Review

Health Risks Associated with Meat Consumption: A Review of Epidemiological Studies

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Abstract: Recent evidence from large prospective US and European cohort studies and from meta-analyses of epidemiological studies indicates that the long-term consumption of increasing amounts of red meat and particularly of processed meat is associated with an increased risk of total mortality, cardiovascular disease, colorectal cancer and type 2 diabetes, in both men and women. The association persists after inclusion of known confounding factors, such as age, race, BMI, history, smoking, blood pressure, lipids, physical activity and multiple nutritional parameters in multivariate analysis. The association has not always been noted with red meat, and it has been absent with white meat. There is evidence of several mechanisms for the observed adverse effects that might be involved, however, their individual role is not defined at present. It is concluded that recommendations for the consumption of unprocessed red meat and particularly of processed red meat should be more restrictive than existing recommendations. Restrictive recommendations should not be applied to subjects above about 70 years of age, as the studies quoted herein did not examine this age group, and the inclusion of sufficient protein supply (e. g. in the form of meat) is particularly important in the elderly.

Key words: meat, processed meat, red meat, poultry, protein, mortality, cardiovascular disease, colon cancer, diabetes type 2

Introduction

Meat is not only a major source of valuable proteins, but also of vitamins such as A, B_1, B_{12} and niacin, and of iron, zinc and other micronutrients. However, recent evidence from the epidemiologic literature suggests that the increasing consumption of red meat, especially in its processed forms, may have adverse health effects, as outlined in this review.

A working group from the Swiss Federal Commission for Nutrition has dealt with the subject by reviewing the scientific literature of recent years and by writing a detailed report, including recommendations for consumption by the public, on behalf of the Federal Food Safety and Veterinary Office [1]. This article is an abridged version.

The report deliberately did not address the environmental, ethical and social aspects of meat consumption. This does not mean that these aspects are not important.

The underlying epidemiologic literature often uses the terms ”red” and ”white” meat. In most cases, the muscle meat from beef, veal, pork, lamb, horse and deer is defined as ”red” meat. ”White” meat refers to

poultry. "Processed meat" includes all types of meat products, such as sausages, cold cuts and other meats, which have undergone a process to extend their shelf life and which have been mixed with ingredients such as curing salt or salt. Not all types of preparations of meat can reliably be allocated to a group, and the selected definitions may vary from those used in individual studies.

Epidemiologic correlations between meat consumption and health

Evidence of the association between meat consumption and the occurrence of disease has been collected mainly from recent large-scale cohort studies in the US and Europe and from meta-analyses of epidemiologic studies. In particular, the relationship between levels of the consumption of meat (red and processed), and mortality and the incidence of important and common diseases such as cardiovascular disease, type 2 diabetes and certain types of cancer, was assessed. A table with a list of all included studies and their main findings can be found in the full report [1]. Randomized controlled intervention studies would indeed be meaningful, but they do not exist and are also unlikely to be feasible in free living individuals.

Total mortality

The prospective cohort study of the "National Institutes of Health-AARP" (NIH-AARP) included half a million participants aged 50–71 years. It found a significant association between the consumption of red and processed meats and total mortality, in both men and women [2]. The risk of death within 10 years was 31 %, and this was 16 % higher in men with the highest compared to the lowest consumption (highest versus lowest quintile) of red meat (hazard ratio 1.31 [95 % CI 1.27 to 1.35]) and of processed meat (HR 1.16 [95 % CI 1.12 to 1.20]), respectively, after adjustment to 13 covariates associated with mortality. The corresponding data for women was a hazard ratio of 1.36 [95 % CI 1.30 to 1.43] for red meat and 1.25 [95 % CI 1.20 to 1.31] for processed meat when the highest and the lowest quintiles of consumption were compared. Lowest vs. highest quintiles of consumption in g per 1000 kcal were: 9.3 vs. 68.1 for men and 9.1 vs. 65.9 for women (red meat), and 5.1 vs. 19.4 for men and 3.8 vs. 16.0 for women (processed meat).

The "Health Professionals Follow-up Study" performed in men and the "Nurses' Health Study" in women repeated detailed nutrition surveys at intervals of 4–6 years for more than 20 years (Fig. 1). The association between meat consumption and mortality persisted after the inclusion of known confounding factors, such as age, race, body mass index (BMI),

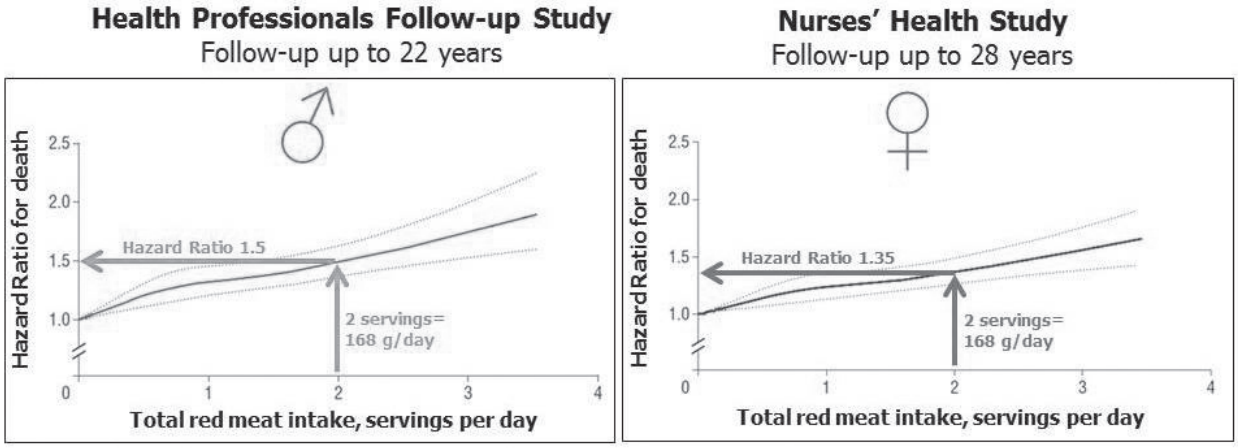

Figure 1: Hazard ratio for death (all-causes mortality) in two US cohort studies with increasing consumption of red meat [3]. With a consumption of 168 g of red meat per day (2 servings) in men the hazard ratio was 1.5, i.e. 50 % higher than with no red meat. The corresponding data for women was a hazard ratio of 1.35 with consumption of 2 servings per day. Data was adjusted in a multivariate model for age; BMI; alcohol consumption; physical activity level; smoking status; race; menopausal status and hormone use in women; family history of diabetes mellitus, myocardial infarction or cancer; history of diabetes mellitus, hypertension, or hypercholesterolemia; and intakes of total energy, whole grains, fruits, and vegetables. Broken lines are 95 % CI.

history of disease, smoking, blood pressure, lipids, physical activity, alcohol consumption and multiple nutritional parameters in multivariate analysis [3]. The overall mortality during the course of follow-up over 22 and 28 years in the two studies indicated an almost linear increase in the hazard ratio (HR) of mortality with increasing consumption of red meat. In men, the increase in risk was more pronounced than in women (HR 1.37 [95 % CI 1.27 to 1.47) vs. 1.24 [95 % CI 1.17 to 1.30]; multivariate model) when comparing the highest quintile of consumption with the lowest (median: 174 g total red meat per day vs. 21 g in men, and 182 g vs. 43 g in women, respectively). In 2013 the results of a large European study (EPIC) of the relationship between meat consumption and mortality in 448,568 men and women from 10 countries was published [4]. They confirmed the findings of the US cohorts [2] [3]. An increased consumption of red meat (>160 g vs. 10–19.9 g per day) was associated with a mean increase of 14 % mortality (HR 1.14 [95 % CI 1.01–1.28]) during a mean follow-up of 13 years. The consumption of processed meat was associated with an even more pronounced 44 % increase in mortality (>160 g compared to 10–19.9 g per day: HR 1.44 [95 % CI 1.24–1.66]). The authors estimated that 3.3 % of deaths could have been prevented if the participants had consumed less than 20 grams of processed meat per day. The consumption of poultry showed no association with mortality. Two recent meta-analyses of prospective cohort studies reporting data on mortality associated with meat consumption yielded similar results [5] [6].

Cardiovascular disease

The US "Health Professionals Follow-up Study" and the "Nurses' Health Study" examined the association between risk of mortality from cardiovascular diseases and meat consumption [3]. Both women and men demonstrated a significant increase in cardiovascular mortality with increasing consumption of unprocessed red meat (18 % increase per serving) and of processed red meat (21 % increase per serving [84 g] per day), (Fig. 2). When men and women were compared, the consumption of unprocessed meat showed a similar increase in risk, while the increase in risk with processed meat was relatively higher in women than in men.

A meta-analysis of studies that examined the association between the consumption of red and processed meat and specific diseases was published in 2010 [7]. It should be noted that meat consumption in some earlier studies was assessed only once, and the associated risk factors evaluated were not as detailed as in the above US cohort studies. The meta-analysis showed a significantly increased risk of incident coronary heart disease with the increasing consumption of processed meat. An intake of 50 g of processed meat per day was associated with a mean increase in risk of 42 %. The consumption of unprocessed red meat showed no significant cor-

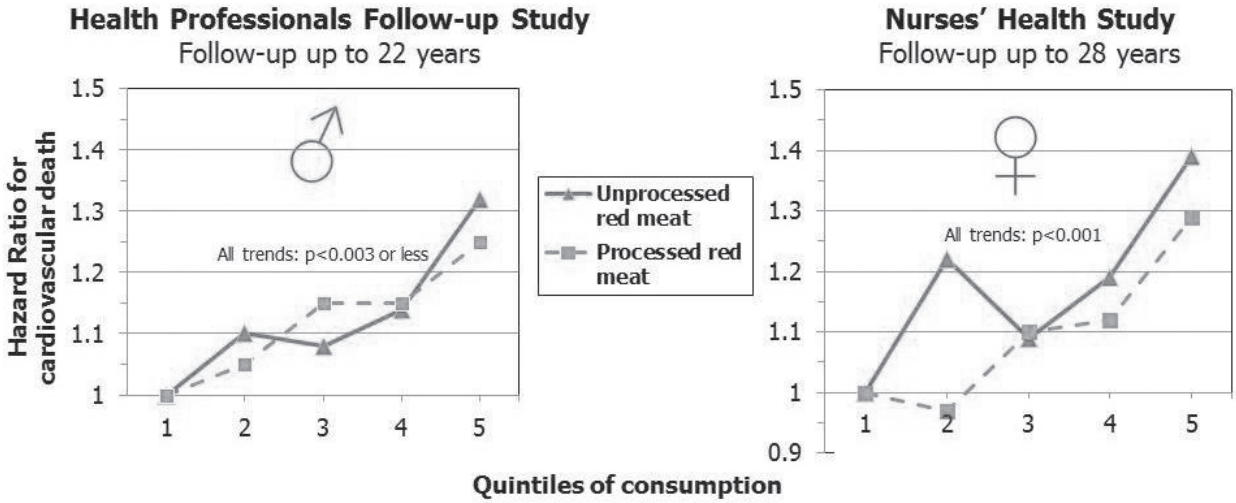

Figure 2: Hazard ratio for mortality from cardiovascular diseases in two US cohort studies of increasing consumption of unprocessed and processed red meat [3]. Data was adjusted in a multivariate model for age; BMI; alcohol consumption; physical activity level; smoking status; race; menopausal status and hormone use in women; family history of diabetes mellitus, myocardial infarction or cancer; history of diabetes mellitus, hypertension, or hypercholesterolemia; and intakes of total energy, whole grains, fruits, and vegetables.

relation with coronary heart disease risk (relative risk [RR] = 1.00), however, several parameters showed a significant heterogeneity between studies (e. g. discordant findings in US and Asian/Australian studies) [7].

The EPIC study showed a significant increase, with increasing consumption of processed meat, in the risk of death due to cardiovascular disease (HR 1.72 [95 % CI 1.29 to 2.30]) when the highest and the second lowest consumption was compared (>160 g per person per day compared to 10–19.9 g). With unprocessed red and with white meat there was no significant correlation with cardiovascular death [4].

Colorectal cancer

Two meta-analyses of the relationship between meat consumption and incidence of colorectal cancer were published in 2011. The first [8] included 21 studies that met the selection criteria (peer review publication, original data of defined cohorts, information on consumption levels and risk; details of unprocessed and processed meat). A significant increase in colorectal cancer risk was found with increasing consumption of red meat (17 % increase in risk per 100 g red meat per day). For processed meat a significant increase in risk by 18 % per 50 g/ day was observed (Fig. 3). The authors concluded from the data that a limited intake of red and processed meat should be recommended for the prevention of colorectal cancer.

The second meta-analysis [9] included 25 studies in which only the consumption of unprocessed red meat was reported. Several of the studies included

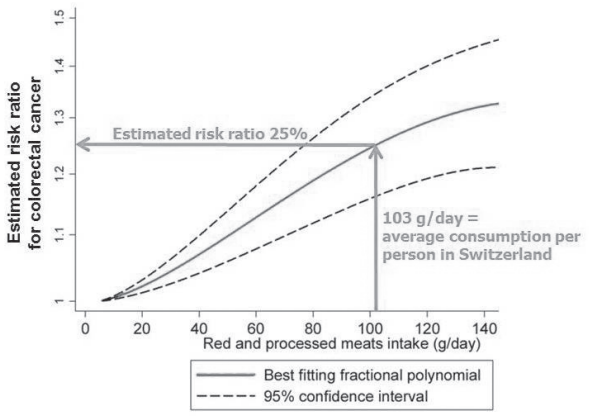

Figure 3: Relative risk of colorectal cancer with an increasing consumption of red meat (processed and unprocessed) [8]. The arrows indicate the estimated risk ratio with the average consumption according to the Sixth Swiss Nutrition Report [48].

did not satisfy the quality features required in the meta-analysis by Chan et al [8]. The increased risk of colorectal cancer at high compared to low consumption of red meat was slightly less than that described in [8](RR 1.12 [95 % CI 1.04 to 1.21]), and the correlation between rectal cancer and the consumption of red meat was not statistically significant. A bias in the authors cannot be excluded since the study was financially supported by the "Beef Checkoff", the "National Cattlemen's Beef Association" and the "National Pork Board".

A recent meta-analysis described the role of red meat consumption compared to other known risk factors for colorectal cancer (inheritance, inflammatory bowel disease, obesity, lack of exercise, etc.) [10]. According to analysis of 14 studies, red meat consumption conferred a low grade but statistically significant increased risk (RR 1.13, 95 % CI 1.09 to 1.16) when comparing five portions (560 g) per week to no consumption. With processed meat (5 studies) the increase was not statistically significant.

Diabetes mellitus type 2

The risk of type 2 diabetes increased with increasing consumption of processed red meat according to a meta-analysis [11]. The hazard ratio for diabetes increased by 51 % [95 % CI 25–83 %] per 50 g of processed red meat per day per person. The increase in risk was statistically significant but relatively low for unprocessed red meat (19 % [95 % CI 4–37 %] increase per 100 g per person per day). The meta-analysis showed significant heterogeneity with the included studies; if the trim and fill method was used to exclude a publication bias, the hazard ratio for diabetes with consumption of processed meat remained 1.23 [95 % CI 1.01–1.52] per 50 g per day.

When changes in meat consumption within four years were assessed in the above-mentioned three large cohort studies, a significant correlation was found between the incidence of diabetes and an increase in the consumption of red meat. An increase of 42 g or more per day compared to no increase, compounded the risk of diabetes in the course of 4 years by 48 % [95 % CI 37–59 %] [12].

The EPIC InterAct study also found a significant correlation between new cases of diabetes and the consumption of red meat [13] [14] in a large European cohort. A 50 g per day increase in the consumption of red and processed meat predicted an increase in risk of 8 % [95 % CI 5–12 %] and 12 % [95 % CI 5–19 %], respectively, in 12 years of follow-up (Fig. 4). In the

French E3N study of 66,180 women there was also a statistically significant association between the risk of new diabetes and consumption of processed red meat, but not with unprocessed red meat [15].

Possible mechanisms for the adverse effects of red meat and processed meat on health

Red meat

The reasons for the apparent adverse effects of red meat in the development or progression of atherosclerosis, diabetes and certain forms of cancer have not been clarified with certainty. It is generally assumed that there are several factors that act individually or in combination. It is also not possible to differentiate between individual sources of red meat (e.g. pork compared to beef or veal) as corresponding data is not available.

Red meat has a higher iron content on average than white meat [16]. An oversupply of heme iron, the storage form of iron found in meat, was considered to be potentially atherogenic [17–19] and growth-promoting in gastrointestinal cancer [20, 21] as well as being diabetogenic [22], however, the fact that processed meats are associated with higher risks compared to unprocessed meats can not be explained thus, as processed meats are to a large extent based on pork with a relatively low iron content.

Recently, other possible mechanisms of the development of atherosclerosis have been described. Phosphatidylcholine [23] and carnitine [24], typical components of meat, are partially degraded by intestinal bacteria into trimethyl-amine-N-oxide (TMAO). This product is potentially atherogenic. Meat-eating individuals produce more TMAO than vegetarians [24]. The concentration of L-carnitine is higher in red than in white meat [25]. The administration of L-carnitine to mice increased the production of TMAO and atherosclerosis [24], however, no similar studies in humans have been reported.

Processed meat

Processed meat differs from non-processed in that the former often contains added ingredients such as curing salt and other salt as preservatives. Salt intake is associated with blood pressure in humans [26]. Curing salt contains nitrite which can produce peroxynitrites in the digestive process. This may promote atheroscle-

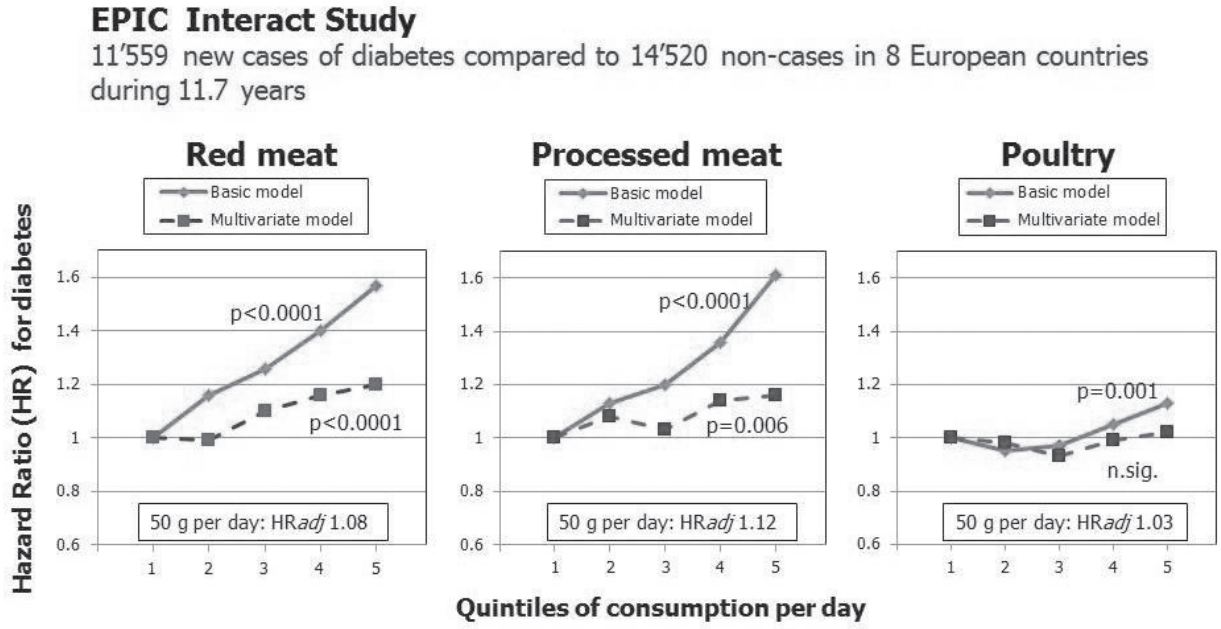

Figure 4: Hazard ratio for new cases of diabetes in the EPIC InterAct Study during increasing consumption of red meat, processed meat and poultry [14]. A 50 g increment of red meat consumption resulted in an 8 % increase in the hazard ratio of diabetes. The data of the multivariate model were adjusted for sex, BMI, energy intake, smoking status, alcohol consumption, physical activity and educational level.

rosis and enhance the development of diabetes [27]. Nitrite concentrations in the blood were correlated with endothelial dysfunction in humans [28] and with impaired insulin sensitivity [29]. Nitrites have also been associated with the development of gastric cancer based on case control studies [30], however, a more recent review of prospective cohort studies failed to confirm this relationship [31]. The carcinogenic effect of nitrites appeared to be diminished by combined consumption with antioxidants [32]. In addition, processed meats provide only small amounts of nitrites compared to endogenous nitrite production and to oral intake of nitrate/nitrite in vegetables [33].

The emergence of colon cancer in rats was, however, enhanced by the interplay of nitrite-containing cooked meat and heme iron [34]. Detailed information about the usual steps in meat processing and possible mechanisms of carcinogenesis can be found in a review article [35].

Health aspects of vegetarianism

Vegetarians have a lower risk of dying from cardiovascular disease or from certain types of cancer compared to meat-eating individuals. This is shown in a meta-analysis of seven studies [36]. The relative risk of death due to coronary heart disease was 29 % lower than that of meat eaters; and for cancer the incidence risk was 18 % lower. Whether vegetarianism is responsible for the decrease in these disease risks is ultimately not clear. There is evidence that vegetarians also differ from meat eaters in other respects that lead to better health [37]. They often have a more health-conscious lifestyle, are less likely to be overweight, smoke less and drink less alcohol [38].

In a meatless diet the sufficient supply of micronutrients such as iron, zinc and vitamin B_{12} may be critical. Meat provides the highest contribution to the iron supply compared with other food groups. Heme iron from meat is better absorbed than non-heme iron in plant foods such as bread. Vegans may be particularly undersupplied with nutrients (including calcium) since they do not eat any animal products; as well as meat they avoid also dairy products, fish and eggs [39]. There are several reports of severe, irreversible neurological damage in the children of vegan mothers who did not supplement with enough vitamin B_{12} [40, 41].

Quality of the evidence and limitations of epidemiological studies

In recent years, published prospective cohort studies from the US and Europe suggest that the increasing consumption of red meat and in particular of processed meat results in an increased risk of mortality, cardiovascular disease, colorectal cancer and type 2 diabetes.

Quality of evidence

Epidemiological studies provide data on associations but no direct evidence of effects and causality. The quality and relevance of the cited epidemiological studies differs significantly. The large cohort studies (HPFS, NHS I and II, NIH-AARP, EPIC, E3N) were carried out in countries with similar lifestyles and eating habits as in Switzerland, and they are thus very relevant since HPFS and NHS I recorded dietary habits over the years, several times. They also took into account all known risk factors such as BMI, smoking status, blood pressure, general nutritional habits, alcohol consumption, ethnicity, diabetes etc. Even after including these risk factors in a multivariate analysis, the relationship was preserved, which supports the suspicion of causality.

Limiting factors in the assessment of the health effects

The aforementioned studies included subjects between 35 and 75 years of age. The effect on people's health of meat and processed meat at ages below or above this age range may lead to a different conclusions than that of this report. In particular, the benefit/risk ratio for the consumption of meat may be more favorable in elderly subjects. The benefits of meat as a valuable source of protein may be greater in older people because the coverage of protein supply plays a particularly important role in the prevention of sarcopenia [42], thereby reducing the risk of falls and osteoporosis (see "Protein Report" [43]). On the other hand, the possible risks associated with consumption of meat in the elderly may be less important as a result of shorter exposure time due to shorter life expectancy. The increase in risk in the quoted studies of this article was found to be mostly below 50 % and often less than 20 %. This may be

interpreted as "large" or "small", depending on personal judgment.

Conclusions

Meat is a valuable source of macro- and micronutrients, particularly of proteins, vitamins A, B_1, B_{12}, niacin, iron, and zinc. Not consuming meat carries certain risks. These are especially present if no animal-based foods at all are consumed (vegan diet).

Evidence from cohort studies leads to the conclusion that long-term consumption of increasing amounts of red meat and particularly of processed meat may result in a certain increase in the risk of mortality, cardiovascular disease, certain forms of cancer such as colon cancer and type 2 diabetes. There is evidence that several mechanisms might be involved, such as curing salt, however, their significance is not yet clearly known.

It is concluded that recommendations for consumption of unprocessed red meat should be more restrictive than existing recommendations in Switzerland [44]. The recommendation for the consumption of processed red meat should be even more restrictive. The Harvard School of Public Health [45] and the World Cancer Research Fund [46] both went further and recommended avoiding processed meat altogether. The present recommendations apply to adults aged about 35–70 years, as the studies quoted in this report examined these age groups. Restrictive recommendations are not warranted for the elderly, as the consumption of sufficient amounts of dietary proteins (e.g. in the form of meat) is particularly important for them [42, 43, 47].

Conflict of interest

The authors declare no conflict of interest in connection with this report.

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