

Impact of meal fatty acid composition on postprandial lipaemia, vascular function and blood pressure in postmenopausal women

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1 **Impact of meal fatty acid composition on postprandial lipaemia, vascular function and blood**
2 **pressure in postmenopausal women**

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23 Running title: Meal fat, lipaemia and vascular function

24

25 **Abbreviations in the text**

26 ACE: angiotensin-converting enzyme; Apo: apolipoprotein; AUC: area under the curve; BMI: body
27 mass index; CETP: cholesteryl ester transfer protein; CM: chylomicron; CMR: CM remnants;
28 CVD: cardiovascular disease; FMD: flow-mediated dilatation; HDL: high density lipoprotein;
29 HDL-C: HDL cholesterol; LDL: low density lipoprotein; LDL-C: LDL cholesterol; LPL:
30 lipoprotein lipase; MUFA: monounsaturated fatty acid; NEFA: non-esterified fatty acids; NO: nitric
31 oxide; PUFA: polyunsaturated fatty acid; RAS: renin-angiotensin system; RCT: randomised clinical
32 trial; RE: Retinyl esters; ROS; reactive oxygen species; Sf: Svedberg flotation rate; SFA: saturated
33 fatty acid; TAG: triacylglycerol; TC: total cholesterol; TRL: TAG-rich lipoprotein; VLDL: very
34 low density lipoprotein.

35

36 **Abstract**

37 Cardiovascular diseases (CVD) are the leading cause of death in women globally, with aging
38 associated with progressive endothelial dysfunction and increased CVD risk. Natural menopause is
39 characterised by raised non-fasting triacylglycerol (TAG) concentrations and impairment of
40 vascular function compared with premenopausal women. However, the mechanisms underlying the
41 increase in CVD risk after women have transitioned through the menopause are unclear. Dietary fat
42 is an important modifiable risk factor in relation to both postprandial lipaemia and vascular
43 reactivity. Meals rich in saturated and monounsaturated fatty acids are often associated with greater
44 postprandial TAG responses compared with those containing n-6 polyunsaturated fatty acids, but
45 studies comparing the effects of these fatty acids on vascular function during the postprandial phase
46 are limited, particularly in postmenopausal women. A systematic search of the literature identified
47 778 publications describing acute postprandial test meal studies including postmenopausal women.
48 The impact of fat-rich meals on postprandial lipaemia was reported in 7 relevant studies, of which
49 meal fat composition was compared in one study described by three papers. An additional study
50 determined the impact of a high fat meal on vascular reactivity. Although there is moderately
51 consistent evidence to suggest detrimental effects of high fat meals on postprandial lipaemia in
52 postmenopausal women (compared with premenopausal women), there is insufficient evidence to
53 establish the impact of meals of differing fat composition. Furthermore, there is no robust evidence
54 to conclude the impact of meal fatty acids on vascular function or blood pressure. In conclusion,
55 there is an urgent requirement for suitably powered robust randomised controlled trials to
56 investigate the impact of meal fat composition on postprandial novel and established CVD risk
57 markers in postmenopausal women, an understudied population at increased cardiometabolic risk.
58

59 **Introduction**

60 Cardiovascular diseases (CVD) which include coronary heart disease (myocardial infarction and
61 angina), stroke and peripheral vascular disease ⁽¹⁾ are a key contributor to the burden of disease
62 globally ⁽²⁾. Over the past 50 years, the prevalence of CVD has fallen in Western populations,
63 however, CVD are currently the major cause of death in women in the UK, accounting for 32% of
64 all deaths ⁽³⁾. Furthermore, the prevalence of CVD is dramatically increasing in other areas,
65 including Eastern Europe, Asia and the Indian subcontinent ⁽⁴⁾.

66 The aetiology for CVD is multifactorial and includes several modifiable risk factors, such as
67 cigarette smoking, a sedentary lifestyle, obesity, elevated blood pressure, dyslipidaemia, type 2
68 diabetes mellitus, and non-modifiable factors, such as advancing ageing, sex, family history of heart
69 disease and ethnicity ^(5; 6). Among the non-modifiable risk factors, ageing is associated with

70 progressive endothelial dysfunction (characterised by a loss of vascular wall homeostasis leading to
71 a decrease in vascular reactivity and raised blood pressure) in both sexes, although it appears to
72 occur earlier in men than women ⁽⁷⁾. The most prominent sex related difference in physiological
73 ageing is the menopause (cessation of menstruation) in women, which usually occurs between the
74 ages of 45 and 55 y, with 51 y being the average age of menopause in the UK ⁽⁸⁾. This natural part
75 of aging in women contributes a significant cardiovascular milestone in terms of both physiology
76 and pathology since oestrogen deficiency is known to impair lipid metabolism and endothelial
77 function, and the menopause is a recognised risk factor for CVD ⁽⁹⁾. It has further been shown by
78 Schouw *et al.* ⁽¹⁰⁾ that for each year of delay in the age of onset of the natural menopause, CVD risk
79 falls by 2%.

80

81 **Postprandial lipaemia**

82 Kolovou *et al.* defined postprandial lipaemia as a complex syndrome characterised by non-fasting
83 hypertriacylglycerolaemia and its augmentation is associated with increased risk of cardiovascular
84 events ⁽¹¹⁾. Following a fat containing meal, there is a transient rise in circulating triacylglycerol
85 (TAG) rich lipoproteins (TRL), such as chylomicrons (CM) and very low density lipoprotein
86 (VLDL). After entering the circulation, the CM TAG is hydrolysed into non-esterified fatty acids
87 (NEFA) by lipoprotein lipase (LPL) forming cholesterol ester rich CM remnants, which are cleared
88 by the liver by receptor-mediated uptake. VLDL follows a similar route of metabolism in the
89 circulation as CM particles, but VLDL are hydrolysed at a slower rate, as the larger CM are
90 preferential substrate for LPL. VLDL TAG depletion produce smaller VLDL (intermediate density
91 lipoprotein or VLDL remnants), ultimately a proportion of which will be metabolised to low density
92 lipoprotein (LDL). LDL particles are cleared from the bloodstream via the hepatic LDL receptor
93 using apoB-100 as a ligand. During the postprandial period, there is an accumulation of TRL in the
94 circulation due to competition between intestinal and hepatic TRL for the same lipolytic and
95 receptor mediated uptake ⁽¹²⁾. A delayed clearance of TRLs in the circulation enhances the
96 accumulation of TRL particles carrying acceptor sites for the cholesteryl ester transfer protein
97 (CETP) which transfers TAG from TRLs (CM and VLDL) and exchanges it with cholesteryl esters
98 from high density lipoprotein (HDL) and LDL. Remodelling of the lipid content of the LDL and
99 HDL particles make them suitable substrates for LPL and hepatic lipase, leading to the formation of
100 smaller denser LDL (LDL₃) and HDL (HDL₃) particles ⁽¹³⁾. HDL₃ is rapidly removed from the
101 circulation decreasing circulating HDL cholesterol (HDL-C) concentrations, which is one proposed
102 mechanism for the inverse association between exaggerated postprandial lipaemia and CVD risk
103 ⁽¹⁴⁾. Another possible mechanism is that LDL₃ has a lower binding affinity to the LDL-receptor,

104 reducing their rate of clearance from the circulation and enabling them to infiltrate the arterial wall
105 ⁽¹³⁾.

106 Since atherosclerosis is now also considered to be a postprandial phenomenon, three large
107 prospective cohort studies aimed to determine the link between cardiovascular events and non-
108 fasting TAG ^(15; 16; 17). In the Norwegian Counties Study, hazard ratios of 1.2 and 1.03 for deaths
109 from CVD per 1 mmol/l increase in non-fasting TAG were reported in women and men,
110 respectively, after 27 years of follow up in a total of 86,261 participants ⁽¹⁷⁾. Furthermore, the
111 Copenhagen City Heart Study that followed 7581 women and 6391 men for 31 years showed that
112 relative to women with non-fasting TAG of <1 mmol/L, hazard ratios for myocardial infarction
113 ranged from 1.5 for women with TAG between 1.0-1.99 mmol/L rising to 4.2 for those with TAG
114 ≥ 5 mmol/L ⁽¹⁶⁾. However, the corresponding hazard ratios for men were 1.3 and 2.1, respectively. In
115 the Women's Health Study, fasting (n=20,118) and non-fasting (n=6391) TAG predicted
116 cardiovascular events after 11.4 years of follow up after adjusting for age, blood pressure, smoking
117 status and hormone therapy. The authors also reported that the strongest association between
118 cardiovascular events and non-fasting TAG occurred 2-4 h after the last meal, with the association
119 declining as the fasting time increased ⁽¹⁵⁾. These studies have demonstrated the greater importance
120 of non-fasting than fasting TAG concentrations as a predictor of CVD risk in women than men.

121 The relationship between postprandial lipaemia and CVD according to menopausal status is
122 a topic of current interest. The impact of menopausal status on the variability of the postprandial
123 lipaemic responses have been reported in a number of studies ^(18; 19; 20; 21) (Supplemental material 1).
124 In general, premenopausal women have lower postprandial triacylglycerol (TAG) responses than
125 men ^(22; 23; 24; 25), which is in contrast to the higher reported responses observed in postmenopausal
126 women compared with men of a similar age ⁽²⁶⁾. In response to a single oral vitamin A fat loading
127 test, van Beek *et al.* ⁽¹⁸⁾ investigated whether a natural menopause was associated with reduced
128 protection from exaggerated postprandial lipaemia. Higher concentrations of postprandial plasma
129 TAG and retinyl palmitate (an indirect marker of CM) were observed in postmenopausal women
130 compared with premenopausal women of similar age, BMI, daily energy and fat intake, *APOE*
131 genotype, LPL activity, and HDL-C concentration, even after adjusting for the confounding effect
132 of fasting TAG. Relative to premenopausal women, Masding *et al.* ⁽²⁰⁾, Schoppen *et al.* ⁽¹⁹⁾ and
133 Jackson *et al.* ⁽²¹⁾ also reported significantly higher postprandial TAG responses after single and
134 sequential fat-rich test meals in healthy postmenopausal women. Although raised LDL cholesterol
135 (LDL-C) is an established risk factor for CVD, large prospective studies have shown non-fasting
136 TAG to be a better predictor of CVD risk in women than fasting LDL-C ^(27; 28; 29). Post-hoc analysis
137 of the The Dietary Studies: Reading Unilever Postprandial Trials (DISRUPT) menopausal groups
138 according to age also revealed a greater increase in non-fasting TAG than fasting LDL-C during the

139 late premenopausal period suggesting that age and the menopause have a differential impact on
140 these two lipid CVD risk biomarkers ⁽²¹⁾.

141 A major biochemical change that occurs in women after the menopause is a reduction in the
142 secretion of endogenous oestrogen and progesterone ⁽³⁰⁾. These hormones not only play a major role
143 in sexual physiology, but are also involved in various physiological processes associated with the
144 vasculature and lipid metabolism. A reduction in oestrogen following the menopause has been
145 shown to have a detrimental impact on lipoprotein metabolism, vascular reactivity and blood
146 pressure (Figure 1). For example, there is much evidence to suggest that oestrogen (endogenous and
147 exogenous) lowers fasting plasma concentrations of total and LDL-C, lipoprotein (a) and
148 apolipoprotein B, whilst elevating HDL-C and apolipoproteins AI and AII ^(31; 32; 33). The impact of
149 oestradiol (the predominant type of oestrogen) on lipid metabolism is reported to contribute 25% of
150 its protective effects for fasting lipid profile ⁽³⁴⁾. One possible mechanism to explain this effect, that
151 was identified in *in vitro* animal studies, was an increase in the number of high affinity LDL
152 receptors on liver cell membranes that enhance LDL uptake by the liver ⁽³³⁾. Exaggerated
153 postprandial lipaemia is observed after the menopause ⁽¹⁸⁾ but the administration of even short term
154 (two to six weeks) oestradiol therapy reduces the menopause-related rise in postprandial TAG in
155 postmenopausal women ^(35; 36). These findings indicate that 17 β -estradiol may accelerate the
156 postprandial clearance of TRL and have a beneficial effect on postprandial lipaemia.

157

158 **Vascular function and blood pressure**

159 Vascular function is a measure of cardiovascular health. The components of impaired vascular
160 function, including hypertension ^(37; 38), arterial stiffness ⁽³⁹⁾ and impaired endothelial dependent
161 vasodilation (endothelial dysfunction) ^(40; 41), are all associated with cardiovascular mortality. In a
162 healthy blood vessel, the endothelium, which is comprised of a monolayer of endothelial cells that
163 lines the blood vessel walls, regulates vascular wall homeostasis by immediately responding to
164 blood-borne and locally produced stimuli to regulate blood flow, blood pressure and vascular tone.
165 It does so by maintaining a precise balance between the release of endothelium-derived vasodilators
166 (such as nitric oxide (NO)), and vasoconstrictors (such as endothelin-I), which actively regulates
167 vascular permeability to plasma constituents, platelets and leukocyte adhesion molecules ⁽⁴²⁾ as well
168 as aggregation and thrombosis ⁽⁴³⁾. However, when the production or bioavailability of NO is
169 reduced, the resulting imbalance of these vasoactive substances disrupts vascular homeostasis. This
170 ‘endothelial dysfunction’ is characterised by vasoconstriction, increased expression of adhesion
171 molecules and pro-inflammatory cytokines, platelet activation and increased oxidative stress ⁽⁴⁴⁾,
172 and is becoming increasingly recognised as an important step for the initiation of coronary
173 atherosclerosis ⁽⁴⁵⁾ and CVD risk in postmenopausal women ⁽⁴⁶⁾. There is supporting evidence of

174 impaired endothelial function after the menopause, which has been associated with a lack of
175 endogenous oestrogen ^(7; 47).

176 There are a number of non-invasive methods which are used to evaluate endothelial function
177 ⁽⁴⁸⁾. Flow-mediated dilatation (FMD) is the gold standard technique that uses ultrasound to assess
178 endothelium-dependent vasodilation in the conduit arteries in the peripheral circulation and is used
179 as a surrogate measure of NO production ⁽⁴⁹⁾. It is now recognised as a screening tool to assess
180 future CVD risk ^(40; 46; 50; 51). Rossi *et al.* reported that postmenopausal women in the lowest tertile of
181 % FMD response (reflective of impaired vascular reactivity) had the greatest relative risk of
182 cardiovascular events. Furthermore, it has been shown that endothelial function is impaired across
183 the stages of the menopause transition in healthy women with the highest % FMD response reported
184 in premenopausal women, with a progressive decline in perimenopausal and postmenopausal
185 women, respectively ⁽⁵²⁾. This suggests the perimenopausal stage (the transition towards the
186 menopause where oestrogen production starts to fall) is a crucial turning point in women where
187 changes in CVD risk commence.

188 Majmudar *et al.* ⁽⁵³⁾ revealed that menopausal status is associated with reduced NO activity,
189 which is restored with oestrogen replacement therapy and may be an important mechanism
190 facilitating the detrimental effect of the menopause on CVD risk and mortality. Another study that
191 acutely administered oestrogen (17 β -oestradiol) to postmenopausal women demonstrated protective
192 effects on forearm microvascular responses to both endothelium-dependent (acetylcholine) and -
193 independent vasodilation (sodium nitroprusside) via improvements in NO activity ⁽⁵⁴⁾. Impaired
194 blood flow in the microcirculation has been proposed to be an indicator of initial endothelial
195 damage in subjects at risk of CVD ⁽⁵⁵⁾. Furthermore, it has been repeatedly shown that 17 β -
196 oestradiol stimulates the production of vasodilatory prostaglandins, such as prostacyclin (PGI₂) ^{(56;}
197 ⁵⁷⁾. These vascular effects are believed to be partly responsible for the long-term benefit of
198 oestrogen therapy on cardiovascular risk in postmenopausal women. However, findings from the
199 Women's Health Initiative study have questioned the benefits of oestrogen therapy, reporting that
200 oestrogen therapy did not protect against myocardial infarction or coronary death after a short (6.8
201 y) or longer-term (18 y) follow-up relative to a placebo, although the findings did show a lower risk
202 of coronary heart disease among the younger postmenopausal women (50 to 59 y) ^(58; 59) ⁽⁵⁹⁾. More
203 recently, a systematic review involving 43,637 women reported the number of cardiovascular
204 events to increase following the long-term (>1 y) use of oestrogen therapy ⁽⁶⁰⁾. In contrast, there is
205 much evidence to suggest that oestrogens (endogenous and exogenous) have several cardio-
206 protective effects (Figure 1) ^(32; 61; 62). These include reductions in plasma markers of endothelial
207 activation (E-selectin) and increased fibrinolytic activity (increased factor VII; reduced fibrinogen,

208 plasminogen activator inhibitor type 1 and tissue plasminogen activator) ^(32; 63). However, increased
209 markers of inflammation (C-reactive protein) and hypercoagulability have also been reported ^(32; 61).

210 Hypertension (high blood pressure) is one of the main age-related disorders in
211 postmenopausal women ^(64; 65), which has been identified as a leading risk factor for myocardial
212 infarction and stroke in women ⁽⁶⁶⁾. The renin-angiotensin system (RAS) is a hormonal cascade,
213 which plays a key role in the regulation of fluid and electrolyte balance, and arterial blood pressure.
214 Upon activation of the RAS cascade, angiotensin II is produced in the liver by angiotensin-
215 converting enzyme (ACE) following conversion of angiotensin I to angiotensin II ⁽⁶⁷⁾. Angiotensin
216 II is a potent vasoconstrictor which degrades bradykinin (a vasodilator) causing arterioles to
217 constrict, resulting in increased blood pressure ⁽⁶⁸⁾. It is well documented in the literature that
218 oestrogen acts on RAS at different points of the cascade including the inhibition of ACE activity. *In*
219 *vitro* and *in vivo* animal studies have also demonstrated the potential effects of oestrogen on the
220 endothelial-dependent vasodilator response to acetylcholine due to oestrogen induced sensitisation
221 measured in coronary and uterine arteries^(69; 70; 71). Loss of oestrogen-dependent cardiovascular
222 protection induces endothelial dysfunction, and may also be involved in the activation of the RAS
223 cascade. Evidence from both clinical and animal studies have shown an inverse association between
224 oestrogen and the activation of RAS ^(72; 73; 74; 75). This has been proposed to occur due to oestrogen
225 induced downregulation of angiotensin receptor I expression leading to an augmented level of
226 angiotensin II ⁽⁷³⁾ (which is a major component of the RAS system) and has several harmful effects
227 on the vascular wall including vasoconstriction, vascular smooth muscle cell proliferation, reactive
228 oxygen species (ROS) generation, and endothelial cell apoptosis ^(76; 77; 78). Oestrogen deficiency has
229 also been reported to lead to an upregulation of ACE activity causing an accumulation of
230 angiotensin II ⁽⁷⁹⁾.

231

232 **Impact of meal fat composition on postprandial lipaemia and vascular function**

233 Diet is one of the most important modifiable risk factors in relation to CVD ⁽⁸⁰⁾. As a strategy to
234 reduce the incidence of CVD, public health policy makers recommend that intakes of dietary
235 saturated fatty acids (SFA) are reduced to <10% total energy in the UK ⁽⁸¹⁾. Substituting SFA with
236 unsaturated fatty acids may provide additional benefits in relation to CVD risk factors, including
237 reductions in the fasting lipid profile and improvements in endothelial function. A systematic
238 review proposed that lowering dietary SFA intake by modifying dietary fat composition rather than
239 reduction in total fat intake, may reduce cardiovascular events by 14% ⁽⁸²⁾. Since individuals spend
240 a large proportion of the day in the fed (postprandial) state, modifications to the fatty acid
241 composition of our meals that are repeated on a daily basis may have a significant impact on
242 postprandial lipaemia and vascular health, which over time could affect CVD risk.

243 The chronic effects of substitution of SFA with polyunsaturated fat (PUFA) on fasting lipid
244 levels have been extensively studied ⁽⁸³⁾, however, the acute affects are less well known. One
245 systematic review and meta-analysis of RCT compared the effects of oral fat tolerance tests with
246 differing fatty acid compositions on postprandial TAG responses in men and women ⁽⁸⁴⁾. Relative to
247 a single SFA-rich meal challenge, a PUFA-rich meal significantly reduced the postprandial
248 lipaemic response over 8 h, whereas a trend for a reduced response was identified following a
249 monounsaturated (MUFA) rich meal challenge. However, differences were not evident at 4 h
250 suggesting that a longer follow-up time after the test meal (i.e. 8 h) is required to observe the acute
251 effects of meal fat composition on postprandial lipaemia. Of the 18 studies included in the review
252 by Monfort-Pires *et al.* ⁽⁸⁴⁾ none of the studies included postmenopausal women which reflects the
253 paucity of postprandial data in this population subgroup.

254 With regards to vascular function, West and colleagues ⁽⁸⁵⁾ reported that consumption of a
255 single high fat meal (50-105 g of fat) can impair postprandial FMD by 45% to 80% with
256 observations of impaired FMD within 2 to 5 h after a high fat meal ^(86; 87; 88; 89). Prolonged
257 postprandial lipaemia is known to induce endothelial dysfunction by promoting the formation of
258 free radicals by accelerating the rate of β -oxidation of free fatty acids (e.g. superoxide radicals).
259 Increased production of ROS or free radicals reduce the amount of bioactive NO by chemical
260 inactivation to form toxic peroxynitrite ⁽⁹⁰⁾. In addition, it has been shown that persisting oxidative
261 stress will render endothelial nitric oxide synthase dysfunctional, markedly reducing NO production
262 ⁽⁹¹⁾. Indeed, high concentrations of TRLs during the postprandial state enhance inflammation by
263 inducing the secretion of pro-inflammatory cytokines ⁽⁹²⁾ and expression of soluble cell adhesion
264 molecules ⁽⁹³⁾.

265 Reviews by Hall ⁽⁹⁴⁾ and Vafeiadou *et al.* ⁽⁹⁵⁾ stated that the acute effects of dietary fats on
266 vascular function is less researched. The authors concluded that high fat meals have a detrimental
267 effect on postprandial vascular function and that there is limited and inconclusive evidence for the
268 comparative effects of test meals rich in MUFA or n-6 PUFA with SFA. Of note, the data derived
269 from these reviews were mainly from studies where the effects of a single high fat meal on
270 postprandial vascular function in different subject groups were determined; however, none of the
271 studies identified in these reviews included only postmenopausal women only.

272 Therefore, we aimed to systematically review and critically evaluate the existing evidence
273 from acute studies comparing meals rich in SFA, MUFA and n-6 PUFA on postprandial lipaemia,
274 vascular reactivity, blood pressure and biomarkers of vascular function and inflammation in
275 postmenopausal women. It is very timely to focus on postmenopausal women since they represent
276 an understudied group within the population at increased CVD risk.

277

278 **Subjects and methods**

279 A systematic approach was used to identify all relevant published literature according to the method
280 used by Vafeiadou *et al.* ⁽⁹⁵⁾. The PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) database was
281 used to perform the literature search, which included all studies published in English until October
282 2016. A protocol that included search terms to conduct the literature search was prepared by two
283 authors (KMR and MW) and then agreed by all authors. Three categories of search terms were
284 identified: i) study group search term (postmenopausal or post-menopausal or post menopause or
285 menopause or menopausal); ii) exposure search terms (which included descriptors of SFA, MUFA
286 and n-6 PUFA, and relevant food sources, e.g. butter, safflower oil and olive oil); iii) outcomes
287 (which included descriptors of vascular function, blood pressure, biomarkers of vascular function
288 and inflammation, and plasma lipids) (Supplementary Information). The Medical Subject Heading
289 Browser (<http://www.nlm.nih.gov/mesh/MBrowser.html>) was used to identify relevant exposures
290 and outcomes. Additional studies (n=2) were identified through hand searching of original articles
291 found using the PubMed search. The titles and abstracts of every paper was assessed for relevance
292 at the initial stage by one author (KMR) and any uncertainties were discussed with other members
293 of the review team until a consensus was reached. This review was restricted to epidemiological
294 studies (cross-sectional, case-control and cohort) and RCT in postmenopausal women with respect
295 to test meals rich in SFA, MUFA and/or n-6 PUFA. Only published peer-reviewed literature was
296 considered (i.e. ‘grey’ literature, such as dissertations, conference proceedings, reports, letters to
297 editors and other non-peer-reviewed research were excluded). Although Hall ⁽⁹⁴⁾ and Vafeiadou *et*
298 *al.* ⁽⁹⁵⁾ previously reviewed the chronic and acute studies on vascular function, they did not
299 specifically address the acute effects in postmenopausal women. In this present review, we only
300 considered acute studies as our objectives were to determine the impact of meal fatty acids on non-
301 fasting TAG responses, vascular function and blood pressure as important CVD risk factor in
302 postmenopausal women. Figure 2 presents a summary of the literature search and reasons for
303 exclusion of the studies.

304

305 **Results and Discussion**

306 This systematic search identified 778 publications in total. Of these, there were nine relevant
307 articles describing seven independent studies in postmenopausal women that examined the acute
308 effects of meals enriched in SFA and/or MUFA and/or n-6 PUFA on postprandial lipaemia ^{(96; 97; 98;}
309 ^{99; 100; 101; 102; 103; 104)}. One of these studies also determined the impact of a single fat containing meal
310 with a low PUFA:SFA ratio on vascular function ⁽¹⁰¹⁾ (Table 1). No studies were identified that
311 reported the acute impact of meal fatty acids on postprandial blood pressure, or biomarkers of
312 vascular function and inflammation in postmenopausal women. Only one single-blind RCT

313 compared the effects of meal fat composition on postprandial lipaemia using a sequential meal
314 protocol, the results of which were presented in three publications ^(97; 98; 100). As opposed to a single
315 meal protocol, the use of a multiple meal design by the researchers is considered superior because it
316 more closely mimics the eating pattern of free-living individuals, particularly in Westernised
317 societies, and provokes a sustained lipaemic response. Five publications described cross-sectional
318 epidemiological studies, which were single arm studies that did not have comparator meals and
319 whose fatty acid compositions varied ^(96; 101; 102; 103; 104). Among these postprandial studies with
320 blood samples collected between 6 to 10 hours after the test meal, two studies ^(96; 102) used a
321 sequential two meal protocol, whereas the other three studies ^(101; 103; 104) incorporated a single meal
322 approach. In addition, one case-control study was identified that considered the responses of
323 normolipaemic, hypercholesterolaemic and mixed hyperlipidaemic postmenopausal women to a
324 single high fat meal ⁽⁹⁹⁾.

325 Data on these human studies will be presented in two sections that address the effects of
326 total fat or fatty acid composition on i) postprandial lipaemia and ii) postprandial vascular function
327 in postmenopausal women.

328

329 **Acute effects of meal fat composition on postprandial lipaemia**

330 The five cross-sectional studies, investigating both single and sequential meals, provided consistent
331 evidence that fat-rich loads, irrespective of fatty acid composition, augment postprandial lipaemia in
332 postmenopausal women, with an increase in TAG being observed in all five studies during the
333 postprandial period relative to baseline ^(96; 101; 102; 103; 104) (Table 1). Furthermore, Pirro *et al.* ⁽⁹⁹⁾
334 investigated the changes in postprandial TAG concentrations after a standardised oral fat load (65g
335 of fat) at baseline, 4, 6 and 8 h in postmenopausal women with hypercholesterolemia and mixed
336 hyperlipidaemia and compared them with a control group of normolipidaemic postmenopausal
337 women. A significantly greater postprandial TAG response was found in the mixed hyperlipidaemic
338 women than in the hypercholesterolaemic and normolipidaemic women which may reflect their
339 higher baseline TAG concentrations. As expected, other factors involved in lipid metabolism,
340 including increases in apo B-48 ⁽¹⁰²⁾, glucose ⁽¹⁰³⁾, and insulin ⁽¹⁰³⁾ as well as reductions in HDL ^{(99;}
341 ^{103; 104)}, glutathione ⁽¹⁰¹⁾ and NEFA ⁽¹⁰³⁾ were also observed postprandially compared with fasting
342 values. However, comparison of the findings from the different studies are challenging due to
343 differences in the nature of the fats and oils used in the test meal, the amount and composition of
344 fat, and postprandial follow up times, as well as the use of both single and sequential test meal
345 protocols. They are also limited in their cross-sectional design in that the lack of comparator meals
346 prevents any conclusions from being made regarding the impact of meal fat composition on
347 postprandial lipaemia. Among all nine articles (seven independent studies) reported in Table 1, only

348 one study that was described in three publications compared the postprandial lipaemic responses to
349 test meals containing oils rich in SFA (palm oil), MUFA (olive oil), n-6 PUFA (safflower oil) and a
350 mixture of n-6 PUFA and n-3 PUFA (safflower and fish oils)^(97; 98; 100). In this study, 10
351 postmenopausal women ingested a high fat breakfast containing 40 g of the assigned test fat
352 followed by a low fat, high carbohydrate lunch (5.4 g total fat) given 5 h later. The authors observed
353 significantly higher levels of plasma NEFA and lower insulin sensitivity following the SFA meal
354 compared with the other test oils. During the postprandial state it has been shown that up to 50% of
355 the liberated NEFA is dietary-derived CM-TAG due to the action of LPL upon TAG to release
356 NEFA⁽¹⁰⁰⁾. Although Robertson *et al.*⁽¹⁰⁰⁾ did not determine the specific fatty acid composition of
357 the circulating NEFA after consumption of the meals, a similar study reported the postprandial
358 change in the plasma NEFA profile to represent the fatty acid composition of the test meals⁽¹⁰⁵⁾.
359 Based on the same sequential meal study, Jackson *et al.* further examined the postprandial TAG and
360 apo B-48 (the apolipoprotein specifically associated with CM) responses, including the responses in
361 three distinct TRL subfractions, and reported significant differences in the apo B-48 time course
362 profiles between the four different test oils⁽⁹⁸⁾. In particular, the MUFA meal resulted in the
363 formation of a greater number of both large (S_f>400 fraction) and
364 moderately (S_f 60-400 fraction) sized apo B-48 particles compared with the other three study meals.
365 The findings from this study suggested that olive oil may enhance CM formation and Jackson *et al.*
366⁽⁹⁷⁾ hypothesised that MUFA may modify the activity or expression of intestinal microsomal TAG
367 transfer protein, which is involved with TRL lipoprotein assembly.

368

369 **Acute effects of meal fat composition on vascular function**

370 Only one study has also examined the acute impact of total fat and/or SFA and/or MUFA and/or n-6
371 PUFA on vascular reactivity in postmenopausal women. A significant decrease in the %FMD
372 response at 2 h ($2.3 \pm 2.6\%$) compared with baseline ($7.7 \pm 2.8\%$, $p < 0.05$) was observed in healthy
373 postmenopausal women after a 65 g oral fat load with a PUFA:SFA ratio of 0.06⁽¹⁰¹⁾ (Table 1).
374 Since a comparator meal of a different fatty acid composition was not included in this study,
375 conclusions regarding the impact of fatty acid composition on vascular function in postmenopausal
376 women cannot be determined.

377

378 **Summary**

379 A systematic approach was used to review the literature on the impact of meal fat composition
380 (SFA, MUFA and n-6 PUFA) on postprandial lipaemia, blood pressure, vascular function and
381 biomarkers of vascular function and inflammation in postmenopausal women. However, there is at
382 present, an extremely limited number of RCT that have investigated the impact of meal fatty acid

383 composition on measures of postprandial lipaemia and vascular function in this population sub-
384 group. Furthermore, differences in study designs (such as the absence of a comparator test meal,
385 and differences in meal fat composition, study duration and outcome measures) prevent any firm
386 conclusions being drawn from this literature review.

387

388 **Conclusions**

389 In conclusion, there is an urgent requirement for suitably powered RCT to investigate the effects of
390 meal fat composition on postprandial lipaemia and vascular function in postmenopausal women.

391 With the increased prevalence of non-communicable diseases in women, especially after the
392 menopause, future studies should consider both healthy postmenopausal women and those at
393 increased cardiometabolic risk using well-standardised measures of vascular function. Since non-
394 fasting TAG is an important CVD risk factor for women, it is essential to use robust test meal
395 protocols that are more reflective of habitual eating patterns to gain a greater understanding of the
396 day-long postprandial handling of different dietary fats.

397

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400 conception of the literature search strategy. KMR undertook the literature search, extracted and
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402 appraised the document at all stages. KGJ and JAL critically appraised the final manuscript. JAL
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404

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Table 1 Acute test meal studies investigating the effects of meal fat content and composition on postprandial lipaemia and vascular function in postmenopausal women

Reference	Subject group, age (mean) and n	Study design	Meal type	Amount of fat (% meal fat if available)	Fatty acid composition	Time of postprandial data	Postprandial measurements (plasma/serum)	Significant outcomes compared to baseline, unless otherwise stated
Postprandial lipaemia								
Westerveld <i>et al.</i> (1996) ⁽¹⁰⁴⁾	59 y n 16 normolipidaemic	Cross sectional*	Single	50 g (40%)	PUFA: SFA 0.06	8 h	TAG, HDL-C and HDL-Apo A-1	↓HDL-C at 3 to 8 h (p<0.05), ↓HDL-Apo A-1 at 3 and 6 h (p<0.05) ↑TAG at 8 h (p<0.05)
Pirro <i>et al.</i> (2001) ⁽⁹⁹⁾	57 y n 17 normolipaemic, 54 y n 17 hypercholesterolaemia and 55 y n 16 mixed hyperlipaemia	Case control	Single	65 g (83%)	PUFA: SFA 0.06	8 h	TC, TAG, HDL-C, HDL ₂ , HDL ₃ , LDL, LDL particle size, and Lp(a)	↑TAG at 4,6 and 8 h, ↓HDL-C at 6 h and ↓Lp(a) at 4 and 6 h in normolipaemic PoM (p<0.05) ↑TAG at 4, 6 and 8 h, ↓HDL-C at 4 and 6 h, ↓HDL ₂ at 4 h and ↓Lp(a) at 4 h in hypercholesterolaemia PoM (p<0.05) ↑TAG at 4, 6 and 8 h, ↓LDL size at 4 and 6 h, ↓HDL-C at 4, 6 and 8 h, ↓HDL ₂ at 6 h and ↓Lp(a) at 4 and 6 h in mixed hyperlipaemia PoM (p<0.05)
Silva <i>et al.</i> (2005) ⁽¹⁰²⁾	52-76 y (62 y) n 17	Cross sectional*	Sequential	Breakfast: 30 g (46%) Lunch: 44 g (52%)	Breakfast (27 %E SFA, 12 %E MUFA, 5 %E PUFA and 2 %E Trans) Lunch (27 %E SFA, 18 %E MUFA, 5 %E PUFA and 2 %E Trans)	10 h	TAG, and apo B-48	↑TAG at 210 min after breakfast and 60 min after lunch ↑Apo B-48 at 150 min after breakfast and 60 min after lunch
Alssema <i>et al.</i> (2008) ⁽⁹⁶⁾	60.1 y n 76	Cross sectional*	Sequential	Both breakfast and lunch compositions: Fat rich meal: 50 g fat,	No information	8 h	TAG, HDL-C and CETP	↑TAG at 8 h (p<0.05), ↓HDL-C at 8 h (p<0.05) in fat rich meal ↑TAG at 8 h (p<0.05), ↓HDL-C at 8 h and ↑CETP in CHO rich meal (p<0.05)

				56 g CHO, 28 g protein					
				CHO rich meal: 4 g fat, 162 g CHO, 22 g protein					
Wassef <i>et al.</i> (2012) ⁽¹⁰³⁾	58 y (45-74 y) n 19 obese PoM	Cross sectional*	Single	¹³ C-labeled breakfast 80 g fat (68%) + 0.017 g ¹³ C-triolein/g fat	25 %E SFA, 26 %E MUFA, 10 %E PUFA and 6 %E other sources	6 h	TAG, glucose, NEFA and Insulin	↑TAG after meal ↓NEFA between 1 to 2 h ↑Glucose at 1 h ↑Insulin AUC at 1 h	
Robertson <i>et al.</i> (2002) ⁽¹⁰⁰⁾	50-63 y (56 y) n 10	Single- blind randomised crossover	Seque ntial	Breakfast: 41 g [†] Lunch: 6 g	High SFA (g/100 g): 10 g n-6 PUFA, 0 g n-3 PUFA, 40 g MUFA and 50 g SFA	8 h	Glucose, NEFA and insulin	High insulin response: SFA > n-6 PUFA > n-3 PUFA > MUFA (p<0.006) Glucose: No significant effect ↑NEFA at 5 h following high SFA breakfast and 30 min after low-fat high-CHO meal ↓insulin sensitivity: SFA < n-6 PUFA < n-3 PUFA < MUFA	
Jackson <i>et al.</i> (2002a) ⁽⁹⁸⁾					High MUFA (g/100 g): 11 g n-6 PUFA, 0 g n-3 PUFA, 72 g MUFA and 17 g SFA				
Jackson <i>et al.</i> (2002b) ⁽⁹⁷⁾					High n-6 PUFA (g/100 g): 74 g n-6PUFA, 0 g n-3 PUFA, 15 g MUFA and 11 g SFA		TAG and apo B-48	↑apo B-48 in MUFA than SFA, n-6 PUFA and n-3/n-6 PUFA meals (p≤0.009)	
					High n-3/n-6 PUFA (g/100 g): 39 g n-6 PUFA, 22 g n-3 PUFA, 22 g MUFA and 19 g SFA		TAG, apo B-48, and in three TAG-rich lipoprotein subfractions	apo B-48 IAUC in the S _r 60-400 fraction greater than in the S _r > 400 fraction for the SFA, n-6 PUFA and MUFA meals (p<0.04) ↑apo B-48 IAUC in the S _f > 400 fraction in MUFA than SFA, n-6 PUFA and n-3/n-6 PUFA meals (p<0.02)	
Postprandial lipaemia and vascular function									
Siepi <i>et al.</i> (2002) ⁽¹⁰¹⁾	57 y n 10	Cross sectional*	Single	65 g	PUFA: SFA 0.06	6 h	TAG and GSH	↑TAG at 4 and 6 h (p<0.05) ↓GSH at 2 h (p<0.05)	
							Brachial FMD	↓FMD at 2 h (p<0.05)	

* No comparator group.

† Values given per 100 g of test oil of which 41 g was included in the breakfast.

Arrows refer to the direction of change over time relative to baseline (fasting), unless otherwise stated.

Abbreviations: AUC; area under the curve, CETP; cholesteryl ester transfer protein, CHO; carbohydrate, E; energy, FMD; flow-mediated dilatation, GSH; glutathione, HDL-C; high density lipoprotein cholesterol, IAUC; incremental area under the curve, LDL; low density lipoprotein, Lp (a); lipoprotein (a), MaxC; maximum concentration, MUFA; monounsaturated fat, NEFA; non-esterified fatty acid, PoM; postmenopausal women, PrM; premenopausal women, PUFA; polyunsaturated fat, RE; Retinyl esters, SFA; saturated fat, TAG; triacylglycerol, TC; total cholesterol.

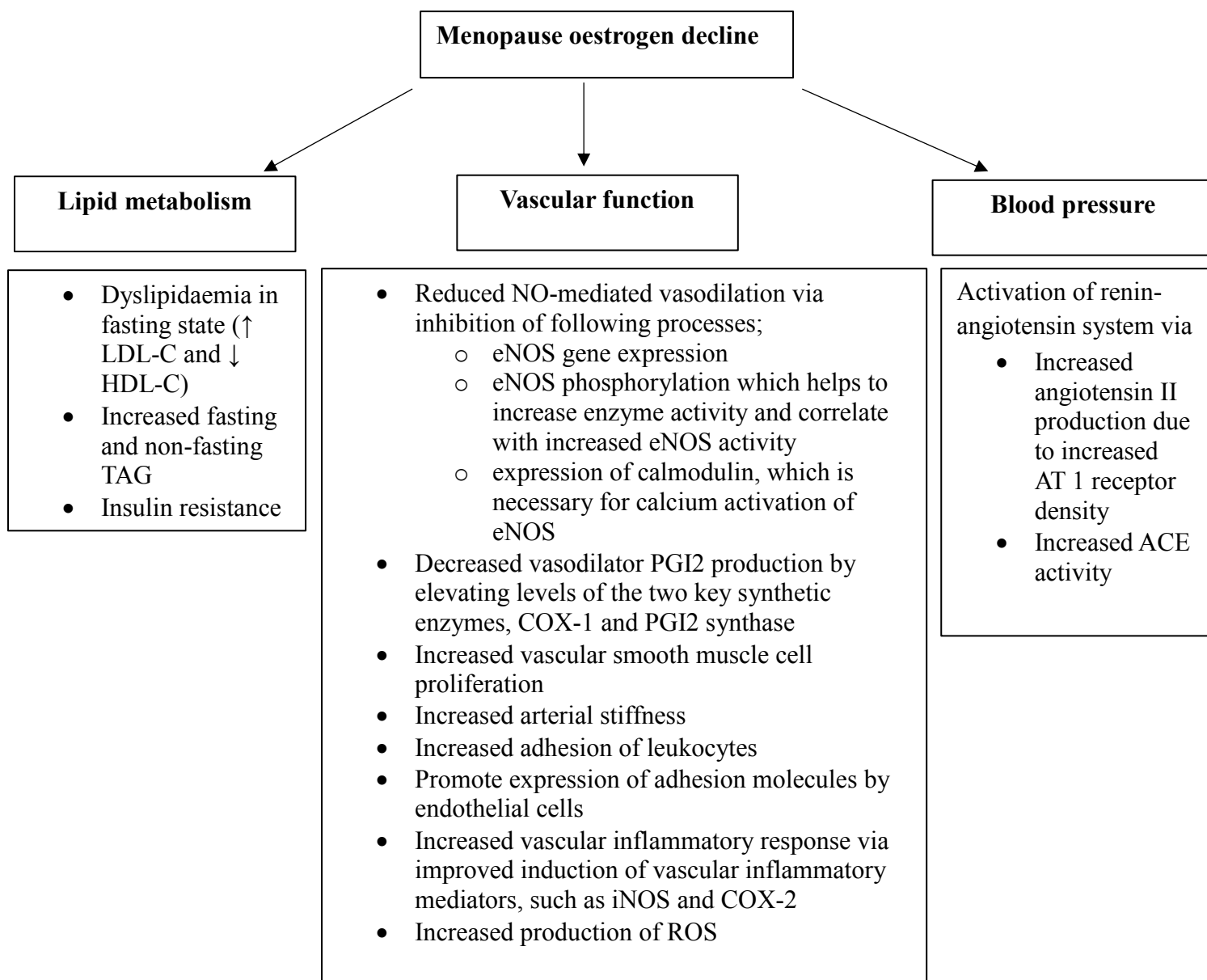


Figure 1: Consequences of the decline in oestrogen during the menopause on the lipid profile, endothelial function and blood pressure. Adapted from Davis *et al.*⁽¹⁰⁶⁾ Abbreviations: ACE; angiotensin converting enzyme, AT-1; angiotensin I receptor, COX; cyclooxygenase, eNOS; endothelial nitric oxide synthase, HDL-C; high density lipoprotein cholesterol, iNOS; inducible NO synthase, LDL-C; low density lipoprotein cholesterol, NO; nitric oxide, PGI; prostaglandin, ROS; reactive oxygen species, TAG; Triacylglycerol

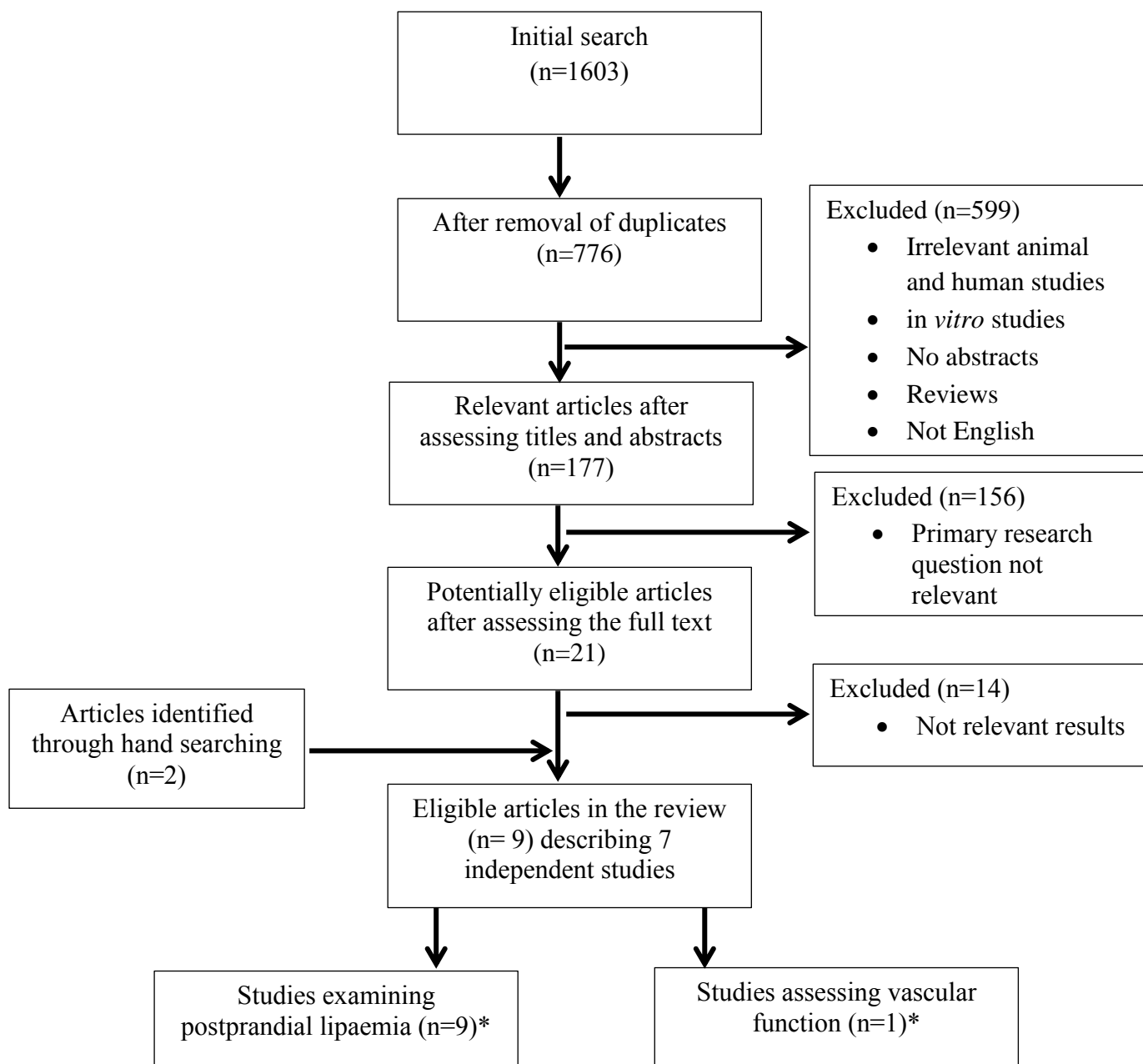


Figure 2: Flow of information through the different phases of the review

*Of the studies included in the review, one publication reported both postprandial lipaemia and vascular function.

Supplementary Table 1 Acute test meal studies investigating the impact of menopausal status on the variability of the postprandial lipaemic responses

* No comparator group.

† Values given per 100 g of test oil of which 41 g was included in the breakfast.

Reference	Subject group, age (mean) and n	Study design	Meal type	Amount of fat (% meal fat if available)	Fatty acid composition	Time of postprandial data	Postprandial measurements	Significant outcomes
van Beek <i>et al.</i> (1999) ⁽¹⁸⁾	47-52 y (50 y) n 23 PoM women and 47-52 y (49 y) n 21 PrM women	Case control	Single	50 g (40%)	PUFA: SFA 0.06	12 h	TAG and Vitamin A/retinyl palmitate	↑TAG AUC at 0-8 h (p=0.024) ↑TAG ΔAUC (p=0.020) in PoM compared to PrM at 0-8 h ↑Vitamin A AUC (p=0.001) in PoM compared to PrM at 0-8 h
Masding <i>et al.</i> (2006) ⁽²⁰⁾	34-56 y (42 y) n 8 PrM and 46-68 y (58 y) n 8 PoM healthy 32-54 y (39 y) n 8 PrM and 53-70 y (61y) n 8 PoM type 2 diabetic	Case and control	Single	45 g	No information	6 h	TAG, NEFA, Glucose, and ¹³ C-palmitic acid	↑TAG AUC in healthy PoM than PrM (p<0.05) ↑ ¹³ C-palmitic acid in healthy PoM than PrM (p<0.01)
Schoppen <i>et al.</i> (2010) ⁽¹⁹⁾	18-36 y (20.9 y) n 20 PrM and 51-59 y (55.7 y) n 18 PoM	Case and control	Single	Breakfast: 75.3 g (62.3%)	11.8 %E SFA, 39.7 %E MUFA and 6.6 %E PUFA	7 h	TAG and TC	↑TAG and TC in PoM than PrM (p<0.0001) Peak TAG at 240 min in PoM and 120 min PrM (p<0.0001)
Jackson <i>et al.</i> (2010) ⁽²¹⁾	42 y n 37 PrM and 60 y n 61 PoM	Case and control	Sequential	Breakfast: 51 g Lunch: 31 g	29 g SFA at breakfast and 14 g SFA at lunch	8 h	TAG	↑TAG IAUC (p=0.002), MaxC (p=0.037) and time to reach MaxC (p=0.009) in PoM than PrM

Arrows refer to the direction of change over time compared with premenopausal women.

Abbreviations: AUC; area under the curve, HDL; high density lipoprotein, IAUC; incremental area under the curve, LDL; low density lipoprotein, Lp (a); lipoprotein (a), MaxC; maximum concentration, MUFA; monounsaturated fat, NEFA; non-esterified fatty acid, PoM; postmenopausal women, PrM; premenopausal women, PUFA; polyunsaturated fat, SFA; saturated fat, TAG; triacylglycerol, TC; total cholesterol.

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