Systematic Review

Annals of Nutrition & Metabolism

Ann Nutr Metab 2011;59:176–186
DOI: 10.1159/000334071

Received: August 25, 2011
Accepted after revision: September 14, 2011
Published online: December 2, 2011

Effects of Monounsaturated Fatty Acids on Cardiovascular Risk Factors: A Systematic Review and Meta-Analysis

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Key Words
Monounsaturated fatty acids · Low fat · Obesity · Cardiovascular risk

Abstract
The appropriate pattern of macronutrient distribution for dietary protocols aimed at treating or preventing obesity and its associated cardiovascular diseases is still a controversial topic of discussion. Recommendations considering a specific percentage or range for monounsaturated fatty acids (MUFA) are rare. It was the aim of this study to analyze long-term, randomized, controlled dietary intervention trials and to investigate the effects of MUFA on the biomarkers of obesity and cardiovascular risk factors. Dietary regimens with a high amount of MUFA (>12%) were compared to those with ≤12%. The biomarkers taken into account were weight, waist circumference, fat mass, total cholesterol, LDL cholesterol, HDL cholesterol, triacylglycerols, systolic and diastolic blood pressure, as well as C-reactive protein. A total of 12 studies met the inclusion criteria. Data analysis was performed using the Review Manager 5.0.25 software. Significant differences between high- and low-MUFA protocols could be observed with respect to fat mass [–1.94 kg (confidence interval –3.72, –0.17), p = 0.03], systolic blood pressure [–2.26 mm Hg (confidence interval –4.28, –0.25), p = 0.03] and diastolic blood pressure [–1.15 mm Hg (confidence interval –1.96, –0.34), p = 0.005] favoring the dietary protocols with >12% MUFA. Therefore, MUFA might represent a useful tool in the design of dietary regimens for obesity and cardiovascular disease.

Introduction

In 2007 and 2008, prevalence of overweight and obesity in the USA was reported to be 32.2% amongst adult men and 35.5% amongst adult women [1]. In comparison with respective data from the National Health and Nutrition Examination Survey (NHANES) studies collected between 1988 and 2000, these numbers increased dramatically by approximately 20% within the last 10 years [2]. Moreover, results derived from large cohort studies revealed a pandemic rise in the prevalence of obesity around the world, which is no longer restricted to industrialized nations [3]. Obesity is regarded to be a serious risk factor for the development of cardiovascular diseases (CVD) which represent the most common cause of death in the Western world since 1970 [4, 5]. An unhealthy choice of

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diet increases the risk of acute myocardial infarction and accounts for about 30% of the population-attributable risk [6]. For European nations, recent data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study indicate that body mass index (BMI) and waist circumference (WC) are strongly associated with death risk. The BMI correlating with the lowest mortality was reported to be 25.3 for men and 24.3 for women [7]. High levels of total cholesterol (TC), LDL cholesterol and triacylglycerols (TG) as well as low levels of HDL cholesterol are evidence-based risk factors of CVD [8–10]. Increases in blood pressure are also associated with mortality risk [11]. Randomized controlled trials (RCTs) have demonstrated a correlation between long-term weight loss or increased physical activity and a reduced incidence of diabetes [12, 13]. However, the appropriate effective dietary protocol to treat obesity and its related CVD is still a matter of debate. In the past, the American Heart Association recommended a diet high in carbohydrates [approx. 55% of total energy consumption, (TEC)] but low in fats (approx. 30% of TEC) in order to prevent overweight, obesity and the associated cardiovascular risks [14, 15]. In 2006, the American Heart Association adjusted its references, permitting a higher maximum value of fat (<35% of TEC) which has meanwhile been adopted by the American Dietetic Association [16, 17].

Considerations of a specific quota of monounsaturated fatty acids (MUFA) within the daily recommendations are scarce. The American Heart Association suggested that less than 15% of TEC should be consumed as MUFA, while the American Dietetic Association proposed the corresponding value to be set to <20% [16, 17]. In the USA, the Dietary Guidelines for Americans included a specific percentage for MUFA in their pattern of macronutrient distribution, i.e. 12% of TEC [18]. In contrast, the European Food Safety Authority concluded that 'Cismonounsaturated fatty acids are synthesized by the body, have no known specific role in preventing or promoting diet-related diseases, and are therefore not indispensable constituents of the diet.' Consequently, the panel did not propose any specific reference value for MUFA at all [19].

Given the obvious potential of dietary regimens in the treatment and prevention of obesity and its associated comorbidities, it is not surprising that there are numerous studies investigating the effects of variations in macronutrient composition on the management of body weight and its metabolic consequences. Previous meta-analyses comparing diets with different amounts of fats in daily nutrition reported an inconclusive impact of MUFA on biomarkers of CVD, suggesting that only long-term intervention trials might adequately address the question of an optimal strategy for the reduction of coronary risk [20, 21].

In our study, we focused on RCTs with a duration of at least 6 months using either high (>12%) or low (≤12%) percentages of MUFA in their daily regimens. As outcome measures, body weight, WC, fat mass (FM), TC, LDL-cholesterol, HDL-cholesterol, TG, C-reactive protein (CRP), as well as systolic and diastolic blood pressure (SBP and DBP) were chosen.

Methods

Research Strategy

For the selection process of adequate publications, methods recommended by the Cochrane Collaboration were used [22]. A wide research strategy was applied to identify as many relevant RCTs investigating the management of obesity and CVD risk factors as possible. Queries were performed in three electronic databases: MEDLINE (between 1966 and December 2010), EMBASE (between 1980 and December 2010) and the Cochrane Trial Register (until December 2010). The research strategy incorporated CVD and obesity-related terms and text terms, adjusted to each database. Key words and Boolean operators were as follows: 'blood pressure AND diet', 'cardiovascular disease AND diet', 'cholesterol AND diet', 'low fat diet', 'Mediterranean diet', 'monounsaturated fatty acids AND diet', 'obesity AND diet' as well as 'triacylglycerols AND diet'. In addition, reference lists of selected studies were reviewed.

To be included, RCTs had to at least assess weight loss or prevention of weight gain during the high-MUFA versus low-MUFA dietary protocol. In accordance with the systematic review of Hession et al. [23] who compared low-carbohydrate diets to low-fat diets, only studies conducted in a population of adult volunteers – as defined by a minimum age of 18 years – were taken into account. The minimum period of dietary intervention and follow-up was set to 6 months, and the nutritional counseling had to be done by a dietician. Since this meta-analysis focused on the prevention of CVD, studies that signed up participants with coronary heart disease (CHD) were excluded.

Types of Intervention

The focus of this review was set on examining high-MUFA versus low-MUFA diets to induce weight loss and/or to prevent weight gain, as well as to induce changes in cardiovascular risk factors. Therefore, the following types of dietary interventions were evaluated: as a primary analysis, we defined high-MUFA diets using the threshold set by the Dietary Guidelines for Americans (>12% of TEC) [18] and low-MUFA to provide ≤12% of TEC in the form of MUFA. Low-MUFA were differentiated to be:

- low-fat diets (LF; total fat content ≤30% of TEC, saturated fatty acids ≤7–10% of TEC)
- low glycemic index diets (LGI)
- high glycemic index diets (HGI)
- high-polyunsaturated fatty acids diets (high-PUFA)
- high-protein diets (HP)
- control diets (total fat content ≥30% of TEC and/or saturated fatty acids ≥10% of TEC).

Outcome Measures

Main outcome parameters of the RCTs included in this study were weight loss or prevention of weight gain, WC and FM. Secondary outcomes included biomarkers of CVD risk:

- serum lipids; including TC, LDL cholesterol, HDL cholesterol and TG
- SBP and DBP
- CRP.

Quality Assessment of Studies

Full copies of studies were independently assessed for methodological quality by two researchers using a standard form using the Jaded score [24]. This 5-point quality scale includes points for randomization (randomized = 1 point; table of random numbers or computer generated randomization = an additional 1 point), double-blinding (double-blind = 1 point; use of a placebo = additional 1 point), and follow-up (numbers and reasons for withdrawal in each group are stated = 1 point) within the report of an RCT. An additional point was accepted if the analysis was by intention-to-treat. Final scores of 0–2 were considered as low quality, while final scores of ≥3 were regarded as representing studies of high quality, since double-blinded study protocols are hard to achieve in these types of interventions.

Data Abstraction and Statistical Analysis

A data abstraction form for this systematic review was created according to Avenell et al. [22]. For each outcome measure of interest, a meta-analysis was performed in order to determine the pooled effect of the intervention in terms of weighted mean differences (WMD) between the postintervention values of the intervention and control groups. All data were analyzed using the Review Manager 5.0.25 software provided by the Cochrane Collaboration (http://ims.cochrane.org/revman). Heterogeneity between trial results was tested with a standard χ^2 test. The I^2 parameter was used to quantify any inconsistency: $I^2 = [(Q - df)] \times 100\%$ (where Q is the χ^2 statistic and d.f. is its degrees of freedom). A value for $I^2 > 50\%$ was considered to represent substantial heterogeneity [25]. Heterogeneity was taken into account by using the random-effects model to estimate WMD and 95% confidence intervals (CIs). Funnel plots were used to assess potential publication bias (i.e. the tendency for studies that yield statistically significant results to be more likely to be submitted and accepted for publication). To determine the presence of publication bias, we assessed the symmetry of the funnel plots in which mean differences were plotted against their corresponding standard errors. A primary analysis of all studies was performed oriented towards the definition of high-MUFA and low-MUFA diets, followed by a subanalysis of the specific kind of dietary intervention as described in the selected studies.

Handling of Missing Data

Data processing for this review required the input of the mean and standard deviation (SD) of post values. Where SD was not available, the authors of the original publication were asked for the missing data. For one trial [26], baseline SD had to be imputed. We assumed that this is a valid procedure since the baseline and postintervention SD were found to be similar within the other trials included in the meta-analysis. In addition, this strategy had been used before in a meta-analysis by Boulé et al. [27].

Results

Characteristics of Studies and Participants

A total of 12 studies recruiting 1,990 participants met the inclusion criteria [26, 28–38]. Four RCTs were performed for a period of 6 months [29, 32, 33, 37], another 4 trials for a period of 12 months [28, 30, 34, 38], 1 lasted 18 months [35], 2 studies executed a 24-month intervention protocol [31, 36], and 1 ran for a period of 4 years [26]. All studies compared a high-MUFA diet to a low-MUFA regime such as LF, LGI, HGI, high-PUFA and HP diets or to unattended controls. Attrition rates did not differ significantly between the intervention groups.

In one trial [33], the high-MUFA diet was approached by two different kinds of intervention: one included the high-MUFA setting in an HGI protocol, while the other combined high MUFA with an LGI regime. Both types of high-MUFA diets were included in the meta-analysis via a separate comparison of high MUFA/LGI versus LF/LGI, high MUFA/HGI versus LF/HGI and high MUFA/HGI versus high saturated fatty acids/HGI (defined as control group). This was done in order to minimize a potential bias of HGI and LGI, respectively, when comparing high-MUFA and low-MUFA diets. The characteristics of all RCTs included in the present meta-analysis are summarized (online supplementary table 1; for all online supplementary material, see www.karger.com/doi/10.1159/000334071).

Outcome Measures

WMD for the effects of high-MUFA versus low-MUFA diets as well as the corresponding subanalyses on all biomarkers of obesity and CVD measured in the RCTs included in our study are summarized (online suppl. table 2).

Weight/Waist Circumference/Fat Mass

The pooled estimates of effects of high-MUFA versus low-MUFA diets on weight were –0.82 kg (95% CI –1.87 to 0.22). Reductions/changes in body weight were not statistically significant (p = 0.16). However, post hoc analysis showed that reduction of body weight was significantly more pronounced following a high-MUFA diet compared to an LF diet [WMD: –1.71 kg (95% CI –3.41 to –0.02), p = 0.05] (fig. 1). FM was assessed in a total of 340 subjects. WMD for the effects of high-MUFA versus low-MUFA regimens was –1.94 kg (95% CI –3.72 to 0.17) which was statistically significant (p = 0.03) (fig. 2). There was no statistically significant effect of a high-MUFA diet on WC compared to control diets.

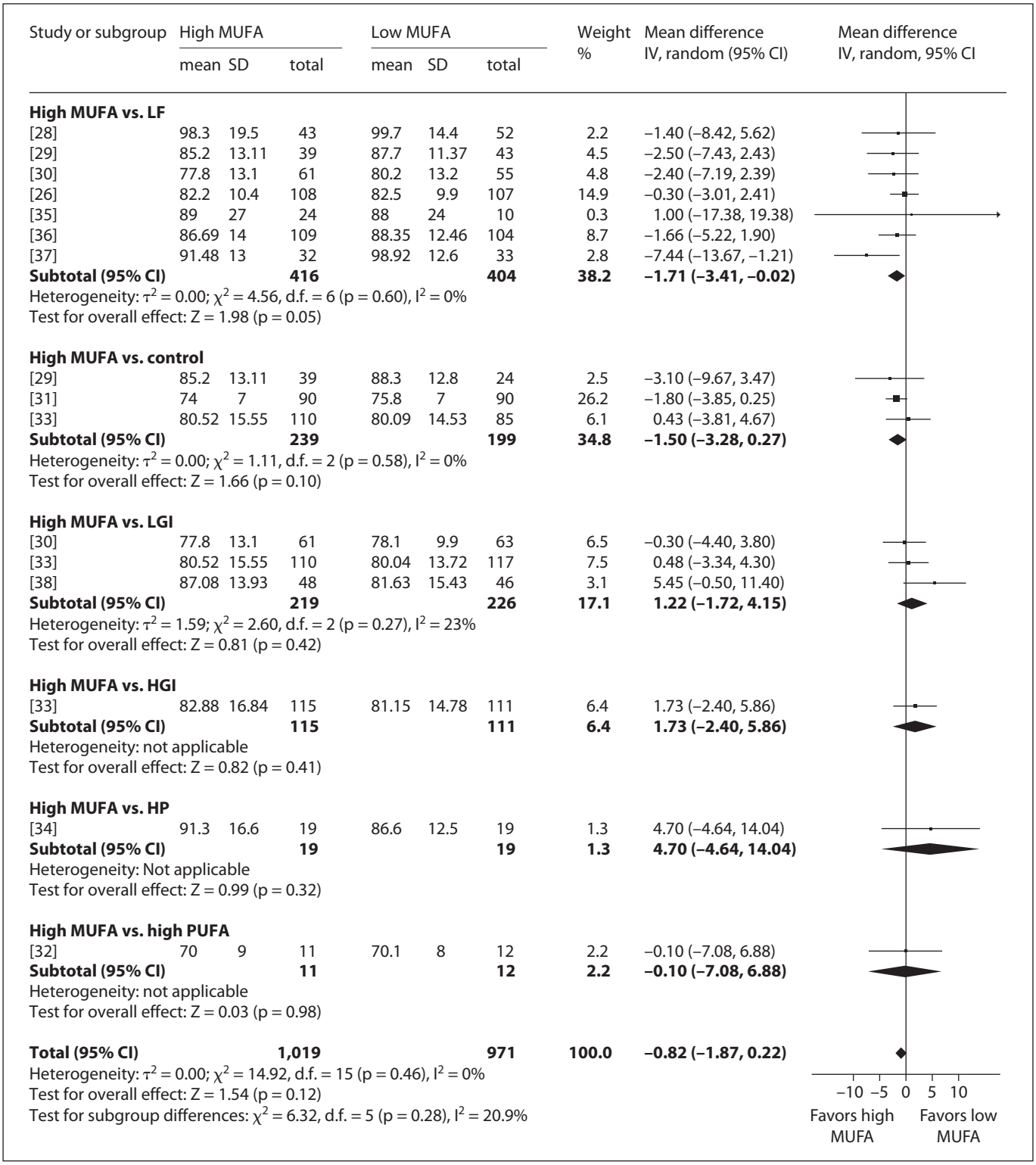

Fig. 1. Forest plot showing pooled WMD with 95% CI for weight (kg) for 12 randomized controlled high-MUFA diets. The different types of low-MUFA diets were separated into subgroups. For each high-MUFA study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study, within the respective meta-analysis. The diamond at the bottom of the graph represents the pooled WMD with the 95% CI for the 12 study groups.

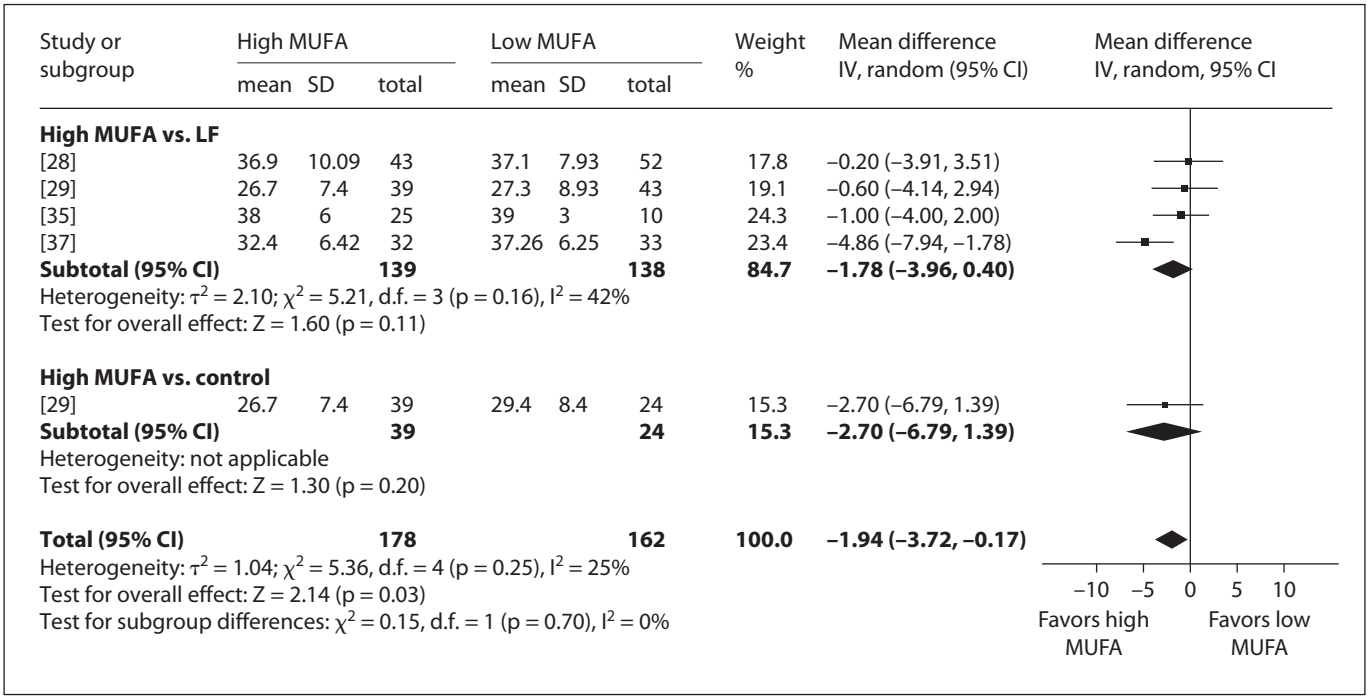

Fig. 2. Forest plot showing pooled WMD with 95% CI for FM (kg) for 4 randomized controlled high-MUFA diets. The different types of low-MUFA diets were separated into subgroups. For each high-MUFA study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study in the respective meta-analysis. The diamond at the bottom of the graph represents the pooled WMD with the 95% CI for the 4 study groups.

Serum Lipids

There were no significant differences between high-MUFA and low-MUFA diets for changes in TC [WMD: –1.33 mg/dl (95% CI –4.45 to 1.78), p = 0.40], LDL cholesterol [WMD: –0.85 mg/dl (95% CI –4.86 to 3.17), p = 0.68], HDL cholesterol [WMD: 0.95 mg/dl (95% CI –0.88 to 2.79), p = 0.31] and TG [WMD: –6.30 mg/dl (95% CI –14.24 to 1.64), p = 0.12].

Blood Pressure

Decreases in SBP were significantly more explicit in subjects adhering to a high-MUFA diet as compared to a low-MUFA diet [WMD: –2.26 mm Hg (95% CI –4.28 to –0.25), p = 0.03]. Comparable results were found when comparing high-MUFA groups to control groups in a post hoc subgroup analysis [WMD: –3.90 mm Hg (95% CI –6.90 to –0.90), p = 0.01] (fig. 3). Our meta-analysis showed that the pooled effect of a high-MUFA diet on DBP was a reduction of 1.15 mm Hg (95% CI –1.96 to –0.34). This is both clinically and statistically significant (p = 0.005) (fig. 4).

C-Reactive Protein

We observed no statistically significant differences between high-MUFA and low-MUFA diets on CRP [WMD: –0.07 mg/dl (95% CI –0.41 to 0.27), p = 0.68].

Discussion

Overweight was found to be associated with an increased relative risk as well as a population-attributable risk for hypertension and CVD, and energy restriction was reported to be the most important factor for weight loss independent of dietary macronutrient composition [5, 39]. In the meta-analysis, reduction of body weight did not differ when comparing high-MUFA with low-MUFA diets. Likewise, decreases in WC following a high-MUFA protocol turned out to be indistinguishable from those detected after low-MUFA diets. However, high-MUFA regimens had a significantly more pronounced impact on FM. Using pooled data from cohort studies and RCTs, de Koning et al. [40] reported a 2% increase in CVD risk for

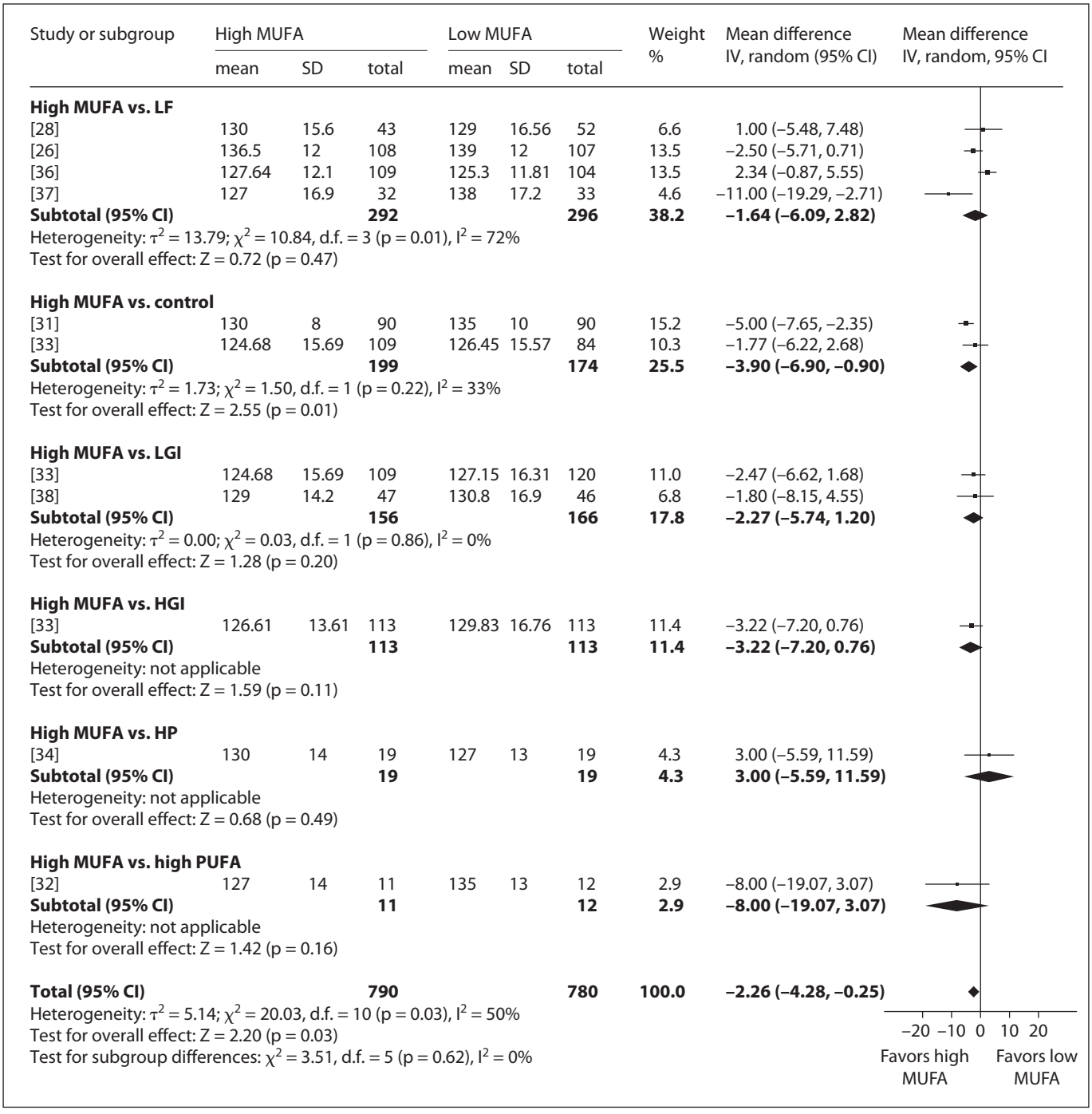

Fig. 3. Forest plot showing pooled WMD with 95% CI for SBP (mm Hg) for 9 randomized controlled high-MUFA diets. The different types of low-MUFA diets were separated into subgroups. For each high-MUFA study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study in the respective meta-analysis. The diamond at the bottom of the graph represents the pooled WMD with the 95% CI for the 9 study groups.

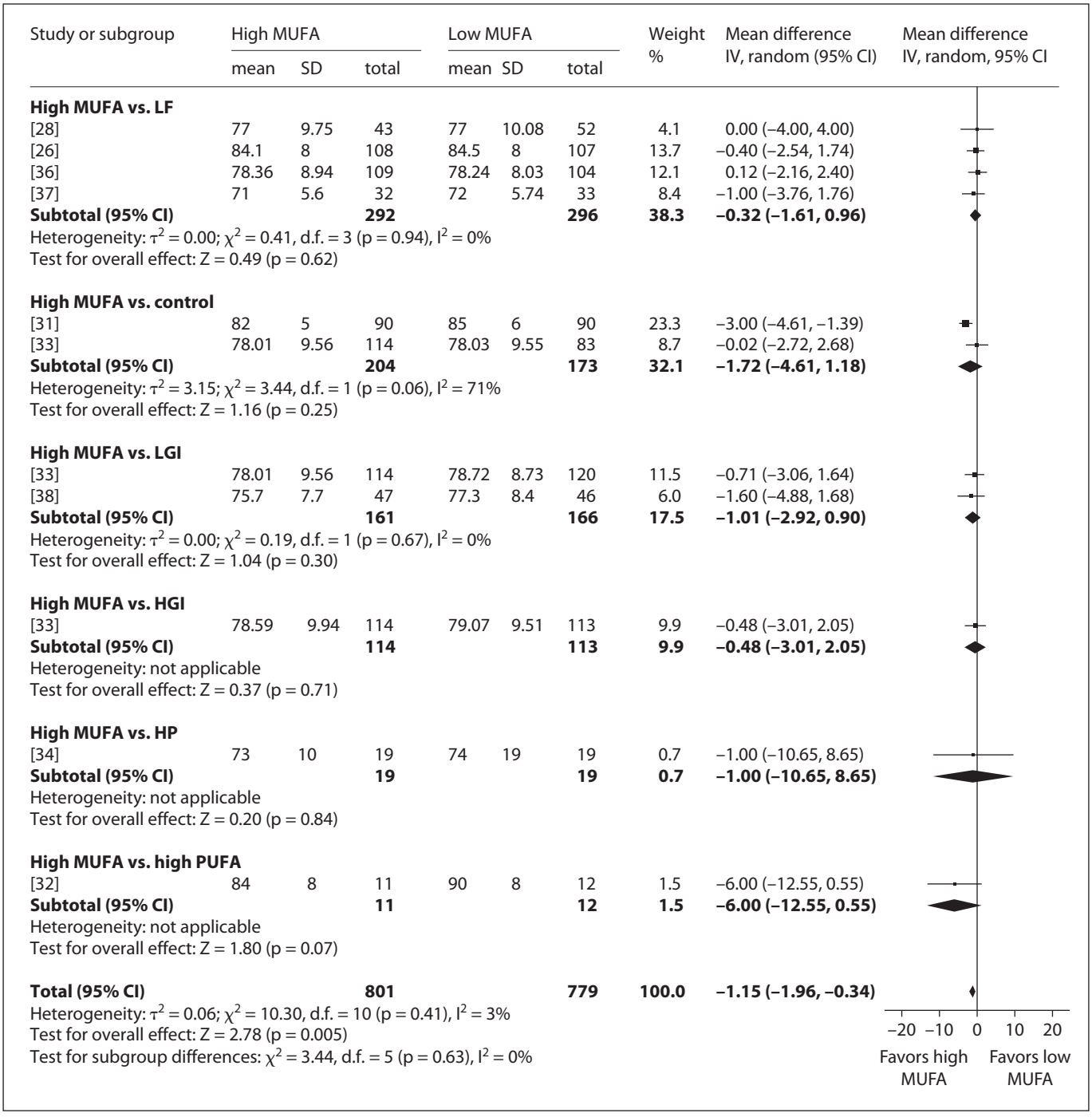

Fig. 4. Forest plot showing pooled WMD with 95% CI for DBP (mm Hg) for 9 randomized controlled high-MUFA diets. The different types of low-MUFA diets were separated into subgroups. For each high-MUFA study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study in the respective meta-analysis. The diamond at the bottom of the graph represents the pooled WMD with the 95% CI for the 9 study groups.

a 2-cm gain in WC. With respect to these observations, our findings remain inconclusive.

Regarding blood lipids, neither HDL cholesterol nor TG was significantly affected by the percentage of MUFA in the RCTs selected for this analysis. Nevertheless, choosing both as outcome measures for CVD is substantiated by a number of studies. Thus, data from the Framingham study showed that for every 0.96-mg/dl rise in HDL cholesterol, the risk of CHD decreased by 2% in men and by 3% in women [41], while TG are considered to be evidence-based risk factors for CVD [42, 43]. In the 10-year follow-up of the Caerphilly and Speedwell cohorts, high levels of TG and low levels of HDL cholesterol were independent risk factors of CVD and a predictor of ischemic heart disease following joined computations [44]. A decrease in mean arterial blood pressure by 3 mm Hg will reduce the risk of CVD by 5–10%, the risk of stroke by 8–15% and overall mortality by 5% [45]. Moreover, a mere 3% reduction of SBP decreased the mortality risk due to myocardial infarction by 8% [46]. In the meta-analysis, reductions in SBP as well as DBP were significantly more pronounced in participants executing a high-MUFA diet as compared to the various low-MUFA protocols. In a previous meta-analysis investigating the effects of high-MUFA versus high-carbohydrate (low-MUFA) diets on blood pressure, the authors concluded that a diet high in carbohydrates may be associated with elevations in blood pressure, which could not be observed following a high-MUFA protocol [47].

In another meta-analysis by Mensink et al. [48], investigating 60 controlled intervention trials, it was found that replacing carbohydrates by MUFA improved the ratio of TC:HDL cholesterol as well as LDL cholesterol, HDL cholesterol and TG values. Similar results were reported in diabetic subjects when comparing a high-MUFA diet to a high-carbohydrate diet [49]. Sofi et al. [50] analyzed cohort studies investigating a Mediterranean diet (which implies a higher amount of MUFA than usual) and observed a significant improvement in health status as indicated by a lower incidence in overall mortality (9%), cancer (6%), dementia (13%) and a decrease in mortality due to CVD (9%). In the Spanish branch of the EPIC study, adherence to a Mediterranean diet was associated with a significantly reduced risk for CHD, supporting its role in primary prevention at least in healthy populations [51].

To be categorized according to this review, high-MUFA diets had to exceed the threshold set by the Dietary Guidelines for Americans (i.e. >12% of TEC) [18]. The final percentage of MUFA in the included studies varied between 12.1 and 25%, posing the question of potential hazards associated with high MUFA contents. Increasing the percentage of MUFA in the diet will most likely result in a higher amount of total fat consumption. Indeed, RCTs using a high-MUFA approach included in this meta-analysis also had a mean fat content of 37% of TEC and, in most cases, exceeded the upper threshold value of 35% [26, 28–30, 33–35, 37, 38] recommended by most international dietary guidelines [16–19]. However, in all studies where the MUFA content exceeded 20% of TEC, no detrimental changes in cardiovascular-related biomarkers were observed [28–30, 34, 37]. Summing up the data of 9 individual trials, Willett postulated that a percentage of fat in the diet at a range of 18–40% will only minimally affect body weight [52]. In addition, the Women's Health Initiative Dietary Modification Trial failed to show a more pronounced weight reduction as well as favorable effects on lipoprotein risk factors in response to an LF diet as compared to a diet with a total fat content of 38.1% of TEC [53, 54]. These data indicate that low-MUFA/low-fat diets are not superior to high-MUFA diets, while vice versa, high-MUFA diets managed to exert beneficial effects that might represent a preventive measure with respect to CVD.

Limitations

This systematic review does not consider unpublished data, and it cannot be excluded that these results may have at least a moderate impact on the effects size estimates. Another limitation lies in the diversity of the publications taken into account. Heterogeneity with respect to study characteristics is a common problem in nutritional intervention trials. Therefore, it is not surprising that the literature chosen for our analysis varies according to the type(s) of diets used, definitions of MUFA diets, the study population, intervention time and long-term follow-up protocols. In the study by Wien et al. [37], MUFA were supplied in the form of almonds. Since energy extraction from nuts is incomplete, this might explain at least in part the positive effects of their high-MUFA protocol on outcome parameters such as body weight. In addition, the study by Shai et al. [36] was included, although a subgroup of participants (46 in the high-MUFA group and 38 in the low-MUFA group, respectively, adding up to approximately 40% of the study population) suffered from CHD. However, a rerun of the analyses without the respective data revealed that the impact of these studies on our results was not significant. Therefore, we decided to keep the data from these studies in the meta-analysis. Another general limitation is given

by the fact that the use of an RCT design in dietary interventions may not be appropriate. Patients within the control group who are not continuously monitored might also change lifestyle aspects of their lifestyle, such as nutrition, of their own accord, perhaps subconsciously or perhaps due to a metabolic response of the body, aiming to return to its initial weight.

Conclusion

This systematic review included long-term RCTs (≥6 months) published until December 2010 which compared high-MUFA and low-MUFA diets. Outcome measures for obesity and its comorbidities were weight, WC, FM, TC, LDL cholesterol, HDL cholesterol, TG, SBP, DBP and CRP. Taken together, the results point to a beneficial effect of diets that contain more than 12% of TEC (in the form of MUFA) on important risk factors such as FM or SBP and DBP. Therefore, international dietary recommendations directed to treat or prevent obesity and its associated CVD could bear in mind specific percentages of MUFA within the range of the current Dietary Guidelines for Americans.

Acknowledgements

The authors are grateful to Susan Jebb, PhD, Iris Shai, PhD, and Thomas Wolever, PhD for providing the raw data of their original studies for this meta-analysis and Cornelia Blank for carefully reading our manuscript.

The authors declare that they have no conflict of interest. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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