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REVIEW

Effects of Ramadan intermittent fasting on lipid and lipoprotein parameters: An updated meta-analysis

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Abstract *Aims:* This systematic review and meta-analysis aimed to clarify several aspects of intermittent fasting during the month of Ramadan on lipid and lipoprotein levels in apparently healthy subjects.
Data synthesis: We searched PubMed, Scopus, and Embase databases and the reference lists of previous reviews, up to Feb 2019 for studies that investigated the effects of Ramadan fasting on fasting levels of triglycerides (TG), total cholesterol (TC), HDL-C, LDL-C, and VLDL-C among healthy subjects including pregnant women and athletic subjects. Studies were selected for quality assessment, meta-analyses, subgroup analyses, and meta-regressions; data of 33 eligible studies, conducted between 1978 and 2019, were included in the analysis.
Results: Intermittent fasting showed no significant effect on circulating TG (WMD = −0.38 mg/dl, 95% CI = −5.33, 4.57), TC (WMD = −1.58 mg/dl, 95% CI = −6.04, 2.88), and LDL-C levels (WMD = 1.85 mg/dl, 95% CI = 0.77, 2.92). Overall, HDL-C (WMD = −2.97 mg/dl; 95% CI = −6.43, 0.48 mg/dl) and VLDL-C (WMD = −1.41 mg/dl; 95% CI = −2.73, −0.10 mg/dl) significantly decreased after Ramadan fasting. A significant increase in LDL-C levels was observed in athletic subjects (WMD = 2.97 mg/dl; 95% CI = 0.80, 5.13) and apparently healthy subjects (WMD = 1.81 mg/dl; 95% CI = 0.55, 3.07). Change in TG levels was associated with age (β = −0.94, $P = 0.043$), its baseline values (β = −0.44, $P = 0.001$), and weight change during the fasting period (β = −0.57, $P = 0.032$).
Conclusion: Ramadan fasting may be accompanied by a moderate improvement of lipid and lipoprotein parameters, especially HDL-C levels; fasting appears to be more beneficial for men and athletic subjects.

List of abbreviations: CKD, Chronic Kidney Disease; CVD, Cardiovascular Disease; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; TC, Total Cholesterol; TG, Triglycerides; VLDL, Very Low-Density Lipoprotein; WMD, Weighted Mean Differences.

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Introduction

There is an increasing interest regarding the health implications of Ramadan fasting, the most common form of intermittent fasting (a restricted feeding period based on religious and spiritual traditions) [1,2]. During Ramadan, healthy adult Muslims abstain from eating, drinking, and smoking from sunrise to sunset [3]. The duration of intermittent fasting in the month of Ramadan (29–30 days) varies between 12 and 22 h (mean 12–14 h) depending on the geographical location and season [4,5].

Major changes in meal timings during fasting days, as well as changes in the quality and quantity of diet, could affect body composition and metabolic profiles [4]. Although some reports indicate that Ramadan fasting results in reduced body weight and fat mass and improved metabolic parameters in healthy individuals [6,7], its effects on different health outcomes remain a challenging issue [8,9].

Effects of intermittent fasting on the plasma level of lipid parameters including serum triglycerides (TGs), total cholesterol (TC), high-density lipoprotein–cholesterol (HDL-C), low-density lipoprotein–cholesterol (LDL-C), and apo-lipoproteins have been documented in several studies [10–14]. Some reports indicate that Ramadan fasting in hyperlipidemic subjects might favorably improve lipid parameters and decrease the risk of coronary heart disease [15]. Results of a meta-analysis of self-controlled cohort studies, conducted by Kul et al., in 2014 showed that Ramadan fasting has some positive effects on some health outcomes in a healthy Muslim population, especially among men [16]. As the effect of Ramadan fasting on lipid profile is affected by several biological and lifestyle mediating factors, current data illustrate a more conflicting picture in healthy subjects [17–23]. In addition, similar conflicting findings have been observed in pregnant women and athletes [24–26].

In this study, therefore, we aimed to conduct an updated systematic review and meta-analysis of both observational studies and clinical trials to assess the potential effects of intermittent fasting during the holy month of Ramadan on traditional lipid profiles in apparently healthy subjects. Moreover, with regard to inconclusive results of previous studies on the effects of Ramadan fasting, especially in athletes and pregnant women as a vulnerable population, we aimed to conduct a sub-group meta-analysis with these two categories. To clarify our hypothesis regarding the possible effects of biological factors, that is, age, sex, weight change during the fasting period, and baseline values of lipid parameters, further sub-group analysis and meta-regressions were also conducted.

Methods

Search strategy, identification, and quality assessment

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to report study findings [27]. All English-language papers were searched using appropriate keywords in PubMed, Scopus, and Embase databases, until Feb 2019. A structured search strategy with the use of various combinations of keywords (Ramadan fasting, intermittent fasting, lipid) and Boolean terms was used to identify records in each database. Gray literature was also searched using Google Scholar. Reference lists from reviews and original studies investigating the potential effects of Islamic fasting on lipid profile were also checked.

In the initial screening phase, reviews and meta-analysis papers were excluded depending on the titles and abstracts, as well as studies conducted on subjects with diabetes, hyperlipidemia, obese individuals, subjects with chronic kidney disease (CKD), cardiovascular disease (CVD), hypertension, or other medical conditions. Irrelevant papers, articles with no access to full texts, and articles in non-English language were also excluded. Articles on subjects with specific diets during Ramadan fasting, and articles with incomplete data for lipid profiles before and after Ramadan were also excluded from the meta-analysis.

To assess study eligibility, all records were independently assessed for initial inclusion and exclusion criteria, and potentially relevant full-text articles were retrieved for data extraction. Flowchart of the literature search is shown in Fig. 1.

The methodological quality of the published papers was independently assessed using the JBI Critical Appraisal Checklist for Quasi-Experimental Studies (nonrandomized experimental studies) [28].

Data collection and synthesis

To complete the data extraction form, we recorded the first authors' name, year of publication, sample size, age, sex, duration of fasting per day, the season of Ramadan fasting, mean (±SDs) baseline (before Ramadan) and final (after Ramadan) levels of TG, TC, LDL-C, HDL-C, and VLDL-C. In studies with subgroup analysis for men and women, each subgroup was included as a separate study.

The primary outcomes of the analysis were mean changes in TGs, TC, LDL-C, HDL-C levels during the holy month of Ramadan in fasting subjects.

Statistical methods

Data were quantitatively assessed based on the weighted mean differences (WMD) and 95% confidence intervals (95% CIs) of lipid parameters relative to baseline values in fasting subjects. To assess the consistency between studies in the meta-analysis, we used I^2 quantity (specific categories such as low = 25%, moderate = 50%, and high = 75%) and Cochran's Q statistic (*P-value* < 0.10 considered as significant) [29]. Both fixed- and random-effects models were used to estimate pooled effect size of intermittent fasting on lipid parameters, and finally, findings from the random-effects model were reported due to significant heterogeneity between the studies.

To investigate potential sources of heterogeneity and to evaluate whether mean differences in lipid profiles might

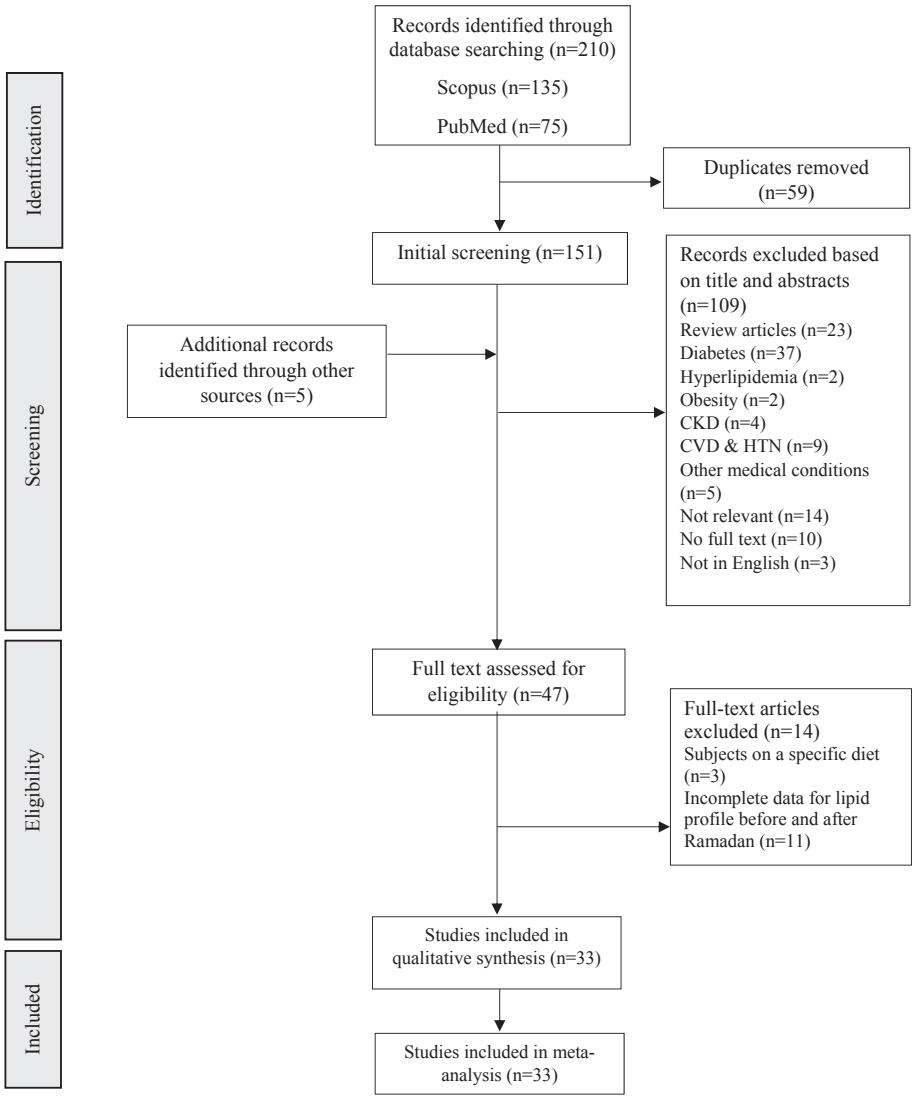

Figure 1 Flowchart of the literature search.

be affected by physiological states, we conducted sub-group analyses according to sex, pregnancy, or training state.

To identify the potential moderators that explain variance in lipid profile values in response to Ramadan fasting, we used random-effects meta-regression models. Accordingly, with the use of meta-regression, we analyzed the effect of baseline values of lipid parameters, age and weight change of the participants, and fasting duration on the pooled-effect size of lipid parameters.

To evaluate potential publication biases, we used funnel plots and Egger's regression test asymmetry. Statistical analyses were conducted using Stata version 11 (Stata Corp.).

Results

Study characteristics

After initially screening and assessing full texts of all 210 published papers identified through our searches, 33 eligible studies (39 study groups) including 33 apparently healthy groups, 4 pregnant women groups, and 4 studies conducted on athletic subjects were included in the final analysis. All studies were conducted between 1978 and 2019. Three studies had a control group of nonfasting participants [30–32], whereas other studies had no control group. Five studies investigated the effect of Ramadan fasting on lipid profile in males and females separately [8,14,33–35]. A total sample of 37 healthy fasting groups (n = 1327) were included in the meta-analysis; 20 studies were conducted only in men (n = 653) and eight studies were conducted only in women (n = 253). Eleven studies have reported results for both sexes. Mean ± SD age of participants ranged from 19.25 ± 3.5 to 43.2 ± 9.4 years, and the fasting duration ranged from 8 to 16 h. The main characteristics of the studies included in the final analysis are provided in Supplementary Table 1.

Meta-analysis

Intermittent fasting showed no significant effect on circulating levels of TG (Fig. 2) (WMD = −0.38 mg/dl, 95% CI = −5.33, 4.57), total cholesterol (WMD = −1.58 mg/dl, 95% CI = −6.04, 2.88) (Fig. 3) and HDL-C (WMD = −2.97 mg/dl; 95% CI = −6.43, 0.48 mg/dl) (Fig. 4). Overall, LDL-C levels (WMD = 1.85 mg/dl, 95% CI = 0.77, 2.92) (Fig. 5) significantly increased and VLDL-C (−1.41 mg/dl; 95% CI = −2.73, −0.10 mg/dl) (Supplementary Fig. 1) significantly decreased after Ramadan fasting.

Change in TG levels was associated with age (β = −0.94, P = 0.043), its baseline values (β = −0.44, P = 0.001), and weight change during the fasting period (β = −0.57, P = 0.032).

Sub-group analysis demonstrated a greater increase in LDL-C levels of athletic subjects (WMD = 2.97 mg/dl; 95% CI = 0.80, 5.13) and apparently healthy subjects (WMD = 1.81 mg/dl; 95% CI = 0.55, 3.07) but not in pregnant subjects. Mean VLDL-C levels in healthy subjects were significantly decreased after Ramadan fasting (WMD = −1.56 mg/dl; 95% CI = −3.08, −0.04). Pooled effect size of intermittent fasting on TG levels displayed higher values in athletic subjects (WMD = −10.48, 95% CI = −29.82, 8.86) than in apparently healthy and pregnant women; however, values were not statistically significant.

Weighted mean changes in TG, TC, LDL-C, HDL-C, and VLDL-C following Ramadan fasting in healthy men and women are shown in Table 1. Intermittent fasting was accompanied by significantly decreased LDL-C levels in men (WMD = −2.65 mg/dl; 95% CI = −5.16,-0.14) but not in women (WMD = −9.50 mg/dl; 95% CI = −21.93, 2.92). Mean VLDL-C levels after Ramadan fasting were significantly decreased in women but not in men (WMD = −5.50 mg/dl; 95% CI = −9.26, −1.74). Although mean change in TC tended to be decreased in men (WMD = −6.48, 95% CI = −13.30, 0.35) and increased in women (WMD = 2.27, 95% CI = −11.63, 16.17), these values were not significant in the random-effects model.

Meta-regression analysis showed that mean changes in TG were directly affected by its baseline values, age, and baseline weight of the participants during the fasting period. Mean changes in TC, LDL-C, HDL-C, and VLDL-C were not significantly associated with baseline values, age, duration of fasting, baseline weight, or weight change of the participants (Table 2).

Publication bias and heterogeneity

An overall symmetric distribution of studies around the mean effect size was observed in funnel plots for lipid profile values, indicating a low risk for publication bias (Supplementary Fig. 2). According to the results of the Egger's regression test, no evidence was observed for TG (coefficient: −0.23, 95% CI: −1.48, 1.01, *P* value = 0.70), LDL-C (coefficient: 0.75, 95% CI: −0.93, 2.44, *P* value = 0.36), HDL-C (coefficient: −0.23, 95% CI: −1.79, 1.33, *P* value = 0.77), and VLDL-C (coefficient: −0.73, 95% CI: −2.83, 1.38, *P* value = 0.45) outcomes regarding publication bias for the total population. Egger's regression test showed a significant publication bias for TC (coefficient: 2.03, 95% CI: 0.45, 3.61, *P* value = 0.013). There was high heterogeneity for TG (I^2 = 85.9%), cholesterol (I^2 = 87.6%), LDL-C (I^2 = 79.3%), and HDL-C (I^2 = 81.1%) in the meta-analysis models for the total population. The subgroup analysis (Table 1) indicated high heterogeneity for TG, cholesterol, and HDL in male and high heterogeneity for all lipid profile values in women.

Discussion

Our meta-analysis of 33 studies, including both apparently healthy and athletic subjects, as well as pregnant women, showed that Ramadan fasting might have beneficial effects on serum HDL-C and VLDL-C concentration, in all three groups. Pregnant women displayed a wide range of changes in lipid parameters with neutral pooled-effect sizes, whereas athletic subjects showed greater improvements in lipid profiles, especially in HDL-C levels and LDL-C-to-HDL-C ratio. We also showed that the effect of intermittent fasting during the holy month of Ramadan on lipid parameters is sex-dependent, especially in the case of HDL-C levels. Even these relatively moderate changes in lipid and lipoprotein levels may be associated with reduced risk of CVD.

To the best of our knowledge, this is the first meta-analysis that has considered athletes and pregnant women as two independent categories in sub-group meta-analysis to assess the potential effects of intermittent Ramadan fasting on lipid profiles. One remarkable finding of our analysis was sex-based differences in lipid parameters in response to intermittent fasting during this month. Sub-group analysis showed greater increases in HDL-C levels among men than among women (2.18 mg/dl *vs.* 0.23 mg/dl). Previous meta-analysis of healthy subjects also showed that Ramadan fasting was accompanied with more beneficial health outcomes in men than in women [16]. Our meta-regression also showed that individuals with higher baseline TG levels exhibited a greater decline in TG concentrations after the fasting period; TG and LDL-C changes during intermittent fasting were also affected by age. We also showed that the magnitude of TG changes was dependent on the degree of weight loss during the fasting period. These novel data provided evidence regarding potential moderators of health-outcomes in response to intermittent fasting.

An overview of related studies published during the past 40 years focusing on health outcomes of Ramadan fasting in healthy subjects reveals conflicting results; different geographical locations, climate conditions, diverse dietary habits, and sleep patterns, as well as different socioeconomic status, may explain, at least in part, some heterogeneities observed in these studies. Similar discrepancies are also highlighted for cardiovascular risk factors, especially for lipid and lipoproteins

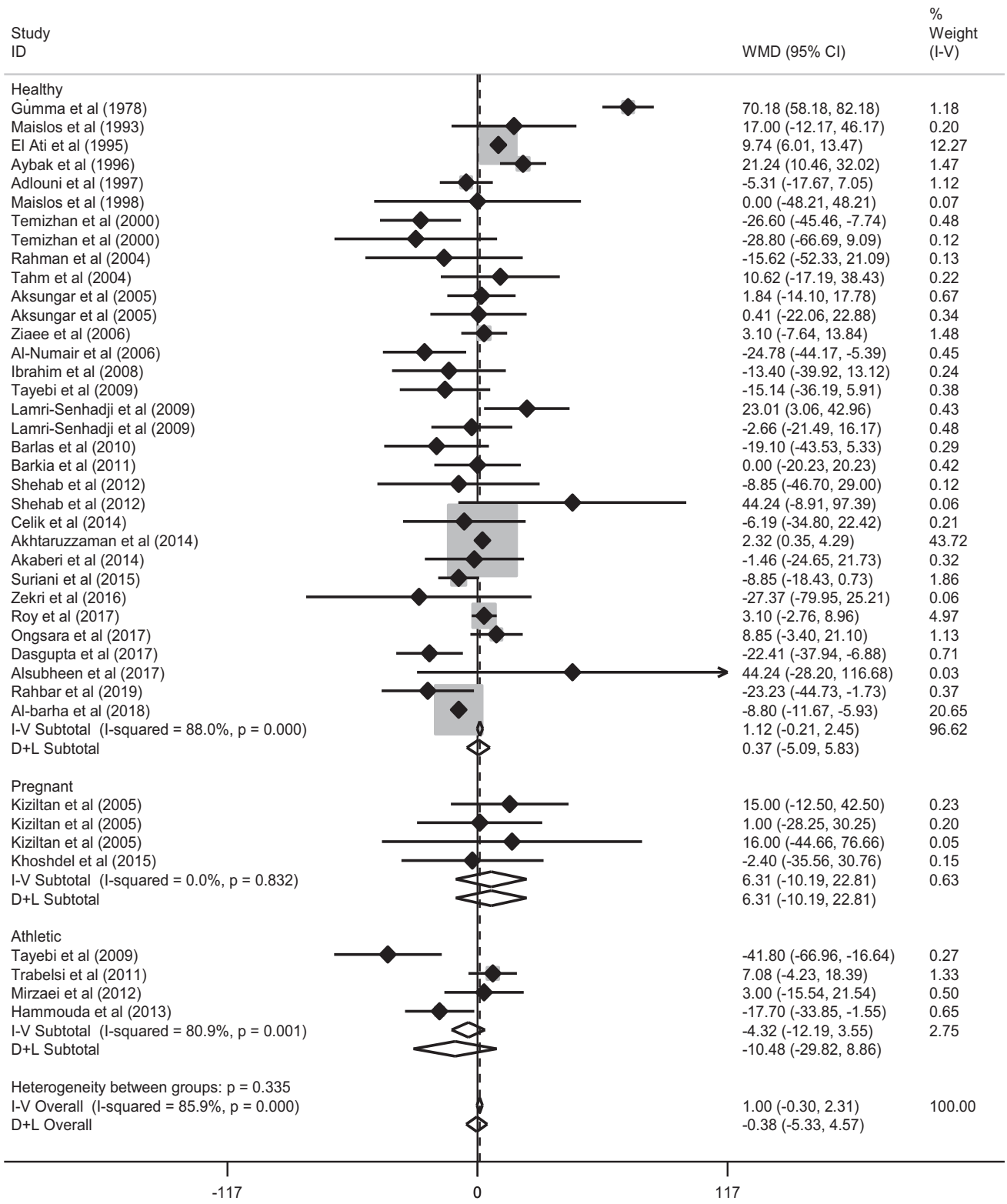

Figure 2 Forest plot of mean differences of TG before and after Ramadan fasting. Ref, reference; WMD, weighted mean difference; I–V overall, fixed effect model; D-L overall, random effect model.

[36]. Overall, a light-to-moderate increase in HDL-C level and decrease in LDL-C level were accompanied by a slight-to-moderate increase in TG levels, reported following intermittent fasting during this month [16,36].

Relatively high heterogeneity observed among the included studies may be explained by several factors including both biological and methodological factors. Moderate increases in TG levels observed during fasting

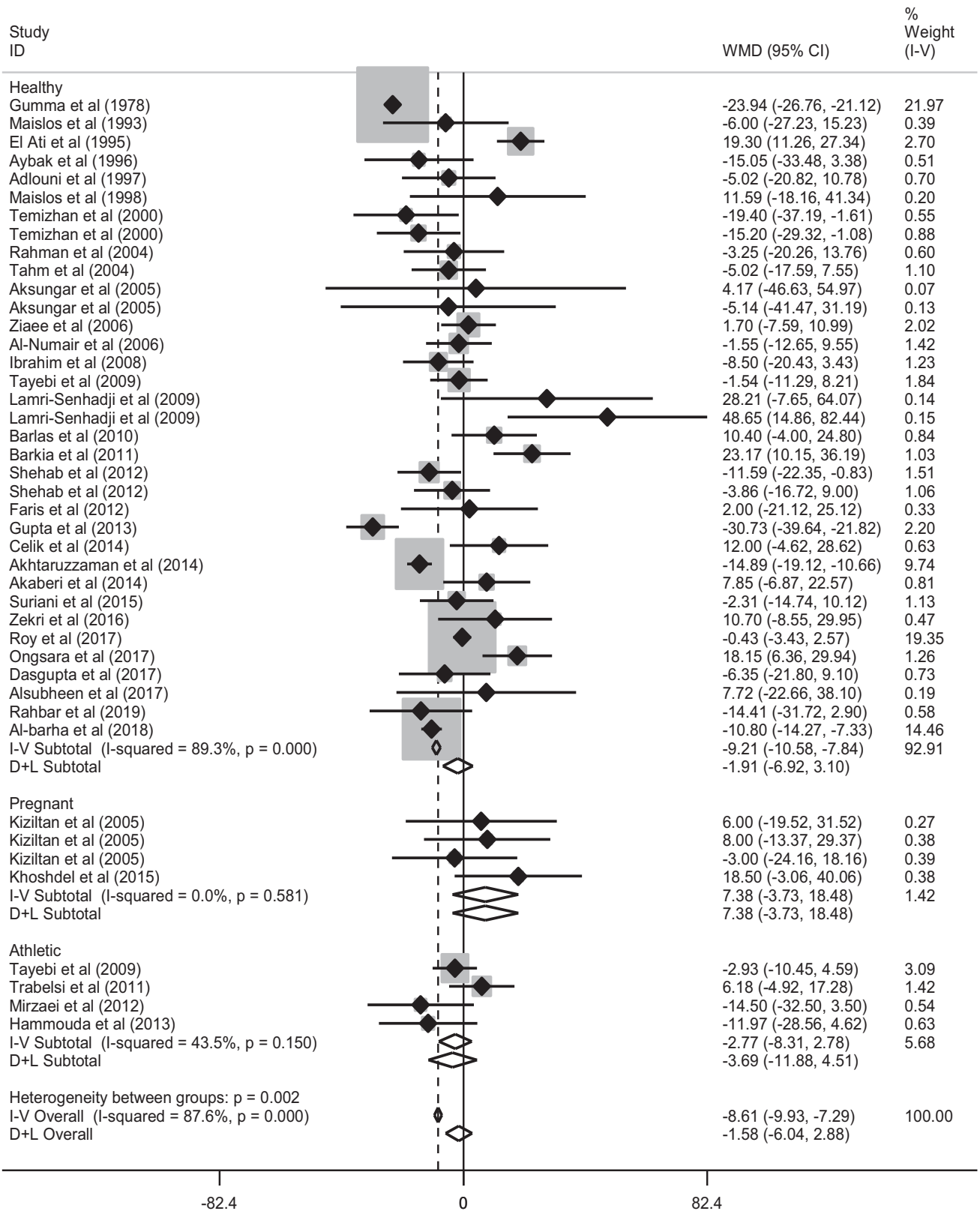

Figure 3 Forest plot of mean differences of cholesterol before and after Ramadan fasting. Ref, reference; WMD, weighted mean difference; I–V overall, fixed effect model; D-L overall, random effect model.

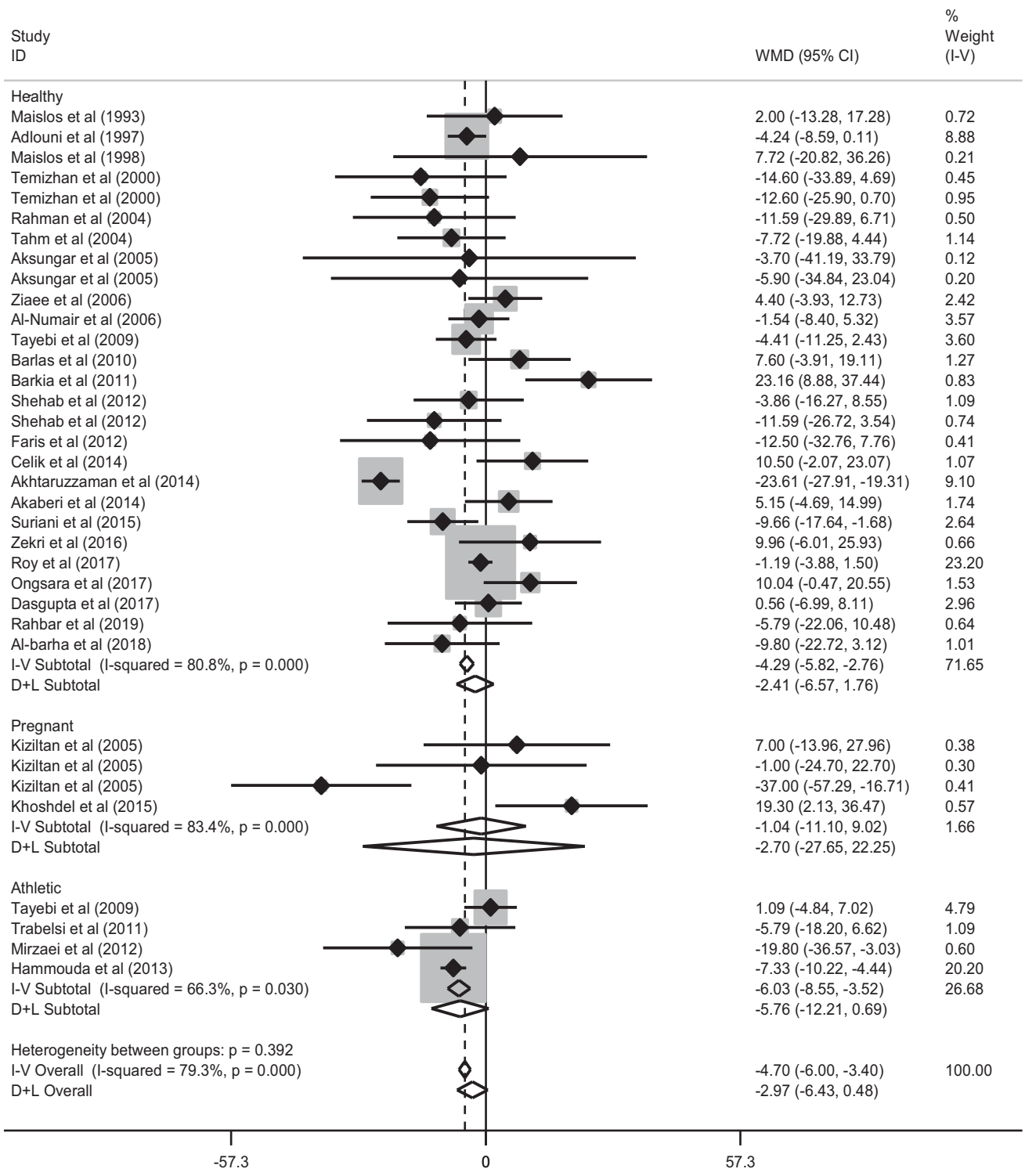

Figure 4 Forest plot of mean differences of HDL before and after Ramadan fasting. Ref, reference; WMD, weighted mean difference; I–V overall, fixed effect model; D-L overall, random effect model.

have been attributed to elevated plasma concentration of free fatty acids released from the adipose tissue during long-term starvation [37]. Increased total fat and carbohydrate intake during Ramadan may also be another reason for the increased level of TGs following intermittent fasting [38].

A major concern in studies that focused on Ramadan fasting and its metabolic outcomes is that these studies

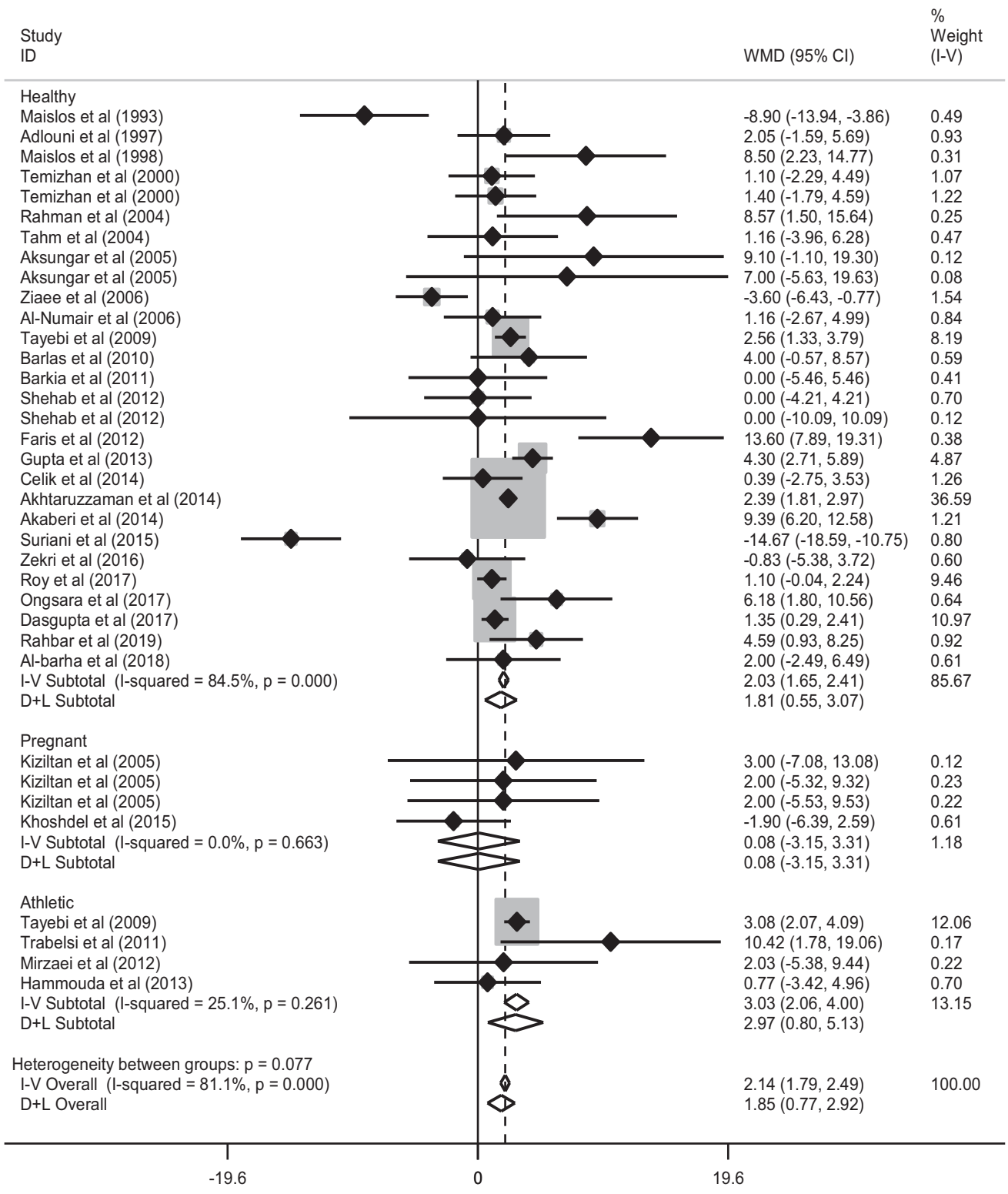

Figure 5 Forest plot of mean differences of LDL before and after Ramadan fasting. Ref, reference; WMD, weighted mean difference; I–V overall, fixed effect model; D-L overall, random effect model.

were conducted in observational settings that lacked proper quality assurance and internal and external validation [1] and could not consider several potential confounders such as dietary habits and sleep patterns during the fasting period.

Discrepancies in the results of these studies may be attributed to the fundamental differences in the study protocol. Time of blood sampling of participants and time points of baseline and final assessments are some of the most important challenges in these studies. In some

Table 1 Meta-analysis of mean differences in lipid profile values before and after Ramadan fasting.

	Number of studies	WMD (95% CI)	I^2
Males			
TG	14	0.94 (−14.72, 16.60)	90.9
Cholesterol	15	−4.98 (−13.46, 3.50)	92.2
LDL	10	−2.32 (−5.06, 0.41)	21.4
HDL	11	2.02 (0.90, 3.14)	46.6
VLDL	3	−2.24 (−5.0, 0.52)	39.7
Females			
TG	8	2.81 (−3.71, 9.33)	80
Cholesterol	8	2.27 (−11.63, 16.17)	90.9
LDL	6	−9.50 (−21.93, 2.92)	87.1
HDL	6	0.23 (−5.58, 6.04)	93.5
VLDL	1	−5.50 (−9.26, −1.74)	–

WMD; Weighted Mean Differences, TG; Triglycerides, LDL; Low-Density Lipoprotein, HDL; High-Density Lipoprotein, VLDL; Very Low-Density Lipoprotein.

Table 2 Meta-regression of potential moderators of changes in lipid profile values in response to Ramadan fasting.

	Slope	95% CIs	*p*-value
MD in TGs			
Age	−0.94	−1.85, −0.03	0.043
Baseline TGs	−0.44	−0.62, −0.27	<0.001
Baseline weight	−0.57	−1.08, −0.05	0.032
Weight change	6.86	−2.64, 16.37	0.510
Duration of fasting	0.95	−1.74, 3.63	0.473
MD in Cholesterol			
Age	−0.30	−1.11, 0.51	0.452
Baseline cholesterol	0.09	−0.26, 0.44	0.611
Baseline weight	−0.34	−0.79, 0.11	0.128
Weight change	−1.22	−7.75, 5.31	0.707
Duration of fasting	−1.67	−4.13, 0.80	0.176
MD in LDL			
Age	−0.17	−0.81, 0.47	0.592
Baseline LDL	−0.15	−0.58, 0.27	0.459
Baseline weight	−0.11	−0.29, 0.07	0.209
Weight change	−1.23	−6.37, 3.92	0.628
Duration of fasting	−0.90	−2.88, 1.07	0.350
MD in HDL			
Age	−0.24	−0.67, 0.19	0.259
Baseline HDL	−0.05	−0.33, 0.22	0.681
Baseline weight	−0.01	−0.24, 0.21	0.915
Weight change	−0.75	−3.46, 1.95	0.571
Duration of fasting	−0.70	−0.38, 1.78	0.192
MD in VLDL			
Age	−0.07	−0.52, 0.38	0.719
Baseline VLDL	−0.25	−0.60, 0.10	0.142
Baseline weight	−0.05	−0.28, 0.19	0.618
Weight change	−0.14	−2.34, 2.06	0.885
Duration of fasting	−0.44	−1.61, 0.73	0.379

MD; Mean Differences, TG; Triglycerides, LDL; Low-Density Lipoprotein, HDL; High-Density Lipoprotein, VLDL; Very Low-Density Lipoprotein.

studies, blood samples were collected in the early hours of the day, after the Sahur meal (postprandial status), whereas in some studies, blood sampling was conducted in the middle or late hours of day, and even after the Iftar meal. Considering the important role of fasting duration in plasma concentrations of lipid profiles, especially TGs [39], the widespread duration of fasting (religious fasting time), reported to be between 10 and 22 h, affects outcomes of the studies, largely limiting the ability to logically compare their results. Although the difference in the results of TC and HDL-C is less affected by the duration of fasting, this difference was reported up to 10% for LDL-C and up to 20% for triglycerides [39]. The best time for blood sampling for measuring blood lipids during fasting is unknown. The National Cholesterol Education Adult Treatment Panel Program III suggests 9- to 12-h fasting before measuring concentrations of plasma lipids [40]; accordingly it is thought that the best time for blood sampling during Ramadan fasting is before dawn (before Sahur meal); blood sampling at the end of the day (before the Iftar meal) may lead to overestimation of serum lipids owing to lack of intake during the day and increased blood concentrations [36].

The absence of a nonfasting control group was another limitation in most studies. Insufficient data on chronobiological changes during Ramadan as a major confounding factor, which affects the association of fasting with biochemical changes and health outcomes [41], could be another limitation of studies. Lack of data regarding physiological status, consumption of Sahur meal (the meal before sunrise) [42], and different dietary habits should also be considered as potential sources of residual amount of heterogeneity in the studies.

Our meta-analysis has some limitations, especially the high levels of heterogeneity, which were unavoidable because of the varying population groups of studies, different methodological approaches, differences in fasting durations, and the physiological status of the study participants. With the use of subgroup analyses, we tried to detect potential sources of heterogeneity of the studies. Moreover, our searches were limited to English-language records, although results of Egger's test showed that this was not the case for most of the lipid profile values, except only TC. In conclusion, findings of this meta-analysis indicate that intermittent fasting during the month of Ramadan may be accompanied by a moderate improvement in lipid and lipoprotein parameters, especially HDL-C levels. Ramadan fasting appears to be more beneficial for men and athletic subjects. Changes in TG levels following intermittent fasting seem to be affected by age, their baseline values, and degree of weight loss during the fasting period.

Further studies with the use of a standardized protocol and controlling for potential confounders (dietary factors, lifestyle habits, and sleep pattern during Ramadan) are required to confirm whether intermittent fasting may be beneficial for the management of cardiometabolic risk factors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.05.056.

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