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Meta-analyses

Effect of vegetarian diets on the presentation of metabolic syndrome or its components: A systematic review and meta-analysis

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SUMMARY

Background & aims: Several studies have examined the effect of vegetarian diets (VD) on metabolic syndrome (MetS) or its components, but findings have been inconsistent. The aim of this study was to perform a systematic review and meta-analysis of randomized controlled trials (RCTs) and observational studies to assess the association between VD and MetS or its components (systolic blood pressure [SBP], diastolic blood pressure [DBP], fasting glucose triglycerides, waist circumference [WC], HDL-cholesterol (HDL-C)) in adults.

Methods: The Cochrane Library, EMBASE, PubMed, Web of Science, and Scopus were searched. RCTs, cohort studies and cross-sectional studies evaluating the effects of VD on MetS or its components in adults, with omnivore diet as control group, were included. Random effects meta-analyses stratified by study design were employed to calculate pooled estimates.

Results: A total of 71 studies (n = 103 008) met the inclusion criteria (6 RCTs, 2 cohorts, 63 cross-sectional). VD were not associated with MetS in comparison to omnivorous diet (OR 0.96, 95% CI 0.50 −1.85, $p = 0.9$) according to meta-analysis of five cross-sectional studies. Likewise, meta-analysis of RCTs and cohort studies indicated that consumption of VD were not associated with MetS components. Meta-analysis of cross-sectional studies demonstrated that VD were significantly associated with lower levels of SBP (mean difference [MD] −4.18 mmHg, 95%CI −5.57 to −2.80, $p < 0.00001$), DBP (MD −3.03 mmHg, 95% CI −4.93 to −1.13, $p = 0.002$), fasting glucose (MD −0.26 mmol/L, 95% CI −0.35to −0.17, $p < 0.00001$), WC (MD −1.63 cm, 95% CI −3.13 to −0.13, $p = 0.03$), and HDL-C (MD −0.05 mmol/L, 95% CI −0.07 to −0.03, $p < 0.0001$) in comparison to omnivorous diet. Heterogeneity of effects among cross-sectional studies was high. About, one-half of the included studies had high risk of bias.

Conclusions: VD in comparison with omnivorous diet is not associated with a lower risk of MetS based on results of meta-analysis of cross-sectional studies. The association between VD and lower levels of SBP, DBP, HDL-C, and fasting glucose is uncertain due to high heterogeneity across the cross-sectional studies. Larger and controlled studies are needed to evaluate the association between VD and MetS and its components.

Abbreviations: MetS, metabolic syndrome; RCTs, randomized controlled trials; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; HDL-C, HDL-cholesterol; ATP III, adult treatment panel III; IDF, international diabetes federation; VD, vegetarian diet; OD, omnivorous diet; WHR, waist-to-hip ratio.

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1. Introduction

Based on the various definitions established by the International Diabetes Federation (IDF) and the Adult Treatment Panel III (ATP III), the worldwide prevalence of metabolic syndrome (MetS) varies between 34% and 39% [1] in developed countries; a lower prevalence of 16–34% has been reported in developing countries [2]. An increasing worldwide prevalence of MetS is associated with an increase in obesity and physical inactivity [3,4]. Patients with MetS are twice as likely to develop cardiovascular disease, and are five times more likely to suffer from type 2 diabetes mellitus compared to an individual without MetS [3]. Globally, MetS and its potential health consequences are now considered as a public health concern [3].

Vegetarian diets (VD) are dietary patterns that exclude meats from the diet. These diets emphasize the consumption of plant foods like legumes, vegetable, grains and fruits. However, some of them include animal derived foods such as milk, eggs, fish and seafood [5]. Among the best-known VD, are the semi-vegetarian diet, which rarely includes meat and poultry, and the vegan diet, which excludes all types of animal products. A few VD are characterized by dietary exceptions of specific food groups such as fish-vegetarian diet, lacto-vegetarian diet, and lacto-ovo-vegetarian diet [6]. VD are usually adopted based on religion and cultural practices, health benefits, and concern towards animals and environmental sustainability [7]. In some cases they are used as dietary strategies in the treatment and prevention of MetS. Randomized controlled trials (RCTs) in adults consuming VD have shown an improvement in weight control [8], glycemic control [9] and other cardiovascular risk factors [10].

Several studies have evaluated the association between VD and a decreased risk of MetS and/or its components. In a study linking VD and health benefits, the prevalence of MetS and its components, including serum triglycerides, fasting glucose, blood pressure and waist circumference (WC), were significantly lower in the vegetarian population when compared with a non-vegetarian population [11]. Lower blood pressure levels have been associated with VD in comparison with omnivores [12]. Also, lower levels of fasting glucose [13,14], WC [13] and triglycerides [14], have been reported in vegetarians. These findings suggest that vegetarian individuals have a lower risk of MetS in comparison to non-vegetarians [13]. In contrast to the beneficial effects of VD, few studies have reported the opposite [13,14], emphasizing lower levels of HDL-C and higher prevalence of MetS [16] in the vegetarian population [15]. In a meta-analysis of RCTs and observational studies assessing the effect of vegan, semi-vegetarian and lacto-ovo-vegetarian on blood pressure, a component of MetS, a significant decrease in systolic blood pressure and diastolic blood pressure was shown in the vegetarian population; nevertheless, this study presented several methodological limitations that should be considered when interpreting the results [5]. The inconsistent reports and the uncertainty of the association between VD and blood pressure and other MetS components, warrants further studies. The objective of this study was to determine the association between VD and the MetS and/or its components in adults.

2. Materials and methods

2.1. Data sources and search strategy

The systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) guidelines [17]. Cochrane Library, EMBASE PubMed, Web of Science, and Scopus were searched from database inception through 24 May 2017. The bibliographies of all identified systematic reviews were also searched for additional relevant studies. The database searches were carried out independently by one author (VP). The search strategies are available as Supplementary data. The search terminologies included search terms relevant to VD and MetS. The inclusion criteria for the study were: 1) RCTs, cohort studies and cross-sectional studies evaluating the effects of VD (lacto-ovo-vegetarian, semi-vegetarian, vegan, pesco-vegetarian) on MetS and/or on one or more of its components (blood pressure, fasting glucose, triglycerides, HDL-C and WC), 2) comparator omnivorous diet group, and 3) adult participants aged 18 years and above. Studies published in languages other than English and German were excluded.

Lacto-ovo-vegetarian diet is defined as a diet that excludes meat, poultry and fish, and includes eggs, dairy products, and plant foods (vegetables, fruits, whole grains and legumes). Semi-vegetarian diet is defined as a diet which contains plant foods and animal foods including meat, poultry, fish, seafood, eggs, and dairy products; though, the consumption of red meat and poultry is very limited in quantity and frequency. Fish-vegetarian or pesco-vegeterian diet is defined as a diet that includes fish, eggs, dairy products and plant foods. Vegan diet is defined as a diet based on plant foods and excludes all type of animal origin foods, including dairy products and eggs. Finally, omnivorous diet is defined as a diet including free consumption of plant and animal foods.

2.2. Study selection and data extraction

Titles and abstracts of the retrieved articles were screened by three authors (MCP, JAL, and JMR) to identify potential relevant articles. All disagreements on selections were discussed with a fourth author (AVH) and resolved by consensus. Three reviewers (MCP, JAL, and JMR) independently extracted relevant data from the selected studies. Another author (AVH) reviewed the extracted data for discrepancies and all four authors (MCP, JAL, JMR and AVH) reached consensus. The articles retrieved from the database searches were saved, shared and screened using myendnoteweb.com. Authors of relevant studies were contacted for additional and missing data.

The primary outcome of interest was MetS as defined by the consensus "Harmonizing the Metabolic Syndrome: A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity" [3]. Secondary outcomes of interest were independent components of MetS: blood pressure, fasting glucose, triglycerides, HDL-C and WC. Data for potential confounders of the association between VD and MetS were also extracted for each study: age, gender, body mass index (BMI), physical activity level, stress, smoking, alcohol, socioeconomic status, and population group.

2.3. Study quality assessment

Risk of bias of RCTs was evaluated using 'The Cochrane Collaboration tool for assessing risk of bias' [18] This tool evaluates the following criteria: 1) sequence generation, 2) allocation concealment, 3) blinding of participants, personnel and outcome assessors, 4) incomplete outcome data, 5) selective outcome reporting, 6) other sources of bias. Risk of bias of cohort studies was evaluated using the Newcastle Ottawa scale (NOS) [19]. NOS scale evaluates the following criteria: 1) Selection: representativeness of the exposed cohort, selection of the non-exposed cohort,

ascertainment of exposure, demonstration that outcome of interest was not present at start of study, 2) Comparability: comparability of cohorts on the basis of the design or analysis, 3) Outcome: assessment of outcome; if the follow-up was long enough for outcomes to occur; adequacy of follow up of cohorts. The NOS assessment was performed per each cohort study; each study was assigned scores based on the 3 criteria (selection, comparability, outcomes). The maximum score was 8, the minimum score 0. A score of 7 was reflective of high methodological quality, a score of 5 or 6 indicated moderate quality and a score of 4 or less indicated low quality. Risk of bias of cross-sectional studies was assessed by using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [20]. Ten out of 14 questions were selected for quality assessment based on their relevance to cross-sectional studies. Each included study was rated as good, fair or poor quality.

2.4. Statistical analysis

Random effects meta-analyses using the inverse variance method were performed to generate forest plots for pooled odds ratios or mean differences [21]. Funnel plots were used to evaluate small study effects, and the Egger's test was performed to measure asymmetry of funnel plots. Cochrane's Chi square test and the I^2 test were used to quantify heterogeneity between studies [22]. Heterogeneity was considered statistically significant at $p < 0.1$ of the Chi square test, and substantial heterogeneity was defined as $I^2 > 60\%$. When the median and interquartile range (IQR) were used, the mean was calculated by the formula $x = (a + 2m + b)/4$ using the values of the median (m), quartiles P25 and P75 (a and b, respectively) and the standard deviation (SD) was estimated using SD = IQR/1.35. Mean Difference (MD) and Standardized Mean Difference (SMD) were reported with 95% confidence intervals. SMD (calculated by dividing the difference in mean outcome between groups over the standard deviation of outcome among participants) was preferred when the units or the scale of the continuous variables was different across studies [23]. Finally, we performed pre-specified subgroup analyses by publication year (before 2001 vs after 2001) and risk of bias (low vs high). As publication year 2001 represents the median year of publication of all included studies, it was chosen as a cut-off for the subgroup analysis. We performed meta-analyses using RevMan 5.3 (Cochrane Collaboration, Denmark).

3. Results

3.1. Study selection

Our search strategy identified 3222 publications. After removal of duplicates, 2660 unique articles remained. Upon screening of studies by title and abstract review, 2466 articles were excluded. After review of 194 full-text articles, 123 studies were excluded: 10 were duplicates, 9 reported more than one intervention diet aside VD, 16 reported no control group, 12 reported insufficient outcome data, 9 were published in other languages (Czech, Russian and Slovak); other reasons for exclusion are presented in Fig. 1. A total of 71 studies were selected for the analysis (six RCTs [14,24–28], two cohorts [29,30], and 63 cross-sectional studies [12,13,15,16,31–88]). One contacted author provided additional information on triglyceride levels, fasting glucose, HDL-C, SBP, and DBP [82].

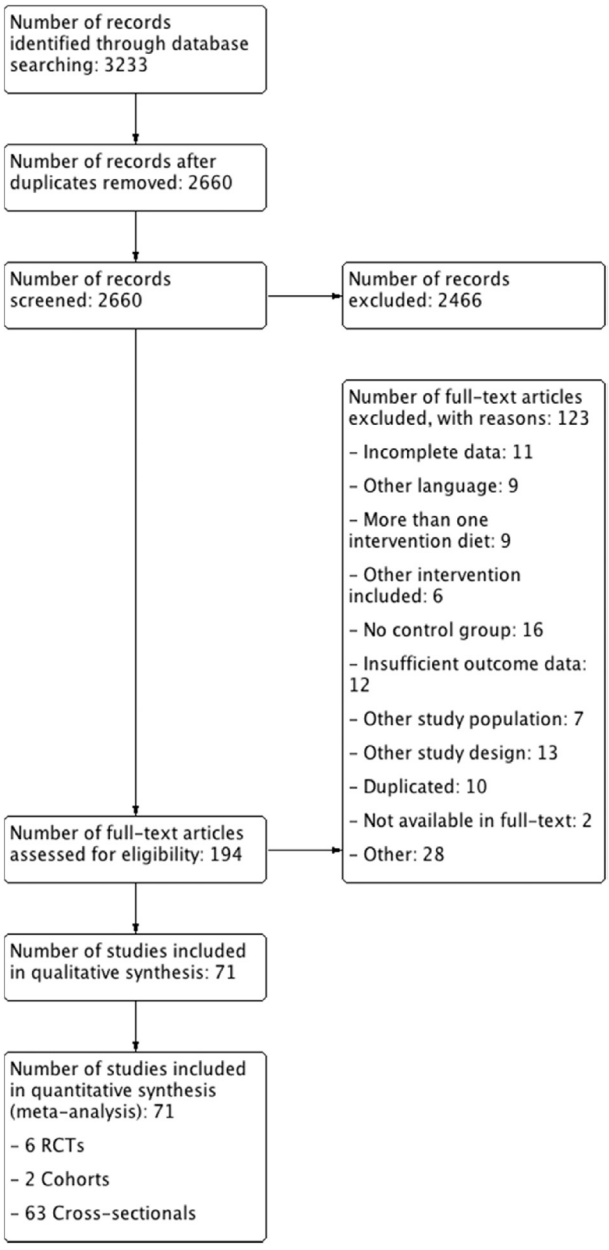

Fig. 1. Flow diagram of study selection.

3.2. Description of studies

Table 1 summarizes the main characteristics of the six included RCTs (n = 706). The population of these studies was mainly composed of women. The mean age of the patients in six RCTs ($n = 597$) was 48.6 years. Vegan diets were used as interventions in three of the studies. The length of the studies ranged from six weeks to seventy-four weeks. Table 2 summarizes the main characteristics of two cohort studies ($n = 352$). The sample of the cohort studies ranged from 50 to 302. The mean age of the included individuals was not provided. Lacto-ovo-vegetarian diets were evaluated in both cohort studies. Table 3 summarizes the main characteristics of 63 included cross-sectional studies ($n = 102{,}000$). Most of the studies used only one type of VD as exposure. The most recent RCT, cohort study and cross-sectional studies were published in 2016, 2011, and 2017, respectively.

The control group in all studies was omnivorous diet. The evaluated outcomes were metabolic syndrome (five cross-sectional studies [13,16,65,74,82]), WC (14 cross-sectional studies [13,15,16,39,41,43,44,59,60,67,81,83,84,87], three RCTs [26–28]), triglycerides (45 cross-sectional studies [13,15,16,31,33,35,38,

Table 1
Characteristics of RCTs studies.

Author, year (reference)	Country	Sample size VD/OD	Length of study (weeks)	Matching for	Mean (SD) age	Gender (male)	BMI	Specific type of population	Types and definition of VD	Definition of omnivorous diet
Sciarrone S, 1993 [24]	Australia	10/10	6	Age, BMI	35.0 (0.7)	100%	25.4 (1.8)	NA	SV: consumption of eggs and cheese. Meat, fish, poultry and animal fats are excluded.	NA
Burke, 2007 [25]	USA	45/48	72	None	25.4 (1.8)	11.7%	34.0 (4.1)	NA	V: meat, poultry, and fish are excluded.	Consuming meat, poultry, or fish
Barnard, 2009 [26]	USA	49/50	74	None	55.6 (10.0)	39.4%	34.9 (7.4)	NA	V: consumption vegetables, fruit, grains and legumes	Conventional diet
Ferdowsian, 2010 [27]	USA	68/45	22	Age, gender, race	NA	17.7%	NA	NA	V: NA	NA
Mishra, 2013 [14]	USA	142/149	18	None	45.2 (14.5)	17.2%	35.0 (0.7)	BMI≥25 or diagnosed previously with diabetes type 2	V: consumption of whole grains, vegetables, legumes, and fruits. Excludes animal products (meat, poultry, fish, dairy products and eggs) and minimizes consumption of added oils, with a target of <3 g of fat per serving. Supplement of Vit. B12	NA
Lee, 2016 [28]	Korea	46/47	12	No	57.9 (7.3)	19.4	23.5 (3.0)	NA	V: Consumption of whole grains, vegetables, fruit, and legumes. Avoid all animal food products (meat, poultry, fish, daily goods, and eggs)	Consuming grains, meat, vegetables, fats and oils, milk, and fruits

Abbreviations: SD, standard deviation; NA, not available; BMI, body mass index; LOV, lacto-ovo-VD, V, vegan; SV, semi-vegetarian.

Table 2
Characteristics of cohort studies.

Author, year (Reference)	Country	Sample size VD/OD	Length of study	Matching for	Mean (SD) Age	Gender (male)	BMI	Specific type of population	Types and definition of VD	Definition of omnivorous diet
Brestrich, 1996 [29]	Germany	151/151	NA	None	54.5 (9.0)	NA	27.7 (4.2)	NA	LOV: NA	NA
Nduka A.G, 2011 [30]	Nigeria	25/25	NA	None	NA	NA	NA	Adventist	LOV: consumption of eggs and dairy products. Animal products are excluded	No meat restrictions

Abbreviations: SD, standard deviation; NA, not available; BMI, body mass index; LOV, lacto-ovo-vegetarian; VD, vegetarian diet; OD: omnivorous diet.

Table 3
Characteristics of cross-sectional studies.

Author, year (reference)	Country	Sample size VD/OD	Matching for	Mean (SD) Age	Gender (male)	BMI	Specific type of population	Types and definition of VD	Definition of omnivorous diet
Sacks F, 1975 [31]	USA	115/115	Age, sex	NA	50%	NA	NA	LOV: NA	NA
Burr, 1981 [32]	UK	85/215	Age, sex	54.5 (14.3)	63%	NA	NA	SV: consumption of meat and fish less than once a month	NA
Liebman, 1983 [33]	USA	36/18	None	30.7 (5.7)	100%	NA	NA	SV: consumption of meat, fish, or poultry no more than once per week	NA
Ophir O, 1983 [34]	USA	98/98	None	60.9 (1.9)	50.50%	NA	Israeli Vegetarian Association	LOV: excluded all kinds of meat and fish. No more than three eggs a week were consumed. Milk and milk derivatives were scarcely used. Diet rich in fruit, vegetables, almonds, peanuts, and nuts.	No meat restrictions
Faber, 1986 [35]	South Africa	33/22	Age, sex	28.2 (30.0)	43.60%	22.6 (3.1)	NA	V: meat, fish or poultry are excluded.	NA
Sanders T, 1987 [36]	England	22/22	Age, height, weight, physical activity and smoking habits	28.8 (21.0)	50%	21.0 (0.7)	NA	V: NA	NA
Thorogood M, 1987 [37]	England	6000/5000	None	38.0	10.50%	NA	NA	V; SV; PV: NA	NA
Nieman, 1989 [38]	USA	23/14	None	NA	NA	NA	Adventists	LOV: excludes meat, fish or poultry	Consumption of meat at least three times per week
Melby, 1989 [39]	USA	219/159	None	53.4 (2.2)	17.70%	26.7 (2.4)	Black and white Adventists	LOV: excludes meat, fish or poultry	NA
Supawan V, 1992 [40]	Thailand	132/68	None	34.0 (12.7)	48%	20.2 (2.9)	Buddhist	V; SV: NA	NA
Melby, 1993 [41]	USA	112/91	None	66.4 (1.7)	NA	27.2 (2.5)	Black and white Adventists	LOV: NA	NA
Pan, W. H, 1993 [42]	China	55/59	Sex, age, BMI	22.1 (4.5)	37.70%	20.5 (2.4)	Chinese Buddhist Vegetarian	LOV: NA	NA
Melby, 1994 [43]	USA	122/45	None	47.6 (2.2)	26.30%	28.1 (1.3)	Seventh Day Adventists	LOV: excludes meat, fish, and poultry; SV: consumption of flesh foods one to three times per week	Consumption of flesh foods daily
Wyatt C, 1995 [44]	Mexico	36/36	Age, sex	NA	NA	24.4 (3.6)	NA	SV: consumption of eggs and milk products	NA
Krajcovicova-Kudlackova, 1996 [45]	Slovakia	81/62	None	27.4 (1.0)	50%	22.1 (1.4)	NA	LOV: NA	NA
Pauletto P, 1996 [46]	Tanzania	654/622	None	NA	58%	NA	NA	LOV: consumption of grains, potatoes, and vegetables.	Eats mainly fish
Ball, 1997 [47]	Scotland	13/20	None	23.4 (4.9)	0%	NA	Premenopausal women	LOV: consumption of some dairy products. Meat is excluded.	NA
Famodu, 1998 [48]	Nigeria	36/40	None	48.6 (1.6)	NA	28.8 (0.9)	Seventh Day Adventist	LOV: consumption of dairy products and eggs; V: meat, eggs and dairy products are excluded.	NA
Richter V, 1999 [49]	Germany	46/49	Age	37.5	NA	NA	German Society of Vegetarians	SV: consumption of milk, eggs, and its derivatives. Meat and fish are excluded.	NA
Kwok, 1999 [50]	China	70/90	None	79.0 (6.1)	NA	22.5 (3.8)	Chinese older women	LOV: NA	Regular consumption of meat
Lee, 2000 [51]	China	60/133	Age, BMI	40.0 (6.1)	36.8%	23.7 (3.5)	NA	LOV: includes dairy products and eggs. Meat and fish are excluded.	NA
Lu, 2000 [52]	Taiwan	109/107	Age, sex	37.7 (4.4)	24.5%	21.4 (2.9)	NA	LOV: includes less than a glass (240 mL) of low-fat or skim milk per day	NA
Hoffmann, 2001 [53]	Germany	242/138	None	NA	NA	NA	Women	LOV: consumption of whole grain products above 1100 g/week, of unheated vegetables above 700 g/week, of highly refined grain products below 1050 g/week, of meat below 300 g/	Consumption of meat between 301 and 1050 g/week, of unheated vegetables between 170 and 852 g/

(*continued on next page*)

Table 3 (*continued*)

Author, year (reference)	Country	Sample size VD/OD	Matching for	Mean (SD) Age	Gender (male)	BMI	Specific type of population	Types and definition of VD	Definition of omnivorous diet
								week, of meat products below 100 g/ week and of alcohol below 70 g/week.	week and of alcohol below 140 g/week
Li, 2001 [54]	Australia	61/78	None	36.0 (8.4)	100.0%	25.2 (3.6)	NA	V: excludes meat, and includes eggs and dairy products <6 times/year; LOV: includes meat no more than six times per year, and eggs and dairy products freely.	Diet includes ≥280g of meat (uncooked weight) per day
Lin, 2001 [55]	Taiwan	20/20	None	57.5 (3.9)	50.0%	24.0 (2.3)	NA	LOV: NA	NA
Appleby, 2002 [12]	UK	5970/4707	None	NA	21.4%	NA	NA	LOV; V; PV: NA	NA
Bedford, 2005 [56]	Canada	106/1711	None	44.6 (1.0)	49.5%	26.1 (0.8)	NA	LOV: NA	NA
Goff, 2005 [57]	UK	21/25	Age, sex, BMI, ethnicity	35.5 (59.0)	50.0%	23.0 (2.6)	NA	V: meat, fish and eggs are excluded.	NA
Fu, 2006 [58]	Taiwan	35/35	Age	55.0 (1.0)	0	23.5 (1.1)	NA	LOV: meat and fish are excluded; but occasionally consumed eggs and dairy products	NA
Hung, 2006 [59]	Taiwan	49/49	Age	36.8 (4.3)	0	21.5 (2.4)	Premenopausal women	LOV: NA	NA
Su, 2006 [60]	Taiwan	58/61	None	58.4 (5.8)	0	23.3 (2.7)	Buddhist	LOV: Diet which avoids meat, fish, and poultry for at least 5 years.	NA
De Biase, 2007 [61]	Brazil	54/22	None	35.4 (12.6)	36.8%	24.2 (4.6)	NA	LOV; V: NA	NA
Teixeira Rde C, 2007 [62]	Brazil	67/134	Age, sex, race, socioeconomic class	47.0 (8.0)	NA	25.3 (4.9)	Adventist	SV: consumption of eggs, milk and dairy products; V: animal products excluded	Consumption of meats
Chen, 2008 [63]	China	99/99	Gender	50.3 (9.3)	43.9%	23.4 (3.2)	NA	LOV: NA	NA
Hung, 2008 [64]	Taiwan	71/388	Age	50.4 (9.8)	57.7%	23.7 (3.1)	Chinese	LOV: NA	NA
Nakamoto, 2008 [65]	Japan	75/47	Age, sex	44.9 (7.6)	40.2%	21.9 (2.3)	NA	LOV: NA	NA
Sambol S, 2009 [66]	Croatia	50/50	None	35.4 (9.3)	32.0%	23.0 (2.8)	NA	V: animal products excluded; VEG: consumption of eggs and dairy products	NA
Pitla, 2009 [67]	India	26/26	None	45.9 (3.9)	56%	24.8 (2.8)	NA	LOV: Not taken any meat, fish or poultry in their lifetime but consumed milk products	NA
Lin, 2010 [68]	Taiwan	102/102	Age, BMI, education level	46.1 (12.4)	0%	23.4 (3.7)	NA	LOV: NA	NA
Chen, 2011 [69]	China	173/190	None	51.9 (9.9)	0%	23.1 (3.2)	NA	LOV: consumption of dairy products and eggs.	NA
Rodenas S, 2011 [70]	Spain	14/12	None	68.4 (9.5)	NA	24.2 (3.2)	Postmenopausal women	SV: Consume certain foods of animal origin but usually exclude red meat from their diet	NA
Yang S, 2011 [71]	China	171/129	None	33.3 (10.4)	100%	23.9 (3.5)	NA	LOV: NA	NA
Dourado, 2011 [72]	Brazil	29/58	Age, sex	40.0 (13.0)	58.6%	24.3 (3.6)	NA	V: meat and fish are excluded.	No meat restrictions
Kim, 2012 [73]	South Korea	59/48	None	62.6 (8.9)	NA	23.8 (3.4)	Postmenopausal women	LOV: NA	NA
Kim, 2012 [74]	Korea	45/30	Age, sex	49.2 (4.6)	50.7%	22.6 (2.8)	NA	LOV: consumption of plant foods, dairy products (goat milk only) and eggs.	NA
Yang S, 2012 [15]	China	169/126	None	33.3 (10.4)	100.0%	24.0 (3.5)	NA	LOV: meat, egg, fish and poultry are excluded	NA
Chiang, 2013 [13]	China	391/315	Age	56.4 (8.4)	0%	23.3 (3.0)	NA	LOV: consumption of a LOV diet at all meals daily and persistently for at least one year	NA
Pettersen, 2012 [75]	USA	302/198	None	67.6 (11.6)	36%	NA	Adventist	SV: consumption of meat and fish less than once a month.	NA
Crowe, 2013 [76]	UK	230/1316	Age, sex	44.4 (13.7)	52.8%	23.6 (3.7)	NA	V: meat and fish are excluded.	Consumption of meat and/or fish
Jung, 2013 [16]	Korea	148/148	Age, sex	52.9 (9.3)	53.4%	24.1 (3.5)	Buddhist	LOV: NA	NA
Vinagre J, 2013 [77]	Brazil	21/29	None	36.2 (9.4)	56.0%	23.3 (2.1)	NA	V: consumption of dairy products and eggs. Animal products are excluded	No meat restrictions

Yadav D, 2013 [78]	India	1096/431	None	NA	57.0%	NA	NA	LOV: NA	NA
Zhang H, 2013 [79]	China	170/126	None	33.2 (10.4)	100.0%	23.9 (3.5)	Buddhist	LOV: consumption of plant foods, milk, and eggs. Meat, poultry and fish are excluded.	No restrictions
Bradbury, 2014 [80]	UK	503/168	None	NA	NA	23.0 (3.3)	NA	V: meat, fish, dairy products, and eggs are excluded; LOV: consumption of dairy products and/or eggs. Meat and fish are excluded; PV: consumption of fish but no meat.	Consumption of meat
Lee, 2014 [81]	Korea	357/357	Age, sex	53.3 (8.6)	42.9%	24.3 (3.2)	Buddhist	LOV: Consumption of dairy products, large amounts of vegetables, fruit, legumes, nuts, grain, and soya protein-food components. Meat, fish and eggs are excluded.	NA
Shridhar K, 2014 [82]	India	2148/4407	None	40.9 (10.3)	58.0%	23.9 (4.5)	NA	SV: consumption of eggs, meat, fish and poultry	NA
Jian Z.H, 2015 [83]	Taiwan	339/6469	Gender, age, exercise, WHR, BP, fasting plasma glucose, uric acid, creatinine	43.4 (17.1)	47.8%	NA	NA	V: Excluded eggs, milk, meat, poultry, seafood and byproducts of animals. LOV: excluded all meat and fish but included eggs and dairy products, for a period of 1 year	NA
Chiu Y.F, 2015 [84]	Taiwan	8183/40, 915	Age, sex, study site	48.9 (14.4)	25.0%	NA	NA	V: NA	NA
Choi S.H, 2015 [85]	Taiwan	615/615	age, gender	48.3 (9.8)	39%	23.9 (3.1)	Buddhist Priests	V: not eat meat and fish but eat vegetarian meals following the Buddhist lessons and eat fruits, vegetables, nuts, and soybean protein foods instead	NA
Patil S, 2015 [86]	India	75/75	None	37.5 (10.6)	46.7%	NA	NA	LOV: Vegetable based diet. Milk and dairy products were considered.	NA
Kuchta A, 2016 [87]	Poland	21/21	None	28 (4.5)	40.5%	21.7 (2.1)	NA	V: Exclude meat, dairy products and eggs from their diet.	Eat plant and animal origin.
Lee YJ, 2016 [88]	Taiwan	54/100	None	60.3 (11.3)	39.6%	25.9 (5.9)	NA	LOV: Consuming dairy products and eggs at least from their diet.	NA
Acosta Navarro, 2017 [89]	Brazil	44/44	None	46.15 (8.7)	100%	25.25 (4.5)	NA	SV: Void of meat, fish, and poultry for at least 4 years. They could be Lacto-Ovo (consuming egg and milk and dairy products) or vegans (consuming no eggs or milk and dairy products)	Consuming any type of meat at least five or more servings by week.

Abbreviations: SD, standard deviation; NA, not available; BMI, body mass index; LOV, lacto-ovo-vegetarian; V, vegan; PV, fish-vegetarian; SV, semi-vegetarian; VD, vegetarian diet; OD, omnivorous diet; WHR, waist-to-hip ratio; BP, blood pressure.

40,42,43,45,46,48–55,57,58,60–63,65–69,71–74,77–79,81,82,84–86,88,89], five RCTs [14,25–28] and cohorts [29,30]), HDL-C (45 cross-sectional studies [13,15,16,32,33,35,37,38,40,43,45,49,51–55,57,58,60–64,66,67,69,71–74,76–89], four RCTs [14,26–28] and two cohorts [29,30]), blood pressure (42 cross-sectional studies [12,13,15,16,31,32,34,36,38,39,41,43,44,46,48,52,54,55,57,58,60,62–65,67–76,79,81–84,87,89] and four RCTs [14,26–28]), and fasting glucose (29 cross-sectional studies [13,15,38,42,43,48,55,57–60,62–64,66,68,69,71,73,74,77,79,81–85,88,89] and three RCTs [24,26,28]).

3.3. Risk of bias of included studies

Risk of bias of RCTs is presented in Suppl. Fig. 1. The six included studies were at high risk of bias. Performance and attrition bias were reported. The two included cohort studies had a high risk of bias; both studies had adequate a representativeness of the exposed cohort, ascertainment of exposure, and assessment of the outcomes (Suppl. Fig. 2). Among the cross-sectional studies, 44 studies had a high risk of bias [12,13,15,16,31–34,36,37,39,41–43,46–48,51–54,56–58,60–62,64–66,68,69,72–75,78,79,81,82,85–88] and 19 studies had a low risk of bias [35,36,38,40,44,45,49,50,55,59,63,67,70,71,76,77,80,83,89]. Most of the cross-sectional studies (93%) presented a clear research question and recruited subjects from similar populations (68%) (Suppl. Fig. 3). However, only 19% of the studies examined different levels of exposure and 59% of included studies did not adjust their results for potential confounding variables. The blinding of outcome assessors was not reported in 75% of the cross-sectional studies. Additional details of the risk of bias are provided in Supplementary Tables 1–3.

3.4. Association between VD and MetS

In five cross-sectional studies ($n = 2282$), VD was not associated with MetS when compared with omnivorous diet (OR 0.96, 95% CI 0.50–1.85, $p = 0.9$) (Fig. 2). Heterogeneity of effects among studies was high ($I^2 = 85\%$, $p < 0.00001$). Additionally, all of the studies reported high risk of bias. No RCTs or cohort studies reported the effect of the association between VS and MetS.

3.5. Association between VD and components of the MetS

In four RCTs ($n = 596$), VD was associated with non-significant lower SBP in comparison with omnivorous diet (MD −0.12 mmHg, 95% CI −1.12 to 0.88, $p = 0.81$) (Fig. 3). There was no evidence of heterogeneity of effects among studies ($I^2 = 0\%$, $p = 0.69$). In 42 cross-sectional studies ($n = 83,943$), VD was associated with significant lower SBP in comparison with omnivorous diet (MD −4.18 mmHg, 95% CI −5.57 to −2.80, $p < 0.00001$). Heterogeneity of effects was high among these studies ($I^2 = 90\%$, $p < 0.00001$). No cohort studies were identified. The funnel plot did not show asymmetry (Suppl. Fig. 4).

In four RCTs ($n = 596$) VD was associated with non-significant higher DBP in comparison with omnivorous diet (MD 0.09 mmHg, 95% CI −1.12 to 1.30, $p = 0.88$) (Fig. 4). There was no evidence of heterogeneity of effects among studies ($I^2 = 0\%$, $p = 0.56$). In 42 cross-sectional studies ($n = 83,943$), VD was associated with significant lower DBP in comparison with omnivorous diet (MD −3.03 mmHg, 95% CI −4.93 to −1.13, $p = 0.002$). Results reported high heterogeneity of effects among included studies ($I^2 = 98\%$, $p < 0.00001$). No cohort studies were identified. The funnel plot did not show asymmetry (Suppl. Fig. 5).

In three RCTs ($n = 212$) VD was associated with non-significant lower fasting glucose levels in comparison with omnivorous diet (MD −0.59 mmol/L, 95% CI −1.36 to 0.18, $p = 0.13$) (Fig. 5). There was no evidence of heterogeneity of effects among studies ($I^2 = 0\%$, $p = 0.97$). In 29 cross-sectional studies ($n = 68,763$), VD was associated with significant lower fasting glucose in comparison with omnivorous diet (MD −0.26 mmol/L, 95% CI −0.35 to −0.17, $p < 0.00001$). There was evidence of high heterogeneity of effects among these studies ($I^2 = 88\%$, $p < 0.00001$). No cohort studies were identified. The funnel plot did not show asymmetry (Suppl. Fig. 6).

In five RCTs ($n = 689$) VD was associated with non-significant higher triglyceride levels in comparison with omnivorous diet (MD 0.11 mmol/L, 95% CI −0.10 to 0.31, $p = 0.30$) (Fig. 6). There was no evidence of heterogeneity of effects among studies ($I^2 = 0\%$, $p = 0.94$). In two cohorts ($n = 352$), VD was associated with non-significant higher triglycerides in comparison with omnivorous diet (MD 0.06 mmol/L, 95% CI −0.22 to 0.35, $p = 0.66$). There was no evidence of heterogeneity of effects among studies ($I^2 = 0\%$, $p = 0.97$). In 45 cross-sectional studies ($n = 70,733$), VD was associated with non-significant higher triglycerides in comparison with omnivorous diet (MD 0.04 mmol/L, 95% CI −0.09 to 0.18, $p < 0.51$). There was high heterogeneity of effects among these studies ($I^2 = 99\%$, $p < 0.00001$). The funnel plot did not show asymmetry (Suppl. Fig. 7).

In three RCTs ($n = 305$) VD was associated with non-significant lower WC in comparison with omnivorous diet (MD −0.41 cm, 95% CI −1.67 to 0.85, $p = 0.53$). In 15 cross-sectional studies ($n = 62,476$),

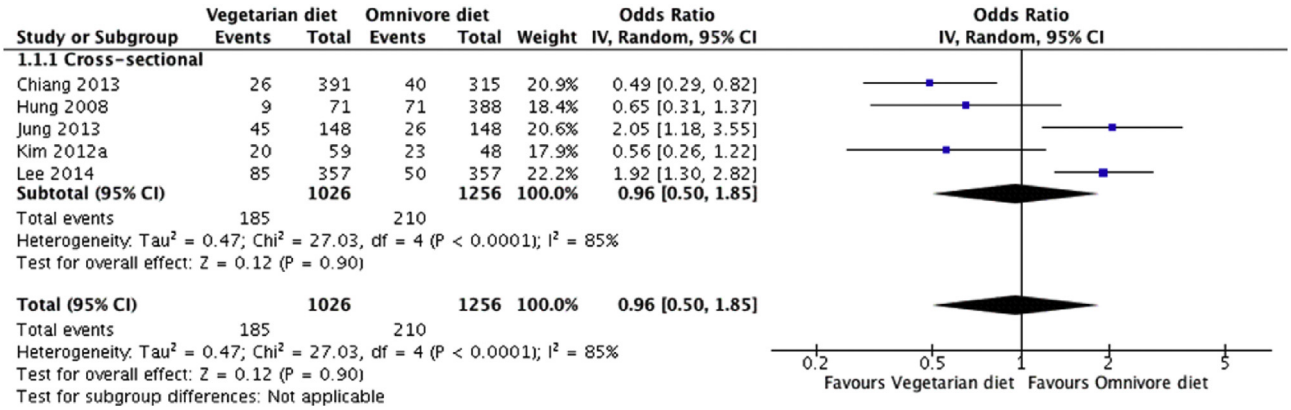

Fig. 2. Association between vegetarian diet and Metabolic Syndrome.

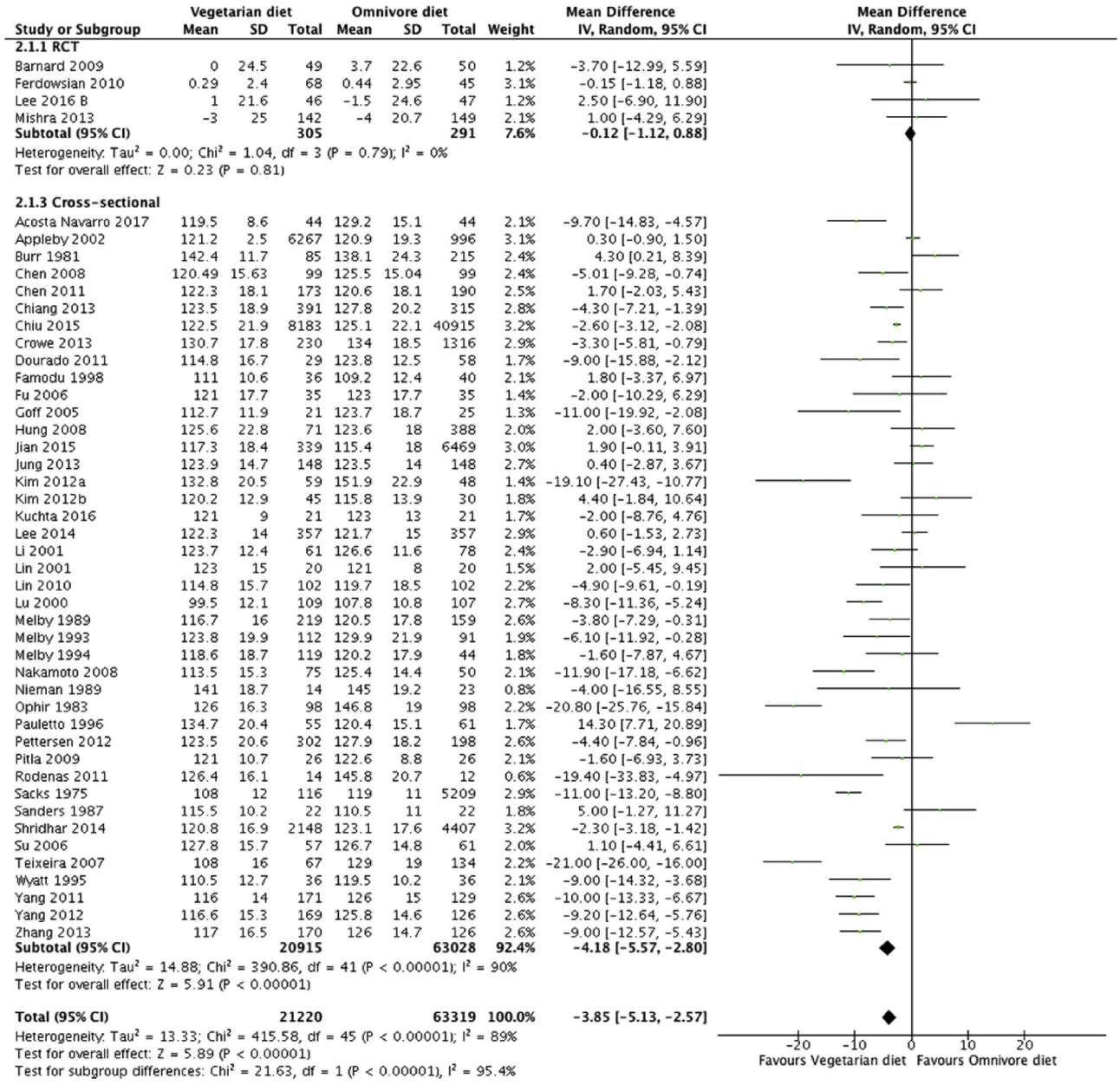

Fig. 3. Association between vegetarian diet and systolic blood pressure.

VD was associated with significant lower WC in comparison with omnivorous diet (MD −1.63 cm, 95% CI −3.13 to −0.13, $p = 0.03$) (Fig. 7). There was high heterogeneity of effects among these studies ($I^2 = 89\%$, $p < 0.00001$). No cohort studies were identified. The funnel plot did not show asymmetry (Suppl. Fig. 8).

In four RCTs ($n = 596$) VD was associated with non-significant lower HDL-C in comparison with omnivorous diet (MD −0.06 mmol/L, 95% CI −0.17 to 0.04, $p = 0.22$) (Fig. 8). There was no evidence of heterogeneity of effects among studies ($I^2 = 0\%$, $p = 0.55$). In two cohorts ($n = 352$), VD was associated with non-significant higher HDL-C in comparison with omnivorous diet (MD 0.16 mmol/L, 95% CI −0.24 to 0.55, $p = 0.44$). There was high heterogeneity of effects among these studies ($I^2 = 91\%$, $p = 0.001$). In 45 cross-sectional studies ($n = 79{,}019$), VD was associated with significant lower HDL-C in comparison with omnivorous diet (MD −0.05 mmol/L, 95% CI −0.07 to −0.03, $p < 0.0001$). There was evidence of high heterogeneity of effects among these studies ($I^2 = 87\%$, $p < 0.00001$). The funnel plot did not show asymmetry (Suppl. Fig. 9).

3.6. Subgroup analyses

In subgroup analyses of cross-sectional studies by year of publication and risk of bias we found significant lower SBP (Suppl. Figs. 10 and 11) and DBP (Suppl. Figs. 12 and 13) in VD in comparison with omnivorous diet, except for cross-sectional studies published before 2001. Subgroup analysis results showed significant lower HDL-C in VD in comparison with omnivorous diet,

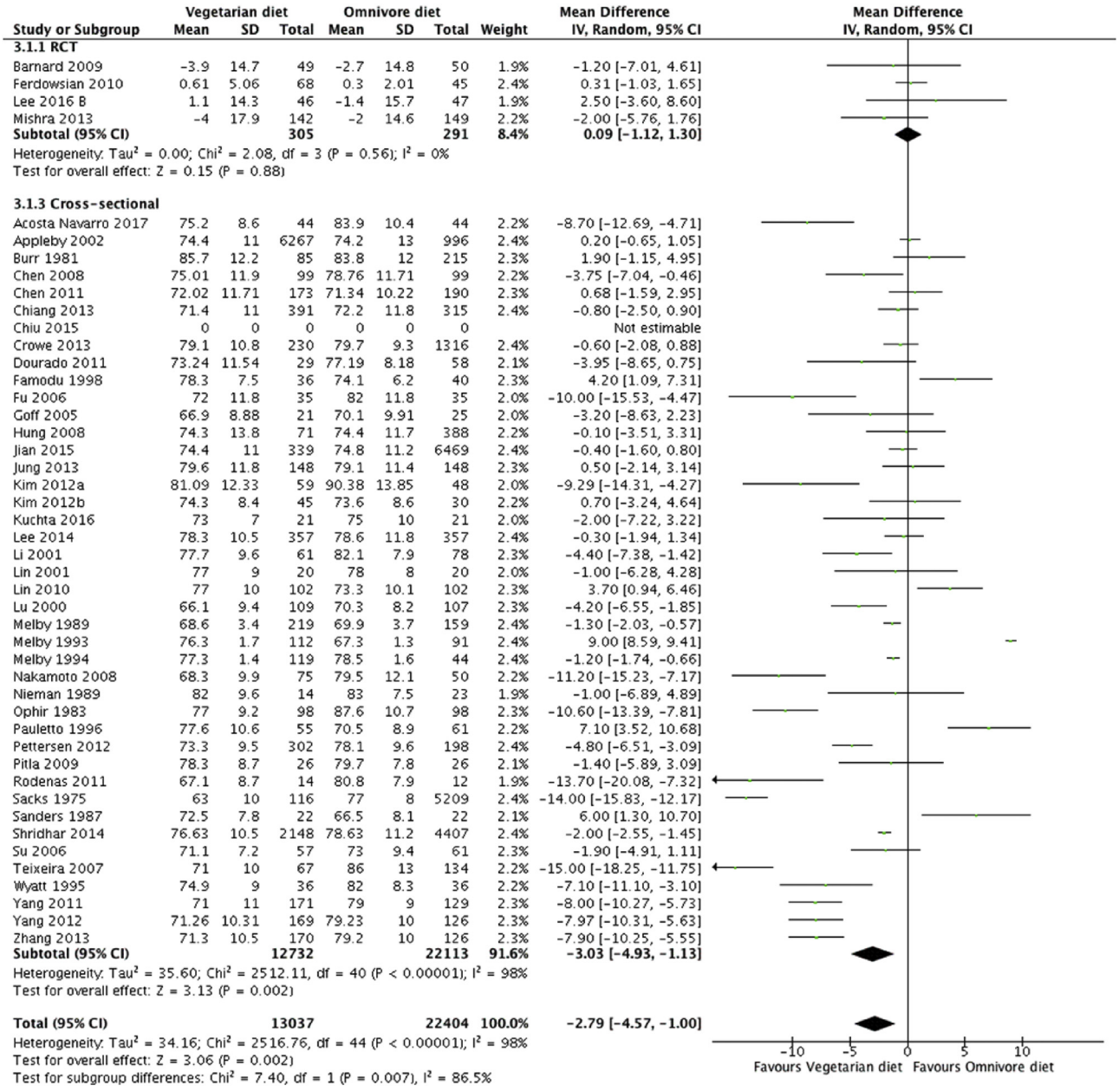

Fig. 4. Association between vegetarian diet and diastolic blood pressure.

only in studies with low risk of bias (Suppl. Fig. 14). Heterogeneity was maintained in subgroup analysis of cross-sectional studies assessing SBP, DBP, triglyceride levels, and decreased in studies evaluating fasting glucose, WC and HDL-C. Sub-group analyses were performed in cross-sectional studies only due to the small number of included RCTs and cohort studies. Of note, results of subgroup analysis are likely to be biased because of the high risk of bias and severe methodological limitations in the cross-sectional studies.

4. Discussion

Our meta-analysis found that the consumption of VD was not associated with MetS when compared with consumption of omnivorous diets. Likewise, meta-analysis of RCTs and cohort studies indicated that consumption of VD were not associated with MetS components when compared with consumption of omnivorous diets. However, meta-analyses of cross-sectional studies showed that the consumption of VD was associated with significant lower levels of systolic and diastolic blood pressure, fasting glucose, WC, and HDL-C. Results showed no significant effects of VD on triglycerides. Heterogeneity of effects among studies was high, and was maintained in most of the subgroup analysis performed. Furthermore, most of the data synthesized in our systematic review are sourced from cross-sectional studies, of which one-half of the studies reported high risk of bias.

Although, a meta-analysis on the efficacy of VD in MetS components has been published, to our knowledge, our meta-analysis is

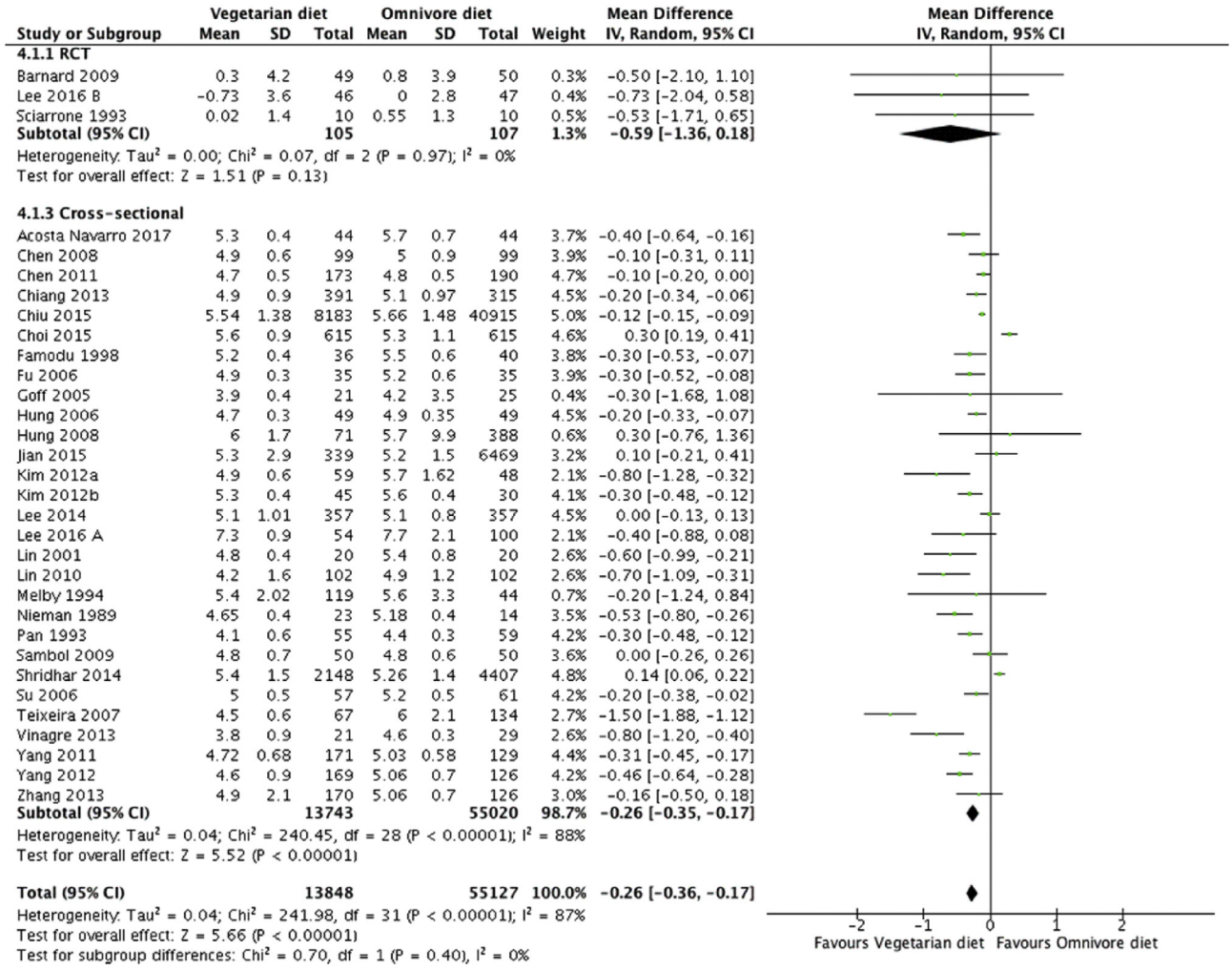

Fig. 5. Association between vegetarian diet and fasting glucose.

a first-of-its-kind that evaluates the effect of VD on the risk of MetS. A previous meta-analysis [90] of RCTs and observational studies suggested evidence of an association between VD (lacto-ovo-vegetarian diet, vegan diet or semi-vegetarian diet) and lower levels of SBP and DBP. Findings from our study corroborate these earlier study results. However, contrary to our results, the earlier meta-analysis did not show an association between VD and lower levels of fasting glucose. Likewise, the meta-analysis of Yokoyama et al. [91] suggests no association between VD (lacto-ovo-vegetarian diet and vegan diet) and the fasting glucose (−0.36 mmol/L; 95% CI, −1.04 to 0.32; $P = 0.301$; $I^2 = 0$; P for heterogeneity = 0.710). The meta-analysis of Yokoyama et al. [91] suggests no association between VD and HDL-C and triglyceride blood levels. Similarly, Zhang et al. [92] showed no effects of VD on levels of HDL-C in a meta-analysis of observational studies, and Wang et al. [93], showed non-significant effect of VD on triglycerides, but a significant lowering effect on the concentrations of blood HDL-C in adults diagnosed with dyslipidemia. Differences in the study eligibility criteria in earlier meta-analyses and our meta-analysis may account for the discordance in these results. An item of differentiation from earlier studies is the evaluation of an association between VD and WC in our study.

The results of our study showed that only meta-analyses of cross-sectional studies had a significant association between the consumption of VD and lower levels of MetS components, with an exception of blood triglycerides. In this context, a review of studies assessing the effects of different type of diets in MetS biomarkers showed that plant-based diets, including vegan diets and ovo-lacto vegetarian, are associated with a reduced risk of MetS, except for its effect on HDL-C and, in some cases, triglycerides blood levels [94]. A few studies measuring the effects of vegetarian diets on MetS reported higher levels of triglycerides in the vegetarian population; findings from these studies highlight the need for caution with regards to the intake of fructose and other simple carbohydrates [84,94]. Results show that VD is associated with a significant decrease in HDL-C. The decrease in HDL-C levels does not contribute to the beneficial effect of these diets on health and, in the long term, it may harm cardiovascular health [95]. Therefore, an appropriate dietary counseling and management is needed for vegetarian individuals to avoid a decrease of HDL-C, a potential increase of serum triglyceride levels, and for the benefit of VD in all aspects of the metabolic profile.

Our meta-analysis showed a non-significant association between VD and MetS. Only cross-sectional studies evaluating an

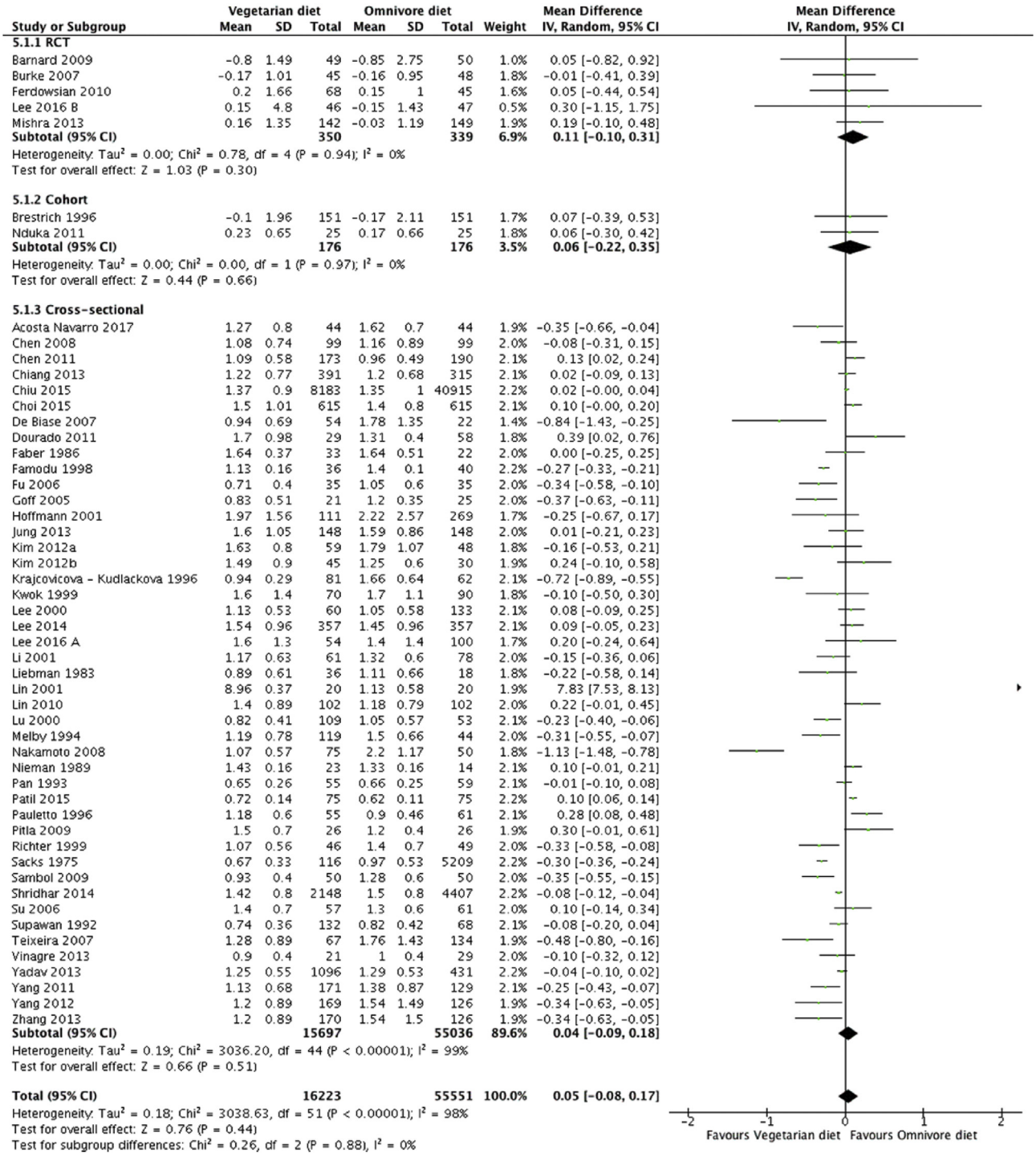

Fig. 6. Association between vegetarian diet and triglycerides.

association between these two variables were found. Few cross sectional studies suggest that VD are associated with a lower risk of MetS when compared with an omnivorous diet [11,13], while few other studies have suggested the opposite effect [16,81]. One plausible reason for these discrepant findings may be the usage of different diagnostic criteria for MetS (ATP III and IDF). Two previous studies [16,81] have used the ATP III, which includes different criteria for WC from the Regional Office for the Western Pacific Region of the World Health Organization (WPRO). The study of Kim and Bae [73] defined MetS according to the ATP III criteria, but applied the Korean guideline for WC. In contrast, the study of Hung et al. [64] was based

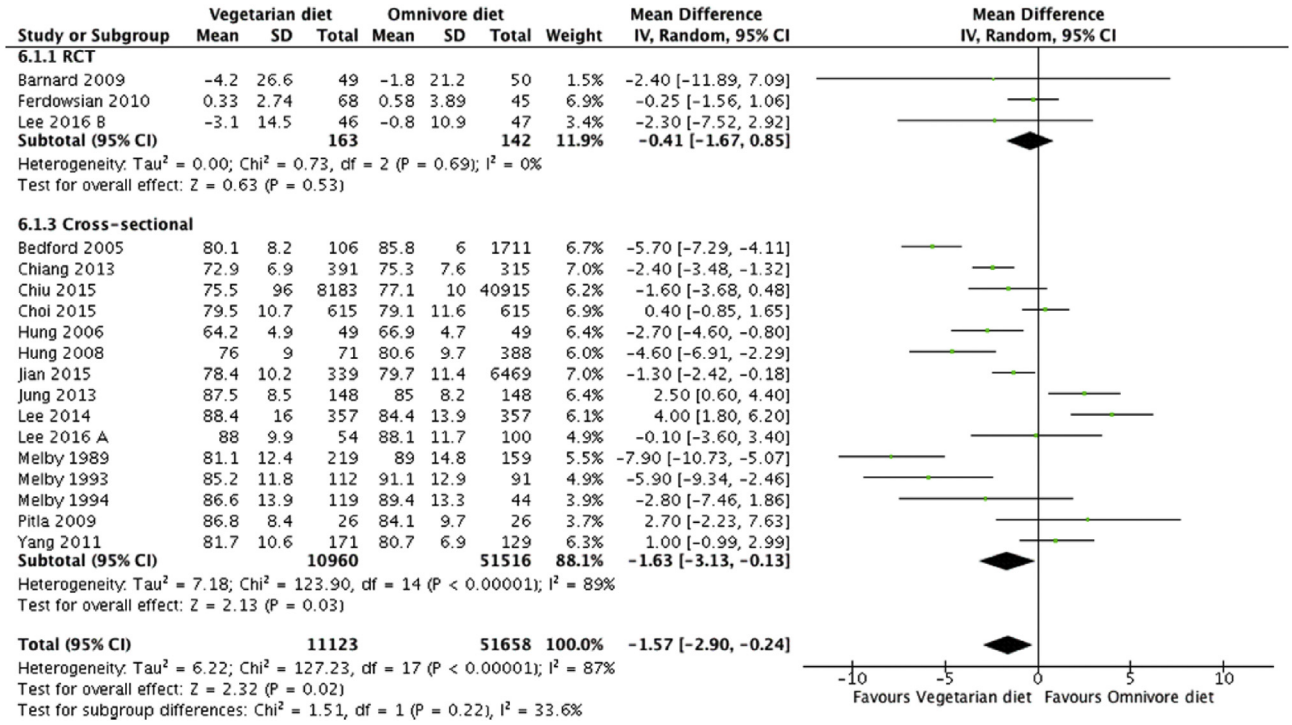

Fig. 7. Association between vegetarian diet and waist circumference.

on the values recommended by the IDF for diagnosing MetS. The study of Chiang et al. [13] used definitions based on both the IDF criteria and the ATP III modified for Asians. The use of different diagnostic criteria for MetS and the low methodological quality of studies are limitations that should be taken into account when interpreting the results of the association between VD and MetS.

It is important to note that the results favor an improvement in MetS components independently, whereas, in studies measuring all the components of MetS together, there is no difference between the two diets. Data from different pools of studies in the Mets variable versus Mets components may partially account for this discrepancy. Also, recent recommendations from literature reviews suggest inclusion of more biomarkers in the diagnosis of MetS [94,96]. These recommendations should be taken into account when interpreting the results.

This is study has several limitations. First, most of the included studies have a cross-sectional design, thus causality between VD and MetS or its components cannot be concluded. In our study, associations between VD and reductions in MetS components were only observed in the meta-analyses of cross-sectional studies. Because of the low quality of evidence and the methodological limitations that characterizes cross-sectional studies, these results should be considered with caution. Second, most of the cross-sectional studies did not adjust their effects for possible cofounders, and therefore there is an increased risk of bias in cross-sectional studies. This is the main limitation in our study. Third, heterogeneity among studies was high, regardless of the study design and subgroup analyses. Possible reasons for heterogeneity include heterogeneous geographical populations, sample size, composition of VD, and health status of participants, among others. Fourth, time of adherence to the diet was not taken into account in the present study, as this information was reported inconsistently throughout studies. Fifth, we could not perform subgroup analysis by type of VD to explore the effect of different type of VD in MetS and its components, due to lack of homogeneity among outcomes. Sixth, composition of VD is unknown in some studies or varies among studies due to the inclusion of datasets from United States, Europe, and various Asian countries, and therefore there is variability in the intervention. Moreover, half of the included studies have high risk of bias; therefore, the quality of evidence is low. Finally, the number of RCTs and cohort studies included for meta-analysis was low. Only one meta-analysis was carried out with four studies, while the others included two or three studies.

In conclusion, VD were not associated with a lower presentation of MetS in comparison to omnivorous diets, based on the meta-analysis of cross-sectional studies. VD were associated with lower levels of SBP, DBP, HDL-C, and fasting glucose in meta-analysis of cross-sectional studies; however, these results are not conclusive due to high heterogeneity and severe methodological limitations found in the included studies. Given most of the studies are cross sectional, large prospective and controlled studies are needed to assess the association between VD and MetS and its components. Moreover, future prospective studies should adjust their results by important cofounders and time of adherence to the diets.

Statement of authorship

The author's responsibilities were as follows – MCP, JAL, JMR, and AVH participated in the conception and design of the project; MCP, JAL, JMR and VP contributed to the study

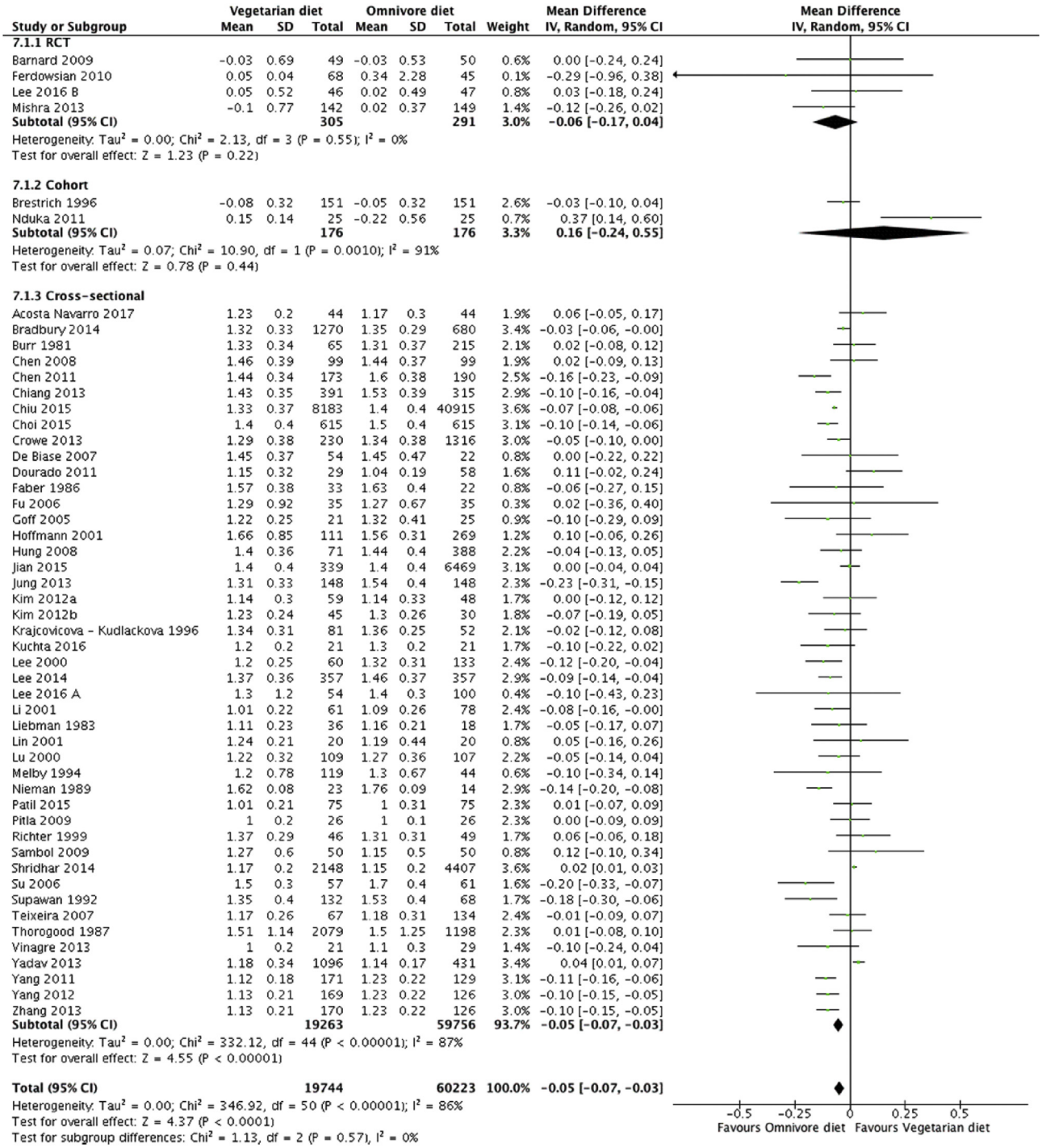

Fig. 8. Association between vegetarian diet and HDL-cholesterol.

selection, data extraction and risk of bias assessment; all authors conducted the statistical analyses; MCP, JAL and JMR contributed in the drafting of manuscript; all authors took part in the writing and final review of the manuscript; and AVH led study supervision.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.05.021.

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