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REVIEW

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# Impact of Fasting Mimicking Diet (FMD) on cardiovascular risk factors: a systematic review and meta-analysis of randomized control trials

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## Abstract

**Introduction** The Fasting Mimicking Diet (FMD) has gained significant attention as a potential intervention for reducing cardiovascular risk factors. While studies have investigated its effectiveness, findings have been inconsistent. Therefore, this systematic review and meta-analysis aimed to clarify evidence on the impact of FMD on cardiovascular risk factors.

**Method** PubMed, Web of Science, Scopus, and Google Scholar were searched for eligible Randomized controlled trials (RCTs) published up to July 2024. Weighted mean differences (WMD) were calculated for the net changes in risk factors using random-effects models.

**Results** Eleven RCTs (with twelve treatment arms) were included. FMD significantly reduced glycated hemoglobin (HbA1c) (WMD = -8.589 mmol/mol, 95% CI: −12.389, -4.769), insulin-like growth factor 1 (IGF-1) (WMD= -19.211 ng/ml, 95% CI: −32.986, -5.437), systolic blood pressure (SBP) (WMD = -4.148 mmHg, 95% CI: −7.584, -0.711), and diastolic blood pressure (DBP) (WMD = -2.263 mmHg, 95% CI: −4.162, -0.364) levels. No significant effects were observed on other cardiovascular risk factors.

**Conclusion** This meta-analysis suggests that FMD can significantly reduce HbA1c, IGF-1, SBP, and DBP levels. Further research is warranted to investigate the long-term and potential clinical implications of FMD on cardiovascular health.

**Prospero registration** The protocol of the study was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration no: CRD42024569426).

**Keywords** Fasting mimicking diet, FMD, Cardiovascular risk factors

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## Introduction

Cardiovascular disease (CVD) persists as the leading cause of mortality worldwide accounting for 32% of all global deaths. A cluster of risk factors, including hypertension, elevated cholesterol, obesity, insulin resistance, and chronic inflammation contribute significantly to CVD development [1]. The management of these risk factors through lifestyle modifications, particularly dietary interventions, represents a fundamental aspect of both the prevention and treatment of CVD. In recent years, Fasting Mimicking Diet (FMD) has gained significant attention as a novel approach that emulates the physiological benefits of traditional fasting while enabling limited caloric intake [2]. The objective of this dietary approach is to provide the metabolic advantages of fasting without the challenges associated with food abstinence. As a result, it has the potential to be a more acceptable and sustainable option for a broader population [1, 2].

FMD is a structured, low-calorie diet that is typically followed for five consecutive days, with a subsequent repetition of the diet every few months. During the fasting phase, the diet is designed to provide an adequate quantity of calories and specific nutrients to prevent the perception of starvation while simultaneously reducing calorie intake to a level that induces a fasting-like state [3, 4]. FMDs often contain low protein, moderate carbohydrate, and a relatively higher proportion of healthy fats, to emulate the physiological responses associated with fasting, including ketosis, cellular autophagy, and enhanced metabolic stress resilience, while inducing calorie restrictions. Following the fasting period, normal eating is resumed, therefore allowing for periodic metabolic reset without continuous caloric deprivation [4–6].

FMD has been demonstrated to exert significant effects on multiple cardiovascular risk factors. For example, FMD may reduce blood pressure, lower blood low-density lipoprotein (LDL) cholesterol and triglycerides, enhance insulin sensitivity, and promote weight loss [7–9]. These beneficial effects are vital in the management of metabolic syndrome, a cluster of conditions that significantly elevate the risk of cardiovascular disease and diabetes [1, 7]. FMD may also mitigate systemic inflammation, which is increasingly recognized as a contributing factor to atherosclerosis and other cardiovascular conditions [1]. FMD also reduces insulin-like growth factor 1 (IGF-1) levels, activates cellular autophagy, and reduces oxidative stress [5, 10], playing a significant role in cellular maintenance and repair, potentially delaying the onset of age-related diseases and improving cardiovascular health. In addition, FMD's influence on hormone regulation and lipid metabolism may contribute to improved endothelial function and vascular health, further reducing the risk of cardiovascular events [9–11].

While preliminary clinical studies suggest the potential benefits of FMD on cardiovascular risk factors, inconsistencies in the findings limit the derivation of conclusive evidence. Therefore, this review aims to synthesise this evidence by systematically pooling the effects of these individual clinical studies, providing a valuable resource for researchers, clinicians and policymakers aiming to reduce the burden of cardiovascular disease.

**Table 1** PICOS criteria for inclusion and exclusion of studies

| Parameters | criteria |
|---|---|
| Participants | Human adults |
| Intervention | Fasting mimicking intervention |
| Comparator | Placebo |
| Outcomes | No limitation |
| Study design | Clinical trials |

## Method

### Search strategy

This meta-analysis was designed following PRISMA guidelines. A comprehensive search of the literature was conducted using PubMed, SCOPUS, and ISI Web of Science databases. The PICOS approach was used to develop search terms using medical and non-medical subject headings and keywords including human adults (Population), fasting mimicking diet (Intervention), control diet (Comparator), cardiovascular risk factor outcomes (Outcome), and clinical trials (setting/design) (Table 1). The search strategy details for PubMed, SCOPUS, and ISI Web of Science databases are provided in Supplementary Table 1.

English-language reports of relevant randomized controlled trials (RCTs) published until July 2024 investigating the impact of fasting-mimicking diets on cardiovascular factors were included. The reference lists of the included articles and relevant reviews were also searched manually. Two reviewers (M.M. and F.A.) independently reviewed each article. Any discrepancies were resolved through discussion with a third reviewer (E.H). PubMed email alert service was also set up to identify any new articles published after our initial search. The protocol of the study was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration no: CRD42024569426).

### Study selection

Studies were included based on the following eligibility criteria: (1) controlled trials with either a parallel or crossover design; (2) reported measurements on anthropometry, blood markers of glycemic status, blood pressure, blood lipids, insulin-like growth factor 1 (IGF-1), and the inflammatory marker C-reactive Protein (CRP) at baseline and end of intervention in both intervention and control groups; (3) an appropriate controlled group

where the sole difference between the control and intervention groups was the fasting-mimicking diet; (4) an intervention duration of at least one complete cycle (four continuous days during one month); and (5) conducted in adults > 18 years old. Studies that did not meet the eligibility criteria were excluded.

### Data extraction

Two investigators (M.M. and H.A.) independently reviewed the eligible RCTs and extracted relevant data using a standardized electronic form. The recorded characteristics of the studies included the first author's name, year of publication, study country, design, number of subjects in each group, and intervention characteristics including cycles of fasting-mimicking diet (FMD), duration, and participant characteristics (i.e. age, gender, and body mass index). Where studies used multiple (two-armed) control groups, each control group was analyzed and reviewed separately.

### Quality assessment

The risk of bias of included studies was systematically assessed using the Cochrane quality assessment tool for RCTs. This tool consists of seven criteria for quality assessment, including random sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. The risk of bias in each study was categorized as low, high, or unclear [12].

### Quantitative data synthesis and statistical analysis

The effect FMD intervention on the following cardiovascular risk factors were recorded: (1) weight (kg); (2) waist circumference (cm); (3) fat mass (kg); (4) fat free mass (kg); (5) BMI ($kg.m^{-2}$); (6) systolic blood pressure (mmHg); (7) diastolic blood pressure (mmHg), (8) fasting blood sugar (mg/dl); (9) HbA1c (mmol/mol); (10) HOMA-IR; 11) IGF-1(ng/ml); 12) triglyceride (mg/dl); 13) total cholesterol (mg/dl); 14) HDL-cholesterol (mg/dl); 15) LDL-cholesterol (mg/dl) and 16) CRP (mg/l). Intervention effects were reported as weight mean difference (WMD) of cardiovascular risk factors along with 95% confidence intervals (CIs). Mean difference was calculated based on net changes from the baseline value of the cardiovascular risk factors. Where the standard deviations (SDs) of change were not reported, the following formula was used: square root [$(SD\ pre\text{-}intervention)^2$ + $(SD\ post\text{-}intervention)^2$ - (2 R × SD pre-intervention– SD post-intervention)], assuming a moderate correlation coefficient (R) = 0.5 [13]. When cardiovascular risk factor values were presented as medians and interquartile ranges (IQR), mean and standard SD were calculated using a previously defined method [14]. To convert the interquartile range (IQR) into a minimum-maximum range, the following equation was used: median + 2 × (Q3-median) and B = median– 2 ×(median-Q1), where A, B, Q1, and Q3 are upper and lower ends of the range, upper and lower ends of the IQR, respectively. Where standard errors (SE) were reported, SDs were calculated using the formula: SD = SE×sqrt (n), where (n) is the number of individuals in each group. Plot digitizer software was used to extract data when the outcome variable was exclusively presented in graphical form.

Heterogeneity among studies was assessed using Cochran's test (with a significance level of (P < 0.1)) and quantitatively through the $I^2$ statistic. An $I^2$ value of ≥ 50% indicated significant heterogeneity across the studies. The pooled effect size was calculated using the random effects model. A sensitivity analysis was performed using the leave-one-out method involving excluding individual studies from meta-analysis and exploring their influence on the overall effect size and heterogeneity [15]. Potential publication bias was assessed using funnel plots, Begg's rank correlation, and Egger's weighted regression tests. To account for this bias in the analyses the Duval and Tweedie 'trim and fill' and 'fail-safe N' methods were used [16]. Subgroup analyses based on population (diabetic and non-diabetic) and BMI (≥ 30 or < 30 $kg/m^2$) were performed to investigate the differences in meta-analysis outcomes based on these variables. Comprehensive Meta-Analysis (CMA) V3 software (Biostat, NJ) was used to perform meta-analyses.

## Results

### Selection and characteristics of included studies

A total of 583 publications were identified through the primary search of literature (Fig. 1). After excluding duplicates and irrelevant articles based on their title and abstracts, 28 studies remained. Following a full-text review, 17 studies were excluded due to the following reasons: no sufficient data ($n = 7$), not having a control group ($n = 2$) [17, 18], animal and in-vitro study ($n = 3$), non-English ($n = 1$), not having a control/placebo group ($n = 1$) [19], full text not accessible ($n = 1$), and insufficient duration of intervention (< 4 continuous days, $n = 2$) [8, 20]. Eleven RCTs met the eligibility criteria and were included in the current systematic review and meta-analysis [3, 7, 9, 10, 21–27]. Of these, 9 studies evaluated anthropometric measurements [7, 9, 10, 21–26], 9 investigated blood glycemic indices [7, 9, 10, 21–25, 27], 7 examined blood lipid profile [7, 9, 10, 21–24], 6 evaluated blood pressure [7, 9, 10, 21, 23, 24], and 6 evaluated CRP [3, 7, 9, 10, 21, 24].

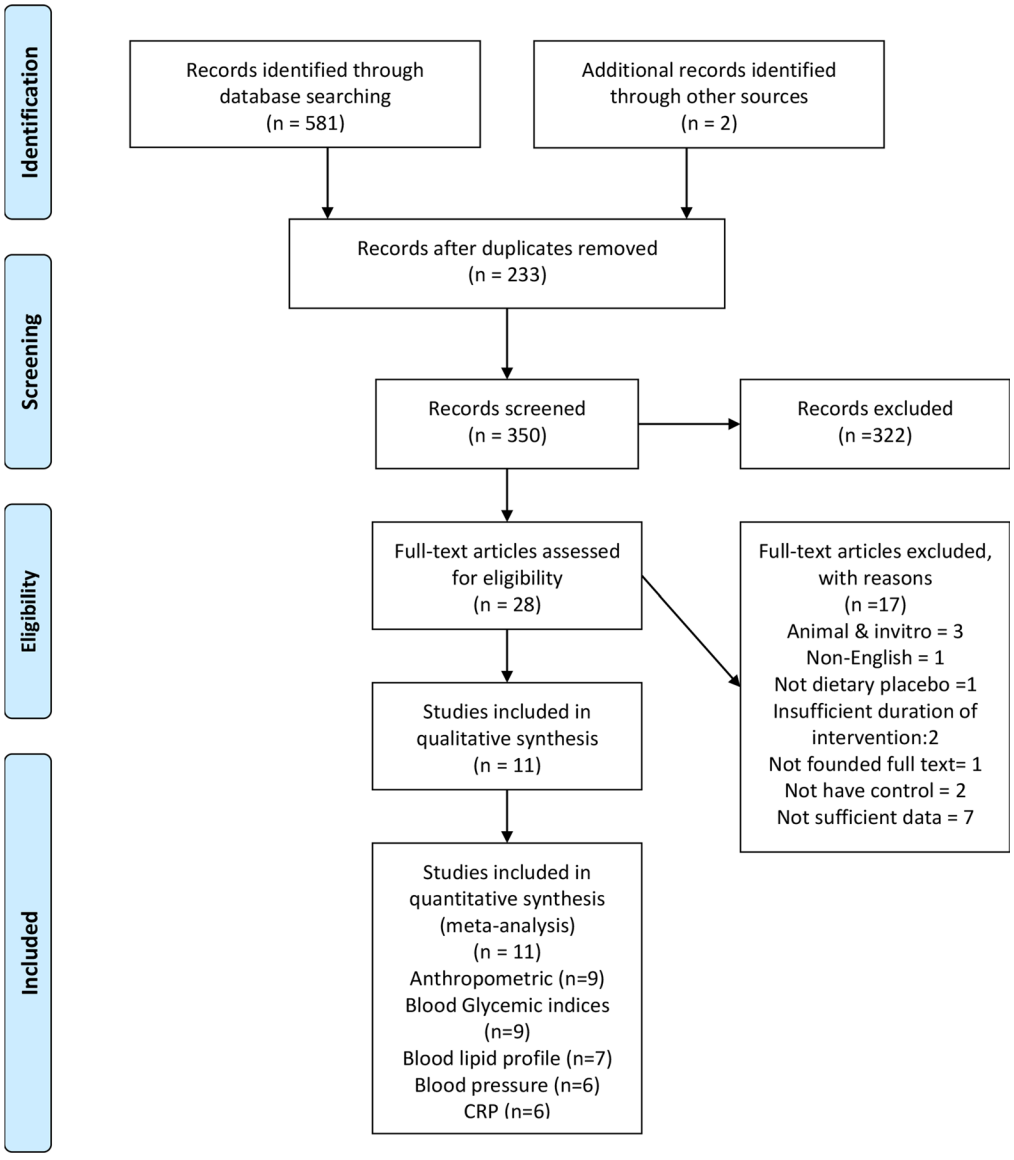


**Fig. 1** Flow chat of literature search process

### Characteristics of included studies

The main characteristics of the 11 qualified studies (12 sub-studies as Van der Velden et al. [9] study had two controls, $n = 761$) are reported in Table 2. Three studies exclusively included female participants [25–27] and others included all genders. FMD cycles varied from 1 to 12 with 1 to 48 weeks intervention durations. Participants aged between 31.1 and 64.9 years old with a BMI of between 25.7 and 33.9 kg/m2. Ten RCTs used a parallel design and one used a crossover design [21]. Studies included individuals with type 2 diabetes ($n = 4$) [9, 10, 23, 24], generally healthy adults ($n = 3$) [3, 21, 22], patients with breast cancer ($n = 2$) [26, 27], and overweight and obese individuals ($n = 2$) [7, 25].

### Data quality

Cochrane risk-of-bias assessment reported high quality with a total low risk of bias for all domains for the majority of studies included. However, two studies reported a moderate quality [3, 9] based on the risk of bias assessment (Table S2).

### Meta-analysis results

Pooled results from the random-effect model analysis suggested a slight but non-significant increase in fat-free mass following FMD (WMD = 0.885 kg, 95% CI: −0.059, 1.830, $p = 0.066$) (Fig. 2). However, there was no significant effect of FMD on other anthropometric measures including body weight (Figure S1), waist circumference (Figure S4), fat mass (Figure S7), and BMI (Figure S12). Heterogeneity was high for BMI ($I^2 = 96.4\%$, $p < 0.001$)

**Table 2** Characteristics of studies that evaluated the effect of FMD on cardiovascular risk factors

| Author, Year | Location | Design | Female % | Duration (week) | Enrolment, *n* | In, *n* | CTRL, *n* | Age, mean | Type of intervention | Type of control diet | Cycle (day) | Population | BMI (Kg/m2) mean |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Brandhorst et al., [2015] | USA | RP | 42 | 12 | 38 | 19 | 19 | IN (F: 41.8, M:42.5) CTRL (F:35.4, M:38.5) | FMD | Normal diet | 3 (5) | Generally healthy adult | NA |
| Wei et al., [2017] | USA | RC | 64 | 12 | 100 | 52 | 48 | IN: 42.2, CTRL: 43.3 | FMD | Normal diet | 3 (5) | Generally healthy adult | 26.6 |
| Stefanie de groot et al., [2020] | The Netherlands | RP | 100 | 12 | 81 | 22 | 59 | IN: 49, CTRL: 51 | FMD | Normal diet | 4 (4) | Breast cancer (HER2-negative) | 25.7 |
| Tang, Fang et al., [2020] | China | RP | 54 | 16 | 100 | 50 | 50 | IN: 50.02, CTRL: 49.84 | FMD | Meal Replacement | 3 (5) | Type 2 Diabetes | 30.15 |
| Lugtenberg et al., [2021] | The Netherlands | RP | 100 | 12 | 74 | 21 | 53 | IN: 49, CTRL: 51 | FMD | Normal diet | 4 (4) | Breast cancer (HER2-negative) | 25.7 |
| Sadeghian et al., [2021] | Iran | RP | 100 | 8 | 60 | 30 | 30 | IN: 34.3, CTRL: 31.17 | FMD | Continuous energy restriction | 2 (5) | Metabolically healthy obese women | 33.26 |
| Sulaj, Alba et al., [2022] | Germany | RP | 27 | 24 | 40 | 21 | 19 | IN: 64.9, CTRL: 31.17 | FMD | Mediterranean diet | 6 (5) | Type 2 Diabetes & diabetic nephropathy | 30.9 |
| Videja, Melita et al., [2022] | Latvia | RP | 65 | 1 | 43 | 24 | 19 | IN: 39, CTRL: 37 | FMD | Normal diet + vegetables | 1 (5) | Generally healthy adult | 28.8 |
| Mishra, Amrendra et al., [2023] | USA | RP | 62 | 16 | 84 | 44 | 40 | IN: 54.86, CTRL: 63.13 | FMD | Mediterranean diet | 4 (5) | Overweight and obese hypertensive subjects | 33.93 |
| Van der Velden et al., [2024] (a) | The Netherlands | RP2A | 68 | 12 | 28 | 13 | 15 | IN: 61, CTRL: 63 | FMD | Placebo | 3 (5) | Type 2 Diabetes | 28.14 |
| Van der Velden et al., [2024] (b) | The Netherlands | RP2A | 77 | 12 | 31 | 13 | 18 | IN: 61, CTRL: 56 | FMD | EndocalyxTM supplement | 3 (5) | Type 2 Diabetes | 29.46 |
| Van den Burg et al., [2024] | The Netherlands | RP | 48 | 48 | 82 | 43 | 39 | IN: 62, CTRL: 64 | FMD | NA | 12 (5) | Type 2 Diabetes | 31.3 |

Abbreviations: RP: Randomized Parallel design, RC: Randomized crossover design, RP2A: Randomized Parallel two-armed design, IN: Intervention group, CTRL: Control group, FFM: Fasting mimicking diet, BMI: Body Mass Index, F: Female, M: Male

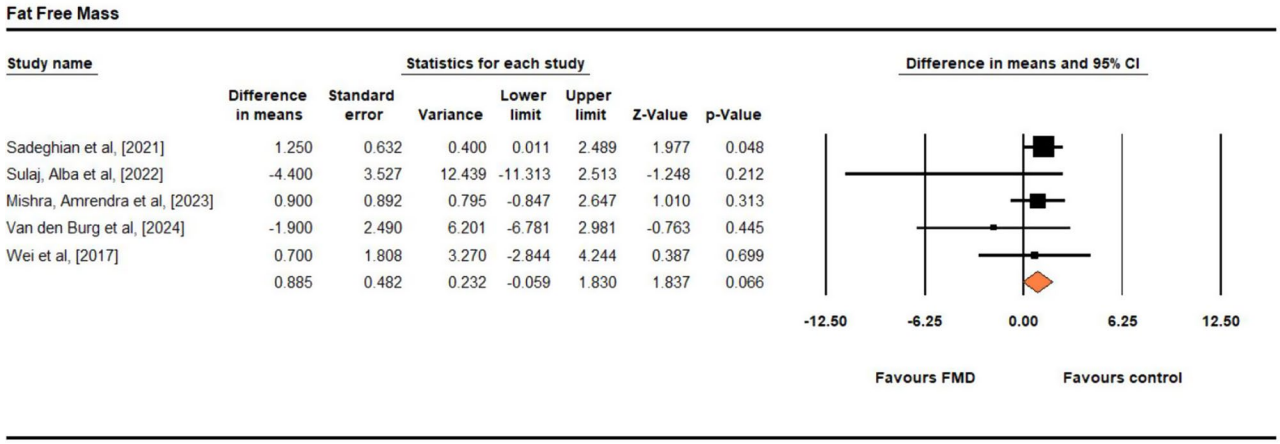


**Fig. 2** Forest plot detailing weighted mean differences and 95% confidence interval for the impact of FMD on Fat Free Mass (kg)

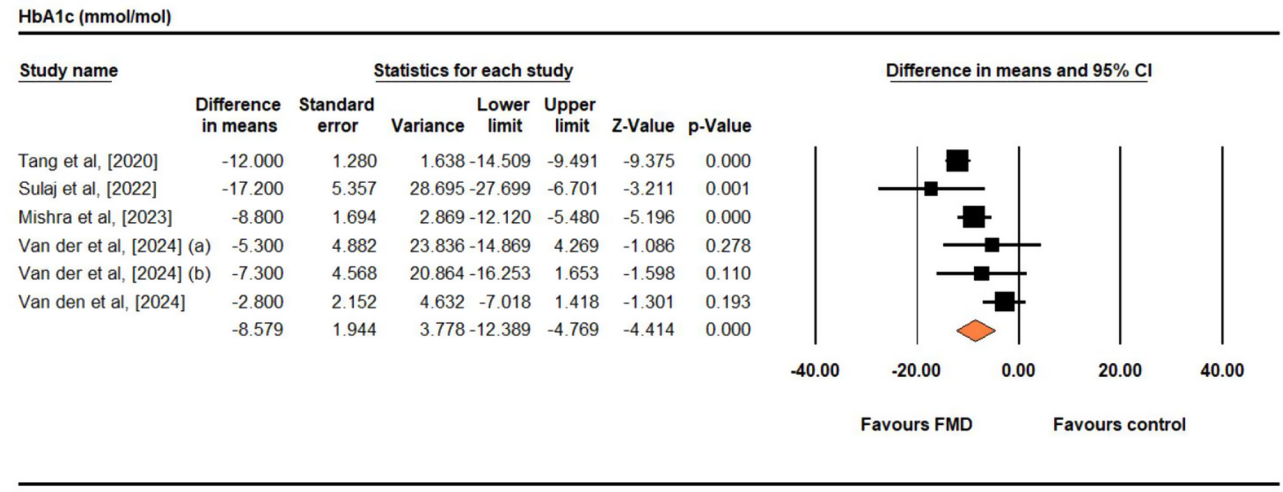


**Fig. 3** Forest plot detailing weighted mean differences and 95% confidence interval for the impact of FMD on Hemoglobin A1c (mmol/mol)

and waist circumference ($I^2 = 93.9\%$, $p < 0.001$), moderate for body weight ($I^2 = 51.1\%$, $p = 0.069$), and low for fat mass ($I^2 = 15.82\%$, $p = 0.313$), and fat-free mass ($I^2 = 0.00\%$, $p = 0.428$) meta-analyses.FMD significantly reduced HbA1c (WMD = -8.589 mmol/mol, 95% CI: −12.389, -4.769, $p < 0.001$) (Fig. 3), and IGF-1 (WMD= -19.211 ng/ml, 95% CI: −32.986, -5.437, $p = 0.006$) (Fig. 4). No significant effect of FMD was observed on FBS (Figure S15), and HOMA-IR (Figure S20). Heterogeneity was high for FBS ($I^2 = 91.54\%$, $p < 0.001$), HbA1c ($I^2 = 70.04\%$, $p = 0.005$), HOMA-IR ($I^2 = 68.44\%$, $p = 0.023$), and IGF-1 ($I^2 = 89.30\%$, $p < 0.001$).

FMD also significantly reduced SBP (WMD = -4.148 mmHg, 95% CI: −7.584, -0.711, $p = 0.018$) (Fig. 5) and DBP (WMD = -2.263 mmHg, 95% CI: −4.162, -0.364, $p = 0.020$) (Fig. 6). Heterogeneity was medium but non-significant for SBP ($I^2 = 50.37\%$, $p = 0.060$)] and DBP ($I^2 = 40.98\%$, $p = 0.118$).

FMD's effects on triglycerides (Figure S29), total cholesterol (Figure S32), LDL-C (Figure S35) and HDL-C (Figure S38) were not significant. However, heterogeneities were high for LDL-C ($I^2 = 90.54\%$, $p < 0.001$), TGs ($I^2 = 93.4\%$, $p < 0.001$), TC ($I^2 = 94.54\%$, $p < 0.001$) and HDL-C ($I^2 = 94.07\%$, $p = 0.007$). FMD effect on CRP level was also non-significant (Figure S41), with low heterogeneity ($I^2 = 0.00\%$, $p = 0.432$).

### Sensitivity analysis

The leave-one-out sensitivity analyses did not significantly affect the overall results of the meta-analysis or the heterogeneity observed for body weight, waist circumference, fat mass, BMI, FBS, HbA1c, HOMA-IR, TGs, TC, LDL-C, and HDL-C meta-analyses. However, the meta-analysis of the effect of FMD on fat-free mass was sensitive to the studies by Sulaj et al. [24] and Van den et al. [10]. Excluding these studies resulted in a significant increase in fat-free mass following FMD

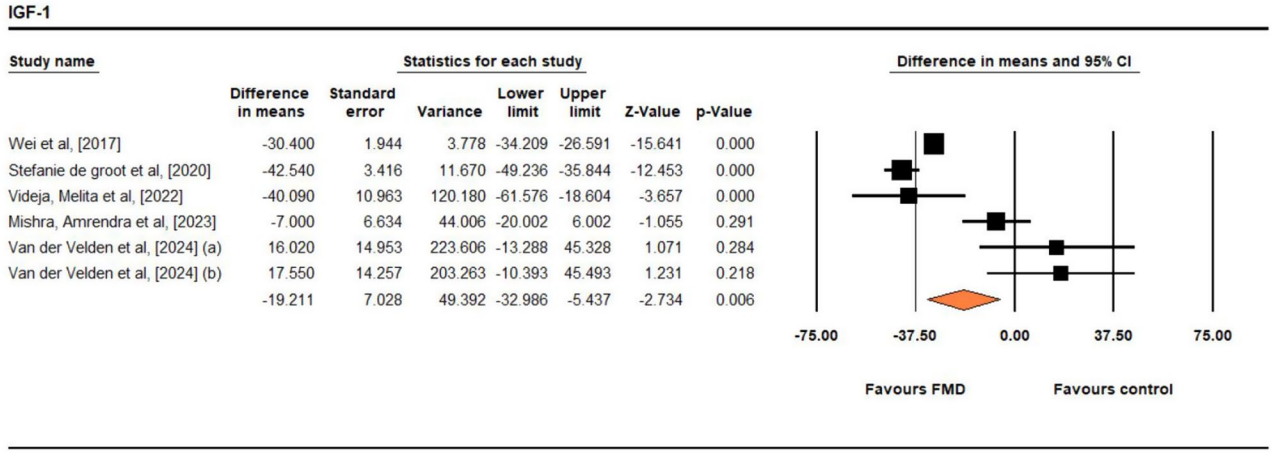


**Fig. 4** Forest plot detailing weighted mean differences and 95% confidence interval for the impact of FMD on IGF-1

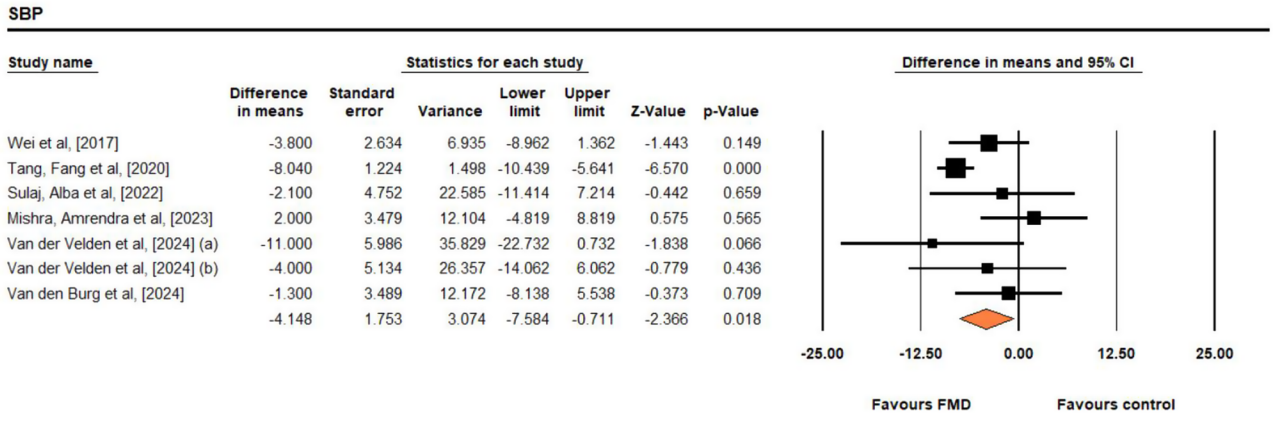


**Fig. 5** Forest plot detailing weighted mean differences and 95% confidence interval for the impact of FMD on Systolic Blood Pressure (mmHg)

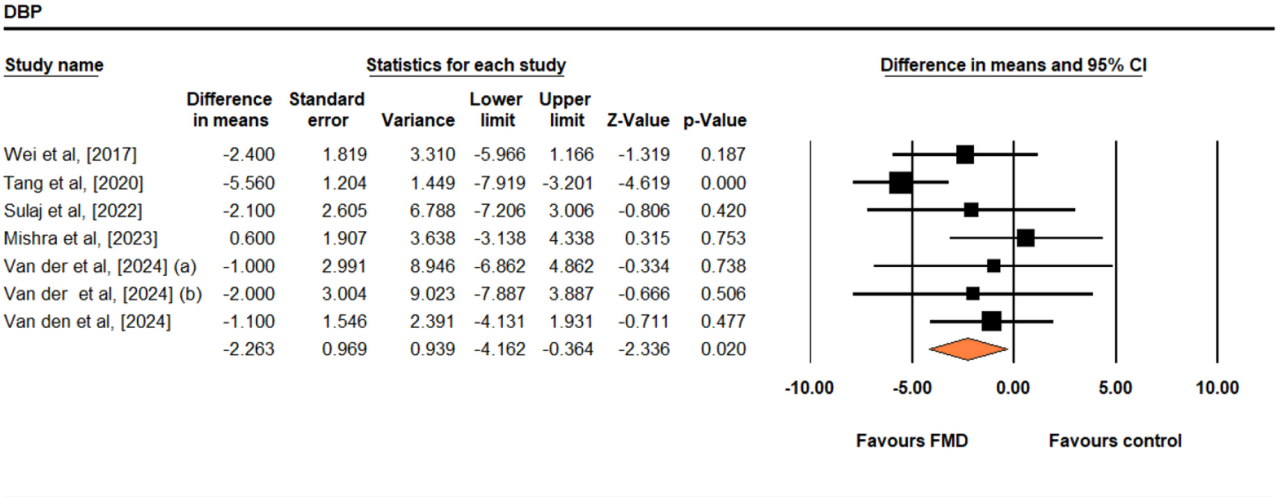


**Fig. 6** Forest plot detailing weighted mean differences and 95% confidence interval for the impact of FMD on Diastolic Blood Pressure (mmHg)

(WMD = 0.486 kg, 95% CI: 0.032, 1.939, $p = 0.043$; and WMD = 0.491 kg, 95% CI: 0.031, 1.956, $p = 0.043$, respectively). Excluding studies by Stefanie de Groot et al. [27] and Wei [21] from meta-analysis resulted in a non-significant effect of FMD on IGF-1 (WMD = -11.565 ng/ml, 95% CI: −30.743, 7.613, $p = 0.237$; and WMD = -13.255 ng/ml, 95% CI: −37.880, 11.370, $p = 0.291$, respectively). SBP and DBP meta-analyses were also sensitive to the study by Tang et al. [23], resulting in a non-significant reduction in SBP (WMD = -2.485 mmHg, 95% CI: −5.512, 0.543, $p = 0.108$), and DBP (WMD = -1.218 mmHg, 95% CI: −2.896, 0.459, $p = 0.155$). Also, the meta-analysis of CRP was sensitive to the exclusion of the Van den et al. [10] study, resulting in a significant reduction following FMD (WMD = -0.577 mg/l, 95% CI: −1.139, -0.015, $p = 0.044$). All figures for sensitivity analyses are presented in the Supplemental File.

### Subgroup analysis

In order to identify sources of heterogeneity and better assess the effects of FMD in different populations, subgroup analyses were performed (Table S3). Subgroup analysis of diabetic group suggested a significant reduction in body weight (WMD = − 6.64 kg, 95% CI: -12.0, -1.22, $p = 0.016$), waist circumference (WMD = -6.72 cm, 95% CI: -10.83, -2.61, $p = 0.001$), BMI (WMD = − 2.47 kg/m2, 95% CI: -4.08, -0.86, $p = 0.003$), SBP (WMD = − 6.01 mm Hg, 95% CI: -9.33, -2.69, $p < 0.001$), and DBP (WMD = -2.86 mm Hg, 95% CI: -5.14, -0.58, $p = 0.014$) following FMD. Among non-diabetic individuals, only a significant reduction was observed in body weight (WMD = 0.88 kg, 95% CI: 0.01, 1.75, $p = 0.045$) following FMD (Table S3).

Subgroup analysis based on BMI suggested a significant decrease in BMI (WMD = − 0.96 kg/m2, 95% CI: -1.77, -0.15, $p = 0.020$), SBP (WMD = -4.79 mm Hg, 95% CI: -9.06, -0.51, $p = 0.028$), CRP (WMD = -0.59 mg/L, 95% CI: -1.18, -0.01, $p = 0.046$), and FBS (WMD = -3.30 mg/dl, 95% CI: -6.20, -0.40, $p = 0.025$) among participants with BMI < 30 kg/m$^2$. However, the meta-analysis effects were not significant for the effect of FMD on any risk factors in a subgroup of participants with BMI ≥ 30 kg/m$^2$ (Table S3).

### Publication bias

Funnel plots suggested a visual asymmetry in the meta-analyses of FMD effects on cardiovascular risk factors (see Supplemental File). Egger's regression tests also suggested a significant publication bias for the effects of FMD on body weight ($p = 0.002$), fat-free mass ($p = 0.027$), and fat mass ($p = 0.025$). However, no evidence of publication bias for the effect of FMD on other risk factors was reported (Egger's regression test p-values ≥ 0.05). Similarly, no publication bias was observed based on Begg's test (p-values ≥ 0.05), with the exceptions of fat-free mass ($p = 0.027$) and TC ($p = 0.035$) (Table S4).

## Discussion

The findings of this systematic review and meta-analysis suggested that FMD cycles may significantly reduce some cardiovascular risk factors including HbA1c, IGF-1, SBP, and DBP. It may also result in a slight but non-significant increase in fat-free mass.

Literature suggests FMD may lead to a reduction in insulin secretion and an increase in glucagon [1, 6, 7, 9], which can facilitate lipolysis and gluconeogenesis, therefore, preventing the utilization of muscle protein as an energy source [1, 6, 7, 9]. During periods of fasting or fasting-mimicking diets, growth hormone levels tend to increase, which facilitates the preservation of lean body mass and enhances fat metabolism [10]. Growth hormone plays a role in the preservation of muscle proteins by facilitating the oxidation of fat and the utilization of stored fat reserves [1]. FMD induces a state of ketosis, whereby the body shifts from utilizing glucose as its primary fuel source to relying on ketones derived from fatty acids. The provision of ketones serves as an alternative energy source for the brain and muscles and helps preserve muscle proteins and maintain fat-free mass [1]. Also, the low protein in FMD triggers adaptive responses that prioritize the preservation of muscle protein [6]. This results in the body becoming more efficient at recycling amino acids and reducing protein breakdown, thus maintaining fat-free mass. FMD is also capable of reducing systemic inflammation and oxidative stress [21]. Chronic inflammation and oxidative stress can contribute to the development of muscle wasting and a reduction in fat-free mass. By reducing inflammation and oxidative stress, FMD helps to safeguard muscle tissue and maintain lean body mass. Also, FMD activates autophagy, a cellular process where damaged proteins and organelles are broken down and recycled. This not only helps in clearing out cellular debris but also ensures that cells maintain their function and integrity. Efficient autophagy contributes to muscle health by preventing the accumulation of damaged proteins and supporting muscle maintenance during periods of low nutrient availability [5, 6, 21, 27].

The findings of this study also suggested that FMD results in a reduction in HbA1c and IGF-1 levels. Evidence indicates that the reduction observed in HbA1c levels following FMD may be more pronounced among individuals with elevated blood glucose levels or an increased risk of developing type 2 diabetes [1, 7, 20]. However, this was not reported in the subgroup of diabetes individuals in the current meta-analysis. The reduction in caloric intake and carbohydrate consumption during FMD periods can result in a decrease in blood glucose levels, which subsequently leads to a reduction

in the glycation of hemoglobin over time [5], therefore potentially helping with HbA1c regulations. The reduction in circulating levels of IGF-1 reported from this meta-analysis could be attributed to the decreased protein intake during fasting mimicking periods, particularly the intake of amino acids such as methionine, which have been demonstrated to stimulate IGF-1 production [22]. FMD exerts influence over a number of pathways associated with the processes of aging and disease, most notably through the downregulation of the growth hormone/IGF-1 axis [26]. A reduction in IGF-1 levels has been linked to a decline in cellular proliferation and an increase in autophagy, a cellular cleansing process that eliminates damaged cells and enhances cellular health [25].

The findings also suggested that FMD can reduce blood pressure. This can have significant benefits for individuals with hypertension or high blood pressure. FMD protocols typically restrict sodium intake [7], which can contribute to a reduction in blood volume and a subsequent lowering of blood pressure. FMD may also improve endothelial function, and facilitate nitric oxide production [7]. Nitric oxide is a vasodilator, facilitating relaxation and dilation of blood vessels and reducing blood pressure [1]. FMD may also reduce markers of inflammation [1]. Lower inflammation levels can enhance endothelial function, which is crucial for NO production [25]. In fact, FMD mimics the effects of fasting, which can lead to metabolic adaptations that enhance the production of NO. Also, the anti-inflammatory effects of FMD may contribute to a reduction in vascular inflammation, which in turn may result in a lowering of systolic blood pressure [1, 7, 25]. Additionally, FMD has the potential to impact the renin-angiotensin-aldosterone system (RAAS), a hormonal regulatory mechanism that oversees blood pressure and fluid balance. By modulating this system, FMD can help reduce vascular resistance and lower blood pressure [1, 7].

A meta-analysis examining the effects of the ketogenic diet in a diabetic population found that the diet can have a positive impact on lipid profiles. However, it did not show significant effects on blood sugar control or weight management [28]. The fasting mimicking diet (FMD), in line with the DASH diet, has the potential to lower blood pressure. This study examining the effect of the FMD, combined with a previous study, has effectively shown that adherence to the DASH diet can lead to significant reductions in blood pressure [29].

This study has several strengths. Major cardiovascular risk factors were investigated in this meta-analysis and subgroup analyses. However, some limitations exist. There were variations in the intervention groups and the control groups' diets across studies. Moderate to high heterogeneities were also observed in the meta-analysis of most risk factors. While subgroup and sensitivity analyses aimed to investigate the source of heterogeneity, the variation and heterogeneity observed may limit the comparability of findings across studies.

## Conclusion

This meta-analysis suggests the Fasting Mimicking Diet (FMD) may significantly reduce HbA1c, IGF-1, SBP, and DBP levels in adults. However, the effect of FMD on other cardiovascular risk factors remains uncertain. Further research is warranted to investigate the potential long-term effect of FMD on cardiovascular risk factors and the underlying mechanisms of action in diverse populations.

### Abbreviations

| | |
|---|---|
| BMI | Body Mass Index |
| CVD | Cardiovascular disease |
| CRP | C-Reactive Protein |
| CIs | Confidence intervals |
| DBP | Diastolic blood pressure |
| FM | Fat mass |
| FFM | Fat free mass |
| FBS | Fasting blood sugar |
| FMD | Fasting Mimicking Diet |
| HDL | High Density Lipoprotein |
| HbA1c | Hemoglobin A1C |
| HOMA-IR | Homeostatic Model Assessment of Insulin Resistance |
| IGF-1 | Insulin-like growth factor 1 |
| LDL | Low Density Lipoprotein |
| RCTs | Randomized controlled trials |
| SBP | Systolic blood pressure |
| SDs | Standard deviations |
| TG | Triglyceride |
| TC | Total cholesterol |
| IQR | Interquartile ranges |
| WMD | Weight mean difference |
| WC | Waist circumference |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01709-5.

Supplementary Material 1

### Author contributions

MM: Conceptualization, Data collection, Validation of results, data analysis, writing original and final draft version, review & editing, MA: writing original, HA: Data collection, FA: Data collection, SK: Review and editing, AB: Review and editing, EH: Review and editing.

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### Data availability

The datasets generated and/or analyzed during the current study are not publicly available due confidential and private information but are available from the corresponding author on reasonable request.

## Declarations

### Ethical approval

No ethical statement was required for this study, no human or animal subjects or materials were used.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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