A single, high-fat meal adversely affects postprandial endothelial function: a systematic review and meta-analysis

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ABSTRACT

Background: Endothelial dysfunction is a predictive risk factor for the development of atherosclerosis and is assessed by flow-mediated dilation (FMD). Although it is known that NO-dependent endothelial dysfunction occurs after consuming a high-fat meal, the magnitude of the effect and the factors that affect the response are unquantified.

Objectives: We conducted a systematic review and meta-analysis exploring the quantitative effects of a single high-fat meal on endothelial function and determined the factors that modify the FMD response.

Methods: Six databases were systematically searched for original research published up to January 2022. Eligible studies measured fasting and postprandial FMD following consumption of a high-fat meal. Meta-regression was used to analyze the effect of moderator variables.

Results: There were 131 studies included, of which 90 were suitable for quantitative meta-analysis. A high-fat meal challenge transiently caused endothelial dysfunction, decreasing postprandial FMD at 2 hours [−1.02 percentage points (pp); 95% CI: −1.34 to −0.70 pp; $P < 0.01$; $I^2 = 93.3\%$], 3 hours [−1.04 pp; 95% CI: −1.48 to −0.59 pp; $P < 0.001$; $I^2 = 84.5\%$], and 4 hours [−1.19 pp; 95% CI: −1.53 to −0.84 pp; $P < 0.01$; $I^2 = 94.6\%$]. Younger, healthy-weight participants exhibited a greater postprandial reduction in the FMD percentage change than older, heavier, at-risk groups after a high-fat meal ($P < 0.05$). The percentage of fat in the meals was inversely associated with the magnitude of postprandial changes in FMD at 3 hours ($P < 0.01$).

Conclusions: A single, high-fat meal adversely impacts endothelial function, with the magnitude of the impact on postprandial FMD moderated by the fasting FMD, participant age, BMI, and fat content of the meal. Recommendations are made to standardize the design of future postprandial FMD studies and optimize interpretation of results, as high-fat meals are commonly used in clinical studies as a challenge to assess endothelial function and therapeutics. This trial was registered at PROSPERO as CRD42020187244. *Am J Clin Nutr* 2022;116:699–729.

Keywords: dietary fats, vascular endothelium, cardiovascular risk, flow-mediated dilation, postprandial

Introduction

Cardiovascular disease (CVD) is the leading cause of death, accounting for more than 33% of all potential years of life lost (1). Impaired function of the endothelium, due to suboptimal NO production, appears to be the first step towards atherosclerosis and CVD (2). As NO measurement is technically challenging (3), flow-mediated dilation (FMD) is the gold-standard noninvasive technique to assess endothelial function and estimate NO bioavailability (4–6). Furthermore, the well-established and strong association between FMD measured after an overnight fast (fasting FMD) and cardiovascular risks indicates that a NO-dependent, fasting FMD measurement is a viable prognostic tool for CVD events (5, 7).

NO is an anti-inflammatory and antiatherogenic essential vasodilator (8), and its production and effectiveness are modulated by health status, age, sex, and diet (9). The typical Western-style diet is characterized by the frequent consumption of highly processed, energy-dense, nutrient-poor meals with a high-fat content (10). Poor diet constitutes a major, preventable risk factor for CVD development (11), partially through its impacts on NO and endothelial health (12). A previous systematic review on meal ingestion that focused solely on the carbohydrate amount (not fat or protein) in the unadjusted linear regression analysis indicated significant decreases in endothelial function, as measured by FMD, and this effect was moderated by participant characteristics such as age, sex, and health status (13). However, only the

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Supplemental Tables 1–3 and Supplemental Figures 1–4 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: CVD, cardiovascular disease; FMD, flow-mediated dilation; FMD%, flow-mediated dilation percentage change; pp, percentage points; RCT, randomized controlled clinical trials; ROS, reactive oxygen species; VIF, variance inflation factor.

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largest postprandial FMD change at a given time point, compared to fasting FMD measurements for each study, was recorded, excluding all other postprandial time points. The ability to respond to a meal and the timing of the response can potentially be a more sensitive CVD risk marker.

In developed countries, adults regularly consume multiple meals and snacks, spending most of their day in the postprandial state with very little time in the fasting state (14, 15). There is evidence that the postprandial metabolism of excess fat is an important initiator in the development and progression of atherosclerotic CVD (16–18). Furthermore, postprandial triglyceride concentrations have been shown to predict CVD risks better than fasting concentrations (19). Elevated postprandial concentrations of triglyceride and lipoprotein remnants after a high-fat meal are a known risk factor for CVD (20) and contribute to endothelial dysfunction, though several possible mechanisms of action exist (18). One proposed mechanism is that an increase in fatty acid oxidation in the endothelium leads to local oxidative stress and, consequently, a reduction in NO bioavailability, resulting in endothelial dysfunction (21–23).

The effect of an acute, high-fat meal on endothelial dysfunction, measured via FMD, has been widely investigated and reported in the literature since 1997 (24). However, although there is endothelial dysfunction after a high-fat meal, the magnitude of the effect and the factors that affect the response are unquantified. This information is essential for both the interpretation of data in cardiovascular studies and the design of future studies on endothelial dysfunction. Therefore, the aim of this systematic review and meta-analysis was to assess the literature and quantify the effects of a high-fat meal on endothelial function, measured by FMD. The secondary aim was to determine the factors that cause variability in the endothelial response.

Methods

Study registration

This systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines (25) and was registered prospectively on PROSPERO, a systematic literature review registration website, as CRD42020187244.

Search strategy

Six databases—MEDLINE in Ovid (Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, and Ovid MEDLINE, from 1946), Embase (from 1947), the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus (from 1788), the Cumulative Index to Nursing and Allied Health Literature (from 1961), and Web of Science Core Collection (from 1900)—were searched with no restrictions from database inception to 20 January 2022. The search strategy was developed around 3 predefined search term groups—"high fat," "postprandial," and "flow-mediated dilation"—to identify studies that measured the effects of a single, high-fat meal on postprandial endothelial function, as measured by FMD. These concept groups were then used as building blocks for mapping all possible keywords. An example of the full search strategy is provided in **Supplemental Table 1**.

Study selection and eligibility criteria

All resultant references were imported into Covidence Systematic Review Software (Veritas Health Innovation) for eligibility screening. Three authors (JJF, ALD, and GW) conducted title and abstract screening followed by full-text screening, with each article requiring assessment by 2 independent researchers for inclusion. One author (JJF) screened all studies at both the title and abstract stage (first pass) and full-text stage (second pass). All disagreements were resolved by group discussion until consensus was reached.

Studies were included if they met the following criteria: *1*) were published in English; *2*) studied adults aged ≥18 with no restrictions on health status; *3*) provided a high-fat meal challenge that contained more than 30 g of total fat or >40% of energy from total fat for meals under 2500 kJ; and *4*) reported acute postprandial endothelial function using brachial artery FMD by ultrasound up to 8 hours after the meal. Studies were excluded if: *1*) the challenge meal contained less than 30 g of total fat or below 40% of energy from fat for meals under 2500 kJ; *2*) FMD was not used to measure endothelial function; or *3*) meals were given with supplements, drugs, or extracts without a control group receiving only a high-fat meal.

Data extraction

A single author (JJF) piloted and completed data extraction, with verification by a second author (SFC). The extracted data included study characteristics (author, year of publication, journal details, country, study design, sample size), participant characteristics (age, sex, BMI, health status), meal characteristics (food type, macronutrient energy composition), measurement protocols for FMD (time of day, placement of cuff and method of measurement), and the means and SDs of FMD at fasting and at postprandial time points. Postprandial FMD responses were extracted from all eligible studies at all time points up to 8 hours after the meal. For the purpose of the meta-analysis, participant groups within the studies were separated. For example, a study that recruited a healthy control group and a group at risk of CVD was considered as 2 separate groups. Additionally, a study that used the same population but evaluated the effects of different meals was considered 2 separate groups. Unless otherwise indicated, if the study only reported that participants arrived fasted, it was assumed that testing was performed in the morning. Where studies only reported fasting and postprandial FMD data in graphical form, data were extracted using WebPlotDigitizer, version 4.3.0 (https://automeris.io/WebPlotDigitizer/), a freely available, validated, Web-based software program (26). The calculation of the SD was conducted according to the Cochrane handbook guidelines, section 6.5.2.8, and previous literature (27, 28). The SD of the mean difference (MD) in the FMD change from fasting was calculated using the following formula:

$$\mathrm{SD} = \sqrt{\left[\left(\mathrm{SD}_{\mathrm{pretreatment}}\right)^2 + \left(\mathrm{SD}_{\mathrm{posttreatment}}\right)^2 - \left(2\mathrm{R} \times \mathrm{SD}_{\mathrm{pretreatment}} \times \mathrm{SD}_{\mathrm{posttreatment}}\right)\right]} \quad (1)$$

We assumed a correlation coefficient (R) of 0.5. If values were missing, the corresponding author was contacted by email, and data were requested. If the author did not respond or values were supplied as the SEMs, medians (IQRs), or 95% CIs, missing values were calculated, converted, or estimated, if possible, using published methods (29, 30) or the Cochrane handbook guidelines, section 6.5.2.2 (27).

Risk-of-bias assessment

Included studies involving randomized controlled clinical trials (RCT) were independently assessed by 2 separate authors (JJF and SFC) for risk of bias using the Cochrane Risk-of-Bias 2.0 tool for randomized trials (31, 32). This tool evaluates potential biases within studies based on a set of 5 domains, including random sequence generation and allocation concealment, blinding of participants and outcome assessors, blinding of the outcome assessment, incomplete outcome data, and selective reporting. Each RCT was classified as having either a low risk, some concerns, or a high risk of bias. Non-RCT studies were individually assessed by 2 separate authors (NJK and SFC) for risk of bias using the Risk Of Bias In Nonrandomized Studies of Interventions tool (33, 34). This tool identifies potential biases within studies based on a set of 7 domains, including confounding, selection of participants, classification of intervention, deviation from interventions, missing outcome data, measurement of outcomes, and selection of reported result. Each non-RCT study was classified as having either no information on the risk of bias or having a low risk, moderate risk, serious risk, or critical risk of bias. Inconsistencies between the reviewers' risk-of-bias assessments at the study level were resolved through discussion until consensus was reached.

Publication bias

Publication bias was assessed by calculation of Egger's regression asymmetry test (35), with a P value ≤ 0.05 considered evidence of small-study effects. Funnel plots were constructed and visually assessed for funnel plot asymmetry.

Statistical analysis

Effects on endothelial function, measured via FMD, were expressed as MDs with 95% CIs. For studies with multiple intervention arms or participant cohorts, each arm or cohort was treated as a separate group for analysis. The change in FMD, defined as the difference between the fasting FMD and the FMD at either 2, 3, or 4 hours after consumption, was subjected to a random-effects restricted maximum likelihood model meta-analysis using Stata, version 17.0 (StataCorp), with the meta, meta regress, and meta bias functions. A meta-analysis was also conducted on the baseline (fasting) FMD, as previous research has shown that the baseline risk can affect postprandial FMD changes (13). Data were evaluated for interstudy heterogeneity using the Cochrane Q statistic and quantified by the I^2 statistic with a P value $\leq$ 0.05. An I^2 value >50% was considered substantial heterogeneity. The 95% CI of I^2 was calculated using the heterogi command in Stata. A sensitivity analysis was conducted on studies with extreme results, where each study was removed individually and together. Where unexplained interstudy heterogeneity was identified, either a random-effects meta-regression analysis was undertaken or a subgroup analysis was performed. The predefined variables of age, BMI, and fasting FMD were tested for associations with the postprandial FMD via unadjusted linear regression. The variables of total energy, total fat, total carbohydrate, total protein, sample size, percentage of male participants, and year of publication were added to the unadjusted linear regression to quantify the relationship between each variable and the postprandial FMD response from fasting. Statistically significant and biologically relevant variables were included in a multivariable meta-regression model. Two-tailed P values $\leq$ 0.05 were considered statistically significant. All variables were tested for collinearity via the vif command in Stata. The final multivariable meta-regression model was selected following inspection of the adjusted R^2 values, where the model with the largest adjusted R^2 value was chosen. Subgroup analyses were conducted based on physiological, theoretical, and empirical associations with FMD (13). In brief, an unadjusted, subgroup-analysis, random-effects model was used to determine whether the relations of differing categorical study ranges of age, BMI, fasting FMD percentage change (FMD%), total fat (percentage of total energy), different study designs (RCT compared with non-RCT), different levels of CVD risk (healthy compared with cardiometabolic disease risk), risk of bias (low risk, some concerns, or high risk), sex (male, female, or mixed population) and FMD analysis method (manual detection compared with edge-detection software) had different associations to each of the FMD% outcome measures (during fasting and 2, 3, and 4 hours after eating).

Results

Study selection

A total of 10,132 articles were identified through database searching (**Figure 1**), with 3500 articles remaining after duplicates were removed. These articles underwent title and abstract screening, with 3244 articles excluded. A full-text screen of the remaining 256 articles resulted in 125 being excluded. Thus, 131 studies were included in the systematic review; 90 of which were considered suitable, based on the information below, for inclusion in the meta-analysis.

Initial evaluation of all 131 identified studies

The FMD technique assesses the vasodilatory response to increased blood flow and shear stress after inflating a blood pressure cuff around a muscular artery for an approximate 4- to 5-minute period. The brachial artery diameter is measured, via high-resolution ultrasound, before and after the cuff inflation. The response to FMD is commonly measured as the relative percentage change in peak reactive hyperemia diameter from baseline (FMD%). Thus, to quantify the effect of a high-fat meal on endothelial function, the MD in the FMD percentage change was calculated as the fasting FMD% subtracted from the postprandial FMD%, termed the FMD change, which is measured in units of percentage points (pp). After a high-fat meal, the measured FMD change was evaluated as a mean value from all studies (**Figure 2**).

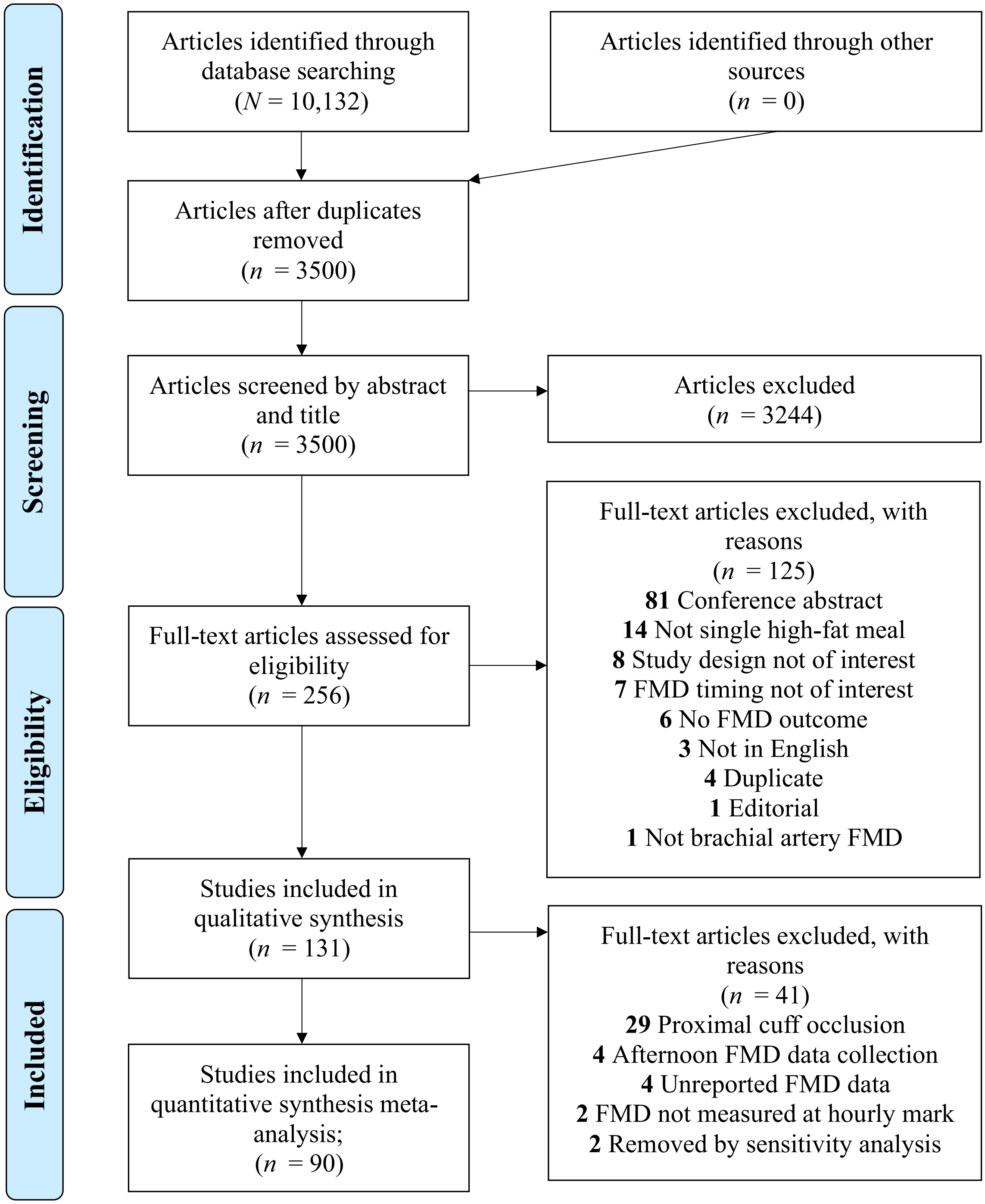

FIGURE 1 Flow diagram showing the progression through the literature search and screening process. Abbreviation: FMD, flow-mediated dilation.

One goal of this work was to assess NO-dependent changes in vasodilation and, based on current FMD protocol guidelines, relative to the ultrasound probe on the brachial artery, distal occlusion cuff placement (i.e., on the forearm) is recommended due to limitations in proximal cuff placement (6). Furthermore, FMD is only ∼30% NO-dependent when the occlusion cuff is placed proximal to the ultrasound probe, compared to ∼70% NO-mediated during distal cuff placement (36). Guidelines also state that testing times should also be standardized to avoid diurnal variations in blood flow and pressure (37). Therefore, studies that deviated from these methods (i.e., did not assess FMD in the morning after an overnight fast or used an occlusion cuff on the upper arm) were excluded from the meta-analysis.

To mitigate the unit-of-analysis error from repeated observations on participants, 3 different outcomes, based on different periods of time, were defined and used for separate analyses as recommended by the Cochrane handbook guidelines, section 6.2.4 (27). The mean value of FMD change was calculated for

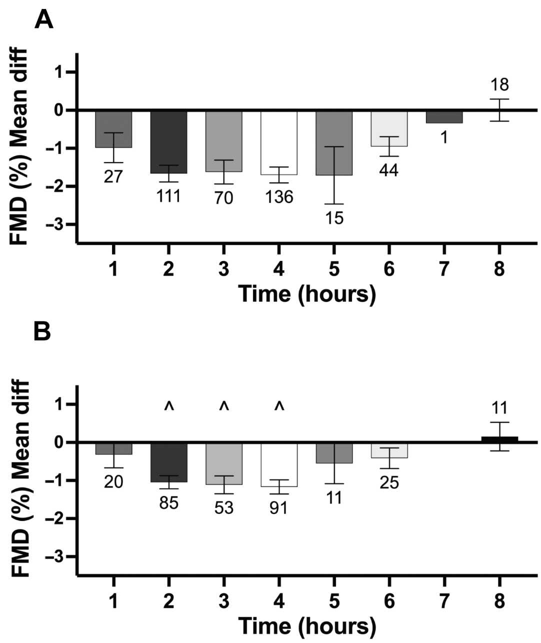

FIGURE 2 A summary of the average mean difference of FMD% between postprandial and fasting measurements (postprandial FMD% − fasting FMD%) after a high–fat meal (mean ± SEM), across (A) all studies and (B) NO-dependent FMD studies. The sample size is indicated above or below the bar. ^Time points at which a meta-regression analysis was performed. Abbreviations: FMD%, flow-mediated dilation percentage change; NO, nitric oxide.

each postprandial hourly time point up to 8 hours. A review of the means demonstrated a postprandial reduction in FMD%, followed by an increase back to baseline 8 hours after mean consumption (Figure 2). The FMD changes at the postprandial time points of 2, 3, and 4 hours were selected for inclusion in the meta-analyses based on an inspection of the graphical data in Figure 2.

Characteristics of studies in all 131 publications

Table 1 summarizes the characteristics of the 131 studies that were included in the systematic review. The ages of the total 4061 participants ranged from 20 to 68.4 years, with an average age of 41.0 years. The median participant BMI was 25.8 kg/m^2 (IQR, 23.6–28.9 kg/m^2; range, 20.5–45.1 kg/m^2). The majority of the studies recruited male and female participants (n = 73), compared with 47 studies conducted only in males, 7 only recruiting females, and 4 that did not present participant sex information. Seventy-six studies recruited participants who were apparently healthy or healthy and overweight, encompassing 1838 individuals. The 2223 participants from 74 studies exhibited a range of cardiometabolic risk factors or disease profiles. These cardiometabolic at-risk populations included individuals who presented with at least 1 CVD risk factor (n = 69 studies; 2062 participants) or had been diagnosed with coronary artery disease (n = 5 studies; 161 participants).

Sixty-three studies measured the FMD at multiple time points and 62 studies only measured the FMD at 1 time point. Of the remaining 6 studies, 4 did not report FMD results (42, 82, 105, 149) and 2 only reported FMD results at fractions of the whole hour (52, 136); thus, all 6 studies were dropped from the meta-analyses (Figure 1). There were 102 studies that performed FMD with the vascular cuff placed on the forearm, distal to the ultrasound probe placed on the brachial artery, compared to 29 studies that placed the cuff on the upper arm. Hence, studies where the cuff was placed proximal to the probe were excluded from the meta-analyses (Figure 1). Most interventions commenced in the morning (n = 127), in comparison to 4 studies that measured FMD in the afternoon (56, 66, 68, 132); these 4 studies were dropped from the meta-analyses (Figure 1). There were 2 studies, Kumar et al. (85) and van Oostrom et al. (146), that had extreme results in FMD changes. As a result of the sensitivity analysis, both studies were removed from the meta-analyses (Figure 1).

Sixty-one studies measured the artery diameter periodically; this manual method of FMD analysis typically averages a small, discrete number of measurements from the precuff inflation period for calculation of the baseline artery diameter and uses only 1 measurement at 60 seconds after cuff deflation. More recent trials (n = 70) have utilized the preferred, edge-detection method for FMD analysis (6). This method can track the artery continuously and determine the diameter over the entire protocol, accurately averaging the baseline artery diameter for the entire 1-minute baseline period, as well as determine the true peak artery diameter after cuff deflation. The FMD changes were reported at 1 hour (n = 27), 2 hours (n = 111), 3 hours (n = 70), 4 hours (n = 136), 5 hours (n = 15), 6 hours (n = 44), 7 hours (n = 1), and 8 hours (n = 18) after consumption. A thorough breakdown of the characteristics of all included studies and NO-dependent-only studies can be found in **Supplemental Table 2**.

Characteristics of the 90 studies included in the meta-analysis and review of NO-dependent FMD

Most of the 90 studies included in the meta-analysis and review of NO-dependent FMDs were randomized (n = 62), with 49 crossover and 13 parallel designs. The median study sample size was 14 (IQR, 10–20; range, 6–93). There was a total of 2856 participants, with a mean age of 41 years (range, 20–68 years). The median BMI was 25.9 kg/m^2 (IQR, 23.8–29.2 kg/m^2; range, 21.9–45.1 kg/m^2). The bulk of the studies recruited mixed-sex populations (n = 48), compared to 35 studies conducted only in males, 5 studies only recruiting females, and 2 studies that did not report participant sex. Eighty-seven groups were apparently healthy or healthy overweight participants, including 1258 individuals. Seventy-nine groups, encompassing 1598 participants, exhibited a spectrum of cardiometabolic risk factors or disease profiles, including diabetes, hypertension, obesity, hypertriglyceridemia, metabolic syndrome, hypothyroidism, or heart disease. These cardiometabolic at-risk populations contained individuals who presented with at least 1 CVD risk factor (n = 76 studies; 1549 participants) or had been diagnosed with coronary artery disease (n = 3 studies; 49 participants). The high-fat meals consumed included fast food meals (n = 16), cream-based meals (n = 16), pastry or bread (n = 25), a milkshake or smoothie (n = 10), or soup (n = 4). Ten studies did not report the meal contents. The mean total energy content of the meals was 4145 kJ, with an average of 64 grams or 58.5% total fat per meal. Postprandial FMD changes were measured at 1 hour (n = 20), 2 hours (n = 85), 3 hours (n = 53), 4 hours (n = 91),

TABLE 1 Characteristics of the studies included in the systematic review[1]

Authors, year	Country	Study design	Cuff placement	FMD timing	FMD analysis method	Risk of bias	N	Male, %	Age, y	BMI, kg/m2	Health status	Main component of high-fat meal	Total energy, kJ	Total fat, En%	Fasting FMD, %
Abubakar et al., 2019[2] (38)	UK	RCT	Forearm	Morning	Edge detection	Low	22	100.0	49.0 ± 2.0	26.9 ± 0.7	CVD risk	Croissant	3210.0	57.8	3.7 ± 0.3
Alqurashi et al., 2016[2] (39)	UK	RCT	Forearm	Morning	Edge detection	Low	23	100.0	46.0 ± 1.9	27.6 ± 0.4	Healthy overweight	NR	3269.0	67.9	5.0 ± 0.5
							23	100.0	46.0 ± 1.9	27.6 ± 0.4	Healthy overweight	NR	3265.6	66.3	5.7 ± 0.5
Anderson et al, 2001[2] (40)	UK	Non-RCT	Forearm	Morning	Edge detection	Moderate	12	58.3	47.3 ± 1.6	32.2 ± 1.2	Diabetes	Cream	5698.6	84.4	2.7 ± 0.3
							12	41.7	43.0 ± 2.9	27.5 ± 0.9	Healthy	Cream	5698.6	84.4	6.3 ± 0.4
Anderson et al., 2005[2] (41)	UK	Non-RCT	Forearm	Morning	Edge detection	Serious	27	66.7	47.6 ± 2.3	29.6 ± 1.0	Diabetes	Cream	5698.6	84.4	NR
Anderson et al., 2006[3] (42)	UK	RCT	Forearm	Morning	Edge detection	Some concerns	10	80.0	53.6 ± 2.5	28.6 ± 1.7	Diabetes	Cream	5698.6	84.4	0.4 ± 0.4
							10	80.0	53.6 ± 2.5	28.6 ± 1.7	Diabetes	Cream	5698.6	84.4	1.3 ± 0.4
Ayer et al., 2010[2] (43)	Australia	Non-RCT	Forearm	Morning	Manual measurement	Moderate	11	63.6	32.1 ± 1.9	45.1 ± 4.7	Obese	Carrot cake and milkshake	4184.0	53.1	6.2 ± 0.5
							11	63.6	31.6 ± 1.6	22.8 ± 0.6	Healthy	Carrot cake and milkshake	4184.0	53.1	4.7 ± 1.2
Bae et al., 2001[2] (44)	South Korea	Non-RCT	Forearm	Morning	Manual measurement	Serious	11	36.4	56.0 ± 1.8	NR	Healthy	Korean barbecue	3359.8	58.8	13.7 ± 1.0
Bae et al., 2001[2] (45)	South Korea	Non-RCT	Forearm	Morning	Manual measurement	Serious	9	66.7	59.0 ± 3.7	NR	CVD	Korean barbecue	3359.8	58.8	9.2 ± 1.0
Bae et al., 2003[2] (46)	South Korea	RCT	Forearm	Morning	Manual measurement	Some concerns	10	100.0	26.0 ± 0.3	NR	Healthy	Korean barbecue	3359.8	58.8	13.30 ± 1.10
Ballard et al., 2008[4] (47)	USA	Non-RCT	Upper arm	Morning	Edge detection	Moderate	10	100.0	20.8 ± 0.6	20.5 ± 0.4	Healthy	Fast food breakfast	4393.2	55.6	11.2 ± 0.8
							10	100.0	20.9 ± 0.7	23.4 ± 1.0	Healthy	Fast food breakfast	4393.2	55.6	9.7 ± 0.8
Benson et al., 2018[2] (48)	USA	Non-RCT	Forearm	Morning	Edge detection	Moderate	10	100.0	26.0 ± 1.0	24.7 ± 1.2	Healthy	Milkshake	3882.8	76.2	6.8 ± 1.0
Berry et al., 2008[2] (49)	UK	RCT	Forearm	Morning	Edge detection	Some concerns	17	100.0	27.1 ± 1.3	24.3 ± 0.7	Healthy	2 muffins and a milkshake	3570.0	51.8	7.3 ± 0.4
							17	100.0	27.1 ± 1.3	24.3 ± 0.7	Healthy	2 muffins and a milkshake	3570.0	51.8	7.3 ± 0.4
Borucki et al., 2009[4] (50)	Germany	RCT	Upper arm	Morning	Manual measurement	High	15	53.3	25.7 ± 0.4	22.3 ± 0.5	Healthy	Cream	2816.1	92.0	8.0 ± 0.7
Brook et al., 2001[2] (51)	USA	Non-RCT	Forearm	Morning	Manual measurement	Serious	32	43.8	34.6 ± 1.7	33.9 ± 1.0	Obese	Fast food burger combo meal w/milkshake	6819.9	38.5	6.3 ± 1.0
Burton-Freeman et al., 2012[5] (52)	USA	RCT	Forearm	Morning	Manual measurement	Some concerns	25	52.0	27.0 ± 1.6	22.0 ± 0.4	Healthy	Bagel w/cream cheese	3562.7	45.0	13.80 ± 1.30
							25	52.0	27.0 ± 1.6	22.0 ± 0.4	Healthy	Bagel w/cream cheese	3547.2	45.4	14.50 ± 1.30

(*Continued*)

TABLE 1 (*Continued*)

Authors, year	Country	Study design	Cuff placement	FMD timing	FMD analysis method	Risk of bias	*N*	Male, %	Age, y	BMI, kg/m2	Health status	Main component of high-fat meal	Total energy, kJ	Total fat, En%	Fasting FMD, %
Ceriello et al., 2002[2] (53)	Italy	RCT	Forearm	Morning	Manual measurement	Some concerns	30	73.3	54.3 ± 2.6	29.7 ± 2.3	Diabetes	Cream	6150.5	94.8	4.5 ± 0.3
							20	60.0	53.5 ± 2.5	28.4 ± 2.1	Healthy	Cream	6150.5	94.8	13.2 ± 0.9
Chaves et al., 2009[4] (54)	USA	Non-RCT	Upper arm	Morning	Manual measurement	Serious	5	100.0	24.0 ± NR	NR	Healthy	Fast food breakfast	3765.6	48.2	NR
Cho et al., 2020[2] (55)	South Korea	RCT	Forearm	Morning	Edge detection	Some concerns	12	58.3	23.5 ± 0.8	23.4 ± 0.8	Healthy	Fast food breakfast w/milkshake	5573.1	47.1	9.7 ± 0.8
Cortés et al., 2006[6] (56)	Spain	RCT	Forearm	Afternoon	Manual measurement	Some concerns	12	75.0	32.0 ± 2.3	24.7 ± 0.9	Healthy	Sandwich w/salami, cheese	5020.8	63.0	4.7 ± 0.4
							12	75.0	32.0 ± 2.3	24.7 ± 0.9	Healthy	Sandwich w/salami, cheese	5020.8	63.0	4.2 ± 0.4
							12	91.7	45.0 ± 3.8	26.3 ± 1.0	CVD risk	Sandwich w/salami, cheese	5020.8	63.0	3.6 ± 0.4
							12	91.7	45.0 ± 3.8	26.3 ± 1.0	CVD risk	Sandwich w/salami, cheese	5020.8	63.0	4.1 ± 0.6
Curtis et al., 2022[2] (57)	UK	RCT	Forearm	Morning	Edge detection	Some concerns	22	59.1	63.2 ± 1.9	31.5 ± 0.6	Metabolic syndrome	Milkshake	4054.3	58.9	2.1 ± 0.3
Das et al., 2018[2] (58)	USA	RCT	Forearm	Morning	Edge detection	Some concerns	11	36.4	27.0 ± 2.0	27.0 ± 1.0	Healthy	Milkshake	3807.4	48.6	9.3 ± 0.9
							12	41.7	27.0 ± 1.0	22.0 ± 0.4	Healthy	Milkshake	3807.4	48.6	6.7 ± 0.7
							13	69.2	26.0 ± 1.0	24.0 ± 1.0	Healthy	Milkshake	3807.4	48.6	7.5 ± 0.6
							9	44.4	26.0 ± 1.0	24.0 ± 1.0	Healthy	Milkshake	3807.4	48.6	7.3 ± 0.8
de Roos et al., 2002[2] (59)	Netherlands	RCT	Forearm	Morning	Edge detection	High	25	100.0	NR	25.4 ± 0.5	Healthy	Bread w/spread and milkshake	4947.0	59.1	2.3 ± 0.4
							25	100.0	NR	25.4 ± 0.5	Healthy	Bread w/spread and milkshake	4947.0	59.1	2.7 ± 0.5
Deveaux et al., 2016[2] (60)	France	RCT	Forearm	Morning	Edge detection	High	33	72.7	45.0 ± 1.6	28.0 ± 0.3	CVD risk	Cream	3765.6	80.0	6.4 ± 0.4
Djoussé et al., 1999[2] (61)	USA	Non-RCT	Forearm	Morning	Edge detection	Serious	13	53.9	32.0 ± 2.5	24.9 ± 0.7	Healthy	Fast food burger combo meal w/Coca-Cola	5020.8	47.2	9.5 ± 1.4
							13	53.9	32.0 ± 2.5	24.9 ± 0.7	Healthy	Fast food burger combo meal w/red wine	5020.8	47.2	8.0 ± 1.1
do Rosario et al., 2021[2] (62)	Australia	RCT	Forearm	Morning	Edge detection	Some concerns	16	18.8	65.9 ± 1.5	30.6 ± 1.0	Obese	Egg, sausage, pastry breakfast w/plum juice	3995.3	60.5	4.1 ± 0.2
							16	18.8	65.9 ± 1.5	30.6 ± 1.0	Obese	Egg, sausage, pastry breakfast w/apricot juice	3986.9	60.6	3.6 ± 0.3
Esser et al., 2013[2] (63)	Netherlands	RCT	Forearm	Morning	Edge detection	Some concerns	20	100.0	22.0 ± 0.5	22.7 ± 0.5	Healthy	Cream	3992.0	88.1	5.1 ± 0.5

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TABLE 1 (*Continued*)

Authors, year	Country	Study design	Cuff placement	FMD timing	FMD analysis method	Risk of bias	*N*	Male, %	Age, y	BMI, kg/m2	Health status	Main component of high-fat meal	Total energy, kJ	Total fat, En%	Fasting FMD, %
Evans et al., 2000[2] (64)	UK	RCT	Forearm	Morning	Edge detection	Some concerns	10	50.0	48.7 ± 1.4	31.3 ± 2.1	Diabetes	Cream	5698.6	84.4	3.3 ± 0.2
							8	50.0	49.6 ± 2.3	31.0 ± 2.2	Diabetes	Cream	5698.6	84.4	3.8 ± 0.2
Evans et al., 2003[2] (65)	UK	Non-RCT	Forearm	Morning	Edge detection	Moderate	10	90.0	53.6 ± 2.5	28.6 ± 1.7	Diabetes	Cream	5698.6	84.4	1.10 ± 0.38
Fahs et al., 2010[6] (66)	USA	RCT	Forearm	Afternoon	Edge detection	Some concerns	20	50.0	25.0 ± 1.0	23.4 ± 0.2	Healthy	Fast food burger combo meal	4294.9	45.23	8.4 ± 0.5
Fard et al., 2000[2] (67)	USA	Non-RCT	Forearm	Morning	Edge detection	Serious	50	68.0	61.8 ± 1.3	30.1 ± 0.6	Diabetes	Cream	5292.8	73.0	6.9 ± 0.6
Fitschen et al., 2011[6] (68)	USA	Non-RCT	Forearm	Afternoon	Manual measurement	Moderate	6	NR	48.2 ± 2.0	33.1 ± 2.7	CVD risk	Sandwich w/salami, cheese	5020.8	63.0	13.50 ± 3.20
							6	NR	48.2 ± 2.0	33.1 ± 2.7	CVD risk	Sandwich w/salami, cheese	5020.8	63.0	9.8 ± 2.1
Gaenzer et al., 2001[2] (69)	Austria	Non-RCT	Forearm	Morning	Manual measurement	Serious	17	100.0	35.7 ± 1.1	24.1 ± 0.4	Healthy	Cream	5803.2	78.8	2.3 ± 0.5
Gokce et al., 2001[4] (70)	USA	RCT	Upper arm	Morning	Edge detection	High	14	57.1	30.0 ± 2.4	NR	Healthy	Eggs and bacon	4464.3	46.4	14.7 ± 2.2
Grassi et al., 2016[2] (71)	Italy	RCT	Forearm	Morning	Edge detection	Some concerns	19	36.8	51.3 ± 1.9	27.1 ± 0.3	CVD risk	Cream	3347.2	79.1	5.2 ± 0.2
Harris et al., 2012[2] (72)	USA	Non-RCT	Forearm	Morning	Edge detection	Serious	10	100.0	23.0 ± 0.9	23.0 ± 1.0	Healthy	Fast food breakfast	3933.0	45.2	6.4 ± 1.00
							15	0.0	20.0 ± 0.5	24.0 ± 1.0	Healthy	Fast food breakfast	3933.0	45.2	12.9 ± 1.1
							15	0.0	20.0 ± 0.5	24.0 ± 1.0	Healthy	Fast food breakfast	3933.0	45.2	12.6 ± 2.0
							15	0.0	20.0 ± 0.5	24.0 ± 1.0	Healthy	Fast food breakfast	3933.0	45.2	11.0 ± 1.4
Hilpert et al., 2007[2] (73)	USA	RCT	Forearm	Morning	Edge detection	Some concerns	15	66.7	53.6 ± 1.9	28.9 ± 1.0	Diabetes	Milkshake	2615.0	70.8	5.2 ± 0.5
Hodgson et al., 2005[2] (74)	Australia	RCT	Forearm	Morning	Edge detection	Some concerns	20	NR	62.1 ± 1.4	28.1 ± 0.8	CVD	Fast food breakfast	3400.0	54.4	5.3 ± 0.7
							20	NR	62.1 ± 1.3	28.1 ± 0.8	CVD	Fast food breakfast w/cup of tea	3400.0	54.4	4.9 ± 0.9
Jahn et al., 2016[2] (75)	USA	Non-RCT	Forearm	Morning	Edge detection	Serious	16	37.5	43.0 ± 3.0	23.0 ± 0.5	Healthy	NR	2489.5	60.0	7.3 ± 1.1
							18	50.0	46.0 ± 3.0	35.0 ± 2.0	Metabolic syndrome	NR	3556.4	60.0	6.0 ± 1.5
Johnson et al., 2011[2] (76)	USA	Non-RCT	Forearm	Morning	Edge detection	Moderate	7	57.1	27.7 ± 2.1	22.0 ± 3.1	Healthy	Fast food breakfast	3933.0	45.2	9.1 ± 1.5
							7	57.1	27.3 ± 3.5	22.5 ± 1.2	Healthy	Fast food breakfast	3933.0	45.2	7.9 ± 1.4
Joris and Mensink, 2013[2] (77)	Netherlands	RCT	Forearm	Morning	Edge detection	Some concerns	20	100.0	61.0 ± 1.6	30.1 ± 0.4	Obese	2 muffins	4695.0	44.6	4.2 ± 0.6
							20	100.0	61.0 ± 1.6	30.1 ± 0.4	Obese	2 muffins w/140 mL beetroot juice	4695.0	44.6	3.8 ± 0.7
Joris et al., 2020[2] (78)	Netherlands	RCT	Forearm	Morning	Edge detection	Some concerns	19	69.0	60.0 ± 1.8	28.3 ± 0.4	CVD risk	2 muffins w/300 mL low-fat milk	4598.0	45.6	4.5 ± 0.8
							22	66.7	60.0 ± 1.5	28.6 ± 2.7	CVD risk	2 muffins w/300 mL low-fat milk	4598.0	45.6	3.4 ± 0.6
Joris et al., 2020[2] (79)	Netherlands	RCT	Forearm	Morning	Edge detection	Some concerns	24	100.0	46.8 ± 5.9	23.3 ± 0.4	Healthy	2 muffins w/300 mL low-fat milk	4598.0	45.6	2.5 ± 0.4
							23	100.0	52.8 ± 2.6	29.9 ± 0.5	Obese	2 muffins w/300 mL low-fat milk	4598.0	45.6	3.5 ± 0.5

(*Continued*)

TABLE 1 (*Continued*)

Authors, year	Country	Study design	Cuff placement	FMD timing	FMD analysis method	Risk of bias	*N*	Male, %	Age, y	BMI, kg/m2	Health status	Main component of high-fat meal	Total energy, kJ	Total fat, En%	Fasting FMD, %
Karatzi et al., 2008[2] (80)	Greece	RCT	Forearm	Morning	Manual measurement	Some concerns	15	46.7	29.5 ± 1.5	23.0 ± 0.7	Healthy	Vegetable soup w/olive oil and red wine	3079.4	64.1	6.6 ± 0.8
							15	46.7	29.5 ± 1.5	23.0 ± 0.7	Healthy	Vegetable soup w/olive oil and white wine	3079.4	64.1	7.2 ± 0.7
							15	46.7	29.5 ± 1.5	23.0 ± 0.7	Healthy	Vegetable soup w/green olive oil and red wine	3079.4	64.1	5.9 ± 0.6
							15	46.7	29.5 ± 1.5	23.0 ± 0.7	Healthy	Vegetable soup w/green olive oil and white wine	3079.4	64.1	7.5 ± 1.1
Karatzi et al., 2013[2] (81)	Greece	Non-RCT	Forearm	Morning	Manual measurement	Moderate	14	100.0	52.7 ± 2.8	27.7 ± 0.6	CVD risk	Vegetable soup w/sesame oil	2163.1	65.6	3.4 ± 0.4
							6	100.0	52.7 ± 4.3	28.5 ± 1.2	CVD risk	Vegetable soup w/corn oil	2163.1	65.6	4.2 ± 0.5
							6	100.0	52.7 ± 4.3	28.5 ± 1.2	CVD risk	Vegetable soup w/olive oil	2163.1	65.6	3.9 ± 0.3
Katz et al., 2001[3] (82)	USA	RCT	Forearm	Morning	Manual measurement	Some concerns	50	50.0	56.7 ± 1.5	28.4 ± 1.2	Healthy overweight	Oatmeal and a milkshake	3424.8	68.3	0.6 ± NR
							50	50.0	56.7 ± 1.5	28.4 ± 1.2	Healthy overweight	Rolled oats and a milkshake	3401.8	69.1	1.1 ± NR
Koemel et al., 2020[2] (83)	USA	Non-RCT	Forearm	Morning	Edge detection	Serious	9	55.6	22.1 ± 0.5	23.8 ± 0.9	Healthy	Chocolate pie	3513.7	63.0	6.4 ± 0.6
							8	62.5	22.6 ± 1.3	25.7 ± 1.3	Healthy overweight	Chocolate pie	3783.2	63.0	4.0 ± 0.6
							8	50.0	68.4 ± 2.7	28.2 ± 1.2	Healthy overweight	Chocolate pie	4007.4	63.0	4.8 ± 0.5
							7	28.6	67.7 ± 2.7	30.4 ± 1.9	Obese	Chocolate pie	4334.6	63.0	3.3 ± 0.5
Krüger et al., 2016[2] (84)	Brazil	RCT	Forearm	Morning	Manual measurement	Some concerns	11	100.0	23.0 ± 0.9	23.3 ± 0.7	Healthy	Bread w/cream and cheese	3877.6	50.0	3.4 ± 0.5
Kumar et al., 2021[7] (85)	India	Non-RCT	Forearm	Morning	Manual measurement	Moderate	13	50.0	53.4 ± 2.5	23.3 ± 0.7	Healthy	Cream	3050.1	79.1	24.7 ± 1.5
							13	50.0	53.4 ± 2.5	23.3 ± 0.7	Diabetes	Cream	3050.1	79.1	14.2 ± 3.3
Lacroix et al., 2016[4] (86)	Canada	RCT	Upper arm	Morning	Edge detection	High	11	100.0	35.5 ± 2.1	26.9 ± 0.9	Healthy	Breakfast sandwich w/hash browns	3589.9	58.7	11.0 ± 1.1
							11	100.0	35.5 ± 2.1	26.9 ± 0.9	Healthy	Fresh salmon	3702.8	51.3	11.0 ± 1.1
							17	100.0	32.7 ± 2.2	24.1 ± 0.6	Healthy	Breakfast sandwich w/hash browns	3589.9	58.7	10.5 ± 0.6
							17	100.0	32.7 ± 2.2	24.1 ± 0.6	Healthy	Fresh salmon	3702.8	51.3	10.5 ± 0.6
Lane-Cordova et al., 2016[2] (87)	USA	RCT	Forearm	Morning	Manual measurement	Some concerns	11	81.8	47.0 ± 5.0	25.5 ± 0.5	Healthy	Soup	2175.7	94.9	3.9 ± 0.9
							11	81.8	47.0 ± 5.0	25.5 ± 0.5	Healthy	Soup	2175.7	94.9	4.5 ± 0.9
Leary et al., 2018[2] (88)	USA	RCT	Forearm	Morning	Manual measurement	Some concerns	30	60.0	26.0 ± 1.0	31.5 ± 0.8	Obese	NR	5092.9	68.0	9.0 ± 0.8

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TABLE 1 (*Continued*)

Authors, year	Country	Study design	Cuff placement	FMD timing	FMD analysis method	Risk of bias	*N*	Male, %	Age, y	BMI, kg/m2	Health status	Main component of high-fat meal	Total energy, kJ	Total fat, En%	Fasting FMD, %
Lin et al., 2008[2] (89)	Taiwan	RCT	Forearm	Morning	Manual measurement	Some concerns	20	100.0	22.0 ± 0.2	23.5 ± 0.3	Healthy	Fast food breakfast	3765.6	49.1	10.5 ± 0.3
Liu et al., 2002[4] (90)	China	Non-RCT	Upper arm	Morning	Manual measurement	Moderate	25	80.0	57.0 ± 1.4	24.3 ± 0.5	CVD risk	NR	3347.2	55.3	6.2 ± 0.2
							37	81.1	57.8 ± 1.4	24.1 ± 0.4	CVD	NR	3347.2	55.3	3.6 ± 0.1
Liu et al., 2017[2] (91)	Australia	RCT	Forearm	Morning	Edge detection	Some concerns	15	100.0	26.7 ± 1.6	31.4 ± 0.8	Obese	Milkshake	5142.1	64.7	5.9 ± 0.6
							15	100.0	26.7 ± 1.6	31.4 ± 0.8	Obese	Milkshake	5012.4	66.2	5.4 ± 0.7
Maggi et al., 2004[4] (92)	Italy	Non-RCT	Upper arm	Morning	Manual measurement	Moderate	15	100.0	49.3 ± 3.1	28.5 ± 0.8	Healthy overweight	NR	6089.0	82.0	16.0 ± 1.3
Marchesi et al., 2000[4] (93)	Italy	Non-RCT	Upper arm	Morning	Manual measurement	Moderate	10	100.0	23.0 ± 0.6	23.0 ± 0.6	Healthy	Cream	5564.7	82.1	14.5 ± 2.1
Marchesi et al., 2001[4] (94)	Italy	Non-RCT	Upper arm	Morning	Manual measurement	Moderate	7	100.0	23.0 ± 1.1	23.0 ± 0.8	Healthy	Cream	5564.7	82.1	9.7 ± 0.8
Marchesi et al., 2002[4] (95)	Italy	Non-RCT	Upper arm	Morning	Manual measurement	Moderate	7	100.0	25.0 ± 2.3	23.0 ± 0.8	Healthy	White bread w/mayonnaise	5564.7	70.0	12.3 ± 0.6
Marchesi et al., 2003[4] (96)	Italy	Non-RCT	Upper arm	Morning	Manual measurement	Moderate	10	70.0	45.0 ± 2.2	26.3 ± 0.2	CVD risk	Cream	5857.6	82.1	4.3 ± 0.5
Marinos et al., 2015[2] (97)	USA	Non-RCT	Forearm	Morning	Edge detection	Moderate	17	0.0	42.0 ± 2.7	38.0 ± 1.4	Obese	Milkshake	6736.2	83.0	6.9 ± 0.2
Markey et al., 2021[2] (98)	UK	RCT	Forearm	Morning	Edge detection	Some concerns	52	59.2	14.4 ± 2.0	25.9 ± 0.5	CVD risk	Sandwich w/cheese and a milkshake	4100.0	45.0	4.7 ± 0.3
McGowan et al., 2016[4] (99)	Ireland	Non-RCT	Upper arm	Morning	Manual measurement	Serious	44	36.4	47.3 ± 1.5	28.1 ± 0.7	Healthy overweight	White bread w/blueberry muffin	3933.0	33.9	5.8 ± 0.6
							28	35.7	47.3 ± 1.6	28.4 ± 0.8	Hypothyroidism	White bread w/blueberry muffin	3933.0	33.9	5.9 ± 0.6
							21	42.9	43.8 ± 2.5	26.4 ± 0.9	Hypothyroidism	White bread w/blueberry muffin	3933.0	33.9	4.5 ± 0.4
Miyoshi et al., 2014[2] (100)	Japan	RCT	Forearm	Morning	Edge detection	Some concerns	10	80.0	31.0 ± 2.2	23.2 ± 0.5	Healthy	Cookie	4931.0	42.8	10.5 ± 2.5
Muggeridge et al., 2019[2] (101)	UK	RCT	Forearm	Morning	Edge detection	Low	7	14.3	57.0 ± 1.1	30.5 ± 1.9	Obese	2 croissants w/cheese and ham	3815.8	55.8	6.4 ± 1.1
							7	14.3	57.0 ± 1.1	30.5 ± 1.9	Obese	2 croissants w/cheese and ham and orange juice	4171.5	51.0	6.7 ± 1.1
							7	14.3	57.0 ± 1.1	30.5 ± 1.9	Obese	2 croissants w/cheese and ham and green tea	3815.8	55.8	6.1 ± 1.4
							7	14.3	57.0 ± 1.1	30.5 ± 1.9	Obese	2 croissants w/cheese and ham and red wine	4610.8	46.1	6.8 ± 1.6
Muniyappa et al., 2012[2] (102)	USA	Non-RCT	Forearm	Morning	Manual measurement	Serious	18	0.0	35.0 ± 2.1	31.0 ± 1.4	Obese	Egg and cheddar omelets w/bagel and orange juice	NR	40.0	8.7 ± 1.1
							18	0.0	38.0 ± 2.8	29.0 ± 1.4	Healthy overweight	Egg and cheddar omelets w/bagel and orange juice	NR	40.0	7.8 ± 1.0
Nagashima and Endo, 2011[2] (103)	Japan	RCT	Forearm	Morning	Manual measurement	Some concerns	12	100.0	39.8 ± 2.7	29.4 ± 0.5	Obese	Cream	1000.7	70.0	11.1 ± 0.7

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TABLE 1 (*Continued*)

Authors, year	Country	Study design	Cuff placement	FMD timing	FMD analysis method	Risk of bias	*N*	Male, %	Age, y	BMI, kg/m2	Health status	Main component of high-fat meal	Total energy, kJ	Total fat, En%	Fasting FMD, %
Nicholls et al., 2006[2] (104)	Australia	RCT	Forearm	Morning	Manual measurement	Some concerns	14	57.1	29.5 ± 2.3	23.6 ± 0.8	Healthy	Carrot cake and milkshake	4184.0	53.1	5.2 ± 1.1
							14	57.1	29.5 ± 2.3	23.6 ± 0.8	Healthy	Carrot cake and milkshake	4184.0	53.1	6.9 ± 0.9
Nierman et al., 2005[3] (105)	Netherlands	Non-RCT	Forearm	Morning	Edge detection	Moderate	15	100.0	50.1 ± 2.0	26.4 ± 0.9	Healthy overweight	Cream	NR	NR	NR
							15	100.0	49.5 ± 2.1	25.4 ± 0.5	Healthy	Cream	NR	NR	NR
Njike et al., 2021[4] (106)	USA	RCT	Forearm	Morning	Edge detection	High	20	50.0	56.1 ± 3.2	31.4 ± 1.3	CVD risk	Smoothie	NR	NR	14.0 ± 1.3
Noda et al., 2013[2] (107)	Japan	RCT	Forearm	Morning	Manual measurement	Some concerns	10	80.0	35.0 ± 3.2	23.9 ± 1.3	Healthy	Cookie	4931.0	42.8	11.8 ± 0.6
Norata et al., 2007[4] (108)	Italy	Non-RCT	Upper arm	Morning	Manual measurement	Moderate	23	100.0	51.8 ± 2.3	26.1 ± 0.7	Healthy overweight	NR	5799.0	82.0	NR
							30	100.0	51.7 ± 2.1	27.5 ± 0.4	CVD risk	NR	5799.0	82.0	NR
Ochiai et al., 2015[4] (109)	Japan	RCT	Upper arm	Morning	Manual measurement	High	13	100.0	44.9 ± 1.4	21.9 ± 0.6	Healthy	2 cookies, cheese, and soup	2359.8	47.0	5.9 ± 1.1
Ohno et al., 2014[2] (110)	Japan	RCT	Forearm	Morning	Manual measurement	Some concerns	10	100.0	43.0 ± 3.2	28.8 ± 0.4	Metabolic Syndrome	Cookie	5450.1	42.8	5.9 ± 0.7
Padilla et al., 2006[2] (111)	USA	Non-RCT	Forearm	Morning	Manual measurement	Serious	8	62.5	25.5 ± 0.8	22.8 ± 0.6	Healthy	Fast food breakfast	3933.0	45.2	5.7 ± 1.2
Papadakis et al., 2020[2] (112)	USA	RCT	Forearm	Morning	Edge detection	Some concerns	15	100.0	31.1 ± 1.4	25.8 ± 0.7	Healthy	Egg, sausage w/pastry and milk	5476.9	59.5	12.6 ± 1.4
Patik et al., 2018[2] (113)	USA	RCT	Forearm	Morning	Edge detection	Some concerns	10	100.0	24.0 ± 1.0	24.3 ± 1.2	Healthy	Fast food breakfast	4142.2	49.1	6.6 ± 0.5
Petersen et al., 2020[2] (114)	USA	RCT	Forearm	Morning	Edge detection	Low	13	100.0	52.0 ± 2.5	29.9 ± 0.9	CVD risk	Corn muffin w/chicken	4502.0	49.3	4.9 ± 0.3
							13	100.0	52.0 ± 2.5	29.9 ± 0.9	CVD risk	Corn muffin w/chicken and 2 g spices blend	4502.0	49.3	5.1 ± 0.5
							13	100.0	52.0 ± 2.5	29.9 ± 0.9	CVD risk	Corn muffin w/chicken and 6 g spices blend	4502.0	49.3	5.7 ± 0.4
Plotnick et al., 1997[4] (115)	USA	RCT	Upper arm	Morning	Manual measurement	High	20	35.0	37.3 ± 2.0	23.0 ± 0.9	Healthy	Fast food breakfast	3765.6	49.1	20.0 ± 1.8
Plotnick et al., 2003[4] (116)	USA	RCT	Upper arm	Morning	Manual measurement	High	10	NR	NR	NR	Healthy	Fast food breakfast	3765.6	49.1	20.2 ± 1.3
Poitras et al., 2014[2] (117)	Canada	Non-RCT	Forearm	Morning	Edge detection	Moderate	10	100.0	23.2 ± 1.0	24.4 ± 0.8	Healthy	Fast food breakfast	4184.0	47.8	5.9 ± 0.8
Raitakari et al., 2000[2] (118)	Australia	Non-RCT	Forearm	Morning	Manual measurement	Serious	12	58.3	33.0 ± 2.0	24.3 ± 0.9	Healthy	2 muffins, sausage and 2 hash browns	4309.5	52.4	4.2 ± 0.7
							12	58.3	33.0 ± 2.0	24.3 ± 0.9	Healthy	2 muffins, sausage and 2 hash browns	4309.5	52.4	5.2 ± 1.1
Ramírez-Vélez, 2011[2] (119)	Colombia	Non-RCT	Forearm	Morning	Manual measurement	Moderate	14	100.0	21.0 ± 0.8	23.7 ± 1.2	Healthy	NR	4389.0	66.6	5.9 ± 0.3

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TABLE 1 (*Continued*)

Authors, year	Country	Study design	Cuff placement	FMD timing	FMD analysis method	Risk of bias	*N*	Male, %	Age, y	BMI, kg/m2	Health status	Main component of high-fat meal	Total energy, kJ	Total fat, En%	Fasting FMD, %
Ramírez-Vélez et al., 2018[2] (120)	Colombia	RCT	Forearm	Morning	Manual measurement	Low	11	72.7	31.8 ± 2.4	24.4 ± 1.3	Healthy	NR	4389.0	66.6	13.5 ± 1.9
							9	55.6	31.4 ± 2.1	23.5 ± 1.0	Healthy	NR	4389.0	66.6	8.1 ± 1.4
Rathnayake et al., 2018[2] (121)	UK	RCT	Forearm	Morning	Edge detection	High	32	0.0	58.0 ± 1.0	25.9 ± 0.7	Healthy overweight	Warm chocolate drink w/white bread	3800.0	52.3	4.7 ± 0.4
							32	0.0	58.0 ± 1.0	25.9 ± 0.7	Healthy overweight	Warm chocolate drink w/white bread	3800.0	51.7	5.0 ± 0.6
							32	0.0	58.0 ± 1.0	25.9 ± 0.7	Healthy overweight	Warm chocolate drink w/white bread	3800.0	51.7	4.7 ± 0.4
Rendeiro et al., 2016[2] (122)	UK	RCT	Forearm	Morning	Edge detection	High	28	100.0	48.0 ± 1.0	28.4 ± 0.4	Healthy overweight	2 croissants w/control drink	3251.0	58.0	4.9 ± 0.3
							28	100.0	48.0 ± 1.0	28.4 ± 0.4	Healthy overweight	2 croissants w/orange juice	3251.0	58.0	4.8 ± 0.3
							28	100.0	48.0 ± 1.0	28.4 ± 0.4	Healthy overweight	2 croissants w/flavanone-rich orange juice	3251.0	58.0	4.8 ± 0.3
							28	100.0	48.0 ± 1.0	28.4 ± 0.4	Healthy overweight	2 croissants w/whole orange juice	3251.0	58.0	4.7 ± 0.2
Rouyer et al., 2019[2] (123)	France	RCT	Forearm	Morning	Manual measurement	High	17	100.0	24.6 ± 0.9	23.6 ± 0.8	Healthy	NR	7655.0	39.2	9.8 ± 0.9
							17	100.0	24.6 ± 0.9	23.6 ± 0.8	Healthy	NR	7655.0	39.2	8.3 ± 0.7
							17	100.0	24.6 ± 0.9	23.6 ± 0.8	Healthy	NR	7655.0	39.2	9.0 ± 0.6
Rudolph et al., 2007[2] (124)	Germany	RCT	Forearm	Morning	Edge detection	Some concerns	24	41.7	32.0 ± 2.3	24.0 ± 1.0	Healthy	Fast food burger combo meal w/soda	5209.1	34.8	9.7 ± 0.5
							24	41.7	32.0 ± 2.3	24.0 ± 1.0	Healthy	Fast food vegetarian burger combo meal w/soda	5087.7	35.6	9.2 ± 0.7
							24	41.7	32.0 ± 2.3	24.0 ± 1.0	Healthy	Fast food vegetarian burger w/vitamin rich sides	4422.5	25.9	8.8 ± 0.7
Rueda-Clausen et al., 2007[2] (125)	Colombia	RCT	Forearm	Morning	Manual measurement	Some concerns	10	100.0	20.8 ± 0.8	21.9 ± 0.8	Healthy	250 mL soup w/potatoes	2494.5	90.7	11.4 ± 1.0
							10	100.0	20.8 ± 0.8	21.9 ± 0.8	Healthy	250 mL soup w/potatoes	2494.5	90.7	11.6 ± 1.2
							10	100.0	20.8 ± 0.8	21.9 ± 0.8	Healthy	250 mL soup w/potatoes	2494.5	90.7	11.4 ± 0.9
							10	100.0	20.8 ± 0.8	21.9 ± 0.8	Healthy	250 mL soup w/potatoes	2494.5	90.7	11.2 ± 0.9
							10	100.0	20.8 ± 0.8	21.9 ± 0.8	Healthy	250 mL soup w/potatoes	2494.5	90.7	10.5 ± 1.0
							10	100.0	20.8 ± 0.8	21.9 ± 0.8	Healthy	250 mL soup w/potatoes	2494.5	90.7	10.7 ± 1.0
							10	100.0	20.8 ± 0.8	21.9 ± 0.8	Healthy	250 mL soup w/potatoes	2494.5	90.7	10.9 ± 1.0
							10	100.0	20.8 ± 0.8	21.9 ± 0.8	Healthy	250 mL soup w/potatoes	2494.5	90.7	11.3 ± 1.0
							10	100.0	20.8 ± 0.8	21.9 ± 0.8	Healthy	250 mL soup w/potatoes	2494.5	90.7	11.4 ± 1.0

(*Continued*)

TABLE 1 (*Continued*)

Authors, year	Country	Study design	Cuff placement	FMD timing	FMD analysis method	Risk of bias	*N*	Male, %	Age, y	BMI, kg/m2	Health status	Main component of high-fat meal	Total energy, kJ	Total fat, En%	Fasting FMD, %
Salden et al., 2016[2] (126)	Netherlands	RCT	Forearm	Morning	Edge detection	High	34	35.3	53.0 ± 2.4	29.7 ± 0.5	Healthy	Milkshake	2600.0	61.0	5.6 ± 0.5
Schillaci et al., 2001[4] (127)	Italy	Non-RCT	Upper arm	Morning	Manual measurement	Moderate	10	0.0	23.0 ± 0.6	22.0 ± 0.6	Healthy	Cream	4979.0	82.1	14.6 ± 1.6
Sejda et al., 2002[2] (128)	Prague	RCT	Forearm	Morning	Manual measurement	Some concerns	11	54.6	24.0 ± 1.4	22.8 ± 0.5	Healthy	Cream cake, doughnut, and cocoa	3496.0	44.8	3.1 ± 0.9
							11	54.6	24.0 ± 1.4	22.8 ± 0.5	Healthy	Cream cake, doughnut, and cocoa	3496.0	44.8	5.3 ± 0.9
Shah et al., 2017[2] (129)	UK	RCT	Forearm	Morning	Edge detection	Some concerns	10	100.0	54.0 ± 1.3	27.0 ± 1.8	Healthy overweight	Fast food breakfast	3933.0	45.2	5.4 ± 1.2
							10	0.0	51.0 ± 1.0	27.0 ± 1.8	Healthy overweight	Fast food breakfast	3933.0	45.2	7.1 ± 1.2
							10	0.0	62.0 ± 1.6	25.3 ± 1.3	Healthy overweight	Fast food breakfast	3933.0	45.2	6.6 ± 1.2
Shige et al., 1999[2] (130)	Japan	Non-RCT	Forearm	Morning	Edge detection	Serious	7	71.4	49.3 ± 3.0	26.0 ± 1.9	Diabetes	Cream	6188.1	47.8	8.1 ± 1.0
Siepi et al., 2002[4] (131)	Italy	Non-RCT	Upper arm	Morning	Manual measurement	Moderate	10	0.0	57.0 ± 2.5	NR	Healthy	Cream	4979.0	82.1	7.7 ± 0.9
Silvestre et al., 2008[6] (132)	USA	RCT	Forearm	Afternoon	Edge detection	Some concerns	12	100.0	21.8 ± 2.5	25.1 ± 3.1	Healthy	Cream	4389.4	95.2	2.7 ± NR
Skilton et al., 2005[2] (133)	Australia	Non-RCT	Forearm	Morning	Manual measurement	Moderate	15	60.0	58.0 ± 2.1	27.4 ± 1.3	Diabetes	2 muffins, 2 hash browns, and a sausage	4309.5	52.4	3.7 ± 0.6
							15	60.0	57.0 ± 2.3	26.3 ± 0.9	Healthy overweight	2 muffins, 2 hash browns, and a sausage	4309.5	52.4	3.2 ± 0.8
							15	60.0	33.0 ± 1.8	24.6 ± 0.9	Healthy overweight	2 muffins, 2 hash browns, and a sausage	4309.5	52.4	4.5 ± 0.9
Smeets et al., 2020[2] (134)	Netherlands	RCT	Forearm	Morning	Edge detection	Some concerns	18	100.0	64.2 ± 1.4	30.8 ± 0.8	Obese	NR	3987.0	52.3	5.1 ± 0.6
Smeets et al., 2021[2] (135)	Netherlands	RCT	Forearm	Morning	Edge detection	Some concerns	18	100.0	60.9 ± 3.1	30.5 ± 0.7	Obese	NR	3987.0	52.3	4.0 ± 0.5
Smolders et al., 2019[5] (136)	Netherlands	RCT	Forearm	Morning	Edge detection	High	44	63.6	60.3 ± 0.8	29.2 ± 0.5	Healthy overweight	Shake, contents NR	4037.6	55.5	4.9 ± 0.4
Stirban et al., 2010[2] (137)	USA	RCT	Forearm	Morning	Edge detection	Some concerns	31	NR	56.8 ± 1.5	31.2 ± 0.7	Diabetes	Bread w/cheese and salami	2510.4	59.0	5.5 ± 0.6
Stonehouse et al., 2015[2] (138)	Australia	RCT	Forearm	Morning	Manual measurement	Low	28	100.0	56.8 ± 1.5	30.0 ± 0.6	Obese	Chicken w/fried white bread and salad	2791.0	58.3	5.8 ± 0.6
							28	100.0	56.8 ± 1.5	30.0 ± 0.6	Obese	Chicken w/fried white bread and salad	2791.0	58.3	5.6 ± 0.6
Swift et al., 2013[2] (139)	USA	Non-RCT	Forearm	Morning	Edge detection	Moderate	8	0.0	55.0 ± 0.6	30.8 ± 2.2	Obese	Egg w/sausage, cheese, orange juice, and milk	2301.2	57.0	5.40 ± 1.19
							8	0.0	57.6 ± 1.8	29.3 ± 1.8	Obese	Egg w/sausage, cheese, orange juice, and milk	2301.2	57.0	4.0 ± 1.7
Tsai et al., 2004[2] (22)	Taiwan	Non-RCT	Forearm	Morning	Manual measurement	Moderate	16	100.0	30.0 ± 1.3	23.1 ± 0.6	Healthy	Fast food breakfast	3765.6	49.1	9.4 ± 0.2
Tucker et al., 2018[2] (140)	USA	RCT	Forearm	Morning	Edge detection	Some concerns	13	100.0	27.0 ± 1.0	25.6 ± 1.1	Healthy	Fast food breakfast	5230.0	44.6	5.1 ± 0.4

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TABLE 1 (*Continued*)

Authors, year	Country	Study design	Cuff placement	FMD timing	FMD analysis method	Risk of bias	*N*	Male, %	Age, y	BMI, kg/m2	Health status	Main component of high-fat meal	Total energy, kJ	Total fat, En%	Fasting FMD, %
Tushuizen et al., 2006[2] (141)	Netherlands	RCT	Forearm	Morning	Edge detection	Some concerns	17	100.0	25.4 ± 0.7	23.6 ± 0.4	Healthy	Fast food breakfast	3765.6	49.1	6.8 ± 0.6
Tushuizen et al., 2007[2] (142)	Netherlands	Non-RCT	Forearm	Morning	Edge detection	Moderate	15	100.0	55.5 ± 1.0	32.7 ± 1.1	Diabetes	NR	3765.6	49.1	5.6 ± 0.2
							12	100.0	55.5 ± 1.2	27.2 ± 0.6	Healthy overweight	NR	3765.6	49.1	8.9 ± 0.3
Tyldum et al., 2009[2] (143)	Norway	RCT	Forearm	Morning	Edge detection	Some concerns	8	100.0	42.0 ± 4.0	28.8 ± 0.9	Healthy	Vegetarian mozzarella pizza	3812.5	46.9	7.1 ± 0.3
van der Made et al., 2017a[2] (144)	Netherlands	RCT	Forearm	Morning	Edge detection	Some concerns	43	32.6	62.0 ± 1.2	26.3 ± 0.6	CVD risk	2 muffins	4095.0	51.1	2.5 ± 0.3
							45	33.3	62.0 ± 0.9	26.9 ± 0.5	CVD risk	2 muffins	4095.0	51.1	2.6 ± 0.3
van der Made et al., 2017b[2] (145)	Netherlands	RCT	Forearm	Morning	Edge detection	Some concerns	37	55.6	61.0 ± 1.0	28.3 ± 0.5	Healthy overweight	2 muffins and 300 mL skim milk	4598.0	45.6	3.0 ± 0.3
van Oostrom et al., 2003[7] (146)	Netherlands	RCT	Forearm	Morning	Edge detection	High	8	100.0	23.0 ± 0.7	21.7 ± 0.5	Healthy	Cream	8325.0	40.0	13.0 ± 1.5
Verwer et al., 2020[2] (147)	Netherlands	Non-RCT	Forearm	Morning	Edge detection	Some concerns	12	100.0	55.3 ± 2.2	27.1 ± 0.8	Healthy	Fast food breakfast	3765.6	49.1	7.9 ± 0.5
							12	100.0	54.6 ± 1.0	32.6 ± 1.3	Diabetes	Fast food breakfast	3765.6	49.1	4.9 ± 0.5
							12	100.0	57.2 ± 1.8	30.6 ± 1.0	Metabolic syndrome	Fast food breakfast	3765.6	49.1	5.7 ± 0.7
Vogel et al., 1997[4] (24)	USA	Non-RCT	Upper arm	Morning	Manual measurement	Serious	10	50.0	39.0 ± 3.2	23.0 ± 0.6	Healthy	Fast food breakfast	3765.6	49.13	21.0 ± 1.6
Vogel et al., 2000[4] (148)	USA	Non-RCT	Upper arm	Morning	Edge detection	Serious	10	50.0	NR	NR	Healthy	Bread w/extra-virgin olive oil	3765.6	49.1	14.3 ± 1.3
							10	50.0	NR	NR	Healthy	Bread w/canola oil	3765.6	49.1	13.0 ± 1.1
							10	50.0	NR	NR	Healthy	Red salmon w/cracker	3765.6	49.1	13.1 ± 1.6
							10	50.0	NR	NR	Healthy	Bread w/extra-virgin olive oil and salad	3765.6	49.1	13.5 ± 1.1
Volek et al., 2008[3] (149)	USA	RCT	Forearm	Morning	Edge detection	Some concerns	30	53.3	30.0 ± 1.5	24.1 ± 0.8	Healthy	Cream w/macadamia nuts	3799.1	84.0	6.6 ± NR
Volek et al., 2009[4] (150)	USA	RCT	Upper arm	Morning	Edge detection	High	20	50.0	32.6 ± 2.5	33.5 ± 1.2	CVD risk	Cream w/macadamia nuts	3799.1	84.0	5.0 ± 0.7
							20	50.0	36.9 ± 2.8	32.1 ± 0.9	CVD risk	Cream w/macadamia nuts	3799.1	84.0	7.1 ± 0.7
West et al., 2005[2] (151)	USA	RCT	Forearm	Morning	Edge detection	Some concerns	18	72.2	55.1 ± 2.1	29.2 ± 0.8	Diabetes	Milkshake	2615.0	70.8	5.1 ± 0.6
							18	72.2	55.1 ± 2.1	29.2 ± 0.8	Diabetes	Milkshake	2615.0	70.8	4.9 ± 0.6
							18	72.2	55.1 ± 2.1	29.2 ± 0.8	Diabetes	Milkshake	2615.0	70.8	5.5 ± 0.6
Westerink et al., 2013[2] (152)	Netherlands	RCT	Forearm	Morning	Manual measurement	Some concerns	93	59.0	57.0 ± 0.9	30.0 ± 0.3	Metabolic syndrome	Cream	9943.8	40.0	4.6 ± 0.3
Westphal et al., 2006[4] (153)	Germany	RCT	Upper arm	Morning	Manual measurement	High	16	50.0	21.0 ± 2.0	22.0 ± 1.1	Healthy	Cream	2759.8	92.0	8.5 ± 0.8
Westphal et al., 2009[4] (154)	Germany	RCT	Upper arm	Morning	Manual measurement	High	27	59.3	59.0 ± 1.5	35.5 ± 1.0	Metabolic syndrome	Cream	4023.0	92.0	5.1 ± 0.3

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TABLE 1 (*Continued*)

Authors, year	Country	Study design	Cuff placement	FMD timing	FMD analysis method	Risk of bias	N	Male, %	Age, y	BMI, kg/m2	Health status	Main component of high-fat meal	Total energy, kJ	Total fat, En%	Fasting FMD, %
Westphal and Luley, 2011[4] (155)	Germany	RCT	Upper arm	Morning	Manual measurement	High	18	11.1	25.2 ± 2.5	22.8 ± 2.0	Healthy	Cream	7072.9	63.6	8.5 ± 0.6
							18	11.1	25.2 ± 2.5	22.8 ± 2.0	Healthy	Cream	7072.9	63.6	8.8 ± 0.5
Widdowson et al., 2017[4] (156)	Ireland	Non-RCT	Upper arm	Morning	Manual measurement	Moderate	50	50.0	49.8 ± 1.1	29.3 ± 0.9	Overweight	NR	3933.0	33.9	6.3 ± 0.6
							50	50.0	50.7 ± 1.1	29.8 ± 0.8	Overweight	NR	3933.0	33.9	4.8 ± 0.6
Williams et al., 1999[2] (157)	New Zealand	RCT	Forearm	Morning	Manual measurement	Some concerns	10	100.0	38.0 ± 1.9	24.6 ± 0.9	Healthy	Milkshake	3754.0	63.5	5.9 ± 0.7
							10	100.0	38.0 ± 1.9	24.6 ± 0.9	Healthy	Milkshake	3754.0	63.5	5.3 ± 0.7
Williams et al., 2001[2] (158)	New Zealand	RCT	Forearm	Morning	Manual measurement	Some concerns	14	100.0	32.0 ± 2.7	24.6 ± 0.8	Healthy	Milkshake	4274.0	67.9	4.9 ± 0.6
							14	100.0	32.0 ± 2.7	24.6 ± 0.8	Healthy	Milkshake	4274.0	67.9	5.1 ± 0.8
Wilmink et al., 1999[2] (159)	Netherlands	RCT	Forearm	Morning	Edge detection	Some concerns	30	50.0	23.0 ± 0.6	22.6 ± 0.5	Healthy	Cream	8325.0	40.0	6.6 ± 0.9
Wilmink et al., 2000[2] (160)	Netherlands	RCT	Forearm	Morning	Edge detection	Some concerns	20	50.0	23.0 ± 0.8	22.8 ± 0.6	Healthy	Cream	8325.0	40.0	10.4 ± 0.7
Wilmink et al., 2001[2] (161)	Netherlands	RCT	Forearm	Morning	Edge detection	Some concerns	15	100.0	25.1 ± 1.1	23.1 ± 0.7	Healthy	Cream	8787.5	40.0	9.1 ± 0.9
Xiang et al., 2012[2] (162)	China	Non-RCT	Forearm	Morning	Manual measurement	Serious	10	0.0	34.6 ± 1.7	23.8 ± 0.6	Healthy	NR	3347.2	62.0	5.9 ± 0.2
							10	0.0	34.2 ± 1.8	24.1 ± 0.7	Hypothyroidism	NR	3347.2	62.0	3.9 ± 0.2
							10	0.0	35.5 ± 2.1	24.3 ± 0.8	Hypothyroidism	NR	3347.2	62.0	3.3 ± 0.2
Yunoki et al., 2011[2] (163)	Japan	RCT	Forearm	Morning	Manual measurement	Some concerns	10	80.0	38.0 ± 3.2	23.9 ± 0.9	CVD risk	Cookie	4931.0	42.8	8.5 ± 0.8
							10	90.0	37.0 ± 1.3	25.3 ± 1.6	CVD risk	Cookie	4931.0	42.8	8.5 ± 0.6
Zhang et al., 2012[4] (164)	China	RCT	Upper arm	Morning	Manual measurement	High	35	51.4	48.3 ± 1.1	24.2 ± 0.3	Healthy	NR	4895.3	60.0	14.6 ± 0.4
							38	55.3	48.4 ± 1.5	25.1 ± 0.4	CVD risk	NR	4895.3	60.0	11.5 ± 0.4
Zhao et al., 2001[4] (165)	China	Non-RCT	Upper arm	Morning	Manual measurement	Serious	50	78.0	57.1 ± 1.0	26.4 ± 0.7	CVD	NR	3347.2	55.3	3.0 ± 0.1
							25	80.0	56.1 ± 1.1	22.6 ± 0.7	Healthy	NR	3347.2	55.3	6.6 ± 0.1
Zhao et al., 2004[4] (166)	China	RCT	Upper arm	Morning	Manual measurement	High	25	56.0	59.1 ± 1.3	25.7 ± 0.4	CVD	NR	3347.2	55.3	7.8 ± 1.7

[1]Edge detection involves the use of computer-automated software to track the artery diameter continuously. Values are mean ± SEM unless otherwise indicated. Each line is an independent group. The majority of the 131 studies were randomized ($n = 83$), with 66 crossover and 17 parallel designs. Studies were conducted in 22 countries, with the majority conducted in the United States ($n = 37$), the Netherlands ($n = 20$), the United Kingdom ($n = 14$), and Italy ($n = 10$). The median study sample size was 15 (IQR, 10–20; range, 5–93). The high-fat meals consumed were varied across the studies, with fast food ($n = 22$) or a cream-based ($n = 32$) meal being most used. Thirty-one studies supplied various pastry-based food items. Twelve studies provided milkshakes. Five studies consumed soup with various plant oils added. A further 5 studies provided dinner meals. Lastly, 6 studies supplied a breakfast meal. Information about the food provided was absent from 17 studies, with authors mostly stating an oral fat load or high-fat breakfast was consumed, without further explanation. Overall, most studies ($n = 131$) reported the total energy content of the meal, with a calculated average total energy of 4197 kJ. However, the extent of information on the macronutrient compositions, especially the types of fat, differed across the studies. The average amount of fat provided in the meals was 66.3 grams or 59.5% of the total meal energy content. Animal products provided the primary type of fat in most test meals, with energy being derived from egg, sausage, bacon, cream, cheese, or milk. The main plant oils used included olive, corn, palm, sesame, soybean, or safflower oil. Abbreviations: CVD, cardiovascular disease; En%, percentage of total meal energy; FMD, flow-mediated dilation; NR, not reported; RCT, randomized controlled trial; w/, with.

[2]Denotes studies that are included in the meta-analysis.

[3]Denotes studies that were excluded due to unreported FMD data.

[4]Denotes studies that were excluded due to use of proximal cuff occlusion FMD protocol.

[5]Denotes studies that were excluded due to FMD not being measured at the hourly mark.

[6]Denotes studies that were excluded due to conducting the clinical trial in the afternoon.

[7]Denotes studies that were excluded by the sensitivity analysis.

5 hours ($n = 11$), 6 hours ($n = 25$), 7 hours ($n = 0$) and 8 hours ($n = 11$) after consumption. The majority of the NO-dependent FMD studies ($n = 57$) employed the edge-detection method for FMD analysis, whereas 33 studies measured the artery diameter periodically.

The overall outcome of the primary aim: random-effects model meta-analysis while fasting and 2, 3, and 4 hours after eating

Forest plots of postprandial FMD changes from fasting to 2, 3, and 4 hours after eating are presented in **Figure 3**. The mean postprandial FMD changes from fasting were −1.02 pp (95% CI: −1.34 to −0.70 pp; $P < 0.01$) at 2 hours, −1.04 pp (95% CI: −1.48 to −0.59 pp; $P < 0.001$) at 3 hours, and −1.19 pp (95% CI: −1.53 to −0.84 pp; $P < 0.01$) at 4 hours. The mean fasting FMD% effect size was 6.31% (95% CI: 5.89%–6.72%; $P < 0.01$); the forest plot for fasting FMD% values is depicted in **Supplemental Figure 1**. Statistical heterogeneity between studies was high at 2 hours (I^2, 93.3%; 95% CI: 93%–94%), 3 hours (I^2, 84.5%; 95% CI: 74%–85%), and 4 hours (I^2, 94.6%; 95% CI: 90%–95%) after eating and while fasting (I^2, 97.8%; 95% CI: 97%–98%).

The outcome of the unadjusted linear regression while fasting and 2, 3, and 4 hours after eating

An unadjusted linear regression analysis was used to identify predictors of change in FMD (postprandial FMD% − fasting FMD%). Bubble plots depicting the unadjusted linear regression analyses at the 2-, 3-, and 4-hour postprandial time points are shown in **Supplemental Figure 2**. The unadjusted linear regression analyses at fasting are shown in **Supplemental Figure 3**. Substantial heterogeneity was observed (I^2 >80%) across all variables and time points in the regression.

The outcome of the secondary aim: multivariable meta-regression while fasting and 2, 3, and 4 hours after eating

The final multivariable meta-regression model was selected following inspection of the adjusted R^2 values. For 82 observations, the independent variables in a 2-hour multivariable meta-regression model were age, fasting FMD%, total energy and fat in the meal, sample size, percentage of male participants, and year of publication (**Table 2**). All other inspected multivariable models are listed in **Supplemental Table 3**. For 53 observations, the 3-hour regression model included the fasting FMD%, total energy and fat in the meal, percentage of male participants, and year of publication. The variables of age, BMI, fasting FMD%, total energy and fat in the meal, sample size, percentage of male participants, and year of publication were included in the 4-hour regression model, with 85 observations. Lastly, age, BMI, sample size, percentage of male participants, and year of publication were included in the fasting regression model, with 158 observations. There was no collinearity identified with a calculated variance inflation factor (VIF) of less than 2.5 for all variables in the regression models, and further investigation of collinearity is only appropriate where the variable VIF value is greater than 10. After adjusting for confounding variables, the multivariable meta-regression showed that at all postprandial time points, the magnitude of the FMD decrease after a meal was still significantly larger when the fasting FMD% was higher [Table 2; 2 hours, $\beta = -0.33$ ($P < 0.001$); 3 hours, $\beta = -0.25$ ($P < 0.001$); 4 hours, $\beta = -0.27$ ($P < 0.001$)]. Participant age was a significant independent predictor of a change in FMD% at 2 hours after the meal ($\beta = -0.02$; $P = 0.039$) when controlling for covariates. In multivariable models, at 2 and 4 hours after eating, there was no significant relation between the meal fat content and vascular function as assessed by FMD [Table 2; $\beta = 0.01$ ($P = 0.493$); $\beta = 0.01$ ($P = 0.491$)]. However, at 3 hours, there was a significant decrease in FMD with an increasing total fat content of the meal ($\beta = -0.03$; $P = 0.016$). At 4 hours after consumption, the total energy content of the meal was inversely related to the FMD response ($\beta = -0.0003$; $P = 0.029$). For the fasting FMD%, only age was determined to be an independent contributor to variation in the FMD effect size ($\beta = -0.10$; $P < 0.001$). The covariates in each model combined explained 35%, 43%, 68%, and 38% of the variance in the fasting FMD% and postprandial FMD% values at 2, 3, and 4 hours, respectively.

The outcome of the secondary aim: subgroup meta-analysis at fasting and 2, 3, and 4 hours after eating

Study and participant characteristics (moderators) that may impact the postprandial FMD response were identified a priori. Subgroup analyses were subsequently undertaken to identify whether moderator variable subcategories had different influences on FMD effect sizes (**Table 3**). The number of observations, MD in FMD, 95% CI: and P value are provided for each subgroup level of the moderator variable. Subgroup meta-analyses indicated a significantly lower fasting FMD% in older, heavier, and at-risk populations ($P < 0.001$). Additionally, these same patterns were seen at 4 hours after high-fat meal consumption for all variables except BMI, where a U-shaped relationship was noted (healthy weight, −1.86 pp [95% CI: −2.49 to −1.22 pp]; overweight, −0.68 pp [95% CI: −1.15 to −0.21 pp]; obese, −1.05 [95% CI: −1.46 to −0.63 pp]). A diagrammatic representation of FMD fasting and postprandial responses between a healthy and an at-risk participant can be seen in **Figure 4**. Participants with a higher fasting FMD% (>10%) had the largest postprandial FMD decrease at all postprandial time points ($P < 0.001$). The study design and risk of bias were not significant across all subgroup analyses ($P > 0.05$).

Risk of bias

The majority of the studies included in this work had a moderate risk of bias ($n = 86$) due to a designation of some concerns in at least 1 risk domain (**Supplemental Figure 4**). Five studies were judged as having a low risk, while 40 were determined to have a high risk of bias. Almost all studies supplied insufficient information about the randomization and allocation concealment procedures, leading to a designation of "no information." Additionally, the risk of bias arose due to inadequate information provided regarding the researcher's prespecified data analysis plan. Overall, studies showed a low

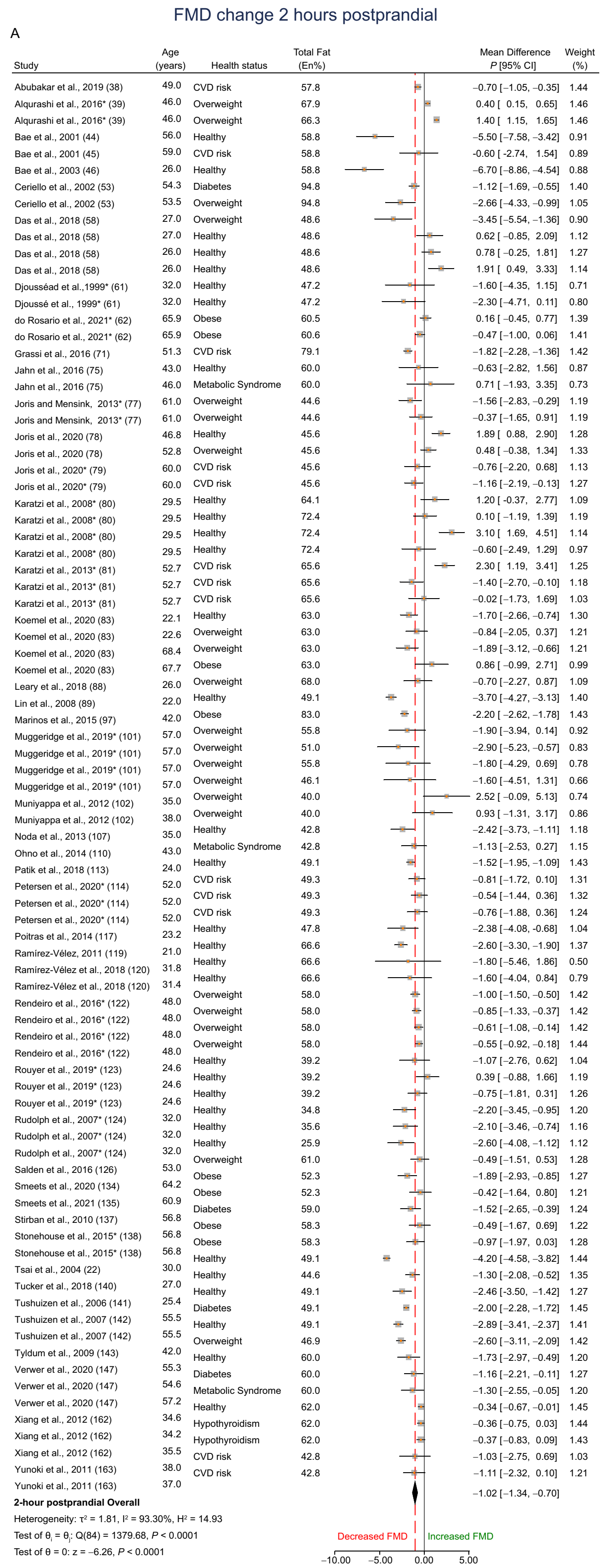
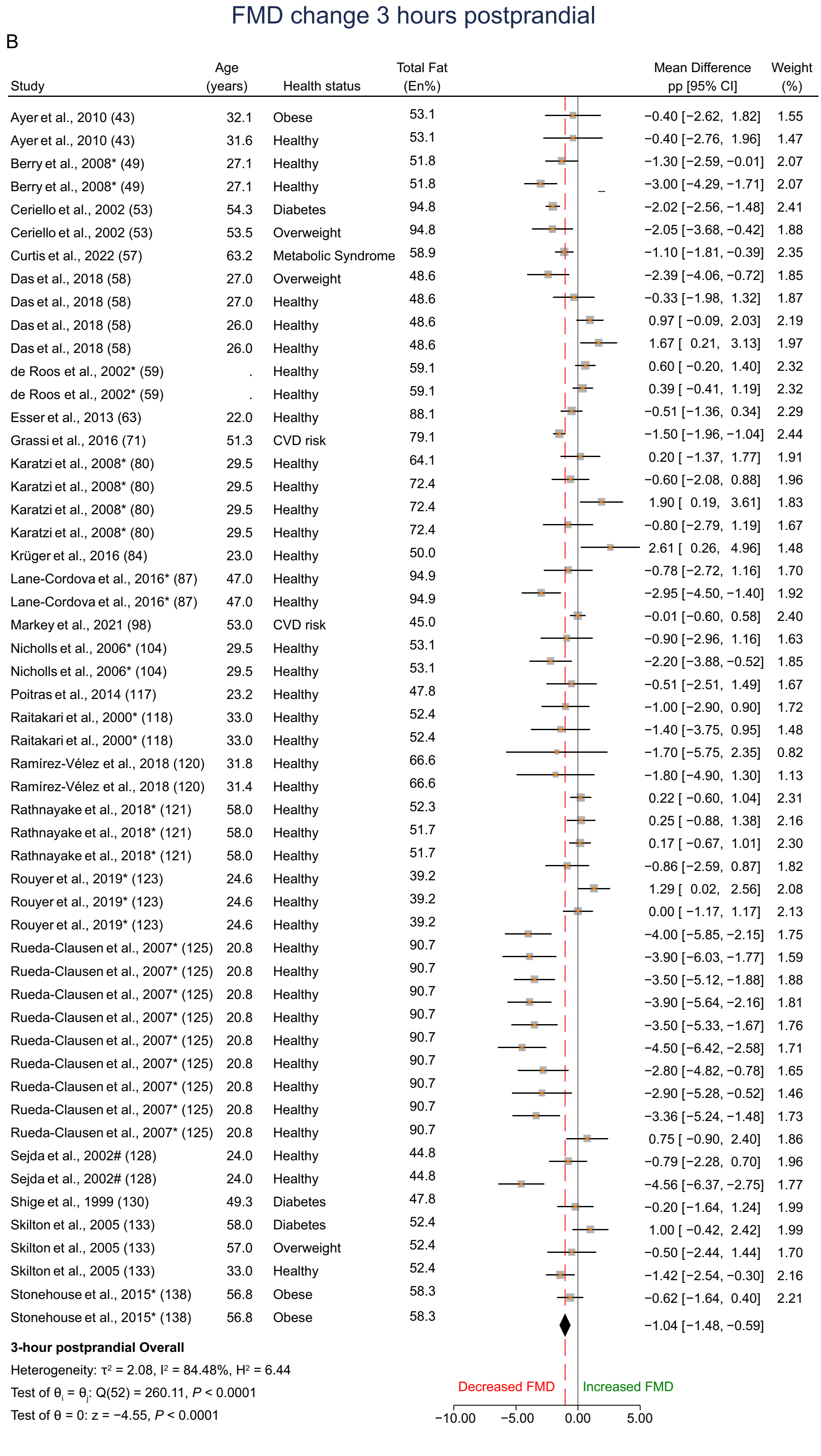


FIGURE 3 Continued.



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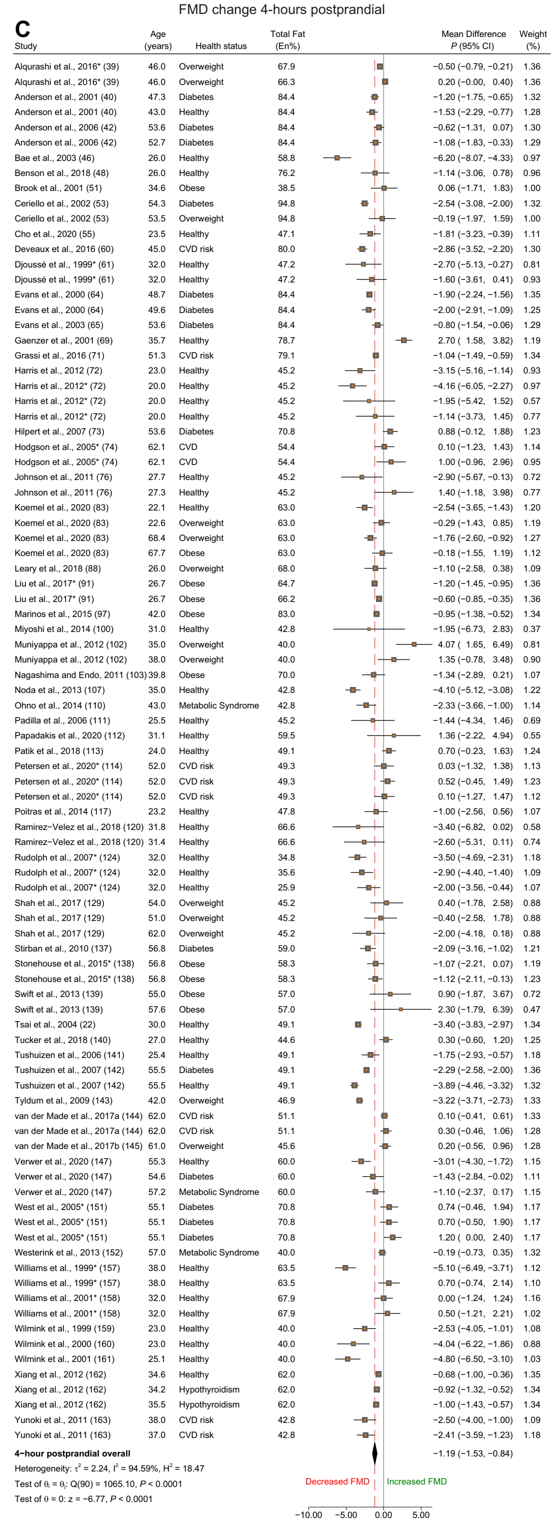

FIGURE 3 Forest plots of the impactof a single, high-fat meal on endothelial function at (A) 2 hours, (B) 3 hours, and (C) 4 hours after consumption. Mean FMD% differences and 95% CIs are indicated by white dots and black horizontal lines. The size of each box is proportionally scaled to the effect size for each group in the restricted maximum likelihood model. The black diamond represents the average mean difference for all groups. FMD is measured as the relative percentage change in the peak reactive hyperemia diameter from the baseline diameter (FMD%). The mean difference in the FMD% was calculated as the fasting FMD% subtracted from the postprandial FMD%, termed the FMD change; the units of the FMD change are pp. The heterogeneity analysis is also presented. *Groups with the same participants consuming different types of meals. Specific meal contents are described in Table 1. #Groups with the same participants consuming the same meal before and after different diet interventions. Abbreviations: CVD, cardiovascular disease; En%, percentage of total meal energy; FMD, flow-mediated dilation; FMD%, flow-mediated dilation percentage change; pp, percentage points; REML, restricted maximum likelihood method.

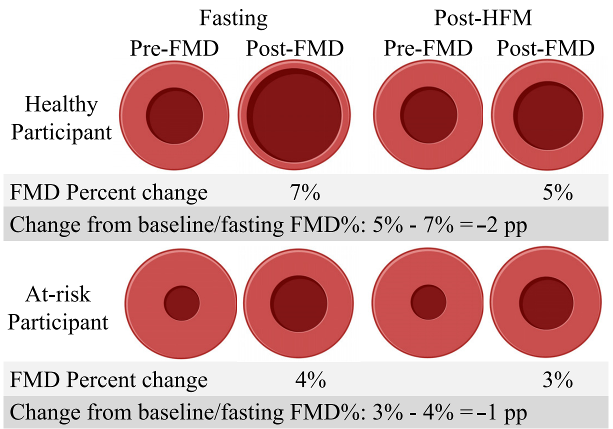

FIGURE 4 Diagrammatic representation of the arterial responses to FMD during fasting and after a high-fat meal in healthy and at-risk participants. Artery cross-sections show the diameter, FMD%, and FMD change. The at-risk participant group included individuals who presented with at least 1 CVD risk factor or were diagnosed with coronary artery disease. Diagrams are not to scale. Abbreviations: CVD, cardiovascular disease; FMD, flow-mediated dilation; FMD%, flow-mediated dilation percentage change; HFM, high-fat meal; pp, percentage points.

risk of bias in the outcome assessment, with most following the expert guidelines available at the time of assessment (167, 168).

Publication bias

A visual inspection of funnel plots showed symmetrical distribution of study effects at each time point. Egger's regression asymmetry test confirmed a lack of publication bias (2 hours, $P = 0.679$; 3 hours, $P = 0.063$; 4 hours, $P = 0.812$; **Figure 5**).

Discussion

Despite variability in participant groups and meal contents, a high-fat meal adversely affects endothelial function, measured by FMD, by mean changes from fasting of −1.02 pp (95% CI: −1.34 to −0.70 pp), −1.04 pp (95% CI: −1.48 to −0.59 pp), and −1.19 pp (95% CI: −1.53 to −0.84 pp) at 2, 3, and 4 hours after consumption. A 1-pp decrease in fasting FMD% is associated with a 9% increase in the risk of cardiovascular events (36). Given the similar reduction in FMD after a high-fat meal, this could indicate an increased CVD risk in the postprandial state. The postprandial endothelial response is modified by the participant's age (2 hours, Table 2; 4 hours, Table 3), BMI (4 hours, Table 3), and health status (4 hours, Table 3). After controlling for confounding variables (multivariable analyses, Table 2), the fat content of a meal was negatively associated with the endothelial function at 3 hours but not at 2 or 4 hours after eating. There was no effect of study design (use of randomization) or risk of bias; thus, these factors did not impact how the analysis was conducted.

Older, at-risk participants were less responsive to FMD during fasting and showed a decreased capacity to respond to FMD after a high-fat meal (2 hours and fasting, Table 2; 4 hours and fasting, Table 3). Ageing causes an imbalance between vasoactive factors, particularly a reduction in NO, brought about by increased reactive oxygen species (ROS) and oxidative stress (169). A reduction in NO bioavailability leads to reduced vascular tone and, thus, an inability to respond to the hemodynamic stimulus. Provision of a high-fat meal with tetrahydrobiopterin, a NO-synthesis cofactor that decreases with ageing (170), has been shown to enhance the FMD response at 4 hours in postmenopausal women and age-matched men compared with a high-fat meal alone (129). This work found interactions between health status and both fasting and postprandial FMDs (Figure 4). Though health status cannot be determined to be an independent predictor of the FMD response, individuals who presented with either cardiometabolic disorders (e.g., participants with diabetes, metabolic syndrome, hypothyroidism, or cardiovascular disease) or cardiometabolic risk factors were more likely to have a lower FMD% at fasting and were less able to respond to the high-fat meal challenge. These conditions are associated with inflammation, which causes activation of NAD(P)H oxidase (171), increased levels of ROS, and subsequent endothelial dysfunction. Thus, certain participant characteristics can modify the endothelial function, both before and after high-fat meal consumption (Figure 4). Therefore, consumption of high-fat meals could further exacerbate endothelial dysfunction in at-risk individuals.

High-fat meals reduce the ability of blood vessels to dilate in response to FMD by reducing NO bioavailability (17). A single, high-fat meal has been hypothesized to cause a reduction in NO bioavailability through an increase in oxidative stress that ultimately leads to endothelial dysfunction through multiple mechanisms (18). Postprandial lipemia has been shown to be associated with increased oxidative stress and decreased FMDs in healthy, male participants (22). Circulating triglyceride-rich lipoproteins and their remnants are also associated with endothelial dysfunction and CVD risks (172, 173). This work showed that the percentage fat content of the meals was inversely associated with the postprandial change in FMD at 3 hours, indicating a reduced vessel response as the fat percentage increased. Total energy intake was also negatively associated with the FMD change at 4 hours after consumption. Therefore, it is likely that the simple act of eating any high-energy meal could result in an increase in ROS, which would reduce FMD. However, no previous studies have measured hourly fasting FMD% results to explore the magnitude of this phenomenon over time.

Phenotypic metabolic flexibility is the ability of an organism to respond and adapt to changes in metabolism and energy demands (174). A high-fat meal challenge enables metabolic flexibility and small changes in endothelial responses to be detected, which might not be apparent at fasting. A systematic review (175) of 61 studies providing various challenge meals showed that utilization of a nutritional stress test enabled the assessment of subtle differences in health status. The current systematic review clearly shows that in older, heavier, and more cardiometabolically at-risk populations, there are smaller changes in FMD from fasting levels at 4 hours after consumption compared to levels in young, healthy-weight populations. At-risk participants showed less capacity to respond to a high-fat meal, exhibiting greater metabolic inflexibility. Thus, we emphasize that there is potential to use the postprandial FMD to

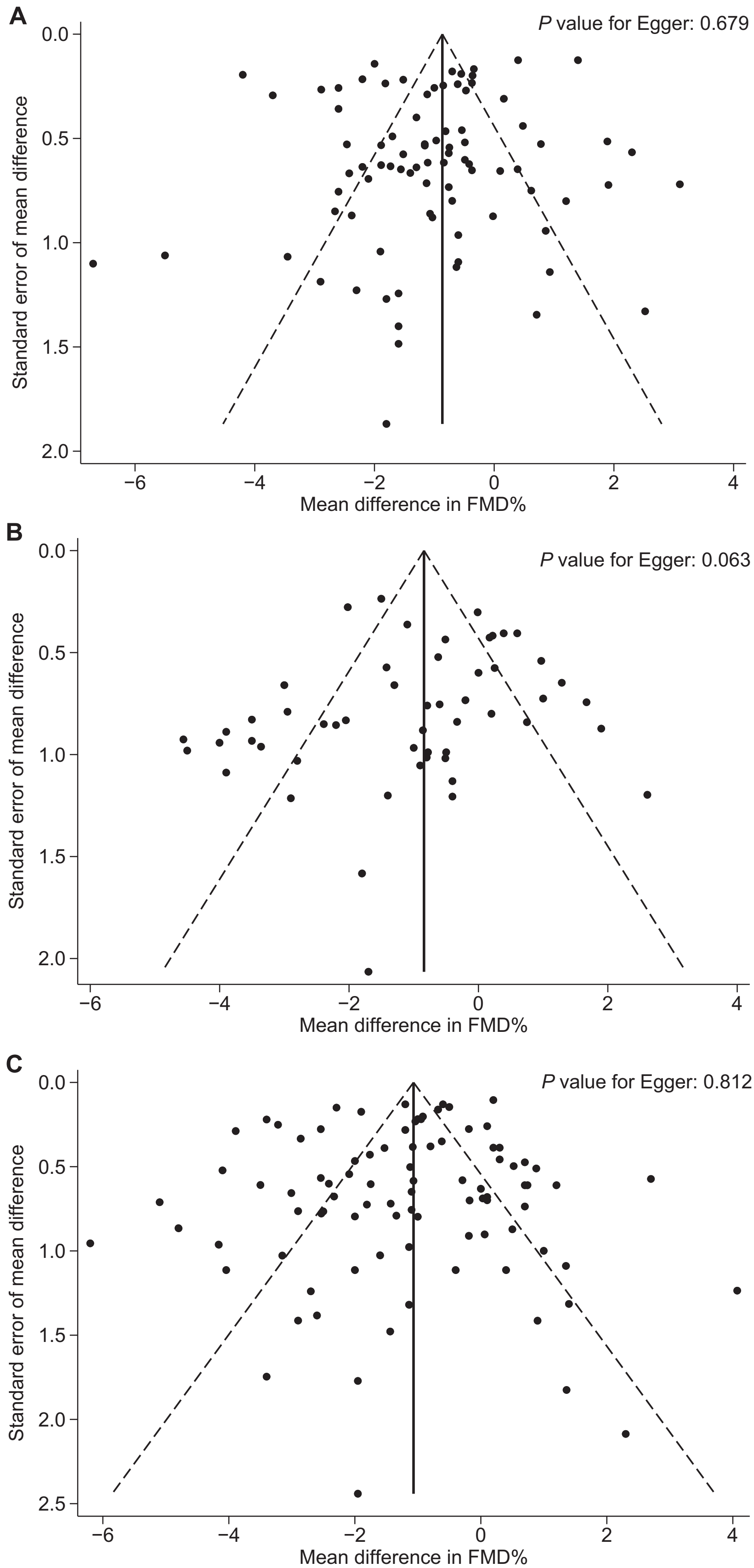

FIGURE 5 Publication bias was assessed by funnel plot of all studies in the meta-analysis at (A) 2 hours, (B) 3 hours, and (C) 4 hours after high-fat meal consumption. Abbreviation: FMD%, flow-mediated dilation percentage change.

TABLE 2 Multivariable meta-regression analysis exploring the effects of moderator covariates on FMD% effect-size variation between studies[1]

Covariate	Slope	SE	Z value	2-sided P value	95% CI: lower	95% CI: upper	Observations, n	I^2	Adjusted R^2
2-hour model									
Intercept	− 104.97	58.52	− 1.79	0.073	− 219.67	9.72	82	88.4	0.428
Age, years	− 0.02	0.01	− 2.06	0.039	− 0.045	− 0.001			
Fasting FMD%	− 0.33	0.08	− 4.28	<0.001	− 0.48	− 0.18			
Total energy, kJ	− 0.00004	0.00	− 0.32	0.745	− 0.0003	0.0002			
Total fat, En%	0.01	0.01	0.69	0.493	− 0.02	0.03			
Sample size, n	0.03	0.02	1.21	0.225	− 0.02	0.07			
Male, %	− 0.003	0.00	− 0.79	0.429	− 0.01	0.01			
Year	0.05	0.03	1.83	0.067	-0.003	0.110			
3-hour model									
Intercept	− 79.33	52.81	− 1.50	0.133	− 182.84	24.17	53	64.9	0.683
Fasting FMD%	− 0.25	0.06	− 3.83	<0.001	− 0.37	− 0.12			
Total energy, kJ	0.0001	0.00	1.05	0.296	− 0.0001	0.0004			
Total fat, En%	− 0.03	0.01	− 2.41	0.016	− 0.05	− 0.01			
Male, %	− 0.004	0.01	− 0.75	0.456	− 0.02	0.01			
Year	0.04	0.03	1.55	0.121	− 0.01	0.09			
4-hour model									
Intercept	− 52.20	46.64	− 1.12	0.263	− 143.61	39.22	85	89.4	0.379
Age, years	− 0.02	0.02	− 1.14	0.254	− 0.05	0.01			
BMI, kg/m^2	0.05	0.06	0.87	0.385	− 0.06	0.17			
Fasting FMD%	− 0.27	0.07	− 4.20	<0.001	− 0.40	− 0.15			
Total energy, kJ	− 0.0003	0.00	− 2.19	0.029	− 0.00051	− 0.00003			
Total fat, En%	0.01	0.01	0.69	0.491	− 0.01	0.03			
Sample size, n	0.03	0.01	1.95	0.052	− 0.0001	0.05			
Male, %	0.00	− 0.001	− 0.23	0.821	− 0.01	0.01			
Year	0.03	0.02	1.12	0.261	− 0.02	0.07			
Fasting model									
Intercept	− 18.29	53.90	− 0.34	0.734	− 123.93	87.34	158	95.3	0.347
Age, years	− 0.10	0.02	− 6.32	<0.001	− 0.13	− 0.07			
BMI, kg/m^2	− 0.03	0.06	− 0.56	0.576	− 0.15	0.09			
Sample size, n	− 0.0002	0.02	− 0.01	0.988	− 0.03	0.03			
Male, %	− 0.003	0.01	− 0.64	0.521	− 0.01	0.01			
Year	0.01	0.03	0.55	0.580	− 0.04	0.07			

[1]Random-effects meta-regression was conducted by restricted maximum likelihood. Abbreviations: En%, percentage of total meal energy; FMD%, flow-mediated dilation percentage change.

detect early endothelial dysfunction before the fasting FMD is impaired.

The sex of the participant independently moderated the postprandial FMD at 3 hours after consumption. No changed postprandial response from fasting could be detected within the female-only studies, compared to reduced postprandial FMD% values in male-only and mixed-sex studies. However, the small sample size for female-only studies suggests that this effect should be further explored. The cardioprotective effect of estrogen has been well established (158, 176). Harris et al. (72) demonstrated that premenopausal women were protected from a high-fat meal challenge during periods of elevated estrogen, during the follicular phase of the menstrual cycle. Moreover, while no differences in 17β-estradiol were observed between male and female participants, females in the menses phase were still protected compared to males. The participant menstrual cycle phase was not consistently reported in the studies in this work, making it difficult to interpret the impact on FMD. The impact of sex differences needs to be interpreted with caution due to the low sample size. In future research, differences between males and females should be considered, and the female menstrual cycle phase should be reported to further understand the cardioprotective nature of estrogen.

Strengths and limitations

The current work is strengthened by the high number and variety of studies, which made a meta-analysis of potential modifiers possible. A rigorous compilation of participant characteristics, study design, FMD methodology, and meal contents was conducted. A conservative statistical approach was adopted to avoid spurious results. Some limitations include the limited number of time points at which the postprandial FMD was measured in the studies. Forty-six out of the 90 studies included in the meta-analysis only measured the FMD at 1 postprandial time point. Thus, conclusions on the FMD response after a meal can only be drawn based on between-subject comparisons, not within-subject comparisons. Second, as there are studies with multiple groups, there is a possibility that any given study might have contributed more than 1 value to the summary metric, leading to repeated estimates. There is a potential increased type I error rate that is associated with multiple statistical tests. Third,

TABLE 3 Subgroup analysis of mean difference in FMD based on study design, age, BMI, CVD risk, quality assessment, sex, FMD analysis method, total fat content, and fasting FMD% at fasting and 2-, 3-, and 4-hour postprandial time points[1]

Time point	Variables and subgroups	Mean difference in FMD%, postprandial FMD% − fasting FMD%			Heterogeneity	
		N	MD (95% CI)	*P* value	I^2, %	Q_B
Age						
Fasting	<31	53	8.04 (7.37–8.71)	<0.001	93.4	<0.001
	31–60	93	5.84 (5.34–6.35)	<0.001	97.2	
	>60	18	4.01 (3.42–4.61)	<0.001	88.9	
2 hours	<31	22	−1.17 (−2.06 to −0.28)	<0.001	94.9	0.664
	31–60	53	−0.10 (−1.35 to −0.64)	<0.001	92.4	
	>60	10	−0.76 (−1.27 to −0.24)	0.008	59.9	
3 hours	<31	29	−1.24 (−1.95 to −0.52)	<0.001	83.2	0.799
	31–60	21	−0.94 (−1.48 to −0.39)	<0.001	77.8	
	>60	1	−1.10 (−1.81 to −0.39)	—	—	
4 hours	<31	23	−1.89 (−2.63 to −1.15)	<0.001	93.7	0.003
	31–60	60	−1.07 (−1.48 to −0.65)	<0.001	94.8	
	>60	8	−0.23 (−0.86 to 0.41)	0.003	68.8	
BMI, kg/m^2						
Fasting	18.5 to <25	70	7.62 (6.99–8.25)	<0.001	95.6	<0.001
	25 to <30	61	5.14 (4.57–5.72)	<0.001	97.9	
	>30	32	5.16 (4.60–5.71)	<0.001	93.6	
2 hours	18.5 to <25	31	−0.97 (−1.59 to −0.35)	<0.001	93.7	0.887
	25 to <30	30	−0.87 (−1.29 to −0.44)	<0.001	92.5	
	>30	21	−1.01 (−1.45 to −0.58)	<0.001	74.2	
3 hours	18.5 to <25	34	−1.17 (−1.80 to −0.54)	<0.001	79.1	0.791
	25 to <30	15	−0.83 (−1.58 to −0.08)	<0.001	89.9	
	>30	4	−1.01 (−1.52 to −0.51)	0.700	0.00	
4 hours	18.5 to <25	35	−1.86 (−2.49 to −1.22)	<0.001	91.4	0.013
	25 to <30	37	−0.68 (−1.15 to −0.21)	<0.001	92.9	
	>30	18	−1.05 (−1.46 to −0.63)	<0.001	88.1	
Fasting FMD%						
2 hours	<10%	79	−0.85 (−1.15 to −0.55)	<0.001	91.8	<0.001
	>10%	6	−3.83 (−5.21 to −2.44)	0.006	78.8	
3 hours	<10%	42	−0.52 (−0.92 to −0.12)	<0.001	78.3	<0.001
	>10%	11	−3.39 (−3.97 to −2.80)	0.812	0.0	
4 hours	<10%	79	−1.02 (−1.36 to −0.68)	<0.001	94.5	0.009
	>10%	12	−2.66 (−3.84 to −1.48)	<0.001	74.0	
Total fat, En%						
2 hours	20–50	37	−1.21 (−1.71 to −0.71)	<0.001	91.3	0.083
	50–80	45	−0.79 (−1.21 to −0.37)	<0.001	93.7	
	>80	3	−1.85 (−2.73 to −0.97)	0.007	78.7	
3 hours	20–50	12	−0.32 (−1.25 to 0.60)	<0.001	82.9	<0.001
	50–80	27	−0.46 (−0.90 to −0.02)	<0.001	68.5	
	>80	14	−2.77 (−3.46 to −2.07)	<0.001	66.5	

(*Continued*)

TABLE 3 (*Continued*)

Time point	Variables and subgroups	Mean difference in FMD%, postprandial FMD% − fasting FMD%			Heterogeneity	
		N	MD (95% CI)	*P* value	I^2, %	Q_B
4 hours	20–50	40	−1.61 (−2.19 to −1.03)	<0.001	91.3	0.027
	50–80	40	−0.71 (−1.20 to −0.21)	<0.001	95.4	
	>80	11	−1.49 (−1.96 to −1.03)	<0.001	83.5	
Study design						
Fasting	RCT	115	6.37 (5.87–6.99)	<0.001	97.9	0.624
	Non-RCT	51	6.15 (5.44–6.87)	<0.001	97.2	
2 hours	RCT	58	−0.92 (−1.29 to −0.55)	<0.001	92.1	0.410
	Non-RCT	27	−1.23 (−1.85 to −0.60)	<0.001	94.6	
3 hours	RCT	44	−1.07 (−1.57 to −0.58)	<0.001	86.6	0.714
	Non-RCT	9	−0.85 (−1.92 to 0.21)	0.002	65.2	
4 hours	RCT	57	−1.20 (−1.63 to −0.77)	<0.001	94.9	0.916
	Non-RCT	34	−1.16 (−1.73 to −0.59)	<0.001	93.7	
CVD risk						
Fasting	Healthy	105	7.24 (6.71–7.77)	<0.001	97.5	<0.001
	Cardiometabolic disease or risk	61	4.76 (4.29–5.22)	<0.001	95.9	
2 hours	Healthy	52	−1.22 (−1.71 to −0.72)	<0.001	95.4	0.150
	Cardiometabolic disease or risk	33	−0.79 (−1.10 to −0.47)	<0.001	81.2	
3 hours	Healthy	44	−0.99 (−1.51 to −0.47)	<0.001	81.4	0.563
	Cardiometabolic disease or risk	9	−1.26 (−1.99 to −0.52)	<0.001	85.4	
4 hours	Healthy	51	−1.55 (−2.11 to −0.99)	<0.001	94.7	0.032
	Cardiometabolic disease or risk	40	−0.83 (−1.17 to −0.50)	<0.001	90.2	
Risk of bias						
Fasting	Low risk	11	6.19 (5.09–7.29)	<0.001	85.5	0.978
	Some concerns	115	6.29 (5.78–6.80)	<0.001	97.3	
	High risk	40	6.34 (5.50–7.18)	<0.001	98.6	
2 hours	Low risk	11	−0.70 (−1.52 to 0.11)	<0.001	93.3	0.129
	Some concerns	51	−1.19 (−1.64 to −0.74)	<0.001	93.3	
	High risk	23	−0.67 (−0.91 to −0.42)	<0.001	46.1	
3 hours	Low risk	4	−1.05 (−1.77 to −0.33)	0.701	0.0	0.146
	Some concerns	38	−1.25 (−1.80 to −0.70)	<0.001	85.1	
	High risk	11	−0.27 (−1.09 to 0.54)	<0.001	81.8	
4 hours	Low risk	6	−0.74 (−1.45 to −0.03)	<0.001	87.1	0.430
	Some concerns	66	−1.26 (−1.66 to −0.86)	<0.001	93.9	
	High risk	19	−0.96 (−1.82 to −0.09)	<0.001	94.0	

(*Continued*)

TABLE 3 (*Continued*)

Time point	Variables and subgroups	Mean difference in FMD%, postprandial FMD% − fasting FMD%			Heterogeneity	
		N	MD (95% CI)	*P* value	I^2, %	Q_B
Sex						
Fasting	Male	67	6.57 (5.91–7.23)	<0.001	98.4	0.452
	Female	16	6.68 (5.30–8.06)	<0.001	97.9	
	Mixed	80	6.05 (5.45–6.65)	<0.001	96.6	
2 hours	Male	39	−1.14 (−1.62 to −0.66)	<0.001	95.8	0.379
	Female	6	−0.34 (−1.36 to −0.68)	<0.001	95.1	
	Mixed	39	−0.99 (−1.48 to −0.51)	<0.001	82.1	
3 hours	Male	21	−1.62 (−2.46 to −0.79)	<0.001	87.2	<0.001
	Female	3	0.21 (−0.31 to 0.73)	0.993	0.0	
	Mixed	29	−0.78 (−1.30 to −0.25)	<0.001	77.8	
4 hours	Male	33	−1.29 (−1.95 to −0.64)	<0.001	97.3	0.364
	Female	13	−0.53 (−1.53 to 0.46)	<0.001	94.3	
	Mixed	42	−1.31 (−1.74 to −0.88)	<0.001	88.2	
FMD analysis						
Fasting	Manual measurement	64	7.22 (6.47–7.98)	<0.001	97.2	0.001
	Continuous edge-detection	102	5.71 (5.27–6.16)	<0.001	97.4	
2 hours	Manual measurement	32	−1.02 (−1.71 to −0.33)	<0.001	94.7	0.986
	Continuous edge-detection	53	−1.01 (−1.34 to −0.68)	<0.001	90.9	
3 hours	Manual measurement	36	−1.30 (−1.87 to −0.73)	<0.001	77.8	0.105
	Continuous edge-detection	17	−0.57 (−1.24 to 0.10)	<0.001	88.4	
4 hours	Manual measurement	27	−1.28 (−2.08 to −0.47)	<0.001	95.7	0.773
	Continuous edge-detection	64	−1.15 (−1.51 to −0.78)	<0.001	93.3	

[1]A maximum likelihood approach was undertaken for a random-effects subgroup meta-analysis. Subgroup analyses were conducted based on physiological, theoretical, and empirical associations with FMD. FMD is measured as the relative percentage change in the peak reactive hyperemia diameter from the baseline diameter (FMD%). The mean difference in the FMD% was calculated as the fasting FMD% subtracted from the postprandial FMD%, termed the FMD change. Heterogeneity was assessed by the I^2 statistic. Q_B, assesed the between-group heterogeneity of effect sizes in studies. Q_B values ≤0.05 were considered as a statistically significant impact of potential modifiers on the difference between subgroups. Abbreviations: CVD, cardiovascular disease; En%, percentage of total meal energy; FMD, flow-mediated dilation; FMD%, flow-mediated dilation percentage change; MD, mean difference; RCT, randomized controlled trial.

results could possibly be affected by regression to the mean. Fourth, meal composition significantly modified the magnitude of the postprandial FMD response. The percentage of carbohydrate and protein of the meal showed an inverse relationship with the FMD compared with the percentage of fat at 3 hours after consumption, suggesting a macronutrient-specific effect on the FMD and endothelial function. However, specific meal contents were often not well reported; specifically, the type of fatty acids was not reported in an overwhelming number of complex, mixed-meal studies.

Recommendations for future research

Standardization of future research methodology would allow for better comparisons and interpretation of studies. In addition, assessing postprandial FMDs would be advantageous to determine the effectiveness of therapies to treat or reduce CVD risks. Based on the findings here, the following recommendations should be considered to assess the benefits of CVD treatment regimens, including drugs, extracts, foods, supplements, or exercise regimens:

1. Follow expert guidelines for FMD protocols (6).
2. Provide a stress-test meal containing at least 60 g of a fat product such as whipped cream or fried food. Alternatively, provide at least 60% energy from fat, less than 30% energy from simple carbohydrates, and less than 10% energy from protein, with a total energy content of at least 3700 kJ. In addition, the macronutrient breakdown of meal challenges should be reported thoroughly.
3. Analyze population groups separately: that is, apparently healthy compared with diabetic populations; older compared with younger cohorts; and men compared with women.
4. Measure endothelial function data while fasting (just before the test meal) and at multiple time points, especially including 3 and 4 hours after consumption.
5. The FMD effects should be compared within populations over standardized periods of time during the intervention period.
6. Researchers seeking to undertake postprandial FMD studies should consider addressing research questions not already answered by the current body of published FMD research.

If feasible, interventions should be run over 6 hours, measuring FMD hourly, to understand the time course of lipid-induced endothelial dysfunction. The measurement of postprandial FMD would be a useful marker to assess the efficacy of potential therapeutics to reduce CVD risks. However, longitudinal cohort studies are required to determine whether this could be used for early detection of CVD risks.

Conclusions

We have, for the first time, collectively quantified the effects of a single, high-fat meal on the postprandial decline in the FMD% compared to fasting, in 164 groups of varying populations, at differing postprandial time points, and with protocols obtained from 90 distinct papers. We are unaware of any other paper that has systematically quantified this relationship. This response was varied across 3 different time points in 3 discrete meta-analyses. Postprandial lipemia reduces NO bioavailability, thereby causing transient endothelial dysfunction, which can be detected and quantified by FMD. These results support the rationale that the postprandial FMD could be a more sensitive risk marker for cardiometabolic disease, offering further insight into endothelial health beyond information gained from the fasting FMD alone.

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Data Availability

Data described in the manuscript will be made available upon request, pending application and approval.

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