

Dietary dilemmas over fats and cardiometabolic risk

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1 **Dietary dilemmas over fats and cardiometabolic risk**

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3 Julie A. Lovegrove¹

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5 ¹Hugh Sinclair Unit of Human Nutrition, Department of Food and Nutritional Sciences, and
6 Institute for Cardiovascular and Metabolic Research (ICMR), University of Reading,
7 Whiteknights, Reading, RG6 6AP, UK.

8

9 ***Corresponding author:** Professor Julie A. Lovegrove, email: j.a.lovegrove@reading.ac.uk,
10 fax: +44 (0)118 931 0080

11

12 **Running title:** Dietary fats, cardiovascular and metabolic risk

13

14 **Key words:** cardiovascular disease; cardiometabolic; saturated fatty acids; polyunsaturated
15 fatty acids; monounsaturated fatty acids; serum lipids; blood pressure, type 2 diabetes

16

17 **Abbreviations:** CVD, cardiovascular disease; CHD, coronary heart disease; COMA,
18 committee on medical aspects of food and nutrition policy; DGAC, US Dietary Guidelines
19 Advisory Committee; FAO, food and agriculture organisation; HbA1c, heamoglobin A1c;
20 HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol;
21 MUFA, monounsaturated fatty acids; NACNE, National Advisory Committee for Nutrition
22 Education; NDNS, National Diet and Nutrition Survey; PUFA, polyunsaturated fatty acids;
23 RNI, recommended nutrient intake; RR, relative risk; RCT, randomised control trial; RNI,
24 Reference Nutrients Intakes; SACN, Scientific Advisory Committee on Nutrition; SFA,
25 saturated fatty acids; TAG, triacylglycerol; TC, total cholesterol; WHO, world health
26 organisation.

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29

30 **Abstract**

31 Cardiovascular diseases (CVD) remain the greatest cause of death globally, and with the
32 escalating prevalence of metabolic diseases, including type-2 diabetes, CVD mortality is
33 predicted to rise. While the replacement of saturated fatty acids (SFA) has been the
34 cornerstone of effective dietary recommendations to decrease CVD risk since the 1980s, the
35 validity of these recommendations have been recently challenged. A review of the evidence
36 for the impact of SFA reduction, revealed no effect on CVD mortality, but a significant
37 reduction in risk of CVD events (7-17%). The greatest effect was found when SFA was
38 substituted with polyunsaturated fatty acids (PUFA), resulting in 27% risk reduction in CVD
39 events, with no effect of substitution with carbohydrate or protein. There was insufficient
40 evidence from randomly controlled trials to conclude upon the impact of SFA replacement
41 with MUFA on CVD and metabolic outcomes. However, there was high quality evidence that
42 reducing SFA lowered serum total, and specifically low-density lipoprotein cholesterol, a key
43 risk factor for CVD, with greatest benefits achieved by replacing SFA with unsaturated fats.
44 The exchange of SFA with either PUFA or monounsaturated fatty acids, also produced
45 favourable effects on markers of glycaemia, reducing HbA1c, a long-term marker of
46 glycaemic control. In conclusion, the totality of evidence supports lowering SFA intake and
47 replacement with unsaturated fats to reduce the risk of CVD events, and to a lesser extent,
48 cardio-metabolic risk factors, which is consistent with current dietary guidelines.

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51

52 **Introduction**

53 Cardiovascular diseases (CVD), which include coronary heart disease (CHD), cerebral
54 vascular disease and peripheral vascular diseases, are the greatest cause of mortality in the
55 world, with an estimated 158,000 deaths annually in the UK alone (1). In parallel, the
56 epidemic of metabolic diseases, principally type 2 diabetes, and obesity contribute to an
57 increase in risk from CVD. In England, 58% of women and 65% of men are overweight or
58 obese, with the prevalence of obesity increasing from 15% to 26% between 1993 and 2016
59 (2). This rise in obesity directly contributes to the prevalence of type 2 diabetes. Of the
60 estimated 6% of the UK population diagnosed with diabetes, 90% have type 2 diabetes, with
61 a rapid increase in prevalence from 2.9% to 7.6%, and 1.9% to 6.2% among men and women
62 respectively between 1994 and 2016 (3).

63 These chronic degenerative diseases are multifactorial, with a number of modifiable lifestyle
64 risk factors. The Global Burden of Disease, Injuries, and Risk Factor study 2013 (4), includes
65 data from 188 countries, and quantified modifiable risk factors to identify emerging threats
66 to population health and opportunities for prevention. In the latest update, the quantified
67 risks accounted for 88.7% disability-adjusted-life years (DALYs) lost from CVD and circulatory
68 diseases and 76.4% from diabetes, the highest of all outcomes. Moreover, it was estimated
69 that dietary risks were the greatest contributor to CVD and diabetes, accounting for 10.4
70 million deaths and 241.4 million DALYs (4). These, and other data, demonstrate the
71 relevance of diet to CVD and metabolic risk and highlights the importance of dietary
72 modulation to reduce this risk. This review will address the impact of dietary fats,
73 particularly saturated fatty acids (SFA), on risk from these diseases.

74

75

76 **Cardiovascular and cardio-metabolic risk factors**

77 There is unequivocal evidence that reduction of total cholesterol (TC), and more specifically
78 low density lipoprotein-cholesterol (LDL- C) significantly reduces the incidence of myocardial
79 infarction and death from cardiovascular causes, without adversely affecting the risk of
80 death from all causes in primary and secondary prevention studies (5). The European
81 Atherosclerosis Society Consensus Panel reviewed the evidence for the effects of high LDL-C

82 on the development of CVD, including CHD and stroke and showed a clear linear causal
83 relationship as illustrated in Figure 1 (5). A consensus was reached that serum LDL-C
84 increased the progression of atherosclerosis in a dose-dependent manner, with greater
85 detriment arising from longer exposure of the vascular endothelium to LDL-C (5). Evidence
86 also clearly demonstrates that small dense LDL particles, which are more likely to move into
87 the vascular intima, undergo oxidation and contribute to the atherosclerotic plaque are
88 more atherogenic and confer a greater risk for CVD (6). In contrast, a low concentration of
89 serum high density lipoprotein-cholesterol (HDL-C) is related to an increased risk of CHD (7),
90 is a key feature of the metabolic syndrome and is highly prevalent in type 2 diabetes and
91 obesity (8). HDL particles are involved in a process of 'reverse cholesterol transport', in
92 which cholesterol is removed from tissues and organs and returned to the liver for
93 metabolism (7). However, recent evidence has shown that increasing serum HDL-C, by use
94 of drugs, may not result in the anticipated reduction in CVD risk, which is more closely
95 related to the functionality, rather than the cholesterol content of HDL particles (9).
96 However, the TC:HDL-C ratio is considered a more sensitive and specific CHD risk predictor
97 than individual cholesterol measures; at all ages in women and the only lipid predictor
98 independently related to CHD in men 65 to 80 years old (7, 10).

99

100 Hypertension is the greatest contributor to death globally and a key CVD and metabolic risk
101 factor that is modifiable by diet (11). While the importance of lowering salt intake to reduce
102 blood pressure is well founded (12), evidence for the impact of dietary fats on blood
103 pressure and vascular function is lacking (13). The health of the vasculature and endothelial
104 function is important for CVD risk reduction and inextricably linked to blood pressure.
105 Endothelial dysfunction occurs when the balance between endothelial injury and repair is
106 disrupted. Circulating bone marrow-derived endothelial progenitor cells play an important
107 role in preserving the structural and functional integrity of the endothelium by inducing
108 neovascularisation at the site of vascular injury (14). Reduced endothelial progenitor cell
109 number and function have been associated with CVD risk factors, including hypertension
110 and hypercholesterolemia, and their potential role as prognostic and/or diagnostic markers
111 of CVD is of considerable value (14). Microparticles are small vesicles released from the
112 surface of many cell types, including endothelial cells and platelets, during activation or
113 apoptosis, which often occurs during endothelial injury. Microparticle numbers are elevated

114 in individuals with CVD and associated risk factors (15), and the addition of endothelial
115 microparticle numbers to the Framingham risk score has been shown to improve its
116 predictive power of future CVD events (16).

117

118 Central obesity and insulin resistance are defining characteristics of the metabolic
119 syndrome, the other two of which can include raised plasma TAG, reduced HDL-C
120 concentrations and hypertension (Table 1) (8). Those with the metabolic syndrome are
121 estimated to have an increased risk of CVD and particularly type 2 diabetes with many
122 shared metabolic risk factors, often presenting with relatively normal TC and LDL-C
123 concentrations (8). There is evidence to suggest that diet and lifestyle interventions may
124 be more effective in preventing the development of the metabolic syndrome than
125 pharmacological agents, and dietary fats may play a key role in this respect (17). The
126 evidence for the impact of dietary fat on cardiovascular and cardio-metabolic risk, with
127 particular reference to SFA, will be reviewed and presented in an attempt to resolve the
128 perceived inconsistencies and confusion.

129

130 **SFA as a strategy to reduce CVD and cardio-metabolic risk factors**

131 SFA reduction has been the mainstay of dietary fat recommendations for coronary heart
132 disease (CHD) risk reduction for many decades. UK public health advice on SFA was officially
133 introduced in 1983 in the National Advisory Committee for Nutrition Education (NACNE)
134 report (18), which recommended reducing SFA to no more than 10% total energy. The
135 Committee of Medical Aspects (COMA) re-evaluated the evidence in 1991 and 1994 and in
136 these reports the advice to reduce SFA intake to no more than about 10% total energy was
137 based on evidence that “increasing or decreasing the contribution of SFA to dietary energy
138 is followed by a rise or fall in low density lipoprotein (LDL) cholesterol and in the
139 commensurate risk of coronary heart disease” (19, 20). Since the 1990’s the evidence for
140 the effects of SFA on a range of health outcomes has increased considerably. This has been
141 reviewed by numerous international organisations with most proposing similar
142 recommendations to limit SFA. Currently, the Australian Government Department of Health
143 and New Zealand Ministry of Health (21) recommend SFA should contribute between 8-10%
144 energy; the Food and Agriculture Organization/World Health Organization (FAO/WHO) (22),

145 Nordic Council of Ministers (23) and US Dietary Guidelines Advisory Committee (DGAC) (24)
146 recommend no more than 10% energy as SFA and the European Food Safety Authority
147 (EFSA) (25) recommend consuming as little as possible. All advise replacement of SFA with
148 polyunsaturated fats (PUFA). In contrast, the French Food Safety Agency (AFSSA) (26)
149 recommended a total SFA intake of no more than 12% energy, but specify a maximum
150 intake of 8% energy from specific SFAs due to their atherogenic potential, namely lauric,
151 myristic and palmitic acids. In 2015, a novel strategy for dietary advice was proposed by the
152 Health Council of the Netherlands (HCN) (27) in which recommendations were designed
153 around foods and dietary patterns rather than specific nutrients. In these
154 recommendations, advice that related to SFA included: i) replace butter, hard margarines,
155 and cooking fats by soft margarines, liquid cooking fats, and vegetable oils; ii) limit the
156 consumption of red meat, particularly processed meat and iii) a few portions of dairy
157 produce daily, including milk or yogurt. The evidence for SFA and health outcomes is
158 currently under review by the Saturated Fats Working Group of the UK Scientific Advisory
159 Committee on Nutrition (SACN). A draft report from SACN was released for public
160 consultation in July 2018 with recommendations that the dietary reference value for SFA
161 remain unchanged at population average of no more than 10% energy from SFA, with
162 recommendations for SFA substitution with unsaturated fats (28).

163

164

165 **Population intake data**

166 Despite long standing dietary recommendations to limit SFA intake, very few populations
167 comply with this advice. A study which included fatty acid intake data from 40 countries
168 throughout the world reported that only 11 met the SFA (<10% energy) and 20 met the
169 PUFA (6-11% E) recommendations. Furthermore, in 18 of 27 countries examined, more than
170 50% of the population had SFA intakes >10% E, whereas in 13 of 27 countries, the majority
171 of the population had PUFA intakes <6% (29). The current SFA intake from the latest data
172 from the UK NDNS (years 7-8) supports these data, with the mean consumption of SFA
173 above recommendations in all age groups with SFA intakes of 11.9%, 12.5% and 14.3% of
174 total dietary energy in adults aged 19-64, 65-74 and 75+ years, respectively. The mean
175 population intakes of different fatty acid classes and the UK Reference Nutrients Intakes
176 (RNI) are shown in Table 2 and Table 3 respectively. The main contributor to SFA intake in

177 adults of all ages were meat and meat products, milk and milk products, and cereals and
178 cereal products (half from pizza, biscuits, buns, cakes, pastries, fruit pies and puddings) with
179 each food group contributing between 20-27% of total SFA intake. Fat spreads contributed
180 9%, 13% and 16% total dietary energy in those of 19-64, 65-74 and 75+ years, respectively.
181 Interestingly intakes of total SFA increased with household available income, although
182 generally these differences were small.

183

184 **Assessment of risk and quality of evidence**

185 The quality of evidence is important to consider when assessing risk. A hierarchy of evidence
186 as represented by a pyramid, is generally accepted, as shown in Figure 2. Data from
187 ecological studies, although helpful for hypothesis generation, is of limited quality and
188 represents associations which are often linked with considerable potential confounding.
189 Data from cohort studies, particularly longitudinal prospective cohort studies, can offer
190 valuable insight into associations between dietary factors and key outcome measures, such
191 as CVD mortality, but do not prove cause or effect. Furthermore, these studies are often
192 associated with confounding including: dietary change over the follow-up period;
193 reformulation of foods throughout the follow-up period (such as removal of trans fatty acids
194 from the food chain which has occurred over the past decade); lifestyle factors including
195 weight change, smoking status, amount of activity which are not fully accounted for;
196 influence of other dietary components; no consideration of the replacing macronutrient or
197 of the quality of macronutrient (i.e wholegrain vs refined carbohydrates or n-3
198 polyunsaturated fatty acids (PUFA) vs n-6 PUFA) and reverse causality.

199

200 In contrast, evidence from randomly controlled trials (RCT) are considered to be of higher
201 quality, with data demonstrating the effect of controlled dietary intervention, such as
202 substitution of SFA with PUFA, on hard clinical outcomes (e.g. CVD mortality) or validated risk
203 markers (e.g. LDL-C). However, all studies investigating dietary fats can be limited by the
204 sample size; duration of follow-up/intervention; study design; confounding by the presence
205 of dietary trans fatty acids in some intervention foods (known to have a significant
206 detrimental effect on CVD) in studies published before 1990s; and residual confounding.
207 Systematic reviews and meta-analyses of particularly RCT, can offer high quality data, which
208 represents the totality of the evidence available. However, there are potential limitations in

209 meta-analyses, such as the quality of the individual studies, criteria for study inclusion,
210 differences in study design, participant inclusion, type and methods of intervention, which
211 can result in inability or inappropriate study comparison and inconsistent findings between
212 meta-analyses addressing the same question. It is therefore apparent that the type of
213 evidence is of paramount importance and wherever possible, rigorous, current and
214 comprehensive systematic reviews and meta-analyse will be used in this review, although
215 individual studies will also be included where appropriate.

216

217 **Challenges to the SFA recommendations**

218 As discussed above, there are consistent global dietary recommendations to limit SFA intake
219 for disease risk reduction, which are based on rigorous assessment of the totality of
220 evidence from RCTs and prospective cohort studies, yet within the last 5 years the validity of
221 SFA reduction has been questioned. This recent challenge to the SFA recommendations has
222 been in response to a number of systematic reviews and meta-analyses which indicate that
223 there is limited evidence for the significant effects of SFA reduction on CVD mortality (30-
224 34). These data will be discussed in the context of the quality and relevance of the evidence.

225

226 **SFA and CVD risk**

227 There is consistent evidence from systematic reviews and meta-analyses of RCTs (35, 36)
228 and prospective cohort studies (30, 32, 33, 37, 38) for the lack of a significant relationship
229 between SFA intake and CVD, CHD and stroke mortality, which has fuelled the recent
230 challenges to SFA recommendations. However, a significant 17% reduction in CVD events in
231 those who reduced their SFA intake compared with usual diet (using a random-effects
232 statistical model) was reported in the most comprehensive, up-to-date and rigorous
233 systematic review and meta-analysis of RCTs (35). This analyse included 11 studies with
234 53,300 participants and 4377 CVD events and used the gold-standard Cochrane protocol for
235 systematic review. Furthermore, a significant 7% or 8% reduction was also observed after
236 using two fixed-effect statistical models (Mantel-Haenszel and Peto, respectively),
237 suggesting that reducing SFA intake to approximately 10% energy significantly reduces CVD
238 events by between 7-17% (35).

239

240 Moreover, Hooper found a significant 7-8% reduction in CHD events when reduced intakes
241 of SFA were compared with usual intakes after fixed effects analysis and a non-significant
242 trend for a 13% reduction after random effects analysis (P=0.07) using 12 RCTs, that
243 included 53,199 participants and 3307 cases. In contrast (30), Chowdhury and colleagues, in
244 their high profile systematic review and meta-analysis of 20 prospective cohort studies
245 (including 283,963 participants and 10,518 CHD cases), concluded there was no association
246 between SFA intake and CHD outcomes, when the top versus the bottom tertiles of SFA
247 intakes were compared using a random effects model. However, the authors also
248 performed a fixed-effect statistical model and found a significant 4% increased risk of CHD
249 outcomes when higher versus lower saturated fat intakes were compared, although this
250 finding was not commented upon in their paper. The reporting of both random and fixed
251 effects models is becoming increasingly popular as recommended in the Cochrane
252 Handbook for Systematic Reviews of Interventions (<http://training.cochrane.org/handbook>).
253 However, within the scientific community there are inconsistencies in the application and
254 relevance of these models to different datasets, with differences in the underlying
255 assumptions and statistical considerations. Fixed-effect models give weight in direct
256 proportion to the size of the primary studies, whereas random-effects models generally give
257 similar weight to all studies, irrespective of size. Although random effects models are used
258 more commonly, fixed-effect models may offer a number of advantages over random-
259 effects models, such as proportionate study weighting, and it would seem prudent to
260 consider both models when reviewing the evidence. The increase in CHD outcomes from
261 higher SFA intake from prospective cohort studies (30) supports the analysis of RCTs using
262 fixed effects analysis (35), and suggests reduction of dietary SFA would be of benefit.

263 Reducing SFA was found to have no effect on the mortality from stroke in a meta-analysis of
264 RCTs (35) and also on ischaemic strokes from the most comprehensive systematic review
265 with meta-analysis of 12 prospective cohort studies with 15 comparisons including
266 n=339,090 participants and 6226 ischaemic stroke deaths (37). In contrast, a systematic
267 review and meta-analysis of 15 prospective cohort studies (n=476,569 including 11,074
268 strokes) reported a significant 11% reduced overall stroke risk and 25% fatal stroke risk with
269 higher SFA intake (39). Interestingly, after subgroup analysis there was no association in
270 non-East Asian populations, but a significant association in East Asian populations (21%

271 lower risk) (39). In another meta-analysis of prospective cohort studies, a significant
272 association was identified between lower SFA intake and higher intracerebral haemorrhagic
273 strokes in Japanese populations only (40). These associations between higher SFA and
274 reduced stroke seem to be isolated to East Asian populations living in East-Asia, who
275 typically consume very low dietary SFA, have distinct differences in dietary patterns, other
276 lifestyle factors and genetic background, in comparison to Western populations in Europe
277 and America.

278 These studies provide vital evidence for the benefits of reducing intake of SFA on CVD and
279 CHD risk, and to address the recent challenges to these recommendations. However, these
280 studies are limited by the lack of consideration of which macronutrient replaced SFA in the
281 diet, and could not distinguish between, or determine whether, there were any differential
282 effects on CVD risk that were dependent on the substitute macronutrient. This is of
283 paramount importance for the development of valid public health advice and guidance on
284 practical strategies of SFA reduction and replacement.

285

286 **Impact of the macronutrient replacement of SFA on CVD risk**

287 Unlike pharmaceutical or supplemental studies, while a drug or supplement can be simply
288 added to a participants' regimen and compared to a placebo, dietary interventions involving
289 macronutrients require careful consideration in terms of the replacement macronutrient,
290 particularly in an iso-energetic study design. This adds complexity to the implementation of
291 the study, data analysis and interpretation of the results of a study. In reality, the
292 intervention outcomes could be the result of reduction of one macronutrient, increase in
293 the replacing macronutrient, or a combination of both.

294

295 *SFA replacement with PUFA*

296 The strongest evidence for the impact of SFA replacement with PUFA is from the
297 comprehensive Cochrane systematic review with meta-analysis of RCTs performed by
298 Hooper (35). This analysis revealed no effect of SFA reduction on CVD or CHD mortality, but
299 a significant 27% lower risk of CVD events and 24% reduction in CHD events when SFA was
300 replaced with PUFA, though no consideration was given to the type of replacement PUFA
301 (35). An earlier meta-analysis also found a significant 21% reduction in risk of CVD mortality

302 when SFA were replaced with PUFA (n-6 and n-3 PUFA combined) and n-3 PUFA alone, but
303 no effect on CVD mortality was observed when SFA was substituted with n-6 PUFA alone
304 (34). Although a more recent systematic review with meta-analysis of 13 prospective cohort
305 studies confirmed a significant 13% and 9% lower risk of CHD mortality and events,
306 respectively, when 5% energy from SFA was replaced by the n-6 PUFA linoleic acid using
307 fixed, but not random, effects models (41). Beneficial effects of SFA replacement with PUFA
308 were also reported after a pooled analysis of 11 prospective cohort studies which showed
309 that a 5% lower SFA and 5% higher PUFA was associated with a significant 26% lower CHD
310 deaths and 13% lower CHD events (42). This was supported by another pooled analysis of 7
311 RCTs and one cross-over trial, in which the average weighted PUFA consumption was 14.9%
312 energy and 5.0% energy in the intervention and control groups respectively. The overall
313 pooled risk reduction was 19%, which was estimated to correspond to a significant 10%
314 reduced risk of CHD events for every 5% of energy from SFA that was replaced with PUFA
315 (43). After meta-regression analysis greater benefit was also shown from longer study
316 duration (43).

317 Collectively these data provide consistent evidence that SFA replacement with PUFA
318 reduces CVD and CHD events, and more limited evidence from prospective cohort studies
319 only for a beneficial effect on CHD mortality. However, here was inadequate evidence on
320 SFA replacement with PUFA on stroke.

321 *SFA replacement with MUFA*

322 Evidence for the impact of replacement of SFA for MUFA is extremely limited, with no
323 systematic review or meta-analysis of RCTs. In the most relevant analysis of prospective
324 cohort studies, a 5% lower energy intake from SFA and concomitant higher energy intake
325 from MUFA was associated with a non-significant trend for higher CHD events, but not CHD
326 deaths (42). The authors commented that there might have been significant confounding by
327 trans fats from spreads, meat and dairy intake. Furthermore, no 'P' value was given and the
328 confidence interval of 1.00 was stated, which suggests this did not reach statistical
329 significance. These data are in stark contrast to the beneficial association reported from
330 modelling of the dietary data from the Nurses Health Study and Health Professional Follow-
331 up Study of 127,536 men and women with 24 to 30 years of follow-up and 7,667 incident

332 cases of CHD (44). This study showed that replacing 5% of energy from SFA with equivalent
333 energy from PUFA or MUFA was associated with a significant 25% and 15% lower risk of
334 CHD, respectively (44). Furthermore, a systematic review and meta-analysis of 32 cohort
335 studies including 841,211 participants revealed a significant overall risk reduction of 12% for
336 CVD mortality, 9% for CVD events and 17% for stroke when comparing the top versus
337 bottom quartiles of MUFA, olive oil, oleic acid, and MUFA:SFA ratio combined. Interestingly,
338 MUFA from mixed origin, animal and vegetable sources, was not associated with significant
339 effects on outcome measures (45). These data support a beneficial impact of MUFA, but
340 also highlight the limited RCT data and potential differential effects of MUFA from different
341 foods, and the overall importance of investigating food sources in relation to CVD risk
342 reduction.

343

344 *SFA replacement with carbohydrate or protein*

345 There is some evidence from the comprehensive Cochrane systematic review and meta-
346 analysis of RCT, that replacement of SFA with total carbohydrate had no effect on CVD and
347 CHD mortality and events, and limited evidence of no effect on strokes (35). A pooled
348 modelling analysis of 11 prospective cohort studies (n=344,696) reported no association on
349 CHD death, but significant 7% higher CHD events when comparing a 5% energy reduction in
350 SFA and equivalent increase in carbohydrate (42). However, none of these analyses
351 considered carbohydrate quality. In the modelling analysis of the Nurses Health Study and
352 Health Professional Follow-up Study (n= 127,536) replacement of 5% energy from SFA with
353 carbohydrates from whole grains was associated with a significant 9% lower risk of CHD,
354 whereas replacing SFA with carbohydrates from refined starches/added sugars was not
355 significantly associated with CHD risk(44). Further support of the importance of the quality
356 of the carbohydrate and CHD risk was illustrated by analysis of n=53,644 participants of
357 prospective cohort studies with a median of 12 year follow-up and 1943 incident MI cases
358 (46). A non-significant inverse association between substitution of SFA with low GI
359 carbohydrates was reported, yet a significant 33% higher MI risk from substitution with high
360 GI carbohydrates was shown. This again highlights that macronutrient type and quality is of

361 key importance, and that SFA substitution with wholegrain intake are associated with
362 beneficial effects on CHD risk.

363 There was limited evidence for a lack of effect of SFA substitution with protein on CVD and
364 CHD mortality and events and strokes in the Cochrane systematic review and meta-analysis
365 of RCTs in which most of the studies were not directly investigating SFA replacement with
366 protein (35).

367

368 **SFA and Cardio-metabolic risk**

369 *Type-2 diabetes*

370 Evidence from systematic reviews and meta-analyses of prospective cohort studies indicate
371 consistent evidence of no association between SFA reduction and risk of type-2 diabetes
372 with the most comprehensive analysis including data from 8 studies (n= 237,454
373 participants and 8739 cases) when the highest vs lowest SFA intakes were compared (37).
374 Only two prospective cohort studies addressed the association between SFA replacement
375 with PUFA on type-2 diabetes, showing inconsistent results (38). One study reported a
376 significant association of 16% reduction in type-2 diabetes risk, whereas the other found no
377 association, unless the model was unadjusted for BMI, when a significant 12% reduction was
378 observed, indicating the significant impact of adiposity on type-2 diabetes risk (38). No
379 evidence was available for SFA replacement with MUFA and protein.

380

381 *SFA and BMI*

382 Reducing the intake of SFA was found to significantly reduce body weight and BMI in a
383 systematic review with meta-analysis in adults (35). However, the majority of the data
384 included in the analysis came from trials in which there were reductions in the intakes of
385 both saturated and total fats, limiting specific attribution to SFA reduction. Furthermore,
386 these anthropometric measures were not primary outcomes throwing considerable
387 uncertainty of the results.

388

389 **Fats, cardiovascular and cardio-metabolic risk markers**

390

391 *Dietary lipids*

392 Dietary fats are key modulators of circulating lipids, with the reduction of serum LDL-C
393 through SFA reduction and higher PUFA, particularly n-6 PUFA (linoleic acid) and shorter
394 chain n-3 PUFA (alpha linoleic acid), and the serum triacylglycerol (TAG) – lowering effects of
395 long chain n-3 PUFA from fish, fish oil or supplements, being central aspects of these dietary
396 fat recommendations (Table 3).

397

398 The most comprehensive analysis investigating the impact of dietary fats, predominantly
399 SFA and replacement macronutrient on serum lipoprotein concentrations was conducted by
400 Mensink for the World Health Organisation (WHO) and published in 2016 (47). Mensink
401 initially performed a systematic review, which identified 84 relevant studies, 211 diet data
402 points and 2353 participants (65% men and 34% women) who had a mean age of 38 years
403 (21 and 72 years), BMI 24.2 kg/m² (20.0 to 28.6 kg/m²), TC 5.1 mmol/L (3.7 to 6.7 mmol/L);
404 LDL-C of 3.3 mmol/L (2.3 to 4.8 mmol/L); HDL-C of 1.2 mmol/L (0.9 to 1.8 mmol/L) and TAG
405 of 1.2 mmol/L (0.7 to 2.2 mmol/L). After performing a number of multiple regression
406 analyses it was shown that reducing SFA and replacing with a mixture of cis-PUFA
407 (predominantly linoleic acid and α -linolenic acid) or cis-MUFA (predominantly oleic acid)
408 was more effective than replacing SFA with a mixture of carbohydrates on the lipoprotein
409 profile (Table 4). More specifically it was estimated that serum TAG increased by a mean
410 0.0011 mmol/L for every 1% energy SFA replacement with mixed carbohydrates, compared
411 to a significant decrease in serum TAG of 0.004 mmol/L and 0.010 mmol/L for 1% energy
412 replacement by *cis*-MUFA and *cis*-PUFA respectively. Furthermore, replacement of 1%
413 energy from SFA with carbohydrate had no effect on serum TC:HDL-C ratio compared to a
414 significant reduction of 0.027 and 0.034 after substitution with *cis*-MUFA and *cis*-PUFA
415 respectively (Table 4). The results were consistent across a wide range of SFA intakes
416 including less than 10% of total energy, consistent for both men and women and not
417 effected by baseline lipid concentrations or type of intervention. Further analysis showed
418 that there were differential lipid responses according to the type of SFA. In comparison to a
419 mixture of carbohydrates, an increased intake of lauric, myristic or palmitic acid raised
420 serum TC, LDL-C and HDL-C and lowered TAG concentrations, while an increased intake of
421 stearic acid had no significant effect on these or other serum lipid values. Lauric acid alone
422 reduced the TC:HDL-C and LDL-C:HDL-C ratios compared with a mixture of carbohydrates

423 (47). These data are supported by metabolic ward studies, which provide high quality data
424 from carefully controlled study which involve provision of total dietary intake, with specific
425 exchange of SFA for other macronutrients (48).

426

427 *Vascular function and blood pressure*

428 Hooper and colleagues offers the most comprehensive analysis on SFA and its replacement
429 with other macronutrients on blood pressure and reported no significant effects (35).

430 However, the evidence from this and a further systematic review without meta-analysis
431 (49), is deemed limited, since blood pressure was a secondary outcome and not included in

432 the search terms of the systematic reviews. More recently a RCT addressed the impact of

433 8% energy replacement of SFA with n-6 *cis*-PUFA or *cis*-MUFA for an 18-week intervention

434 period in 195 men and women with 1.5-fold elevated CVD risk compared with the general

435 population, with vascular function measures as the primary outcomes. It was reported that

436 a high SFA diet (17% energy) increased night SBP ($+3.8 \pm 1.5$ mmHg), while replacing 8%

437 energy from SFA with n-6 PUFA and MUFA attenuated the elevated night SBP, which

438 reached significance for replacement with *cis* MUFA (-1.1 ± 1.3 mmHg) (50). Furthermore,

439 relative to the SFA-rich diet, replacing with *cis*-MUFA and *cis*-n-6 PUFA significantly

440 decreased endothelial (-47.3%, -44.9% respectively) and platelet (-36.8%, -39.1%

441 respectively) micro-particle numbers and increased endothelial progenitor cell numbers

442 (+28.4%) when SFA was replaced with *cis*-MUFA (51). These data suggest that replacement

443 of SFA with MUFA may beneficially affect endothelial repair and maintenance leading to

444 reduced CVD risk. Moreover, an acute intervention in 32 post-menopausal women showed

445 that postprandial DBP (incremental area under the curve-iAUC) was significantly lower when

446 meal SFA was replaced with MUFA, with a similar trend for SBP reduction, and a

447 corresponding lower plasma nitrite response (iAUC) (52). This evidence suggests a potential

448 beneficial effect of replacing SFA with unsaturated fats, particularly *cis*-MUFA, although

449 further robust RCT with vascular measures as primary outcomes are required to confirm

450 these findings.

451

452 Glycaemic control

453 The most comprehensive evidence for SFA and glycaemic measures is by Imamura and
454 colleagues in which a number of meta-regression analyses of various glycaemic and insulin
455 resistant measures are presented (53). Data from 99 RCTs with 4144 participants, including
456 individuals with and without type-2 diabetes were analysed and a significant lower fasting
457 glucose (-0.04 mmol/L) was reported when 5% energy as SFA was iso-energetically
458 substituted with PUFA, though no effect was shown with MUFA or carbohydrate
459 substitution. A further meta-regression analysis of data from 23 RCTs with 618 participants
460 reported that substitution of SFA with PUFA and MUFA significantly lowered serum HbA1c
461 (a longer-term marker of glycaemic control) by a mean difference of -0.15% and -0.12%,
462 respectively, with no effect of replacement with carbohydrate (53).

463 Data from 3 RCTs with 249 participants (with and without type 2 diabetes), reported a
464 significant increase in the rate of clearance of blood glucose in a 2-hour oral glucose
465 tolerance tests (OGTT) (a recognised measure of glucose tolerance) reporting a mean
466 difference of -1.69 mmol/L (35). However, this was a secondary analysis and measures of
467 glycaemic control were not included in the search terms. A more comprehensive systematic
468 review with meta-regression analysis included data from 11 RCT with 615 participants, and
469 showed that substitution of SFA with either PUFA, MUFA or carbohydrate had no effect on a
470 2-hour OGTT, or infusion measures (including hyperglycaemic or euglycaemic clamp and
471 FSIGTT) (53). This finding is consistent with data from two of the largest RCTs that measured
472 insulin sensitivity with an intra-venous glucose tolerance test as the primary outcome to
473 investigate the effects of SFA replacement, with MUFA or carbohydrates of different quality
474 (54, 55). However, meta-regression analysis of data on HOMA, a fasted marker of insulin
475 resistance, from 30 RCTs with 1801 participants showed significant lower insulin resistance
476 when SFA was substituted with PUFA and MUFA (mean difference -4.1% and -3.1%
477 respectively) but not with carbohydrate (53).

478

479 **Conclusions**

480 There is consistent evidence that mortality from total CVD, CHD and stroke are not affected
481 by SFA intake, and importantly no detriment to mortality from other causes from lower
482 intakes (with the possible exception of strokes, particularly haemorrhagic strokes, in

483 population living in East Asia). However, there is good evidence for a reduction in CVD
484 events with lower SFA intakes from RCTs and some evidence for risk reduction of CHD
485 events for lower SFA intake from RCT and prospective cohort studies. Replacement with
486 unsaturated fats, rather than carbohydrates or protein, has greater benefit to both CVD and
487 metabolic risk, with more evidence for PUFA replacement. CVD and CHD events have a
488 serious adverse impact on health and quality of life, and while mortality from CVD has
489 decreased over the past 50 years in many Western populations, the prevalence of CVDs is
490 increasing. With the escalating aging population, more people are living with cardiovascular
491 and metabolic diseases, resulting in a major adverse impact on health, quality of life and a
492 significant increase in financial burden to the NHS. Reduction in events would therefore
493 have a significant benefit to society and beyond. This evidence supports our current
494 recommendation to reduce SFA to promote public health. However, refinement of this
495 guidance will require a greater understanding of how the sustainable replacement of SFA
496 with different types of carbohydrates and unsaturated fats impacts on hard clinical
497 endpoints, with address of the influence of sex and age.

498

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501

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504

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508 the author.

509

510 **Authorship**

511 JAL is the sole author of this manuscript.

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Adiposity	Must have central obesity Waist > 94 cm males > 80 cm females Plus 2 of the following:
Glycaemia	Fasting plasma glucose > 5.6 mmol/L
Dyslipidaemia	TAG >1.7 mmol/L Low HDL-C <1.03 mmol/L males < 1.29 mmol/L females or specific treatment
Hypertension	Systolic blood pressure > 130 mmHg Diastolic blood pressure > 85 mmHg

	or treatment
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Table 2. Mean daily intake of saturated (SFA), monounsaturated (MUFA) and polyunsaturated (PUFA) fatty acids (%total energy) intake for UK children and adults by age. (NDNS RP survey years 7-8 (2014/15-2015/16) Bases unweighted).

Age Group	SFA (%total eng)	MUFA (%total eng)	n-6 PUFA (%total eng)	n-3 PUFA (%total eng)
Children 4-10 y n=514	10.0 ± 2.7	11.8 ± 2.1	4.3 ± 1.1	0.8 ± 0.3
Children 11-18 y n=542	12.4 ± 2.9	12.4 ± 2.4	4.7 ± 1.4	0.9 ± 0.3
Adults 19-64 y n=1082	11.9 ± 3.4	12.1 ± 3.0	4.7 ± 1.6	0.9 ± 0.4
Adults 65-74 y n=181	12.5 ± 3.6	11.3 ± 2.6	4.3 ± 1.4	1.0 ± 0.4
Adults 75+ y n=174	14.3 ± 3.9	11.6 ± 2.4	4.2 ± 1.6	1.0 ± 0.4

SFA: saturated fatty acid; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids;
%total eng: % total energy

Table 3. UK Dietary Reference Nutrient Intakes (RNI) for fats for adults as a percentage of total energy intake.

	Individual Minimum	Population Mean	Individual Maximum
SFA		10%	
<i>cis</i> -PUFA	n-3 PUFA 0.2% n-6 PUFA 1.0% LC n-3 PUFA 0.45g	6%	10%
<i>cis</i> -MUFA		12%	
<i>trans</i> fatty acids		2%	
Total fatty acids		30%	
Total fat		33%	

SFA: saturated fatty acid; PUFA: polyunsaturated fatty acids; MUFA: monounsaturated fatty acid; LC n-3 PUFA, long chain n-3 polyunsaturated fatty acids. Taken from ⁽¹⁹⁾

Table 4. Estimated multiple regression equations for the mean changes in serum lipids when 1% of dietary energy from SFA is isoenergetically replaced by carbohydrates, *cis*-MUFA or *cis*-PUFA

Lipid	SFA for CHO	SFA for <i>cis</i> -MUFA	SFA for <i>cis</i> -PUFA	No ¹
Change TC ² (mmol/L) CI (95%)	-0.041 -0.047 to -0.035 P <0.001	-0.046 -0.051 to -0.040 P <0.001	-0.064 -0.070 to -0.058 P <0.001	177/74
Change LDL-C (mmol/L) CI (95%)	-0.033 -0.039 to -0.027 P <0.010	-0.042 -0.047 to -0.037 P <0.001	-0.055 -0.061 to -0.050 P <0.001	165/69
Change HDL-C (mmol/L) CI (95%)	-0.010 -0.012 to -0.008 P <0.011	-0.002 -0.004 to -0.000 P = 0.014	-0.005 -0.006 to -0.003 P <0.001	163/68
Change in TAG (mmol/L) CI (95%)	0.011 0.007 to 0.014 P <0.001	-0.004 -0.007 to -0.001 P = 0.022	-0.010 -0.014 to -0.007 P <0.001	172/72
Change in TC:HDL-C ratio CI (95%)	0.001 -0.006 to 0.007 P = 0.842	-0.027 -0.033 to -0.022 P <0.001	-0.034 -0.040 to -0.028 P <0.001	159/66

SFA: saturated fatty acids; CHO: carbohydrates; *cis*-MUFA: *cis*-monounsaturated fatty acids; *cis*-PUFA: *cis*-polyunsaturated fatty acids; CI, confidence interval; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol;

¹Number of diets/number of studies

²The 95% confidence intervals (CI) refer to the regression coefficients on the line directly above
Adapted from (47)

Figure 1 Log-linear association per unit change in low-density lipoprotein cholesterol (LDL-C) and the risk of cardiovascular disease as reported in meta-analyses of Mendelian randomization studies, prospective epidemiologic cohort studies, and randomised trials. The increasingly steeper slope of the log-linear association with increasing length of follow-up time implies that LDL-C has both a causal and a cumulative effect on the risk of cardiovascular disease. Taken from (5)

Figure 2. Pyramid depicting hierarchy of evidence.