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Animal and Plant Protein Sources and Cardiometabolic Health

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Running title: protein sources and cardiometabolic health

1 **Abstract**

2 The sources or types of protein in the diet have long been overlooked regarding their link to
3 cardiometabolic health. The picture is complicated by the fact that animal and plant proteins
4 are consumed along with other nutrients and substances which make up the “protein package”
5 so plant/animal protein come with clear nutrient clusters. This review aimed at deciphering the
6 relation between plant and animal protein and cardiometabolic health by examining different
7 nutritional levels (such as amino acids, protein type, protein foods, protein patterns and
8 associated overall dietary and nutrient patterns) and varying levels of scientific evidence (basic
9 science, RCT, observational data). Plant protein in western countries is a robust marker of
10 nutrient adequacy of the diet, whereas the contribution of animal protein is highly
11 heterogeneous. Yet recent data from large cohorts have confirmed that total and animal proteins
12 are associated with the risk of CVD and diabetes, even when fully adjusting for lifestyle and
13 dietary/nutritional factors. Here again, there is marked variability depending on the type of
14 animal protein. Protein from processed red meat and total red meat on the one hand, and from
15 legumes, nuts and seeds on the other, are often reported at the extremes of the risk range. RCTs
16 using purified proteins have contributed little to the topic to date, inasmuch as the findings
17 cannot readily be extrapolated to current or near-future diets, but RCTs studying whole protein
18 foods have shown a beneficial effect of pulses. Despite many of the benefits of plant protein
19 reported in observational or interventional studies may stem from the protein package that they
20 convey and the nutrients that they displace, there are also important indications that protein per
21 se may affect cardiometabolic health via the many amino acids that are present at typically
22 contrasting levels in plant vs animal proteins.

23 Key words: cardiometabolic health, animal protein, plant protein.

24 **Introduction**

25 As compared to lipid and carbohydrates, protein is the macronutrient that makes the smallest
26 observed contribution to energy intake and the lowest level of recommended intake (1). Protein
27 also has the specific feature that its dietary reference intake has been set on the basis of a strict
28 nutritional requirement. Further, because protein is found in very large amounts in a limited
29 number of foods, very high intakes are infrequent, and this results in the usual intake ranging
30 from 12% to 20% (of energy intake) in economically developed countries (1, 2). While there
31 is a longstanding debate on the levels of fat and carbohydrate that are best for long-term health,
32 the issue of protein is more recent, and indeed there are still limited definitive data to address
33 the question.

34 As with fat and carbohydrates, the question of the total amount of protein may seem
35 outdated and somewhat misplaced: as I will illustrate in this paper, the type of protein may
36 matter much more than the total amount. As far as cardiometabolic health is concerned, much
37 progress has been achieved in understanding that the total amount of fat is of much less
38 importance than the type of fatty acids (mostly making a distinction between saturated and
39 polyunsaturated fatty acids) and the foods that convey them (distinguishing basically animal
40 foods from vegetal oils) (3-6). Likewise, total carbohydrates now seem a useless descriptor that
41 should be definitely broken down in order to consider different types of carbohydrates and their
42 sources (so making a distinction in particular between low glycemic index foods and those
43 containing added sugars) (7, 8). As for proteins, classic distinctions between sources or types
44 of protein are only made on the basis of digestibility and indispensable amino acid contents,
45 and with respect to the primary criterion of the protein requirement. Future efforts to define
46 protein quality need to focus on studying dietary proteins in terms of health related outcomes,
47 thus encompassing long-term outcomes relative to cardiometabolic health (9). However, this
48 has mostly remained an emerging area of research and, until recently, what mattered in terms

49 of dietary protein was being above the nutritional allowance and of overall “good quality”,
50 which means an ability to supply sufficient indispensable amino acids to renew body protein
51 (1, 9, 10). Interestingly, by defining protein quality in this way, it becomes dependent on
52 quantity. Therefore, in industrialized countries using varied sources of protein at surfeit levels
53 of intake, this viewpoint cannot take account of the potential influence on health of the type or
54 source of dietary protein. However, the growing importance and urgency of considering dietary
55 protein in terms of sustainability (11-13) means it is now necessary to revise this persistent
56 viewpoint and consider the spectrum of the relationship between the type of protein in the diet
57 (animal vs plant protein, and different protein sources) and long-term health. In this review, I
58 intend to focus on the relation with animal / plant protein sources and cardiometabolic risk.

59 The topic of protein sources or types and cardiovascular health can be traced back more
60 than a century. That of animal protein and atherosclerosis was the subject of further study
61 during the 1960s. Considerable progress has been made during the past ten years and in
62 particular recently, based on an increasing body of evidence from randomized controlled trials
63 (RCTs) and cohort studies. Our aim in this article is to review the literature on animal/plant
64 protein and cardiometabolic health by consider varying levels of scientific evidence (basic
65 science, RCT, observational data). Furthermore, since animal and plant proteins are consumed
66 along with other nutrients and substances which make up the “protein package”, plant/animal
67 protein come with clear nutrient clusters. Therefore, one specific objective of this review was
68 to explore the relation between the intake of animal and plant protein and cardiovascular risk
69 by considering different nutritional levels for “protein” (such as amino acids, protein type,
70 protein foods, protein patterns and their association with overall dietary patterns and clusters
71 of nutrient intakes).

72

73 **The protein package and dietary protein intake as a marker of diet quality**

74 Protein intake goes with the “protein package” and results from complex dietary behaviors

75 There are two reasons for the associations between intakes of proteins of different types
76 and the overall dietary and nutrient patterns seen in individuals. This arises first of all from the
77 nutritional characteristics of the foods containing protein. To take a trivial example, animal
78 protein tends to be accompanied by saturated fatty acids, whereas plant protein tends to come
79 with fiber and phenolic compounds. This is usually referred to as the “whole food package”,
80 or to be more specific the “protein package”; this is important if we are to understand the
81 protein issue with respect to long-term health (14). The more intricate and specific the
82 association between a food protein and other nutrients/substances supplied in the food offer,
83 the stronger the relationship between their intakes in the diet will tend to be (15, 16). The
84 second reason stems from the overarching behavioral or social factors that govern food choices.
85 In western countries, specific protein foods may be chosen over other protein foods which they
86 therefore displace and will be accompanied by different associated foods. For instance, a higher
87 protein intake from fish is usually associated with a lower intake of red meat and high-fat dairy
88 products, a higher intake of vegetables, and a lower intake of sweets as has been reported in
89 the USA (17). These dietary features are also associated with more physical activity along with
90 other markers of a health-conscious set of attitudes (such as less cigarette smoking and a greater
91 use of vitamin supplements). Fish intake is also associated with other features of dietary
92 behavior such as eating three meals a day more frequently, consuming fewer prepared meals
93 and more organic foods, and thus implies a more favorable nutrient profile intake and of course,
94 higher sociodemographic and economic categories, as has been shown in France (16, 18, 19).

95 Plant and animal protein sources and diet quality: the case of meat eating

96 It is therefore not surprising that the literature contains numerous reports of associations
97 between protein sources and markers of diet quality. Because of the protein package, animal
98 proteins have long been blamed for their contribution to an inadequate nutrient intake profile,

99 which may explain the association with cardiovascular risk (14, 20). This has been reported
100 comprehensively with respect to meat intake in different populations and countries. The
101 relationship between meat intake and diet quality has also been considered in studies comparing
102 an omnivorous population qualified as “meat-eaters” versus non-meat eaters who eat fish
103 (pesco-vegetarians) and vegetarians. As discussed by others (21), meat-eaters in the European
104 Prospective Investigation into Cancer and Nutrition (EPIC)-Oxford study (22) had a higher
105 energy intake and a different nutrient intake profile, with a higher qualitative contribution of
106 SFAs and less fiber and PUFAs. However a simple direct comparison of the nutrient profile
107 remains difficult since “meat-eaters” had also a higher intake of vitamin B-12, vitamin D, Zinc
108 and iodine, as found in the EPIC-Oxford study and other studies on vegetarians (22-24). When
109 considering overall profiles of dietary quality, such as those assessed using dietary quality
110 indexes that are mostly based on food groups (such as Healthy Eating Indexes), the quality is
111 much higher for non-meat-eating diets than in the general population (25). However, any direct
112 comparison between vegetarian and non-vegetarian diets is largely confounded by behavioral
113 factors affecting food choices (26, 27). Finer comparisons have been made with populations
114 displaying less extensive ranges of meat consumption and behaviors than the general
115 population, such as the US Adventists (24, 28), or when comparing high-meat eaters, low-meat
116 eaters, poultry-eaters, fish-eaters (and vegetarians) (29, 30). In more general populations that
117 are almost entirely composed of meat-eaters, meat intake has also been associated with poorer
118 diet quality, as assessed from the profile of intake of certain important food groups: higher
119 intakes of total meat were associated with lower intakes of vegetables, fruits and cereals in
120 Europe (20); red meat intake was associated with lower intakes of fruits, whole grains and nuts
121 in Finland (31), and a lower meat:fish ratio was a strong determinant of diet quality and nutrient
122 profiles in Japan (32).

123 Protein patterns are strong markers of diet quality

124 The relationship between some specific animal proteins and diet quality indeed extends
125 beyond the case of meat, and a more general link has been reported overall for plant vs animal
126 proteins. Plant and animal protein intakes, both as a whole and in detail, show strong inverse
127 associations with each other and strong associations with patterns of nutrient intake, as was
128 clearly shown recently by Shang et al. (33) when studying the Melbourne Cohort. In more
129 detail, and as shown in Figure 1, animal protein and total protein intakes were strongly
130 associated, and animal protein was associated with lower intakes of plant proteins (including
131 grains), fiber and vitamins E and C, and higher intakes of saturated fats. By contrast, plant
132 protein was associated negatively with all animal proteins except fish, positively with fiber and
133 vitamin E, and negatively with energy and SFAs. Indeed, the associations were much stronger
134 regarding the intake of meat protein rather than total animal protein, and contrasted with fish
135 protein when compared to total animal protein. Phillips and colleagues found in the USA that
136 animal-based protein foods such as meat contributed more to the intake of protein and several
137 “positive” nutrients (notably, zinc, vitamin B-12 and highly-bioavailable iron) as well as
138 several “negative” nutrients (cholesterol and SFAs) than did plant-based protein foods (34).
139 Conversely, the authors found that plant-based protein foods contributed more to the intake of
140 other positive nutrients (notably dietary fiber, vitamin E, magnesium and PUFAs) (34). This
141 confirms that animal-derived nutrients are an important component of the overall pattern of
142 nutrient intake (35). To gain further insight into the nutrient profile associated with animal vs
143 plant protein intake, we analyzed plant and animal protein intakes and the probabilistic overall
144 nutrient adequacy of the diet of French adults (36, 37). We showed that as a general rule, total
145 plant protein and each type of plant protein intake (cereals, legumes, nuts and grains, etc.) were
146 strongly associated with nutrient adequacy (36, 37). The association between plant/animal
147 protein intake and overall nutrient adequacy was explained by a large set of nutrients, including
148 SFAs, sugars, potassium, sodium, folate, vitamin C, manganese, cholesterol and fiber (36). It

149 is important to note that this list includes many nutrients that are deemed to be of particular
150 importance to cardiometabolic health, and in particular fiber, SFAs, magnesium, potassium and
151 sugars. Some nutrients on this list clearly arise from the “protein package” (such as fiber,
152 magnesium, potassium and SFAs) whereas others (namely sugar) come from a much more
153 complex and indirect association between the nature of protein intake and food choices in the
154 diet. Indeed, it is likely that rather than resulting from a displacement by plant protein foods, a
155 lower sugar intake is due to a smaller contribution of added sugar to the diet of individuals who
156 make healthier choices in general, although we adjusted for potential confounding factors (such
157 as energy, alcohol intake, age and socioeconomic factors). Unlike the robust association with
158 plant protein intake, we found in this population that there was a marked heterogeneity within
159 the animal protein intake with respect to nutrient intakes and adequacy. This was expected
160 because, as mentioned above, meat intake was not associated with the same protein package
161 and dietary behaviors than fish or dairy intakes. In this respect, we found important contrasts
162 between protein from fish and low-fat dairy (positively associated with the nutrient cluster
163 related to global nutrient adequacy) and protein from processed meat, cheese and eggs
164 (negatively associated). These associations also varied according to gender, with a negative
165 association between red meat protein and nutrient adequacy in men only (36). Such a difference
166 in gender with respect to meat intake was also reported by Fogelholm et al. (31) who found a
167 positive association between red meat and vegetables in men only, and by Vergnaud et al. (20)
168 who reported an opposite association between the intakes of meat and ”sugar and
169 confectionery” or ”added fat”, depending on gender. When analyzing protein intake patterns
170 in the general French population, we recently reported that individuals with a protein pattern
171 with the largest contribution from eating pork had low overall scores for nutrient adequacy
172 whereas the population with a dominant contribution from fish protein had the highest scores
173 (16). In this general population, “pork eaters” and “poultry eaters”, were the groups with the

174 highest animal:plant protein ratio, whereas fish eaters had the lowest ratio. Likewise, “milk
175 eaters” (i.e. individuals with high intakes of protein from milk) had a high animal:plant protein
176 intake and their diet displayed relatively good nutrient adequacy (16). This further illustrates
177 the definite heterogeneity within animal proteins regarding their associated clusters of
178 nutrients. By contrast, our analysis showed that plant proteins, whatever their source (i.e.
179 grains, legumes, seeds and nuts) and gender were consistently associated with nutrient
180 adequacy.

181 Issues when interpreting current and future diet quality in terms of plant vs animal protein
182 patterns.

183 The complex links between animal:plant protein intake and the overall characteristics
184 of the diet were also found when examining the design of dietary interventional trials. The
185 Dietary Approach to Stop Hypertension (DASH) diet, Omniheart diet and others such as the
186 “Beef in an Optimal Lean diet” (BOLD) could be compared on the basis of their different levels
187 of plant:animal proteins but neither the composition of these diets, nor their nutrient contents,
188 were indeed simply related to this ratio (38, 39). The diets were indeed designed to increase
189 the levels of certain nutrients (such as potassium, magnesium and fiber) and were based on an
190 overall healthy dietary pattern which included fruits and vegetables and low-fat versions of
191 dairy and meat products (40). The levels of plant versus animal proteins per se were secondary
192 to the design of these diets and the results of these studies cannot be compared using this
193 parameter alone (39).

194 It remains unclear whether the association between plant protein intake and overall
195 nutrient adequacy can be ascribed mainly to the intrinsic characteristics of the foods that are
196 currently available to compose our diet (i.e. to the “protein package” of the usual protein food
197 groups), or if this might be largely confounded by the healthy behaviors of individuals who
198 purposely adopt a diet containing more plants (i.e. linked to overarching factors of diet quality)

199 (41). Dietary diversity is an overarching factor in diet quality which we found was associated
200 with both overall nutrient adequacy and plant protein intake in French adults (37). When
201 analyzing this relationship in more detail, we found that the association between plant protein
202 intake and nutrient adequacy was independent of overall dietary diversity (37). This result
203 further strengthens the view that plant protein intake is a robust marker of the nutritional
204 adequacy of the diet (36). Satija et al. (42) studied the relation between health and overall score
205 of adherence to a plant-based diet or to a healthy plant-based diet (as measured using a plant-
206 based diet index that positively counts plant food groups that are not fruit juices, sweetened
207 beverages, refined grains, potatoes and sweets/dessert. The authors found that the negative
208 association between a plant-based diet and a risk of diabetes in three USA cohorts was stronger
209 when the healthy plant-based diet was considered). Similar findings were reported recently
210 regarding the cardiovascular disease (CVD) mortality risk in the general US adult population
211 (43). It is important to note that food groups that contribute negatively to a healthy plant-based
212 diet are not rich in protein. When looking more closely at the data on the relationship with
213 protein intake, it can be seen that contrary to other indexes, the healthy plant-based diet index
214 is positively associated with total protein intake (42, 43). This association appears to be the
215 result of a higher intake of plant protein and a moderately lower intake of animal protein.
216 Therefore, plant/animal protein intake appears to be tightly associated with diet quality, even
217 across different types of plant-based or animal-based diets in the general population.

218 However, what is difficult to infer from the present literature is the extent to which the
219 association between plant protein intake and the intake patterns for nutrients that are important
220 to cardiometabolic health may depend on the characteristics of the plant protein foods that are
221 traditionally available, and whether this may change in the near future when new products
222 come onto the market. This indeed reflects the classic nutrients-foods-patterns complexity (44).
223 As pointed out in the analysis by Satija and colleagues, not all plant foods are healthy but the

224 plant protein foods currently available are mostly good contributors to healthy diets. This is
225 typically the case of legumes, nuts and seeds, for instance. By contrast, it remains unclear
226 whether the development of new plant protein products to be used as substitutes for meat
227 products by the general population will cause a healthy revision of the plant protein food
228 benchmark; there could be a risk that it will lead to a more heterogeneous relationship between
229 plant protein intake and a healthy nutrient intake, and hence long-term health.

230 Finally, this intricate association between intakes of various protein sources, the overall
231 dietary pattern and the profile of nutrient intake means that we should be very cautious when
232 analyzing and interpreting observational data. There are indeed two types of confusion that
233 should be borne in mind and do not have the same implications. The first concerns the
234 association between the intake of plant/animal proteins, dietary patterns and overall health-
235 related behaviors. This is indeed a classic pitfall in nutritional epidemiology. Carefully
236 designed models for very large samples are good solutions to overcome this issue using
237 residualization (45), but because the associations with protein intakes are strong, there will
238 always be an important risk of residual confusion. The second type of confusion arises from
239 the fact that when referring to “protein” in the diet we do indeed mean protein-rich products,
240 i.e. protein plus the “protein package”, along with nutrients and other substances that are more
241 or less closely associated with the protein per se. This second issue has implications when
242 interpreting the results of observational studies. It means that it may not be possible to
243 extrapolate the association found for “protein” in a given study to either another dietary context
244 (another population not sharing the same dietary background). It also means that it may not be
245 possible to extrapolate in the future if the population changes the nature of the foods conveying
246 their protein, after a change in the food offer. Beyond observational data, this issue also has
247 implications regarding the setting and interpretation of RCTs, as I shall discuss further below.

248

249 **Plant and animal proteins in observational studies**

250 Until recently, only a few studies had specifically examined the association between dietary
251 plant protein (versus animal protein) and the cardiovascular or diabetic risk, and they produced
252 a mixed picture. When modelling the data from the Iowa Women's Health Study, Kelemen et
253 al. (46) reported that plant protein could have potentially favorable effects on coronary heart
254 disease mortality when compared with both animal protein and total carbohydrate. Indeed, an
255 inverse association was observed when plant protein replaced either carbohydrate or animal
256 protein whereas no association was observed when animal protein replaced carbohydrates.
257 When analyzed in the context of low-carbohydrate diets, plant (vs animal) -based diets were
258 associated with lower rates of mortality from CVD in US cohorts (47), but there was little
259 evidence for such a contrast in European cohorts (48). This difference could thus be ascribed
260 to countries with different background diets and metabolic statuses of individuals, and different
261 types of dietary substitutions between dietary proteins and carbohydrates (49). Because the
262 models were adjusted to take account of numerous potential confounding factors (such as
263 physical activity, BMI, energy intake, alcohol intake, smoking) but to take little or no account
264 of the dietary factors associated with animal vs plant protein intakes, the associations with plant
265 and animal protein could rather have been ascribed to some association with plant-based or
266 animal-based diets, and the amount of animal/plant protein and fat that they conveyed. In other
267 words, plant and animal proteins could in this case be taken as markers of underlying dietary
268 patterns.

269 More recently, positive findings regarding plant vs animal proteins and cardiovascular
270 risk have been reported by major cohort studies. After combining the large Harvard cohorts,
271 Song et al. (50) reported significant associations between plant vs animal protein intake and
272 CVD mortality. In models adjusting for lifestyle risk factors and for numerous dietary and fatty
273 acid intakes, the authors found that a 10% increase in energy intake from animal protein would

274 translate into an 8% increase in CVD mortality. Conversely, a 3% increase in energy from plant
275 protein would reduce this risk by 12%. When compared to the energy contribution of animal
276 protein (mean: 14%, 5th-95th percentile: 9%-22%) and plant protein (4%, 2%-6%) in the
277 population, the impact of equally rebalancing plant and animal protein could therefore be
278 important. These associations were confined to participants with at least one unhealthy lifestyle
279 factor (based on smoking, heavy alcohol intake, overweight or obesity and physical inactivity)
280 and were not evident among those without any of these risk factors. In a Mediterranean
281 population at high cardiovascular risk, animal protein (and not plant protein) was also
282 associated with a higher risk of CVD events and mortality (51). In the large cohort of the
283 Adventist Health Study 2, we found an association between CVD mortality and animal protein
284 intake, but not total plant protein intake. An 18g increment of animal protein was associated
285 with a 7% increase in CVD mortality, which is a higher estimate of the risk than that previously
286 found. In the Adventist cohorts, the mean and range of animal protein was lower than in the
287 general population, and the population had a better overall dietary and nutrient pattern, with
288 fewer differences in lifestyle confounding factors across the different types of diet. Therefore,
289 the results could mean that even at low/moderate levels of intake in a population with a good
290 overall health status, an intake of animal protein is associated with a higher CVD risk.

291 An association between animal/plant protein and type-2 diabetes has also been
292 confirmed by recent studies. In a very large cohort of type 2 diabetics in eight European
293 countries (EPIC-InterAct), it was found that animal protein was associated with a higher risk
294 of diabetes, after adjusting for dietary and nutrient intakes. The relationship tended to be
295 attenuated but persisted after adjustment for BMI and waist circumference, suggesting that the
296 effect of animal protein intake was not entirely mediated by its association with body weight
297 and composition (52, 53), a classical association in the literature (52, 53). Similar results were
298 found in Chinese women, with evidence for mediation by insulin resistance, independently of

299 BMI (54). Genetic susceptibility to diabetes did not change the associations (55). Based on the
300 Melbourne Cohort (21,523 participants), Shang et al. (56) also reported a higher risk of incident
301 diabetes in individuals with a higher animal protein intake. These positive associations
302 appeared to be stronger in individuals with normal baseline plasma glucose, BMI or blood
303 pressure, and were more marked in men. An association with plant protein intake and diabetes
304 was only found in women. In another recent analysis of USA cohort studies that included a
305 large number of diabetics, the relationship was confirmed for animal protein, but it was also
306 found that plant protein was inversely associated with risk, irrespective of gender (57). A recent
307 meta-analysis (58) confirmed that the data overall clearly demonstrate an association between
308 total and animal protein intake and diabetes risk, but do not reveal a significant association
309 with plant protein, as reported previously (56). Interestingly, it has been argued that the relation
310 with animal protein may be non-linear, with important effects only being observed under high
311 intakes, and may only be mediated in part by BMI (59). It was recently found that total and
312 animal protein intake, and the animal:plant protein ratio was strongly and positively associated
313 with insulin resistance in a cross-sectional analysis of middle aged and older people from the
314 Adventist Health Study 2 (60). These results suggest that the effect of animal protein on insulin
315 sensitivity can also occur at the low levels of intake seen in this population.

316 Overall, these results on diabetes risk and CVD mortality are generally in line with the
317 findings regarding intermediary endpoints for cardiometabolic health. A relation between the
318 type of protein intake and incident metabolic syndrome was recently documented in the
319 Melbourne Cohort study (33). The authors reported a higher risk with higher total and animal
320 protein intakes and lower plant protein intakes. A higher energy intake from animal protein was
321 associated with increases in systolic blood pressure, waist circumference and body weight over
322 11 years, whereas a higher plant protein intake was associated with reductions in waist
323 circumference and weight (33).

324 Considerable study over many years has focused on the relation between animal/plant
325 protein intake and blood pressure (61). A number of transversal or longitudinal studies reported
326 negative associations between plant protein and blood pressure (62-66). However, total protein
327 intake was shown to be inversely associated with blood pressure in many studies, and some
328 reported inverse associations between animal protein intake and blood pressure or the risk of
329 hypertension (67-69). Some of the heterogeneity affecting these findings could be linked to the
330 background dietary context and the type of animal protein consumed, which would explain the
331 contrasting findings in Asian vs Western populations. Taken together, however, the difference
332 between the effects of plant or animal protein on blood pressure does not appear to be so marked
333 (70-72), unlike the harder endpoints discussed above.

334

335 **Beyond total plant and total animal protein: the type of animal/plant protein matters**

336 It has become clear in the last decade that plant protein and animal protein are overly coarse
337 descriptors of protein intake. When reviewing the epidemiological studies that have attempted
338 to analyze in detail the association between more specific protein sources and some health
339 endpoints, we can see dramatic differences between specific protein sources within the “animal
340 protein” type. In a recent meta-analysis of diabetes risk, the intake of proteins from red meat
341 and processed meat was associated with a higher risk, whereas the intake from dairy products
342 was associated with a lower risk (58). Studies with fully adjusted models of substitution have
343 been helpful in further analyzing this heterogeneity. When modeling the effect of replacing one
344 portion of animal protein food with one portion of average plant protein food (comprised of
345 whole grains, legumes, peanuts, peanut butter and other nuts), Malik et al. (57) found that
346 substitution for processed meat was associated with a greater benefit with respect to diabetes
347 risk (a 21% reduction in risk) while the association with dairy protein was not significant
348 (Figure 2). Red meat was intermediate in this gradation. Interestingly, high-glycemic index

349 foods such as refined grains and potatoes were also associated with a higher risk when
350 compared to plant protein foods (Fig. 2). In the Melbourne Cohort, Shang et al. (33) ascribed
351 the positive effect of animal protein on incident metabolic syndrome and its components to red
352 meat and chicken, and the negative effect of plant protein to legumes and nuts. Red meat was
353 the animal protein which was found to be significantly associated with diabetes risk in a
354 Chinese cohort (54). In the context of low carbohydrate diets, red and processed meats have
355 been implicated in the positive association between intakes of animal protein and fat and a
356 higher risk of diabetes (73). Since these studies adjusted for BMI, there could be additional
357 effects of meat on diabetes risk than those mediated by changes to BMI (74-76). An elucidation
358 of the underlying mechanisms supports the causal role of processed and total red meat
359 consumption in increasing risk of type 2 diabetes (77). These possible mechanism include role
360 of saturated fatty acids, sodium, advanced glycation end products, nitrates/nitrites for
361 processing, heme iron, trimethylamine N-oxide, branched amino acids, and endocrine disruptor
362 chemicals (77).

363 As far as cardiovascular mortality is concerned, and using the same approach of protein source
364 substitution in the Harvard cohorts, it was found that replacing processed meat by plant protein
365 was the most beneficial (39% reduction in risk), while replacing unprocessed meat (17%
366 reduction in risk) or dairy (11% reduction) procured the most modest benefits (50). These
367 findings have clarified earlier reports regarding the association between the risk of coronary
368 heart disease and the consumption of protein food groups in the Nurses' Health Study in 2010.
369 In this report, Bernstein et al. (78) found that in a model controlling statistically for energy
370 intake, one serving/day of nuts was associated with a 30% lower risk when compared to one
371 serving/day of red meat. Similarly, when compared to one serving/day of red meat, a lower risk
372 was associated with one serving/day of low-fat dairy (13% lower risk), poultry (19%) or fish
373 (24%). This was also in line with the recent report from the *Prevención con Dieta Mediterránea*

374 (PREDIMED) study, where portions of red and processed meats involved the highest risk of
375 incidence of metabolic syndrome, when compared to legumes, poultry and rabbit, fish or eggs
376 (79). Because intakes of protein from various food groups are indeed much multicollinear, our
377 first aim was to analyze the underlying structure of the protein pattern in order to identify the
378 most salient component. Therefore, we analyzed the pattern of protein intake in the Adventist
379 Health Study 2 and found five protein factors (independent of each other), which we then used
380 in models to analyze cardiovascular mortality. We found significant and strong associations
381 with two of these factors. Comparing the highest vs lowest quintiles of factor scores, we found
382 a 61% higher risk for the "Meat" protein factor and a 40% lower risk for the "Nuts & Seeds"
383 protein factor. These estimates were little influenced by other characteristics of the diet, such
384 as vegetarian dietary patterns or nutrients related to CVD health. These associations were
385 particularly strong among young adults aged 25–44 (with a 100% higher risk for the "Meat"
386 protein factor and a 60% lower risk for the "Nuts & Seeds" protein factor); Figure 3.

387 Finally, although there is a very important body of evidence for their effects on diabetes
388 and CVD risk, it should be kept in mind that red meat, and especially processed meat, are
389 strongly associated with health-oriented behaviors that still make it difficult to disentangle the
390 causal effects of red meat from observational studies (80).

391

392 **Lessons from clinical trials**

393 Clinical trials offer another line of evidence regarding the specific effects of some plant and
394 animal proteins. The literature proposes a large body of studies that have examined the effects
395 of specifically manipulating plant proteins on intermediary endpoints related to
396 cardiometabolic health. The studies can be divided into two different types. The first contains
397 studies that manipulate protein in quite a specific manner by using purified proteins that can be
398 included in experimental foods with a closely controlled composition. The second type

399 concerns studies that test the utilization of protein foods as included in individual diets, usually
400 controlling for the macronutrient content of the diets. In a clinical trial, if a “plant protein” is
401 tested using foods that are rich in that protein, the trial will refer to the effect of consuming
402 certain plant protein-rich foods along with the protein package of these foods and not
403 specifically the plant protein. It would be erroneous to assign the results to either a particular
404 protein or to the protein food group in general, i.e. irrespective of variations in the nutrient
405 contents of these protein foods (81). However, the findings of such studies have important
406 implications for public nutrition, because they can be extrapolated to how individuals actually
407 consume dietary proteins or would eat more of a dietary protein if willing to do so, using the
408 protein foods that are available. By contrast, if a trial uses a protein ingredient that is purified
409 (e.g. protein isolate) and used to prepare experimental foods, the results will apply more to
410 “protein” but are less extrapolable to real life. Furthermore, it should be kept in mind that
411 proteins are never pure and they usually convey >10% nutrients and other substances intimately
412 associated with them (notably in the case of plant protein) (82). Even if they are intimately
413 associated, there may be variations in the amounts and nature of the substances involved, thus
414 making the “protein” quite heterogeneous. This has long been discussed regarding the amounts
415 of isoflavones in soy protein, the opinion being that isoflavones may convey a large part of the
416 benefit associated with “soy protein” (83-85). Another point (which might seem a detail and is
417 often overlooked) is that protein ingredients may be isonitrogenous but differ regarding the
418 amount of amino acids they contain, as we discussed several years ago (86). In any case, the
419 more the trial design aims to decipher a specific effect of the protein isolated, the more the
420 results will apply to protein per se, but the less they will readily apply to public nutrition, unless
421 the food industry can rapidly deliver new food products containing purified protein that
422 individuals are prepared to consume. In that case, it is questionable whether such trials are
423 relevant to the actual situation where individuals would incorporate these new protein foods in

424 their diet, because these new protein foods would be expected to replace the other protein foods
425 that they are currently consuming, in a way that has not been analyzed by the design of the
426 RCT.

427 I do not intend to review all the literature concerning RCT on specific protein and
428 protein sources and cardiometabolic health, but I would like to discuss certain aspects of this
429 literature.

430 Briefly, as far as purified protein ingredients are concerned, much as been published on
431 soy protein, and the reader is directed to some interesting reviews and opinions (85, 87, 88). I
432 would like to use this example to consider the amounts (“doses”) of soy protein that could be
433 expected to convey the effects reported in the literature. The effects of soy protein on blood
434 lipids and blood pressure have mostly been observed with high intakes of protein, generally
435 around ~35g/day (83, 89), while the effects of soy protein at intakes below 25g/day are either
436 weak or found not statistically significant; this was discussed recently in a meta-analysis
437 concerning the effects on blood pressure (84). In order to judge the practical implications of
438 such levels of intake, it is worth mentioning that the high soy protein intake of Adventist vegans
439 in the USA averages only 13g (24). Other plant proteins, which have been less studied, may
440 have effects on cholesterol or blood pressure, as was suggested for lupin protein (90-92), but
441 the data are scarce. It may therefore be difficult to determine whether a combination of purified
442 plant proteins in large quantities (~50g/day) could result in reproducing some of the findings
443 regarding soy protein at high doses reported in RCT.

444 It is more likely that plant protein might benefit cardiometabolic risk factors when
445 consumed as a protein food. This would not be surprising because some components in the
446 plant protein package could favorably replace others that are associated with animal protein
447 (e.g. fatty acid types), but also because some of them have been shown to be effective in
448 modulating cardiometabolic risk factors, such as fiber. In RCT, the positive effects of plant

449 protein when using plant foods or unpurified protein ingredients have been ascribed to the
450 effects of protein and fiber that are found at high levels in the unrefined ingredients. For
451 instance, this is the case for lupin (93, 94), although there have been some conflicting results
452 (95). Indeed, as shown in the literature when comparing the results with soy products against
453 those obtained with soy protein ingredients, the evidence generally appears much stronger
454 when studying whole plant foods or raw ingredients than purified proteins (96-98). Overall, a
455 recent analysis reported that the evidence available from randomized controlled trials suggests
456 that 1 to 2 servings of plant protein foods instead of animal protein foods decreases low-density
457 lipoprotein cholesterol, non-high-density lipoprotein cholesterol and apolipoprotein B by ~4%
458 in adults with and without hyperlipidemia. (99). Because of inconsistencies or inaccuracies in
459 the estimates the overall certainty of the evidence is moderate and suggests that more research
460 will be required to refine these estimates (99). The effect of pulses on cardiovascular risk
461 factors in RCT is reviewed elsewhere in the same volume of this journal [add Sievenpeper's
462 review reference]. In my view, further studies are needed to assess the effects of plant protein
463 on various cardiometabolic risk factors, such as low-grade inflammation, endothelial vascular
464 function and insulin sensitivity, because there have been some null results (e.g., 100) and the
465 field has not been studied sufficiently. These studies would be better served by the use of
466 different types of plant protein and different types of substitution.

467 When considering even more general changes to food consumption involving foods
468 rich in plant proteins, a consensus has now been reached that legumes improve cardiometabolic
469 risk factors (as compared to various diets controlled for energy nutrients). For a full review on
470 legumes and beans and cardiometabolic risk, the reader can refer to the review by Salas Salvado
471 in the same volume of this journal [add Salas Salvado's review reference here]. By contrast, it
472 is difficult to draw any conclusions from RCTs that have tested the effects of meat consumption
473 because the dietary treatments and results have varied. O'Connor et al.'s recent meta-analysis

474 (101) reported no effect of total red meat intake >0.5 servings/day on blood lipids and blood
475 pressure. It had already been found that substituting red meat for poultry or fish did not affect
476 blood lipids (102) and substituting protein in general for some types of carbohydrates in a
477 healthy diet could benefit CVD risk factors (103, 104). However, this information from RCTs
478 contrasts with observational findings that associated red meat intake and CVD risk factors
479 (105) or CVD events and mortality (106-114).

480 Approaches that rely on simultaneous changes to several foods in a diet, such as a more
481 food-based and dietary pattern method, are useful to clarify dietary recommendations aimed to
482 achieve a reduction in cardiometabolic risk (115). If trying to summarize the findings of
483 observational and interventional studies, what stands out is that a healthier protein pattern
484 would consist in reducing the consumption of processed and red meats and preferring more
485 protein sourced from legumes, nuts and seeds. This general conclusion would also fall in line
486 with the common features of generally prudent diets such as the Mediterranean diet (116-118).
487 More data are required to investigate the specific effects of other animal based protein products
488 (such as chicken and dairy) and other plant-based products (such as grains), and the factors
489 which modulate their effects on cardiometabolic health.

490

491 **Could amino acids form part of the relationship?**

492 As I discussed at the beginning of this paper, one might consider that a large part of the
493 relationship between plant and animal protein intakes and cardiometabolic risk could be
494 ascribed to the large cluster of nutrients and other substances (e.g. phytochemicals) that they
495 convey, either directly or indirectly (39, 119). Indeed, in observational studies, it remains
496 difficult to separate the effects of a specific protein from that of the closely associated “protein
497 package”, and also from other characteristics of the overall diet, as I have argued. It also seems
498 clear that the literature is more conclusive when RCTs involve whole protein plant foods rather

499 than purified proteins. Nonetheless, it should also be considered that the type of protein per se
500 (i.e. the relative amounts of amino acids that it supplies) may affect cardiometabolic risk.
501 Support for this proposal can be found in human and animal studies that manipulated amino
502 acid intakes, and also from an analysis of observational studies. Many studies have reported a
503 significant association with cardiometabolic outcomes, even when fully adjusted models were
504 used, i.e. including dietary/nutrient intakes and despite classic confounding factors related to
505 behaviors and socioeconomic status. For example, this was the case regarding a recent report
506 on plant/animal protein intake and the risk of diabetes, which used a model that, as well as
507 numerous genetic and lifestyle factors, also adjusted for total energy intake, percentages of
508 energy from trans-fats, saturated fats, monounsaturated fats and polyunsaturated fats, dietary
509 cholesterol, dietary fiber, and the glycemic index (57). Song et al. (50) also recently found
510 significant relations between CVD mortality and plant vs animal protein intakes when adjusting
511 for dietary intakes (e.g. whole grains, fruits and vegetables, glycemic index) and the intakes of
512 different fatty acids. Likewise, in the Adventist Health Study-2 cohort, we found that the strong
513 association between protein intake factors was not modified when account was taken of
514 potential confounders such as the vegetarian diet category and the intake of a series of nutrients
515 considered as being relevant to cardiovascular risk (e.g. PUFAs, SFAs, sodium and vitamins A,
516 C, E, B-6, folate and B-12) (120).

517 As well as their utilization for protein synthesis or oxidation, amino acids enter specific
518 metabolic pathways that lead to the synthesis of metabolites which play key roles in physiology
519 and pathophysiology. For this review, I would like to mention a few amino acids that are present
520 at varying levels in plant and animal proteins and have been studied widely for their probable
521 impacts on physiology: arginine, cysteine and branched chain amino acids.

522 Arginine provides the substrate for the synthesis of nitric oxide, the key mediator of
523 vascular homeostasis (121-123). Indeed, an impairment of NO production and/or bioactivity

524 has been largely reported as a central feature associated with cardiometabolic risk, including
525 that of coronary artery disease, stroke and diabetes (124). As shown by a meta-analysis,
526 arginine supplementation improves endothelial function when its levels are low at baseline
527 (125). The beneficial effects of arginine supplementation on endothelial function can be
528 achieved with a low intake (such as that seen by modifying the amount or type of protein in the
529 diet) as has been demonstrated by its ability to blunt postprandial endothelial function after a
530 high-fat meal (126, 127). The kinetics of arginine bioavailability may also play an important
531 role inasmuch as arginine that is made available slowly – as is the case for dietary, protein-
532 bound arginine – is directed more towards nitric oxide synthesis than arginine that is rapidly
533 available (for example, in a dietary supplement) (128). The potential of arginine-rich proteins
534 to prevent alterations to postprandial endothelial function has been documented (129, 130) and
535 arginine may mediate some of the beneficial effects of arginine-rich proteins in the diet (90,
536 130). Arginine may also have other benefits on cardiometabolic health (131-135). The benefits
537 of high arginine intake have also been studied for many years in association with lysine intakes,
538 stemming from seminal works on plant and animal proteins and atherosclerosis (136, 137).
539 More recently, in a closely controlled trial, Vega-Lopez et al. (138) found that a low (vs high)
540 lysine:arginine ratio lowered fasting and postprandial C-reactive protein and lowered
541 postprandial plasma levels of triglycerides in moderately hypercholesterolemic subjects.
542 Sulfur amino acids, and particularly cysteine, have also been studied for their potential effects
543 on cardiometabolic risk, because of their links with homocysteine (a probable risk factor for
544 CVD) and glutathione (a pivotal molecule in redox homeostasis). The relationship between
545 cysteine intake, glutathione metabolism and cardiometabolic health has been widely studied
546 and reviewed elsewhere (139-141). In brief, dietary cysteine supplementation has been reported
547 to reduce diet-induced oxidative stress and insulin resistance in rats (142). This protective effect
548 was notably accompanied by an alteration of glutathione redox status, which has been reported

549 as being an early marker of atherosclerosis in healthy humans (143). In humans, variations in
550 sulfur amino acid intakes affect fasting plasma free cysteine concentrations and the redox
551 status, as shown by the extracellular cysteine/cysteine redox potential (144). Supplementation
552 with a cysteine donor lowers plasma homocysteine, improves glutathione levels and redox
553 status, and lowers blood pressure (145). Cysteine intake has also been inversely associated with
554 the incidence of stroke (146).

555 BCAAs have been widely studied for their relation with insulin resistance since it was
556 reported that high BCAAs plasma levels formed part of a metabolic signature correlated with
557 insulin resistance in obese individuals. BCAAs concentrations are elevated in obese subjects
558 with insulin resistance and/or metabolic syndrome (147). They are associated with plasma
559 acylcarnitines and cardiovascular risk factors (147-152) and they are predictive of diabetes and
560 CVD (153-155). BCAAs intake has been associated with the incidence of insulin resistance
561 and diabetes, although this intake could simply be a marker of total and animal protein intake
562 (156, 157). BCAAs supplementation has also been reported to modulate insulin sensitivity,
563 notably in the context of diet-induced obesity (158-160) or in individuals with low baseline
564 levels of intake (161). These findings remain controversial, because opposite results were
565 reported with leucine alone in mice (162, 163) and high plasma BCAAs concentrations resulted
566 from a complex change in their metabolism (150, 164). Importantly, dietary BCAAs largely
567 interplays with fatty acid oxidation, and we recently showed that this could explain why the
568 type of protein in a high-fat meal modulates the extent of postprandial mitochondrial overload
569 and incomplete substrate oxidation (165). However, it remains difficult to ascertain whether
570 dietary and plasma BCAAs contribute to the onset of the dysregulations contributing to
571 cardiometabolic risk, or if high plasma BCAAs concentration is a marker of dysregulated
572 metabolism (166, 167). Recent Mendelian randomization analyses suggested a causal role of

573 BCAAs metabolism, which is impaired by insulin resistance, in the etiology of type 2 diabetes
574 (166, 168, 169).

575 Based on experimental studies in animal or humans, or associations found in
576 epidemiological studies, other amino acids have been studied for their links with cardiovascular
577 risk factors and identified as candidates for mediating the effects of protein intakes. For
578 instance, oral glycine was shown to be particularly efficient in potentiating the action of insulin
579 (170, 171). Intakes of glutamic acid have been associated with lower systolic blood pressure,
580 independently of other amino acids (172). Plasma glycine and glutamine are inversely
581 associated with the incidence of type-2 diabetes (153). Other candidate amino acids include
582 histidine, phenylalanine and tyrosine (135, 173).

583 It would be interesting to study both the separate and combined effects of amino acid
584 intakes, to identify the most influential amino acids when taken together (with additive or
585 synergetic effects) and try to determine how they might account for the effects of plant proteins.
586 Because amino acid intakes are not independent of each other, and are also associated with
587 other characteristics of the diet, the analysis of observational data needs to take account of this
588 complexity and ways must be found to reduce it to the most salient components. In this regard,
589 Teimoori et al. (174) recently analyzed patterns of amino acid intake using models with
590 multiple dietary/nutritional confounders. They found that an amino acid factor with high
591 loadings from BCAAs, aromatic amino acids, serine and threonine was strongly associated
592 with the incidence of hypertension in a model adjusting for fatty acid types, calcium, sodium,
593 magnesium, potassium and fiber. In the study by Jenning et al. (173), the association between
594 the intake of several amino acids and blood pressure was found to depend on whether they
595 originated from plant or animal protein sources, which is indicative of the complexity of this
596 issue. Further analysis of this complex situation is necessary in the context of large cohorts.

597 Although it is much too soon to draw any definite conclusions, the amino acids
598 identified in the literature that I have reviewed here as possibly being detrimental to
599 cardiometabolic health are found at higher levels in animal protein and their intake are more
600 contributed by animal protein intake. These are mostly BCAAs and aromatic amino acids, –
601 indispensable amino acids (175). Conversely, the amino acids identified as being potentially
602 beneficial are mainly found at higher levels in plant proteins. These are mostly arginine,
603 cysteine, glutamine/glutamate, and glycine, or – non-indispensable amino acids (173). These
604 findings warrant further study to understand patterns of amino acid intake and cardiometabolic
605 health. This research may indeed change our vision of amino acids as being classified as
606 “indispensable” vs “non-indispensable”, and drive attempts to shift our understanding of
607 protein quality for human health.

608 **Conclusion**

609 Plant protein in western countries is a robust marker of nutrient adequacy of the diet, whereas
610 the contribution of animal protein largely varies according to animal source. Plant and animal
611 proteins are indeed consumed with other nutrients and substances that makes the ‘protein
612 package’ and this may explain their relation to cardiometabolic health in the current dietary
613 patterns. Yet recent data from large cohorts have confirmed that total and animal proteins are
614 associated with the risk of CVD and diabetes, even in models that are largely adjusted for
615 lifestyle and dietary/nutritional factors. Here again, there is marked variability depending on
616 the type of animal protein. Protein from processed red meat and total red meat on the one hand,
617 and from legumes, nuts and seeds on the other, are often reported at the extremes of the risk
618 range. RCTs using purified proteins have contributed little to the topic to date, inasmuch as the
619 findings cannot readily be extrapolated to current or near-future diets, but RCTs studying whole
620 protein foods have shown a beneficial effect of pulses. Despite many of the benefits of plant
621 protein reported in observational or interventional studies may stem from the protein package

622 that they convey and the nutrients that they displace, there are also important indications that
623 protein *per se* may affect cardiometabolic health via the many amino acids that are present at
624 typically contrasting levels in plant vs animal proteins.

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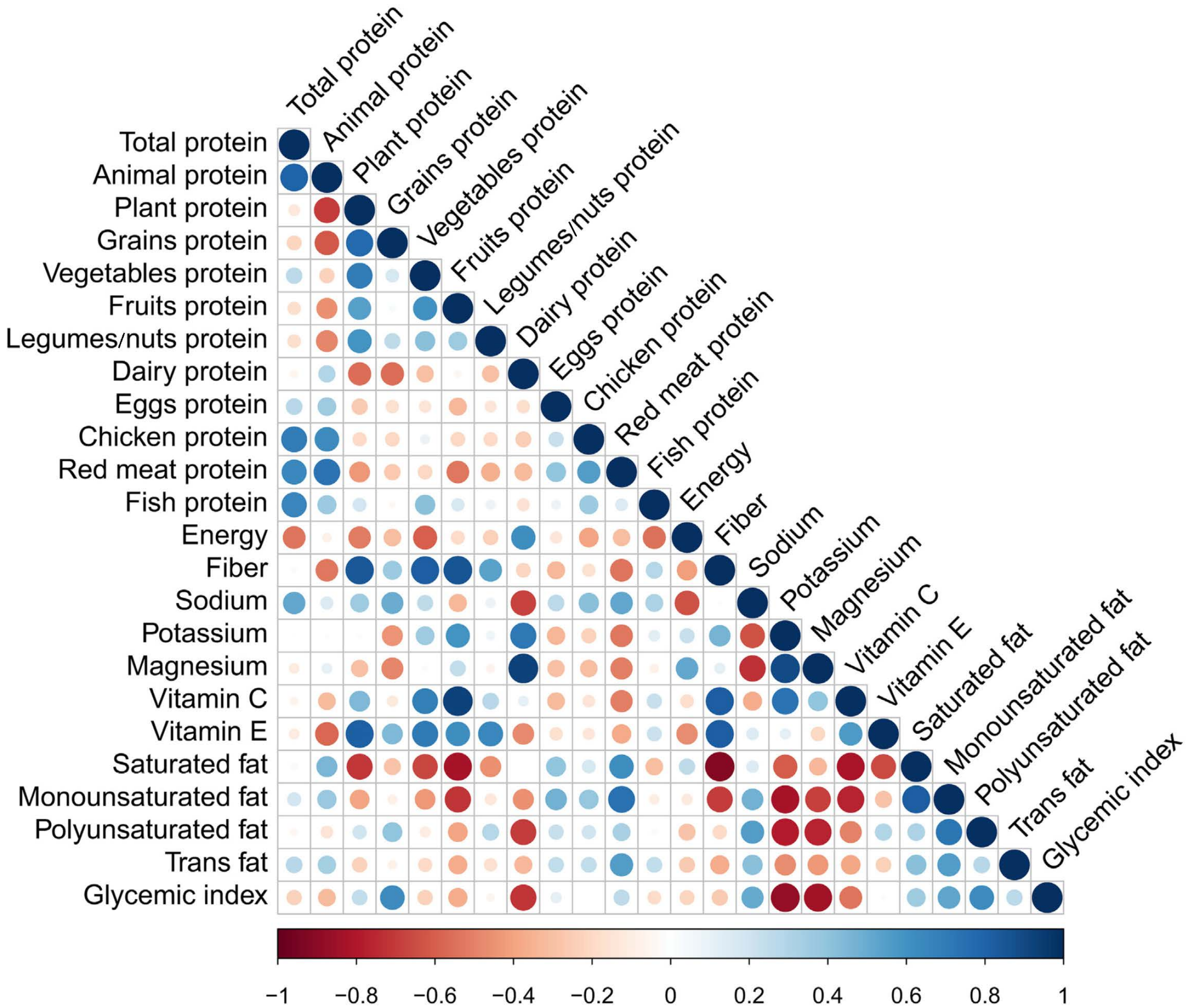
Legends for Figures

Figure 1. Partial correlation analysis between intakes of protein according to sources and intakes of nutrients in the Melbourne Cohort study. Pearson's correlation analysis was used to calculate age- and gender- adjusted partial correlation coefficients. Blue and red colors indicate positive and negative correlations, respectively, and color intensity and the size of the circle are proportional to the correlation coefficient. Adapted with permission from Shang et al. (33).

Figure 2. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) for type 2 diabetes associated with replacement of 1 serving of individual animal protein foods (dairy foods, poultry, eggs, red meat, and processed meat), refined grains, and potatoes with 1 serving of vegetable protein foods (composite variable comprised of whole grains, legumes, peanuts, peanut butter, and other nuts) in the Nurses' Health Study (1984–2008), Nurses' Health Study II (1991–2009), and the Health Professionals Follow-up Study (1986–2008). The models adjusted for age, family history of diabetes, smoking, alcohol intake, physical activity, race/ethnicity, total energy intake, postmenopausal hormone use (Nurses' Health Study, Nurses' Health Study II), oral contraceptive use (Nurses' Health Study II), intakes of sugar-sweetened beverages, fruit, and vegetables, and body mass index. Results were mutually

adjusted for other food sources of animal protein, refined grains, and potatoes. Reproduced with permission from Malik et al. (57).

Figure 3. Multivariate-adjusted hazard ratio (HR) of CVD mortality by quintile of the "Meat" protein factor (Panel A) and "Nuts & Seeds" protein factor (Panel B) in 81,337 participants in the Adventist Health Study-2, presented at two age categories. The model was adjusted for age, sex, race, BMI, individual socioeconomic factors, health-related lifestyle, energy intake and the type of diet in the vegetarian spectrum. Significant age interactions were found for the "Meat" and "Nuts & Seeds" protein factors. HRs were estimated at the mean age of each age category. Adapted from Tharrey et al. (120).



Type of Food Replaced

HR (95% CI)

Dairy

0.98 (0.96, 1.00)

Refined grains

0.94 (0.91, 0.96)

Poultry

0.91 (0.86, 0.96)

Eggs

0.89 (0.83, 0.95)

Red meat

0.89 (0.86, 0.93)

Fish

0.87 (0.81, 0.94)

Potatoes

0.84 (0.78, 0.91)

Processed meat

0.79 (0.74, 0.84)

