grow, the corresponding profit margins, and consequences of crop husbandry (pesticides) on non-target organisms (bees) |
| Dr. Guiseppe Grosso[a] | Integrated Cancer Registry, Azienda Ospedaliera Universitaria Policlinico Vittorio Emanuele | Italy | Strong evidence is required to inform public health messages when researching the impact of food and nutrition in humans |
| Dr. John Ingram | University of Oxford | UK | Food systems can provide the link between food production and good nutrition, including food security and nutrition security, when there is good communication between plant breeders, agronomists, farmer education, and public health messaging |
| Kiringai Kamau | University of Nairobi | Kenya | Data driven, student led, agricultural extension models can align infrastructure to support the governments' efforts to address producer community knowledge delivery gaps |
| Professor Louis Levy | Public Health England (PHE) | UK | Nutrition research fits into the policy cycle of identifying needs, options, implementation, monitoring, and evaluation review and requires evidence at each stage of the cycle |
| **Day 1 (PM): role of health-care providers in delivering nutritional care and nutrition skills in practice** | | | |
| **Moderator: Nida Ziauddeen[a]** | | | |
| Melissa Adamski | Monash University | Australia | Monash University has a suite of online courses, Food as Medicine. The Food as Medicine MOOC is an educational tool aimed at the general public, which provides free, flexible online learning in areas of food, nutrition, and health. The suite of for-fee flexible online courses are for HCP to provide relevant and useful nutrition information that can be used in health-care practice |
| Celia Laur[a] | University of Waterloo | Canada | NNEdPro's Global Innovation Panel supports individuals and groups to enhance the skills of HCP and translate evidence into practice |
| Dr. Jennifer Crowley[a]<br>Professor Eleanor Beck[a] | University of Auckland<br>University of Woollongong | NZ<br>Australia | The Australia New Zealand Network supports medical nutrition educators progress medical/health-care nutrition research |
| James Bradfield[a]<br>Shivani Bhat[a]<br>Professor Sumantra Ray[a] | University College Cork<br>NNEdPro<br>NNEdPro | UK<br>Canada<br>UK | NNEdPro has developed a multipronged educational strategy ranging from e-learning for health care and related professionals to educational interventions in poorly resourced settings. I-KANN-25 will serve as an international knowledge exchange platform to bring together existing knowledge and also provide a platform to share best practice within and across regions |
| Eritia Abulu<br>Miranda van Emmenis<br>Pauline Douglas[a]<br>Candice Ward | University of Hereford<br>University of Cambridge<br>University of Ulster<br>Cambridge Diabetes Education Programme (CDEM) | UK<br>UK<br>UK<br>UK | Student and health-care professionals illustrated different approaches to the key role pharmacists could provide at the interface between the public and HCP to deliver nutrition advice to patients |
| Dr. Robert Winwood | Royal DSM | UK | Some drug nutrient interactions adversely affect micronutrient status in human tissue, while others can benefit micronutrient interactions |
| Selvarani Elahi[a] | Laboratory of the Government Chemist (LGC) | UK | The Food Authenticity network is a virtual initiative to bring together those involved in food authenticity testing across the UK, and in other countries access to a network of food authenticity testing laboratories |

(*Continued*)

**TABLE 1** | Continued

| Speaker name | Organization | Country | Key message |
|---|---|---|---|
| **Day 1 (mini symposium): translating novel data on polyphenols onto practice** | | | |
| **Moderator: Professor Daniele Del Rio[a]** | | | |
| Dr. Christina Khoo | Ocean Spray | USA | Ocean Spray is associated with universities and government agencies to understand the nutritional and health benefits of the cranberry |
| Dr. Daniela Martini | University of Parma | Italy | The three main pillars used to judge health food claims provide guidance for the research required to have claims substantiated |
| Dr. Donato Angelino | University of Parma | Italy | Emerging evidence suggests that polyphenols, particularly procyanidins, found in tea, cocoa, grapes, nuts, and berries are beneficial for cognitive function |
| Professor Nathalie Tufenkji | McGill University | Canada | Emerging evidence suggests that cranberry may be an alternative to use of antibiotics for the prevention and treatment of infections |
| Geoffrey Istas | Kings College London | UK | Emerging evidence suggests that cranberry polyphenols provide beneficial effects to the vascular health of healthy men |
| Professor Kalpana Gupta | Boston University School of Medicine | USA | Recent research demonstrates that cranberry lowers urinary tract infections in women |
| **Day 2: Implementation science-moving research into practice** | | | |
| **Moderators: Dr. Margaret Ashwell (AfN), Dr. Glenys Jones[a], Professor Martin Kohlmeier[a]** | | | |
| Celia Laur[a] | University of Waterloo | Canada | Finding effective ways of getting evidence into routine practice using implementation science and practice. Examples from the More-2-Eat implementation project |
| Harrison Carter[a] | University of Cambridge | UK | Practicable solutions are being sought to address barriers that challenge implementation policy to address hospital malnutrition |
| Pauline Douglas[a] | NNEdPro | UK | The cow's milk allergy project aims to bring best practice from hospital care into primary care and community care practice |
| Dr. Glenys Jones[a] | NNEdPro | UK | |
| Dr. Minha Rajput Ray[a] | NNEdPro | UK | |
| Associate Professor Suzanne Piscopo[a] | Society for Nutrition Education and Behavior (SNEB)<br>University of Malta | Malta | To promote healthy eating behaviors that are effective, interventions need to be based on behavior change theory, target specific audiences, and go beyond disseminating information to nurturing a willingness to improve food intake and creating an enabling environment |
| Dr. Laura Thomas | Laura Thomas Ph.D.<br>"Don't Salt My Game" | UK | Intuitive eating principles can create behavior change in practice |
| Victor Mogre | University for Development Studies, Tamale | Ghana | Educational interventions should emphasis building skills, self-efficacy, and role modeling of nutrition care by leaders in the practice setting to improve nutrition practice behavior. Future studies should measure improved clinical outcomes that result from change in nutrition practice behavior |
| Victoria Avery | Yakult | UK | There is potential for probiotics, given in conjunction with an educational programme for care home staff, to counter the effects of age-related changes to gut microbiota, and enhance the health of care home residents |
| Anthony Warner | The Angry Chef | UK | "Fake news" related to nutrition illustrates the importance of evidence-based and easily understood nutrition communication and public health messaging |
| Dr. Giles Yeo | University of Cambridge | UK | Academics have a duty to stand up for and be passionate about the truth, but how it is told also matters |
| **Day 2: panel discussion: the creation of the nutrition data strategy** | | | |
| **Moderator: André Laperrière[a]** | | | |
| Ruthie Musker[a] | Global Open Data for Agriculture and Nutrition (GODAN) | UK | The need for and benefits of open access data were supported by most summit attendees who provided suggestions how NNEdPro and GODAN can continue to advocate for it/open access data |
| Nida Ziauddeen[a] | University of Southampton | UK | |
| Dr. Glenys Jones[a] | NNEdPro | UK | |

[a]*NNEdPro Member.*

*GTA, Global Training Academy; HCP, health-care professionals; NELICO, Nutrition Education and Leadership for Improved Clinical Outcomes; NZ, New Zealand; MOOC, Massive Open Online Course; USA, United States of America.*

agronomists,[1] extension services (farmer education),[2] raw material processors, final product processors, through to nutritionists, anthropologists, and behavioral psychologists) to link agriculture to nutrition outcomes. Policy makers should also acknowledge the need to educate farmers about which crops to grow/produce, as discussed by farmer and agricultural economist, Kiringai Kamau.

From a cross-border legal perspective, the evolving nature of the international right to food, and its relevance within nutrition research and education was presented by Bosko Stankovski. Policy makers should know that the right to food is progressive and should be seen as dynamic, not static, as evidenced in three UN documents (5–7). Giuseppe Grosso discussed the need for strong evidence to inform policy and public health messages, recognizing the limitations of some studies, including the ethical challenges when researching the impact of food and nutrition in humans.

Louis Levy (LL) of Public Health England (PHE) presented a UK perspective on nutrition evidence, policy development, and implementation. LL discussed how nutrition research fits into the policy cycle of identifying needs and options, following through to implementation, monitoring, and evaluation/review. Evidence is required at each stage of the cycle and is accompanied by consultation when applicable.

## HEALTH-CARE PROVIDERS HAVE A KEY ROLE IN DELIVERING NUTRITIONAL CARE

To put nutrition policies into practice, one approach is to focus on educating health-care providers and developing their skills to deliver safe and effective nutrition care. For example, the Food as Medicine, Massive Open Online Course, presented by Melissa Adamski, provides free, flexible, online learning for the general public, with education on the relationship between food, nutrition, and health. Under this Food as Medicine brand, a suite of for-fee online courses have also been developed for health-care professionals (HCP) without a nutrition background, or as refresher courses for nutrition professionals (8), a number of which have been externally quality assured by the UK Association for Nutrition.

To further encourage international shared learning in nutrition education, the NNEdPro's Global Innovation Panel (GIP) supports individuals and groups to work and learn together to enhance the skills of HCP and translate evidence into practice. For example, within GIP, the Australia and New Zealand Network (ANZ Network) aims to support medical nutrition educators progress medical/health-care nutrition research. NNEdPro is also developing e-learning materials for the University of Cambridge, School of Clinical Medicine, which is also included as pre-learning material for the NNEdPro Summer School Foundation Certificate Course in Applied Human Nutrition. The global application of such teaching methods was illustrated in NNEdPro's Urban Slum Project that delivered a series of workshops to educate local HCP and lay volunteers on delivering nutrition advice to the urban slum population in India (9).

Another way that NNEdPro supports HCP education is through the International Knowledge Application Network in Nutrition 2025 initiative (I-KANN-25), which uses the global increase in NCDs as an example to illustrate its application. I-KANN-25 is part of NNEdPro's education and training academy, which facilitates: nutrition education at the University of Cambridge; the Summer School in Applied Human Nutrition (Cambridge); the annual International Summit (Cambridge); and e-learning initiatives. I-KANN-25 seeks to connect materials from these initiatives and more, to be used internationally, such as through the development of an online portal, which will encourage regional adaptations and opportunities for international interaction to facilitate learning. The I-KANN-25 online network will be modeled on the Food Authenticity Network, developed by the Department for Environment, Food and Rural Affairs (Defra). The Defra initiative spans 21 countries to bring together those involved in food authenticity testing (10).

### The Role of Nutrition in Pharmacy

Pharmacists play a key role within primary care, often having more contact with members of the community than other HCP (11). For this reason, pharmacists are a key group that should be aware of the importance of nutrition. To highlight this opportunity/need, NNEdPro ran an essay competition entitled, "*The role of nutrition in pharmacy settings*." The competition, the third in a series of annual NNEdPro essay competitions (12, 13), was open to those working in or studying pharmacy, and those attending the NNEdPro Summer School. The pharmacy winner was University of Herefordshire student, Eriata Abulu who presented ideas from her essay, as did Summer School student winner, Miranda Van Emmenis. Both competition winners and a panel of speakers highlighted that with additional training, pharmacists could fulfill a key role at the interface between the public and HCP to deliver evidence-based nutrition messages.

To demonstrate a specific example of how nutrition science integrates with pharmacists' clinical role, Robert Winwood presented on drug nutrient interactions.

## TRANSLATING NOVEL DATA ON POLYPHENOLS ONTO PRACTICE

The emerging evidence regarding the benefits of polyphenols provided an interesting case study on how evidence-based nutrition that has proven clinical effectiveness can be translated into practice. To present this case, Daniele Del Rio (DDR) provided an introduction to polyphenols, while Christina Khoo set the scene by outlining Ocean Spray's history and collaboration of research with universities, government agencies, and other companies to highlight evidence regarding the impact of cranberries on health.

A series of researchers outlined emerging evidence for polyphenols in health. Daniela Martini presented on requirements for scientific substantiation of health claims, indicating the

[1] Works with the science and technology of producing and using plants for food, fuel, fiber, and land reclamation.

[2] Agricultural extension is the application of scientific research and knowledge to agricultural practices through farmer education.

benefits of using the three main pillars on which food claims are judged to provide guidance for the quality research required to have claims substantiated (14, 15). Donato Angelino presented evidence suggesting that polyphenols, in particular, proanthocyanidins, found in tea, cocoa, grapes, nuts, and berries, are beneficial for cognitive function. However, lack of robust biomarkers of dietary intake hampers progress in this field. Geoffrey Istas presented on the effects of polyphenols on vascular function in healthy men. Nathalie Tufenkji discussed cranberry as an alternative for prevention of urinary tract infections (UTIs), an infection that contributes to global spread of antibiotic resistance. Kalpana Gupta focused on the impact of cranberry on UTIs, the most common bacterial infection in women (16). KG's research among women with recent history of UTI demonstrates a lowered number of symptomatic UTI episodes for those consuming cranberry juice (17), suggesting an alternative preventative measure.

## IMPLEMENTATION—MOVING RESEARCH INTO PRACTICE

### What Is Implementation Science and How Can It Improve Nutritional Care?

With the expanding evidence in nutrition research, knowing when and how to get that research into practice is key. Knowledge translation, implementation, behavior change, and communication of nutrition messages are important components when translating this research into practice. Celia Laur presented an example of an effective implementation project from the Canadian More-2-Eat project, which improved nutrition care in five Canadian hospitals. By working with hospital champions and support teams, and using a variety of implementation and behavior change strategies, all five hospitals successfully implemented nutrition screening, and a method of triaging at risk patients to receive appropriate care. A toolkit to support implementation is available online (18), and plans are underway to sustain change and spread nationally and internationally, including in the UK.

In the UK context, a barrier to addressing hospital malnutrition is the confusion and misunderstanding about who is responsible for malnutrition. Harrison Carter (HC) explained the need for HCP to understand how to get policy into practice, including how it may require a whole system/service change, such as staff contractual alterations and workforce agreements. He also mentioned the costs associated with implementation to improve hospital malnutrition as another barrier. Medical nutrition education at all levels was one practical recommendation to address policy implementation barriers.

Another UK example of an implementation project underway focused on nutritional management of cow's milk allergy, currently, a neglected clinical area. The aim is to bring examples of best practice from hospital care into primary and community practice for this most common food allergy in infants and young children. Focus groups and interviews are being conducted to inform what needs to be done and how, with a theory of change model being created.

### Connecting Implementation, Education, and Behavior Change

Presenting accurate nutrition messages in a way that is easy to understand is another important aspect within public health. Anthony Warner, a well-known blogger with a "temperament," presented on bad science and the truth about healthy eating. Faddish diets from insta-food stars thrive in a world that favors easy explanation. People are attracted to these easy explanations over real science, potentially making decisions harmful to health. In a world of "fake news" with many providing their opinion on nutrition, qualified nutrition professionals have an important role in providing information that is evidenced based and easily understood.

While messaging is important, we also need to change behavior. To effectively promote healthy eating behaviors, Suzanne Piscopo discussed how nutrition interventions should be based on behavior change theory, target specific audiences, and go beyond disseminating information to nurturing willingness to improve food intake and creating enabling environments (19). Laura Thomas provided an example of this, describing use of intuitive eating principles in practice to create changes in behavior (20). A broader perspective was taken by Victor Mogre who explained the evidence from across several countries regarding educational interventions to improve nutrition care competencies and delivery by doctors and other HCP (21). When it comes to medical nutrition education, there is far more in common across regions than there are differences. Needs assessments should inform the design of interventions in order to improve nutrition practice behavior.

### Bringing It All Together

Giles Yeo's (GY) presentation, although focused on the genetics of body weight and several unique examples, provided a strong emphasis on nutrition communication, and transmission of that message from trusted sources. GY argued that academics have a duty to be passionate about the truth, but how the truth is told also matters.

Continuing with the translation of nutrition evidence into practice, another area with growing evidence is the use of probiotics in a care home environment, which was presented by Victoria Avery. This educational programme is used to increase care home staff knowledge of the potential benefits that probiotics can provide. Caryl Nowson provided another example of nutrition translation and the promotion of healthy aging through bringing together the training of medical, nursing, nutrition, and physical activity HCP. Many HCP include professional domains for lifestyle approaches to reducing disease, which enables nutrition in care of the older person to be made part of everyone's business. To translate this approach into action, examples were provided including a project to increase muscle mass and strength in women living independently in retirement villages (22). The recommendation was that if all HCP curricula included nutrition competencies, skills learned would provide opportunities to develop real-world interdisciplinary approaches for: disease prevention and management to identify nutritional risk; the importance of lifestyle to patients for health; and support nutritional self-management of patients.

## THE NEED FOR OPEN DATA

There is a need for open nutrition data in all of its forms (i.e., source data, descriptive collated information, research intelligence, and evidence synthesis) to be available for relevant experts to access and analyze. A discussion, chaired by AL and led by Ruthie Musker, Nida Ziauddeen, and Glenys Jones, outlined the need for and use of open data. A significant challenge raised during the discussion was ethics; the need for consent from participants, through to challenges of ethical approval at organization level. For example, whether university ethics review boards would approve collection and future use as open data. Most people recognized the need for and benefits of open data and provided suggestions for how NNEdPro and GODAN can continue to advocate and develop systems for open data access, such as the use of trials registries and repositories, formats for standardizing the anonymization of subject data, and ways to link data sources.

## CONCLUSION

Nutrition education provides the means to connect the ever-expanding and changing body of research-based evidence to policy and practice. This year, the Summit focused more broadly on how to impact policy and the need to concentrate on the full food system from "pre-farm to post-fork." Once it is clear that strong evidence exists and the timing is right for translation into policy and practice, implementation and behavior change techniques should be employed, targeting HCP and the public. In all areas within nutrition and health, clear and effective messages are needed along with strong measures of impact centered on an ultimate goal: to improve nutritional health and wellbeing for patients and the public with a longer term view to link nutritional interventions, both at population and individual levels, to measureable health outcomes.

## ETHICS STATEMENT

Ethical approval was not required for this article because the risk to summit participants was deemed minimal, and all speakers consented to the inclusion of their details and key messages.

## AUTHOR CONTRIBUTIONS

JC and CL led on writing the manuscript, while JC, CL, HC, GJ, and SR were involved in editing and finalizing this article. SR provided senior oversight. All authors were involved in organizing the Summit. All speakers in **Table 1** were provided the opportunity to review this article to ensure accurate reflection of their presentations, however, were not involved in writing.

## ACKNOWLEDGMENTS

The Royal College of Physicians and the Royal Society of Biology accredited this event for Continuing Professional Development points. The programme from the Summit is available online. CL and HC chaired the event, with leadership from all NNEdPro directors including SR, Pauline Douglas (PD), DDR, Minha Rajput-Ray (MRR), and AL. The authors extend thanks to all speakers, moderators, and attendees for their informative and insightful contributions to the Summit. The authors also wish to thank all those involved in coordinating the Summit, including NNEdPro Directors, SR, PD, MRR, DDR, as well as team members Dr. Lauren Ball, Shivani Bhat, James Bradfield, and Francesca Ghelfi. Thanks also to partner organizations of the NNEdPro Group including the British Dietetic Association (BDA), Global Open Data for Agriculture and Nutrition (GODAN), Society for Nutrition Education and Behaviour (SNEB), Ulster University School of Biomedical Sciences, and Cambridge University Health Partners (including Cambridge University Hospitals and the School of Clinical Medicine).

## FUNDING

This Summit was supported by: *Platinum Level:* GODAN and DSM; *Key supporters:* Mead Johnson, and Yakult; *Symposium Supporter:* Ocean Spray; *Associated Supporters and Knowledge Partners:* American Society of Nutrition (ASN), British Nutrition Foundation (BNF), Cambridge Diabetes Education Programme, Lead Government Chemist (LGC), MyFood24, Parenteral Enteral Nutrition (PEN), The Nutrition Society. The annual Summit is also made possible by support in kind from NNEdPro's strategic partners, including, the British Dietetic Association, University of Cambridge, Ulster University, and the Society for Nutrition Education and Behaviour.

## REFERENCES

1. United Nations. *Sustainable Development Goals* (2015). Available from: http://www.un.org/sustainabledevelopment/development-agenda/ (accessed September 2017).
2. United Nations. *United Nations Decade of Action on Nutrition 2016-2025* (2017). Available from: http://www.who.int/nutrition/decade-of-action/en/ (accessed September 2017).
3. Food and Agricultural Organization. *The State of Food and Agriculture*. Available from: http://www.fao.org/docrep/003/w1358e/w1358e00.htm
4. Committee on World Food Security. *Report of the 39th Session of the Committee on World Food Security* (2012). Available from: http://www.fao.org/bodies/cfs/cfs39/en/ (accessed September 2017).
5. United Nations. *Universal Declaration of Human Rights* (1948). Available from: http://www.un.org/en/universal-declaration-human-rights/ (accessed September 2017).
6. United Nations. *International Covenant on Cultural, Economic and Social Rights* (1966). Available from: http://www.ohchr.org/EN/ProfessionalInterest/Pages/CESCR.aspx (accessed September 2017).
7. United Nations. *Food Assistance Convention* (2003). Available from: http://www.ifrc.org/docs/idrl/I1060EN.pdf (accessed September 2017).
8. Monash University. *Food as Medicine* (2017). Available from: https://www.futurelearn.com/courses/food-as-medicine (accessed September 2017).
9. Rajput-Ray M, Bhat S, Roy AR, Banerjee R, Ray S. Is there a solution to tackle child malnutrition in urban slums? *CN Focus* (2016) 8:3.
10. Food Authenticity Network. *Food Authenticity a Virtual Network for Food Authenticity Analysis 2017* (2017). Available from: http://www.foodauthenticity.uk/ (accessed September 2017).
11. World Health Organization Consultative Group. *The Role of the Pharmsist in the Healthcare System* (1994). Available from: http://apps.who.int/medicinedocs/en/d/Jh2995e/1.6.2.html#Jh2995e.1.6.2 (accessed September 2017).

12. The NNEdPro Group. Strengthening doctors nutrition knowledge and education. *CN Focus* (2015) 15:2.
13. Bhat S, Laur C, Ball L, Ray S. Nursing essay competition 2016. *CN Focus* (2016) 8:2.
14. Martini D, Rossi S, Biasini B, Zavaroni I, Bedogni G, Musci M, et al. Claimed effects, outcome variables and methods of measurement for health claims proposed under European Community Regulation 1924/2006 in the framework of protection against oxidative damage and cardiovascular health. *Nutr Metab Cardiovasc Dis* (2017) 27:473–503. doi:10.1016/j.numecd.2017.01.008
15. Martini D, Biasini B, Rossi S, Zavaroni I, Bedogni G, Musci M, et al. Claimed effects, outcome variables and methods of measurement for health claims on foods proposed under European Community Regulation 1924/2006 in the area of appetite ratings and weight management. *Int J Food Sci Nutr* (2017):1–21. doi:10.1080/09637486.2017.1366433
16. Gupta K, Hooton TM, Roberts PL, Stamm WE. Patient-initiated treatment of uncomplicated recurrent urinary tract infections in young women. *Ann Int Med* (2001) 135:9–16. doi:10.7326/0003-4819-135-1-200107030-00004
17. Beerepoot M, Ter Riet G, Nys S. Lactobacilli versus antibiotics to prevent urinary tract infections. A randomized double-blind non-inferiority trial in postmenopausal women. *Arch Int Med* (2012) 172:704–12. doi:10.1001/2013.jamainternmed.111
18. Canadian Malnutrition Taskforce. *More-2-Eat Implementation Project*. Available from: http://nutritioncareincanada.ca/research/more-2-eat-implementation-project
19. Michie S, Atkins L, West R. The behaviour change wheel: a guide to designing interventions. *Implement Sci* (2011) 6:42. doi:10.1186/1748-5908-6-42
20. Tribole E, Resch E. *Intuitive Eating*. New York: St Martin's Press (2012).
21. Mogre V, Scherpbier A, Stevens F, Aryee P, Cherry M, Dornan T. Realist synthesis of educational interventions to improve nutrition care competencies and delivery by doctors and other healthcare professionals. *BMJ Open* (2016) 6:e010084. doi:10.1136/bmjopen-2015-010084
22. Daly R, O'Connell S, Mundell N, Grimes C, Dunstan D, Nowson C. Protein-enriched diet, with the use of lean red meat, combined with progressive resistance training enhances lean tissue mass and muscle strength and reduces circulating IL-6 concentrations in elderly women: a cluster randomized controlled trial. *Amer J Clin Nutr* (2014) 99:899–910. doi:10.3945/ajcn.113.064154

**Conflict of Interest Statement:** JC, CL, HC, GJ, and SR are core members of the NNEdPro group, which hosted the Summit.

frontiers in Public Health

MINI REVIEW
published: 03 May 2018
doi: 10.3389/fpubh.2018.00129

# Hypertension in Children: Role of Obesity, Simple Carbohydrates, and Uric Acid

*Antonina Orlando[1]*, Emanuela Cazzaniga[1], Marco Giussani[2], Paola Palestini[1] and Simonetta Genovesi[1,3]*

*[1] Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy, [2] Family Pediatrician, Azienda Sanitaria Locale della Provincia di Milano, Milan, Italy, [3] Department of Cardiovascular, Neural and Metabolic Sciences, S. Luca Hospital, IRCCS, Istituto Auxologico Italiano, Milan, Italy*

Over the past 60 years there has been a dramatic increase in the prevalence of overweight in children and adolescents, ranging from 4% in 1975 to 18% in 2016. Recent estimates indicate that overweight or obese children and adolescents are more than 340 million. Obesity is often associated with hypertension, which is an important cardiovascular risk factor. Recent studies show that the presence of hypertension is a frequent finding in the pediatric age. Hypertensive children easily become hypertensive adults. This phenomenon contributes to increasing cardiovascular risk in adulthood. Primary hypertension is a growing problem especially in children and adolescents of western countries, largely because of its association with the ongoing obesity epidemic. Recently, it has been hypothesized that a dietary link between obesity and elevated blood pressure (BP) values could be simple carbohydrate consumption, particularly fructose, both in adults and in children. Excessive intake of fructose leads to increased serum uric acid (SUA) and high SUA values are independently associated with the presence of hypertension and weaken the efficacy of lifestyle modifications in children. The present review intends to provide an update of existing data regarding the relationship between BP, simple carbohydrates (particularly fructose), and uric acid in pediatric age. In addition, we analyze the national policies that have been carried out over the last few years, in order to identify the best practices to limit the socio-economic impact of the effects of excessive sugar consumption in children.

**Keywords: obesity, cardiovascular disease, hypertension, fructose, uric acid**

OPEN ACCESS

***Edited by:***
*Sumantra Ray, NNEdPro Global Centre in Cambridge, United Kingdom*

***Reviewed by:***
*Roberto Pontremoli, Università di Genova, Italy*
*Iain Stephen Pratt, Cancer Council Western Australia, Australia*

****Correspondence:***
*Antonina Orlando*
*antonina.orlando@unimib.it*

***Specialty section:***
*This article was submitted to Public Health Policy, a section of the journal Frontiers in Public Health*

***Received:*** *23 October 2017*
***Accepted:*** *16 April 2018*
***Published:*** *03 May 2018*

***Citation:***
*Orlando A, Cazzaniga E, Giussani M, Palestini P and Genovesi S (2018) Hypertension in Children: Role of Obesity, Simple Carbohydrates, and Uric Acid. Front. Public Health 6:129. doi: 10.3389/fpubh.2018.00129*

## OBESITY: A WORLD DISEASE

In the world, obesity rages like an epidemic that involves millions of people each year. The World Health Organization (WHO) has declared that around 39% of the world's population is overweight and that worldwide obesity has nearly tripled since 1975. This alarming evidence shows that obesity is one of the major public health problems of the twenty-first century (obesity complications are the cause of about 3 million deaths per year) and the most frequent nutritional disorder in the developed countries. The infants with excess weight, in 2016, were 41 million. This problem mainly concerns the urban zone of developing countries.[1]

The prevalence of people with excess weight in Europe differs among countries: in the Mediterranean area it ranges from 20 to 40%, and in the northern countries it lies between 10

[1] http://www.who.int/mediacentre/factsheets/fs311/en/.

and 20% (1). These figures are alarming, especially when one considers that Mediterranean countries, which are traditionally supposed to follow a Mediterranean diet, classified as a healthy food regime, have the highest prevalence of overweight children. In 2015 in Italy, children and adolescents in excess of weight reached a proportion of 30.6%.[2]

Childhood overweight is a very common problem in high-income countries, but it has also spread in medium and low-income areas, and it is mostly due to low-quality diet and poor physical activity (2).

There are, therefore, several factors contributing to the onset of overweight; besides, genetic predisposition, socio-environmental, and psychological factors also contribute (3).

The social cost of obesity is increasing (4), but the health costs may turn out to be even higher if, on top of the cost of hospitalizations, other indirect costs attributable to obesity, such as those due to lower school performance, psychosocial problems, and poor quality of life, are added.

## OBESITY AND CARDIOVASCULAR DISEASES (CVD)

Until a few years ago, body fat was considered an energy storage, without hormonal and metabolic functions, and its increase represented only an esthetic problem or an obstacle to physical performance, rather than a real health problem (5). Current epidemiological data show, with increasing force, that the obesity and overweight epidemic and its early onset in childhood make it necessary to consider excess weight as a cardiovascular risk factor also in pediatric age (6). Indeed, numerous studies documented an independent association between obesity and ischemic heart disease (angina and myocardial infarction) in adulthood (7). Furthermore, it has been clearly demonstrated that obesity favors heart failure, atrial fibrillation, stroke, and sudden death (7, 8). The INTERHEART study, a case–control study that looked at 29,972 patients in 52 countries, showed that the relationship between waist circumference and waist-to-hip ratio and myocardial infarction was stronger than the one between myocardial infarction and body mass index (BMI) (9). Therefore, central obesity increases the risk of developing CVD and premature deaths. Worldwide, CVD is the major cause of death and disability. In fact, in 2012 the deaths caused by CVD were 17.5 million, representing about 30% of global deaths.[3] Even in the pediatric population, the phenomenon of obesity is widespread and, if not corrected, it can determine the onset and progression of CV complications, leading to enormous social and health costs.

## OBESITY AND HYPERTENSION

Obesity is often associated with other CV risk factors such as hypertension, type 2 diabetes, endothelial dysfunction and left ventricular hypertrophy. In particular, in the pediatric population, hypertension is by far the major risk factor associated with obesity. Hypertension has been recognized globally for more than 50 years as an important risk factor for CVD in the adult population (10, 11), and its estimated prevalence is of about a half billion hypertensive subjects in 2025 (12). The literature showed that in children hypertension is not as rare as it was believed. This has led to a systematic approach to the problem in children and adolescents, with the publication of US and European recommendations on this subject (13–15). Excess weight in childhood and adolescence is the most common cause of hypertension (16–18). The first major study on pediatric hypertension stated that "the detection and management of hypertension in children and hypertension precursors in adults are the next big public health frontier" (19).

Unfortunately, to date, the diagnosis of childhood hypertension is still absent in most cases, and the knowledge of pediatric hypertension among physicians is still insufficient. The obstacles for optimum recognition of childhood hypertension include not only the limited knowledge but also the difficulty of performing multiple measurements over the years, which are essential for proper diagnosis (20, 21). In the American continent, according to the latest estimates, 74 million children under the age of 18 are hypertensive (22).

In Italy, 4% of schoolchildren have high blood pressure (BP) (16). Only 1–3% of hypertensive children are normal weight (23), while approximately 37% are overweight. An obese child is three times more at risk of developing hypertension than a normal-weight child (24).

Central obesity plays an important role in determining hypertension in the child: waist circumference, and waist-to-height ratio are in fact independent determinants of high BP beyond BMI in childhood (25). The presence of hypertension in childhood raises the probability of being hypertensive in adulthood (26).

The advances in diagnostic techniques for revealing early organ damage in the subclinical phase of hypertension have made it possible to understand that, even in pediatric age, high BP can be associated with alterations of some target organs, like left ventricular hypertrophy and increased carotid intima-media thickness (27, 28).

## HYPERTENSION: ROLE OF URIC ACID

In 1972, Kahn and colleagues demonstrated that increased serum uric acid (SUA) was an independent risk factor for hypertension. In particular, they found that 25–40% of adults with hypertension had SUA > 6.5 mg/dl and more than 60% had >5.5 mg/dl, and that SUA and systolic BP were linearly related. In the Multiple Risk Factor Intervention study in normotensive men, the presence of SUA levels greater than 7 mg/dl increased the risk of developing hypertension by 80%. The association between hyperuricemia and hypertension was more common in young people. High SUA was observed in about 90% of adolescents with recent onset hypertension and the SUA level correlated with BP values (29). Viazzi and colleagues found a correlation between SUA and hypertension in children with risk factors for CVD (30).

[2]http://www.epicentro.iss.it/okkioallasalute/dati2016.asp.
[3]http://www.who.int/mediacentre/factsheets/fs355/en/.

No clear causal or mechanical correlation between elevation of uric acid and hypertension development had yet been described, until in a rat model with mild hyperuricemia high uric acid levels were shown to be associated with the development of initial hypertension.

It was already known that humans and monkeys have higher SUA levels than most other mammals, due to the lack of the liver enzyme uricase that degrades uric acid to allantoin. With this knowledge, at the end of the 1990s, Johnson and colleagues developed a model of hyperuricemic rats using a pharmacological uricase inhibitor The hyperuricemic rats developed systemic hypertension, demonstrating that the increase of SUA was the cause of the increase in BP (31).

Two randomized studies showed that SUA lowering drugs were able to reduce BP values in adolescent pre-hypertensive and hypertensive individuals, demonstrating that hypertension is related with uric acid (32, 33).

Moreover, experimental studies have clarified the mechanism through which hyperuricaemia leads to increased BP. The basis of this mechanism has been hypothesized to be renal vasoconstriction that is mediated by the increase in SUA through reduction of endothelial nitric oxide release and activation of the renin–angiotensin system with consequent vascular and renal damage (34–36).

A significant association between hyperuricemia, endothelial dysfunction, and activation of the renin–angiotensin system has also been documented in humans (37, 38).

The development of CVD may be caused by elevated values of SUA which induce inflammation at the vascular level (**Figure 1**).

In conclusion, all these data together suggest that uric acid promotes the development of hypertension through a two steps mechanism (39). Uric acid increases the vascular resistance by activating the renin–angiotensin–aldosterone system and suppressing the vascular nitric oxide production. Consequently, the development of the arteriosclerosis process is promoted. This process involves structural changes and is thus hardly reversible (40).

## HYPERTENSION: ROLE OF FRUCTOSE CONSUMPTION

The epidemic increase in hypertension and hyperuricemia may be partly due to the increase of sugar consumption (41).

Many epidemiological and experimental data have recently allowed to hypothesize that high consumption of sugar with the diet may be the mediator of the observed association between hypertension and hyperuricemia (41, 42).

The consumption of added sugars, in particular fructose, and high fructose corn syrup has drastically increased (41). Excess weight and associated metabolic pathologies may be caused by the excessive intake of fructose and give rise to systemic hypertension (43). Fructose metabolism has been reviewed extensively elsewhere (44) and will be only briefly outlined here. Fructose is absorbed into the enterocytes of the small intestine by the transporter GLUT5 and successively poured into the blood by GLUT2 (45). The liver absorbs most of the fructose present in the systemic circulation and hepatic fructokinase catalyzes the phosphorylation reaction to produce fructose-1-phosphate and to initiate fructose catabolism (46). Unlike the phosphorylation of glucose by glucokinase, where a feedback system prevents excessive phosphorylation and ATP depletion, fructokinase is not inhibited by its product (fructose-1-phosphate). Consequently, the fructose metabolism leads to a fast reduction in intracellular ATP, and the AMP produced is metabolized to uric acid (**Figure 2**). In fact, within 30 min after fructose ingestion, a rise in uric acid can be found in the circulation (43).

Studies demonstrated that elevated fructose intake and, consequently, hyperuricemia induce inflammation in renal tubular epithelial cells leading to renal injury and development of hypertension. Indeed, drugs used to treat hyperuricemia (i.e., allopurinol) prevent this effect (47–49).

The association between fructose consumption and increase of BP levels is demonstrated by clinical and epidemiologic studies in adolescents and adults. In the National Health and Nutrition Examination Survey study population, a correlation between consumption of sugar-sweetened beverages (SSB) and

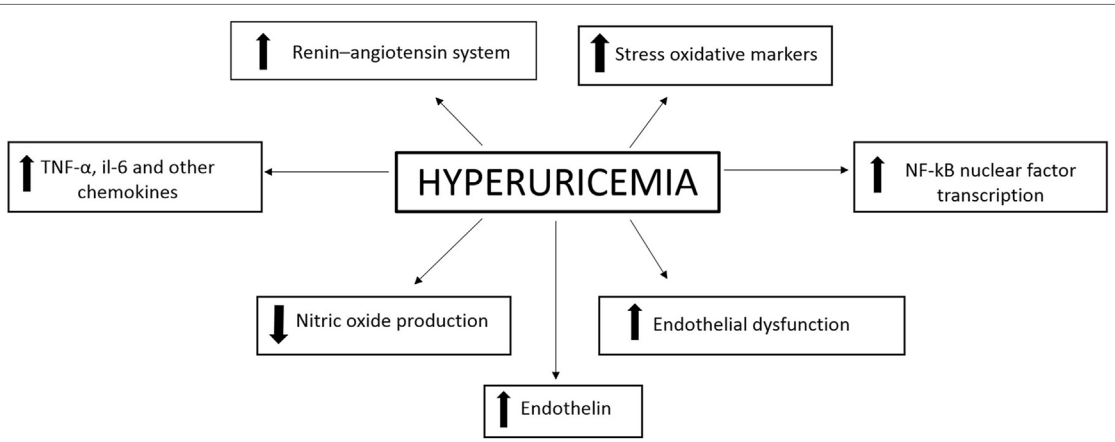



**FIGURE 1** | Mechanisms through which hyperuricaemia leads to cardiovascular damage.

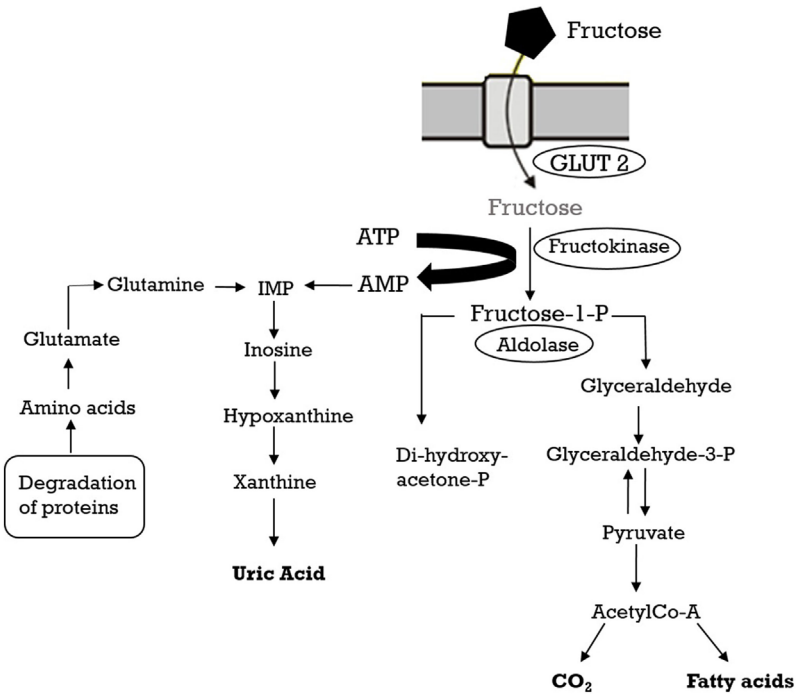



**FIGURE 2** | Fructose metabolism.

higher levels of SUA and BP was shown (50, 51). Furthermore, Jalal and colleagues showed that allopurinol prevented the increase in BP values induced by the assumption of 200 g of fructose (52). In addition, a prospective study in healthy adults showed that a significant reduction of BP values was obtained by reducing intake by one SSB serving per day, independently of weight loss (53).

In adults, the correlation between sugar intake, excess weight, and cardiovascular risk was demonstrated by several epidemiologic studies. The consumption of SSB causes weight gain or increases the risk of overweight or obesity (54–56). These data emphasize the public health importance of reducing the intake of these beverages and other sweets.

## WORLD PREVENTION STRATEGY

To manage the obesity epidemic, local and international administrations have implemented different national programs (57), in particular to fight childhood obesity.

It is complicated to evaluate the effectiveness of national public health programs (PHP) because of the number of people involved (58).

The success of a PHP requires a combination of synergistic and complementary actions, measures, regulations, and laws. Among the goals, increase in fruits and vegetables consumption, reduction in intake of simple sugars (in particular SSB), and increase in daily physical activity should not be missing.

A key strategy of the program could be to disseminate clear and simple information about its objectives and to provide dietary reference guidelines for the target population. Moreover, the collaboration between governments and the food industry should be encouraged in order to improve the quality of supplied food, as has been done in France during the French National Nutrition and Health Program. It should be noted, however, that some authors have shown that there is no evidence of the effectiveness or safety of these public–private partnerships (59).

To fight childhood obesity, the programs must affect the school settings. In France, a "Regulation on the Composition of School Meals and Food Safety" is provided to encourage school food service managers to offer fresh foods, quality products, and well-balanced meals as well as to take an active role in developing nutrition education and banning school vending machines (60).

Many authors (61–64) agree that schools are important for nutrition education because they give opportunities for experiential learning and are responsible for communication with the family and the wider community (3).

Few obesity intervention programs have targeted preschool-aged children. Lim et al. (64) tested the feasibility and effectiveness of the NASA MX project among South Korean children in kindergarten in order to promote early prevention of obesity. Their intervention program consisted in 4 weeks of fitness training and 2 weeks of nutrition education and they demonstrated that this PHP was feasible and resulted in favorable changes in eating behavior and nutritional knowledge among children.

Interestingly, different projects reported a reduction in sweet drinks (65), carbonate beverage (61), and SSB (66) consumption.

Currently, about 35–40 states in the US and the District of Columbia have sales taxes on sodas sold in grocery stores and in vending machines with the goal of decreasing caloric intake from nutrient poor foods. However, such small taxes seem to be ineffective in reducing the consumption of soda (67).

Unfortunately, some researchers (65, 68) reported the failure of a project regarding overweight children. In particular, the children involved continued with their bad habits, including excessive consumption of sweet foods, low fruit consumption, and sedentary behavior. On the other hand, the overweight children showed an improved knowledge of the attitudes to healthy eating and physical activity (68).

Some researchers (69, 70) launched the "Paying less for health" trials and showed that the price of food items influenced the purchase at the refectory or at the vending machine.

Schools should plan PHP for the prevention of obesity (61), in particular to teach how to reduce the consumption of SSBs in favor of clean drinking water (71, 72).

Ministries, research, and educational institutions are in the right position to contribute, each with their own skills, to prevent cardiovascular risk factors in children to reduce the incidence of CVD in adulthood because "cardiovascular prevention is a thing of children!"

## AUTHOR CONTRIBUTIONS

AO and EC performed the literatures work and drafted of the article, MG, PP, and SG have done the work of review and correction.

## REFERENCES


1. Speiser P, Rudolf M, Anhalt H, Camacho-Hubner C, Chiarelli F, Eliakim A, et al. Childhood obesity. *J Clin Endocrinol Metab* (2005) 90(3):1871–87. doi:10.1210/jc.2004-1389
2. Ebbeling C, Pawlak D, Ludwig D. Childhood obesity: public-health crisis, common sense cure. *Lancet* (2002) 360:473–82. doi:10.1016/S0140-6736(02)09678-2
3. Lobstein T, Baur L, Uauy R. Obesity in children and young people: a crisis in public health. IASO International Obesity TaskForce. *Obes Rev* (2004) 5(Suppl 1):4–104. doi:10.1111/j.1467-789X.2004.00133.x
4. Trasande L, Liu Y, Fryer G, Weitzman M. Effects of childhood obesity on hospital care and costs, 1999–2005. *Health Aff* (2009) 28(4):w751–60. doi:10.1377/hlthaff.28.4.w751
5. Manios Y, Moschonis G, Karatzi K, Androutsos O, Chinapaw M, Moreno LA, et al. Large proportions of overweight and obese children, as well as their parents, underestimate children's weight status across Europe. The ENERGY (EuropeaN Energy balance Research to prevent excessive weight Gain among Youth) project. ENERGY Consortium. *Public Health Nutr* (2015) 18(12):2183–90. doi:10.1017/S136898001400305X
6. Ayer J, Charakida M, Deanfield JE, Celermajer DS. Lifetime risk: childhood obesity and cardiovascular risk. *Eur Heart J* (2015) 36(22):1371–6. doi:10.1093/eurheartj/ehv089
7. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med* (2002) 162:1867–72. doi:10.1001/archinte.162.16.1867
8. Lawlor DA, Lean M, Sattar N. ABC of obesity: obesity and vascular disease. *BMJ* (2006) 333:1060–3. doi:10.1136/bmj.333.7577.1060
9. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, et al. Obesity and the risk of myocardial infarction in 27.000 participants from 52 countries: a cas-control study. *Lancet* (2005) 366:1640–9. doi:10.1016/S0140-6736(05)67663-5
10. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J III. Factors of risk in the development of coronary heart disease – six year follow-up experience. The Framingham Study. *Ann Intern Med* (1961) 55(1):33–50. doi:10.7326/0003-4819-55-1-33
11. Lo JC, Chandra M, Sinaiko A, Daniels SR, Prineas RJ, Maring B, et al. Severe obesity in children: prevalence, persistence and relation to hypertension. *Int J Pediatr Endocrinol* (2014) 3(1):3. doi:10.1186/1687-9856-2014-3
12. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* (2005) 365:217–23. doi:10.1016/S0140-6736(05)70151-3
13. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation and treatment of high blood pressure in 92 children and adolescents. *Pediatrics* (2004) 114:555–76. doi:10.1542/peds.114.2.S2.555
14. Lurbe E, Cifkova R, Cruickshank JK, Dillon MJ, Ferreira I, Invitti C, et al. Management of high blood pressure in children and adolescents: recommendations of the European Society of Hypertension. *J Hypertens* (2009) 27:1719–42. doi:10.1097/HJH.0b013e32832f4f6b
15. Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A, Erdine S, Hirth A, et al. European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. *J Hypertens* (2016) 34(10):1887–920. doi:10.1097/HJH.0000000000001039
16. Genovesi S, Giussani M, Pieruzzi F, Vigorita F, Arcovio C, Cavuto S, et al. Results of blood pressure screening in a population of school-aged children in the province of Milan: role of overweight. *J Hypertens* (2005) 23(3):493–7. doi:10.1097/01.hjh.0000160203.35910.9f
17. Genovesi S, Antolini L, Giussani M, Brambilla P, Barbieri V, Galbiati S, et al. Hypertension, prehypertension, and transient elevated blood pressure in children: association with weight excess and waist circumference. *Am J Hypertens* (2010) 23(7):756–61. doi:10.1038/ajh.2010.50
18. Spagnolo A, Giussani M, Ambruzzi AM, Bianchetti M, Maringhini S, Matteucci MC, et al. Focus on prevention, diagnosis and treatment of hypertension in children and adolescents. *Ital J Pediatr* (2013) 19(39):20. doi:10.1186/1824-7288-39-20
19. Blumenthal S, Epps RP, Heavenrich R, Lauer RM, Lieberman E, Mirkin B, et al. Report of the task force on blood pressure control in children. *Pediatrics* (1977) 59(Suppl 2):I–II,797–820.
20. Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of hypertension in children and adolescents. *JAMA* (2007) 298(8):874–9. doi:10.1001/jama.298.8.874
21. Riley M, Dobson M, Sen A, Green L. Recognizing elevated BP in children and adolescents: how are we doing? *J Fam Pract* (2013) 62(6):294–9.
22. Rao G. Diagnosis, epidemiology, and management of hypertension in children. *Pediatrics* (2016) 138(2):e20153616. doi:10.1542/peds.2015-3616
23. Brambilla P, Antolini L, Street ME, Giussani M, Galbiati S, Valsecchi MG, et al. Adiponectin and hypertension in normal-weight and obese children. *Am J Hypertens* (2013) 26(2):257–64. doi:10.1093/ajh/hps033
24. Herouvi D, Karanasios E, Karayianni C, Karavanaki K. Cardiovascular disease in childhood: the role of obesity. *Eur J Pediatr* (2013) 172(6):721–32. doi:10.1007/s00431-013-1932-8
25. Genovesi S, Antolini L, Giussani M, Pieruzzi F, Galbiati S, Valsecchi MG, et al. Usefulness of waist circumference for the identification of childhood hypertension. *J Hypertens* (2008) 26(8):1563–70. doi:10.1097/HJH.0b013e328302842b
26. Sorof JM, Lai D, Turner J, Poffenbarger T, Portman RJ. Overweight, ethnicity, and the prevalence of hypertension in school-aged children. *Pediatrics* (2004) 113:475–82. doi:10.1542/peds.113.3.475
27. Sorof JM, Alexandrov AV, Cardwell G, Portman RJ. Carotid artery intimal-medial thickness and left ventricular hypertrophy in children with elevated blood pressure. *Pediatrics* (2003) 111(1):61–6. doi:10.1542/peds.111.1.61
28. Pieruzzi F, Antolini L, Salerno FR, Giussani M, Brambilla P, Galbiati S, et al. The role of blood pressure, body weight and fat distribution on left ventricular

mass, diastolic function and cardiac geometry in children. *J Hypertens* (2015) 33(6):1182–92. doi:10.1097/HJH.0000000000000552
29. Krishnan E, Kwoh CK, Schumacher HR, Kuller L. Hyperuricemia and incidence of hypertension among men without metabolic syndrome. *Hypertension* (2007) 49(2):298–303. doi:10.1161/01.HYP.0000254480.64564.b6
30. Viazzi F, Antolini L, Giussani M, Brambilla P, Galbiati S, Mastriani S, et al. Serum uric acid and blood pressure in children at cardiovascular risk. *Pediatrics* (2013) 132(1):e93–9. doi:10.1542/peds.2013-0047
31. Johnson RJ, Kivlighn SD, Kim YG, Suga S, Fogo AB, Metz C. Reappraisal of the pathogenesis and consequences of hyperuricemia in hypertension, cardiovascular disease, and renal disease. *Am J Kidney Dis* (1999) 33(2): 225–34. doi:10.1016/S0272-6386(99)70295-7
32. Feig I, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *JAMA* (2008) 300(8):924–32. doi:10.1001/jama.300.8.924
33. McMullan CJ, Borgi L, Fisher N, Curhan G, Forman J. Effect of Uric Acid Lowering on Renin-Angiotensin-System Activation and Ambulatory BP: A Randomized Controlled Trial. *Clin J Am Soc Nephrol* (2017) 12(5):807–16. doi:10.2215/CJN.10771016
34. Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, et al. Hyperuricemia induces endothelial dysfunction. *Kidney Int* (2005) 67(5):1739–42. doi:10.1111/j.1523-1755.2005.00273.x
35. Zharikov S, Krotova K, Hu H, Baylis C, Johnson RJ, Block ER, et al. Uric acid decreases NO production and increased arginase activity in cultured pulmonary artery endothelial cells. *Am J Phyiol Cell Physiol* (2008) 295(5): C1183–90. doi:10.1152/ajpcell.00075.2008
36. Sánchez-Lozada LG, Tapia E, López-Molina R, Nepomuceno T, Soto V, Avila-Casado C, et al. Effects of acute and chronic L-arginine treatment in experimental hyperuricemia. *Am J Physiol Renal Physiol* (2007) 292(4): F1238–44. doi:10.1152/ajprenal.00164.2006
37. Doehner W, Schoene N, Rauchhaus M, Leyva-Leon F, Pavitt DV, Reaveley DA, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. *Circulation* (2002) 105(22):2619–24. doi:10.1161/01.CIR.0000017502.58595.ED
38. Mercuro G, Vitale C, Cerquetani E, Zoncu S, Deidda M, Fini M, et al. Effect of hyperuricemia upon endothelial function in patients at increased cardiovascular risk. *Am J Cardiol* (2004) 94(7):932–5. doi:10.1016/j.amjcard.2004.06.032
39. Feig DI. Uric acid and hypertension. *Semin Nephrol* (2011) 31(5):441–6. doi:10.1016/j.semnephrol.2011.08.008
40. Strambi M, Giussani M, Ambruzzi MA, Brambilla P, Corrado C, Giordano U, et al. Novelty in hypertension in children and adolescents: focus on hypertension during the first year of life, use and interpretation of ambulatory blood pressure monitoring, role of physical activity in prevention and treatment, simple carbohydrates and uric acid as risk factors. *Ital J Pediatr* (2016) 42(1):69. doi:10.1186/s13052-016-0277-0
41. Johnson RJ, Segal MS, Sautin Y, Nakagawa T, Feig DI, Kang DH, et al. Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. *Am J Clin Nutr* (2007) 86(4):899–906. doi:10.1093/ajcn/86.4.899
42. Brown CM, Dulloo AG, Yepuri G, Montani JP. Sugar ingestion, in the form of fructose, acutely elevates blood pressure in healthy young humans. *Am J Physiol Regul Integr Comp Physiol* (2008) 294(3):R730–7. doi:10.1152/ajpregu.00680.2007
43. Madero M, Perez-Pozo SE, Jalal D, Johnson RJ, Sánchez-Lozada LG. Dietary fructose and hypertension. *Curr Hypertens Rep* (2011) 13(1):29–35. doi:10.1007/s11906-010-0163-x
44. Tappy L, Le KA. Metabolic effects of fructose and the worldwide increase in obesity. *Physiol Rev* (2010) 90(1):23–46. doi:10.1152/physrev.00019.2009
45. Jones HF, Butler RN, Brooks DA. Intestinal fructose transport and malabsorption in humans. *Am J Physiol Gastrointest Liver Physiol* (2011) 300(2):G202–6. doi:10.1152/ajpgi.00457.2010
46. Mayes PA. Intermediary metabolism of fructose. *Am J Clin Nutr* (1993) 58(5):S754–65. doi:10.1093/ajcn/58.5.754S
47. Sánchez-Lozada LG, Tapia E, Bautista-García P, Soto V, Avila-Casado C, Vega-Campos IP, et al. Effects of febuxostat on metabolic and renal alterations in rats with fructose induced metabolic syndrome. *Am J Physiol Renal Physiol* (2008) 294(4):F710–8. doi:10.1152/ajprenal.00454.2007
48. Cirillo P, Gersch MS, Mu W, Scherer PM, Kim KM, Gesualdo L, et al. Ketohexokinase-dependent metabolism of fructose induces proinflammatory mediators in proximal tubular cells. *J Am Soc Nephrol* (2009) 20(3):545–53. doi:10.1681/ASN.2008060576
49. Hu QH, Wang C, Li JM, Zhang DM, Kong LD. Allopurinol, rutin, and quercetin attenuate hyperuricemia and renal dysfunction in rats induced by fructose intake: renal organic ion transporter involvement. *Am J Physiol Renal Physiol* (2009) 297(4):F1080–91. doi:10.1152/ajprenal.90767.2008
50. Nguyen S, Choi HK, Lustig RH, Hsu CY. Sugar-sweetened beverages, serum uric acid, and blood pressure in adolescents. *J Pediatr* (2009) 154(4):807–13. doi:10.1016/j.jpeds.2009.01.015
51. Jalal DI, Smits G, Johnson RJ, Chonchol M. Increased fructose associates with elevated blood pressure. *J Am Soc Nephrol* (2010) 21(9):1543–9. doi:10.1681/ASN.2009111111
52. Perez-Pozo SE, Schold J, Nakagawa T, Sánchez-Lozada LG, Johnson RJ, Lillo JL. Excessive fructose intake induces the features of metabolic syndrome in healthy adult men: role of uric acid in the hypertensive response. *Int J Obes (Lond)* (2010) 34(3):454–61. doi:10.1038/ijo.2009.259
53. Chen L, Caballero B, Mitchell DC, Loria C, Lin PH, Champagne CM, et al. Reducing consumption of sugar-sweetened beverages is associated with reduced blood pressure: a prospective study among United States adults. *Circulation* (2010) 121(22):2398–406. doi:10.1161/CIRCULATIONAHA.109.911164
54. Hu FB, Malik VS. Sugar-sweetened beverages and risk of obesity and type 2 diabetes: epidemiologic evidence. *Physiol Behav* (2010) 100(1):47–54. doi:10.1016/j.physbeh.2010.01.036
55. Malik VS, Popkin BM, Bray GA, Després JP, Hu FB. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation* (2010) 121(11):1356–64. doi:10.1161/CIRCULATIONAHA.109.876185
56. Malik VS, Pan A, Willett WC, Hu FB. Sugar-sweetened beverages and weight gain in children and adults: a systematic review and meta-analysis. *Am J Clin Nutr* (2013) 98(4):1084–102. doi:10.3945/ajcn.113.058362
57. Lobstein T, Baur LA. Policies to prevent childhood obesity in the European Union. *Eur J Public Health* (2005) 15(6):576–9. doi:10.1093/eurpub/cki068
58. Péneau S, Salanave B, Maillard-Teyssier L, Rolland-Cachera MF, Vergnaud AC, Méjean C, et al. Prevalence of overweight in 6- to 15-year-old children in central/western France from 1996 to 2006: trends toward stabilization. *Int J Obes (Lond)* (2009) 33(4):401–7. doi:10.1038/ijo.2009.31
59. Moodie R, Stuckler D, Monteiro C, Sheron N, Neal B, Thamarangsi T, et al. Profits and pandemics: prevention of harmful effects of tobacco, alcohol, and ultra-processed food and drink industries. *The Lancet* (2013) 381:670–9. doi:10.1016/S0140-6736(12)62089-3
60. Hercberg S, Chat-Yung S, Chaulia M. The French national nutrition and health program: 2001-2006-2010. *Int J Public Health* (2008) 53(2):68–77. doi:10.1007/s00038-008-7016-2
61. James J, Thomas P, Cavan D, Kerr D. Preventing childhood obesity by reducing consumption of carbonated drinks: cluster randomised controlled trial. *BMJ* (2004) 328(7450):1237. doi:10.1136/bmj.38077.458438.EE
62. Taylor RW, McAuley KA, Williams SM, Barbezat W, Nielsen G, Mann JI. Reducing weight gain in children through enhancing physical activity and nutrition: the APPLE project. *Int J Pediatr Obes* (2006) 1:146–52. doi:10.1080/17477160600881247
63. Li J, Hooker NH. Childhood obesity and schools: evidence from the national survey of children's health. *J Sch Health* (2010) 80(2):96–103. doi:10.1111/j.1746-1561.2009.00471.x
64. Lim H, Kim J, Wang Y, Min J, Carvajal NA, Lloyd CW. Child health promotion program in South Korea in collaboration with US National Aeronautics and Space Administration: improvement in dietary and nutrition knowledge of young children. *Nutr Res Pract* (2016) 10(5):555–62. doi:10.4162/nrp.2016.10.5.555
65. Taylor RW, McAuley KA, Barbezat W, Strong A, Williams SM, Mann JI. APPLE Project: 2-y findings of a community-based obesity prevention program in primary school age children. *Am J Clin Nutr* (2007) 86(3):735–42. doi:10.1093/ajcn/86.3.735
66. Rauba J, Tahir A, Milford B, Toll A, Benedict V, Wang C, et al. Reduction of sugar-sweetened beverage consumption in elementary school students using

an educational curriculum of beverage sugar content. *Glob Pediatr Health* (2017) 4:2333794X17711778. doi:10.1177/2333794X17711778
67. Dilk A, Savaiano DA. Sugar price supports and taxation: a public health policy paradox. *Nutr Today* (2017) 52(3):143–50. doi:10.1097/NT.0000000000000217
68. Sahota P, Rudolf MC, Dixey R, Hill AJ, Barth JH, Cade J. Evaluation of implementation and effect of primary school based intervention to reduce risk factors for obesity. *BMJ* (2001) 323:1027–9. doi:10.1136/bmj.323.7320.1027
69. Hanna P, French SA, Story M, Fulkerson JA. A pricing strategy to promote sales of lower fat foods in high school cafeterias: acceptability and sensitivity analysis. *Am J Health Promot* (2002) 17:1–6. doi:10.4278/0890-1171-17.1.1
70. French SA. Pricing effects on food choices. *J Nutr* (2003) 133:841S–3S. doi:10.1093/jn/133.3.841S
71. Levy DT, Friend KB, Wang YC. A review of the literature on policies directed at the youth consumption of sugar sweetened beverages. *Adv Nutr* (2011) 2(2):182S–200S. doi:10.3945/an.111.000356
72. Godin KM, Chacón V, Barnoya J, Leatherdale ST. The school environment and sugar-sweetened beverage consumption among Guatemalan adolescents. *Public Health Nutr* (2017) 14:1–8. doi:10.1017/S1368980017001926

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Public Health

PERSPECTIVE
published: 18 December 2017
doi: 10.3389/fpubh.2017.00331

# Survival Mediterranean Style: Lifestyle Changes to Improve the Health of the US Fire Service

*Maria Korre[1,2], Mercedes Sotos-Prieto[1,3,4] and Stefanos N. Kales[1,2]**

[1] Environmental & Occupational Medicine & Epidemiology Program, Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, United States, [2] Cambridge Health Alliance, Harvard Medical School, Cambridge, MA, United States, [3] The Diabetes Institute, Ohio University, Athens, OH, United States, [4] Department of Food Sciences and Nutrition, School of Applied Heath Sciences and Wellness, Ohio University, Athens, OH, United States

Cardiovascular disease (CVD) causes almost half of all on-duty deaths in US firefighters and is an important and costly cause of morbidity. In addition, cancer is a growing health concern in this population. Obesity and obesity-associated, cardiometabolic risk clustering are major, modifiable risk factors for fire service CVD and cancer risk. The Mediterranean diet (MedDiet) is proven effective in primary and secondary CVD prevention. It is also associated with a decreased risk of cancer and other chronic diseases. Moreover, it can be adapted into successful workplace interventions. Emerging data from our group regarding the US Fire Service show that greater compliance with the MedDiet is associated with improved CVD risk profiles and less weight gain among career firefighters. Moreover, the fact that career firefighters take a considerable number of meals communally on the job also represents an excellent opportunity for a workplace Mediterranean Diet Nutritional Intervention (MDNI). The devastating effects of obesity, CVD, and cancer on the US fire service are recognized, but currently few effective preventive programs exist. The consistently positive health benefits from following a MedDiet and promising preliminary data in the fire service justify translational research to determine the most effective means of delivering MDNIs to US firefighters. Therefore, a high priority should be assigned to efforts, which can help further disseminate and implement our program of novel behavior change strategies, "Survival Mediterranean Style," throughout the US fire service and eventually to other occupations.

**Keywords: Mediterranean diet, lifestyle, firefighters, workplace health, obesity, cardiovascular health, cancer**

OPEN ACCESS

***Edited by:***
*Alessandra Lafranconi, Università degli studi di Milano Bicocca, Italy*

***Reviewed by:***
*Christopher Alan Birt, University of Liverpool, United Kingdom*
*Katerina Stylianou, University of Michigan, United States*
*Giuseppe Grosso, NNEdPro Global Centre for Nutrition and Health, United Kingdom*

***Correspondence:**
*Stefanos N. Kales*
*skales@hsph.harvard.edu*

***Specialty section:***
*This article was submitted to Public Health Policy, a section of the journal Frontiers in Public Health*

***Received:*** *10 August 2017*
***Accepted:*** *22 November 2017*
***Published:*** *18 December 2017*

***Citation:***
*Korre M, Sotos-Prieto M and Kales SN (2017) Survival Mediterranean Style: Lifestyle Changes to Improve the Health of the US Fire Service. Front. Public Health 5:331. doi: 10.3389/fpubh.2017.00331*

## INTRODUCTION

Today, as a result of the worldwide epidemics of obesity and diabetes, we are witnessing a strong and renewed interest in the traditional Mediterranean diet (MedDiet). A nutritional approach that derives its appeal not only from its many proven health benefits but also from its delicious meals combining diverse flavors, colors, and aromas fresh from the land and sea.

The MedDiet has consistently been associated with decreased all-cause mortality, less chronic disease, and better quality of life (1–6). Robust evidence in the general population consistently demonstrates the benefits of MedDiet on cardiovascular risk factors including obesity, hypertension, diabetes, and metabolic syndrome (4, 7–13). Therefore, it also decreases the risk for cardiovascular disease (CVD) morbidity and mortality (2, 8, 14–18).

Variants of the MedDiet have been consumed in more than 15 countries surrounding the Mediterranean Sea (19). The MedDiet includes high consumption of extra-virgin olive oil, fruits, vegetables, nuts, and legumes, unrefined whole grain and fish; a moderate intake of yogurt and fermented dairy, eggs, and poultry; moderate wine consumption with meals and low intake of processed and red meats and sweets (5, 14).

After a successful proof of concept, MedDiet has been shown to be applicable in non-Mediterranean countries as well, with supportive evidence for carrying on its cardioprotective role (20). From Australia to Japan, Chile and Iran as well as North-European countries, following the key principles of MedDiet has given great opportunities to various food types of local cuisines that can serve as great substitutes of food items that can be more easily found only in the Mediterranean region, thus enhancing its adherence on a global scale (20). Although a challenge, the applicability and transferability of the MedDiet in non-Mediterranean countries is desirable and supported by the current scientific evidence on its health benefits in non-Mediterranean countries. Some approaches such as the alternative MedDiet (16), and the recognition of this dietary pattern in the latest 2015 Dietary Guidelines for Americans are clear examples.

Emerging data from firefighters in the US, a population with significant health concerns, also support beneficial effects and potential for greater adoption of this eating pattern, despite living in a non-Mediterranean country. While less than 2% of firefighters currently follow the MedDiet, over 60% want to learn more about it and over 70% would be interested in an online nutritional platform (21). Controlled trials can quantify these benefits and determine the cost-effectiveness of implementation (22).

This paper will provide the rationale and need for Mediterranean Diet Nutrition Interventions (MDNI) in the US fire service. First, we will summarize data on CVD in firefighters and demonstrate that a major proportion of CVD morbidity and in particular, mortality is attributable to obesity and cardiometabolic risk clustering. We will then discuss nutritional challenges and opportunities in the fire service; the role of healthy diet in CVD prevention; in particular, the proven benefits of MedDiet; as well as the success of workplace interventions to change eating and lifestyle behavior. Moreover, we examine data revealing the role of obesity in increasing the risk of many cancers, while MedDiet reduces the risks of obesity, cancer, and other chronic diseases. Finally, we will use preliminary data from the fire service to support that an MDNI should improve key dietary habits, decrease weight gain, and improve firefighters' CVD risk factor profile.

## CVD IN THE US FIRE SERVICE

Cardiovascular disease is the predominant cause of on-duty death and lifetime mortality in the US fire service. Sudden cardiac death (SCD) causes about 45% of on-duty fatalities. Strokes, aneurysms, and other CVD pathologies result in another 5% of on-duty deaths (23–26). There are an estimated 17–25 non-fatal, line-of-duty CVD events in the US fire service for every fatal on-duty CVD event (25). Thus, CVD is also a major cause of morbidity and disability (25, 27, 28). As in the general population, these CVD events are largely due to coronary heart disease (CHD) (23–25, 27). Finally, CHD accounts for 30% of all deaths and, thus, is the leading cause of lifetime mortality among US firefighters (29). Thus, interventions which prevent CVD are clearly the top priority for US fire service research. In this regard, the effect of MedDiet in CVD prevention is roughly equivalent to statin medications (e.g., Lipitor, Crestor) (30), while having added benefits on weight control, preventing diabetes, and decreasing the risk of cancer (31, 32).

Obesity and cardiometabolic risk clustering are well-established CVD risk factors in the general population, and as well obesity strongly promotes risk factor clustering as mediated by negative effects on blood pressure, metabolism, sleep-disordered breathing, and cardiac enlargement (28). In the fire service, obesity has documented adverse effects on: fitness, metabolic syndrome, left ventricular hypertrophy/cardiomegaly, incident CHD; on-duty CHD events, including SCD; injury risks/workers' compensation costs; job-related disability and CVD retirements (24, 25, 27, 33–36).

The obesity problem in the US fire service has been increasing. Steadily within the worldwide obesity epidemic, about 40% of firefighters are now obese (25). A recent population-based investigation of both career and volunteer firefighters proved that the high obesity prevalence was due to excess adiposity rather than the misclassification of increased muscle mass (37). In fact, obesity was more prevalent when assessed by body fat measures compared to body mass index (BMI).

Even in a study of young fire recruits (mean age 26 years), 44% were overweight and 33% were obese. The obese subjects, compared to normal weight subjects, had an almost sevenfold greater risk of hypertensive blood pressure readings (38). Another recent investigation of young firefighters found 67% to be overweight or obese. Again, high BMI was associated with higher central blood pressure and increased arterial stiffness (39).

While the effects of excess weight on CVD are usually thought of as manifesting in middle-aged and older firefighters, we have recently linked obesity, hypertension, and other modifiable risks to fire service deaths in young firefighters. Among firefighters $\leq$45 years of age, at least two-thirds of on-duty SCD was related to preventable factors such as obesity and CHD (36). Moreover, we found surprising preliminary evidence of excess obesity among on-duty trauma deaths (burns, asphyxiation, and blunt trauma) compared with occupationally active control firefighters (36). These data suggest effective dietary intervention within an overall wellness strategy could reduce both CVD- and non-CVD-related morbidity and mortality.

## EXISTING DIETARY CHALLENGES AND OPPORTUNITIES

The high prevalence of obesity and CVD risk clustering in the fire service is multifactorial. First, shift work has been associated with weight gain, increased blood pressure, and worsening insulin resistance (25, 28). Moreover, shift work and unscheduled emergency calls, lead to irregular meal times, which increase the likelihood of choosing fast foods and other takeout foods. Thus, career firefighters are more likely to consume meals higher in

sugars and saturated fats (40–42). These factors likely contribute to certain traditions around over-eating and less healthy choices common in fire service culture.

According to one of our recent studies, the two dietary factors that differed the most between obese and non-obese firefighters were obese firefighters' higher consumption of sugary drinks and fast-food (41). These findings are consistent with those from the general population. Sweetened beverages are the largest contributors to added-sugar consumption in the US (43–45). In addition, investigations have associated increased fast-food consumption with obesity (46–48) and cardiometabolic risk (49).

Nonetheless, there are also good opportunities for intervention in the fire service and successes have been achieved with workplace approaches. Promoting Healthy Lifestyles: Alternative Models' Effects was a prospective randomized controlled study of firefighter wellness, examining individual (one-on-one motivational counseling), and team health promotion approaches. Both interventions had beneficial effects on LDL cholesterol and exercise habits, compared with the control group (50). Moreover, after 1 year, both intervention groups demonstrated better weight control; more fruit/vegetable consumption and perceived greater well-being compared to controls (51). Even 4 years after the 12-month interventions, physical activity and nutrition remained improved compared with baseline (52).

There is also evidence that less intense wellness strategies have positive effects on fire service health. Poston et al. compared 10 fire departments that had implemented key Wellness Fitness Initiative (WFI) components (53) and compared them to 10 otherwise similar departments that had not implemented WFI approaches. Firefighters in the WFI departments had significantly lower BMI, body fat, waist circumference, and were over 40% less likely to be obese (53).

## MedDiet AND CVD AND CANCER REDUCTION

Numerous studies have demonstrated the effectiveness of MedDiet in reducing all-cause mortality (54–56), CVD morbidity and mortality, and cancer mortality (1–6, 57). These benefits likely derive from effects on intermediate states such as inflammation hypertension, obesity, metabolic syndrome, and diabetes mellitus (4, 7–10). Given these clear benefits, the latest US government nutritional guidelines recognize and recommend the MedDiet as a healthy option for Americans (58). Most nutrition experts recognize that there are many healthy eating patterns found across the globe, including Asian and vegetarian options, but there is a consensus that the "Mediterranean diet reigns supreme" considering all the evidence and pros and cons of each (59).

Consistent evidence of benefits from MedDiet has inspired MDNI. In the classic Lyon Heart study, subjects with a history of myocardial infarction were randomized to an MDNI or control diet (59). The MDNI mimicked a traditional Cretan diet with less red meat, but more fruit, vegetables, fish, and margarine. The randomized controlled trial (RCT) was stopped early because of excessive morbidity/mortality in the control arm, while the MDNI lowered the risk of recurrent heart disease by 50–70% during follow-up (60).

Mediterranean Diet Nutrition Intervention trials for primary prevention have also provided very promising results. Metabolic syndrome, a precursor of heart disease, affects over 25% of career firefighters (61). A 2-year randomized trial of MDNI reversed metabolic syndrome in 2/3 of the intervention group, whereas metabolic syndrome persisted in more than 80% of the controls (62). The most notable MDNI trial to date is PREDIMED in Spain (17). Beginning in 2003, PREDIMED ultimately randomized over 7,000 participants at high CVD risk, but without known CVD, to one of three interventions: an MDNI supplemented with extra-virgin olive oil; an MDNI supplemented with mixed nuts or a low-fat diet. The most recent data from PREDIMED provide the highest quality scientific evidence thus far of MedDiet benefits. After an average of 4.8 years of follow-up, subjects given the MDNI with extra-virgin olive oil had a 40% reduction in the incidence rate of new-onset diabetes (63), and a 30% decrease in major CVD events compared to control subjects prescribed a low-fat diet (14). In addition, PREDIMED has already documented other benefits, including decreased risk of breast cancer (64) and cognitive decline (65).

It is important to note that MedDiet is associated with significantly decreased cancer risks (6, 66, 67). First, although there are diverse workplace exposure and other causes of cancer, obesity is a major and modifiable risk factor for many types of cancer (34). Second, obesity is highly prevalent among US firefighters (25, 37) and third, MedDiet can reduce body weight and help maintain lower body weights. Finally, following a MedDiet produces large and significant decreases in cancer risks (1, 68–70). According to the most recent study, cancer is the second leading cause of lifetime mortality among US firefighters and accounts for over 25% of deaths (29). Therefore, long-term Mediterranean dietary changes in the fire service should positively impact firefighters' cancer burden.

## MedDiet AND WORKPLACE BEHAVIORAL CHANGE

As we recently summarized in published reviews of MedDiet and the workplace, experience with worksite MDNIs is limited, but the evidence is quite positive (66, 67). Shai et al. have completed the only RCT at an Israeli nuclear facility, where over 300 obese participants were randomly assigned to: a low-fat, restricted-calorie diet; a Mediterranean, restricted-calorie diet; or a low-carbohydrate diet without calorie restriction (71). The 2-year intervention included a spousal education program and changes in the workplace cafeteria (72). After 6 years, the total weight loss was greatest and most significant for the Mediterranean group (3.1 kg), whereas the other two groups gained back most of their weight (73). Moreover, the Mediterranean group had the greatest persistent reductions in triglyceride and cholesterol levels from baseline.

In a Chilean factory, a 1-year, uncontrolled MedDiet intervention using education and changing the employer's cafeteria significantly improved MedDiet scores, waist circumference, HDL, blood pressure, and metabolic syndrome prevalence among the participants (2).

Carey et al. performed an uncontrolled pilot study of a 12-week low-glycemic nutritional program including some MedDiet principles in 10 men from one platoon of the Buffalo, NY Fire Department (74). At baseline, 70% had metabolic syndrome and an average of 3.2 metabolic syndrome risk factors. Upon completion of the pilot, the prevalence of metabolic syndrome and risk factors had decreased significantly: 30% and 1.9 metabolic syndrome risk factors, respectively.

## PRELIMINARY DATA

### Modified MedDiet Score and Cardiovascular Risk in Midwestern Firefighters

We previously investigated the dietary habits of 780 Midwestern firefighters using a modified Mediterranean diet score (mMDS) derived from a comprehensive lifestyle questionnaire. Greater adherence to MedDiet as measured by the mMDS was significantly associated with improvements in body fat, metabolic syndrome, LDL- and HDL-cholesterol, weight gain, and aerobic fitness (41). Firefighters with greatest adherence to MedDiet showed a 35% decreased risk of metabolic syndrome and 43% lower risk of weight gain compared to the bottom quartile of mMDS. Associations for improved HDL, total cholesterol/HDL, and body fat remained significant even after adjustments for age, BMI, and physical activity levels (36).

### National Surveys of International Association of Fire Fighters (IAFF) Members

Dietary change is more likely to happen if the change strategy is acceptable to the target population and addresses perceived knowledge gaps. Therefore, in collaboration with the IAFF (21), we have conducted national surveys of firefighters. We found that 71% of IAFF members do not currently follow any particular dietary plan, and less than 2% report that they currently follow the MedDiet. However, over 70% want to learn more about the MedDiet; and they most frequently rated the MedDiet description as their favorite and gave it better rankings ($p < 0.001$) compared to the Paleo, Atkins, and other popular diets. Diverse and colorful flavors; the ability to enjoy lean meats in moderation; healthy fats and proteins from olive oil, nuts, fish, and the temperate wine consumption in moderation make the MedDiet an attractive and enjoyable option. Most important, the MedDiet does not require completely giving up any specific food and is, therefore, accessible and acceptable for adoption and long-term adherence among diverse groups, including the fire service. The weight status and the opinions expressed by career firefighters results strongly support the need for and a positive reception to potential MDNIs.

## DISCUSSION

We know that more than one of every three firefighters in the US is obese and SCD is the number one line of duty killer-far ahead of burns and dangerous gases in fire smoke. We are also aware that fire department environments may promote and reinforce poor eating habits and thus, may inadequately increase CVD and obesity risks. Obviously, given the positive effects of MedDiet on CVD, obesity control, and cancer, it is more important than ever to more widely disseminate and implement MedDiet in the US fire service to improve firefighter health and longevity. We step–step provided the evidence necessary to promote behavioral change strategies in the fire service and modify the existing food culture, with the ultimate purpose to be getting more firefighters and their families to adopt the principles of the MedDiet to decrease their risks of chronic disease.

All our research stated above has provided the evidence needed and put the rationale and the basis; and with an unprecedented success, the US Department of Homeland Security awarded our team in 2015 with a $ 1.5-million, 3-year, competitive research grant entitled "Feeding America's Bravest: MedDiet-Based Interventions to Change Firefighters' Eating Habits and Improve Cardiovascular Risk Profiles" to conduct Mediterranean Diet Nutritional Interventions in selected US firefighters. Namely, our trials consist of two parallel designs. First, regarding the career firefighters, we have developed multi-pronged, MDNI behavior change strategies including: diet/lifestyle education; discounted access to key MedDiet foods; electronic education platforms and reminders. MDNI components have been refined *via* surveys, literature review, and local/national firefighter input including labor/management and fire service focus groups, and as a result of the above refinements, our team has developed original firefighter-specific MedDiet pyramid, food shopping guides and recipes many of which were designed and created based on firehouse favorites. Second, we have developed an online, open trial as a demonstration project to help change volunteer firefighters' health habits and improve cardiovascular risk profiles using a MedDiet intervention strategy. The online tools include firefighter-centered guidelines for eating and exercise, firefighter-favorite recipes, food shopping tips, guides for eating out and on the go, running healthy meetings and a series of short instructional videos, among other resources.

Nutrition and medical experts agree that following a Mediterranean-style diet improves health. However, the health system has had very limited effectiveness in changing Americans' eating and other lifestyle behaviors, while limited evidence suggests that workplace-based nutrition interventions can be beneficial. Building on our prior work with firefighters and the above rationale, our funded projects seek to establish the effectiveness of behavioral change strategies in the fire service to modify the existing food culture. Our goal is to motivate firefighters and their families to adopt key features of the MedDiet at work and home through education, participation, and incentives.

Overall, our team aims to create comprehensive, accessible, and sustainable programs around the time-honored and scientifically proven principles of the Traditional MedDiet that after a successful proof of concept, can be disseminated to nationally to the rest of the US fire service, as well as other workplaces and schools in the future. Already, we are working with two other outstanding employers who are preparing to adopt and incorporate healthy dietary workplace initiatives: overall, our team aims to create a comprehensible, approachable, and sustainable program around the time-honored and scientifically proven principles of the Traditional MedDiet that after a successful proof of concept,

can be disseminated to the rest of the fire service and other workplaces and schools in the future: law enforcement officers at the Broward County Sheriff's Office (Florida) and the automobile manufacturer, SEAT, in Spain (75).

## CONCLUSION

The ultimate purpose of this work is to get more firefighters and their families to adopt the principles of the MedDiet to decrease their risks of chronic disease.

## AUTHOR CONTRIBUTIONS

All authors contributed equally to designing and drafting the manuscript.

## FUNDING

This investigation was supported by the Federal Emergency Management Agency (FEMA) Assistance to Firefighters Grant (AFG) Program's Award EMW-2014-FP-00612 (PI: SK).

## REFERENCES


1. Mitrou PN, Kipnis V, Thiebaut AC, Reedy J, Subar AF, Wirfalt E, et al. Mediterranean dietary pattern and prediction of all-cause mortality in a US population: results from the NIH-AARP Diet and Health Study. *Arch Intern Med* (2007) 167(22):2461–8. doi:10.1001/archinte.167.22.2461
2. Leighton F, Polic G, Strobel P, Perez D, Martinez C, Vasquez L, et al. Health impact of Mediterranean diets in food at work. *Public Health Nutr* (2009) 12(9A):1635–43. doi:10.1017/S1368980009990486
3. Trichopoulou A, Bamia C, Trichopoulos D. Anatomy of health effects of Mediterranean diet: Greek EPIC prospective cohort study. *BMJ* (2009) 338: b2337. doi:10.1136/bmj.b2337
4. Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, Gnardellis C, Lagiou P, Polychronopoulos E, et al. Diet and overall survival in elderly people. *BMJ* (1995) 311(7018):1457–60. doi:10.1136/bmj.311.7018.1457
5. Trichopoulou A, Orfanos P, Norat T, Bueno-de-Mesquita B, Ocke MC, Peeters PH, et al. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. *BMJ* (2005) 330(7498):991. doi:10.1136/bmj.330.7503.1329-b
6. Knoops KT, de Groot LC, Kromhout D, Perrin AE, Moreiras-Varela O, Menotti A, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. *JAMA* (2004) 292(12):1433–9. doi:10.1001/jama.292.12.1433
7. Babio N, Bullo M, Salas-Salvado J. Mediterranean diet and metabolic syndrome: the evidence. *Public Health Nutr* (2009) 12(9A):1607–17. doi:10.1017/S1368980009990449
8. Vincent-Baudry S, Defoort C, Gerber M, Bernard MC, Verger P, Helal O, et al. The Medi-RIVAGE study: reduction of cardiovascular disease risk factors after a 3-mo intervention with a Mediterranean-type diet or a low-fat diet. *Am J Clin Nutr* (2005) 82(5):964–71.
9. Panagiotakos DB, Pitsavos CH, Chrysohoou C, Skoumas J, Papadimitriou L, Stefanadis C, et al. Status and management of hypertension in Greece: role of the adoption of a Mediterranean diet: the Attica study. *J Hypertens* (2003) 21(8):1483–9. doi:10.1097/00004872-200308000-00011
10. Kafatos A, Diacatou A, Voukiklaris G, Nikolakakis N, Vlachonikolis J, Kounali D, et al. Heart disease risk-factor status and dietary changes in the Cretan population over the past 30 y: the Seven Countries Study. *Am J Clin Nutr* (1997) 65(6):1882–6.
11. Garcia-Fernandez E, Rico-Cabanas L, Rosgaard N, Estruch R, Bach-Faig A. Mediterranean diet and cardiodiabesity: a review. *Nutrients* (2014) 6(9): 3474–500. doi:10.3390/nu6093474
12. Babio N, Toledo E, Estruch R, Ros E, Martinez-Gonzalez MA, Castaner O, et al. Mediterranean diets and metabolic syndrome status in the PREDIMED randomized trial. *CMAJ* (2014) 186(17):E649–57. doi:10.1503/cmaj.140764
13. Godos J, Zappala G, Bernardini S, Giambini I, Bes-Rastrollo M, Martinez-Gonzalez M. Adherence to the Mediterranean diet is inversely associated with metabolic syndrome occurrence: a meta-analysis of observational studies. *Int J Food Sci Nutr* (2017) 68(2):138–48. doi:10.1080/09637486.2016.1221900
14. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* (2013) 368(14):1279–90. doi:10.1056/NEJMoa1200303
15. Martinez-Gonzalez MA, Garcia-Lopez M, Bes-Rastrollo M, Toledo E, Martinez-Lapiscina EH, Delgado-Rodriguez M, et al. Mediterranean diet and the incidence of cardiovascular disease: a Spanish cohort. *Nutr Metab Cardiovasc Dis* (2011) 21(4):237–44. doi:10.1016/j.numecd.2009.10.005
16. Fung TT, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, Hu FB. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. *Circulation* (2009) 119(8):1093–100. doi:10.1161/CIRCULATIONAHA.108.816736
17. Estruch R, Martinez-Gonzalez MA, Corella D, Salas-Salvado J, Ruiz-Gutierrez V, Covas MI, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Ann Intern Med* (2006) 145(1):1–11. doi:10.7326/0003-4819-145-1-200607040-00004
18. Grosso G, Marventano S, Yang J, Micek A, Pajak A, Scalfi L, et al. A comprehensive meta-analysis on evidence of Mediterranean diet and cardiovascular disease: are individual components equal? *Crit Rev Food Sci Nutr* (2017) 57(15):3218–32. doi:10.1080/10408398.2015.1107021
19. Keys A, Menotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R, et al. The diet and 15-year death rate in the seven countries study. *Am J Epidemiol* (1986) 124(6):903–15. doi:10.1093/oxfordjournals.aje.a114480
20. Mocciaro G, Ziauddeen N, Godos J, Marranzano M, Chan M-Y, Ray S. Does a Mediterranean-type dietary pattern exert a cardio-protective effect outside the Mediterranean region? A review of current evidence. *Int J Food Sci Nutr* (2017) 24:1–12. doi:10.1080/09637486.2017.1391752
21. Yang J, Farioli A, Korre M, Kales SN. Dietary preferences and nutritional information needs among career firefighters in the United States. *Glob Adv Health Med* (2015) 4(4):16–23. doi:10.7453/gahmj.2015.050
22. Sotos-Prieto M, Cash SB, Christophi C, Folta S, Moffatt S, Muegge C, et al. Rationale and design of feeding America's bravest: Mediterranean diet-based intervention to change firefighters' eating habits and improve cardiovascular risk profiles. *Contemp Clin Trials* (2017) 61:101–7. doi:10.1016/j.cct.2017.07.010
23. Kales SN, Soteriades ES, Christophi CA, Christiani DC. Emergency duties and deaths from heart disease among firefighters in the United States. *N Engl J Med* (2007) 356(12):1207–15. doi:10.1056/NEJMoa060357
24. Smith DL, Barr DA, Kales SN. Extreme sacrifice: sudden cardiac death in the US fire service. *Extrem Physiol Med* (2013) 2(1):6. doi:10.1186/2046-7648-2-6
25. Soteriades ES, Smith DL, Tsismenakis AJ, Baur DM, Kales SN. Cardiovascular disease in US firefighters: a systematic review. *Cardiol Rev* (2011) 19(4): 202–15. doi:10.1097/CRD.0b013e318215c105
26. Fahy R. *U.S. Firefighter Fatalities Due to Sudden Cardiac Death, 1995-2004*. Quincy, MA: USA National Fire Protection Association (2005).
27. Holder JD, Stallings LA, Peeples L, Burress JW, Kales SN. Firefighter heart presumption retirements in Massachusetts 1997-2004. *J Occup Environ Med* (2006) 48(10):1047–53. doi:10.1097/01.jom.0000235909.31632.46
28. Kales SN, Tsismenakis AJ, Zhang C, Soteriades ES. Blood pressure in firefighters, police officers, and other emergency responders. *Am J Hypertens* (2009) 22(1):11–20. doi:10.1038/ajh.2008.296
29. Daniels RD, Kubale TL, Yiin JH, Dahm MM, Hales TR, Baris D, et al. Mortality and cancer incidence in a pooled cohort of US firefighters from San Francisco, Chicago and Philadelphia (1950-2009). *Occup Environ Med* (2014) 71(6):388–97. doi:10.1136/oemed-2013-101662
30. Estruch R. Cardiovascular mortality: how can it be prevented? *Nefrologia* (2014) 34(5):561–9. doi:10.3265/Nefrologia.pre2014.Apr.12481
31. Kales SN, Smith DL. Firefighting and the heart: implications for prevention. *Circulation* (2017) 135(14):1296–9. doi:10.1161/CIRCULATIONAHA.117.027018
32. Willett WC. The Mediterranean diet: science and practice. *Public Health Nutr* (2006) 9(1A):105–10. doi:10.1079/PHN2005931
33. Willett WC. Food for thought. *Harv Public Health* (2013) 3:34–5.

34. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer – viewpoint of the IARC Working Group. *N Engl J Med* (2016) 375(8):794–8. doi:10.1056/NEJMsr1606602
35. Korre M, Porto LG, Farioli A, Yang J, Christiani DC, Christophi CA, et al. Effect of body mass index on left ventricular mass in career male firefighters. *Am J Cardiol* (2016) 118(11):1769–73. doi:10.1016/j.amjcard.2016.08.058
36. Yang J, Teehan D, Farioli A, Baur DM, Smith D, Kales SN. Sudden cardiac death among firefighters </=45 years of age in the United States. *Am J Cardiol* (2013) 112(12):1962–7. doi:10.1016/j.amjcard.2013.08.029
37. Poston WS, Haddock CK, Jahnke SA, Jitnarin N, Tuley BC, Kales SN. The prevalence of overweight, obesity, and substandard fitness in a population-based firefighter cohort. *J Occup Environ Med* (2011) 53(3):266–73. doi:10.1097/JOM.0b013e31820af362
38. Tsismenakis AJ, Christophi CA, Burress JW, Kinney AM, Kim M, Kales SN. The obesity epidemic and future emergency responders. *Obesity (Silver Spring)* (2009) 17(8):1648–50. doi:10.1038/oby.2009.63
39. Fahs CA, Smith DL, Horn GP, Agiovlasitis S, Rossow LM, Echols G, et al. Impact of excess body weight on arterial structure, function, and blood pressure in firefighters. *Am J Cardiol* (2009) 104(10):1441–5. doi:10.1016/j.amjcard.2009.07.009
40. Lowden A, Moreno C, Holmback U, Lennernas M, Tucker P. Eating and shift work – effects on habits, metabolism and performance. *Scand J Work Environ Health* (2010) 36(2):150–62. doi:10.5271/sjweh.2898
41. Yang J, Farioli A, Korre M, Kales SN. Modified Mediterranean diet score and cardiovascular risk in a North American working population. *PLoS One* (2014) 9(2):e87539. doi:10.1371/journal.pone.0087539
42. Esquirol Y, Bongard V, Mabile L, Jonnier B, Soulat JM, Perret B. Shift work and metabolic syndrome: respective impacts of job strain, physical activity, and dietary rhythms. *Chronobiol Int* (2009) 26(3):544–59. doi:10.1080/07420520902821176
43. Malik VS, Popkin BM, Bray GA, Despres JP, Hu FB. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation* (2010) 121(11):1356–64. doi:10.1161/CIRCULATIONAHA.109.876185
44. Guthrie JF, Morton JF. Food sources of added sweeteners in the diets of Americans. *J Am Diet Assoc* (2000) 100(1):43–51, quiz 49–50. doi:10.1016/S0002-8223(00)00018-3
45. Nielsen SJ, Popkin BM. Changes in beverage intake between 1977 and 2001. *Am J Prev Med* (2004) 27(3):205–10. doi:10.1016/j.amepre.2004.05.005
46. Pereira MA, Kartashov AI, Ebbeling CB, Van Horn L, Slattery ML, Jacobs DR Jr, et al. Fast-food habits, weight gain, and insulin resistance (the CARDIA study): 15-year prospective analysis. *Lancet* (2005) 365(9453):36–42. doi:10.1016/S0140-6736(04)17663-0
47. Duffey KJ, Steffen LM, Van Horn L, Jacobs DR Jr, Popkin BM. Dietary patterns matter: diet beverages and cardiometabolic risks in the longitudinal Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr* (2012) 95(4):909–15. doi:10.3945/ajcn.111.026682
48. Nettleton JA, Polak JF, Tracy R, Burke GL, Jacobs DR Jr. Dietary patterns and incident cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis. *Am J Clin Nutr* (2009) 90(3):647–54. doi:10.3945/ajcn.2009.27597
49. Odegaard AO, Koh WP, Yuan JM, Gross MD, Pereira MA. Western-style fast food intake and cardiometabolic risk in an Eastern country. *Circulation* (2012) 126(2):182–8. doi:10.1161/CIRCULATIONAHA.111.084004
50. Elliot DL, Goldberg L, Duncan TE, Kuehl KS, Moe EL, Breger RK, et al. The PHLAME firefighters' study: feasibility and findings. *Am J Health Behav* (2004) 28(1):13–23. doi:10.5993/AJHB.28.1.2
51. Elliot DL, Goldberg L, Kuehl KS, Moe EL, Breger RK, Pickering MA. The PHLAME (Promoting Healthy Lifestyles: Alternative Models' Effects) firefighter study: outcomes of two models of behavior change. *J Occup Environ Med* (2007) 49(2):204–13. doi:10.1097/JOM.0b013e3180329a8d
52. MacKinnon DP, Elliot DL, Thoemmes F, Kuehl KS, Moe EL, Goldberg L, et al. Long-term effects of a worksite health promotion program for firefighters. *Am J Health Behav* (2010) 34(6):695–706. doi:10.5993/AJHB.34.6.6
53. Poston WS, Haddock CK, Jahnke SA, Jitnarin N, Day RS. An examination of the benefits of health promotion programs for the national fire service. *BMC Public Health* (2013) 13:805. doi:10.1186/1471-2458-13-805
54. Sotos-Prieto M, Bhupathiraju SN, Mattei J, Fung TT, Li Y, Pan A, et al. Association of changes in diet quality with total and cause-specific mortality. *N Engl J Med* (2017) 377(2):143–53. doi:10.1056/NEJMoa1613502
55. Buil-Cosiales P, Zazpe I, Toledo E, Corella D, Salas-Salvado J, Diez-Espino J, et al. Fiber intake and all-cause mortality in the Prevencion con Dieta Mediterranea (PREDIMED) study. *Am J Clin Nutr* (2014) 100(6):1498–507. doi:10.3945/ajcn.114.093757
56. Guasch-Ferre M, Babio N, Martinez-Gonzalez MA, Corella D, Ros E, Martin-Pelaez S, et al. Dietary fat intake and risk of cardiovascular disease and all-cause mortality in a population at high risk of cardiovascular disease. *Am J Clin Nutr* (2015) 102(6):1563–73. doi:10.3945/ajcn.115.116046
57. Sotos-Prieto M, Bhupathiraju SN, Mattei J, Fung TT, Li Y, Pan A, et al. Changes in diet quality scores and risk of cardiovascular disease among US men and women. *Circulation* (2015) 132(23):2212–9. doi:10.1161/CIRCULATIONAHA.115.017158
58. Office of Disease Prevention and Health Promotion. *Scientific Report of the 2015 Dietary Guidelines Advisory Committee* (2015). Available from: https://health.gov/dietaryguidelines/2015-scientific-report/
59. Mineo L. *To Age Better, Eat Better*. Harvard Gazette (2017). Available from: https://news.harvard.edu/gazette/story/2017/05/much-of-life-is-beyond-our-control-but-dining-smartly-can-help-us-live-healthier-longer/
60. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* (1999) 99(6):779–85. doi:10.1161/01.CIR.99.6.779
61. Baur DM, Christophi CA, Kales SN. Metabolic syndrome is inversely related to cardiorespiratory fitness in male career firefighters. *J Strength Cond Res* (2012) 26(9):2331–7. doi:10.1519/JSC.0b013e31823e9b19
62. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA* (2004) 292(12):1440–6. doi:10.1001/jama.292.12.1440
63. Salas-Salvado J, Bullo M, Estruch R, Ros E, Covas MI, Ibarrola-Jurado N, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. *Ann Intern Med* (2014) 160(1):1–10. doi:10.7326/M13-1725
64. Toledo E, Salas-Salvado J, Donat-Vargas C, Buil-Cosiales P, Estruch R, Ros E, et al. Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED trial: a randomized clinical trial. *JAMA Intern Med* (2015) 175(11):1752–60. doi:10.1001/jamainternmed.2015.4838
65. Martinez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvado J, San Julian B, et al. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. *J Neurol Neurosurg Psychiatry* (2013) 84(12):1318–25. doi:10.1136/jnnp-2012-304792
66. Korre M, Kalogerakou T, Sotos-Prieto M, Kales SN. What is the Mediterranean diet and how can it be used to promote workplace health? *J Occup Environ Med* (2016) 58(3):e111–3. doi:10.1097/JOM.0000000000000681
67. Korre M, Tsoukas MA, Frantzeskou E, Yang J, Kales SN. Mediterranean diet and workplace health promotion. *Curr Cardiovasc Risk Rep* (2014) 8(12):416. doi:10.1007/s12170-014-0416-3
68. Schwingshackl L, Hoffmann G. Adherence to Mediterranean diet and risk of cancer: a systematic review and meta-analysis of observational studies. *Int J Cancer* (2014) 135(8):1884–97. doi:10.1002/ijc.28824
69. Reedy J, Krebs-Smith SM, Miller PE, Liese AD, Kahle LL, Park Y, et al. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. *J Nutr* (2014) 144(6):881–9. doi:10.3945/jn.113.189407
70. Grosso G, Buscemi S, Galvano F, Mistretta A, Marventano S, La Vela V, et al. Mediterranean diet and cancer: epidemiological evidence and mechanism of selected aspects. *BMC Surg* (2013) 13(Suppl 2):S14. doi:10.1186/1471-2482-13-S2-S14
71. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* (2008) 359(3):229–41. doi:10.1056/NEJMoa0708681
72. Golan R, Schwarzfuchs D, Stampfer MJ, Shai I; DIRECT Group. Halo effect of a weight-loss trial on spouses: the DIRECT-spouse study. *Public Health Nutr* (2010) 13(4):544–9. doi:10.1017/S1368980009991273
73. Schwarzfuchs D, Golan R, Shai I. Four-year follow-up after two-year dietary interventions. *N Engl J Med* (2012) 367(14):1373–4. doi:10.1056/NEJMc1204792

74. Carey MG, Al-Zaiti SS, Liao LM, Martin HN, Butler RA. A low-glycemic nutritional fitness program to reverse metabolic syndrome in professional firefighters: results of a pilot study. *J Cardiovasc Nurs* (2011) 26(4):298–304. doi:10.1097/JCN.0b013e31820344d7
75. thebuzzbusiness. *Mediterranean Cuisine Comes to the Car Plant*. (2017). Available from: http://www.thebuzzbusiness.com/mediterranean-cuisine-comes-to-the-car-plant/

**Conflict of Interest Statement:** SK reports grants from US Dept. of Homeland Security, non-financial support from Barilla America, non-financial support from California Almond Board, non-financial support from Arianna Trading Company, non-financial support from Innoliva/Molina de Zafra, during the conduct of the study; personal fees from Medicolegal Consulting, personal fees from Mediterranean Diet Roundtable, outside the submitted work (22). MK and MS-P declare no competing interests.

frontiers in Nutrition

ORIGINAL RESEARCH
published: 12 July 2018
doi: 10.3389/fnut.2018.00054

# The Cambridge Intensive Weight Management Programme Appears to Promote Weight Loss and Reduce the Need for Bariatric Surgery in Obese Adults

*Rajna Golubic[1,2*], Celia Laur[2,3], Megan Kelsey[2], Alana Livesy[1], Joanna Hoensch[1], Adrian Park[1†] and Sumantra Ray[1,2†]*

[1] Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom, [2] NNEdPro Global Centre for Nutrition and Health, St John's Innovation Centre, Cambridge, United Kingdom, [3] Faculty of Applied Health Sciences, University of Waterloo, Waterloo, ON, Canada

OPEN ACCESS

**Edited by:**
Lidia Santarpia,
Università degli Studi di Napoli Federico II, Italy

**Reviewed by:**
Miguel Luiz Batista Junior,
University of Mogi das Cruzes, Brazil
Sharon Ross,
National Cancer Institute (NCI), United States

***Correspondence:**
Rajna Golubic
r.golubic@gatesscholar.org

[†]Joint senior authors.

**Specialty section:**
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

**Received:** 17 December 2017
**Accepted:** 07 June 2018
**Published:** 12 July 2018

**Citation:**
Golubic R, Laur C, Kelsey M, Livesy A, Hoensch J, Park A and Ray S (2018) The Cambridge Intensive Weight Management Programme Appears to Promote Weight Loss and Reduce the Need for Bariatric Surgery in Obese Adults. Front. Nutr. 5:54. doi: 10.3389/fnut.2018.00054

**Objectives:** To investigate the impact of the Cambridge Intensive Weight Management Programme (IWMP) on weight change, eligibility for bariatric surgery, HbA1c, and blood pressure.

**Design:** Prospective non-randomized intervention.

**Setting:** The IWMP is a multi-disciplinary weight loss intervention for severely obese patients to avoid or optimize their physiological state thus enabling bariatric surgery. It uses dietary interventions, pharmacotherapy, and physical activity along with behavior change counseling.

**Participants:** Severely obese patients (Body Mass Index, BMI$\geq$40 kg/m$^2$).

**Interventions:** IWMP is a prospective intervention conducted in a National Health Service Tier 3 obesity service. It includes 3 phases of 8 weeks each: weight loss, weight stabilization, and weight maintenance. In each phase, patients adhered to a prescribed dietary regime and attended regular clinic visits. Data included in this analysis are from those who enrolled in IWMP between 2009 and 2013.

**Primary and secondary measures:** The primary outcome was weight change between baseline and completion of the programme. Secondary outcomes included changes in blood pressure, HbA1c and eligibility for bariatric surgery pre-assessment. Changes in outcomes were compared by age, sex, smoking status, and employment.

**Results:** Of $n = 222$ eligible patients, complete data were available for $n = 141$ patients (63.5%). At baseline, the mean (SD) BMI was 49.7 (9.2) kg/m$^2$ for women, and 47.9 (7.2) kg/m$^2$ for men. Mean (SD) weight change for women was −18.64 (8.36) kg and −22.46 (10.98) kg for men. $N = 97$ (69%) of patients achieved $\geq$10% weight loss. Individuals aged $\leq$50 years lost significantly more weight than those aged >50 years [mean (SD) weight loss: 22.18 (10.9) kg vs. 18.32 (7.92) kg, $p = 0.020$]. Changes in weight were non-significant by smoking status or employment. Median (IQR) change in systolic and

diastolic blood pressure was −6 (−14.6) mmHg and 0 (−8.6) mmHg (non-significant), respectively. There was ∼50% reduction in the need for bariatric surgery.

**Conclusions:** For the majority of the patients, IWMP is promoting weight loss and allowing for avoidance of, or optimization before, bariatric surgery.

**Keywords: obesity, diabetes mellitus, hypertension, policy making, bariatric surgery, behavior change, dietary intervention, physical activity adherence**

## INTRODUCTION

Obesity and related disorders, such as type 2 diabetes, are reaching epidemic prevalence worldwide (1). In England, the prevalence of obesity increased from 15% in 1993 to 26% in 2014 (2). For severe obesity (defined as body mass index (BMI) $\geq$40 kg/m$^2$ according to the World Health Organization), the prevalence has more than tripled since 1993, with 2% of men and 4% of women being severely obese in 2014 (2). Findings of the Prospective Studies Collaboration suggest that every 5 kg/m$^2$ increase in BMI is associated with a 30% higher overall mortality, 40% higher for vascular mortality and 60–120% higher for diabetic, renal and hepatic mortality (3). Evidence also suggests that those who are overweight or obese are at increased risk of developing type 2 diabetes, cardiovascular disease, musculoskeletal disorders and certain cancers (4). Furthermore, people who are obese are seven times more likely to develop diabetes than those within the normal BMI range (5).

Recent literature has demonstrated effectiveness of bariatric (weight loss) surgery for the treatment of obesity. According to a Cochrane review of 22 randomized controlled trials (RCTs) of surgery for weight loss in adults, the direction of effect across studies suggests that those who had surgery had greater weight loss than those who underwent non-surgical management of obesity, one to two years later (6). Improved health-related quality of life and improved diabetes were also reported (6). Picot *et al.* in 2016 suggested that bariatric surgery appears to be a clinically and cost-effective intervention for moderately to severely obese people (4).

Despite the clear NICE guidance (BMI $\geq$40 kg/m$^2$, or between 35 and 40 kg/m$^2$ and other significant co-morbidities such as diabetes, hypertension or severe obstructive sleep apnoea that could be improved if they lost weight) (7), the effectiveness of bariatric surgery, and the rising prevalence of obesity, the availability of bariatric surgery in the UK remains poor. Welbourn *et al.* indicated that in the UK, <1% of individuals who could benefit from bariatric surgery get the treatment (8). One of the potential explanations for this observation is that general practitioners are not able to refer patients directly to surgical services, but instead, there is a tiered system (Tier 1 covers universal services such as health promotion or primary care; Tier 2 covers lifestyle interventions; Tier 3 covers specialist weight management services; and Tier 4 covers bariatric surgery). In the UK, there were 6,032 Finished Consultant Episodes in National Health Services (NHS) hospitals in 2014/15 with a primary diagnosis of obesity and a main or secondary procedure of bariatric surgery (2). Of bariatric surgery patients, 60% were between the ages of 35–54, and 76% of patients were female (2).

In those who are severely obese, intense action may be taken, with support of healthcare professionals, to decrease weight as a way to avoid bariatric surgery or prepare individuals so they are more suitable for surgery (9). The Cambridge Intensive Weight Management Programme (IWMP) is a multi-disciplinary weight loss intervention designed for severely obese patients to lose weight with the support of a multi-disciplinarily healthcare team within a Tier 3 Obesity service. To support this weight loss, the IWMP uses a structured and well-supervised combination of dietary interventions (low calorie diet), pharmacotherapy, and physical activity (written and verbal advice) all underpinned by continual counseling for behavioral change (targeting diet and activity) during 24-week follow-up divided in 3 8-week phases with a different diet composition in each phase.

The aim of the IWMP is to promote weight loss or weight loss maintenance, and behavior changes for people who are severely obese. The ultimate goal for those in IWMP is to avoid bariatric surgery, or to be in a more optimal physiological state prior to bariatric surgery. This paper aims to explain the IWMP and its impact on weight change in severely obese individuals. Secondary measures include: change in eligibility for bariatric surgery, diabetes risk (HbA1c), and blood pressure measured across the strata of age, sex, and employment.

## METHODS

### Study Population

The IWMP is a prospective multi-component intervention conducted by the Tier 3 Obesity Services, at Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, in Cambridge, UK. Although this service is ongoing, data for this intervention was collected from 2009 to 2013.

Patients were recruited from the Addenbrooke's hospital obesity hospital service, which provides healthcare to the patients from East Anglia region. Individuals who were eligible for the IWMP were being treated in the obesity clinic and then agreed to complete the intensive programme with fortnightly clinic visits. The eligibility typically meant that patients were severely obese (BMI $\geq$40 kg/m$^2$) but wanted to avoid bariatric surgery or had been recommended for patient optimization prior to bariatric surgery. Any contraindication to a low energy diet was used as exclusion criteria, including: pregnancy, significant renal or hepatic disease, unstable coronary heart disease, uncontrolled

diabetes, active eating disorder, unstable psychological status, or inability to attend clinic visits.

Prior to entering the study, patients underwent a rigorous pre-programme screening that consisted of comprehensive medical and psychological assessments. A detailed medical assessment designed to review any medical or surgical contraindications was required to select eligible patients as well as identify potential obesity-related co-morbidities to be optimized (10). The Epworth Sleepiness Scale was used to assess for the symptoms of obstructive sleep apnoea (11). Psychological assessments were taken prior to the intervention, and throughout the programme, however results will not be presented here. Since this work is based on hospital service data, a specific ethics committee approval was not required.

## Intervention

The IWMP was delivered by a multi-disciplinary team, which included consultant physicians, a clinical (obesity) psychologist, clinical nurse specialists, advanced specialist dietitians, and specialist dietitians. The IWMP consisted of a 24-week weight loss programme divided into three 8-week phases (**Figure 1**). In each phase, patients were required to adhere to a prescribed dietary regimen, record food intake and physical activity, and attend regular clinic visits. Additional medical and psychological management of related comorbidities using a multidisciplinary team approach ensure clinical safety for patients enrolled on the programme.

### Phase 1 (Weight Loss)

Patients consume an all-liquid diet of 4–5 pints (1,136–1,420 kcal) of semi-skimmed milk per day or 800–1,000 mL of an alternate supplement (1,280–1,600 kcal) of Nutricia Fortisip Extra® if volume is not tolerated. The Nutricia Fortisip Extra® is a dietary supplement used in individuals with malnutrition. The dietary composition of 100 mL of semi- skimmed milk included proteins (3.6 g), carbohydrates (4.8 g, of which sugars 4.8 g), and fat (1.8 g) while 100 mL of Nutricia Fortisip Extra® included proteins (6 g), carbohydrates (18.4 g, of which sugars 6.7 g), and fat (5.8 g). The volume prescribed was dependent on protein requirement (12), ensuring a minimum of 50 g a day to meet with Low Calorie Diet guidelines (13). Patients also took a complete multivitamin and mineral supplement as well as fiber and sodium supplements (in a form of sodium chloride) as the liquid diet is typically low in sodium chloride. Medications for diabetes that may cause hypoglycaemia and antihypertensive medications were reduced in order to minimize risks of hypoglycaemia and symptomatic postural hypotension which might otherwise occur with the lifestyle intervention. There were solid and lactose free choices for those who were unable to tolerate the milk or supplements of the programme.

### Phase 2 (Weight Stabilization)

Patients transitioned to a diet of 50% milk and 50% solid food. Weight loss medication was added (Orlistat and Sibutramin).

### Phase 3 (Weight Maintenance)

Patients returned to a 100% solid diet and individualized energy-balanced nutritionally complete diet. Patients received guidance on weight maintenance including relapse management and a focus on an overall healthy diet.

### Follow-Up

Patients were followed up for 3 months after completion of the IWMP before care was transferred back to the general practitioners.

## Outcome Measures

To monitor patient's progress, the following outcomes were measured at the fortnightly clinic visits: weight (kg), height (m), and blood pressure (mmHg). Weight was measured using standardized Seca® (Hamburg, Germany) weight scales. Height was measured using a Seca® (Hamburg, Germany) stadiometer. BMI was calculated as weight divided by high squared and expressed as $kg/m^2$. HbA1c, an indicator of diabetic control, was assessed at the beginning and at the end of the intervention using a standard microprocessor controlled HPLC system dedicated to A1C analysis (TOSOH A1c Analyser). Physical activity was assessed using the Baecke's Questionnaire (14) in a small subset of patients at baseline (results not shown due to small sample size of the participants responding to the questionnaire which is a voluntary part of the multifarious monitoring activities which patients need to conduct in this service). Smoking status was self-reported as a dichotomous variable (smoker/non-smoker). Employment status was self-reported (employed/unemployed/retired) with employed patients also providing details about their occupation (no standard occupation coding was used). The employed patients were further classified according to occupational physical activity (sedentary/non-sedentary job). This classification was performed in an arbitrary fashion based on the common qualitative descriptions of the jobs reported.

## Statistical Analysis

As this is a service evaluation of exploratory nature rather than a primary research study, power calculations were not performed nor were strict hypotheses formulated prior to the onset of the IWMP. IWMP is a complex clinical service intervention with tailoring to the needs of individual patients, rather than a controlled study intervention.

Descriptive statistics for continuous variables including weight, height, BMI and HbA1C, are shown as mean (SD) when distribution was normal or median (IQR) in the case of substantial departure from normality, and *N* (%) for categorical variables including smoking, employment, and occupational physical activity. An *a priori* decision was made to present baseline characteristics, and rate in the weight or BMI change, by sex for comparability with the studies that include women or men only. To test the differences in weight change and BMI change across 2 or $\geq$3 categories of socio-demographic variables, *t*-test and ANOVA were performed, respectively. The Mann-Whitney *U*-test and the Kruskall-Wallis test were conducted to assess the difference in non-normally distributed variables according to 2

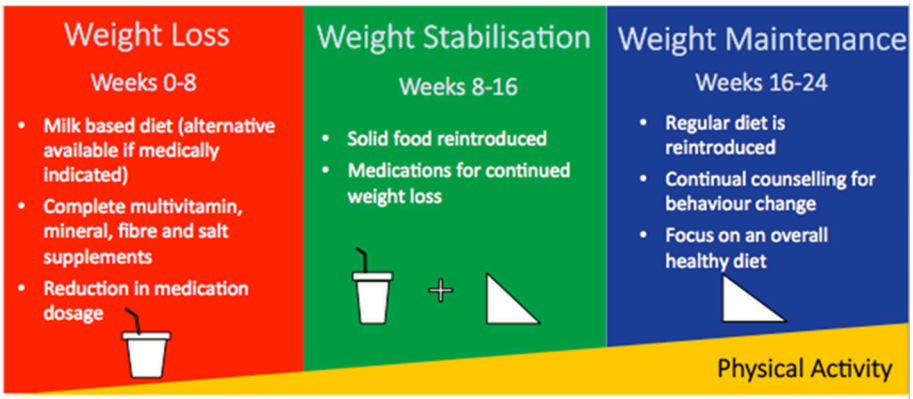



**FIGURE 1 |** Overview of the 3 phases within the 24-week intensive weight management programme.

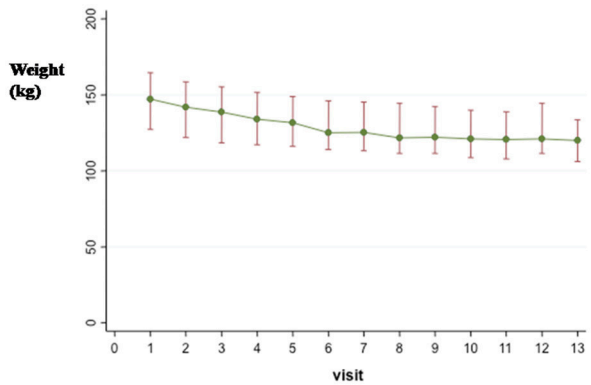



**FIGURE 2 |** Median (IQR) body weight (kg) by visit and at the 3-month follow-up (visit 13).

**TABLE 1 |** Baseline characteristics by sex.

| | Men ($N = 74$) Mean (*SD*) | Women ($N = 67$) Mean (*SD*) |
|---|---|---|
| Age (y) | 47.0 (10.7) | 50.5 (12.1) |
| Weight (kg) | 151.7 (26.9) | 132.8 (29.2) |
| BMI (kg/m$^2$) | 47.9 (7.2) | 49.7 (9.2) |
| Systolic blood pressure (mmHg) | 129.5 (16.9) | 122.9 (16.9) |
| Diastolic blood pressure (mmHg) | 72.5 (12.1) | 71.6 (12.1) |
| HbA1c (%) | 8.63 (1.75) | 7.7 (1.6) |
| Type 2 diabetes diagnosis, *N* (%) | 44 (66%) | 54 (73%) |
| **EMPLOYMENT STATUS** | | |
| Employed, *N* (%) | 31 (63%) | 26 (50%) |
| Unemployed, *N* (%) | 12 (25%) | 22 (42%) |
| Retired, *N* (%) | 6 (12%) | 4 (8%) |
| **SMOKING STATUS** | | |
| Non-smoker, *N* (%) | 40 (83%) | 42 (81%) |
| Smoker, *N* (%) | 8 (17%) | 10 (19%) |

*Data on employment and smoking status were available for 101 and 100 patients, respectively.*

or ≥3 categories of socio-demographic variables, respectively. The rate of weight or BMI change between the 3 phases of the programme was assessed using Kruskall-Wallis test.

The above-mentioned socio-demographic variables were considered to be potential predictors of the outcomes of interest. Each predictor was entered in a univariable linear regression model with weight change and BMI change being continuous outcomes in separate models. A $p$-value $< 0.10$ was considered statistically significant in these univariable models and $p < 0.05$ in all other analyses. Only age-category and sex reached statistical significance and were used in the further multivariable model.

# RESULTS

## Participant Characteristics

Baseline characteristics are shown in **Table 1**. Of $n = 222$ eligible patients, complete data were available for $n = 141$ patients (63.5%), with 48% women (**Table 1**). The average age was 47 years and 50.5 years of age for women and men, respectively. All participants qualified as severely obese with the mean (SD) BMI at 49.7 (9.2) and 47.9 (7.2) kg/m$^2$ for women and men, respectively. Sixty-six percent of men and 73% of women had a confirmed diagnosis of type 2 diabetes. Follow-up data was collected, however responses were only received from $N = 45$ at 3 months and $n = 0$ at 6 months. The prevalence of unemployment was high, with 25% ($N = 12$) in men and 42% ($N = 22$) in women. $N = 8$ (17%) men and $N = 10$ (19%) women reported being current smokers.

## Primary Outcome—Weight Change

There was an average (SD) weight loss of 20.5 (9.8) kg following completion of the intervention. Sixty-nine percent ($N = 97$) had lost 10% or more of their body weight.

Comparisons between weight loss, percentage weight loss, and BMI change are presented in **Table 2**, stratified by sex, smoking status and employment status. A statistically significant difference was found in mean (SD) weight loss between men and women with men losing more weight than women [women: 18.64

(8.36) kg; men: 22.46 (10.98) kg, $p = 0.021$]. This did not remain significant for BMI change and percent weight loss. Significance was also found for age group, with results suggesting that patients who are 50 years old or less have greater mean weight loss [≤50 years, 22.18 (10.9) kg; >50 years, 18.32 (7.92) kg, $p = 0.020$] and mean BMI change [≤50 years, −7.58 (3.45) kg/m$^2$; >50 years, −6.26 (2.78) kg/m$^2$, $p = 0.016$] than their older counterparts. There were no significant differences in weight loss, percentage weight loss, or BMI change according to smoking or employment status.

The rate of weight change is presented in **Table 3**, including the three phases of IWMP. There was a significant difference in the rate of weight change between the phases ($p < 0.001$). The highest rate of weight change was observed in the first phase of the intervention with median (IQR) −11.2 (−14.7, −8.2) kg. The magnitude of the change decreased to −4.8 (−7.1, 2.4) kg and −1.2 (−3.2, 0.2) kg in the second and third phase, respectively.

**Figure 2** details the median (IQR) weight for every visit and 3-month follow-up (visit 13 in the figure). The median (IQR) body weight dropped from 147.2 (127.4, 164.6) kg at baseline to 121.0 (111.4, 144.4) kg at the end of the third phase and reached 120.0 (106.2, 133.6) kg at the 3-month follow-up. The greatest weight reduction was noted in the first month of the study and was followed by a slower weight loss and finally stabilization. Similar trends were observed for BMI (Supplementary Information, Figure 1).

Univariate regression models with weight loss as the outcome showed significance for sex and age group (**Table 4**). These two predictors were then entered in a multivariable (i.e., mutually adjusted) model and the significance remained for both predictors with the same direction and similar magnitude of the association as in univariate models, i.e., male sex (β = 4.32, 95% CI: 1.14–7.50) and being younger than 50y (β = 4.36, 95% CI: 1.16–7.55) were associated with significantly greater weight loss compared to being female of older than 50y (Supplementary Information Table 1). This model suggests independent associations of age and sex with weight loss. As no statistical significance was reached in univariate models with other socio-demographic variables, these were not entered in the multivariable model and their effects on the weight loss are interpreted only from univariate models.

**TABLE 2 |** Mean weight loss, percentage weight loss, and BMI change by sex, age, smoking status, and employment status.

| | Weight loss (kg) Mean *(SD)* | % Weight loss Mean *(SD)* | BMI change Mean *(SD)* |
|---|---|---|---|
| **SEX** | | | |
| Women ($n = 74$) | 18.64 (8.36) | 14.08 (6.19) | −6.94 (3.19) |
| Men ($n = 67$) | 22.46 (10.98) | 14.59 (6.55) | −7.04 (3.28) |
| *p*-value | 0.021 | 0.634 | 0.849 |
| **AGE GROUP** | | | |
| ≤50 years ($n = 77$) | 22.18 (10.9) | 15.22 (6.97) | −7.58 (3.45) |
| >50 years ($n = 62$) | 18.32 (7.92) | 13.21 (5.31) | −6.26 (2.78) |
| *p*-value | 0.020 | 0.062 | 0.016 |
| **SMOKING STATUS** | | | |
| Non-smoker ($n = 81$) | 22.20 (10.05) | 15.1 (6.57) | −7.51 (3.35) |
| Smoker ($n = 18$) | 19.54 (13.12) | 13.3 (7.08) | −6.71 (7.08) |
| *p*-value | 0.339 | 0.263 | 0.377 |
| **EMPLOYMENT STATUS** | | | |
| Employed ($n = 57$) | 22.52 (12.08) | 14.7 (7.38) | −7.45 (3.74) |
| Unemployed ($n = 34$) | 20.42 (8.73) | 14.4 (6.38) | −7.31 (3.20) |
| Retired ($n = 9$) | 19.09 (4.43) | 14.9 (3.77) | −6.27 (1.98) |
| *p*-value | 0.495 | 0.967 | 0.635 |

**TABLE 3 |** Rate of weight change (kg) throughout the phases of the programme.

| Phase | Mean | *SD* | Median | Interquartile range 25th; 75th percentiles |
|---|---|---|---|---|
| Weeks 1–8 | −11.9 | 7.5 | −11.2 | −14.7; −8.2 |
| Weeks 9–16 | −4.8 | 4.3 | −4.8 | −7.1; −2.4 |
| Weeks 17–24 | 0.1 | 12.7 | −1.2 | −3.2; 0.2 |

*$p < 0.001$ for the Kruskal-Wallis test across the 3 phases.*

## Secondary Outcomes

### Bariatric Surgery

At the time of analysis, bariatric surgery guidelines for the East of England Specialised Commissioning Group indicated that eligible patients must have a BMI ≥40 kg/m$^2$ with either type 2 diabetes or severe obstructive sleep apnoea. Of the $n = 32$ IWMP patients who met the BMI criteria for bariatric surgery at baseline, only $n = 17$ were still eligible by the end of the intervention (46.7% reduction). Of the $n = 26$ patients who met the BMI and age criteria (18–65 years) for bariatric surgery (15), only $n = 13$ were still eligible at post-intervention (50% reduction).

### Diabetes (HbA1c)

Of the patients with diabetes ($n = 66$ for type 2 diabetes; $n = 2$ for type 1 diabetes) there was a median (IQR) reduction in HbA1c of 8.6 (0–17.8)%. This equates to a median (IQR) unit reduction of HbA1c of 0.6% (0–1.6) according to Diabetes Control and Complications Trial (DCCT) and −8.0 (−17.0, −1.0) mmol/mol according to the International Federation for Clinical Chemistry (IFCC). A greater reduction in HbA1C was observed among men, those older than 50 years, non-smokers and retired compared to the counterparts without

**TABLE 4 |** Univariable linear regression models assessing the associations of sex, age, smoking status, and occupation with weight loss (IWMP, baseline $N = 141$).

| | β-coefficient | 95% Confidence interval | *p*-value |
|---|---|---|---|
| Sex (male) | 3.82 | 0.59 – 7.05 | 0.021 |
| Age (≤50y) | 3.85 | 0.61 – 7.10 | 0.020 |
| Smoking (yes) | −2.67 | −8.17 – 2.84 | 0.339 |
| Occupation (Employed) | 2.10 | −2.43 – 6.63 | 0.359 |
| Occupation (Retired) | −1.331 | −8.85 – 6.19 | 0.726 |

*NB, the following reference categories were used: sex- female, age–>50 years, smoking-no, occupation- unemployed.*

these characteristics (Supplementary Information, Table 2). However, none of these differences were statistically significant (Supplementary Information, Table 2).

### Blood Pressure

There were no significant changes in blood pressure outcomes based on demographic variables assessed. The median (IQR) change in systolic and diastolic blood pressure was−6 (−14 to 6) and 0 (−8 to 6) mmHg, respectively (Supplementary Information, Table 3, Supplementary Information, Figures 2, 3).

## DISCUSSION

The findings of this intervention in severely obese individuals suggest that the completion of the IWMP is associated with an average (SD) weight loss of 20.5 (9.8) kg over 24 weeks. Sixty-nine percent ($n = 97$) of the patients had lost 10% or more of their body weight. Sex and age were significant independent predictors of weight loss, with men and those younger than age 50 achieving significantly greater weight loss than their counterparts. The significant weight loss associated with the IWMP shows the potential of this programme to help severely obese patients. It must remain clear that this programme must only be followed under strict supervision of several healthcare providers working as a multidisciplinary team, and it is not advised for individuals to follow this regime on their own. As the number of severely obese people increases, more programmes must be available to help them lose weight to help avoid bariatric surgery or to optimize patients before surgery, thus reducing deleterious health effects of obesity.

### Clinical Significance

The clinical effectiveness of the IWMP is demonstrated by the substantial weight loss, which is greater than in some similar weight management programmes, as described below. Although not statistically significant, there was also a clinically appreciable reduction in HbA1c at individual patient level. There was a substantial drop in the need for bariatric surgery in relation to the local referral guidelines. Although the absolute magnitude of the reduction in systolic blood pressure was small and did not reach statistical significance, there was an overall decrease in the use of antihypertensive medications.

Many people in IWMP are on several medications, however due to the nature of the data, there was no way to quantify medication change in a consistent way. Experiences of IWMP clinicians indicate an overall reduction in hypertension medication. Since blood pressure remained unaffected despite this reduction in medication, the lack of change may indicate a positive outcome. Although not discussed due to the small sample size, observation from IWMP clinicians indicate the IWMP has been effective in controlling obstructive sleep apnoea and to an extent hypercholesterolemia.

### Comparison With Other Weight Management Programmes

The Danish RCT, the CAROT study (16) ($N = 192$) found that low energy diet (LED; 800–1,200 kcal/day) and very low energy diet (VLED; <800 kcal/day) resulted in an average weight loss of 10.7 kg and 11.4 kg over 16 weeks, respectively which is a smaller weight reduction than IWMP. The observed differences could be explained by the differences in the baseline characteristics of the patients (those in the CAROT were somewhat older [mean age 63 years] and leaner [mean (SD) for baseline weight was 103.2 (15.0) kg and for baseline BMI was 37.3 (4.8) kg/m$^2$] compared to the IWMP) (16). Furthermore, the different nature (i.e., dietary content) and the duration of the interventions (16 weeks for the CAROT vs. 24 weeks for the IWMP) could possibly account for the observed differences in the weight loss (16).

A feasibility study ($N = 91$) in the primary care setting in the UK (17) with similar baseline characteristics as the IWMP reported a mean (SD) weight loss of 14.7 (10.8) kg over the period of 12 months. The study used the same 3 phases as the IWMP (weight loss with low energy liquid diet for 12 weeks, food reintroduction for 6–8 weeks and weight maintenance until 12 months) but the intervention lasted for one year.

Recently published results of the DiRECT trial (18) have demonstrated that the primary care intervention comprising of total diet replacement (825–853 kcal/day formula diet for 3–5 months), stepped food reintroduction (2–8 weeks), withdrawal of antidiabetic and antihypertensive medications and structured support for long-term weight loss maintenance was associated with a remission to a non-diabetic state after 12 months among obese adults with type 2 diabetes. This study indicates that effective weight management interventions may be performed in primary care thus translating the findings from the tertiary centers to the community.

In a review of very low calorie or low-energy liquid-formula diets in people with and without type 2 diabetes, all trials reported weight loss for all participants, with our without diabetes (19). In another review focused on people with diabetes, the mean weight loss from the 17 studies was 13.2 kg (range 4.1–24 kg), with the duration ranging from 5 days to 6 months (20). In the STAMPEDE trial, Schauer et al, demonstrated that in obese patients with type 2 diabetes, bariatric surgery plus intensive medical therapy was more effective than medical therapy alone (21).

### Strengths and Limitations

The strengths of this study include the unique multidisciplinary team approach with fortnightly follow-ups and support to the patients with severe obesity. As this is a service-based intervention, it is likely that the majority of the individuals with severe obesity in the geographic region which the hospital serves have been captured, thus increasing generalisability of our findings. As this is a service based intervention it was not possible to have a control group, thus there is no randomization of participants.

As this programme is conducted in a clinical NHS setting with a multi-faceted team over several years, there are changing bariatric surgery criteria [lower BMI cut-offs for the consideration of bariatric surgery, i.e., 35 kg/m$^2$ in those with diabetes or significant co-morbidities including hypertension, or obstructive sleep apnoea (15)], as well as changes to staffing and procedures. These are all limiting factors of data collection. Some of the available data was not sufficient for analysis due

to missing data or inconsistent entry, thus limiting sample size. Further analysis may be conducted to examine the changes in medications and psychological status, however this is currently outside the remit of this study.

As with any participant intensive study, it is challenging to determine how well participants followed the diet and physical activity recommendations. The pre-determined commitment, the fortnightly clinic visits, and diet and physical activity records were all strategies used to measure adherence, however it is still difficult to account for this factor. There is also no objective measure of physical activity.

Although follow-up with participants was attempted at 3 months, there was a minimal response rate and thus follow-up data is lacking. Beyond 3 months, there was no follow-up. Due to this lack of follow-up, it was not possible to assess the potential weight regain after post-intervention weight loss. Reviewing long term weight loss maintenance is an important next step for IWMP.

It is widely acknowledged that screening for various psychological measures (including depression and anxiety, self-esteem, eating behavior and attitudes, and quality of life) should be used as part of weight management assessment. IWMP used standardized and validated instruments (11, 22–25) to measure each of these constructs. However, we did not include them in this analysis due to missing data for a large proportion of the participants.

As this is a small group of patients, it is difficult to have studies with a large sample size. Data were collected to monitor individual progress, and when viewed together the sample size may appear small. For this reason, analysis focused on weight change and a small number of secondary outcomes. Furthermore, we identified only age and sex to be significant predictors of weight loss thus limiting the multivariable analysis for other factors considered to be possibly associated with weight loss.

## CONCLUSION

The IWMP is a service designed for severely obese individuals who have the ultimate goal of avoiding the need for bariatric surgery or to optimize the patient before surgery. IWMP patients lost an average (SD) of 20.5 (9.8) kg over the course of an intensive 24-week programme. There was around a 50% reduction in the need for bariatric surgery. When used appropriately under direct professional supervision, the IWMP has the potential to significantly decrease weight of severely obese individuals. Further research into the clinical effectiveness of IWMP would include the addition of long term follow-up to assess weight maintenance as well as measures of vascular function and genotype to assess inter-individual difference in physiological and clinical response to the IWMP intervention.

## AUTHOR CONTRIBUTIONS

RG analyzed data, drafted the manuscript and made subsequent revisions according to co-authors' comments. CL contributed to data collection and manuscript preparation. MK performed part of the analysis. JH lead data collection and study management. AP conceived the study, oversaw all stages of the project, provided critical input to all drafts of the manuscript. SR conceived the study, oversaw all stages of the project, provided critical input to all drafts of the manuscript. AL contributed to data collection.

## FUNDING

This project was conducted by the NNEdPro Global Centre for Nutrition and Health in Cambridge and funded in part by Cambridge University Hospitals NHS Foundation Trust.

## ACKNOWLEDGMENTS

Claire Connell (clinic visits); Mike Newell design of **Figure 1**.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2018.00054/full#supplementary-material

## REFERENCES

1. World Health Organization. *Obesity and Overweight* (2016).
2. Health, Social Care Information Centre. *Statistics on Obesity, Physical Activity and Diet*. London: Health and Social Care Information Centre (2016).
3. Prospective Studies Collaboration, Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* (2009) 373:1083–96. doi: 10.1016/S0140-6736(09)60318-4
4. Picot J, Jones J, Colquitt JL, Gospodarevskaya E, Loveman E, Baxter L, et al. The clinical effectiveness and costeffectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation. *Health Technol Assess.* (2016) 13:1–190, 215–357, iii–iv. doi: 10.3310/hta13410
5. Abdullah A, Peeters A, de C, de Courten M, Stoelwinder J. The magnitude of association between overweight and obesity and the risk of diabetes: a meta-analysis of prospective cohort studies. *Diabetes Res Clin Pract.* (2010) 89:309–19. doi: 10.1016/j.diabres.2010.04.012
6. Colquitt JL, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults (Review). (2014) 8:CD003641. doi: 10.1002/14651858.CD003641
7. National Institute for Health and Care Excellence(UK). *Obesity: Identification, Assessment and Management* (2014).
8. Welbourn R, le Roux CW, Owen-Smith A, Wordsworth S, Blazeby JM. Why the NHS should do more bariatric surgery; how much should we do? *BMJ* (2016) 353:i1472. doi: 10.1136/bmj.i1472
9. Royal College of Surgeons of Engalnd. *Commissioning guide:Weight Assessment and Management Clinics (tier 3*) (2014).
10. Aronne LJ. Classification of obesity and assessment of obesity-related health risks. (2002) 10(Suppl. 2):105S—15. doi: 10.1038/oby.2002.203
11. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. (1991) 14:540–5.
12. The Parenteral & Enteral Nutrition Group of the British Dietetic Association. *A Pocket Guide to Clinical Nutrition* (2011).
13. Thai AG, Wadden TA. The evolution of very-low-calorie diets: an update and meta-analysis. *Obesity* (2006) 14:1283–93. doi: 10.1038/oby.2006.146

14. Richardson MT, Ainsworth BE, Wu HC, Jacobs DR Jr, Leon AS. Ability of the Atherosclerosis Risk in Communities (ARIC)/Baecke Questionnaire to assess leisure-time physical activity. *Int J Epidemiol.* (1995) 24:685–93.
15. NHS Commissioning Board Clinical Reference Group for Severe and Complex Obesity. *Clinical Commissioning Policy: Complex and Specialised Obesity Surgery* (2013).
16. Christensen P, Bliddal H, Riecke BF, Leeds AR, Astrup A, and Christensen R. Comparison of a low-energy diet and a very low-energy diet in sedentary obese individuals: a pragmatic randomized controlled trial. *Clin Obes.* (2011) 1:31–40. doi: 10.1111/j.1758-8111.2011.00006.x
17. Lean M, Brosnahan N, McLoone P, McCombie L, Higgs AB, Ross H et al. Feasibility and indicative results from a 12-month low-energy liquid diet treatment and maintenance programme for severe obesity. *Br J Gen Pract.* (2013) 63:e115–24. doi: 10.3399/bjgp13X663073
18. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* (2017) 391:541–51. doi: 10.1016/S0140-6736(17)33102-1
19. Leslie WS, Taylor R, Harris L, Lean MEJ. Weight losses with low-energy formula diets in obese patients with and without type 2 diabetes: systematic review and meta-analysis. *Int J Obes.* (2017) 41:96–101. doi: 10.1038/ijo.2016.175
20. Sellahewa L, Khan C, Lakkunarajah S, Idris I. A systematic review of evidence on the use of very low calorie diets in people with diabetes. *Curr Diabetes Rev.* (2017) 13:35–46. doi: 10.2174/1573399812666151005123431
21. Schauer P, Bhatt DL, Kirwan J, Wolski K, Aminian A, Brethauer S, et al. Bariatric surgery versus intensive medical therapy for diabetes — 5-year outcomes. *N Engl J Med.* (2017) 376:641–51 doi: 10.1056/NEJMoa1600869
22. Kolotkin RL, Crosby RD. Psychometric evaluation of the impact of weight on quality of life-lite questionnaire (IWQOL-lite) in a community sample. *Qual Life Res.* (2002) 11:157–71.
23. Rosenberg M. *Society and the Adolescent Self-Image*. Princeton, NJ: Princeton University Press (1965).
24. Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *J Psychos Res.* (1985) 29:71–83. doi: 10.1016/0022-3999(85)90010-8
25. Zigmoid AS, Snaith RP. The hospital anxiety and Depression Scale. *Acta Psychiatr Scand.* (1983) 67:361–70.

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

# Advantages of publishing in Frontiers

**OPEN ACCESS**
Articles are free to read for greatest visibility and readership

**FAST PUBLICATION**
Around 90 days from submission to decision

**HIGH QUALITY PEER-REVIEW**
Rigorous, collaborative, and constructive peer-review

**TRANSPARENT PEER-REVIEW**
Editors and reviewers acknowledged by name on published articles

**Frontiers**
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

**Visit us:** www.frontiersin.org
**Contact us:** info@frontiersin.org | +41 21 510 17 00

**REPRODUCIBILITY OF RESEARCH**
Support open data and methods to enhance research reproducibility

**DIGITAL PUBLISHING**
Articles designed for optimal readership across devices

**FOLLOW US**
@frontiersin

**IMPACT METRICS**
Advanced article metrics track visibility across digital media

**EXTENSIVE PROMOTION**
Marketing and promotion of impactful research

**LOOP RESEARCH NETWORK**
Our network increases your article's readership