

# Dietary inflammatory index significantly affects lipids profile among adults: An updated systematic review and meta-analysis

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**Abstract:** *Background:* The available data on the relationship between dietary inflammatory index (DII<sup>®</sup>) and serum lipids are controversial. This systematic review and meta-analysis aimed to investigate the relationship between DII<sup>®</sup> and serum lipids, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) in general populations. *Methods:* PubMed, Web of Science, SCOPUS, and Cochrane electronic databases were systematically searched from inception to December 2019. Case-control, cohort or cross-sectional studies that evaluated the relationship between DII<sup>®</sup> and serum lipids were included. The random-effects model was applied to evaluate the pooled weighted mean difference (WMD) and 95% confidence intervals (CI). *Results:* In total, twenty-four cross-sectional and one case-control studies with a total sample size of 129,759 were included in the meta-analysis. The pooled results showed that the highest category of DII<sup>®</sup> was associated with 5.16 mg/dl increase in TC (Pooled WMD: 5.16; 95% CI: 0.58–9.73,  $p = 0.02$ ) and 3.99 mg/dl increase in LDL-C (Pooled WMD: 3.99; 95% CI: 1.16–6.81,  $p = 0.006$ ). However, no significant association between DII<sup>®</sup> scores, HDL-C and TG was found. In subgroup analysis, the geographical region, gender, and dietary assessment methods were potent sources of heterogeneity. *Conclusion:* This study showed that a higher level of DII<sup>®</sup> was associated with higher levels of TC and LDL-C in apparently healthy populations. Since the included studies had observational designs, therefore, no conclusion of causality was possible. More studies with interventional designs are required to elucidate the causality of the observed association between DII<sup>®</sup> and the risk of abnormal lipid profile.

**Keywords:** Dietary inflammatory index, serum lipid profile, cardio-metabolic risk factors, meta-analysis

## Introduction

Dyslipidemia, defined as abnormal lipid profiles including high levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL-C) and low high-density lipoprotein-cholesterol (HDL-C) concentrations, is associated with adverse health consequences including atherosclerosis, stroke, cardiovascular diseases (CVD), and coronary heart disease (CHD) [1]. The majority of lipid disorders are associated with poor dietary behaviors [2]. Therefore, dietary modification is one of the most important therapeutic strategies to combat against dyslipidemia. Several studies have revealed the effectiveness of dietary changes and life-style interventions in reducing CVD risk factors [3, 4].

It has been reported that dietary patterns might be better predictors of disease risk rather than individual food items [5, 6]. The nutrient and food items action in combination with each other in a usual diet is different from their isolate

action [7]; numerous studies have revealed that chronic and continuous inflammation is related to adverse health outcomes such as cancer, obesity, hypertension, metabolic syndrome, CVD, and mortality [8–10]. Several indices have been developed to investigate the inflammatory properties of diet such as adapted Mediterranean Diet Score (MDS), Inflammatory Score of the Diet (ISD), Empirically Derived Inflammatory Pattern (EDIP) and dietary inflammatory index (DII<sup>®</sup>) [11, 12]. DII<sup>®</sup> is a priori-defined dietary pattern with 45 components (36 anti-inflammatory food items and 9 pro-inflammatory food items), while empirical dietary inflammatory pattern (EDIP) is a posteriori index developed based on prospective data with 18 components (9 anti-inflammatory food items, 9 pro-inflammatory food items). Also, EDIP uses foods or food groups instead of nutrients, and its direct association with three inflammatory markers, including C-reactive protein (CRP), tumor necrosis factor alpha receptor (TNFaR)-2, and interleukin (IL)-6

has been established [13]. Indeed, DII® was developed to assess the overall pro-inflammatory and anti-inflammatory potential of diet [14, 15]. DII® is derived from 1,943 peer-reviewed researches and evaluates whether dietary quality has a negative or positive impact on inflammatory status of body by predicting the levels of inflammatory parameters, such as TNF- $\alpha$ , CRP, IL-6, IL-1 $\beta$ , IL-4, and IL-10 [14]. Numerous studies have been published that evaluated the relationship between DII® and several diseases, such as cancers [16–20], CVD [21, 22], obesity [23], and even mortality [24–26]. Several studies reported the relations between DII® and the risk of dyslipidemia [27], elevated serum TG and LDL-C levels [28], low HDL-C level [29], and hypercholesterolemia [30]; however, there are inconsistencies in the results of other studies regarding the association between DII® and lipids [31–33]. Moreover, to our knowledge, there is no summarized systematic review and meta-analysis study that evaluated the association between DII® and serum lipids in general population. Therefore, in the present systematic review and meta-analysis, we summarized the results of all studies that examined the relationship between DII® and serum lipids including TC, HDL-C, LDL-C, and TG.

## Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to perform and report the results of the current study [34] [Table E1 in Electronic Supplementary Material 1 (ESM 1)]. The protocol of the present systematic review and meta-analysis has also been approved and registered in the ethics committee of Tabriz University of Medical Sciences (identifier: IR.TBZMED.VCR.REC.1397.298).

### Search strategy

To identify relevant studies on the association between DII® and lipid profile, electronic databases including Web of Sciences, PubMed, Cochrane and Scopus were searched without language restriction from inception to December 2019. Moreover, references of the retrieved studies were manually screened to find additional articles. The literature was searched using a combination of the MeSH (Medical Subject Headings) and free-text terms from the PubMed database (Table E2 in ESM 1). The PICOs components (participants, intervention, comparison, and outcome) for the present study are summarized in Table E3 in ESM 1. The protocol was registered in the International prospective

register of systematic reviews (PROSPERO; Identifier: CRD42018110588).

### Inclusion criteria

In the present systematic review and meta-analysis, observational studies with case-control, cohort, or cross-sectional designs that evaluated the relationship between dietary DII® and serum lipids were included. Observational studies with apparently healthy participants of more than 18 years old were included. The studies that evaluated the relationship between DII® and chronic kidney disease, cancers, multiple sclerosis, and diabetes mellitus or gestational diabetes mellitus were excluded. Moreover, we excluded studies among children, adolescents and pregnant women. To be included in the current meta-analysis, the study must have reported the mean  $\pm$  standard deviation (SD) of continuous variables, or relative risk (RR), odds ratio (OR) along with 95% confidence intervals or prevalence of abnormal serum lipids in highest DII® category (pro-inflammatory diet) compared with the lowest DII® (anti-inflammatory diet) as the reference group. The retrieved articles were uploaded into EndNote software (version X8, for Windows, Thomson Reuters, Philadelphia, PA, USA), and duplications were removed. Accordingly, titles and abstracts of all studies had been assessed independently by two authors (MAF and MV). Studies that did not meet the inclusion criteria were excluded. Full texts of potentially relevant studies were retrieved and were examined to identify any additional relevant studies. Any discrepancies were discussed and resolved through consensus and discussion with third investigator (MM).

### Data collection and extraction

Data extraction from all studies that met the inclusion criteria was carried out independently by two researchers (MAF and MV) using a predefined extraction form. The following information was extracted from the included studies: publication year, first author's name, geographical area, study design, the mean age of the participants, number of case and controls, diet assessment, sample size, setting, gender, and adjusted covariate. Any discrepancies between the two researchers were resolved by discussion.

### Quality assessment

The quality assessment of the relevant included studies was performed by the Newcastle-Ottawa scale (NOS) adopted for cohort and cross-sectional studies [35]. The 9-point NOS scale has scoring ranges from 0 to 9. Studies with  $\geq 7$  scores were categorized as high quality.

## Data synthesis and analysis

In the present study, the ORs and 95% confidence intervals for the odds of having higher serum lipid in the highest DII<sup>®</sup> category compared with the lowest DII<sup>®</sup> category were used. The Ln of ORs and its standard error (s.e.) as the effect size were estimated. The random-effects model was applied to achieve the overall effect sizes. Pooled OR and 95% confidence interval (CI) was estimated using a weighted random-effects model (the DerSimonian-Laird approach). Subgroup analysis was conducted to identify possible sources of heterogeneity if required. To investigate the heterogeneity of pooled effect sizes, I-squared test and Cochran's Q test was used;  $I^2 < 25\%$ , no heterogeneity;  $I^2 > 50\%$  large heterogeneity;  $I^2 = 25\text{--}50\%$ , moderate heterogeneity [36]. The heterogeneity was considered significant if either the Q statistic had p value less than 0.1 or  $I^2$  was greater than 50%. Sensitivity analysis was used to identify the robustness of our results. Funnel plots along with Egger's and Begg's tests were used to evaluate the publication bias. Meta-analysis was performed using the STATA version 12 (STATA Corp, College Station, TX, USA), and *p*-values less than 0.05 were considered as statistically significant.

## Results

### Study selection

The flow chart of the study selection is shown in Figure 1. Totally, 10,860 studies were retrieved; after removing of 779 duplicates, 10,081 studies remained. Then, 9,862 irrelevant articles were excluded based on the title and abstract screening. In the next step, the remained 219 relevant articles were selected for the evaluation of full-texts. Finally, from the remained 219 studies, 34 eligible studies were included in the systematic review [7, 27–33, 37–62] while only 25 studies were included in our meta-analysis [29, 32, 33, 37, 39, 40, 42, 44–60, 62].

### Study characteristics

The characteristics of the included studies are presented in Table 1. From those studies, two studies had cohort design [7, 31], thirty-one had cross-sectional design [27–30, 32, 33, 37–56, 58–62], and one had case-control design [57]. These studies were published between 2013 and 2019, and the sample size varied from 50 to 70,991 participants with an overall number of 232,846 participants. Thirty studies included combination of both genders, while four studies included only female or male subjects [31, 41, 45, 46]. Most

of the included studies were conducted in USA [29, 31, 51, 52, 58, 62] and Iran [28, 32, 38, 49, 50, 53]. The remaining studies were performed in Spain [7, 46, 61], Italy [27], Korea [44, 48, 54], Brazil [42, 43], France [41, 60], China [39], Poland [40], Scotland [30], Sweden [45], Ireland [37], Indonesia [47], Australia [59], Mexico [55], Lebanon [56], Colombia [57], and Luxembourg [33].

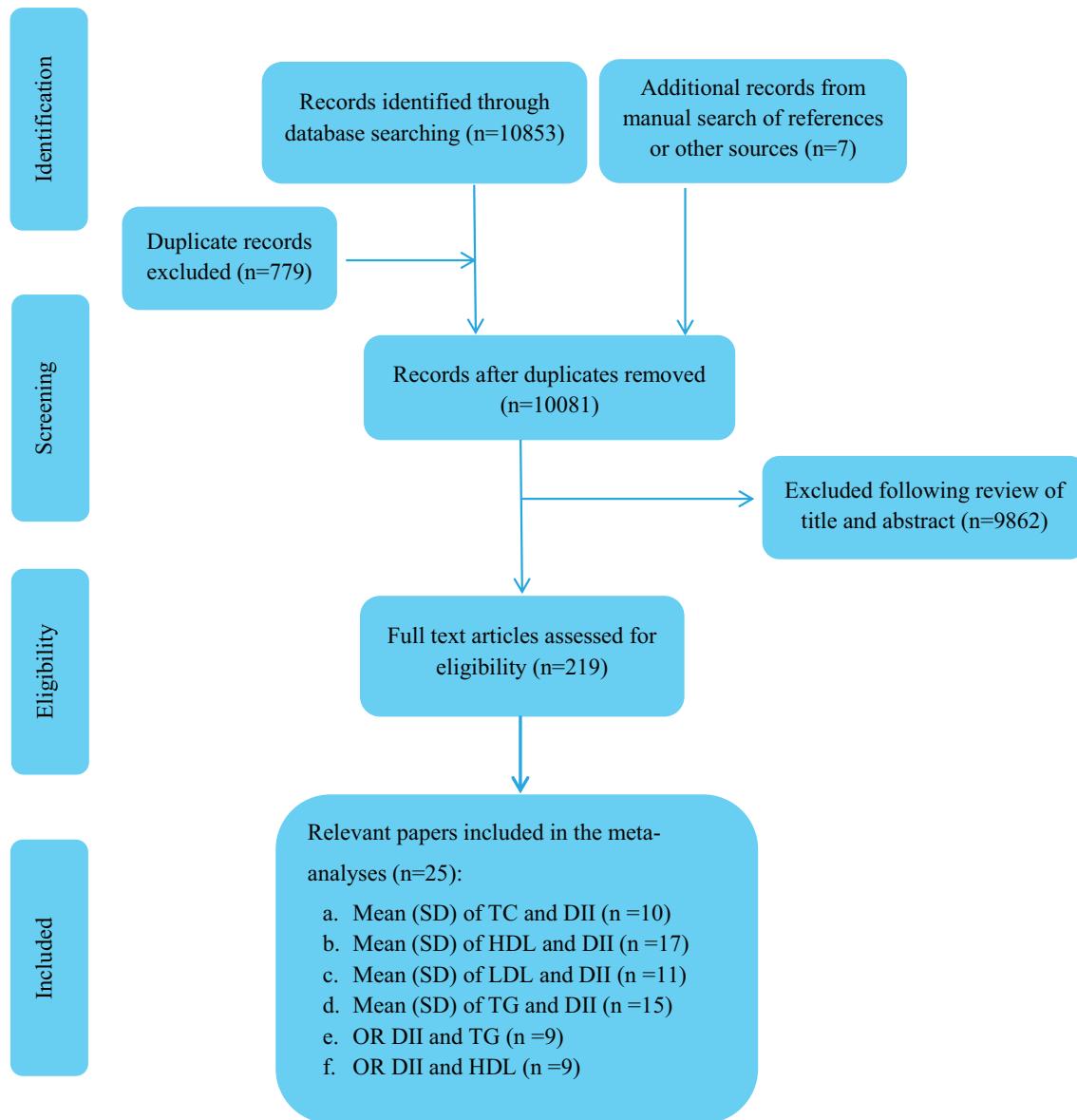
Among those studies ( $n = 34$ ) that have examined the association between lipid profile (TC or HDL-C or LDL-C or TG) and DII<sup>®</sup>, nineteen studies reported no significant difference between serum lipids or no difference in the prevalence of dyslipidemia across different DII<sup>®</sup> categories [7, 27, 31, 32, 39, 42, 43, 45–49, 52–54, 56, 58, 59, 61]. Sokol et al. [40] reported a negative association between the OR of low HDL-C and DII<sup>®</sup> only among women. Shivappa et al. [51] found a higher prevalence of hypercholesterolemia among subjects in the lowest tertiles of DII<sup>®</sup> in subjects without metabolic syndrome; Park et al. [52] reported higher TG and lower HDL-C in subjects of the lowest quartile of DII<sup>®</sup> among metabolically healthy and unhealthy overweight or obese adults.

Alkerwi et al. [33] found that the prevalence of high TG or low HDL-C concentrations between tertiles of DII<sup>®</sup> was not significantly different while the odds ratio of having low HDL-C concentrations was observed in the top tertile of DII<sup>®</sup>. Na et al. [44] reported higher TG and lower HDL-C concentrations in the highest quartile of DII<sup>®</sup> versus lowest quartile of it. Corley et al. [30] reported a significant difference in hypercholesterolemia between different tertiles of DII<sup>®</sup>. Among the included studies, higher TG, TC or LDL-C and lower HDL-C concentrations were reported in the highest DII<sup>®</sup> category in nine studies [28, 29, 37, 38, 50, 55, 57, 60, 62]. Additionally, the NOS scores of all included studies ranged from 6 to 9 points, and 33 studies had a score of 7 or above (Table 1).

### Meta-analyses results

#### Results from the meta-analysis of mean TC, HDL-C, LDL-C, and TG across different DII<sup>®</sup> categories

In the comparison of the TC between DII<sup>®</sup> categories, a total of 10 studies were included [33, 42, 44, 46, 49, 51, 55, 57, 59, 60]. Figure 2 shows the Forest plot of the included studies. The results showed that the highest category of DII<sup>®</sup> was associated with a 5.16 mg/dl increase in TC (Pooled weighted mean difference [WMD]: 5.16; 95% CI: 0.58–9.73; *p* = 0.02). However, significant heterogeneity between the studies was observed (Chi-squared = 124.27 (d.f. = 5) *p* < 0.0001;  $I^2 = 96.0\%$ ;  $Tau^2 = 17.08$ ). Because of the great source of heterogeneity between studies, the subgroup analysis has been performed and identified the sample size and dietary assessment tools as heterogeneity sources (Table E4 in ESM 1).



**Figure 1.** Flow diagram of study screening and selection process.

In the comparison of HDL-C between DII<sup>®</sup> categories a total of 17 studies were included (Figure 3) [29, 33, 42, 44–53, 55, 57, 60, 62]; the study by Park et al. [52] was included as two independent studies among healthy and unhealthy overweight and obese adults. The study by Shivappa et al. [62] involved dietary assessment tools of seven-day food record and 24 hours recall method, so it was included as two independent studies. The results showed that no significant association was identified between HDL-C and DII<sup>®</sup> (Pooled WMD:  $-0.16$ ; 95% CI:  $-0.87$ – $0.56$ ;  $p = 0.66$ ). However, considerable heterogeneity between the studies was observed ( $\chi^2 = 22294.40$  (d.f. = 18);  $p < 0.0001$ ;  $I^2 = 99.9\%$ ;  $\tau^2 = 1.46$ ). The sample size and continent were sources of heterogeneity (Table E5 in ESM 1).

Sensitivity analysis couldn't change the overall effect size. All of the included studies were performed in a combination of both genders and therefore, subgrouping according to gender, was not possible.

In the comparison of LDL-C between DII<sup>®</sup> categories a total of 11 studies were included [42, 44, 46, 49, 51, 55, 57, 60, 62]. Figure 4 shows the Forest plot of the included studies. Our results indicated that the highest category of DII<sup>®</sup> was associated with  $3.99$  mg/dl increase in LDL-C (Pooled WMD =  $3.99$ ; 95% CI:  $1.16$ – $6.81$ ;  $p < 0.01$ ) and considerable heterogeneity between the studies was observed ( $\chi^2 = 105.53$  (d.f. = 10)  $p < 0.001$ ;  $I^2 = 96.2\%$ ;  $\tau^2 = 21.32$ ). Continent, dietary assessment tool, and sample size were the sources of heterogeneity (Table E6 in ESM 1).

**Table 1.** Characteristics of studies included in the systematic review owing to reporting the association between DII® and serum lipids

First author	Year	Country	Study design	Sex	Age range	Total sample size	Number of cases/controls	Dietary intake assessment method	Result	Adjusted variables	NOS
Farhangi MA [32]	2019	Iran	Cross-sectional	Both	37.97 ± 8.80	150	42/37	FFQ	There was no significant difference between OR of HDL-C, LDL-C, TC and TG in different quartiles of DII®	WHR and DBP	8
Farhangi MA [32]	2019	Iran	Cross-sectional	Both	37.97 ± 8.80	50	12/12	FFQ	Subjects in third quartile had significantly higher TC and TG concentrations compared with subjects in second quartile	WHR and DBP	8
Corley J [30]	2019	Scotland	Cross-sectional	Both	70	928	309/309	FFQ	Significant difference in hypercholesterolemia between different tertiles of DII® was observed	–	8
Corley J [30]	2019	Scotland	Cross-sectional	Both	73	765	254/256	FFQ	Significant difference in hypercholesterolemia between different tertiles of DII® was observed	–	8
Godos J [27]	2019	Italy	Cross-sectional	Both	> 18	1936	484/484	FFQ	No significant difference in dyslipidemia (%) between different quartile of DII® was observed	–	7
Guinter MA [31]	2019	USA	Cohort	men	20–48	6016	1503/1503	3-day diet record	No significant difference in hypercholesterolemia (%) between different quartile of DII® was observed	–	8
Laouali N [41]	2019	France	Cross-sectional	Women	53 ± 6.7	70991	14199/14199	FFQ	With increasing DII® quintile frequency of hypercholesterolemia decreased	–	8
Meneguelli TS [42]	2019	Brazil	Cross-sectional	Both	> 20	248	83/82	24-h recall	No significant difference in TG, Age, sex, income, smoking, PAL, TC, LDL-C and HDL-C in highest statin use, antihypertensive use, versus lowest DII® tertiles	7	
Morimoto M [43]	2019	Brazil	Cross-sectional	Both	≥ 40	2269	567/568	24-h recall	No significant difference in dyslipidemia (%) between different quartile of DII® was observed (both men and women)	–	8

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**Table 1.** (Continued)

First author	Year	Country	Study design	Age range	Total sample size	Number of cases/controls	Dietary intake assessment method	Result	Adjusted variables	NOS
Na W [44]	2019	Republic of Korea	Cross-sectional	Both	40–72	7795	1949/1948	24-h recall	Significant difference in TG and HDL-C and no significant difference in TC and LDL-C in highest versus lowest DII® quintile	–
Nilsson A [45]	2019	Sweden	Cross-sectional	Women	65–70	112	37/38	Food record	No significant difference in TG and HDL-C in highest versus lowest DII® quintile	8
Poccov-Gerardino G [46]	2019	Spain	Cross-sectional	Women	18–80	105	35/35	24-h recall	No significant difference in TG, TC, LDL-C and HDL in highest versus lowest DII® tertiles.	8
Muhammad HFL [47]	2019	Indonesia	Cross-sectional	Both	19–56	503	169/164	FFQ	No significant difference between TG and HDL-C versus lowest DII® tertiles	7
Shin D [48]	2018	Republic of Korea	Cross-sectional	Both	>19	3014	603/602	24-hour dietary recall	No significant difference between TG and HDL-C in highest versus lowest DII® was observed	8
Mirmajidi S [49]	2018	Iran	Cross-sectional	Both	18–60	150	75/75	FFQ	No significant difference in TG, TC, LDL-C and HDL-C between different subgroups of DII® was observed	8
Abdurrahman AA [50]	2018	Iran	Cross-sectional	Both	19–59	300	72/63	FFQ	Significantly higher TG and no difference in HDL-C in highest versus lowest DII® quartiles	8
Shivappa N [51]	2018	USA	Cross-sectional	Both	≥ 35	20823	4164/4164	FFQ	The prevalence of hypercholesterolemia in lowest quintile was significantly higher than highest. No significant difference between serum lipids across quintiles of DII® was observed	9
Ren Z [39]	2018	China	Cross-sectional	Both	18–75	1690	579/566	24-h dietary recall	There was no significant difference between OR of HDL-C and TG in different tertiles of smoking, BMI	8

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**Table 1.** (Continued)

First author	Year	Country	Study design	Sex	Age range	Total sample size	Number of cases/controls	Dietary intake assessment method	Result	Adjusted variables	NCS
Phillips CM [37]	2018	Ireland	Cross-sectional	Both	50–69	1992	–	FFQ	The mean of LDL-C, TG was higher and HDL-C was lower in higher than median EDII® group compared with lower than median E DII®. TC was not different	–	7
Park YM [52]	2018	USA	Cross-sectional	Both	20–90	1815	634/570	24 hour recall method	Mean HDL-C was higher and TG, BMI and age was lower in highest versus lowest DII® tertile among metabolically healthy overweight/obese individuals	–	7
Park YM [52]	2018	USA	Cross-sectional	Both	20–90	1918	610/674	24 hour recall method	There was no significant difference between HDL-C and TG in different tertiles of DII among metabolically unhealthy overweight/obese individuals	–	7
Niknizaz L [53]	2018	Iran	Cross-sectional	Both	18–64	606	151/151	FFQ	No significant difference between HDL-C and TG in different quartiles of DII and no association between OR of HDL-C and TG and DII®	Smoking status (smoker and non-smoker), PAL (low, moderate, high), sex, age, BMI	8
Mazidi M [29]	2018	USA	Cross-sectional	Both	≥ 18	17689	550/454/73	FFQ	Mean TG and HDL-C were significantly higher and lower in highest quartile of DII was compared with lowest	Age, race, sex and income to poverty ratio	9
Kim HY [54]	2018	Korea	Cross-sectional	Male	19–65	3682	1010/2672	24 hour recall method	There was no association between OR of TG and HDL-C with DII® quartiles	Age, BMI, education, alcohol consumption, smoking, physical activity, and total calorie intake	8
Kim HY [54]	2018	Korea	Cross-sectional	Female	19–65	5609	1044/4565	24 hour recall method	There was no association between OR of TG and HDL-C with DII® quartiles	Age, BMI, education, alcohol consumption, smoking, physical activity, and total calorie intake	8
Denova-Gutiérrez E [55]	2018	Mexico	Cross-sectional	Both	20–69	1174	234/235	FFQ	Mean TC in highest quartile was significantly higher than lowest. Other lipids were not different	–	7
Vahid F [28]	2017	Iran	Cross-sectional	Both	Mean aged	414	214/200	168 item FFQ	Significantly higher LDL-C, TG and lower HDL in highest tertile versus lowest	Age, BMI, education, smoking, alcohol, diabetes, LDL, TG	7

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**Table 1.** (Continued)

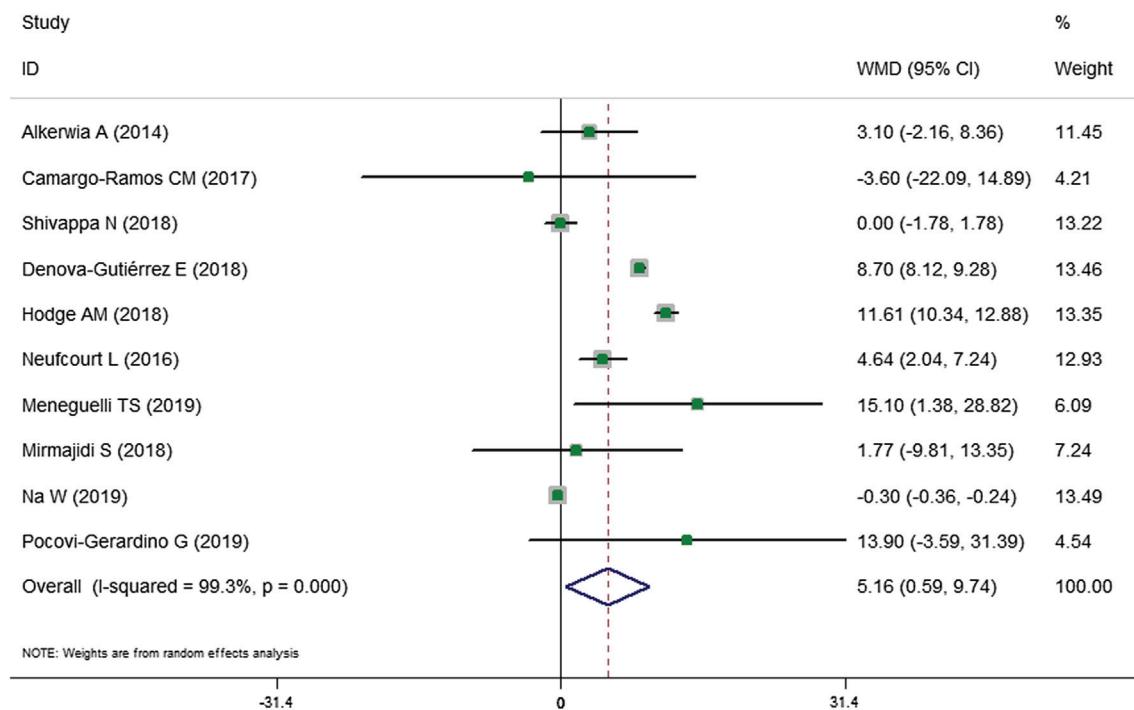
First author	Year	Country	Study design	Sex	Age range	Total sample size	Number of cases/controls	Dietary intake assessment method	Result	Adjusted variables	NOS
Naja F [56]	2017 Lebanon	Cross-sectional	Both	> 18	331	159/171		FFQ	No significant difference between mean DII® in subjects with normal compared with elevated blood lipids. OR of having elevated lipids was not associated with DII®	Age, sex, marital status, education, crowding index, PAL smoking	9
Camargo-Ramos CM [57]	2017 Colombia	Case-control	Both	Mean aged 40	90	77/13		24 hour recall method	HDL-C was significantly lowered in subjects with pro-inflammatory compared with anti-inflammatory diet	Age and sex	7
Sokol A [40]	2016 Poland	Cross-sectional	Both	45–64	3862	965/964		24 hour recall method and FFQ	No significant association between OR of being central obese with DII® quartiles (combination analysis)	BMI and age	7
Sokol A [40]	2016 Poland	Cross-sectional	Male	45–64	1290	–		24 hour recall method and FFQ	No significant association between OR of serum lipids with DII® quartiles	BMI and age	7
Sokol A [40]	2016 Poland	Cross-sectional	Female	45–64	2572	–		24 hour recall method and FFQ	Women in lowest quartile of DII® have higher OR of low HDL-C compared with women in top quartile	BMI and age	7
Wirth M [58]	2014 USA	Cross-Sectional	Both	Mean aged 42	447	112/112		FFQ	No significant association between HDL-C and TG with DII® quartiles was observed	Sex and years of police work	6
Alkenwi A [33]	2014 Luxembourg	Cross-Sectional	Both	18–69	1432	450/450		FFQ	The prevalence of raised TG or low HDL-C between tertiles of DII® was not different. No significant difference between mean of lipids in different tertiles. OR of low HDL-C was associated with top tertiles of DII®	Age (continuous variable), sex, education, income smoking status, PAL	8
Hodge AM [59]	2018 Australia	Cross-sectional	Both	40–69	41513	7906/7907		FFQ	No significant difference in TC between quintiles of DII®	–	8
Farhangi MA [38]	2018 Iran	Cross-sectional	Both	Mean aged 454 ≈ 57–60	113/113			FFQ	TC and TG were positively and HDL-C negatively associated with DII® in patient's candidate diabetes and myocardial infarction for CABG	Age, gender, BMI, educational attainment and presence of diabetes and myocardial infarction	9

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**Table 1.** (Continued)

First author	Year	Country	Study design	Sex	Age range	Total sample size	Number of cases/controls	Dietary intake assessment method	Result	Adjusted variables	NOS
Neufcourt L [70]	2018	France	Cross-sectional	Both	35–60	7743	1935/1935	24-hour dietary record	Serum TC in highest quartile was significantly higher compared with lowest LDL-C or HDL-C was not statistically significant	–	8
Ramallal R [7]	2015	Spain	Cohort	Both	Mean aged ≈ 37–39	18794	4698/4699	FFQ	No association between OR of hypercholesterolemia and DII® after two years follow-up	Family history of CVD, smoking status, total energy intake, PA <sub>1</sub> , BMI, educational level, total alcohol intake, snacking, average time sitting, and average time spent watching television	8
Garcia-Calzon S [61]	2015	Spain	Cross-sectional	Both	55–80	520	173/174	FFQ	No association between the prevalence of dyslipidemia across tertiles of DII®	–	7
Shivappa N [62]	2013	USA	Cross-sectional	Both	20–70	495	165/165	24 hours recall method	Mean LDL-C in highest tertiles of DII® was significantly higher than lowest. No significant difference in HDL-C between tertiles of DII® was observed	–	8
Shivappa N [62]	2013	USA	Cross-sectional	Both	20–70	559	186/187	7 days food record	Mean LDL-C in highest tertiles of DII® was significantly higher than lowest. No significant difference in HDL-C between tertiles of DII® was observed	–	8

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting surgery; DBP, diastolic blood pressure; DII®, dietary inflammatory index; EDII, empirically developed dietary inflammatory index; FFQ, food frequency questionnaire; FR, Food record; HDL-C, high density lipoprotein cholesterol; NOS, Newcastle-Ottawa scale; PAL, physical activity level; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WC, waist circumference.



**Figure 2.** Forest plot illustrating weighted mean difference in TC among participants in highest versus lowest DII®; positive and negative values represent increase and decrease of TC in highest versus lowest DII® category respectively. WMD, weighted mean difference; CI, confidence interval.

In the comparison of TG between DII® categories, a total of 15 studies were included [29, 33, 37, 42, 44–47, 49–53, 55, 57]. Figure 5 shows the Forest plot of the included studies and no significant association was observed (Pooled WMD = 4.29; 95% CI: -12.22–20.79;  $p = 0.61$ ; Heterogeneity chi-squared = 4.8e + 05 (d.f. = 15)  $p < 0.0001$ ;  $I^2 = 100.0\%$ ;  $Tau^2 = 1.0 e + 03$ ). The sample size and continent were all sources of heterogeneity (Table E7 in ESM 1). All of the included studies were performed in a combination of both genders. Therefore, the subgrouping according to gender was not possible.

#### Results from the meta-analysis of OR for the association between elevated TG and reduced HDL-C with DII®

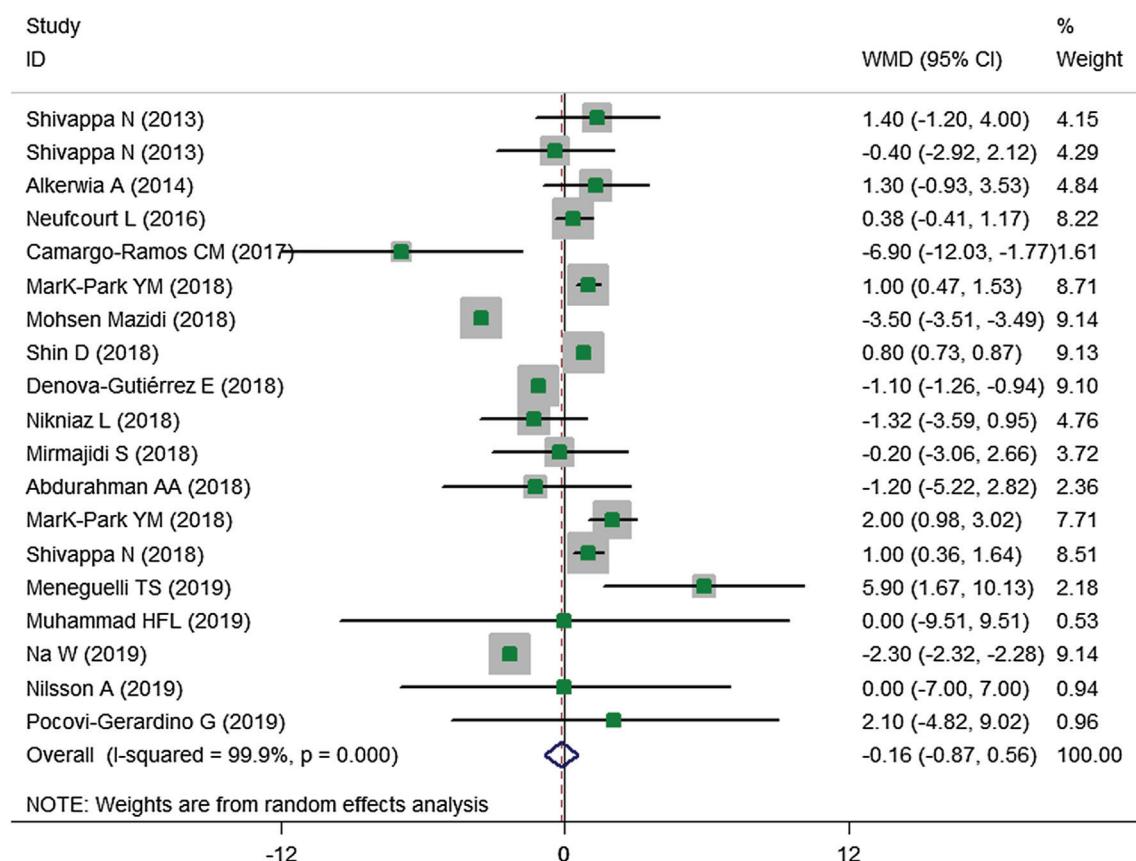
In the meta-analysis of the relationship between OR of elevated TG and DII® nine studies were included [32, 33, 39, 40, 42, 53, 54, 56, 58]. Figure 6 shows the Forest plot of the included studies. The study by Farhangi et al. [32] reported the results for men and women separately; therefore, each of them was included as two independent studies. Among all of the included studies that assessed the OR of elevated TG characterized by TG > 150 mg/dl no relationship was seen between elevated TG and DII® in the random effect model (OR = 1.00; 95% CI: 0.99–1.00;  $p = 0.20$ ). No heterogeneity was also observed (Heterogeneity chi-squared = 8.81 (d.f. = 10)  $p = 0.55$ ;

$I^2 = 0.0\%$ ;  $Tau^2 < 0.001$ ). Therefore, no subgroup analysis was performed.

In the meta-analysis of the association between OR of HDL-C and DII® nine studies were included [32, 33, 39, 40, 42, 53, 54, 56, 58]. Figure 7 shows the forest plot of the included studies. Among all of the included studies that assessed the OR of reduced HDL-C characterized by HDL-C < 50 and 40 mg/dl in women and men respectively, no relationship was seen between reduced HDL-C and DII® in random effect model (OR = 0.97; 95% CI: 0.86–1.09;  $p = 0.60$ ; Heterogeneity chi-squared = 23.47 (d.f. = 10)  $p < 0.01$ ;  $I^2 = 57.4\%$ ;  $Tau^2 = 0.01$ ). The country and continent were the sources of heterogeneity (Table E8 in ESM 1), and sensitivity analysis made no change to these results.

#### Publication bias

The Funnel plots showed moderate asymmetry, proposing the possible role of publication bias in the current study (Figures E1–6 in ESM 1). However, the Begg's and Egger's tests provided no evidence of substantial publication bias for all of the included variables. The provided values are as follows: TC, Egger's test ( $p = 0.35$ ) and Begg's test ( $p = 0.34$ ); TG, Egger's test ( $p = 0.30$ ) and Begg's test ( $p = 0.06$ ); HDL-C, Egger's test ( $p = 0.39$ ) and Begg's test ( $p = 0.48$ ); LDL-C, Egger's test ( $p = 0.54$ ) and Begg's test ( $p = 0.45$ ). TG (OR), Egger's test ( $p = 0.27$ ) and Begg's test ( $p = 0.36$ ). HDL-C (OR), Egger's test ( $p = 0.46$ ) and Begg's test ( $p = 0.38$ ).

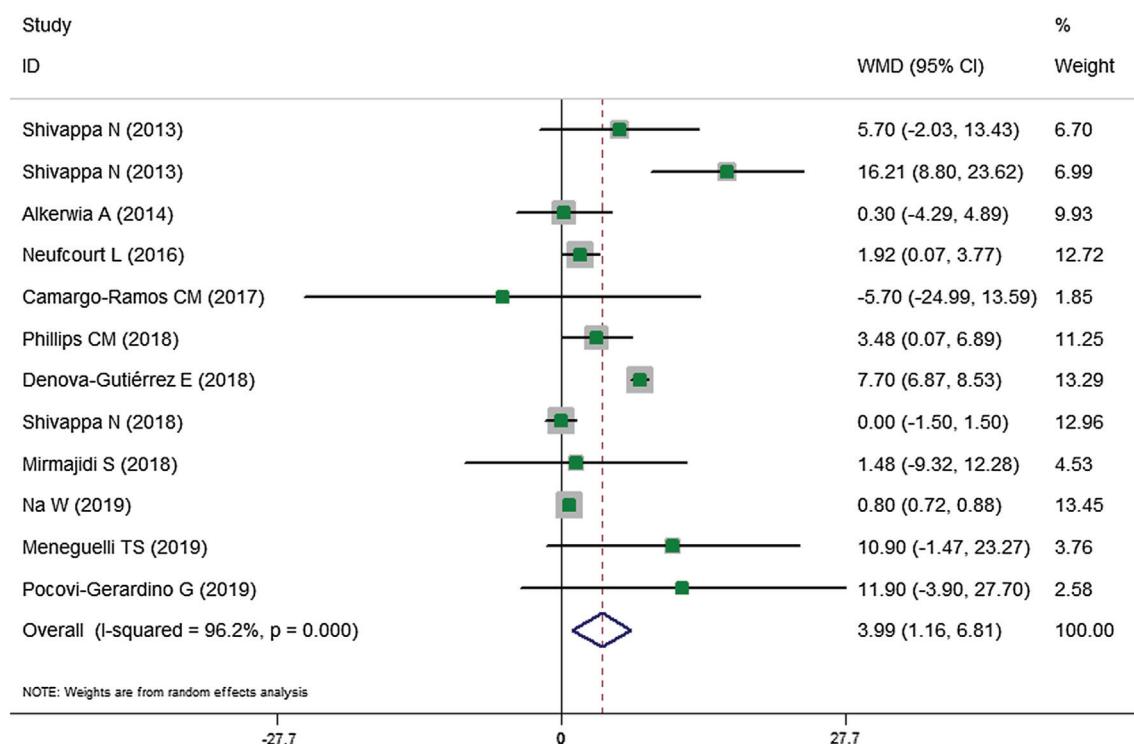


**Figure 3.** Forest plot illustrating weighted mean difference in HDL-C among participants in highest versus lowest DII®; positive and negative values represent increase and decrease of HDL-C in highest versus lowest DII® category respectively. WMD, weighted mean difference; CI, confidence interval.

## Discussion

In the present meta-analysis, serum TC and LDL-C were positively related to higher DII® scores in two-class meta-analysis. However, no association between TG and HDL-C with DII® was observed. In our meta-analysis, the most pro-inflammatory diet was associated with 5.16 mg/dl and 3.99 mg/dl increased concentrations of TC and LDL-C, respectively. There is a large body of evidence suggesting immune-modulatory effects of foods, food components, nutrients, and non-nutrients in improving inflammatory status [51, 62]. Therefore, a more pro-inflammatory diet with a high DII® score leads to low-grade inflammation, and is associated with adverse metabolic outcomes including higher VLDL, small dense LDL, and lower HDL particles and high serum levels of TC and LDL-C [37]. The underlying mechanisms of abnormal lipid metabolism due to high inflammatory potential of diet is well established in rodents [63]. Pro-inflammatory cytokines in hepatocytes lead to reduced expression of ApoAI, and decreased HDL-C concentrations [63]. Also, it has been shown that inflammation changes the HDL composition and function as a cholesterol acceptor, impairs cholesterol

efflux, apoAI/HDL cholesterol acceptor activity and hepatic sterol metabolism and inhibits transporters of macrophage cholesterol [64, 65]. Moreover, it has been reported that inflammation reduces paraoxonase 1 (PON1) activity, and as a consequence, increased LDL oxidation [66]. Increased ceruloplasmin level and reduced transferrin as a result of inflammation, lead to higher LDL oxidation [66]. Also, the association between serum lipids and DII® may be related to dietary patterns. Previous studies have revealed that an unhealthy dietary pattern affects lipid profile and other cardiovascular risk factors [67, 68]. Consumption of an anti-inflammatory diets such as the Mediterranean diet characterized by increased consumption of vegetables, whole grains, nuts, fruits, and legumes are associated with reduces risk of cardiovascular diseases and overall mortality [69]. DII® aimed to use different food parameters to estimate the inflammatory potential of an individual's diet [14, 15] and it is used for evaluating the association between dietary inflammatory potential and the risk of different diseases [14]. To our knowledge, the current study is the first meta-analysis focused on the association between the DII® and serum lipids in general populations.



**Figure 4.** Forest plot illustrating weighted mean difference in LDL-C among participants in highest versus lowest DII®; positive and negative values represent increase and decrease of LDL-C in highest versus lowest DII® category respectively. WMD, weighted mean difference; CI, confidence interval.

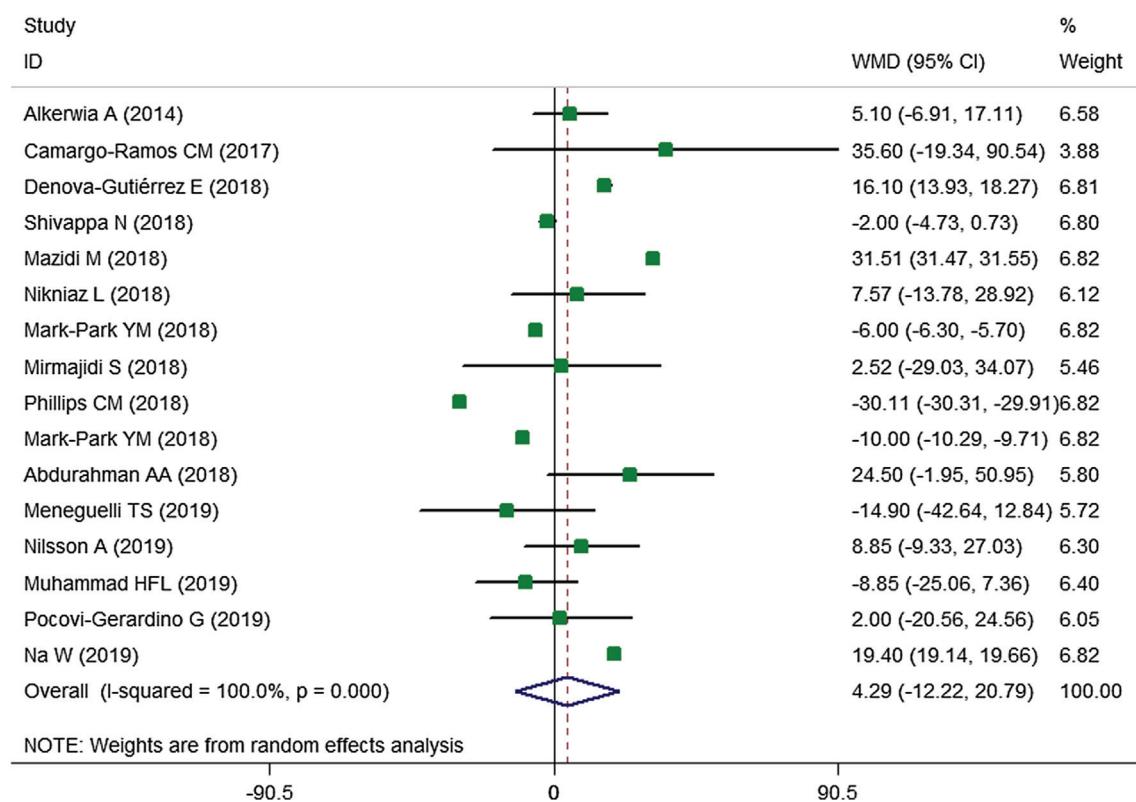
Previous studies revealed that DII® scores were related to inflammatory cytokines, colorectal and prostate cancers, and the components of metabolic syndrome (MetS) such as higher blood pressure, obesity, higher waist circumference, and elevated serum TG [70–72]. Also, Alkerwi et al. [73] in a population-based cohort study with 1,352 participants showed that higher DII® scores were associated with low HDL-C levels. A previous large cohort study reported that after 13 years of follow-up, a pro-inflammatory diet was positively associated with higher TG and lower HDL-C concentrations [70]. Camargo-Ramos et al. [57] reported that higher DII® values were associated with lower HDL-C concentrations. Wirth et al. [40], in a cross-sectional study of 447 U.S. police officers, reported no significant association between DII® scores and TG concentrations. Shivappa et al. [62] found a higher LDL-C concentration in higher teriles of DII® compared with the lowest tertile in data extracted from both seven-day dietary record and 24-hour recall method.

Neufcourt et al. [70] also found a significantly higher TC in higher DII® quartile. However, in other cross-sectional studies conducted in Spain [46], Iran [32], Brazil [42], Luxembourg [33], and China [39] no association was reported. A cross-sectional study in Scotland performed by Corley et al. [30] reported significant differences in the prevalence of hypercholesterolemia between different

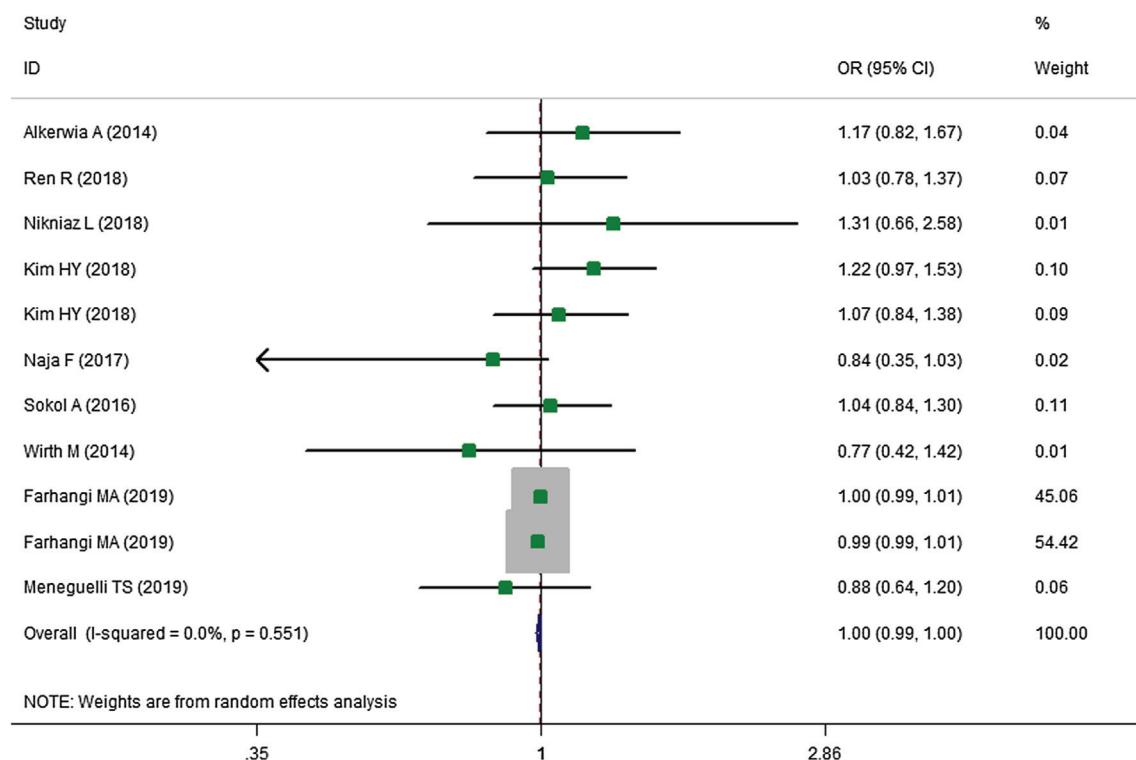
teriles of DII®. In contrast, in the study of Godos et al. [27] and Morimoto et al. [43] in 2019, no significant difference was observed in the prevalence of dyslipidemia between different quartiles of DII®. In the study by Kim et al. [54], being in the highest DII® category increased the odds of MetS among men (OR = 1.40; 95% CI = 1.06–1.85;  $p = 0.008$ ) and postmenopausal women (OR = 1.67; 95% CI = 1.15–2.44;  $p = 0.008$ ); while no significant association between odds of hypertriglyceridemia ( $p = 0.41$ ) and low HDL-C ( $p = 0.11$ ) with DII® was reported.

According to our results, higher DII® was associated with  $-6.8$  mg/dl lower HDL-C and  $7.19$  mg/dl higher TG concentrations among studies that were conducted in Asia. In contrast, among studies that were conducted in the USA, higher DII® scores were associated with  $-0.14$  mg/dl reduction in TG and  $0.31$  increase in the HDL-C concentrations. These discrepancies might be due to differences in race, gender, diet quality, and genetic background of the population. Although, the overall effects size of the association between DII® and TG or HDL-C was not statistically significant. Same as our results, previous meta-analysis also reported no association between these components and DII® [21].

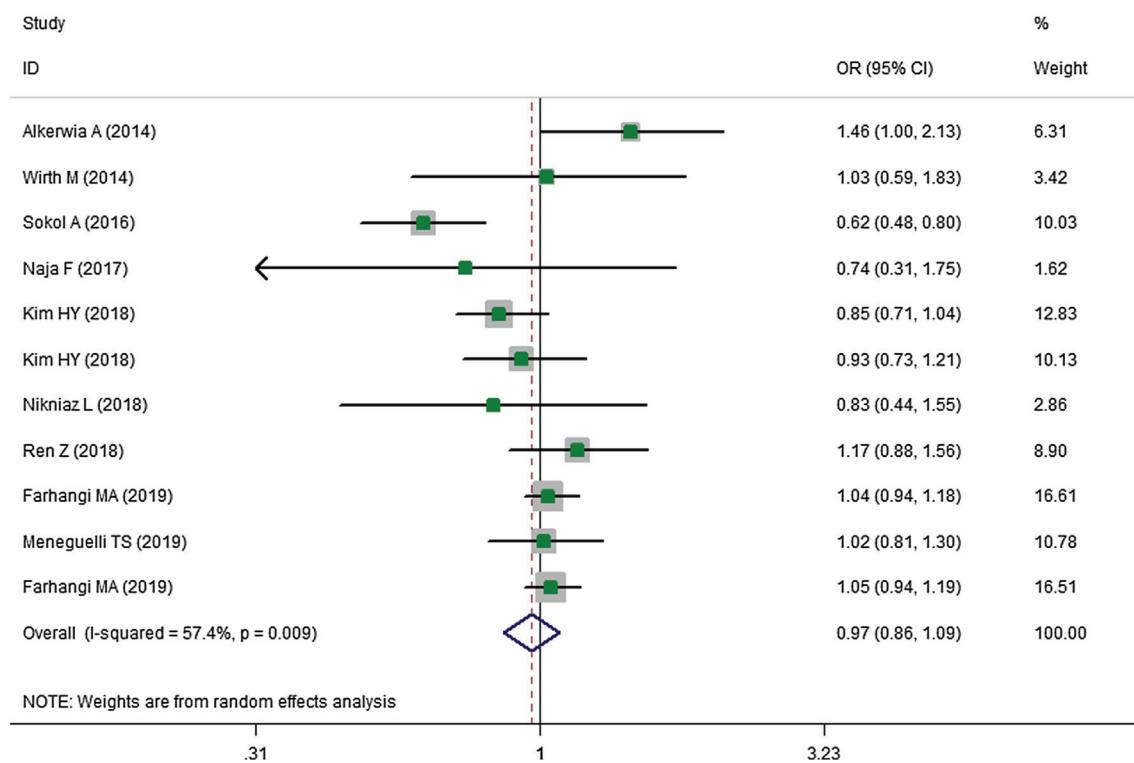
Several potential limitations of the current review should be addressed; first, the findings of the current review were based on observational studies, and therefore no causality



**Figure 5.** Forest plot illustrating weighted mean difference in TG among participants in highest versus lowest DII®; positive and negative values represent increase and decrease of TG in highest versus lowest DII® category respectively. WMD, weighted mean difference; CI, confidence interval.



**Figure 6.** Forest plot illustrating OR of TG among participants with highest versus lowest DII®.



**Figure 7.** Forest plot illustrating OR of HDL-C among participants with highest versus lowest DII<sup>®</sup>.

inference could be elucidated. Second, DII<sup>®</sup> scores were derived from self-reported food frequency questionnaire (FFQ) or 24 hours recall method, which might be a potent source of recall bias. Additionally, the diverse food items of the FFQs might be a source of heterogeneity. Third, one of the factors included in the dietary inflammatory index is energy intake and therefore, at least part of the observed relations may be attributed to total calorie intake. Using energy-adjusted values of DII might reduce the source of bias. Moreover, a great between-study heterogeneity might reduce the validity of findings, although a detailed subgrouping has been performed that is a strength. Finally, because of the wide age range of the participants in the included studies, subgrouping according to age was not possible. To our knowledge, it is the first summarized study about the relation between DII<sup>®</sup> and lipid profile among a reasonable number of adult population which further highlights the strength of our work.

## Conclusion

In conclusion, in the current summarized study, we observed a positive association between DII<sup>®</sup> and serum TC and LDL-C levels among general population. However, no significant association between DII<sup>®</sup> and TG or HDL-C in the current study was reported. Further interventional

studies are warranted to better clarify the association between DII<sup>®</sup> and health risk factors.

## Electronic supplementary material

The electronic supplementary material is available with the online version of the article at <https://doi.org/10.1024/0300-9831/a000688>

**ESM 1.** Including information about PRISMA checklist, subgroup analysis and Begg's Funnel plots.

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## History

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## Conflict of interest

The authors declare that there is no conflict of interest.

## Ethical approval and consent to participate

The study protocol was approved and registered by the ethics committee of Tabriz University of Medical Sciences (identifier: IR.

TBZMED.VCR.REC. 1397.298). The protocol of the current work has been registered in the PROSPERO system (Registration number: CRD42018110588).

## Authors' contributions

All authors have read and approved the final manuscript. MAF contributed in study concept and design, statistical analysis, and drafting of the manuscript. Data extraction and quality assessment were performed independently by MAF, and MV. MV and MM read and revised the manuscript final submitted draft. The authors declare that there is no conflict of interest. MAF also performed the final revision of paper.

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