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Original article

The impact of type of dietary protein, animal versus vegetable, in modifying cardiometabolic risk factors: A position paper from the International Lipid Expert Panel (ILEP)

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SUMMARY

Proteins play a crucial role in metabolism, in maintaining fluid and acid-base balance and antibody synthesis. Dietary proteins are important nutrients and are classified into: 1) animal proteins (meat, fish, poultry, eggs and dairy), and, 2) plant proteins (legumes, nuts and soy). Dietary modification is one of the most important lifestyle changes that has been shown to significantly decrease the risk of cardiovascular (CV) disease (CVD) by attenuating related risk factors. The CVD burden is reduced by optimum diet through replacement of unprocessed meat with low saturated fat, animal proteins and plant proteins. In view of the available evidence, it has become acceptable to emphasize the role of optimum nutrition to maintain arterial and CV health. Such healthy diets are thought to increase satiety, facilitate weight loss, and improve CV risk. Different studies have compared the benefits of omnivorous and vegetarian diets. Animal protein related risk has been suggested to be greater with red or processed meat over and above poultry, fish and nuts, which carry a lower risk for CVD. In contrast, others have shown no association of red meat intake with CVD.

The aim of this expert opinion recommendation was to elucidate the different impact of animal *vs* vegetable protein on modifying cardiometabolic risk factors. Many observational and interventional studies confirmed that increasing protein intake, especially plant-based proteins and certain animal-based proteins (poultry, fish, unprocessed red meat low in saturated fats and low-fat dairy products) have a positive effect in modifying cardiometabolic risk factors. Red meat intake correlates with increased CVD risk, mainly because of its non-protein ingredients (saturated fats). However, the way red meat is cooked and preserved matters. Thus, it is recommended to substitute red meat with poultry or fish in order to lower CVD risk. Specific amino acids have favourable results in modifying major risk factors for CVD, such as hypertension. Apart from meat, other animal-source proteins, like those found in

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dairy products (especially whey protein) are inversely correlated to hypertension, obesity and insulin resistance.

Abbreviations

AI	augmentation index
ApoB	apolipoprotein B
A/P	animal to plant protein ratio
BC	body composition
BD	balanced diet
BF%	body fat percentage
BMI	body mass index
BP	blood pressure
CHD	coronary heart disease
CHO	carbohydrate
CI	confidence interval
CRP-	C-reactive protein
CTPro	change in total protein
CV	cardiovascular
CVD	cardiovascular disease
DALY	disability adjusted life years
DASH	dietary approaches to stop hypertension
DBP	diastolic blood pressure
DII	dietary inflammatory index
DM	diabetes mellitus
DRI	dietary reference intakes
EAR	estimated average requirement
E-DII	energy adjusted dietary inflammatory index
eGFR	estimated glomerular filtration rate
eNOS	endothelial Nitric oxide synthase
EPIC	European Prospective Investigation into Cancer and Nutrition
FDA	Food and Drug Administration
FFQ	Food Frequency Questionnaire
FG	fasting glucose
FL	free-living weight loss
FMD	flow mediated dilation
GLP1	glucagon like peptide 1
HAD	Healthy American Diet
HC	high carbohydrate
HDL-C	high-density lipoprotein cholesterol
HELENA	Healthy Lifestyle in Europe by Nutrition in Adolescence
HMG-CoA	hydroxy-methyl-glutaryl coenzyme A
HOMA-B	homeostatic model assessment of B-cell function
HOMA-IR	homeostatic model assessment of insulin resistance
HOMA-S	homeostatic model assessment of insulin sensitivity
HP	high protein
hsCRP	high sensitivity C-reactive protein
HTN	hypertension
iAUC	incremental Area Under the Curve
IHD	ischemic heart disease
IHLs	intrahepatic lipids
IMAT	intermuscular adipose tissue
INTERMAP	International Population Study on Macronutrients and Blood Pressure
INTERSALT	International Study of Electrolyte Excretion and Blood Pressure
ILEP	International Lipid Expert Panel
IL-6	interleukin 6
IR	insulin resistance
ISF	isoflavones
LC/HP	low carbohydrate/high protein
LDL-C	low density lipoprotein cholesterol
MCP1	monocyte chemoattractant protein 1
MC-SFA	medium chained saturated fatty acids
MetS	metabolic syndrome
MR	meal replacement
mRNA	messenger ribonucleic acid
MUFA	monounsaturated fatty acids
NA	not available
NCEP	National Cholesterol Education Program
NEAP	net endogenous acid production
NHANES	National Health and Nutrition Examination Survey
NO	nitric oxide
OB	obesity
OmniHeart	Optimal Intake Trial to Prevent Heart Disease
OR	odds ratio
PAD	peripheral artery disease
PBD	plant based diet
PRAL	potential renal acid load
PUFA	poly unsaturated fatty acids
PWV	pulse wave velocity
RCT	randomized controlled trial
RDA	recommended dietary allowance
RR	relative risk
SBP	systolic blood pressure
SFA	saturated fatty acids
sICAM	soluble intercellular adhesion molecule 1
Soy+	isoflavone-rich soy
Soy	isoflavone-poor soy
SP	standard protein
sVCAM	soluble vascular adhesion molecule 1
T2DM	type 2 diabetes mellitus
TAG	triacylglycerol
TC	total cholesterol
TG	triglycerides
TNF	tumour necrotizing factor
TPro	total protein
TyG	index-triglyceride-glucose index
VLDL	very low-density lipoprotein
WC	waist circumference
WHO	world health organization
WL	weight loss
WM	weight maintenance

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1. Introduction

Proteins are well known for their kinetic, catalytic, structural and signalling roles [1,2]. Proteins also play a crucial role in fluid and acid-base balance as well as antibody synthesis [1,2]. Unlike lipids and carbohydrates, proteins contain nitrogen that creates amino groups found in amino acids (essential and non-essential), nucleotides and hormones [1]. Dietary proteins are important nutrients and are classified as animal (meat, fish, poultry, eggs and dairy) and plant proteins (beans, lentils, nuts and soy) [2]. While animal proteins tend to contain a good balance of required amino acids (i.e. complete sources) some plant proteins are low in certain amino acids (i.e. incomplete sources) [1,2].

The cardiovascular (CV) disease (CVD) burden has been shown to be reduced by optimum, well-balanced diet, with more plant proteins in addition to low saturated fatty acids (SFA) and unprocessed animal proteins [3]. According to the World Health Organization (WHO), 17.9 million people die every year from CVD, representing 31% of worldwide deaths [4]. CVD affects several arterial vessels (e.g. coronary and peripheral). Dietary modification has been shown to significantly decrease the risk of coronary heart disease (CHD), by attenuating related risk factors, such as hypertension (HTN), hyperglycemia, elevated low-density lipoprotein cholesterol (LDL-C) level, oxidative stress and inflammation [5,6].

In view of the above-mentioned facts, it has become acceptable to emphasize the role of optimal nutrition to maintain arterial health. There is however considerable debate regarding which diet is optimal for specific patients, especially taking into account any existing risk factors or concomitant disorders [7–9]. Different studies have compared the benefits of omnivorous and vegetarian diets [8–12]. Plant proteins may have a different impact on CVD compared with animal proteins [3]. Epidemiological and interventional studies attempted to evaluate the respective benefits of these two types of proteins, but a strict separate impact is difficult to prove because of the natural mix of dietary proteins people usually consume in addition to the effect of other non-protein compounds on CVD risk factors [3]. Some studies suggested that diets rich in animal protein with low fiber increase CVD risk [3] via their adverse effects on blood lipids and blood pressure (BP), but this effect has not been demonstrated in controlled trials [3,8,10–12]. Furthermore, animal protein related risk has been suggested to be greater with red or processed meat compared with poultry, fish and nuts, which carry a lower risk for CHD. In contrast to these findings, other studies demonstrated no association between red meat and CHD [2,4,10]. Such inconsistent data might be associated with the fact that animal protein might modulate CVD risk factors by different amino acids, with cysteine, glutamate, arginine, taurine and tryptophan having a modifying effect on BP, by reducing weight, increasing glomerular filtration rate (GFR), reducing vascular resistance and other actions [3,8,10–12].

The aim of the present expert opinion recommendation of the International Lipid Expert Panel (ILEP), presented in the form of the Position Paper, is to elucidate the different impact of animal *vs* vegetable protein on cardiometabolic risk factors. We also provide recommendations on the protein content of the optimal healthy diet.

1.1. Comprehensive literature search and clinical evidence of dietary protein in modifying cardiometabolic risk factors

A comprehensive literature search was conducted using the electronic databases: PubMed-Medline, EMBASE, Scopus, Google Scholar, Web of Science by Clarivate, the Cochrane Central Registry of Controlled Trials and ClinicalTrial.gov, up to October 2019, using the following terms: dietary protein OR protein OR animal proteins OR vegetable proteins AND coronary artery disease AND cardiometabolic risk factors AND outcome AND randomized controlled trial (RCT) AND clinical trials AND/OR obesity AND/OR hypertension AND/OR stroke AND/OR diet AND/OR milk/dairy proteins OR nuts OR soy OR red meat OR fish AND/OR insulin resistance. The literature search was limited to studies in humans and articles published in English. Two reviewers (FZB and GB) independently evaluated each article. No filters were applied. Additionally, the abstracts from the most important conferences on the topic were searched.

The level of evidence and the strength of recommendation of different protein diets have been weighed and graded according to predefined scales and are presented in Tables 1 and 2.

Physicians and medical professionals of other specialties treating patients at different CV risk are encouraged to consider the Position Paper in the process of evaluating the clinical status of their patients and to implement lifestyle changes including well-balanced healthy diet with the optimal protein content. However, the Position Paper does not override in any way the individual responsibility of physicians to make appropriate decisions taking into account the condition of a given patient and in consultation with that patient, or, where necessary, with the patient's guardian or caretaker. The authors of the Position Paper are aware that the use of recommendations depends on several judgment calls that take into account values and preferences of patients.

2. Dietary animal proteins *vs* plant proteins

The recommendations for protein intake in USA are based on the Dietary Reference Intakes (DRIs) [13]. The DRIs for protein are presented as the Estimated Average Requirement (EAR) and the Recommended Dietary Allowances (RDAs) [13]. For individuals older than 18 years, the EAR is 0.66 g/kg of body weight and the RDA is 0.8 g/kg of body weight. A 57 kg woman and a 70 kg man are considered as the references for EAR and RDA. The values of EAR 38 g/day and the RDA 46 g/day for women and EAR of 46 g/day and RDA 56 g/day for men are considered as reference values for protein intake. Based on current evidence, an RDA of 1.0–1.2 g of protein/kg of body weight to maintain normal calcium and nitrogen metabolism, and to maintain normal renal function, was considered as normal value in the elderly [13]. On the other hand, in children and pregnant women the DRIs for protein intake/kg of body weight are considered to be higher, because of growth needs in this age. For children aged 1–3 years the RDA is 1.05 g/kg of body weight/day, for those aged 4–13 years it is 0.95 g/kg of body weight/day, and 14–18 years aged children it is 0.85 g/kg of body weight/day [13]. Whereas, for pregnant women of all ages the RDA is 1.1 g/kg of body weight/day [13]. Athletes also have an increased need for daily protein, mainly because of their interest to gain muscle mass and to support higher levels of daily activities. Based on previous studies, it was suggested that protein intake in athletes should be between 1.2 and 1.7 g/kg/day [13].

Smit et al. [14] calculated age and gender specific estimates of protein intake using the National Health and Nutrition Examination Survey (NHANES) 1988–1991 cohort. This study found that in adults, the average daily protein intake was 80 g/day, from which 69% originated from animal food. In addition, the authors found that the energy intake values were 2591 ± 39 kcal for men and 1746 ± 18 kcal for women [14]. The recent data from NHANES 2013–2014 showed that the average of protein consuming per day from the USA inhabitants was 80 g/day: 94 g of protein/day for men, and 67 g of protein/day for women. However, the data from this study could not analyse the breakdown of animal food *vs* plant food protein [15] (Table 3).

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Table 1
Classes of recommendation.

Classes of recommendation	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective	Is recommended/Is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful	Is not recommended

Table 2
Level of evidence.

Level of evidence	Definition
Level A	Data derived from multiple randomized clinical trials or their meta-analysis
Level B	Data derived from single randomized clinical trial or large non-randomized studies
Level C	Consensus or opinion of the experts and/or small studies, retrospectives studies, registries

Table 3
Recommendations for average and dietary allowance for protein.

Class	Level	Estimated average requirement for protein	Dietary allowances for protein	Safety issues
I	**B**	0.60 g/kg/day[a] 0.71–1.0 g/kg/day[b] 1.1–1.4 g/kg/day[c]	0.80 g/kg/day[a] 0.85–1.1 g/kg/day[b] 1.2–1.6 g/kg/day[c]	No safety issues
III	**B**		>2.0 g/kg/day	May accelerate disease progression (e.g. preexisting kidney disease), reduce glycogen levels, and be detrimental for optimal performance.

[a] General healthy adult male and female.
[b] Children and pregnant women.
[c] Endurance athletes.

A protein-rich-diet can limit the consumption of other nutrients (e.g. refined sugars and saturated fat); this should be factored in when assessing the impact of protein intake on CVD risk [3]. In the recent paper prepared by the ILEP an increase of saturated fats and animal proteins consumption was observed in individuals on low carbohydrate diets (carbohydrate level intake <200 g/day) [16]. Many observational studies provided evidence for the health benefit from vegetable proteins, particularly in BP control and achieving optimum lipid profile [17–19]. Having evaluated BP in a Seven Days Adventist population, Armstrong et al. suggested that the lower BP in a vegetarian community might have been related to them being thin, consuming little alcohol and a healthy diet as well as a tendency not to smoke [19]. It should be mentioned that the effects of dietary plant protein are usually not in isolation but integrated with other plant-based-food components, such as magnesium, potassium and fiber [20,21]. The Nurses' Health Study found that replacing 1 standard serving of red meat [3oz (85 g)] with different vegetable protein sources reduced CHD risk by 13–30% [22], similar to the effect of soy food on CHD in women [23].

In male patients with hypercholesterolemia and normal body mass index (BMI), the cholesterol level was decreased by replacement of animal protein with soy protein in their diet [24]. In these patients, 60% of the animal proteins were substituted by soy, after a diet with 25–30% of energy from fats, 10–12% from proteins, and the rest from carbohydrates. In addition to basic blood tests, lipid parameters, anthropometric measurements and endothelial function were evaluated at baseline and 6 weeks after soy protein diet replacement. Endothelial function was assessed by flow-mediated endothelium-dependent dilatation (FMD) and plasma thrombomodulin levels [24]. After using a soy protein intake of 19.9 ± 2.2 g/day during the study period, the plant source protein was greater compared with animal source protein ($p < 0.001$), but the weight, waist-hip ratio (WHR) and skin fold thickness of the subjects were not changed by the soy protein diet. On the other hand, BMI decreased significantly (25.3 ± 1.3 *vs* 25.1 ± 1.3 kg/m^2, $p = 0.03$). Plasma total cholesterol (TC), LDL-C and triglycerides (TG) levels were also significantly decreased (by 15%, 20% and 14%, respectively) whereas high-density lipoprotein cholesterol (HDL-C), apolipoprotein (Apo) A1 and lipoprotein (a) (Lp(a)) levels did not change after the soy protein diet [24]. Leslie et al., in a randomized study, assessed the effect of plant-based diet (PBD) using specific dietary advice on vascular function in peripheral artery disease (PAD) patients [25]. In addition to the lipid profile, C-reactive protein (CRP), nitric oxide (NO), superoxide dismutase (SOD), vascular function assessment by brachial artery FMD, carotid intima-media thickness (cIMT), carotid-femoral pulse wave velocity (PWV), and brachial-ankle PWV were measured. After 4 months on PBD, TC and LDL-C were decreased by 7.6% and 13.6%, respectively ($p = 0.01$), NO level increased from 7.7 ± 5.3 μmol/L at baseline to 18.7 ± 13.7 μmol/L after 4 months PBD ($p < 0.01$), whereas there were no such changes in the control group. After 4 months, FMD was significantly improved in the PBD group compared with the control group (8.7 ± 5.6 *vs* 5.1 ± 0.5%; $p = 0.03$); moreover, the ankle-brachial index was also significantly improved by 7.6% [25].

Van Bussel et al. studied dietary intake by food-frequency questionnaire (FFQ) and measured plasma biomarkers of endothelial dysfunction in 557 participants (aged 59.6 ± 6.9 years) at increased CVD risk from the CODAM (Cohort on Diabetes and Atherosclerosis Maastricht) study, who were followed-up for 7

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years [26]. A higher consumption of fish (per 100 g/week) was associated with a lower endothelial dysfunction score (β: −0.027; 95% confidence interval [CI]): (−0.051, −0.004), whereas consumption of vegetables, fruit, dairy products, alcohol-containing beverages, or meat, were not related with endothelial dysfunction over 7 years follow-up. These results showed that consumption of more lean fish (per 100 g/week), more raw vegetables (per 100 g/d), and fewer high-fat dairy products (per 100 g/day) were associated with lower level of endothelial dysfunction [(β: −0.038; 95% CI: −0.072, −0.005), (β: −0.095; 95% CI: −0.191, 0.000), and (β: −0.070; 95% CI: −0.131, −0.009), respectively]. On the other hand, consumption of more fresh fruit (per 100 g/day), wine (per 100 mL/week) and poultry (per 100 g/day), and fewer high-fat dairy products (per 100 g/day) were associated with much lower grade of inflammation [(β: −0.074; 95% CI: −0.133, −0.015), (β:−0.006; 95% CI: −0.013, 0.001), (β:−0.247; 95% CI: −0.479, −0.014), and (β:−0.100; 95% CI: −0.182, −0.019), respectively [26].

Most of the available studies have also correlated red meat intake with increased CV risk and mortality. In a study [22] which included >80,000 women, red meat intake was related to an increased CHD risk, but the impact was different with nuts, poultry, fish and milk protein intake, which lowered the CHD risk in the same subjects. The consumption of nuts (1 serving/day) lowered by 30% the risk of CHD compared with consumption of red meat (1 serving/day). Consumption of low-fat dairy was associated with 13%, poultry with 19% and fish with 24% lower risk of CHD compared with consumption of red meat (1 serving/day for all) [22]. Similar results were reported by Preis et al. who concluded that high animal protein intake correlated with increased CHD risk in men [27]. In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, only processed meat increased the risk for CVD and all-cause mortality but not red meat or poultry [28]. These findings were also reproduced by Micha et al. [29]. The likely explanation for the worse effect of processed meat is the 400% more sodium and 50% more nitrates they contain compared with unprocessed meat [30]. It was shown in an experimental study that nitrates and their products (e.g. peroxynitrite) promote vascular dysfunction and atherosclerosis, impair glucose tolerance and reduce insulin secretion, while streptozocin (a nitrosamine-related compound), has diabetogenic effect [31]. A nitrite concentration has been showed to be associated with endothelial dysfunction and impaired insulin response in adults and was used as a biomarker of these impairments [32]. On the other hand, salt intake is positively correlated with BP (through its water retention mechanism) and is a predictor of left ventricular (LV) mass, which is an important risk factor for premature CVD [33]. This is the reason for considering preservatives and sodium content of processed meat as having the strongest link with CHD risk [22,30–33] (Figs. 1–4, Table 4, Suppl. Table 1).

3. Dietary protein intake and obesity

Proteins may prevent weight gain and may also have beneficial effect on weight maintenance, mainly by increasing the thermogenesis and satiety [34]. The total protein and protein from animal sources had positive correlation with subsequent body weight change in the general population, and this correlation was stronger in women than in men [34]. In contrast, plant protein did not show any correlation with weight changes. The EPIC study [34], which included 89,432 subjects followed up for 6.5 years, showed that higher intake of total protein and protein from animal sources correlated with subsequent weight gain, particularly in women. Those women who had 150 kcal higher daily intake had a yearly weight increase of 78 g (95%CI: 35–120) and 82 g (95%CI: 41–124) for total and animal protein, respectively. In contrast, the yearly weight increase was much lower for men compared with women - 29 g (95%CI:1–59) and 30 g (95%CI:8–68), respectively. The diet with protein sourced from red and processed meat, as well as poultry were associated with increased weight, whereas the protein from fish and dairy sources did not correlate with any weight changes. No significant association of plant protein and protein from unknown origin consumption with weight changes was also observed [34].

In another study participants consumed 500–1000 calories less from the usual daily amount, but with a minimum daily amount of 1000 kcal. Based on the proportion of protein consumption, participants were divided into 2 groups: (1) the high protein (HP) group (22–30% protein, 50–55% carbohydrate and 20–25% fat), and, (2) standard protein (SP) group (12–20% protein, 55–60% carbohydrates and 20–30% fats). The waist circumference (WC) was significantly decreased, from 96.13 ± 8.19 to 90.09 ± 8.62 cm ($p < 0.001$), after 8 weeks of protein-rich low-calorie diet intervention [35]. This study showed that the specific dietary intervention reduce visceral fat and it is recommended as a possible treatment or prevention of visceral obesity [35].

The HELENA (Healthy Lifestyle in Europe by Nutrition in Adolescence) RCT study [36] was undertaken to assess the role of plant protein intake in preventing obesity among adolescents in European countries. Mean total protein intake among subjects was 96 g/day, from which 59% derived from animal protein. Female participants consumed less total, animal and plant protein male, and the consumption of these proteins was lower in younger participants (between 12.5 and 14.9 years of age). Females consumed 50 g/day animal proteins, compared with 33 g/day plant proteins, whereas males consumed 66 g/day animal proteins and 43 g/day plant proteins [36]. Underweight subjects consumed less protein than obese participants. The plant protein intakes had stronger inverse association with BMI z-score and body fat percentage (BF%) compared with animal protein intakes. Animal protein intake had inverse association with TC, TG, VLDL-C and leptin, whereas there was a positive association with serum fasting glucose. On the other hand, absolute plant protein intake had inverse association with TC, HDL-C, and leptin, but positive association with serum fasting glucose. After adjustments for fat intake, animal protein intake had a positive association with BMI z-score [36]. Based on these results, the authors suggested that extra high protein intake may cause imbalance in energy intake and food consumption. These findings indicate that despite weak positive association of HDL-C with absolute animal protein intake, plant protein had stronger protective effect against obesity compared with animal protein. It was considered that these results were influenced by the facts that participants of this study exceeded protein intake based on WHO requirement, and almost 2/3 of them consumed protein sources were from animal origin rather than from plants, which could influence to the body weight and body composition [36].

A parallel-design, RCT showed that after a 12-week eucaloric high protein (HP) diet with 3 whole eggs/day (equivalent of 1.4 g protein/kg/day), changes in muscle composition, and cardiometabolic health were minimal *vs standard* protein (SP) diet void of eggs (0.8 g protein/kg/day). The subcutaneous fat to muscle volume ratio was decreased over time in participants with HP diet but not in those with SP diet ($p = 0.031$) [37]. After 12-week dietary intervention, both body weight (−3.00 ± 2.43 kg, $p = 0.022$, partial

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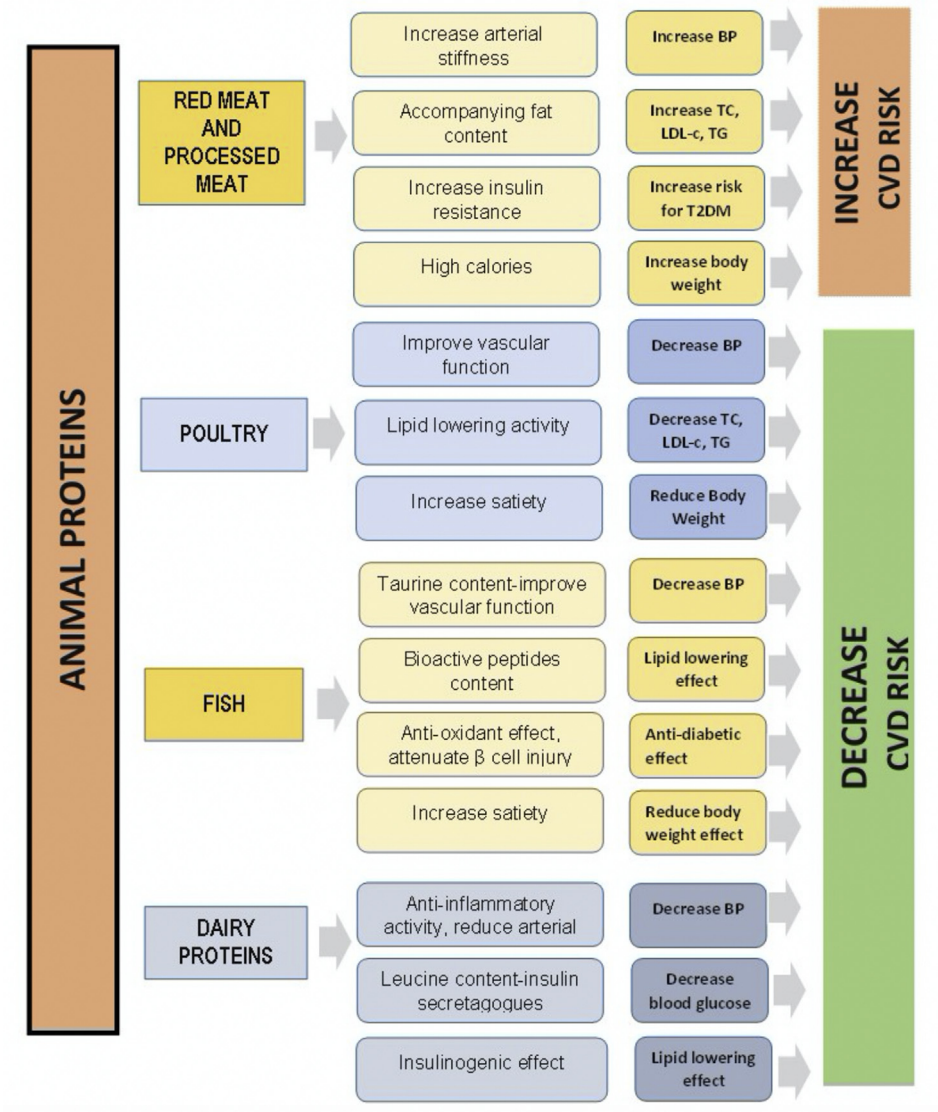

Fig. 1. The effect of animal proteins on CVD risk factors and their possible mechanisms. *CVD, cardiovascular disease; BP, blood pressure; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; T2DM, Type 2 Diabetes Mellitus.*

$r^2 = 0.246$) and body fat (-2.25 ± 1.67 kg, $p = 0.011$, partial $r^2 = 0.266$) were reduced in both HP and SP diet groups [36]. On the other hand, LDL-C concentration ($p = 0.015$, partial $r^2 = 0.274$) and hip circumference ($p = 0.003$, partial $r^2 = 0.450$) were decreased only after dietary intervention with the SP diet. Moreover, fasting glucose, insulin concentrations and other cardiometabolic markers were not influenced by these diets [37].

In the study by Campbell et al. [38], in middle-aged overweight and obese adults, who were on a 36 weeks resistance and aerobic exercise intervention, an inverse association of total protein intake (TPro) and change in total protein intake (CTPro) with body mass, fat mass (FM) and BMI changes was registered. The authors observed an inverse association of TPro and CTPro with changes in body mass, FM and BMI in this study. Changes in body composition were different ($p < 0.05$) among study groups that consumed protein <1.0 g/kg/day (n = 43) vs ≥ 1.0 to <1.2 g/kg/day (n = 29) vs ≥ 1.2 g/kg/day (n = 45). After a 36-week exercise training intervention, the participants of TPro study group with ≥1.0 to <1.2 g/kg/day reduced FM and %FM increased percentage of lean mass (%LM) compared with the lowest TPro, whereas the TPro group with ≥1.2 g/kg/day had intermediate responses on changes in FM, %FM and %LM [38]. However, the gain in LM did not differ between study groups. In addition, there was no relation observed of TPro and CTPro with metabolic syndrome (MetS) indexes [38].

In the study by Tang et al. [39], men who aimed weight maintenance reducing their daily energy needs for 750 kcal/day with either SP (0.8 g protein/kg/day) or HP (1.4 g protein/kg/day) for 12 weeks, lost more lean body mass compared with men that consumed either standard or high protein content. The weight reduction in SP group was -10.6 ± 0.6 kg, whereas in HP group was -9.1 ± 0.7 kg. However, both diet groups had not significant differences regarding body weight and fat, TC, HDL-C, TG, glucose, insulin, LDL-C and TC-to-HDL-C ratio. This study also showed that energy restriction in general effectively improves several clinical CV health indicators, improves glucose control, but these improvements were not different between SP and HP groups [39].

The findings of the Belgian National Food Consumption Survey suggest that in a Belgian population, fresh meat, cheese and milk products are the most important contributors to animal protein intakes [40]. In the participants of the study from 72 g/day of total

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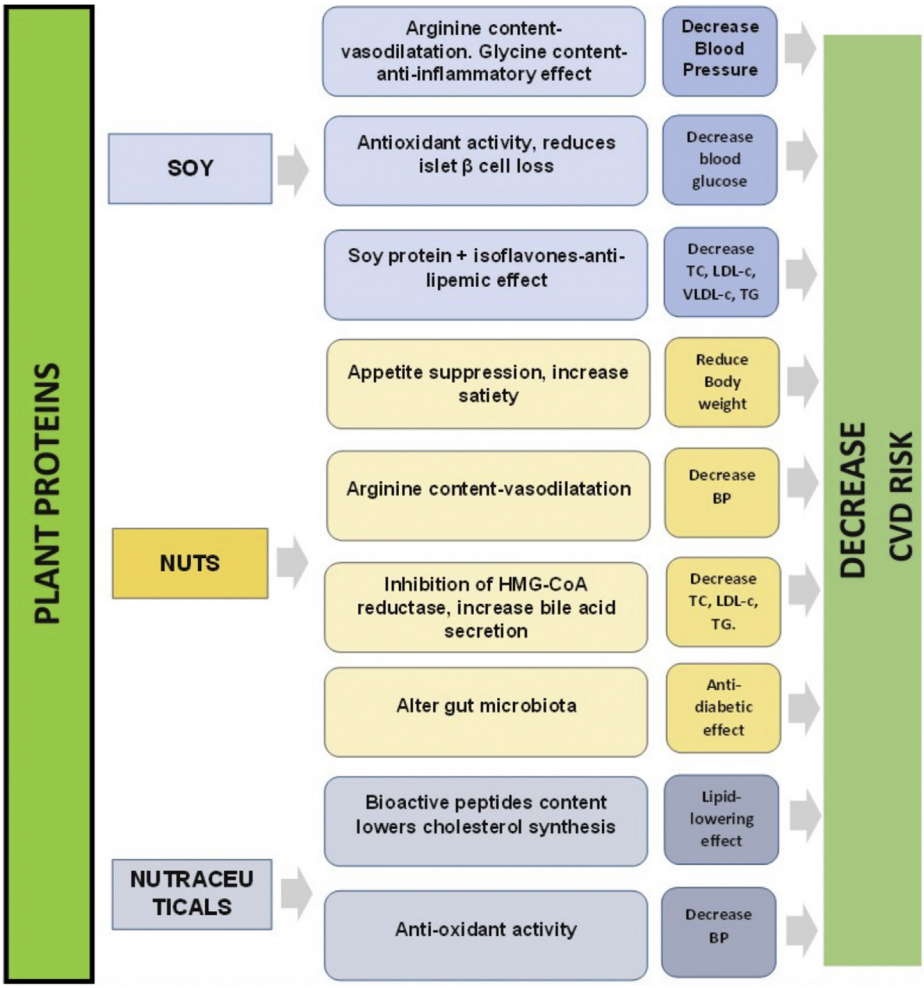

Fig. 2. The effect of plant proteins on CVD risk factors and their possible mechanism. *CVD, cardiovascular disease; BP, blood pressure; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; T2DM, Type 2 Diabetes Mellitus; VLDL-C, very-low density lipoprotein cholesterol; HMGCoA, 3-hydroxy-3-methylglutaryl coenzyme A.*

protein intakes, 47 g/day were from animal protein source whereas 25 g/day from plant protein source. Total animal protein intakes were mainly from meat and meat products (53%), whereas plant protein intakes were from cereals and cereal products (54%). Females had lower animal and plant protein intakes compared with males ($p < 0.001$). Legume and soya protein intakes were low in the whole population (0.101 and 0.174 g/day, respectively). Animal protein intake had positive correlation with BMI ($\beta = 0.013$; $p = 0.001$) and WC ($\beta = 0.041$; $p = 0.002$) in male participants of this study. In contrast, in participants of both genders, plant protein intake was inversely associated with BMI (males: $\beta = -0.036$; $p < 0.001$; females: $\beta = -0.046$; $p = 0.001$) and WC (males: $\beta = -0.137$; $p < 0.001$; females: $\beta = -0.096$; $p = 0.024$). Based on these findings, plant proteins could have important protective effect in general population in the prevention of overweight and obesity [40].

Another study compared the effect of different diets (low-fat, high carbohydrate [HC] and low-fat, high protein [HP] *ad libitum* diets) on metabolic and CV risk factors in healthy obese subjects. In addition, this study assessed the effect of these diets on weight maintenance (WM) after weight loss (WL) induced by a very low-calorie diet [41]. In the overweight and obese postmenopausal women, the diet compound with low-fat, HP or HC did not reduce BP, arterial stiffness or inflammatory markers during the 6 h postprandially follow-up period, compared with the normal protein diet. During the WM period, participants received dietary counselling from a dietician, maintaining the fat intake of approximately 30% of total energy intake in all groups. In HC study group, the participants had carbohydrate intake of at least 55% of total energy intake, whereas the protein intake of at least 25% of energy intake was in both HP groups. The participants of HC group consumed also maltodextrin supplements twice a day (50 g/day), whereas the HP group consumed intact casein or whey supplements twice a day (50 g/day). The WM (2.3 kg difference, $p = 0.04$) and fat mass reduction (2.2 kg difference, $p = 0.02$) were significantly better in HP diet group compared with the HC group, after their weight loss. TG and glucagon concentrations were increased more in the HC diet group (0.6 mmol/L difference, $p = 0.01$ and 9.6 pg/ml difference, $p = 0.02$, respectively), while glucose concentration was increased more in the HP diet group (0.3 mmol/L difference, $p = 0.02$) [41]. The authors concluded that low-fat, high-casein or whey protein diets are more effective for WM after WL compared with low-fat, HC diets and these diets do not adversely affect metabolic and CV risk factors [41]. However, it is very difficult finally to answer the question which component finally influenced the weight in a causative way [41].

The postprandial effects of whey protein isolate on BP, vascular function and inflammatory markers in overweight and obese

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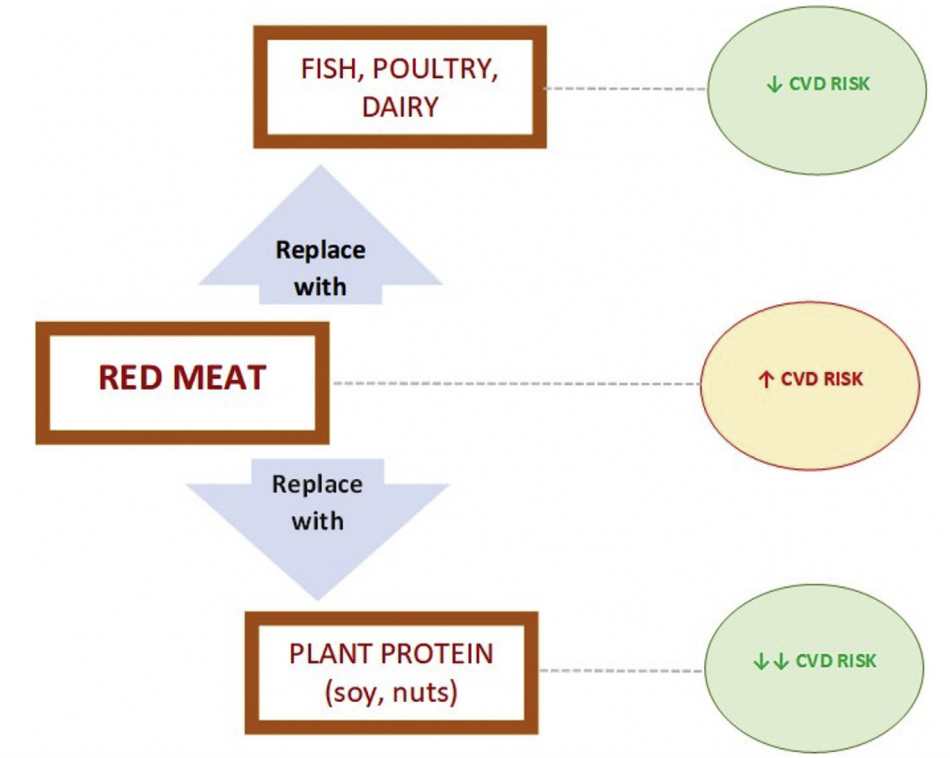

Fig. 3. Meal replacement and its effect on cardiovascular disease (CVD) risk.

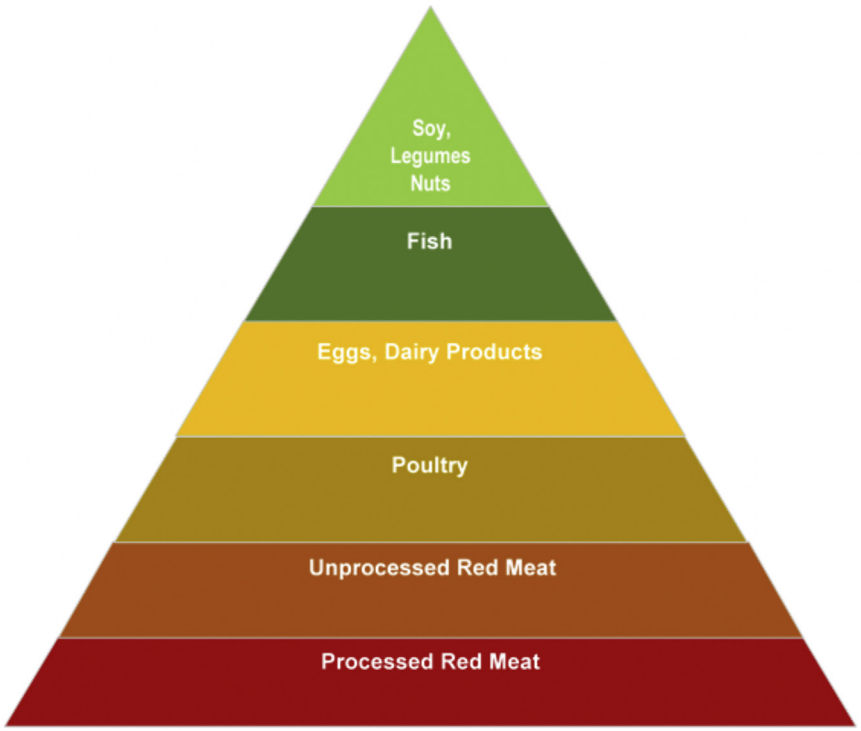

Fig. 4. Protein source pyramid.

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Table 4
Recommendations for dietary animal protein vs. plants protein.

Class	Level	Daily dose of types of proteins	Effect on CV risk	Cardiovascular effects
I	**B**	>50% plant protein/day of total protein intake	↓ BP, insulin resistance, weight, CV risk	↓ diastolic dysfunction
I	**B**	Reduction of red meat (≤100 kcal/day and ≤3 servings/week)	↓ BP, insulin resistance, obesity, CHD, CV risk	↓ diastolic dysfunction, ↑sICAM-1, sVCAM-1

Abbreviations: CV, cardiovascular; BP, blood pressure, CHD, coronary heart disease, sICAM-soluble intercellular adhesion molecule 1; sVCAM-soluble vascular adhesion molecule 1.

postmenopausal women were investigated by Pal et al. [42]. The women included in the study consumed a breakfast, which included 1 of 3 supplements: 45 g whey protein isolate, 45 g sodium caseinate or 45 g of a glucose control. It was shown that both systolic and diastolic BP, and augmentation index (AIx) were decreased initially after consumption of the meal, irrespective of the supplement they receive, but these measurements gradually returned to baseline levels after 6 h. Moreover, there were no significant differences in the above measurements between the study groups. These findings suggest that the effects will be better observed from the long-term whey proteins consumption studies [42]. In contrast, in another RCT the authors demonstrated that different heart-healthy weight-loss dietary patterns with the animal and plant protein improved MetS indicators in a similar way [43]. This study investigated the effects of 3 different diets with different amounts of protein from plant and animal sources on MetS indicators: (1) a modified-DASH (M-DASH) diet rich in plant protein (18% protein, two-thirds plant sources), (2) M-DASH diet rich in animal protein [Beef in an Optimal Lean Diet (BOLD): 18.4% protein, two-thirds animal sources], and, (3) a moderate-protein diet [Beef in an Optimal Lean Diet Plus Protein (BOLD+): 27% protein, two-thirds animal sources]. These diets were compared at 3 phases of energy balance: (1) controlled WM, (2) controlled WL with an exercise component, and (3) prescribed free-living (FL) weight loss. All groups achieved about 5% weight loss and all study groups MetS indices were improved irrespective of diet composition. MetS criteria were decreased after the WL phase [Healthy American Diet (HAD) compared with WL, $p < 0.01$], and these changes were maintained during the FL phase [Healthy American Diet (HAD) compared with FL, $p < 0.01$]. In all study groups the prevalence of MetS was 100% at the beginning of screening, but dropped to 70% in the BOLD group, to 81% in the BOLD + group and to 90% M-DASH group after the HAD phase. After the WM phase, the participants had a prevalence of MetS 80–90% [HAD *vs* WM, p = NS], which was decreased to 50–60% by WL and was maintained through FL (HAD, WM *vs* WL, FL, $p < 0.01$) [43].

A Chinese study showed that the replacement of standard-protein diets (SP, 1.1 g protein/kg/day) with high-protein diets (HP, 2.2 g protein/kg/day) in obese individuals with hyperlipidemia (TG > 1.7 and < 5.4 mmol/L) that were not under cholesterol-lowering drug treatment did not affect WL and BMI reduction, whereas the waist-hip ratio was decreased significantly in subjects under HP diet compared with those with SP diet (-0.03 ± 0.03 *vs* -0.01 ± 0.04; $p < 0.05$) [44]. TGs decreased from baseline in both groups, but this decrease did not differ between groups. This study demonstrated that in patients with hyperlipidemia, a protein-enriched meal replacement (MR) diet significantly reduce WC compared with a standard protein diet [44] (Figs. 1–4, Table 5, Suppl. Table 1).

4. Dietary protein intake and lipid disorders

Based on the current guidelines, the modification of CV risk factors in general, and dyslipidemia particularly, by diet and lifestyle is the basis of treatment [3,5]. Therefore, plant-based diets for CVD prevention have attracted considerable interest. However, the effect of plant protein and the specific substitution for animal protein on blood lipids and prevention of CV disorders still remains unclear, despite the opinion that this protein mediate the prevention of dyslipidemia [45–47].

In a 12-week follow-up RCT, overweight women underwent a hypocaloric diet [calculated-deficit diets (−500 kcal/day)]. These women were randomized to a beef-consumption or chicken-consumption dietary group, in addition to a regular fitness walking program. In both study groups the WL was significant from baseline to the end of the study ($p < 0.05$, for both), but did not differ between groups (5.6 ± 0.6 kg, in the beef-consumption group and 6.0 ± 0.5 kg in the chicken-consumption group) [48]. Body fat percentage, TC and LDL-C was reduced significantly ($p < 0.05$ for all), in both groups, with no significant differences between groups. On the other hand, HDL-C did not change significantly in both groups. Therefore, a high protein diet and exercise affect WL and improve the lipid profile, irrespective of animal protein source [48].

A systematic review and meta-analysis of RCTs performed by the Nutrition Committee of the American Heart Association (AHA), assessed the effect of animal protein substitution with plant protein on LDL-C, non-HDL-C and ApoB [49]. The pooled data from 112 RCTs (randomized, long-term, dietary intervention trials), showed that

Table 5
Recommendations for dietary intake and obesity.

Class	Level	Daily doses of dietary proteins	The effect on obesity	Direct (cardio)vascular effect
I	**A**	Plant proteins 25–43 g/day	↓BMI, ↓Body weight, ↓Waist circumference	Not demonstrated
III	**A**	Animal proteins ≥42 g/day	↑BMI, ↑Body weight, ↑Waist circumference	Not demonstrated
I	**A**	Standard protein diet (preferably plant-based) 0.8 g/kg/day	↓WC 6.78–8 cm ↓Body weight ↓Body fat %	Not demonstrated
IIb	**B**	High protein diet (preferably plant-based) 1.4 g/kg/day[a]	↓ WC 3–5.22 cm ↓Body weight ↓Body fat %	Not demonstrated

Abbreviations: BMI, body mass index, WC, waist circumference.
[a] It is not recommended for subjects with kidney diseases.

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substitution of animal protein with plant protein decreased LDL-C by 0.16 mmol/L (6.2 mg/dl; $p < 0.00001$; $I^2 = 55\%$), non-HDL-C by 0.18 mmol/L (7 mg/dl; 95%CI, −0.22 to −0.14 mmol/L; $p < 0.00001$; $I^2 = 52\%$), and ApoB by 0.05 g/L (95%CI, −0.06 to −0.03 g/L; $p < 0.00001$; $I^2 = 30\%$) [49].

Data from epidemiological studies suggest that soy consumption may reduce the incidence of certain chronic diseases [5,50,51]. Furthermore, some clinical studies showed that ingestion of soy proteins might reduce the CVD risk [5,50,51]. It was demonstrated that soybeans contain other additional components, such as isoflavones, lecithins, saponins and fiber, which may improve CV health and reduce CV risk factors through independent mechanisms [5,50,51]. These data were a reason that in 1999 U.S. Food and Drug Administration (FDA) approved the food-labelling health claim for soy proteins in the prevention of CHD [50,51]. Similarly, in the United Kingdom, Brazil, South Africa, the Philippines, Indonesia, Korea and Malaysia, the use of the soy proteins for the same indications was also been approved thereafter. However, in different studies the health benefits are variable and still inconsistent [5,50,51].

The effect of soy protein on the lowering of cholesterol level in a human study was reported for the first time in 1967, and demonstrated that in men with hypercholesterolemia, the replacement of mixed proteins mainly by isolated soy protein products at an intake of 100 g/day reduced TC level by 2.59 mmol/L (100 mg/dl) [52]. A meta-analysis of 30 studies published later suggested that the mean intake of isolated or textured soy protein of 47 g/day (ranging from 17 to 124 g/day) of isolated or textured soy protein resulted in significant reduced TC by 9.3%, LDL-C by 12.9%, and TG by 10.5%, compared with animal protein intake. Based on this data the FDA approved a food-labelling health claim for soy protein in the prevention of CHD [53]. In addition, the AHA has acknowledged the data regarding the efficacy of soy protein in CVD risk factors reduction as still limited and insufficient [51]. In a study that randomly compared diets with milk protein (Milk), isoflavone-poor soy (Soy-), or isoflavone-rich soy (Soy+), it was demonstrated that the soy-consumption increases the postprandial triacylglycerol (TAG), suggesting that the absence of isoflavones in soy protein may have adverse effects on cardiometabolic risk factors [51]. The usual diets in these study participants were supplemented for 28 days with 25 g/day of protein. In addition to baseline measurements of TAG and other cardiometabolic parameters, they were additionally measured after supplementation in a fasted state and postprandially at 30, 60, 120, 240, and 360 min after a high fat 1000 kcal shake. Postprandial TAG increased after Soy-consumption in participants, suggesting that the postprandial state is a more sensitive indicator of soy ingestion effects on CVD risk factors compared with the fasting lipid profile [51].

The Nutrition Committee of AHA published the pooled data from 22 RCT that analyzed dietary effects of isolated soy protein in comparison with casein protein, wheat protein and mixed animal proteins [54]. The range of soy protein used in these RCTs was from 25 to 135 g/day, whereas the range of isoflavones was from 40 to 318 mg/day. The meta-analysis showed that LDL-C or non-HDL-C concentrations were significantly decreased by soy protein intake [54]. In a study that included 60 postmenopausal hypertensive women, who were followed for 8 weeks, daily supplementation of 25 g of soy protein and 101 mg of aglycone isoflavones reduced LDL-C and ApoB levels by 11% and 8%, respectively, and reduced systolic and diastolic BP by 9.9% and 6.8%, respectively [55].

For the initial treatment of hypercholesterolemia, the National Cholesterol Educational Program (NCEP) step I diet is usually recommended, which consist in the restriction of fat and cholesterol intake [56]. In a randomized crossover study, normocholesterolemic and hypercholesterolemic men consumed either NCEP step I soy protein diet or an NCEP step I animal protein diet for 5 weeks, to evaluate the possible hypocholesterolemic effect of the soy protein. Regardless of plasma lipid status, the soy-protein diet significantly decreased plasma concentrations of LDL-C for approximately 6% ($p = 0.029$) and plasma LDL-C to HDL-C ratio by 11% ($p = 0.005$). This study concluded that the NCEP step I soy protein diet enhances the hypocholesterolemic effect in both normocholesterolemic and hypercholesterolemic men [56].

Whether intact of milk proteins lowers 24 h ambulatory BP and other risk factors of CVD was investigated in a double-blinded, randomized, 3 way-crossover intervention study [57]. Participants randomly consumed 28 g whey protein 2 times/day, 28 g calcium-caseinate, or 27 g maltodextrin (as a control group) for 8 weeks with a 4-week washout period. Besides significant reductions in SBP and DBP, as well as the peripheral, central systolic, and mean pressures after whey-protein supplementation compared with controls, the authors also noted significant changes in lipids. Both whey-protein and calcium-caseinate intakes increased FMD (1.31%; $p < 0.001$, and 0.83%; $p = 0.003$, respectively), lowered TC [−0.26 mmol/L ($p = 0.013$) and −0.20 mmol/L ($p = 0.042$), respectively], but only whey protein decreased TG (−0.23 mmol/L; $p = 0.025$) compared with controls. The soluble intercellular adhesion molecule 1 and soluble vascular cell adhesion molecule 1 were also reduced by both whey protein and calcium-caseinate consumption ($p = 0.011$ and $p = 0.039$, respectively) compared with controls. In conclusion, unhydrolyzed milk proteins consumption (56 g/d) for 8 week improved vascular reactivity, endothelial function and lipid risk factors, whereas whey-protein supplementation lowered both systolic and diastolic BP [57].

A crossover RCT [58] studied the effect of diet with increased protein intake (HP), at the expense of carbohydrates, in healthy humans consuming a high fat, hypercaloric diet. The effect of this diet was observed on intrahepatic lipids (IHLs), circulating TGs, and it was indicated that HP, high fat, hypercaloric diet significantly affects lipid metabolism. After a 2-week run-in period, participants were randomized to: (1) the control diet [(27.8 energy % [en%] fat, 16.9 en% protein, 55.3 en% carbohydrates)] for 4 weeks, or, (2) the high-fat, hypercaloric diet (>2 MJ/day). The crossover trial was designed with 2 periods of 2 weeks, with either HP (37.7 en% fat, 25.7 en% protein, 36.6 en% carbohydrates) or SP (39.4 en% fat, 15.4 en% protein, 45.2 en% carbohydrates) diets. A trend toward lower intrahepatic lipids (IHL) and plasma TG concentrations during the HP condition compared with the SP condition was observed (IHL: 0.35 ± 0.04 *vs* 0.51 ± 0.08%, $p = 0.08$; TG: 0.65 ± 0.03 *vs* 0.77 ± 0.05 mmol/L, $p = 0.07$, for HP and SP, respectively). On the HP diet the fat mass was lower (10.6 ± 1.72 *vs* 10.9 ± 1.73 kg; $p = 0.02$), whereas fat-free mass was higher (55.7 ± 2.79 *vs* 55.2 ± 2.80 kg; $p = 0.003$), compared with the SP diet. This study found that a HP, high fat, and hypercaloric diets affect the lipid metabolism. This diet lowers fat mass and increases fat-free mass and tends to lower the IHL and circulating TG concentrations compared with an SP, high fat, hypercaloric diet [58].

In a RCT, healthy overweight women, in addition to the regular aerobic clubs exercise, received a HP diet during an 8-week investigation (45% of energy from carbohydrates, 25% from proteins, and 30% fat) or balanced diets (BDs; carbohydrates 55%, proteins 15%, and fat 30%). It was shown that in these overweight and obese women with regular aerobic exercise lipid profiles and hsCRP levels were improved after administration of both HP and BD, irrespective of the type of diet. Concentrations of LDL-C ($p < 0.001$ in the BD group *vs* $p = 0.023$ in the HP group) and HDL-C ($p < 0.001$ in BD group *vs* $p = 0.002$ in the HP group) were improved significantly in both groups. Circulating TGs levels improved in both interventions groups, but the change in the HP group was not significant ($p = 0.007$ in BD group *vs* $p = 0.099$ in the

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HP group), whereas TC concentration decreased, however without significant differences ($p = 0.53$ in BD group *vs* $p = 0.73$ in the HP group). There were marginally significant decreases in the hsCRP levels due to both diets ($p = 0.057$ in the BD group *vs* $p = 0.086$ in the HP group) [59].

In a randomized crossover study [60], the effects of diets high in vegetable protein (specifically, wheat gluten) on lipids, uric acid and renal function was investigated. In subjects with HP diet, 11% of the total dietary energy from starch in the control bread was replaced by vegetable protein (wheat gluten). The diets differ between groups only regarding the percentage of protein within total energy; 27% in HP group compared to 16% in the control group. The HP diet resulted in lower triacylglycerol, uric acid and creatinine concentrations compared with controls (by 19.2 ± 5.6%; $p = 0.003$, by 12.7 ± 2.0%; $p < 0.001$ and by 2.5 ± 1.1%; $p = 0.035$, respectively), whereas urea and 24-h urinary urea output had higher concentrations (by 42.2 ± 5.8%; $p < 0.001$ and by 99.2 ± 17.2%; $p < 0.001$, respectively). TC, HDL-C and the renal clearance of creatinine did not differ significantly between groups [60].

In a 12-weeks RCT diet intervention study, the effect of dietary supplementation with whey protein and medium chained SFA (MC-SFA) on postprandial lipid metabolism in subjects with abdominal obesity was investigated [61]. The diet contained 60 g milk protein (whey or casein) and 63 g milk fat, with high or low MC-SFA content daily. It was found that the postprandial ApoB-48 (as a specific marker for chylomicrons of intestinal origin) response decreased significantly after whey consumption by 4310 mg/L (95%CI: 559–8060) compared with casein consumption ($p = 0.025$) independently of fatty acid composition. Furthermore, supplementation with casein increased postprandial glucagon-like peptide 1 (GLP-1) response compared with supplementation with whey ($p = 0.003$). However, no interactions of milk protein and milk fat with postprandial lipidemia were observed. The authors concluded that in subjects with abdominal obesity, a whey protein supplement decreases the postprandial chylomicron response compared with casein supplementation, thereby indicating that whey protein may have a beneficial impact on CVD risk [61].

An interest in the effect of nutraceuticals on improvement and optimization of dyslipidemia control and treatment was introduced in recent years [62]. It was shown that some nutraceuticals have lipid-lowering properties and possible positive effects on non-lipid CV risk factors, improving markers of vascular dysfunction (e.g. endothelial function and pulse wave velocity). The lipid-lowering activity in hypercholesterolemic patients of plant proteins (lupin protein or pea protein) associated with soluble fibers (oat fiber or apple pectin), who received these nutraceuticals for primary prevention of CVD, was confirmed: TC were decreased in all groups, particularly in patients that had diet with lupin protein + cellulose (−0.3 mmol/l (11.6 mg/dl), −4.2%), casein + apple pectin (−0.39 mmol/l (15 mg/dl), −5.3%), pea protein + oat fiber (−0.35 mmol/l (13.5 mg/dl), −4.7%) and pea protein + apple pectin (−0.43 mmol/l (16.6 mg/dl), −6.4%) ($p < 0.05$). Moreover, LDL-C was significantly reduced in subjects that had diet with pea protein + apple pectin combinations (−0.27 mmol/l (10.4 mg/dl), 9.2%) ($p < 0.004$ *vs* controls) [62,63] (Figs. 1–4, Table 6, Suppl. Table 1).

5. Dietary protein intake and hypertension

Hypertension remains the leading cause of morbidity and mortality worldwide [1], being a key risk factor of heart disease, stroke and kidney failure [1,4]. Genetic and lifestyle factors have important roles in the development of hypertension. It is known that reducing carbohydrates and salt intake can help to lower BP, but also adequate protein intake may attenuate hypertension [1]. A significant inverse association between protein intake and BP, was documented in several RCTs and observational studies [1,64–66]. Moreover, some animal and human studies have shown that some amino acids may have antihypertensive effects. It was shown that glutamate, cysteine, glutathione and arginine may attenuate and prevent alterations that cause hypertension, including increased insulin resistance, increased oxidative stress, decreased NO bioavailability, and altered renin angiotensin system function [1,11,12]. While, leucine enhanced protein synthesis in skeletal muscle and improved insulin resistance, taurine and tryptophan attenuated the activity of sympathetic nervous system, whereas soy protein lowered BP through its high arginine content and antioxidant activity by isoflavones [1,11,12].

A diet containing an ample amount of protein per day may be beneficial for individuals with hypertension, serving as a part of lifestyle changes in these patients. The Dietary Approaches to Stop Hypertension (DASH) diet, includes high amount of vegetables, fruits, whole cereal products and low-fat dairy products; low in salt and saturated fat; moderately high in protein; and includes whole grains, poultry, fish and nuts [64]. This diet lowered BP more than typical North American diet [54], even after modifications made to have both diets lower and similar sodium contents in DASH study [64].

The Optimal Macronutrient Intake Trial to Prevent Heart Disease (OmniHeart) trial studied 3 diet patterns that differed in macronutrient composition: (1) the diet rich in carbohydrates (58% carbohydrate, 15% protein, and 27% fat), (2) HP diet (48% carbohydrate, 25% protein, and 27% fat), and (3) the diet with higher unsaturated fat (48% carbohydrate, 15% protein, and 37% fat) [65]. The results of this trial showed that among those with hypertension, the protein diet decreased mean SBP by 3.5 mmHg ($p = 0.006$), LDL-C by 3.3 mg/dl (0.09 mmol/L; $p = 0.01$), HDL-C by 1.3 mg/dl (0.03 mmol/L; $p = 0.02$) and TGs by 15.7 mg/dl (0.18 mmol/L; $p < 0.001$), compared with the carbohydrate diet. On the other hand, the unsaturated fat diet among those with hypertension decreased SBP by 2.9 mmHg ($p = 0.02$), increased HDL-C by 1.1 mg/dl (0.03 mmol/L; $p = 0.03$) and lowered TGs by 9.6 mg/dl (0.11 mmol/L; $p = 0.02$), compared with the carbohydrate diet. This diet had no significant effect on LDL-C. Moreover, compared with the carbohydrate diet, the estimated 10-year CHD risk was lower and similar on the protein and unsaturated fat diets [65]. The results from most relevant studies that investigated the effect of dietary protein on BP, including the OmniHeart [65], International Study of Salt and Blood Pressure (INTERSALT) [60] and DASH studies [64] demonstrated an inverse relationship between dietary protein and BP. The nonessential amino acid cysteine, as a component of dietary protein, was introduced as in important amino acid for its antihypertensive effects. Studies have shown that N-acetylcysteine, a stable cysteine

Table 6
Recommendations for dietary protein intake and lipid disorders.

Class	Level	Plant protein	Effects on LDL-C	Effects on non-HDL-C	Effects on Apo-B	Direct vascular effect
I	**A**	15–52 g/day plant proteins	−12 to −20%	−14 to −22%	−3 to −6%	Not demonstrated

Abbreviations: LDL-C, low density lipoprotein cholesterol, HDL-C, high density lipoprotein cholesterol, ApoB, apolipoprotein B.

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analogue, lowers BP in hypertensive humans and animal models of hypertension [12]. The possible mechanisms of the antihypertensive effects of cysteine are through decreasing oxidative stress, lowering advanced glycation end products, improving insulin resistance (IR) and glucose metabolism, and by modulating levels of NO and other vasoactive molecules. Therefore, a balanced diet containing cysteine-rich proteins was proposed as a beneficial lifestyle choice for patients with hypertension [12].

It was documented that the diet rich in protein that contains the semi-essential amino acid arginine, lowers BP in humans and in animal models [11]. The possible mechanism of the lowering BP is through improvement of endothelial cell function and decreasing peripheral vascular resistance, due to the ability of arginine to decrease insulin resistance, to decrease glycation end products formation, to increase NO production, and decrease angiotensin II levels and oxidative stress [11]. The DASH study demonstrated that the DASH diet, which is rich in protein, lowered BP more than a typical North American diet with similar reduced sodium content. The mechanism of the BP lowering by DASH diet may be addressed to its higher arginine-containing protein, higher antioxidants and low salt content [11].

The INTERMAP study, which included 4680 men and women, aged 40–59 years, from 17 randomly selected population samples in Japan, China, United Kingdom and United States assessed the relationship of animal, plant and total protein intake to BP, by measuring their BP 8 times at 4 visits. Significant inverse relationship between vegetable protein intake and BP was registered [66] - higher vegetable protein intake by 2.80% kilocalories (i.e. 2 SD of vegetable protein intake) was associated with −2.72 mmHg lowering of SBP and −1.67 mmHg of DBP. When these values were adjusted for height and weight, there were −1.95 mmHg for SBP and −1.22 mmHg for DBP ($p < 0.001$ for both). Patients with high vegetable and low animal protein intake diets had different amino acid contents compared with subjects with low vegetable and high animal protein intake diets. The BP was registered in individuals from the country-specific top quartiles of vegetable protein intake and bottom quartiles of animal protein intake (who consumed 9.1% of their total calories from vegetable protein and 4.3% from animal protein), and in individuals from the country-specific bottom quartiles of vegetable protein intake and top quartiles of animal protein intake (who consumed 5.4% of their total calories from vegetable protein and 12.0% from animal protein). The individuals from the country-specific top quartiles of vegetable protein intake and bottom quartiles of animal protein intake had lower BP adjusted for sample, age and sex (−4.15 mmHg for SBP, $p < 0.001$ and −2.15 mmHg for DBP, $p < 0.01$). Based on these findings, a diet high in vegetable products, as a part of healthy lifestyle for prevention of high BP and related diseases, was recommended [66].

The INTERSALT cross-sectional multicentre study, performed in 32 countries worldwide, evaluated the impact of dietary protein in BP, by measuring 3 dietary protein parameters in 24 h urine all study included participants: nitrogen and urea, which were used as indexes of total protein intake, and sulfate, which was used as an index of sulphur-containing dietary amino acids [67]. Both 24 h urinary total nitrogen and urea nitrogen had significant independent inverse relationship with systolic and diastolic BP. SBP and DBP were 3.0 and 2.5 mmHg lower, respectively, in subjects who had dietary total protein intake 30% above the overall mean compared with subjects who had dietary protein intake 30% below the overall mean, supporting the hypothesis that higher dietary protein intake has favourable influences on BP [67]. A Japanese cross sectional study with >7500 subjects aged from 40 to 69 years showed that an increment by 25.5 g/day in total protein intake decreased SBP for 1.14 mmHg ($p < 0.001$) and DBP for 0.65 mmHg ($p < 0.001$), an increment by 19.9 g/day in animal protein intake decreased SBP for 1.09 mmHg ($p < 0.001$) and DBP for 0.41 mmHg ($p = 0.003$) and an increment by 13.1 g/day in plant protein intake reduce only DBP by 0.57 mmHg ($p < 0.001$) [68]. The Isfahan Healthy Heart Program [69] evaluated the effect of different protein intake diets on BP in 9660 randomly selected Iranian adults and found that more frequent total, animal and plant protein intake was significantly related to lower SBP and DBP in a crude model ($p < 0.001$); however, after adjusting for potential confounders in the fully-multivariable adjusted model, only more frequent plant protein consumption was significantly associated with lower SBP and DBP ($p = 0.04$). The ORs (95%CI) of crude and multivariate adjusted models revealed a greater risk of HTN for participants with less frequent total protein intake (OR = 0.43; 0.36–0.51; p-for-trend<0.001). All multivariate adjusted models demonstrated significant inverse relationships between higher category of total protein consumption and risk of HTN, which was decreased 19% in subjects with the highest quintile of total protein consumption in fully adjusted model (0.81 [0.65–0.96]; p-for-trend = 0.004). Animal protein consumption had a marked effect in lowering the risk of HTN (0.59; 0.50–0.70; p-for-trend<0.001 only in a crude model). The lower risk of HTN occurrence was associated with more frequent consumption of plant protein in crude and fully adjusted models. ORs demonstrated that the highest quintile of plant protein intake was related to 60% reduction in the occurrence of HTN (0.40 [0.34–0.48]; $p < 0.001$). ORs attenuated marginally by excluding all potential confounder effects (0.82 [0.67–0.94]; $p = 0.03$). The authors concluded that more frequent protein intake, particularly plant protein, was inversely associated with BP and risk of HTN development among Iranian adults [69].

The PREMIER study [21] had similar results to the above studies where plant proteins where inversely linked with systolic and diastolic BP during the 6- and 18-months follow-up period, irrespective of change in body weight and WC. This study demonstrated a strong inverse association of plant protein intake with both systolic ($p = 0.0045$) and diastolic BP ($p = 0.0096$) after adjusting for all covariates and other intakes (fat, fibre, calcium and potassium). Fruit/vegetable intake was also had significant inverse association with systolic BP ($p = 0.0003$) and diastolic BP ($p = 0.0157$) after adjusting for all covariates and other intakes (dairy, meat and fat) at 6 months. On the other hand, the 6 months changes in plant protein intake were inversely associated with changes in systolic BP ($p = 0.0486$), but there were not significant changes in diastolic BP ($p = 0.0759$). The odds of having hypertension were lowered for 25% with every 1-unit (% of kcal) added in dietary plant protein intake (OR = 0.75; 95%CI: 0.60, 0.95). In addition, every extra serving of fruit/vegetable, the decreased the odds of having HTN by about 23% (OR = 0.77; 95%CI: 0.79, 0.97) [21].

In the Chicago Western Electric Study [70], which included 1700 middle-aged employed men followed for 8 years, systolic and diastolic BP had inverse correlation with vegetable protein intake and positive correlation with animal protein intake and total protein intake. In men who consumed 14–42 cups of vegetables a month (0.5–1.5 cups/day) the SBP was increased for 2.8 mmHg less than in those who consumed <14 cups a month (<0.5 cups/day) in 7 years ($p < 0.01$). On the other hand, men who consumed 14–42 cups of fruit a month the SBP was increased for 2.2 mmHg less than in those who consumed <14 cups a month in 7 years ($p < 0.05$). Moreover, there was observed a direct relationship between beef-veal-lamb and poultry intakes with the SBP/DBP increase ($p < 0.05$). The results of this study support the concept that the risk of developing high BP may be reduced with diets higher in fruits and vegetables and lower in meats (except fish) [70].

Data from epidemiological studies suggest that, in populations who consume large amounts of soy protein, the incidence of CHD is

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reduced [71]. A soy protein-rich diet during gestation and adult life decreased oxidative stress and improved endothelial function, reducing BP in vivo in rats. The mechanism of this vascular reactivity improvement was considered to be through increased mitochondrial glutathione and mRNA levels for endothelial NO synthase (eNOS). It is considered that the reduced eNOS and antioxidant gene expression, impaired endothelial function, and elevated BP in animals fed a soy-deficient diet, which was reversed with refeeding rats with an SP diet for the period of 6 months [71]. The findings of this study suggest that an SP diet reduce oxidative stress and increases NO bioavailability, through eNOS and antioxidant gene expression in the vasculature and other tissues. These effects cause lowering of BP, considering soy isoflavones as an alternative therapy for BP lowering and control, particularly in postmenopausal women and patients at risk of CHD [71]. In contrast, Teede et al. conducted a double-blind, placebo controlled crossover trial where 40 subjects received soy cereal (40 g soy protein, 118 mg isoflavones) and gluten placebo cereal, each for 3 months [72]. Subjects that had soy protein diet had a higher 24 h systolic BP by 2.3 mmHg ($p = 0.003$), a higher daytime systolic BP by 3.4 mmHg ($p = 0.0002$) and a higher daytime diastolic BP by 1.4 mmHg, compared with subjects that had gluten protein diet ($p = 0.008$). However, there was not observed significant difference between diet groups in overall 24 h diastolic BP, night systolic BP and night diastolic BP. Furthermore, subjects with soy protein diet had higher 24 h heart rates by 3.5 bpm ($p < 0.0001$) compared with gluten protein diet [72].

The Shanghai Women's Health Study examined the association of usual soy foods intake and BP in 45,694 participants of, measuring BB at baseline and after 2–3 years of this diet [73]. Soy protein intake had inverse correlation with both systolic BP (p-for-trend = 0.01) and diastolic BP (p-for-trend = 0.009) after adjusting for age, BMI, lifestyle and other dietary factors. The adjusted mean systolic and diastolic BP were for 1.9 mmHg and for 0.9 mmHg lower, respectively, in women who consumed ≥25 g soya protein/d than in women consuming <2.5 g/day. These associations became stronger with increasing age (p for interaction <0.05 for both BPs) [73]. Among women >60 years old, the corresponding differences were −4.9 mmHg (95%CI: −8.0, −1.9 mm Hg) for systolic BP and −2.2 mmHg (95%CI: −3.8, −0.6 mmHg) for diastolic BP [73]. Similar results were achieved in another RCT, conducted by He et al., where 40 g/day of soya bean protein were given to 302 participants with an initial untreated systolic BP of 130–159 mmHg, diastolic BP of 80–99 mmHg, or both [74]. After the 12-week intervention, the net changes in SBP and DBP were −4.31 mmHg (95%CI, −2.11 to −6.51 mmHg; $p < 0.001$) and −2.76 mmHg (95% CI, −1.35 to −4.16 mmHg; $p < 0.001$), respectively. The net changes in systolic and diastolic BP reductions were −7.88 mmHg (95% CI, −4.66 to −11.1 mmHg) and −5.27 mmHg (95%CI, −3.05 to −7.49 mmHg), respectively, in persons with hypertension and −2.34 mmHg (95%CI, 0.48 to −5.17 mmHg) and −1.28 mmHg (95%CI, 0.52 to −3.07 mmHg), respectively, in those without hypertension [74]. A meta-analysis of 27 RCTs that examined the effects of soya protein on BP showed participants in the soya protein group had a mean decrease of 2.21 mmHg (95%CI 24.10, 20.33; $p = 0.021$) for SBP and 1.44 mmHg (95%CI 22.56, 20.31; $p = 0.012$) for DBP, compared with controls. Soya protein consumption reduced SBP and DBP in both hypertensive and normotensive subjects, but these reductions were markedly greater in hypertensive subjects [75].

Another double-blinded, 3-way-crossover, RCT concluded that intact milk proteins, particularly whey protein, decrease 24 h ambulatory BP and other risk markers of CVD [57]. The study found that after whey-protein supplementation (2 × 28 g/day) compared with control intake (2 × 27 g maltodextrin (control)/day), significant reductions in 24-h BP [SBP: −3.9 mmHg; for DBP: −2.5 mmHg; $p = 0.050$ (for both)] were observed. Peripheral, central and mean systolic pressures [-5.7 mmHg ($p = 0.007$), −5.4 mmHg ($p = 0.012$), and −4.0 mmHg ($p = 0.019$), respectively] were also lowered by whey-protein supplementation compared with controls [57]. FMD was increased after both whey-protein and calcium-caseinate intakes (2 × 28 g calcium caseinate/day) compared with control intake [1.31 and 0.83%, respectively]. TC was lowered by both whey protein and calcium caseinate [for −0.26 and −0.20 mmol/L, respectively], whereas triacylglycerol was decreased (for −0.23 mmol/L) only by whey protein, compared with controls. In conclusion, this study found that unhydrolyzed milk proteins consumption (56 g/day, for 8 weeks) affected biomarkers of endothelial function and lipid risk factors, and also improved vascular reactivity. Therefore, the 24 h ambulatory SBP and DBP were lowered by whey-protein supplementation [57].

Apart from the studies that showed the inverse association between BP and dairy consumption, there is few data on the postprandial effects of milk proteins on BP [76]. The lunch diet with 28 g whey protein was compared with diet of 28 g calcium-caseinate or 27 g maltodextrin effect in adults there were taking of a high fat, isoenergetic breakfast and the outcomes on BP and other CVD risk factors were observed. Up to 5 h post-ingestion, the whey protein significantly reduced systolic BP compared with calcium-caseinate (−15.2 ± 13.6 mmHg) and maltodextrin (−23.4 ± 10.5 mmHg). In addition, the arterial stiffness was improved by whey protein compared to maltodextrin (incremental Area Under the Curve-$iAUC_{0-8h}$: +14.4 ± 6.2%) [76]. The insulin response was higher in subjects with whey protein diet compared with those on a calcium-caseinate diet ($iAUC_{0-8h}$: +219.5 ± 54.6 pmol/L), despite similar glucose levels in both diet groups. The suppression of non-esterified fatty acids was induced less in subjects who received calcium-caseinate than those with whey protein ($iAUC_{0-5h}$: −58.9 ± 135.5 μmol/L) and maltodextrin ($iAUC_{0-5h}$: −106.9 ± 89.4 μmol/L). In these subjects, calcium-caseinate induced also a smaller postprandial triacylglycerol response than in subjects with whey protein ($iAUC_{0-8h}$: −1.68 ± 0.6 mmol/L). The authors concluded that milk proteins might have beneficial effect on the maintaining and improvement of CVD risk factors [76].

In overweight and obese postmenopausal women, a breakfast meal with 1 of 3 supplements: 45 g whey protein isolate, 45 g sodium caseinate or 45 g of a glucose control, lowered both SBP and DBP, and decreased AIx decreased initially, irrespective from the supplement they receive, but these changes returned to baseline levels by 6 h [77]. These different supplements also did not have different effects on plasma inflammatory markers (IL-6, TNF-α and CRP). This study concluded that the beneficial effects on BP, vascular function or inflammatory markers previously seen with chronic whey protein ingestion were not seen in the acute postprandial period, suggesting long-term consumption of whey proteins [77].

Another randomized study compared the effects of whey protein with casein supplementation, using glucose supplementation as control group, on BP, vascular function and inflammatory markers in overweight/obese individuals [78]. The SBP was decreased significantly at week 6 in the whey and casein groups, ($p = 0.028$ and $p = 0.020$, respectively) and at week 12 ($p = 0.020$, and $p = 0.017$, respectively) compared with baseline. On the other hand, whey and casein decreased DBP at 12 weeks compared with baseline ($p = 0.038$ and $p = 0.042$, respectively), and compared with controls ($p = 0.025$, $p = 0.038$, respectively). The whey supplement also lowered AIx 12 weeks ($p = 0.021$) compared with baseline and compared with controls ($p = 0.006$) and casein ($p = 0.006$). There changes of inflammatory markers did not differ

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Table 7
Recommendations for dietary protein intake and hypertension.

Class	Level	Daily dose of Dietary protein	Effect on SBP	Effect on DBP	Vascular effect
IIa	**A**	20–50 g/day (soy protein)	−1.28 to −17.0 mmHg	−0.9 to −12.2 mmHg	↑NO, improve systemic arterial compliance, contains ACE inhibitory peptides.
IIa	**A**	28–70 g/day (whey protein)	−3.8 to −15.2 mmHg	−2.1 to −2.5 mmHg	↑Flow mediated dilatation ↓Augmentation Index

Abbreviations: SBP, systolic blood pressure, DBP, diastolic blood pressure, NO, nitric oxide, ACE, angiotensin converting enzyme.

within or between groups. This study concluded that the whey protein improves BP and vascular function in overweight and obese subjects [78] (Figs. 1–4, Table 7, Suppl. Table 1).

6. Dietary protein intake and diabetes mellitus (DM)

DM is one of the most common endocrine diseases worldwide, and also the most important conventional risk factor of CVD, which prevalence was increased in adults from 4.7% in 1980 to 8.5% in 2014 [79]. DM is also a major cause of myocardial infarction, stroke, chronic kidney failure, blindness and lower limb amputation [79].

Mirmiran et al. [80] analyzed the associations of total protein intake and the animal-to-plant (A/P) protein ratio with cardiometabolic risk factors. BMI correlated with total protein intake in men ($\beta = 0.14$, $p = 0.01$) and A/P protein ratio in women ($\beta = 0.075$, $p = 0.01$), whereas WC correlated with total protein intake ($\beta = -0.048$, $p = 0.03$) and A/P protein ratio ($\beta = 0.031$, $p = 0.05$) in women. On the other hand, the fasting glucose was associated with both total protein intake ($\beta = 0.061$ and 0.11, $p < 0.05$) and the A/P protein ratio ($\beta = -0.078$ and -0.056, $p < 0.05$) in both men and women, respectively. The total protein intake was associated with serum HDL-C ($\beta = 0.107$ and 0.07, $p < 0.05$) in both men and women, and with DBP in women ($\beta = -0.125$, $p = 0.01$). The conclusions of this study were the higher dietary protein intake associate with enhanced HDL-C levels, WC, and DBP, and a higher A/P protein ratio was associated with lower serum fasting glucose and WC [80].

In addition to obesity, which is considered the most important risk factor for type 2 DM (T2DM), the certain foods and dietary factors are shown to be associated with DM [81]. A prospective study of 69,554 women aged 38–63 years without a history of DM, CVD or cancer, the associations between two major dietary patterns (Prudent" and "Western") and risk of T2DM was assessed [81]. The prudent pattern is characterized by higher intakes of fruits, vegetables, fish, legumes, poultry and whole grains, while the Western pattern contained higher intakes of meats (red and processed), sweets, desserts and refined grains. The highest quartile of Western pattern had higher relative risk (RR) for DM by 1.49 (95%CI, 1.26–1.76, p for trend <0.001) compared to its lowest quintile. The read and processed meats intake also had a positive association with T2DM. One-serving of red meat and of processed meat increased RR for T2DM by 1.26 (95%CI, 1.21–1.42) and 1.38 (95%CI, 1.23–1.56), respectively. This increased RR for T2DM was increased also for bacon and hot dog intakes, by 1.73 (95%CI, 1.39–2.16) and 1.49 (95% CI, 1.04–2.11), respectively [81]. In conclusion, the Western pattern of diet (high in red and processed meats, refined grains, sweets and deserts) elevates risk of T2DM development in women. Therefore, it is recommended to reduce the consumption of these food items to decrease the risk of T2DM [81].

The prospective EPIC-InterAct case-cohort study, which investigated the association of protein intake with T2DM incidence [82], found that high total and animal protein intake is associated with a modestly elevated risk of T2DM in European adults. In this contest, limiting iso-energetic diets high in dietary proteins, particularly those from animal sources, should be considered [82]. A study which involved 6822 participants aged ≥45 years without DM, found a significant association of higher animal protein intake (from meat, dairy and fish food sources) increased IR and increased risk of pre-DM and T2DM, which are partly mediated by obesity over time [83]. Higher total protein intake was associated with increased longitudinal homeostatic model assessment of IR (HOMA-IR) and with increased risk of pre-diabetes and T2DM. The association of total animal protein with HOMA-IR was 0.10 (0.07, 0.12), and that for prediabetes was 1.35 (1.24, 1.45), whereas T2DM was 1.37 (1.26; 1.49). The harmful associations of total animal protein were contributed to by protein from meat, fish, and dairy (e.g. for HOMA-IR: protein from meat, 0.13 (0.10, 0.17); from fish, 0.08 (0.03, 0.13); from dairy, 0.04 (0.0003, 0.08)) [83]. On the other hand, the total plant protein, proteins from legumes and nuts, those from grains, potatoes, or from fruits and vegetables did not associate with any of the outcomes. Furthermore, plant protein from legumes and nuts, from grains, from potatoes, or from fruits and vegetables of different sources did not correlate with insulin resistance, and risk of pre-DM and T2DM. The findings of this study highlight the role of specific protein from different food sources, particularly high animal protein intake, which may be harmful in the development of T2DM even already in early stages [83].

Over an average of 8.8 years, 37,309 participants in the Women's Health Study aged ≥45 years were prospectively assessed for the effect of red meat intake at the incidence of T2DM [84], and the positive associations between red and processed meat intake and the risk development of T2DM were found. Women in the highest quintile of red and processed meat intake had higher multivariate-adjusted RRs of T2DM by 1.28 (95%CI 1.07–1.53, $p < 0.001$ for trend) and 1.23 (1.05–1.45, $p = 0.001$ for trend), respectively, compared with those in the lowest quintile of red and processed meat intake. Furthermore, the frequent consumption of total processed meat (RR 1.43, 95%CI 1.17–1.75 for ≥5/week *vs* < 1/month, $p < 0.001$ for trend) and 2 major subtypes, which were bacon (1.21, 1.06–1.39 for ≥2/week *vs* < 1/week, $p = 0.004$ for trend) and hot dogs (1.28, 1.09–1.50 for ≥2/week *vs* < 1/week, $p = 0.003$ for trend) significantly increased risk of DM development [84]. In contrast, there was no association between consumption of unprocessed red meat and poultry with T2DM development risk, irrespective of their amount, (RR 1.05, 95%CI 0.85–1.30 for highest *vs* lowest quintile, and RR1.12, 95%CI 0.95–1.32 for highest *vs* lowest quintile, respectively) in a large 12 years follow-up study [85]. Only consumption of the 3 processed meat items and hamburgers (RR 1.27, 95%CI 0.99–1.62 for ≥2/week *vs* < 1/month) had significant association with T2DM risk. Frequent consumption of processed meat was associated with a higher risk for T2DM (RR 1.46, 1.14–1.86 for ≥5/week *vs* < 1/month, p for trend <0.0001) [85].

In 24,182 participants from The United States National Health and Nutrition Examination Survey (NHANES), 3 dietary patterns (DP) were studied: 1) with dominant content of saturated fat (SFA), total fat, mono-unsaturated fatty acids (MUFA) and carbohydrate (CHO), 2) with high level of vitamins, trace elements and dietary fiber, and, 3) mainly based polyunsaturated fatty acids (PUFA), cholesterol and protein [86]. The first and third DP had better association with higher likelihood for developing IR, whereas the

second DP had a lower likelihood for the developing of IR. Across quarters of the first DP, the significant increase of mean levels of markers of glucose and insulin homeostasis was observed - for plasma insulin (12.3 *vs* 15.5 μU/mL), HbA_{1c} (5.6 *vs* 5.8%), HOMA-IR (3.3 *vs* 4.1), homeostatic model assessment of β-cell function (HOMA-B) (143.5 *vs* 164.7), and decreased for homeostatic model assessment of insulin sensitivity (HOMA-S) (0.58 *vs* 0.49) (all $p < 0.001$) [86]. The opposite pattern was observed across quarters of the second DP, as FBG (102.2 *vs* 99.1 mg/dl), plasma insulin (14.5 *vs* 12.7 μU/mL), HbA_{1c} (5.8 *vs* 5.4%), 2 h glucose (123.1 *vs*115.4 mg/dl), HOMA-IR (3.9 *vs* 3.3) decreased while HOMA-S (0.50 *vs* 0.58) increased (all $p < 0.001$). The profiles of parameters of glucose and insulin homeostasis were similar across quarters of the first and third DP, and the changes in HOMA-B and HOMA-S were not significant. This finding documented that the DP based on carbohydrates, SFA, PUFA, protein, total fat, MUFA, and high-cholesterol-load foods are linked to impaired glucose tolerance. In contrast, the healthy pattern (DP2) may have favourable effects on insulin sensitivity and glucose tolerance [86].

After extracting and analyzing data from NHANES (n = 16,784), Mazidi et al. concluded that energy intake and race-adjusted mean of serum CRP (0.49–0.26 mg/dl), apo B (95.6–90.8 mg/dl), glucose/insulin homeostasis parameters and TG-glucose index (TyG) index (8.32–7.95) significantly decreased with the increased of nut intake ($p < 0.001$ for all) [87]. In a systematic review of RCTs, the relation of nut consumption and their effect on IR and other cardiometabolic risk factors were studied [88]. The possible mechanism of nuts in glucose control and appetite suppression was considered to be the activity of unsaturated fatty acids (MUFA and PUFA) that are present in nuts. On the other hand, the fiber and polyphenols that are compounds of nuts may also have an anti-diabetic effect by altering gut microbiota. Nuts also lower serum cholesterol by reducing cholesterol absorption, and through inhibition of HMG-CoA reductase and increasing bile acid production by stimulation of 7-α hydroxylase. Moreover, the arginine and magnesium that are present in nuts improve inflammation, oxidative stress, endothelial function and BP [88]. In a randomized parallel trial, in the subjects with prediabetes who consumed for 16 weeks almonds (60 g/day of pre-packaged raw or dry roasted almonds) the fasting insulin concentrations (−23 *vs* + 19%; $p = 0.002$), HOMA-IR (−25 *vs* + 0.3%; $p = 0.007$) and the homeostasis model analysis for beta-cell function (HOMA-B; −18 *vs* + 30.0%; $p = 0.001$) were significantly reduced. Also, the glucose levels were improved by a Mediterranean diet rich in pistachios (−8.8 ± 8.5% $p < 0.001$) [88] (Figs. 1–4, Table 8, Suppl. Table 1).

7. Dietary protein intake and CVD

Protein-based diets have become more popular with the rise of low-carbohydrate diets. People who consume high-protein diets often miss out on the other nutrients including vegetables, legumes and whole grains. On the other hand, some high-protein diets also contain higher levels of saturated and trans-fats, which have been documented to associate with CHD [3,19,89,90]. Furthermore, when the intake is in excess, proteins increase muscle tissue acidity, which itself contribute to oxidative stress and therefore deteriorate vascular function and myocardial contractility. In some experimental studies, the animal protein ingestion raised serum cholesterol level, but it was not consistent in other studies. Some ecologic studies suggested a positive association between animal protein intake and increased risk of CHD, but the prospective data on this association are not definite [3,8,19,90].

According to recent data [89], globally dietary risks were responsible for 11 million deaths, or 22% of all deaths among adults, with CV disease being the leading cause. Moreover, the healthy foods and nutrients consumption based on recent data was suboptimal worldwide. While, the daily intake of some unhealthy foods and nutrients (e.g. sugar-sweetened beverages, processed meat and sodium) exceeded the optimal level globally, the healthy foods (nuts and seeds, milk, and whole grains) were observed to be far from optimal intake [89]. High intake of sodium was evidenced to be responsible for more than half of diet-related deaths and two-thirds of diet-related disability-adjusted life-years (DALYs) in (3 million [95%Cl: 1–5] deaths and 70 million DALYs), followed by low intake of whole grains (3 million deaths and 82 million DALYs), and low intake of fruits (2 million deaths and 65 million DALYs). These data documented that the improvement of diet can potentially prevent 1 in every 5 deaths worldwide [84]. It was shown that the suboptimal diet is responsible for more deaths than any other risk globally, including smoking, highlighting the need for urgent improvement worldwide. This data also showed among dietary risk factors for mortality, the diets high in sodium, low in whole grains, low in fruit, low in nuts and seeds, low in vegetables, and low in omega-3 fatty acids are the leading factors; each accounting for >2% of global deaths [89].

The Nurse's Health prospective study followed 84,136 women aged 30–55 years without known cancer, DM, ischaemic heart disease, stroke, stroke or other CVD for 26 years follow-up [22]. A standardized and validated questionnaire, which was updated every 4 years, was used to assess the diet in study patients. From study subjects, 2210 incident nonfatal myocardial infarctions and 952 deaths from CHD were documented [22]. In another study, higher intakes of red meat and high-fat dairy products significantly increased risk of CHD, whereas higher intakes of poultry, fish, and nuts were significantly lowered risk [19]. In a model controlled statistically for energy intake, 1 serving/day of nuts lower risk of CHD for 30% (95% CI, 17–42%) compared with 1 serving/day of red meat. Similarly, 1 serving/day of low-fat dairy (13%; 95%CI, 6–19%), poultry (19%; 95%CI, 3–33%) and fish (24%; 95%CI, 6–39%) lowered the risk for CHD compared with 1 serving/day of red meat. From the above data, it is suggested that high red meat intake increases the risk of CHD, which may be reduced by shifting sources of protein in the US diet. However, there was no relationship between animal or

Table 8
Recommendations for dietary protein intake and diabetes mellitus.

Class	Level	Daily dose of plants vs. animal	Effect on DM parameters	Additional effects	Vascular effect
I	**A**	14.2–68 g/day (nuts)	↓FG, ↓HbA1C, ↓HOMA-IR, ↓HOMA-B	↓SBP, ↓DBP, ↓TC, ↓LDL-C, ↓TG, ↓BW, ↓hsCRP	↓oxidative stress, ↑NO, ↑vasodilation, modulate gene expression of leucocyte adhesion molecule.
III	**A**	1-7 servings/week (red and processed meat)	↑ risk for T2DM up to 50%	↑BW, ↑WC, ↑LDL-C, ↑TC, ↑risk of stroke	Iron-mediated oxidative stress, ↑vascular stiffness

Abbreviations: DM, diabetes mellitus; FG, fasting glucose; HbA1C, glycated haemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-B, homeostatic model assessment of B-cell function; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; BW, body weight; hsCRP, high sensitivity C-reactive protein; WC, waist circumference; NO, nitric oxide.

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vegetable protein and CHD risk, when polyunsaturated, monounsaturated and saturated fats were included in multivariable model analysis. But, the analyses of individual protein sources showed that higher intake of the red and processed meats increased, whereas higher intakes of fish, nuts, and beans decreased the risk for CHD [22].

In another prospective cohort study, 80,082 women aged 34–59 years and without a previous diagnosis of cancer, stroke, CHD, hypercholesterolemia or DM, the association between dietary protein intake and incidence of CHD was examined [90]. Validated dietary questionnaires were used to assess the intakes of protein and other nutrients. During 14 years of follow-up, 939 major CHD events had the study subjects [90]. After adjustment for age, higher intake of protein lowered the risk of CHD (RR; 0.75 (95%CI: 0.61, 0.92)) differed between extreme quintiles of total protein intake [90]. These data did not confirm the hypothesis that a high protein intake increases the risk of CHD. In contrast, the findings of this study suggest that replacing carbohydrates with protein may lower the risk for CHD. However, the application of public dietary advice for these findings should be cautious, because the high protein diet is often accompanied by intakes with increased amount of saturated fat and cholesterol [90].

The Women's Lifestyle and Health cohort study [91] with e follow-up for 12 years of 42,237 random volunteer women (30–49 years old) in Sweden completed an extensive questionnaire. The results of this study showed that decreasing carbohydrate or increasing protein intake by one decile increased total mortality for 6% (95%CI: 0–12%) and 2% (95%CI: −1 to 5%), respectively [86]. The investigators of this study mainly draw attention to the potential for long-term adverse health effects of diets low in carbohydrates and high in protein, related to the CV health. However, the main limitation of this study was that it did not address questions concerning the potential effects of low carbohydrate and/or high protein diets on the body weight or IR [91].

The NHANES 1999–2000 provides evidence that lower carbohydrate diets have an unfavourable association with overall and cause-specific mortality [16]. Nearly 25,000 subjects were followed up (mean follow-up 6.4 years) and it was found that participants with the lowest carbohydrate intake had the highest risk of overall (32%), CVD (50%), cerebrovascular (51%) and cancer (36%) mortality, particularly among obese participants [16]. Also, the pooled data from 9 prospective studies [16] showed that there was an important association between low-carbohydrate/high protein diet and overall (RR 1.22, 95%CI 1.06–1.39, $p < 0.001$), CVD (RR 1.13, 95%CI 1.02–1.24, $p < 0.001$), and cancer mortality (RR 1.08, 95%CI 1.01–1.14, $p = 0.02$) [16].

The Health Professionals Follow-Up Study investigated the intakes of protein and other nutrients and the incidence of CHD in 43,960 men using a validated food-frequency questionnaire at 4 time points during the 18 years follow-up [27]. The RR of CHD was 1.08 (95%CI: 0.95, 1.23; p for trend = 0.30) when the top and the bottom quintiles of percentage of energy from total protein were compared. The RRs for animal and vegetable protein were 1.11 (95% CI: 0.97, 1.28; p for trend = 0.18) and 0.93 (95%CI: 0.78, 1.12; p for trend = 0.49), respectively. When the population was restricted to subjects free of HTN, hypercholesterolemia, and DM at baseline, the RR of CHD was 1.21 (95%CI: 1.01, 1.44; p for trend = 0.02) for total protein, 1.25 (95%CI: 1.04, 1.51; p for trend = 0.02) for animal protein, and 0.93 (95%CI: 0.72, 1.19; p for trend = 0.65) for vegetable protein [27].

The Shanghai Women's Health Study, a prospective population-based cohort study, investigated the effect of soya food intake on the incidence of CHD among 75,000 Chinese women, of whom 64,915 were without previously diagnosed CHD, DM, stroke or cancer at baseline, using a validated food-frequency questionnaire in an in-person interview on usual intake of soya food (40–70 years) [23]. There was a significant dose-response relationship between soy food intake and risk of total CHD (p-trend = 0.003) with an adjusted RR of 0.25 (95%CI, 0.10–0.63) when the highest *vs* the lowest quartiles of total soya protein intake were compared. This association was highly significant for nonfatal myocardial infarction (RR = 0.14; 95%CI, 0.04–0.48; p for trend = 0.001). In conclusion, this study found that soy food consumption may reduce the risk of CHD in women [23].

Kelemen et al. prospectively followed for 15 years the incidence of cancer and mortality from CHD, cancer, and all causes in 29,017 postmenopausal Iowa women without previous CHD, CHD or DM, who responded to a mailed questionnaire for their medical information, dietary and lifestyle [92]. The risk ratios from a simulated substitution of dietary protein with carbohydrate and of vegetable with animal protein were estimated by nutrient density models. The authors found that the highest vegetable protein intake decreased CHD mortality by 30% among women, from an isoenergetic substitution of vegetable protein for carbohydrate and for animal protein [(95%CI: 0.49, 0.99) and (95%CI: 0.51, 0.98), respectively] following multivariable adjustment [92]. Moreover, the red meat intake was associated with CHD mortality (Risk Ratio 1.44, 95%CI: 1.06, 1.94) and dairy products (Risk Ratio 1.41, 95%CI: 1.07, 1.86) when substituted for servings per 1000 kcal (4.2 MJ) of carbohydrate foods. The results of this study showed that the long-term adherence to high-protein intake diets, without discrimination toward protein source, may have potentially adverse health consequences [92].

According to a study by Mazidi et al., dietary patterns play an important role on serum hsCRP levels, as a risk factor for CVD [93]. More than 17,000 participants were selected and analyzed. It was found that dietary fiber intakes, PUFA, vitamins A, E, B family, C and K total folate magnesium, iron, copper and potassium decreased hsCRP ($p < 0.001$ for all), whereas sugar intake increased hsCRP levels ($p < 0.001$) [93]. The data from the selected participants of US NHANES were used to assess the association of the Dietary Inflammatory Index (DII) scores with different cardio-metabolic risk factors and their combination as MetS [94]. The energy-adjusted-DII (E-DII) expressed per 1000 kcal was calculated from 24 h dietary recalls. Of the 17,689 participants (mean age was 45.8 years), 48.3% were men, who were slightly younger than women (44.9 *vs* 46.5 years, $p = 0.05$). The odds of MetS, its components, as well as obesity, elevated hsCRP, TG/HDL-C ratio, apo B and HbA_{1c} rose across increasing quartiles of E-DII ($p < 0.001$). In the models that were adjusted for age, sex, race and income-to-poverty ratio, the CVD risk factors (TG/HDL-C ratio, apo B and HbA_{1c}) were increased across quartiles of the E-DII (all $p < 0.001$), while HDL-C levels decreased ($p < 0.001$) [94].

In a study with national representative sample of American adults, the association between dietary acid load, potential renal acid load (PRAL) and net endogenous acid production (NEAP) on one hand, and PAD on the other hand, was investigates [95]. Of 4864 eligible participants (40–85 years old), (5.5%) had PAD confirmed by ankle brachial index <0.9 in either limb. Patients with PAD had higher mean of PRAL and NEAP (16.2 *vs* 9.1 mEq/d and 56.2 *vs* 50.1 mEq/d), p < 0.001 for both, compared with PAD-free participants. The top, more acidic, quarter of PRAL was associated with 31% higher odds compared with the bottom quarter (more alkaline) [OR: 1.31, 95%CI: 1.11–1.57] regarding the presence of the PAD. The findings of this study suggest that dietary acids load, which is an index of acid-base balance, may contribute to the pathogenesis of PAD [95].

From 24,474 participants, 3520 deaths occurred during follow-up in cohort study [96], which examined the association of total dairy and dairy subgroups consumption of with total and cause

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specific (CHD, cerebrovascular and cancer) mortality. Total mortality risk was lower when the top quartiles were compared with the lower quartiles of total dairy (hazard ratio [HR] 0.98, 95%CI: 0.95–0.99) and of cheese (HR: 0.92, 95%CI: 0.87–0.97) consumption. Using a similar model, the total dairy and milk consumption had a negative association with the risk of cerebrovascular mortality (HR: 0.96, 95% CI: 0.94–0.98, HR: 0.93, 95% CI: 0.91–0.96, respectively), while milk consumption was associated with increased CHD mortality (HR: 1.04, 95%CI: 1.02–1.06) [96]. The authors next carried out a systematic review and meta-analysis with 636,726 participants of prospective studies to check the consistency with their cohort study. The results of this meta-analysis documented a significant inverse association between fermented dairy products and all-cause mortality (RR: 0.97, 95%CI: 0.96–0.99), while milk consumption was associated with higher CHD mortality (RR: 1.04, 95%CI: 1.01–1.05) [96] (Figs. 1–4, Table 9, Suppl. Table 1).

8. Dietary protein intake and stroke

The results from 4 cohort studies [97–100], which evaluated the relationship between dietary protein consumption and strokes, showed that higher consumption of red meat (both processed and unprocessed), refined grains and full-fat dairy products intakes were associated with a higher risk of stroke. On the other hand, higher intakes of fruits, vegetables, whole grains, fish, and poultry lowered the risk of stroke events. A study that involved 84,010 women and 43,150 men, compared the effects of red meat with different protein sources, found that the risk of stroke was lowered by 1 serving/day of: poultry for 27% (95%CI, 12–39%), nuts for 17% (95%CI 4–27%) fish for 17% (95%CI, 0–30%), low-fat dairy for 11% (95%CI, 5–17%), and whole-fat dairy for 10% (95%CI, 4–16%), compared with 1 serving/day of red meat [97]. On the other hand, there was no significant associations were seen with exchanging legumes or eggs for red meat [97]. In the 3 other studies, with 150,000 individuals, the interaction of total, animal, and vegetable protein on one hand, with HTN, DM, hypercholesterolemia and high BMI on the other hand, were examined [98–100]. In the study, with 34,670 women without CVD and cancer at baseline who were prospectively followed up for 10.4 years, 1680 incident cases of stroke (cerebral infarctions, intracerebral haemorrhages, subarachnoid haemorrhages and unspecified strokes) were ascertained [98]. The diets with high total red meat and processed meat intake increased the risk of cerebral infarction, but not of total stroke, intracerebral haemorrhage or subarachnoid haemorrhage. The multivariable RR of cerebral infarction, when the highest quintile was compared with the lowest quintile of consumption was 1.22 (95%CI, 1.01–1.46) for red meat and 1.24 (95%CI, 1.04–1.49) for processed meat. However, unprocessed (fresh) meat consumption did not correlated with total stroke or with any stroke subtypes [98].

In a study, which assessed the association between dietary protein, intake and risk of stroke among middle-aged men (43,960 participants followed up for 18 years) 1057 stroke events were identified [100]. When the risk for total stroke, the top quintile of percentage energy from protein were compared with the bottom, the RR was 1.14 (95%CI: 0.90, 1.43; p for linear trend: 0.43) for total protein, 1.11 (95%CI: 0.87, 1.41; p for linear trend: 0.52) for animal protein, and 0.82 (95%CI: 0.60, 1.12; p for linear trend: 0.17) for vegetable protein. There was no difference between protein intake and subtypes of stroke - ischemic and haemorrhagic ones [100].

The prospective study by Fung et al., investigated major dietary patterns and stroke risk in 71,768 women (38–63 years old) without a previous history of CVD or DM [99]. The results demonstrated that a high Western dietary pattern score (high intake of red and processed meats, refined grains, high-fat dairy products, and sweets and desserts) increased the risk of ischemic stroke. In contrast, a reduced risk of ischemic stroke was observed in participants that used a high prudent pattern score (higher intakes of fruits, vegetables, whole grains, fish and poultry). During 14 years of follow-up, when comparing the highest with lowest quintiles of the Western pattern, after adjusting for potential confounders, a RR of 1.58 (95%CI, 1.15 to 2.15; $p = 0.0002$ for trend) for total strokes and 1.56 (95%CI, 1.05 to 2.33; $p = 0.02$ for trend) for ischemic stroke. On the other hand, in participants that used prudent pattern, when the extreme quintiles were compared the RRs were 0.78 (95%CI, 0.61 to 1.01) for total stroke and 0.74 (95%CI, 0.54 to 1.02) for ischemic stroke [99].

The relationship between the red meat consumption and the risk of stroke was assessed among 40,291 Swedish men (45–79 years old), without previous history of CVD or cancer at baseline [101]. The consumption of processed meat increased the risk of stroke, whereas the consumption of fresh red meat has no relationship with the risk of stroke. The multivariable RRs of total stroke were 1.23 (95%CI: 1.07, 1.40; p for trend = 0.004) for processed meat and 1.07 (95%CI: 0.93, 1.24; p for trend = 0.77) for fresh red meat, when comparing the highest with the lowest quintiles of these intakes. The results of this study documented that processed meat consumption was positively associated with risk of cerebral infarction, when the highest with the lowest quintile of these

Table 9
Recommendations for dietary protein intake and CV risk.

Class	Level	Substitute 1 serving/day of red meat	The effect on the risk of CHD	Mechanism of action
I	**B**	Substitute with fish	↓ 24%	↓ Saturated fat content ↓ Heme iron content ↓Salt content ↑Polyunsaturated fat
I	**B**	Substitute with poultry	↓ 19%	↓ Saturated fat content ↓ Heme iron content ↓Salt content ↑Polyunsaturated fat
I	**B**	Substitute with low-fat dairy	↓ 13%	↓ Saturated fat content ↓ Heme iron content ↓Salt content ↑Polyunsaturated fat
IIa	**B**	Substitute with nuts	↓ 20–30%	↓ Saturated fat content ↓ Heme iron content ↓Salt content ↑Polyunsaturated fat

Abbreviations: CHD, coronary heart disease, CV, cardiovascular.

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Table 10
Recommendations for dietary protein intake and stroke.

Class	Level	Daily doses of dietary proteins	The effect on the risk of stroke	Vascular effects
III	**A**	100 g increment/day in total meat consumption	↑10%	Iron-mediated oxidative stress, ↑vascular stiffness
III	**A**	100 g increment/day in red meat consumption	↑13%	Iron-mediated oxidative stress, ↑vascular stiffness
III	**A**	50 g increment/day in processed meat consumption	↑11%	Iron-mediated oxidative stress, ↑vascular stiffness
I	**B**	Substitute 1 serving of red meat with poultry/day	↓ 27%	↓ saturated fat, ↓ vascular fragility
I	**B**	Substitute 1 serving of red meat with fish/day	↓ 17%	↓saturated fat, ↓ vascular fragility
I	**B**	Substitute 1 serving of red meat with nuts/day	↓ 17%	↓saturated fat, ↓ vascular fragility
I	**B**	Substitute 1 serving of red meat with low-fat dairy/day	↓ 11%	↓saturated fat, ↓ vascular fragility
I	**B**	Substitute 1 serving of red meat with whole-fat dairy/day	↓ 10%	↓saturated fat, ↓ vascular fragility

consumptions were compared [(RR: 1.18; 95%CI: 1.01, 1.38; p for trend = 0.03) 101].

A meta-analysis of pooled data from prospective cohort studies evaluated the association between consumption of red and processed meat and risk of stroke [102]. This analyses documented that in individuals with the highest intakes of total, red or processed meat increased the risk of stroke, compared with individuals with the lowest intakes; the RRs were: 1.15 (95%CI, 1.05–1.25) for total meat, 1.09 (95%CI, 1.01–1.18) for red meat and 1.14 (95%CI, 1.05–1.25) for processed meat. The relationship between red meat consumption and ischemic and haemorrhagic strokes had pooled RRs 1.13 (95%CI, 1.01–1.25) and 0.99 (95%CI, 0.77–1.28), respectively. The RRs of the relationship between processed meat consumption and ischemic and haemorrhagic strokes were 1.19 (95%CI, 1.08–1.31) and 1.23 (95%CI, 0.96–1.58), respectively [102]. The results from this analysis showed that each 100 g/day increment in total meat consumption increased the risk of stroke by 10% (RR = 1.10; 95%CI, 1.05–1.15), each 100 g/day increment in red meat consumption by 13% ($n = 5$; RR = 1.13; 95%CI, 1.03–1.23) and by 11% for each 50 g/day increment in processed meat consumption ($n = 5$; RR = 1.11; 95%CI, 1.02–1.20) [102]. Another meta-analysis of prospective studies evaluated the effects of red meat consumption on the risk for stroke [103]. There were 10,630 cases of stroke among 329,495 participants from 6 prospective studies with follow-up from 11 to 26 years. The RR (95%CI) of all strokes were 1.11 (1.03–1.20), 1.13 (1.03–1.24), and 1.11 (1.06–1.16), respectively, for each serving/day increase in fresh red meat, processed meat and total red meat consumption. The stroke subtypes, however had different results regarding these associations: while the risk of ischemic stroke was positively associated with consumption of fresh red meat (RR, 1.13; 95%CI, 1.00–1.27), processed meat (RR, 1.15; 95%CI, 1.06–1.24), and total red meat (RR, 1.12; 95%CI, 1.05–1.19); these intakes had no significant associations with haemorrhagic stroke [103] (Figs. 1–4, Table 10, Suppl. Table 1).

9. Conclusions and implications for future studies

Many observational and interventional studies confirmed that increasing protein intake, especially plant-based proteins and some selected animal-based proteins (poultry, fish, unprocessed red meat low in saturated fats and low-fat dairy products) have a positive effect in modifying cardio-metabolic risk factors. Nevertheless, the existing evidence is not consistent enough. Vegetarians have a tendency to have lower BP, healthier lipid profiles and almost near normal body weight, compared with omnivores, even though this may be a result of their overall healthier lifestyle. In many studies red meat intake has been correlated with increased CVD risk, mainly because of its non-protein ingredients (saturated fats) and the way it was cooked and preserved matters. So, there are recommendations to substitute red meat for poultry or fish, in order to lower CVD risk. As specific amino acids have antihypertensive effect, foods that contain these amino acid-rich-proteins have favourable results in modifying a major risk factor for CVD, such as hypertension.

A considerable number of RCTs attribute cardioprotective properties to soya consumption. Soya might improve the lipid profile and adjust BP, even though it is not clear whether this is the effect of soybean proteins or isoflavones. Despite that, soya remains a favourable protein source. Regarding dairy products, proteins found there (especially whey protein) are inversely correlated with hypertension, obesity and insulin resistance. In order to reduce CVD risk factors, evidence-based dietary patterns should be promoted. Replacing carbohydrates and unprocessed red meat with protein-sufficient foods that have been shown to have advantageous outcomes, is advised. Dietary recommendations should provide emphasis to both the amount and sources of protein.

As it is very difficult to determine the effect of a specific protein in a certain food, without the interference of the effects of other accompanying ingredients, there is a lack of human or animal studies that provides definitive results regarding their effects. There is also a need for more studies that evidence the health outcomes of other plant-based proteins, other than soy and nuts. Due to the fact that it is impossible to investigate the effect of dietary proteins only on health outcomes, we still cannot exclude the possibility that their favourable effects in lowering CVD risk could be due to isoflavones or unsaturated fats (or other dietary components) [104–106].

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Conflict of interest

Maciej Banach: speakers bureau: Abbott/Mylan, Abbott Vascular, Actavis, Akcea, Amgen, Biofarm, KRKA, MSD, Sanofi-Aventis, Servier and Valeant; consultant to Abbott Vascular, Akcea, Amgen, Daichii Sankyo, Esperion, Lilly, MSD, Resverlogix, Sanofi-Aventis; Grants from Sanofi and Valeant; *Dimitri P. Mikhailidis:* has given talks and attended conferences sponsored by Amgen, Novo Nordisk and

Libytec; *Gani Bajraktari:* speakers bureau: KRKA, Bosnalijek, Novartis, LEK-Sandoz, Boston-Scientific, Trepharm and Alkaloid; consultant to Novartis; *Michael Y. Henein, Fjolla Zhubi-Bakija, Ibadete Bytyçi, Zarife Rexhaj and Esra Zhubi*, have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2020.05.017.

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With the endorsement of

1. Argentina Lipid Society
2. Association of Cardiologists of the Republic of Uzbekistan
3. Association of Preventive Pediatrics of Serbia
4. Baltic Society of Atherosclerosis
5. Belgian Lipid Club
6. Belgian Association for Patients with Familial Hypercholesterolemia
7. Chinese Atherosclerosis Society
8. Collegium of Family Physicians in Poland
9. Croatian Atherosclerosis Society
10. Czech Society for Atherosclerosis
11. Egyptian Association for Endocrinology, Diabetes and Atherosclerosis (EAEDA)
12. Egyptian Association of Atherosclerosis, Vascular Biology and Research (EAVA)
13. Emirates Cardiac Society
14. Estonia Society of Hypertension
15. German Atherosclerosis Society
16. Hellenic Atherosclerosis Society
17. Hellenic Lipidology Society
18. Hellenic Society of Lipidology, Atherosclerosis and Vascular Disease
19. Hungarian Atherosclerosis Society
20. International Natural Product Sciences Taskforce (INPST)
21. Israeli Society for Treatment and Prevention of Atherosclerosis
22. Italian Nutraceuticals Society (SINut)
23. Italian Society for Cardiovascular Prevention
24. Kosovo Society of Cardiology
25. Kyrgyz Atherosclerosis Society
26. Latvian Society of Cardiology
27. Lipid and Atherosclerosis Society of Southern Africa
28. Lipid and Blood Pressure Meta-Analysis Collaboration (LBPMC) Group
29. Lipid Association of India
30. Lithuanian Heart Association
31. Mighty Medic
32. New French Atherosclerosis Society (NSFA)
33. Polish Lipid Association (PoLA)
34. Romanian National Forum for Prevention
35. Romanian Society of Cardiology
36. Russian National Atherosclerosis Society
37. Saudi Group for Cardiovascular Prevention and Rehabilitation
38. ScreenPro-FH
39. Serbian Association for Arteriosclerosis, Thrombosis and Vascular Biology Research (SAATVBR)
40. Slovak Association of Atherosclerosis
41. Slovenian Society of Cardiology
42. Society on Sarcopenia, Cachexia and Wasting Disorders
43. Swiss Society for Familial forms of Hypercholesterolemia (SSFH)
44. Taiwan Society of Lipids and Atherosclerosis
45. Tunisian Association of Study and Research on Atherosclerosis
46. Ukrainian Atherosclerosis Society
47. Working Group for Lipidology, Vascular biology and Research (WGLVR)
48. Venezuelan Society of Atherosclerosis
49. Very Large Database of Lipids (VLDL)

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