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*Review Article*

# A review of the evidence for the effects of total dietary fat, saturated, monounsaturated and *n*-6 polyunsaturated fatty acids on vascular function, endothelial progenitor cells and microparticles

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## Abstract

Vascular dysfunction is recognised as an integrative marker of CVD. While dietary strategies aimed at reducing CVD risk include reductions in the intake of SFA, there are currently no clear guidelines on what should replace SFA. The purpose of this review was to assess the evidence for the effects of total dietary fat and individual fatty acids (SFA, MUFA and *n*-6 PUFA) on vascular function, cellular microparticles and endothelial progenitor cells. Medline was systematically searched from 1966 until November 2010. A total of fifty-nine peer-reviewed publications (covering fifty-six studies), which included five epidemiological, eighteen dietary intervention and thirty-three test meal studies, were identified. The findings from the epidemiological studies were inconclusive. The limited data available from dietary intervention studies suggested a beneficial effect of low-fat diets on vascular reactivity, which was strongest when the comparator diet was high in SFA, with a modest improvement in measures of vascular reactivity when high-fat, MUFA-rich diets were compared with SFA-rich diets. There was consistent evidence from the test meal studies that high-fat meals have a detrimental effect on postprandial vascular function. However, the evidence for the comparative effects of test meals rich in MUFA or *n*-6 PUFA with SFA on postprandial vascular function was limited and inconclusive. The lack of studies with comparable within-study dietary fatty acid targets, a variety of different study designs and different methods for determining vascular function all confound any clear conclusions on the impact of dietary fat and individual fatty acids on vascular function.

**Key words: Dietary fatty acids: CVD: Vascular function: Progenitor cells: Microparticles**

CVD remains the major cause of death in Western societies. Although CVD is a multi-factorial disease, diet has been shown to play an important role in both the development and progression of the disease. Dietary strategies aimed at reducing the incidence of CVD include the recommendation to reduce SFA in the diet. In 1994, the Committee on Medical Aspects of Food Policy (COMA) published a report on Nutritional Aspects of CVD which included a recommendation to reduce the average intake of SFA from 16 % to no more than 11 % of food energy. Although the dietary intake of SFA has fallen, current intakes for 19–64-year-olds assessed in the first year of the National Diet and Nutrition Survey (NDNS) rolling programme (February 2008 to March 2009) exceed the COMA recommendation, at approximately 12·8 % of food energy[(1)]; total fat intake at 35·1 % of dietary energy is at the recommended level of intake for the population. A key question that needs to be addressed is whether the further desired reduction in SFA intake should be achieved through

**Abbreviations:** %E, percentage of energy; ALNA, α-linolenic acid; COMA, Committee on Medical Aspects of Food Policy; DVP, digital volume pulse; EDV, endothelium-dependent vasodilation; FBF, forearm blood flow; FMD, flow-mediated dilatation; LDI, laser Doppler imaging with iontophoresis; NDNS, National Diet and Nutrition Survey; PWA, pulse wave analysis; PWV, pulse wave velocity.

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replacement of dietary fat with carbohydrate (low-fat diets), or whether substitution of SFA with *n*-6 PUFA or MUFA is a more desirable population target. There is evidence for potentially detrimental metabolic effects of low-fat, high-carbohydrate diets in some population groups, such as type 2 diabetics[2,3], and it is argued that *n*-6 PUFA and MUFA substitution is preferable since both would achieve further reductions in LDL-cholesterol that cannot be achieved with the removal of SFA alone. However, the benefits of *n*-6 PUFA or MUFA substitution compared with low-fat diets on new and emerging risk factors for CVD, including vascular function, are unclear. Therefore, it is timely to assess a wider body of evidence on SFA substitution with fat of differing fatty acid profiles in an attempt to inform and strengthen the evidence base for public health recommendations of dietary SFA replacement.

Endothelial dysfunction is strongly associated with increased CVD risk and has emerged as a critical early modifiable event in the development of coronary atherosclerosis[4]. Since endothelial dysfunction results from the collective effects of both traditional (age, smoking, blood pressure and lipid abnormalities) and emerging (genetic make-up, insulin resistance and inflammation) risk factors, it offers considerable utility as an integrated and early measure of the effects of diet and lifestyle on CVD risk[5]. Numerous studies have highlighted the prognostic value of *in vivo* measures of vascular reactivity, of both the coronary and peripheral arteries, in predicting future coronary events[4,6]. Although there is currently no 'gold-standard' technique for measuring vascular function, flow-mediated dilatation (FMD) involving post-ischaemic wall tracking of brachial artery dilatation by ultrasound has been extensively used as a surrogate marker of coronary vascular function[7]. Other techniques include measurement of forearm blood flow (FBF) in response to vasoactive substances using strain gauge plethysmography[8] and laser Doppler imaging with iontophoresis (LDI), a non-invasive technique to assess endothelial function in the peripheral microcirculation[9,10]. Arterial stiffness is commonly measured as an estimate of the elasticity of the vessels and has been associated with atherosclerosis and CVD incidence[11]. Methods for the measurement of arterial stiffness include pulse wave analysis (PWA), pulse wave velocity (PWV) and digital volume pulse (DVP).

The relationships between traditional markers of endothelial function, such as von Willebrand factor and adhesion molecules, have been well described in the literature[12–14], and reviewed in relation to dietary fat intake[15–19]. In contrast, while endothelial progenitor cells and microparticles are now recognised as potential novel biomarkers of vascular function, there is still only limited data on the impact of dietary fat and fatty acid intake on their circulating levels[20]. Endothelial progenitor cells originate in the bone marrow and are seen in small numbers in healthy individuals, but tend to increase following vascular injury[21]. This increase has been suggested to be related to angiogenesis, repair and maintenance of the integrity of existing vessel walls[22]. In addition to the classical risk factors, emerging risk factors linked to inflammation and vascular reactivity (as assessed by FMD) have been associated with endothelial progenitor cell number and/or function[23,24]. Endothelial microparticles are small vesicles that are released from endothelial cells and can be found circulating in the blood. Several studies have shown raised levels of endothelial microparticles, and in some cases platelet microparticles, to be associated with endothelial dysfunction and obesity[25–27].

The effects of substituting SFA with MUFA and *n*-6 PUFA on plasma lipid levels and inflammatory biomarkers have been extensively studied, yet the influence of these dietary manipulations on vascular function remains unclear. Therefore, the main scientific question in this review addressed the effects of total dietary fat and individual fatty acids (SFA, MUFA and *n*-6 PUFA) on vascular function, cellular microparticles and endothelial progenitor cells by critically evaluating the existing evidence from epidemiological, human dietary intervention and postprandial test meal studies of the quantity and quality of dietary fat (SFA, MUFA and *n*-6 PUFA) on vascular function, endothelial progenitor cells and microparticles. The impact of *n*-3 PUFA, in particular long-chain *n*-3 PUFA (DHA and EPA), on vascular function has not been specifically addressed in this instance due to the number of reviews that already exist in this subject area[15,19,28]. Nevertheless, the importance of long-chain *n*-3 PUFA as a dietary strategy to reduce CVD incidence and mortality should not be underestimated since its consumption is associated with a lower risk of CVD development[29,30], blood pressure and vascular function[31,32].

## Subjects and methods

A systematic approach was used to identify all relevant published literature. Database searching was performed exclusively using the Medline database (US National Library of Medicine, Bethesda, MD, USA) following a similar approach to Dangour *et al.*[33]. The search period covered all studies published in English until November 2010. A protocol that specified the method in which to conduct the literature search was initially prepared and agreed by the review team. The search strategy consisted of an initial identification of relevant search terms for exposures (which included descriptors of SFA, MUFA and *n*-6 PUFA, and relevant food sources) and outcomes (which included descriptors of vascular function). The Medical Subject Heading Browser (http://www.nlm.nih.gov/mesh/MBrowser.html) was used to identify relevant Medical Subject Heading descriptors that were included in the search strategy as terms and combined with a list of relevant outcome terms. The Scientific Advisory Committee on Nutrition Framework for the Evaluation of Evidence that Relates Food and Nutrients to Health[34] was used as a basis to identify and assess evidence on the effects of dietary fats on vascular function. The titles and abstracts of all papers were assessed for relevance by three reviewers. The evidence base of this review is restricted to epidemiological (cross-sectional and cohort) and randomised controlled trials in human subjects with respect to total fat, SFA, MUFA and/or *n*-6 PUFA intake and measures of vascular function, as well as novel circulating biomarkers of vascular function, microparticles and endothelial progenitor cells. Data from animal and *in vitro* studies were collated, but not included in the review. In addition, studies or results on the effects of total

fat, SFA, MUFA and/or *n*-6 PUFA on blood pressure and other traditional biomarkers of vascular dysfunction (such as von Willebrand factor and cell adhesion molecules) were not included since these have been reviewed elsewhere[15,35,36].

Only published peer-reviewed literature was accepted, whereas 'grey' literature, such as dissertations, conference proceedings, reports, letters to editors and other non-peer-reviewed research, were excluded. Relevant reviews were collated but not included in the review. Hand-searching was performed on the reference lists of review articles to confirm the completeness of initial electronic searches. All researchers agreed on a common data extraction procedure. Extracted data included all study characteristics such as study type and design, volunteers' characteristics, type of dietary intervention, type/amount of fatty acids incorporated in the diet, any vascular function outcomes and statistical significance. Data extraction was performed in duplicate by two reviewers for the first ten publications and the extracted data were compared for any inconsistencies.

Evidence from both epidemiological studies and randomised controlled trials is generally included in the evaluation process of the relationship between diet and health. Although epidemiological studies can offer informative data on possible associations between environmental exposures, such as dietary components, and mortality, morbidity, disease risk or biomarkers of risk, cause and effect cannot be determined. These studies have been of paramount importance in hypothesis generation, yet consideration of significant confounding factors in such studies is essential. In comparison, randomised controlled trials are considered the 'gold standard' in terms of the strength of the scientific evidence supporting dietary recommendations for populations. Long-term controlled dietary intervention studies in free-living populations are well recognised to be highly demanding, particularly when the study requires changes to a major component of the diet, such as dietary fat content and/or quality, but these studies are very informative. In addition to the importance of the chronic impact of different diets, it is becoming increasingly apparent that since individuals spend the majority of the day (approximately 18 h) in the postprandial state, determination of the metabolic effects after the ingestion of a meal is of greater physiological relevance than the post-absorptive, fasting state. In 2007, two prospective cohort studies reported postprandial, non-fasting plasma TAG concentrations to be an independent risk factor for CVD, further adding weight to the argument that the postprandial phase is an important factor in relation to cardiovascular health[37,38]. Postprandial test meal studies provide information on the daily stress imposed on the endothelium by exposure to post-meal levels of metabolites such as lipids, glucose and insulin, therefore enabling the determination of the optimal amount and type of fat in the meal that have beneficial effects on vascular health.

Due to the small number of relevant studies and the large heterogeneity in study design, time of exposure, measures of vascular function and types of statistical analysis, a formal meta-analysis could not be performed. Therefore, a qualitative systematic approach was undertaken to search and evaluate the literature.

## Results and discussion

The literature search identified 4687 publications in total. From these studies, we identified fifty-nine relevant articles describing fifty-six studies that examined the effects of total fat and/or SFA and/or MUFA and/or *n*-6 PUFA on vascular function, endothelial progenitor cells and microparticles. These included six publications describing five epidemiological studies, eighteen publications describing the equivalent number of long-term dietary intervention studies and thirty-five publications describing thirty-three postprandial test meal studies. Data from these human studies will be presented in two sections; the first addressing total fat quantity and the second, the effects of individual fatty acids.

## Effects of dietary fat quantity on vascular function

### *Epidemiological associations from cross-sectional and cohort studies*

Of the two studies identified in the literature, inconsistent findings were observed in the cross-sectional[39] and longitudinal cohort[40] studies, both conducted in children (Table 1). Schack-Nielsen *et al.*[40] reported a significant positive relationship between total energy from fat (estimated from 7 d diet diaries) and arterial stiffness measured by PWV (aorto-radial: correlation coefficient ($r$) 0·32 ($P$=0·004) and aorto-femoral: $r$ 0·20 ($P$=0·051)) in healthy Danish children followed up at the age of 10 years. However, no association between total fat intake and arterial compliance was observed by Schutte *et al.*[39] in South African children aged 10–15 years. The atherosclerotic process that is normally exacerbated by an impaired endothelium function begins early in childhood[41,42]. Furthermore, there is evidence to suggest that the presence of atherosclerotic risk factors in childhood is predictive of CVD risk later in life[43]. Therefore, although the evidence is not conclusive, future nutritional studies in children may provide valuable information about the effect of dietary fat intake at early stages in life on the prevention of CVD development in adulthood.

### *Dietary intervention studies investigating dietary fat intake*

Details of the thirteen studies, identified between 1997 and 2010, which examined the effects of a low-fat diet only or compared diets of differing fat contents, are presented in Table 2. In two studies, low-fat diets were associated with an improvement in vascular function when compared with baseline[44,45], while six studies showed that low-fat diets either improved[46–48] or attenuated the reduction in vascular function observed with high-fat diets[49–51]. Conversely, two studies that compared the postprandial vascular responses to test meals representative of the previous intervention diet reported the high-fat diets to have beneficial effects[52,53]. However, with this type of study design, it is not possible to conclude whether the responses observed reflect the effects of the long-term dietary intervention, since differences have been observed with test meals of differing fatty acid composition[54], independent of background diet.

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**Table 1.** Epidemiological studies investigating the associations between total dietary fat and vascular function

| Reference | Subject group, age and *n* (M/F) | Assessment of dietary status | Fatty acids intake (g/d or %E) | | | | Vascular function measure | Association | Significant outcomes |
|---|---|---|---|---|---|---|---|---|---|
| | | | Total fat | SFA | MUFA | PUFA | | | |
| Cross-sectional | | | | | | | | | |
| Schutte *et al.* (2003)[39] | South African and African Caribbean HT and NT children aged 10–15 years *n* 631 (296/335) | 24 h dietary recall* | Boys: NT: 55·9 HT: 59·8 | Boys: NT: 18·6 HT: 19·8 | Boys: NT: 19·7 HT: 20·8 | Boys: NT: 12·2 HT: 12·8 | Systemic arterial compliance | Systemic arterial compliance *v.* dietary fatty acids | No association† |
| | | | Girls: NT: 50·6 HT: 52·4 | Girls: NT: 16·7 HT: 17·8 | Girls: NT: 17·8 HT: 19·2 | Girls: NT: 11·1 HT: 10·6 | | | |
| Cohort | | | | | | | | | |
| Schack-Nielsen *et al.* (2005)[40] | Danish healthy infants followed up at 10 years *n* 93 (44/49) | 7 d food diary‡ | Girls: 35·2 Boys: 35·7 | Girls: 15·6 Boys: 15·7 | Girls: 10·1 Boys: 10·1 | Girls: 4·3 Boys: 1·3 | PWV | Fat intake *v.* arterial stiffness | Aorto-radial ($r$ 0·32; $P$= 0·004)§ |
| | | | | | | | | | Aorto-femoral ($r$ 0·20, $P$= 0·051)§ |
| | | | | | | | | SFA, MUFA or PUFA *v.* arterial stiffness | No association |

%E, percentage of energy; M, male; F, female; HT, hypertensive; NT, normotensive; PWV, pulse wave velocity.
* Values are g/d.
† Adjusted for age, sex and height.
‡ Values are %E.
§ Adjusted for sex, height and weight.

Overall, there is weak evidence to suggest that low-fat diets have beneficial effects on vascular function. However, the evidence becomes stronger when the fatty acid composition of the intervention diets is taken into consideration. Of the seven studies comparing low-fat (<30 percentage of energy (%E) total fat) with high-fat, SFA-rich (29·7–35·9 %E total fat) diets, three reported an improvement in vascular function with the low-fat diet[46–48], whereas two studies showed a low-fat diet to attenuate the decline in vascular function observed with the high-fat, SFA-rich diet[49,51]. In addition, a further study reported an improvement in arterial stiffness with a low-fat (30 %E), low-cholesterol (<200 mg/d) diet, which followed a habitual diet high in SFA[45]. Nestel *et al.*[47] reported that the fatty acid composition of a low-fat diet (26 %E) may influence the improvement in arterial elasticity relative to high-fat diets (46·9–50·7 %E). In overweight/obese men and postmenopausal women, a low-fat, PUFA-rich diet led to a significantly greater improvement in arterial elasticity, with only a tendency for an improvement with a low-fat, MUFA-rich diet, which did not reach statistical significance. Interestingly, in studies that incorporated a dietary intervention and test meal challenge, a high-fat (38 %E), SFA-rich diet and test meal showed a similar postprandial vascular response (measured by ischaemic reactive hyperaemia) to the low-fat (<30 %E) diet and low-fat test meal[52,53]. In addition to these studies, Keogh *et al.*[44] found no change in FMD, but an improvement in PWV relative to baseline, 8 weeks after two weight-loss diets, a high-fat (61 %E), SFA-rich, low-carbohydrate Atkins diet or a low-fat (30 %E), high-carbohydrate diet, in obese adults. A further study by this group[51] revealed that the consumption of identical diets for 1 year led to an impairment in FMD with the high-fat, SFA-rich, low-carbohydrate diet, whereas PWV was shown to be improved following both diets. The significant weight loss in these two groups of obese subjects after ingestion of the diets for 8 weeks[44] and 52 weeks[51] (7·5 and 14·9 kg, respectively) was thought to contribute to the improvement in PWV as opposed to the differences in dietary fat intake.

Of the five studies that compared the effects of a low-fat diet (18–28 %E) relative to a high-fat (37–44 %E), MUFA-rich diet, three showed no significant effect of dietary fat content[49,55,56], whereas two studies reported beneficial effects on postprandial vascular function with a high-fat, MUFA-rich diet and test meal compared with a low-fat diet and test meal[52,53]. However, while these data provide support for acute beneficial effects of MUFA-rich test meals, it cannot be concluded that these responses were dependent on the MUFA-rich background diet, since comparisons of the responses to the MUFA-rich test meal following background diets of differing fat content and composition were not made. Keogh *et al.*[49] suggested that even though the amounts of dietary fat in the high-fat, SFA-rich and high-fat, MUFA-rich diets were identical (36–37 %E), only the high-fat, SFA-rich diet reduced the FMD response relative to the low-fat (18 %E) and high-fat, MUFA-rich diet after 8 weeks in healthy adults[49]. This finding highlights the importance of the fatty acid composition of the high-fat diet on vascular

**Table 2.** Chronic dietary intervention studies investigating the effects of total dietary fat on vascular function in healthy and non-healthy volunteers

| Reference | Subject group, age and *n* (M/F) | Study design and duration | Description of dietary intervention (total fat, %E) | Dietary fat composition (%E, unless specified) SFA | MUFA | *n*-6 PUFA (PUFA*) | Other | Vascular function measure | Significant outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Healthy volunteers | | | | | | | | | |
| Ashton *et al.* (2000)[55] | 35–55 years (M) and 50–60 years (PMW)<br>*n* 28 (14/14) | CO, R<br>4 weeks per diet | HF, MUFA-rich diet (40–42 %E) | 7–8 | 26–28 | 7–8* | CHO: 40–45 mg/d; Chol: 112 mg/d | Arterial elasticity | NS |
| | | | LF, high CHO diet (22–25 %E) | 7–8 | 7–8 | 7–8* | CHO: 55–60 mg/d; Chol: 103 mg/d | | |
| de Roos *et al.* (2001)[106] | 19–59 years<br>*n* 32 (11/21) | CO, R, C<br>3·5 weeks per diet | LF, high CHO diet (25·7 %E) | 10·3 | 7·8 | 6·9* | CHO: 59·7 mg/d; Chol: 294 mg/d | FMD | NS |
| | | | HF, MUFA diet (44·4 %E) | 15·5 | 19·3 | 8·8* | CHO: 37·8 mg/d; Chol: 386 mg/d | | |
| Raitakari *et al.* (2005)[48] | Infants (7 months old), followed up at 11 years<br>*n* 369 (182/187) | PAL, R, C<br>10·5 years | LF, low SFA diet (about 30 %E) | Boys: 10·8<br>Girls: 11·5 | ND<br>ND | ND<br>ND | | FMD | ↑ LF, low SFA *v.* control diet ($P$=0·003) in boys only |
| | | | Control diet (ND) | Boys: 13·2<br>Girls: 12·8 | ND<br>ND | ND<br>ND | | | |
| Keogh *et al.* (2005)[49] | 20–75 years<br>*n* 40 (19/21) | CO, R<br>3 weeks per diet | HF, SFA-rich diet (37 %E) | 19 | 12 | 4* | CHO: 45 mg/d; Chol: 326·5 mg/d | FMD | ↓ HF, SFA-rich *v.* HF, MUFA-rich, HF, PUFA-rich and LF, high CHO diets ($P$=0·01) |
| | | | HF, MUFA-rich diet (37 %E) | 8 | 19 | 7* | CHO: 44 mg/d; Chol: 206·9 mg/d | | |
| | | | HF, PUFA-rich diet (36 %E) | 9 | 10 | 15* | CHO: 45 mg/d; Chol: 174·3 mg/d | PWV | NS |
| | | | LF, high CHO diet (18 %E) | 7 | 6 | 3* | CHO: 65 mg/d; Chol: 167·3 mg/d | | |
| Fuentes *et al.* (2008)[52] (chronic and acute study) | Apo E3/E3 genotype 18–30 years<br>*n* 20 (20/0) | CO, R, C<br>4 weeks per diet | Chronic diets and acute test meal: | | | | | IRH | ↓ SFA-rich and LF ALNA-rich meals at 4 ($P$=0·031) and 6 h ($P$=0·013) *v.* MUFA-rich meal |
| | | | HF, SFA-rich Western diet (38 %E) | 22 | 12 | 4* | ALNA: 0·4 %E | | |
| | | | SFA-rich meal (60 %E) | 35 | 22 | 4* | ALNA: 0·7 %E | | |
| | | | HF, MUFA-rich Mediterranean diet (38 %E) | <10 | 24 | 4* | ALNA: 0·4 %E | Total nitrites | ↑ fasting level with HF, MUFA-rich *v.* HF, SFA-rich ($P$<0·05) or LF, ALNA-rich diets ($P$<0·05) |
| | | | MUFA-rich meal (60 %E) | 22 | 38 | 4* | ALNA: 0·7 %E | | |
| | | | LF, ALNA-rich diet (<30 %E) | <10 | 12 | 8* | ALNA: 2 %E | | |
| | | | ALNA-rich meal (60 %E) | 20 | 24 | 16* | ALNA: 4 %E | | |
| Miller *et al.* (2009)[46] | >20 years Mean age 30·6 ± 9·6 years<br>*n* 18 (9/9) | CO, R<br>4 weeks per diet | HF, low CHO Atkins diet (29·7 %E†) | 15·4† | ND | ND | Chol: 567 mg/d | FMD | ↑ Ornish *v.* Atkins diet (*P* value ND) |
| | | | Mediterranean South Beach diet (17·0 %E†) | 7·7† | ND | ND | Chol: 202 mg/d | | |
| | | | LF, high CHO Ornish diet (4·9 %E†) | 1·6† | ND | ND | Chol: 114 mg/d | | |
| Non-healthy volunteers | | | | | | | | | |
| Nestel *et al.* (1997)[47] | OB and OW (BMI 25–36 kg/m$^2$)<br>Mean age 54 ± 6 years<br>*n* 15 (8/7) (PMW) | C<br>4 weeks per diet | | % total fat | % total fat | % total fat | | Arterial elasticity | ↑ LF-MUFA-rich *v.* HF-S1 diet ($P$<0·05)<br>↑ LF-ALNA-rich *v.* HF-S1 ($P$<0·0001), HF-S2 ($P$<0·005) and LF-MUFA-rich ($P$<0·05) diets |
| | | | HF, SFA-rich diet 1 (HF-S1) (35·9 %E) | 50·7 | 35·3 | 14·3* | CHO: 42·5 mg/d; Chol: 295 mg/d | | |
| | | | LF, MUFA-rich diet (26·4 %E) | 25·8 | 58·1 | 16·1* | CHO: 57·9 mg/d; Chol: 206 mg/d | | |
| | | | LF, ALNA-rich diet (26·3 %E) | 23·4 | 27·5 | 49·1* | CHO: 58·4 mg/d; Chol: 210 mg/d | | |
| | | | HF, SFA diet 2 (HF-S2) (34·7 %E) | 46·9 | 36·2 | 16·4* | CHO: 46·6 mg/d; Chol: 287 mg/d | | |

**Table 2.** *Continued*

| Reference | Subject group, age and *n* (M/F) | Study design and duration | Description of dietary intervention (total fat, %E) | Dietary fat composition (%E, unless specified) SFA | MUFA | *n*-6 PUFA (PUFA*) | Other | Vascular function measure | Significant outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Fuentes *et al.* (2001)[56] | Caucasian HC (plasma Chol >5·2 mmol/l) aged 18–65 years *n* 22 (22/0) | CO, R, C 4 weeks per diet | HF, SFA-rich diet (run-in diet) (38 %E) | 20 | 12 | 6* | CHO: 47 | FMD | ↑ HF, MUFA-rich *v.* HF, SFA-rich diet ($P$=0·027) |
| | | | LF, high CHO diet (28 %E) | <10 | 12 | 6* | CHO: 57 | | |
| | | | HF, MUFA-rich diet (38 %E) | <10 | 22 | 6* | CHO: 47 | | |
| Pirro *et al.* (2004)[45] | HC (LDL >4·1 mmol/l) Mean age 58 ± 4 years *n* 35 | UC 8 weeks | LF diet (low Chol and low SFA) (30 %E) | 5 | ND | ND | Chol: <200 mg/d | PWV | ↓ LF diet *v.* baseline ($P$=0·02) |
| Keogh *et al.* (2008)[44] | OW and OB (BMI 27–44 kg/m$^2$) Abdominally obese and ≥1 extra risk factor for MS 24–64 years *n* 66 | PAL, R, C 8 weeks | Energy-restricted diets: | | | | | FMD | NS |
| | | | HF, very low CHO diet (HF) (61 %E) | 20 | ND | ND | CHO: 4 | | |
| | | | LF, high CHO diet (LF) (30 %E) | <8 | ND | ND | CHO: 46 | PWV | ↓ HF, low-CHO and LF, high-CHO diets *v.* baseline (both $P$<0·001) |
| | | | Estimate from 12 d food diaries: | | | | | | |
| | | | HF (58·5 %E) | 21 | 25 | 8* | CHO: 5·1 mg/d; Chol: 598 mg/d | | |
| | | | LF (27·8 %E) | 6 | 12 | 7* | CHO: 46·7 mg/d; Chol: 140 mg/d | | |
| Bradley *et al.* (2009)[50] | OW and OB (mean BMI 33·6 ± 3·7 kg/m$^2$) Mean age 39 ± 10 years *n* 24 (9/15) | PAL, R, C 8 weeks | Energy-restricted diets: | | | | | | |
| | | | HF, low CHO (60 %E) | ND | ND | ND | CHO: 20 | PWA | ↓ LF, high CHO diet *v.* HF, low CHO diet ($P$=0·04) |
| | | | LF, high CHO (20 %E) | ND | ND | ND | CHO: 60 | | |
| Perez-Martinez *et al.* (2009)[53] (chronic and acute study) | MS 35–70 years *n* 74 | PAL, R, C 12 weeks | Chronic diet and acute test meal: | | | | LC *n*-3 PUFA (g/d or g/meal) | IRH | ↑ IRH 4 h after HF, MUFA-rich *v.* other diets ($P$<0·05) |
| | | | HF, SFA-rich diet (38 %E) | 16 | 12 | 6* | 0 | | |
| | | | HF, SFA-rich meal (65 g) | 38 | 21 | 6* | 0 | Total nitrites | NS |
| | | | HF, MUFA-rich diet (38 %E) | 8 | 20 | 6* | 0 | | |
| | | | HF, MUFA-rich meal (65 g) | 12 | 43 | 10* | 0 | | |
| | | | LF, high CHO diet and *n*-3 PUFA (LFHCC *n*-3) (28 %E) | 8 | 11 | 6* | 1·24 | | |
| | | | LFHCC *n*-3 PUFA-rich meal (65 g) | 21 | 28 | 16* | 1·24 | NO synthase | ↑ NO synthase 4 h after HF, MUFA-rich *v.* HF, SFA-rich and LFHCC diets ($P$=0·035) |
| | | | LF, high CHO diet and high oleic sunflower-seed oil (LFHCC) (28 %E) | 8 | 11 | 6* | 0 | | |
| | | | LFHCC meal (65 g) | 21 | 28 | 16* | 0 | | |

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**Table 2.** *Continued*

| Reference | Subject group, age and *n* (M/F) | Study design and duration | Description of dietary intervention (total fat, %E) | Dietary fat composition (%E, unless specified) | | | | Vascular function measure | Significant outcomes |
|---|---|---|---|---|---|---|---|---|---|
| | | | | SFA | MUFA | *n*-6 PUFA (PUFA*) | Other | | |
| Wycherley *et al.* (2010)[51] | OW and OB (mean BMI 33·7 ± 0·6 kg/m$^2$) Abdominally obese and ≥ 1 extra risk factor for MS Mean age 50·0 ± 1·1 years *n* 49 | PAL, R, C 52 weeks | Energy-restricted diets: HF, SFA-rich, very low CHO (61 %E) | 20 | ND | ND | CHO: 4 | FMD | ↓ HF, very low CHO diet *v.* LF, high CHO diet ($P$=0·045) |
| | | | LF, high CHO (30 %E) | <8 | ND | ND | CHO: 46 | | ↓ HF, very low CHO diet *v.* baseline ($P$ value ND). |
| | | | | | | | | PWV | ↓ HF, very low CHO diet and HF, low CHO diet *v.* baseline ($P$=0·001). |
| | | | | | | | | PWA | NS |

%E, percentage of energy; M, male; F, female; PMW, postmenopausal women; CO, cross-over; R, randomised; HF, high-fat; CHO, carbohydrates; Chol, cholesterol; LF, low-fat; C, controlled; FMD, flow mediated dilatation; PAL, parallel; ND, not determined; ↑, increased; PWV, pulse wave velocity; IRH, ischaemic reactive hyperaemia; ALNA, α-linolenic acid; ↓: decreased; OB, obese; OW, overweight; HC, hypercholesterolaemic; UC, uncontrolled; MS, metabolic syndrome; PWA, pulse wave analysis.

*Data for total PUFA.

†%E calculated from energy and total fat or SFA (g/d) using dietary data from study.

function, which will be discussed in more detail in the second part of this review.

In the study by Ashton *et al.*[55], no differences were observed between the high-fat (40–42 %E), MUFA-rich and low-fat (22–25 %E) diets, but it was unclear whether improvements in arterial elasticity were observed in response to both diets as baseline values were unavailable. Bradley *et al.*[50] compared two weight-loss regimens, one a high-fat, low-carbohydrate (60 % fat; 20 % carbohydrate) diet containing equal proportions of SFA (21 %E) and MUFA (21 %E), and the other a low-fat, high-carbohydrate (20 % fat; 60 % carbohydrate) diet. After 8 weeks, the low-fat diet was shown to improve the aortic augmentation index (arterial stiffness) in overweight and obese subjects compared with the high-fat diet. Only one study, conducted in healthy adults, has compared the effects of a high-fat (36 %E), PUFA-rich diet (type of PUFA not reported) *v.* a low-fat (18 %E) diet[49], but no differences were observed in vascular function, assessed using FMD and PWV, between the diets (Table 2).

## *Effects of meal fat quantity on postprandial vascular function*

Substantial differences in study design were observed between the twenty test meal studies published between 1996 and 2010 (Table 3). These included differences in the type of test meal (for example, fat-containing drinks *v.* mixed meals), meal fat content, frequency of blood sampling during the postprandial period and vascular function outcomes. Of the twenty studies, eight examined the effects of high-fat meals only without including a comparator meal in their design[57–64], whereas the remaining twelve studies compared high-fat with low-fat meals[65–76].

Irrespective of the differences in study design, the majority of the studies in healthy volunteers reported a clear impairment in postprandial vascular function following a high-fat meal (36–80 g fat). The only study to report no effect[71] was conducted in eight young adults and may have been confounded by the small sample size and failing to control for the menstrual cycle in women, a factor known to influence FMD measurements[77]. It should also be highlighted that although there were no significant changes from baseline following the high-fat meal in this study, the endpoint measure of FMD was significantly higher after the low-fat meal (0 g fat) compared with the high-fat (48 g fat) meal[71]. In contrast, Phillips *et al.*[76] reported an improvement in arterial stiffness in healthy, obese and type 2 diabetic subjects 6 h after a high-fat meal, with the return to baseline levels of arterial stiffness shown to be delayed in type 2 diabetics (297 min from baseline) compared with healthy subjects (161 min from baseline). Interestingly, in two studies, similar vascular responses to a high-fat meal were observed in both lean and obese subjects[63,76], leading the authors to conclude that alterations in postprandial vascular reactivity may be unlikely to contribute to the increased CVD risk in obese adults[63].

Similar deleterious effects of high-fat meals on vascular function were reported in three studies that included type 2 diabetic subjects[58,61,64]. In one of these studies, the vascular

**Table 3.** Acute test meal studies investigating the effects of meal fat content on vascular function in healthy and non-healthy subjects

| Reference | Subject group, age and *n* (M/F) | Study design | Description of test meal (total fat, g or %E) | Fatty acid composition of test meal (g or %E) | | | | Vascular function measure (time points) | Significant outcomes |
|---|---|---|---|---|---|---|---|---|---|
| | | | | SFA | MUFA | *n*-6 PUFA (PUFA*) | Other | | |
| Healthy subjects | | | | | | | | | |
| Plotnick *et al.* (1997)[67] | 24–54 years<br>*n* 20 (7/13) | CO, R, C | HF meal (50 g) | ND | ND | ND | Chol: 255 mg; VitC: 1000 mg | FMD (0, 2, 4 and 6 h) | ↓ 2, 3 and 4 h after HF meal |
| | | | LF meal (0 g) | ND | ND | ND | Chol: 13 mg; VitC: 1000 mg | | |
| Vogel *et al.* (1997)[69] | 39 ± 10 years<br>*n* 10 (5/5) | CO, R, C | HF meal (50 g)<br>LF meal (0 g) | 14 g<br>14 g | ND<br>ND | ND<br>ND | Chol: 255 mg<br>Chol: 13 mg | FMD (0, 1, 2, 3, 4, 5 and 6 h) | ↓ 2 ($P$=0·05), 3 ($P$=0·02) and 4 h ($P$=0·03) after HF *v.* LF meal |
| Ong *et al.* (1999)[66] | 30 ± 5 years<br>*n* 16 (16/0) | CO, R, C | HF meal (50 g)<br>LF/H-CHO meal (5 g) | 4 g<br>0·4 g | 38 g<br>3·8 g | 5 g<br>0·5 g | CHO: 48 g<br>CHO: 218 g | FMD (0 and 3 h) | ↓ HF than LF/H-CHO meal ($P$=0·02) |
| Marchesi *et al.* (2000)[59] | 21–25 years<br>*n* 10 (10/0) | UC | HF meal (65 g) | ND | ND | ND | CHO: 25 g | FMD (2, 4, 6 and 8 h) | ↓ HF meal at 2 ($P$<0·05) and 4 h ($P$<0·05) only |
| Gaenzer *et al.* (2001)[60] | 29–43 years<br>*n* 17 (17/0) | R, C | HF drink (65 g/m$^2$ BSA) | 41 g | 20 | 4 | CHO: 24 g;<br>Chol: 240 mg | EDV (4 and 8 h) | Fasting EDV showed a diurnal variation ($P$<0·001). EDV at 4 h (12·00) less than fasting EDV at 12.00 hours ($P$=0·027) and correlated inversely with the magnitude of postprandial triacylglycerolaemia (8 h TAG AUC) ($r$ −0·81, $P$<0·001) |
| Ng *et al.* (2001)[65] | Chinese students aged 22 ± 2 years<br>*n* 10 (10/0) | CO, R, C | Asian HF meal (50 g)<br>Western HF meal (50 g)<br>LF meal (0 g) | 40 g<br>14 g<br>0 g | ND<br>ND<br>ND | ND<br>ND<br>ND | Chol: 255 mg<br>Chol: 255 mg<br>Chol: 0 mg | FMD (0, 4 h) | ↓ Western and Asian HF meals *v.* LF meal ($P$<0·006, $P$<0·001, respectively) |
| Sarabi *et al.* (2001)[68] | *n* 10 (10/0) | C | HF meal (34 %E)<br>Fat-free meal | 26 % fat<br>0 | 38 % fat<br>0 | 36 % fat*<br>0 | CHO: 51 %E | FBF (0, 1 and 2 h) | ↓ EDV 1 h after HF meal ($P$<0·001) and return to fasting levels at 2 h ($P$<0·001 *v.* 1 h) |
| Healthy subjects | | | | | | | | | |
| Bae *et al.* (2003)[70] | 25–27 years<br>*n* 10 (10/0) | CO, R, C | HF meal (53·4 g)<br>LF meal (3 g) | ND<br>ND | ND<br>ND | ND<br>ND | CHO: 50 g<br>CHO: 178 g | FMD (0, 2, 4 and 6 h) | ↓ 2 and 4 h after HF meal *v.* baseline ($P$<0·05) and LF meal ($P$<0·001) |
| Steer *et al.* (2003)[73] | 20–30 years<br>*n* 26 (13/13) | PAL, R, C | Western HF meal (34 %E)<br>LF meal (20 %E)<br>MF meal (3 %E) | 8·9† %E<br>6† %E<br>0·9† %E | 12·9† %E<br>7·4† %E<br>0·5† %E | ND<br>ND<br>ND | CHO/Trans FA/VitC<br>51 %E/12·3 %E/147 mg<br>66 %E/6·6 %E/78 mg<br>84 %E/1·7 %E/114 mg | FBF (0, 1 and 2 h) | ↓ EDV ($P$<0·01) 1 h after HF meal<br>↑ EDV ($P$<0·01) 1 h after MF meal |
| Tsai *et al.* (2004)[57] | 21–39 years<br>*n* 16 (16/0) | UC | HF meal (50 g) | 14 g | ND | ND | Chol: 225 mg | FMD (0, 2, 4 and 6 h) | ↓ 2, 4 and 6 h after HF meal *v.* baseline ($P$<0·001) |
| Padilla *et al.* (2006)[71] | 26 ± 1 years<br>*n* 8 (5/3) | CO, C | LF meal (0 g)<br>HF meal (48 g) | 0 g<br>16·5 g | ND<br>ND | ND<br>ND | CHO/Trans FA/Chol<br>209 g/0 g/5 mg<br>91 g/4·5 g/280 mg | FMD (0 and 4 h) | ↑ after LF *v.* HF meal ($P$=0·001) |

**Table 3.** *Continued*

| Reference | Subject group, age and *n* (M/F) | Study design | Description of test meal (total fat, g or %E) | Fatty acid composition of test meal (g or %E) | | | | Vascular function measure (time points) | Significant outcomes |
|---|---|---|---|---|---|---|---|---|---|
| | | | | SFA | MUFA | *n*-6 PUFA (PUFA*) | Other | | |
| Tushuizen *et al.* (2006)[62] | Caucasian aged 20–35 years<br>*n* 17 (17/0) | CO, R, C | Two consecutive HF meals at breakfast (0 h) and lunch (4 h) (50 g each) | 60 % of fat (14 g) | ND | ND | CHO: 55 g | FMD (0, 2, 4, 6 and 8 h) | ↓ 6 h after HF meal *v.* baseline ($P<0·05$) |
| | | | Water only | 0 g | 0 g | 0 g | CHO: 0 g | | |
| Shimabukuro *et al.* (2007)[72] | 30–42 years<br>*n* 12 (6/6) | CO, R, C | High-CHO meal (0 %E) | ND | ND | ND | CHO: 100 %E | FBF (0, 2 and 4 h) | Peak FBF and total reactive hyperaemic flow ↓ 2 and 4 h after HF meal ($P<0·01$) |
| | | | HF meal (35 %E) | ND | ND | ND | CHO: 0 %E | | |
| | | | Standard meal (control; 32·7 %E) | ND | ND | ND | CHO: 50·4 %E | | |
| Bui *et al.* (2010)[75] | Asian aged 26·4 ± 4·2 years<br>*n* 11 (11/0)<br>Caucasian aged 26·8 ± 4·6 years<br>*n* 8 (8/0) | CO, R | HF meal (50·1 g fat) | 14 g | ND | ND | CHO: 43·8 g; Chol: 443 mg | FBF (2 and 4 h) | Compared with LF meal, FBF ↓ with HF meal in Asians only ($P=0·02$)<br>FBF attenuated in Asians compared with Caucasians (19·3 %, $P=0·09$) |
| | | | LF meal (5·1 g fat) | 1 g | ND | ND | CHO: 135·8 g; Chol: 0 mg | | |
| Healthy and non-healthy subjects | | | | | | | | | |
| Anderson *et al.* (2001)[58] | T2D aged 35–53 years<br>*n* 12 (7/5)<br>Healthy controls aged 30–63 years<br>*n* 12 (5/7) | PAL | Standard fat-containing drink | 80 g | ND | ND | | FMD (0 and 4 h) | ↓ in control and T2D patients *v.* baseline ($P<0·05$)<br>↓ in T2D patients at baseline and 4 h *v.* controls ($P<0·05$) |
| Tushuizen *et al.* (2007)[61] | Caucasian T2D (*n* 15) and Caucasian healthy controls (*n* 12)<br>Mean age 55 ± 2 years<br>*n* 27 (27/0) | PAL | Three isoenergetic meals (0, 4 and 8 h) (50 g) | 60 % total fat | ND | ND | CHO: 75 g | FMD (0, 2, 4, 6, 8, 12, 16, 20 and 24 h) | ↓ in T2D *v.* healthy group ($P<0·01$) at baseline<br>Over 24 h, ↓ in both groups ↓ in T2D group *v.* healthy group ($P<0·01$) |
| Tousoulis *et al.* (2010)[74] | Young adults<br>*n* 37 (26/11) | PAL, R | Extra virgin olive oil (45·8 g) | 6·4 g | 35·3 g | 4·2 g* | | FBF (0, 1, 2 and 3 h) | ↓ 1 h after maize oil *v.* baseline and water control ($P<0·05$)<br>↑ 1 h after soya oil *v.* baseline and water control ($P<0·05$) |
| | | | Maize oil (46 g) | 6 g | 12·5 g | 27·5 g* | | | |
| | | | Soya oil (46 g) | 7 g | 11·5 g | 27·5 g* | | | |
| | | | Water control | 0 g | 0 g | 0 g | | | |
| Ayer *et al.* (2010)[63] | Obese (*n* 11) and healthy controls (*n* 11) aged 22 ± 6 years<br>*n* 22 (22/8) | PAL | HF meal (60 g) made of coconut oil (24 g), olive oil (24 g) and sunflower-seed oil (12 g) | 25·2 g† | 21·4 g† | 10 g†* | | FMD<br>FBF<br>PWV<br>PWA<br>DVP<br>(0, 1 and 3 h) | NS<br>NS<br>NS<br>NS<br>NS |

**Table 3.** *Continued*

| Reference | Subject group, age and *n* (M/F) | Study design | Description of test meal (total fat, g or %E) | Fatty acid composition of test meal (g or %E) | | | | Vascular function measure (time points) | Significant outcomes |
|---|---|---|---|---|---|---|---|---|---|
| | | | | SFA | MUFA | *n*-6 PUFA (PUFA*) | Other | | |
| Neri *et al.* (2010)[64] | T2D (*n* 40) aged 43 ± 3 years<br>Subjects with IGT (*n* 40) aged 41 ± 4 years<br>Healthy controls (*n* 40) aged 41 ± 2 years<br>Total *n* 120 (60/60) | PAL | HF milkshake | 80 g | ND | ND | | FMD (0, 4 and 8 h) | ↓ in T2D and IGT subjects at 4 h compared with baseline (however, absolute values and *P* values not mentioned) |
| Philips *et al.* (2010)[76] | T2D (*n* 10) aged 56 (SD 10) years; obese (*n* 10) aged 41 (SD 10) years; and lean (*n* 8), aged 46 (SD 11) years | CO, R | HF meal (57·5 g) | 11·4 g | ND | ND | CHO: 83 g | PWA (0, every 10 min for 1 h, every 15 min for 2 h and every 30 min for 3, 4, 5 and 6 h) | ↓ augmentation index in all groups after HF meal<br>↓ augmentation index in lean and T2D after HF meal compared with obese ($P<0·05$) |
| | | | Water control | 0 g | 0 g | 0 g | | | |

%E, percentage of energy; M, male; F, female; CO, cross-over; R, randomised; C, controlled; HF, high-fat; ND, not determined; Chol, cholesterol; VitC, Vitamin C; FMD, flow-mediated dilatation; ↓, decreased; LF, low-fat; H-CHO, high carbohydrate; CHO, carbohydrates; UC, uncontrolled; BSA, body surface area; EDV, endothelium-dependent vasodilation; AUC, area under the curve; FBF, forearm blood flow; PAL, parallel; Trans FA; *trans*-fatty acids; ↑, increased; MF, minimal fat; T2D, type 2 diabetics; PWV, pulse wave velocity; PWA, pulse wave analysis; DVP, digital volume pulse; IGT, impaired glucose tolerance.

*Data for total PUFA.

†Values calculated from original paper.

response to three consecutive high-fat meals (50 g fat) was impaired to a greater extent in type 2 diabetics compared with healthy control subjects[61], suggesting that individuals with increased CVD risk may handle fat differently during the postprandial phase (Table 3).

The findings from studies that investigated the effects of high-fat *v.* low-fat meals support the hypothesis that ingestion of a high-fat meal leads to an impairment of vascular function. Only one study has attempted to examine the dose-dependent effect of increasing the test meal fat content on postprandial vascular function. Steer *et al.*[73] reported a decrease in the FMD response with a high-fat meal (34 %E) only, with little effect of moderate (20 %E) or minimal (3 %E) fat meals. There is also limited evidence relating to the maximum amount of dietary fat, ingested in a single sitting that can influence FMD or other vascular measures. This may vary with health status, since the activation of the endothelial response appears to be related to, among other factors, the degree of elevation in circulating plasma TAG levels[59,60,76], which are known to be significantly higher in subjects with type 2 diabetes and those at risk of CVD (for example, metabolic syndrome)[78]. Of the studies that examined the effect of a single high-fat meal, four showed a fat-induced impairment in vascular function when the meals were rich in SFA[57–59,64], with three further studies reporting an impairment in vascular function after sequential ingestion of both two[60,62] and three[61] high-fat, SFA-rich meals.

There were two studies in which the high-fat meal (50 g fat) was MUFA-rich[66,74]. While a test meal enriched with high-oleic sunflower-seed oil was shown to decrease the postprandial FMD response compared with the baseline and low-fat meal (5 g fat)[66], 50 g of extra-virgin olive oil were found to have no effect on reactive hyperaemia compared with water[74]. In the latter study, the change in reactive hyperaemia from baseline at 1 h was lower after maize oil, but higher after soya oil. This finding suggests that the type of fat given in the high-fat test meal, and especially the PUFA-rich meal, may have differential effects on postprandial vascular function when compared with water. The effect of fat quality on postprandial vascular function will be discussed in the second part of this review.

The impact of ethnicity on the postprandial vascular response to a high-fat (50·1 g fat) *v.* a low-fat (5·1 g fat) meal has been studied by Bui *et al.*[75]. Although there was a tendency for FBF to be attenuated in healthy Asian males compared with Caucasian males after the high-fat meal, Asian males were more sensitive to the fat content of the test meals. In this group, the FBF was greater after the low-fat meal (336·9 ml/100 ml tissue per min) compared with the high-fat meal (287·4 ml/100 ml tissue per min), suggesting that genetic differences between the ethnic groups may have contributed to the variation in response to the test meals.

### *Effects of meal fat quantity on cellular microparticle number*

Only five studies were published between 2004 and 2010[61,62,79–81], three of which studied the effects of meal

fat content on endothelial microparticles[61,79,80]: two studies on total microparticles[61,62] and another on platelet microparticles[81]. A summary of these studies is presented in Table 4.

All of these studies were consistent in reporting a significant increase in circulating microparticle number following a high-fat meal (50–100 g fat), both in healthy subjects and those at a higher CVD risk, suggesting that a high-fat meal may be associated with vascular injury. In healthy volunteers, all three studies reported an increase in circulating endothelial[79,80] or platelet-derived microparticles[62] following a high-fat meal. Although the complete fatty acid profiles of the high-fat meals were not reported in these studies, two stated that SFA contributed 28 % of total fat, suggesting that SFA accounted for the deleterious effects on the vascular wall. In the study by Ferreira *et al.*[79], the high-fat meal also contained higher cholesterol levels compared with the low-fat meal (255 *v.* 5 mg). However, two studies have reported that daily egg consumption, equivalent to approximately 200 mg of dietary cholesterol, had little impact on endothelial function in both healthy[82] and hyperlipidaemic adults[83], suggesting that differences in the SFA content of the high-fat (14 g) and low-fat meals (0 g) in the Ferreira study[79] may have been responsible for the observed effects on FMD.

Studies on the effects of meal fat content on microparticles in non-healthy volunteers showed similar increases in circulating numbers of cellular microparticles in both type 2 diabetics and patients with established ultrasound-assessed atherosclerotic plaques[61,81]. Tushuizen *et al.*[61] reported a greater increase in cellular microparticle levels following consecutive high-fat meals (50 g fat each) in type 2 diabetics than in healthy controls. However, Michelsen *et al.*[81] showed no difference in response to a high-fat meal (70 %E fat) between healthy individuals and patients with established atherosclerotic plaques. These data strongly suggest that there may be differences in cellular microparticle response to high-fat meals between healthy populations and those at high CVD risk, which warrants further investigation.

### *Summary*

The outcomes of epidemiological (cross-sectional and cohort) and dietary intervention studies have been inconsistent, making it difficult to draw clear conclusions with respect to the long-term effects of dietary fat quantity on vascular function. However, there does appear to be modest evidence for a weak beneficial effect of low-fat diets, which was most apparent when the comparator diet was high in SFA. It is also worthy of note, that high-fat, MUFA-rich diets tend to improve vascular function in a similar way to low-fat, high-carbohydrate diets. Nevertheless, it should be taken into consideration that when the MUFA-rich diets are based on virgin olive oil, the reported beneficial effects on vascular function may be mediated in part by its high phenolic content[84].

In comparison, evidence to support an association between a high-fat meal and impairment of postprandial vascular function in both healthy subjects and in those with increased CVD risk (for example, type 2 diabetics) is more consistent. There are limited data to suggest that high-fat meals may modestly increase the levels of circulating microparticles (a novel and emerging biomarker of vascular function), with no data available on endothelial progenitor cells. However, data should be viewed with caution since in the majority of the postprandial studies, the fat content of the test meals was significantly higher, and thus unrepresentative of an amount of fat normally ingested at a single sitting.

## Effects of dietary fat quality on vascular function

### *Epidemiological associations from cross-sectional and cohort studies*

Of the five epidemiological studies (three cross-sectional studies and two longitudinal cohort studies) published between 2001 and 2010, two examined the relationship between both dietary fat quantity and fatty acid quality with vascular function[39,40] (see previous section and Table 1). The remaining three (described in four publications) studied associations between dietary fat composition and vascular function (Table 5)[85–88]. Significant associations between fatty acid intake and vascular function were reported in the three cross-sectional[39,85–87] and two longitudinal cohort studies[40,88] (Tables 1 and 5). However, these studies had limitations, including small sample sizes (*n* 56–174) and sample population, with only one of the two cohort studies being conducted in adults. There were also differing methods of assessing dietary intake, including 24 h dietary recalls[39], 7 d intakes[40] or biomarkers of intake, such as serum phospholipids[85], cholesteryl esters[85] and plasma/serum fatty acids[87,88]. The studies of Schutte *et al.*[39] and Sarabi *et al.*[85] suggested that sex interactions may have masked associations with vascular function, and that these interactions warrant further attention. Furthermore, 24 h dietary recalls were used to determine dietary intake, which, as a dietary assessment tool that relies on memory, has major limitations which could lead to inaccuracy.

There is a conflict in the associations between vascular function and different types of SFA in cross-sectional studies. The study reported by both Sarabi *et al.*[85] and Lind *et al.*[86] showed palmitic acid to be negatively associated ($r$ −0·29; $P<0·05$) with the endothelial function index (as assessed by the ratio of endothelium-dependent vasodilation (EDV): endothelium-independent vasodilation (EIDV) by venous occlusion plethysmography, reflecting the activity of endothelial NO synthase), with stearic acid positively associated with the endothelial function index ($r$ 0·27; $P<0·05$) and FBF at recovery after hyperaemia ($r$ 0·41; $P<0·01$). Steer *et al.*[87] revealed the total proportion of SFA, and in particular lauric and myristic acid, to have a negative association with the endothelial function index in healthy young men ($r$ −0·37 and $r$ −0·36 respectively, $P<0·05$), but not in women. In addition, Schutte *et al.*[39] reported a negative association of SFA (regression coefficient $\beta = -0·98$; $P=0·008$) and a positive association of MUFA ($\beta = 1·34$; $P=0·003$) with pulse pressure in hypertensive girls, whereas the intake of dietary PUFA was negatively associated with pulse pressure ($\beta = -0·53$; $P=0·007$) in hypertensive boys. Sarabi *et al.*[85] analysed associations

**Table 4.** Acute test meal studies investigating the effects of meal fatty acids on microparticles in healthy and diseased subjects

| Reference | Subject group, age and *n* (M/F) | Study design | Description of test meal (total fat, g or %E) | Fatty acid composition of test meal (g or %E) | | | | Vascular function measure (time points) | Significant outcomes |
|---|---|---|---|---|---|---|---|---|---|
| | | | | SFA | MUFA | *n*-6 PUFA (PUFA*) | Other | | |
| Fat quantity: healthy subjects | | | | | | | | | |
| Ferreira *et al.* (2004)[79] | Healthy aged 22–30 years<br>*n* 18 (10/8) | CO, UC | LF meal (0 g) | 0 g | ND | ND | Chol: 5 mg | EMP (0, 1 and 3 h) | ↑ 1 ($P$=0·0007) and 3 h ($P$<0·0001) after HF meal |
| | | | HF meal (50 g) | 14 g | ND | ND | Chol: 255 mg | | ↑ 1 ($P$=0·001) and 3 h ($P$<0·0001) after HF *v.* LF meal |
| Tushuizen *et al.* (2006)[62] | Healthy aged 20–35 years<br>*n* 17 (17/0) | CO, R, C | Two consecutive HF meals (50 g each) | 14 g | ND | ND | CHO: 55 g | Total MP (0, 2, 4, 6 and 8 h) | ↑ HF meal *v.* water ($P$ < 0·05) |
| | | | Water only | 0 g | ND | ND | CHO: 0 g | | |
| Harrison *et al.* (2009)[80] | Healthy aged 23–31 years<br>*n* 8 (8/0) | CO, R, C | HF meal (97 g fat/2 $m^2$ BSA) | ND | ND | ND | CHO: 124 g/2 $m^2$ BSA | EMP (0, 2, 4 and 6 h) | ↑ HF meals ± exercise ($P$=0·05 for both) |
| Fat quantity: healthy and non-healthy subjects | | | | | | | | | |
| Tushuizen *et al.* (2007)[61] | Caucasian uncomplicated T2D (*n* 15) and healthy (*n* 12)<br>Aged 53–57 years<br>Total *n* 27 (27/0) | UC | Three consecutive isoenergetic meals given at 0, 4 and 8 h (50 g/meal) | 30 g | ND | ND | CHO: 75 g | Total MP, EMP (0, 2, 4, 6, 8, 12, 16, 20 and 24 h) | ↑ CD144-EMP in T2D *v.* healthy group at baseline ($P$ < 0·05) and 12 h ($P$<0·05) |
| Michelsen *et al.* (2009)[81] | Patients with atherosclerotic plaques (echolucent (*n* 20) and echogenic (*n* 20)) and healthy (*n* 20)<br>Aged 56–80 years<br>Total *n* 60 (31/29) | UC | HF meal (70 %E) | 66 %E | 32 %E | 2 %E* | | PMP (0 and 4 h) | ↑ all groups |
| Fat quality: healthy subjects | | | | | | | | | |
| Sutherland *et al.* (2010)[104] | Healthy aged 20–70 years<br>*n* 22 (13/9) | CO, R, C | HF (sunflower-seed oil) meal (41 g) | 5 g | 9 g | 26 g | CHO: 33 g | EMP (0, 1 and 3 h) | ↑ HF (sunflower-seed oil) compared with baseline ($P$<0·05) |
| | | | HF (cream) meal (41 g) | 26 g | 12 g | 2 g | CHO: 36 g | | |

%E, percentage of energy; M, male; F, female; CO: cross-over; UC, uncontrolled; LF, low-fat; ND, not determined; Chol, cholesterol; EMP, endothelial microparticles; ↑, increased; HF, high-fat; R, randomised; C, controlled; CHO, carbohydrates; MP, microparticles; BSA, body surface area; T2D, type 2 diabetics; PMP, platelet microparticles.
* Data for total PUFA.

**Table 5.** Epidemiological studies investigating the associations between dietary fatty acids and vascular function

| Reference | Subject group, age and *n* (M/F) | Assessment of dietary status | Fatty acid intake | | | Vascular function measure | Significant outcome |
|---|---|---|---|---|---|---|---|
| | | | SFA | MUFA | PUFA | | |
| Cross-sectional | | | | | | | |
| Sarabi *et al.* (2001)[85] | Swedish healthy aged 20–69 years *n* 56 (31/25) | Serum lipids* | | | | | |
| | | PL | 0·4 (MA)<br>30·5 (PA)<br>14·4 (SA) | 0·7 (POA)<br>12·4 (OA) | 20·3 (LA) | FBF | Negative associations<br>PA in PL *v.* EFI ($r$ −0·29, $P$<0·05)<br>PA in CE *v.* EFI ($r$ −0·35, $P$<0·01) |
| | | CE | 0·9 (MA)<br>0·2 (PDA)<br>11·3 (PA)<br>0·9 (SA) | 3·7 (POA)<br>21·7 (OA) | 50·0 (LA)<br>0·8 (GLA)<br>0·7 (DHGLA)<br>6·6 (AA) | | POA in PL *v.* EFI ($r$ −0·32, $P$<0·01)<br>POA in CE *v.* EFI ($r$ −0·35, $P$<0·01)<br>POA in CE *v.* EDV ($r$ −0·32, $P$<0·05)<br>OA in CE *v.* EDV ($r$ −0·28, $P$<0·05)<br>Positive associations<br>SA in PL *v.* EFI ($r$ 0·27, $P$<0·01)<br>LA in CE *v.* EFI ($r$ 0·35, $P$<0·01)<br>LA in CE *v.* EDV ($r$ 0·30, $P$<0·05) |
| Lind *et al.* (2002)[86] | Same group as Sarabi *et al.* (2001)[85] above | CE | 0·9 (MA)<br>0·2 (PDA)<br>11·3 (PA)<br>0·9 (SA) | 3·7 (POA)<br>21·7 (OA) | 50·0 (LA)<br>0·8 (GLA)<br>0·7 (DHGLA)<br>6·6 (AA) | FBF | Resting FBF *v.* SA ($r$ 0·31; $P$<0·05)†<br>FBF at 80 s *v.* SA ($r$ 0·41; $P$<0·01)†<br>Resting FBF *v.* DHGLA ($r$ 0·32; $P$<0·05)†<br>FBF at 80 s *v.* DHGLA ($r$ −0·35; $P$<0·05)† |
| Steer *et al.* (2003)[87] | Swedish healthy aged 20–30 years *n* 74 (36/38) | Whole serum lipids* | 1·3 (MA)<br>25·0 (PA)<br>7·3 (SA)<br>0·2 (LAU)<br>34·1 (SFA) | 2·9 (POA)<br>23·0 (OA) | 26·8 (LA)<br>0·4 (GLA)<br>1·8 (DHGLA)<br>6·0 (AA) | | LA *v.* EFI in males ($r$ −0·37; $P$<0·05)<br>MA *v.* EFI in males ($r$ −0·36; $P$<0·05)<br>SA *v.* EFI in males ($r$ −0·31; $P$=0·07)<br>Total SFA *v.* EFI in males ($r$ −0·41; $P$<0·05) |
| Cohort | | | | | | | |
| Anderson *et al.* (2009)[88] | Adults from London health centres | Total plasma lipids‡ | | | | PWV | PWV *v.* AA ($r$ −0·25, $P$=0·007) |
| | 45–74 years *n* 174 (89/85) | White European | 1·1 (MA)<br>22·0 (PA)<br>6·3 (SA) | 3·1 (POA)<br>22·6 (OA) | 26·0 (LA)<br>6·2 (AA)<br>1·4 (DHGLA) | | Partial correlation analyses: PWV *v.* AA ($r$ −0·17; $P$=0·07) |
| | | African Caribbean | 0·8 (MA)<br>20·6 (PA)<br>6·4 (SA) | 2·0 (POA)<br>19·1 (OA) | 26·8 (LA)<br>8·0 (AA)<br>1·5 (DHGLA) | | No differences between ethnic groups |
| | | Gujarati | 1·2 (MA)<br>20·2 (PA)<br>6·4 (SA) | 1·5 (POA)<br>17·2 (OA) | 34·4 (LA)<br>7·2 (AA)<br>1·6 (DHGLA) | | |

M, male; F, female; PL, phospholipids; MA, myristic acid; PA, palmitic acid; SA, stearic acid; POA, palmitoleic acid; OA, oleic acid; LA, linoleic acid; FBF, forearm blood flow; EFI, endothelial function index; CE, cholesteryl esters; EDV, endothelium-dependent vasodilation; PDA, pentadecyclic acid; GLA, γ-linolenic acid; DHGLA, dihomo-γ-linolenic acid; AA, arachidonic acid; LAU, lauric acid; PWV, pulse wave velocity.

* Data are mean NEFA (%).

† Adjusted for age and sex.

‡ Data are weight %.

between palmitic acid, oleic acid and linoleic acid with the endothelial function index and EDV. Linoleic acid was positively associated with both the endothelial function index ($r$ 0·35; $P<0·01$) and EDV ($r$ 0·30; $P<0·05$), suggesting increased vasodilation as a result of greater quantities of linoleic acid in cholesteryl esters and hence, an improvement in vascular function. In contrast, palmitic acid was negatively associated with the endothelial function index ($r$ −0·35; $P<0·05$) and oleic acid with EDV ($r$ −0·28; $P<0·05$) which implied a decrease in vasodilation, as concentrations of these plasma fatty acids increased in cholesteryl esters, to the detriment of vascular function.

Data from the two longitudinal cohort studies were inconsistent. Although differences between the dietary fatty acid classes and PWV were not observed in children[40], Anderson *et al.*[88] reported an inverse association between the proportion of arachidonic acid in total plasma lipids and arterial stiffness ($r$ −0·25; $P=0·007$) in adults, which was independent of ethnicity.

### *Dietary intervention studies investigating dietary fat quality*

Between 2000 and 2010, seven studies compared the effects of high-fat, SFA-rich diets with either high-fat, MUFA-rich and/or *n*-6 PUFA-rich diets[46,49,52,53,56,86,89] (since five of these studies compared both dietary fat quantity and quality, they are summarised separately in Table 2[46,49,52,53,56]), one study examined the effects of MUFA-rich diets only[90] and a further study compared the effects of supplements enriched with SFA, MUFA and *n*-6 PUFA[91] (Table 6). Relative to a SFA-rich diet, a MUFA-rich diet was shown to improve vascular function[56] or attenuate the reduction in the vascular response observed with a SFA-rich diet[49]. Similar effects on postprandial vascular function were observed with MUFA-rich diets and acute test meals, with an improvement observed by Perez-Martinez *et al.*[53] and an attenuation of the reduction in vascular response by a SFA-rich diet and test meal reported by Fuentes *et al.*[52]. These studies provide consistent evidence that the substitution of SFA with MUFA in the background diet leads to modest improvements in vascular function. However, the studies upon which this conclusion is based varied in their design, and were potentially confounded by the effects of other dietary components such as the quantity of fruits and vegetables, α-linolenic acid (ALNA) and carbohydrate. As already mentioned, it should also be noted that for two studies[52,53], measures of vascular function were made following a test meal, the composition of which was the same as the background diet. Since postprandial FMD measurements have been shown to vary according to the meal fatty acid composition, one should be cautious in concluding that these findings result from the background diet, rather than the fatty acids in the test meal.

Beneficial effects of MUFA-rich diets on vascular reactivity either compared with baseline[90] or a SFA-rich meal[49,52,53,56] cannot necessarily be attributed to the increased MUFA intake in all of these studies. For example, Rallidis *et al.*[90] showed an improvement in FMD following a Mediterranean-style diet with intensive dietary counselling (intervention group) compared with general advice to follow a Mediterranean-style diet (control group). The intervention group was shown to increase their intake of whole grains, fruits, vegetables, nuts, red wine and fish, in addition to extra-virgin olive oil, which were significantly higher in total fat, MUFA, fibre and vitamin C compared with the control group[90]. Even studies that used oil as a source of MUFA, used a variety of oils, including extra-virgin olive oil[52,90], olive oil[56,89] and rapeseed oil margarine and almonds[49]. Additionally, the potential impact of the polyphenolic compounds within the extra-virgin olive oil may have influenced the results. In the study by Keogh *et al.*[49], the MUFA-rich diet included rapeseed oil-based margarine which also contains ALNA, as well as almonds. Since almonds contain L-arginine, this may have enhanced the bioavailability of NO and contributed to an improvement in FMD[92]. It is also difficult to determine whether the vascular effects of replacing SFA with MUFA are due to the increase in MUFA or simply a result of reducing dietary SFA.

In comparison with a SFA-rich diet, only two studies reported that MUFA-rich Mediterranean-style diets[46,89] had no effect on vascular function. However, the lack of effect observed by Ambring *et al.*[89] could have been a consequence of the small difference in MUFA content between the diets (2 %E), whereas in the study of Miller *et al.*[46], the contribution of dietary fat of the Mediterranean South Beach diet (17 %E) was lower than the SFA-rich Atkins diet (29·7 %E). An additional study, which supplemented the diet with 10 g/d of high-oleic sunflower-seed oil for 8 months, produced no effect on ischaemic reactive hyperaemia when compared with the SFA-rich placebo (a mixture of soyabean oil and fractionated coconut oil)[91]. However, the dosage of MUFA was relatively low (equivalent to 1·5 g oleic acid/d) and, unlike most of the other studies, there was no exchange of dietary SFA with MUFA. Only one study analysed the effects of a diet rich in both MUFA and PUFA relative to a SFA-rich diet[86]. A significant improvement in FBF was observed with the intervention diet, but this study did not allow for conclusions to be made on the individual classes of unsaturated fatty acids.

Only one study has compared the effects of a SFA-rich diet with a PUFA-rich diet on vascular function, with the PUFA-rich diet (containing ALNA) attenuating the decrease observed in FMD with the SFA-rich diet[49] (Table 2). Limitations of this study included the PUFA content of the diet (15·2 %E), which was twice as high as the current recommendation in the UK and three times higher than the population intake recorded in the 2008–9 NDNS. In addition to this study, Khan *et al.*[91] failed to show any significant changes in ischaemic reactive hyperaemia relative to baseline following supplementation for 8 months with 10 g/d of either *n*-6 PUFA-rich evening primrose oil or soyabean oil in 173 healthy men and women. No studies to date have addressed the impact of *n*-6 PUFA substitution for SFA.

Inconsistent findings were observed in the two dietary intervention studies that compared the effects of high-fat, MUFA-rich diets with PUFA-rich diets on vascular function[49,93]. Of these, a MUFA-rich diet significantly improved FMD compared

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**Table 6.** Chronic dietary intervention studies investigating the effects of dietary fatty acid composition on vascular function in healthy and non-healthy volunteers

| Reference | Subject group, age and *n* (M/F) | Study design and duration | Description of dietary intervention (total fat, %E) | Dietary fat composition (%E, unless specified) SFA | MUFA | *n*-6 PUFA (PUFA*) | Other | Vascular function measure | Significant outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Healthy volunteers | | | | | | | | | |
| Lind *et al.* (2002)[86] | 30–65 years (M) and 50–65 years (F) *n* 19 (13/6) | CO, R, C 4 weeks per diet | HF, MUFA- and PUFA-rich diet (37 %E) | ND | ND | ND | | FBF | ↑ relative maximal FBF after MUFA/PUFA-rich *v.* SFA-rich diet ($P=0·02$) |
| | | | HF, SFA-rich diet (37 %E) | ND | ND | ND | | | |
| Khan *et al.* (2003)[91] | 40–65 years (PMW) *n* 173 (118/55) | PAL, R, C, DB 8 months | Supplements | PA/SA† | OA† | LA/AA/GLA† | EPA/DHA/ALNA† | LDI | ↑ EDV after FO *v.* baseline ($P=0·02$) |
| | | | SFA-rich placebo | 64/20 | 166 | 231/0/0 | 0/2/34 | | |
| | | | MUFA-rich, high-oleic sunflower-seed oil | 119/75 | 1448 | 318/0/2 | 0/0/7 | | |
| | | | *n*-6 PUFA-rich EPO | 79/24 | 146 | 666/0/66 | 0/0/22 | | |
| | | | *n*-6 PUFA-rich soyabean oil | 171/25 | 327 | 622/0/0 | 0/0/112 | | |
| | | | LC *n*-3 PUFA-rich tuna FO | 174/53 | 206 | 223/16/3 | 35/188/27 | | |
| | | | EPO and FO (EPO/FO) | 274/56 | 188 | 418/14/78 | 35/197/10 | | |
| Ambring *et al.* (2004)[89] | 20–51 years *n* 22 (12/10) | CO, R, C 4 weeks per diet | | | | | CHO/fibre (g/d)/*n*-3 PUFA | FBF | NS |
| | | | SFA-rich diet (36 %E) | 17 | 12 | ND | 48/19/1 | Arterial elasticity | NS |
| | | | MUFA-rich Mediterranean-style diet (34 %E) | 8 | 14 | ND | 48/40/2 | | |
| Non-healthy volunteers | | | | | | | | | |
| Ryan *et al.* (2000)[93] | Irish Caucasian T2D aged 40–65 years *n* 11 (11/0) | UC 8 weeks per diet | *n*-6 PUFA-rich run-in diet | ND | ND | ND | | FMD | ↑ MUFA-rich intervention *v.* PUFA run-in diet ($P<0·0001$) Positive correlation with cholesteryl ester OA:LA ratio ($r=0·61$, $P<0·001$) |
| | | | MUFA-rich intervention diet | ND | ND | ND | | | |
| Rallidis *et al.* (2009)[90] | Abdominally obese with waist circumference >102 cm (M) and > 88 cm (F) < 70 years *n* 82 | PAL, R, C 8 weeks | Mediterranean-style diets: (intakes estimated from 3 d food diaries) | | | | CHO/β-carotene/ α-tocop./vitamin C | FMD | ↑ Intervention diet *v.* baseline ($P<0·001$) |
| | | | Specific food plan and close supervision (intervention; 47·4 %E) | 9·5 | 26·4 | 6·2* | 38·8/595·9/4·9/167·8 | | ↑ Intervention diet *v.* control diet ($P=0·042$) |
| | | | General advice (control; 40·3 %E) | 11·8 | 19·8 | 5·7* | 42·1/418·4/4·4/117·1 | | |

%E, percentage of energy; M, male; F, female; CO, cross-over; R, randomised; C, controlled; HF, high-fat; ND, not determined; FBF, forearm blood flow; ↑, increased; PMW, postmenopausal women; PAL, parallel; DB, double blind; PA, palmitic acid; SA, stearic acid; OA, oleic acid; LA, linoleic acid; AA, arachidonic acid; GLA, γ-linoleic acid; ALNA, α-linolenic acid; LDI, laser Doppler imaging; EDV, endothelium-dependent vasodilation; FO, fish oil; EPO, evening primrose oil; LC, long chain; CHO, carbohydrates; T2D, type 2 diabetics; UC, uncontrolled; FMD, flow-mediated dilatation; tocop., tocopherol.

* Data for total PUFA.

† Values are given as mg/10 g emulsion.

with a run-in diet rich in *n*-6 PUFA and showed a significant association between the ratio of oleic acid:linoleic acid in adipocyte membranes and FMD in type 2 diabetics[93] (Table 6). However, this study did not include another diet for comparison, which limits the strength of these findings. In contrast, Keogh *et al.*[49] failed to find a significant difference in FMD between groups consuming high-fat (36–37 %E), MUFA-rich and PUFA-rich diets. It is worth noting that the source of MUFA and PUFA varied between these studies; Ryan *et al.*[93] compared diets rich in olive oil and linoleic acid, whereas Keogh *et al.*[49] compared rapeseed oil margarine and PUFA-enriched margarine, with the addition of almonds to both diets. It is possible that the improvements in vascular function observed by Ryan *et al.*[93] could be attributed, in part, to the increased consumption of phenolic compounds in olive oil[84]. The PUFA-rich diet used by Keogh *et al.*[49] contained sources of ALNA, which may explain the lack of effect relative to the MUFA-rich diet. Therefore, no controlled study to date has compared the impact of MUFA and *n*-6 PUFA on vascular function.

## *Effects of meal fat quality on postprandial vascular function*

Of the studies published between 2000 and 2010, ten articles compared the effects of moderate- or high-fat meals of differing fat composition with an equal amount or %E from total fat on vascular function. The study by Tousoulis *et al.*[74] included a comparison of different test oils with water and therefore is summarised in Table 3, and the remaining nine studies are summarised in Table 7. Substantial differences in study design were observed between studies (as discussed in the previous section), which make drawing firm conclusions difficult. Of these ten studies, seven were performed in healthy volunteers[74,94–99], one in a mixed group of healthy and hypercholesterolaemic subjects[100] and two in type 2 diabetics[101,102] (Tables 3 and 7).

In studies that compared the postprandial effects of SFA with either MUFA or *n*-6 PUFA in healthy subjects, two studies reported significant impairment in FMD response following SFA-rich meals[96,99], whereas two studies observed no significant change in FMD[94,98]. However, the lack of an effect of the SFA-rich meal on FMD response and improvement in arterial stiffness in the study of Berry *et al.*[98] should be viewed with caution since a shea butter blend, rich in stearic acid, was used in the test meal. Stearic acid has been reported to be neutral with respect to CVD risk due to its minimal cholesterol-raising effects[103], and so may not be representative of all types of SFA. Furthermore, in the study by Raitakari *et al.*[94], the proportion of SFA in the SFA-rich meal was much lower than the proportion of SFA in the study by Nicholls *et al.*[96], in which a detrimental effect of SFA on postprandial vascular function was evident (48 *v.* 89·6 %E). Only one study investigated the effects of SFA in individuals at high risk of CVD and, in particular, type 2 diabetic patients[101]. This study reported a significant decline in FMD following the SFA-rich meal (60 %E SFA), which was apparent as early as 2 h after meal ingestion and was maintained up to 6 h postprandially, suggesting that a SFA-rich meal may have deleterious effects on vascular function in type 2 diabetics.

Of the studies that have examined the effects of a MUFA-rich meal or oil alone on postprandial vascular function, six have been performed in healthy subjects and three in subjects at high risk of CVD. In healthy subjects, three studies reported a reduction in postprandial FMD[95,98,99], whereas the remaining three studies reported no significant changes in FMD[94,97] or FBF[74]. However, in the study by Raitakari *et al.*[94], both the MUFA-rich and SFA-rich control meals were shown to enhance peripheral vasodilation assessed using FBF. The effects of the type of MUFA-rich oil incorporated into the test meal on vascular function were conflicting in subjects at high risk of CVD. In the study by Cortés *et al.*[100], FMD was impaired following a meal containing olive oil (38 %E MUFA) in both healthy and hypercholesterolaemic subjects[100], whereas West *et al.*[102] reported an improvement in FMD following a meal rich in high-oleic sunflower-seed oil (50 g fat of which 32·6 g MUFA)[100,102]. In contrast, no significant alterations in FMD were observed with a meal containing extra-virgin olive oil[101], or extra-virgin olive oil given alone[74]. It is highly possible that the conflicting outcomes on the postprandial effects of MUFA on vascular function in both healthy and non-healthy subjects may be due to the varying sources of MUFA-rich oils used in the test meals.

Of the five studies that examined the effects of *n*-6 PUFA on postprandial vascular function in healthy subjects, three reported no significant effect on FMD[95–97], with two studies observing an impairment in vascular function with an *n*-6 PUFA-rich meal[99] and *n*-6 PUFA-rich maize oil given alone[74]. Furthermore, in the study by Nicholls *et al.*[96], the PUFA-rich meal (safflower oil, 75 %E PUFA) resulted in an increase in post-ischaemic hyperaemia, suggesting a non-endothelium-dependent increase in microvascular blood flow. Interestingly, in the study of Tousoulis *et al.*[74], ingestion of soya oil alone was shown to improve reactive hyperaemia 1 h after ingestion, suggesting that oils rich in ALNA and linoleic acid (maize oil) may have opposing effects on vascular function.

In the only study performed in a mixed group of healthy and hypercholesterolaemic subjects[100], FMD was significantly improved in the hypercholesterolaemic individuals, but was unchanged in healthy subjects, suggesting that fasting lipid levels may influence the impact of the *n*-6 PUFA meal in the different subject groups. However, in this study, walnuts were the main source of PUFA, and it is not clear whether ALNA *per se* or other components in walnuts (such as L-arginine) were responsible for the observed effects. This warrants further investigation.

## *Effects of meal fat quality on cellular microparticle number*

Only one study has compared the effects of SFA-rich (cream) and *n*-6 PUFA-rich (sunflower-seed oil) test meals on circulating numbers of endothelial microparticles positive to CD144 (a more specific marker of endothelial microparticles; Table 4). Although ingestion of the SFA-rich meal was associated with a greater increase in TAG concentration

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**Table 7.** Acute test meal studies investigating the effects of meal fatty acid composition on vascular function in healthy and non-healthy subjects

| Reference | Subject group, age and *n* (M/F) | Study design | Description of test meal (total fat, g or %E) | Fatty acid composition of test meal (g or %E) | | | | Vascular function measure (time points) | Significant outcomes |
|---|---|---|---|---|---|---|---|---|---|
| | | | | SFA | MUFA | *n*-6 PUFA (PUFA*) | Other | | |
| Healthy subjects | | | | | | | | | |
| Vogel *et al.* (2000)[95] | 28–55 years<br>*n* 10 (5/5) | CO, R, C | HF OO meal (50 g)<br>HF rapeseed oil meal (CO) (50 g)<br>HF salmon meal (S) (50 g) | ND<br>ND<br>ND | ND<br>ND<br>ND | ND<br>ND<br>ND | | FMD<br>(0 and 3 h) | ↓ OO meal *v.* baseline ($P$=0·008) |
| Raitakari *et al.* (2000)[94] | 18–45 years<br>*n* 12 (7/5) | CO, C | HF SFA meal (61 g)<br>HF MUFA meal (61 g) | 48 %E<br>10 %E | 40 %E<br>85 %E | 7·4 %E*<br>5 %E* | Trans FA: 4·6 %E<br>Trans FA: 0 %E | FMD<br>FBF<br>(0, 3 and 6 h) | ↑ resting FBF ($P$<0·001) and stimulated FBF ($P$<0·001) after both meals |
| Williams *et al.* (2001)[97] | 23–53 years<br>*n* 14 (14/0) | CO, R, C, DB | OO-rich drink (78·4 g)<br>SO-rich drink (78·4 g) | 18 g<br>12·4 g | 40·7 g<br>11·1 g | 9·5 g*<br>44·1 g* | CHO: 62·5 g; Chol: 210 mg<br>CHO: 62·5 g; Chol: 210 mg | FMD<br>(0 and 4 h) | NS |
| Nicholls *et al.* (2006)[96] | 18–40 years<br>*n* 14 (8/6) | CO, R, C, DB | SO-rich meal (1 g fat/kg BW)<br>Coconut oil-rich meal (CO) (1 g fat/kg BW) | 8·8 %E<br>89·6 %E | 13·6 %E<br>5·8 %E | 75·0 %E<br>1·9 %E | | FMD<br>FBF<br>(0, 3 and 6 h) | ↓ 3 h after CO meal ($P$<0·05)<br>↑ post-hyperaemic FBF after SO meal (45 %) and CO meal (21 %) ($P$=0·02) |
| Rueda-Clausen *et al.* (2007)[99] | 18–23 years<br>*n* 10 (10/0) | CO, R, C, DB | Soup with OO<br>Soup with palm oil<br>Soup with soyabean oil | 14·3 %<br>43·6 %<br>16·3 % | 77·8 %<br>46·4 %<br>24·4 % | 6·55 %*<br>9·97 %*<br>52·78 %* | CHO: 50·6 kcal<br>CHO: 50·6 kcal<br>CHO: 50·6 kcal | FMD<br>(0 and 3 h) | ↓ all meals ($P$ < 0·00001) |
| Berry *et al.* (2008)[98] | 18–40 years<br>*n* 17 (17/0) | CO,R | HF stearic acid-rich meal (50 g)<br>HF oleic acid-rich meal (50 g) | 26·7 g<br>0·8 g | 16·4 g<br>42·5 g | 4·5 g<br>4·0 g | CHO: 89 g<br>CHO: 89 g | FMD<br>PWV<br>PWA<br>(0 and 3 h) | ↓ FMD 3 h after oleic acid-rich meal *v.* baseline ($P$<0·001)<br>↓ PWA and PWV 3 h after both meals *v.* baseline ($P$<0·001) |
| Healthy and non-healthy subjects | | | | | | | | | |
| West *et al.* (2005)[102] | T2D aged 55 ± 2 years<br>*n* 18 (13/5) | CO, R, C, DB | MUFA meal (50 g)<br>MUFA meal with ALNA (50 g)<br>MUFA meal with EPA/DHA (50 g) | 4·5 g<br>3·5 g<br>5 g | 32·6 g<br>31·2 g<br>30·7 g | 9·2 g<br>9·2 g<br>6·1 g | CHO/ALNA/EPA/DHA<br>24 g/0·5 g/0 g/0 g<br>24 g/3·3 g/0 g/0 g<br>24 g/0·2 g/2·8 g/1·2 g | FMD<br>(0 and 4 h) | ↑ all meals ($P$=0·01)<br>Inverse correlation between Δ in TAG and Δ in FMD ($r$ = -0·50, $P$<0·05) with the MUFA meal<br>↑ TAG associated with ↑ FMD ($r$ = 0·49, $P$=0·046 and $r$ = 0·49, $P$=0·052) after MUFA meals with ALNA and EPA/DHA |
| Cortés *et al.* (2006)[100] | HC aged 45 ± 13 years<br>*n* 12 (11/1)<br>Healthy controls aged 32 ± 8 years<br>*n* 12 (9/3) | CO, R | HF OO meal (80 g)<br>HF walnut meal (80 g) | 35 %E<br>35 %E | 38 %E<br>23 %E | 7 %E*<br>23 %E* | CHO/ALNA/Chol<br>22 %E/0 g/120 mg<br>22 %E/5·4 g/120 mg | FMD<br>(0 and 4 h) | ↓ OO meal *v.* baseline in healthy and HC subjects<br>↑ in HC group after walnut meal ($P$=0·006) |

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**Table 7.** *Continued*

| Reference | Subject group, age and *n* (M/F) | Study design | Description of test meal (total fat, g or %E) | Fatty acid composition of test meal (g or %E) | | | | Vascular function measure (time points) | Significant outcomes |
|---|---|---|---|---|---|---|---|---|---|
| | | | | SFA | MUFA | *n*-6 PUFA (PUFA*) | Other | | |
| Tentolouris *et al.* (2008)[101] | T2D aged 58 ± 9 years *n* 33 (21/12) | CO, R | H-SFA meal (butter) (35·6 g) H-MUFA meal (extra-virgin OO) (35·8 g) | % total fat 62·9 14·6 | % total fat 31·9 77·0 | *% total fat 0·3* 7·9* | CHO: 50·1 g CHO: 50·1 g | FMD 0, 2, 4 and 6 h | ↓ H-SFA meal ($P<0·001$) Overall, Δ in FMD was significantly different between meals (↑ after MUFA and ↓ after SFA) ($P=0·008$) |

%E, percentage of energy; M, male; F, female; CO, cross-over; R, randomised; C, controlled; HF, high-fat; OO, olive oil; ND, not determined; FMD, flow-mediated dilatation; ↓, decreased; Trans FA, *trans*-fatty acids; FBF, forearm blood flow; ↑, increased; DB, double-blind; CHO, carbohydrates; Chol, cholesterol; SO, safflower oil; BW, body weight; PWV, pulse wave velocity; PWA, pulse wave analysis; T2D, type 2 diabetics; ALNA, α-linolenic acid; HC, hypercholesterolaemics; Δ, change from baseline; H-SFA, high SFA; H-MUFA, high MUFA.
*Data for total PUFA.

within the chylomicron-enriched fraction at 1 and 3 h postprandially, the *n*-6 PUFA-rich meal led to higher circulating levels of endothelial microparticles compared with the SFA-rich meal. It has been proposed that the fat content of a test meal may increase the numbers of circulating endothelial microparticles as a result of the increased lipaemia. However, the findings from this study suggest that the fatty acid composition of a test meal may also play an important role in the shedding of endothelial microparticles positive to CD144 during the postprandial state[104].

## Summary

There is, at present, insufficient epidemiological evidence (three cross-sectional studies and two longitudinal cohort studies) to draw any firm conclusions on the association between dietary fat composition and vascular function. There are a number of limitations of published studies, including study size, relevance of the population studied and methods of assessment of vascular function.

Data were also limited on which to draw conclusions regarding the chronic effects of dietary fatty acid composition on measures of vascular function. However, there is moderately consistent evidence to suggest a small improvement in vascular function when MUFA-rich diets were compared with SFA-rich diets in healthy and non-healthy individuals, whereas data regarding the effects of *n*-6 PUFA diets are extremely limited. The current data suggest that a reduction in dietary SFA may have beneficial effects on vascular function, and that a MUFA-rich diet may provide an alternative to the low-fat, high-carbohydrate diet.

For the test meal studies, there was weak evidence to suggest a modest reduction in vascular function following a SFA-rich meal, whereas inconsistent effects were observed with both MUFA-rich and PUFA-rich meals. Nevertheless, meal fatty acid composition has previously been shown to exert differential effects on plasma lipids and other metabolic measures that might be responsible for these findings. To date, only one study has examined the impact of meal fatty acid composition on circulating levels of endothelial microparticles, with no data available on endothelial progenitor cells or platelet microparticles.

## Conclusions

A systematic approach was used to review the literature on the impact of both the quantity and quality of specific dietary fats (SFA, MUFA and *n*-6 PUFA) on vascular function and circulating levels of cellular microparticles. The role of *n*-3 PUFA was not considered in the present review as the effects of this class of fatty acids on vascular function, including potential mechanisms of action, have been covered in depth elsewhere[15,19,28,105]. Few studies were designed to directly compare the substitution of SFA with MUFA and *n*-6 PUFA on vascular function, with the majority comparing diets/meals rich in SFA, MUFA or PUFA. The measurement of novel biomarkers of vascular function such as endothelial progenitor cells, endothelial microparticles and platelet

microparticles was also extremely limited, especially after meals of differing fatty acid composition. Differences in the designs of both the chronic intervention and postprandial test meal studies rendered comparisons difficult. In particular, studies of the effects of high-fat, MUFA-rich diets used either a combination of MUFA-rich oils or complex dietary strategies such as the Mediterranean diet. The majority of the studies investigating the chronic and postprandial effects of PUFA used diets/meals that contained a mixture of both *n*-3 (ALNA) and *n*-6 PUFA.

The nature and health status of subjects and the method of assessment of vascular function were other variables that could have influenced outcome. Men were the most frequently investigated group. However, when premenopausal women were included, no consideration was given to the potential impact of the menstrual cycle phase and sex hormone concentrations on vascular function measures. FMD was used in the majority of studies, while FBF, arterial stiffness (PWV/PWA and DVP) and reactivity of the peripheral microcirculation (LDI) were used in a smaller number of studies. These techniques evaluate a diverse range of vascular endpoints, which makes the comparison of the data from the various studies difficult, since the reactivity of the macro- and microcirculation is known to be influenced by different physiological factors. Some studies failed to include a suitable control or comparator group, and two studies were of a mixed design, incorporating both a dietary intervention and postprandial test meal protocol. There were also issues relating to the type of statistical analysis performed, with very few studies investigating how the intervention diet(s) influenced the measure of vascular function over the time course of the study.

In conclusion, there is a requirement for suitably powered, robust randomised controlled trials to investigate the substitution of dietary SFA with both MUFA and *n*-6 PUFA on vascular function in adults. A dose–response study design would provide strong evidence for the effects (or lack) of dietary fats on vascular function. With the increased prevalence of obesity within the population, future studies should not only be conducted in healthy adults but also in adults at increased cardiometabolic risk, using well-standardised measures of vascular function. Future test meal studies should consider examining meals with a fat content that is more reflective of habitual eating patterns. Data from controlled and sufficiently powered investigations, in targeted populations, will be essential to enable development of the optimum dietary strategy to reduce SFA intake in the diet.

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