The Mediterranean Diet and Cardiovascular Disease: A Multilevel Meta-Analysis

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The Mediterranean Diet and Cardiovascular Disease: 
A Multilevel Meta-Analysis

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The Mediterranean Diet and Cardiovascular Disease: A Multilevel Meta-analysis

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**Introduction**

Cardiovascular diseases (CVD) are serious public health problems with growing substantial concern. As the leading cause of death worldwide for both biological sexes, The Centers for Disease Control estimate that in the United States alone, 610,000 Americans die from cardiovascular diseases each year\(^1\). Unfortunately, due to the complex physiology of the circulatory system as well as the complicated pathogenesis involved in diseases of the heart\(^2\), a gold standard for effective primary and secondary prevention is uncertain. Needed are evidence-based prevention programs designed to optimize health and vascular wellness.

Cardiovascular diseases are defined broadly as disorders pertaining to the heart and or blood vessels\(^3\). As an umbrella term for several complications, diseases of the heart vary in regards to symptomology and levels of potential irreversible damage\(^3,4\). Diseases of the blood vessels supplying the heart, brain, and appendages can lead to myocardial infarction, stroke, and oxygen deprived tissue death\(^3,4\). The complexity of the risk factors contributes to the development and pathogenesis of CVD, making direct causes elusive. Multiple risk factors act synergistically to cause the hallmark signs of CVD, including chronic inflammation and abnormal lipid metabolism\(^2,4\). Atherosclerosis, a precursor to many cardiovascular complications, is recognized as a chronic low-grade inflammatory disease of human arteries\(^2,5\) beginning within damaged vascular endothelium. In a systematic review published in 2016, Gimbrone et al\(^6\) referred to endothelial tissue as the “continuous cellular lining of the cardiovascular system”. This tissue becomes damaged by various stressors including bacterial toxins, tobacco smoke, elevated blood glucose,
and poor diet. The vessel wall becomes vulnerable with increased permeability, allowing for low density lipoprotein (LDL) molecules to become trapped within the layers of the arterial wall. This interaction triggers a complex pathogenic cascade into motion to signal the accumulation of macrophages, which modify the LDL particle into a premature fatty lesion or simply, a foam cell. The endothelial cells become activated by this chemical cascade, increasing the expression of multiple chemicals secreted from damaged vessel cells and macrophages. Continued structural maturing of fatty lesions result in the synthesis of a fibrous outer layer that protects a lipid dense, toxic core. Gimbrone notes that within one individual, multiple atherosclerotic plaques may coexist within the circulatory system. With that, each lesion may progress at its own stage of evolution beginning with an initial phase of endothelial dysfunction. Dysfunction localized within the endothelial cells may signal various developmental changes within the lesion(s). Continuing this discussion of lesion progression, this introduction will outline the integration of inflammatory processes and lipid metabolism in the development of an atherosclerotic lesion, paying specific attention to various biomarkers of dysfunction.

In a scientific statement written by health professionals from the Centers for Disease Control regarding inflammatory molecules and CVD, authors note that all stages of development of an atherosclerotic lesion from initial injury to complication are pieces of inflammatory response to injury. The established lesion signals the body’s primal response to tissue injury and contains multiple types of inflammatory cells that contribute to instability within the plaque. An increase in instability by pro-inflammatory cells may cause the plaque to dislodge itself from the arterial wall. A ruptured plaque may travel from
its location of origin and ultimately occlude arteries and block blood flow to various vital organs or appendages\textsuperscript{2-10}. As a result, vital tissues stop receiving nutrients and oxygen thus contributing to various heart disease related events, including cerebral vascular accidents, peripherary artery disease, and myocardial infarction. Two specific inflammatory cell types involved in atherosclerosis, cellular adhesion molecules (CAMs) and pro-inflammatory cytokines, are secreted from endothelial and inflammatory cells and contribute to lesion progression\textsuperscript{2,4-10}. Due to their influence on various mechanisms of cellular function, CAMs may serve as important diagnostic markers of early endothelial injury\textsuperscript{7}. Specific CAMs of interest include intracellular adhesion molecule (ICAM) and vascular cellular adhesion molecule (VCAM). In addition to CAMs, cytokines contribute to plaque instability\textsuperscript{2,4}, overall inflammatory response\textsuperscript{2,4} and may serve as early biomarkers of cardiovascular risk as well as fully developed CVD\textsuperscript{2,4}. Specific CVD-related cytokines of interest include C-reactive protein (CRP) and interleukin-6 (IL-6).

\textit{Cellular Adhesion Molecules.} In 1997, Devaux, et al.\textsuperscript{11} published a tissue study that reported significant expression of cellular adhesion molecules in tissue samples from failing human hearts\textsuperscript{11}. Furthermore, Devaux notes how cellular adhesion molecules interact with immune cells to allow for the migration of white blood cells to the site of inflammation\textsuperscript{11}. Since 1997, several studies note the selective adhesive properties of CAMs for pre-macrophage cells, as they are overlying the atherosclerotic plaque causing an increase in migration of immune cells to the site of vessel damage\textsuperscript{6-11}. Components of oxidized LDL particles may act as triggers for CAM expression inducing the atherosclerotic inflammation process\textsuperscript{6-11} suggesting that persistent ICAM expression could be a characteristic of chronic
inflammatory disorders. Soluble VCAM may be present in acute damage to the endothelium within major vessels and has been reported to be correlated with severity or “lesion burden” in atherosclerosis.

**Inflammatory Cytokines.** In 2004, Kanda et al. published a systematic review focusing on inflammatory cytokines and their clinical significance for cardiac patient care. Researchers noted the importance of understanding cytokines for clinicians to determine the severity of atherosclerosis as well as the role cytokines play in viral infections of the heart muscle and cardiac tissue rejection after grafting or transplant. Produced by damaged endothelial cells and the immune system, the IL6 cytokine may be a potent activator of immune response as well as a potential stimulator of CRP and other acute phase proteins. Clinicians reported elevated IL6 levels within the diseased cardiac muscle as well as in systemic circulation in the presence of heart failure while other inflammatory biomarkers were normal. Increased levels of circulating IL6 have been associated with disease severity and therefore could serve as important biomarkers of heart disease related outcomes such as unstable angina and heart failure. In addition, elevated levels of IL6 associated with less ability for the heart to pump blood, lower cardiac function, and poor prognosis. IL6 may also be an important predictor of localized cardiac dysfunction and endothelial deterioration as it is secreted during several developmental events noted in the timeline of maturing plaques. Due to the involvement in a localized inflammatory response, researchers speculate that this cytokine may be a crucial marker of multiple atherosclerotic lesions; with each lesion potentially progressing at independent rates, IL6 may be an important determinant of biological lesion stage.
While researchers note that IL6 may serve as a better predictor of localized early endothelial dysfunction, inflammatory cytokine CRP may serve as a more accurate indicator of systemic wide inflammation in patients with cardiac complications\textsuperscript{2,6-9,11}. Researchers note that these two cytokines may be connected since IL6 has been found to act as a potent stimulus of CRP production in the liver\textsuperscript{6,11}. In 2013, Stoner and colleagues investigated inflammatory biomarkers and their contribution to cardiovascular disease\textsuperscript{2}. In a systematic review, Stoner et al\textsuperscript{2} corroborates other research studies by noting that CRP can be viewed as a predictor for future CVD events, including myocardial infarction\textsuperscript{2,6,11}. Researchers also note that due to the complexities of CVD, certain cytokines and other inflammatory biomarkers may offer more insight to prognostic information while others may be more instrumental in predicting cardiovascular disease events\textsuperscript{2}. It is evident that chronic inflammatory cytokines have some influence on various cardiovascular disease complications. A reduction in inflammatory mediated pathways may contribute to improved arterial function thus possibly contributing to a healthier heart and therefore, a reduction in mortality.

\textit{Serum Lipid Disruption}. Similar to the primal response of the inflammatory process, the presence of tissue injury or chronic inflammation has been reported to trigger the disruption in serum lipid levels as well as the inherent biochemical composition of lipid molecules\textsuperscript{14,15}. In 2004, Esteve et al published an article examining the relationships with dyslipidemia, inflammation, and atherosclerosis. With activation of the inflammatory cascade, an increase in triglycerides\textsuperscript{14} is also noted. Inflammation may also affect enzyme activity of lipoprotein lipase, a vital player in lipoprotein metabolism\textsuperscript{14,16}. Cytokines including
CRP and IL6 have been noted to be elevated with serum lipid disruption and to normalize with resolving TG levels\textsuperscript{14}. In addition, rising IL6 levels have been associated with decreasing HDL and reverse cholesterol transport. Interleukin 6 may trigger composition changes of lipoproteins by increasing ratios of cholesterol and TG rich substances\textsuperscript{14,15}. The inflammatory process may also result in dysregulation of the LDL receptor resulting in accumulation of particles, which are prone to oxidation\textsuperscript{14,15}. Oxidized LDL is more pathogenic and may serve as important precursors to foam cells, a premature atherosclerotic lesion\textsuperscript{14}. Together these findings further reinforce the proposed integration of lipid metabolism within the inflammatory cascade.

It is evident that the inflammatory response to endothelial injury acts synergistically with molecules of lipid metabolism thus contributing to cardiovascular disease related outcomes. Lifestyle approaches for both primary and secondary prevention of CVD as well as chronic inflammation and dyslipidemia that highlight healthy dietary intake have become the focus of many treatment modalities. Recently praised in the Scientific Report of 2015-2020 Dietary Guidelines\textsuperscript{17}, the Mediterranean diet is a dietary pattern with promising health benefits. In addition, Mediterranean areas have lower morbidity rates and increased longevity\textsuperscript{18}. The Mediterranean Diet (MD) refers to the dietary pattern of its location. First introduced by Dr. Ancel Keys in the 1960s\textsuperscript{18}, the MD combines a variety of minimally processed food groups in moderation to provide a balanced, satiating meal pattern\textsuperscript{18}. The MD emphasizes the consumption of monounsaturated and polyunsaturated fats (primarily in the form of olives, olive oil, and nuts) as well as the daily consumption of vegetables, fruits, low fat dairy products, and whole grains\textsuperscript{18,19}. In addition to these guidelines,
consumption of fish twice weekly, poultry, legumes, and tree nuts are recommended. Eggs may be consumed 7 days a week. Individuals following the MD are encouraged to reduce the servings of processed items and red meat to at least 1-2 times per week. Moderate consumption of alcohol (in the form of wine at 1 drink/day for women and 2 drinks/day for men) is allowed. Physical activity to promote health and overall well-being is encouraged. In addition, the nutritional guidelines note that these dietary factors specific to the Mediterranean diet are contributors to a reduction in metabolic disturbances commonly seen in individuals that consume a poor quality diet\textsuperscript{17}. The report defines a suboptimal diet is as a dietary pattern with low fruit and vegetable intake, infrequent consumption of seafood, nuts, and legumes with increased consumption of sodium rich and processed foods\textsuperscript{17}. These characteristics of poor diet quality are eliminated when one follows a Mediterranean diet.

The Mediterranean diet and various health complications have been a focus of many types of research efforts including retrospective, prospective, and clinical trials. Among important literature, both the Lyon Heart Study (LHS)\textsuperscript{20} and the Prevención Con Dieta Mediterránea (PREDIMED)\textsuperscript{21} have been sources of promising evidence in relation to reducing and preventing CVD events. These studies were the first to investigate the cardio-protective effect of the Mediterranean diet on cardiovascular disease events using a randomized and controlled setting. The LHS compared a traditional MD to a control diet while the PREDIMED trial investigated the effect of enhanced Mediterranean diets with olive oil and nuts versus a low fat diet only. The PREDIMED trial extended MD investigation by questioning key food components of the MD pyramid\textsuperscript{21}. One of the first randomized
control trials with a longitudinal premise to investigate the cardio protective effect of the Mediterranean diet, the PREDIMED study spanned eleven primary care facilities across Spain and continues to deliver positive results. Cited in many research reports, these rather historical studies have outline beneficial effects of the MD for both cardiovascular disease and inflammation. Chiva-Branch et al\textsuperscript{5} cites PREDIMED results in a systematic review: greater adherence to MD is associated with a reduction in CVD events and related deaths\textsuperscript{5,21}. After 5 years, a relative risk reduction of major CVD events (MI, stroke, death) by 30\%\textsuperscript{5,21}. In addition, Chiva-Branch notes that two sub-studies of the PREDIMED trial revealed that after a 3-month MD dietary intervention a reduction in serum expression of CRP was observed\textsuperscript{5}. In another sub-study of PREDIMED, researchers were able to attribute these serum reductions to increased adherence to the MD as well as increased consumption of extra virgin olive oil, nuts, fruits, and vegetables\textsuperscript{5}.

Many research efforts in addition to the PREDIMED\textsuperscript{21} study have taken further steps to look closer at the specific roles of olive oil and tree nuts in the beneficial responses observed by individuals following the Mediterranean diet. As mentioned above, both olive oil and tree nuts are principal sources of dietary fat within the Mediterranean diet pattern\textsuperscript{18,19}. In a report published by Rigacci et al\textsuperscript{75}, the nutraceutical properties of olive oil in particular are discussed as well as their proposed benefits noted specifically for inflammatory atherosclerosis and CVD. Olive oil contains strong antioxidant properties that pose as a potent combator of localized and systemic inflammatory responses seen in atherosclerotic disease\textsuperscript{75}. Specific polyphenols isolated in the olive plant have been noted to favor longevity while reducing the inherent inflammatory response\textsuperscript{75}. In regards to tree
nuts, Souza et al\textsuperscript{76} notes a nutrient profile containing high levels of bioactive substances that influences a reduction in oxidative stress causing a protective effect against cardiovascular alterations\textsuperscript{76}. In addition to these findings, Souza et al\textsuperscript{76} discusses the importance of consuming a mixture of nuts to help intensify the cardio-protective and anti-inflammatory benefits attributed to nuts\textsuperscript{76}. Researchers describe a “balancing effect of nutrients” such as mono- and poly-unsaturated fats and minerals to target specific disease related markers involved in atherosclerotic cardiovascular disease\textsuperscript{76}. Due to the growing body of evidence pertaining to the Mediterranean diet pattern and its principal sources of dietary lipid (olive oil and nuts specifically), it is important to consider these key components of the MD as they do not diminish the overall dietary quality.

Taken together, these positive findings in regards to the MD dietary pattern, its key sources of lipid, and CVD support the beneficial effect of a Mediterranean diet pattern. However, it still remains unclear which particular characteristics of the MD interventions influence the greatest beneficial effect on cardiovascular disease events, inflammatory biomarkers, and serum lipid measures. It is also important to note that many of the current reports on MD and CVD yield controversial results and make it difficult for researchers to observe the efficacy of a dietary pattern over time and across multiple populations. These findings suggest further investigation is warranted to understand the connection between the Mediterranean diet patterns, cardiovascular disease events, and inflammatory cytokines.

\textit{Purpose and Specific Aims}

The purpose of this work is to study the relationship of the MD and cardiac related
events as well as potential diagnostic markers of disease severity by conducting a high quality meta-analysis. Due to the nature of the extracted data, two researchers and a third party expert (TBHM) recommended two different Meta analytic approaches a univariate (using fixed and random-effects assumptions) and a multivariate (using random-effect assumptions) approach; both approaches will include mixed-effects assumptions when predictors are included in the models. In addition to CVD related events and inflammation, the majority of studies included serum lipid measures as outcomes. Due to the apparent integration of inflammation and lipid metabolism as well as the increasing burden of CVD related complications, the following outcome measures were chosen for evaluation under both random-effect assumptions: 1) total CVD related events, 2) myocardial infarction, 3) CVD related death, 4) c-reactive protein, 5) interleukin 6, 6) intracellular adhesion molecule, 7) vascular cellular adhesion molecule, 8) triglycerides, 9) low density lipoprotein, and 10) high density lipoprotein. Due to the nature of included data as there are multiple subgroups per study, researchers determined a multilevel meta-analytic model was implemented to account for dependencies within the dietary comparisons. Therefore, under multivariate assumptions the following outcome measures were chosen for further investigation: CRP, IL6, ICAM, VCAM, TG, LDL, and HDL.

Several specific aims under each Meta analytic approach are outlined in detail below with the analysis performed.

Univariate Meta-Analytic Aims.

1. to obtain overall effect sizes under fixed- and random-effects assumptions for each outcome of interest (total CVD related events, MI, CVD death, CRP, IL6, ICAM,
VCAM, TG, LDL, and HDL)

2. to evaluate the variability/consistency across current available literature pertaining to this topic

3. to explain the variability across the study population using the moderator or predictor variable, intervention length

Multivariate Meta-analytic Aims.

1. to obtain overall random effect sizes for each outcome of interest (CRP, IL6, ICAM, VCAM, TG, LDL, and HDL) while accounting for multiple dietary comparision groups within each included study

2. to evaluate the variability/consistency across current available literature pertaining to this topic by examining the differences between each dietary comparision group

3. to further explain the variability across the study population using moderator or predictor variables coded during the data extraction process

The primary hypothesis for this paper is that both random and multilevel effects for outcomes of interest (CVD related events, inflammatory biomarkers, and serum lipid markers) will favor the Mediterranean diet interventions compared to baseline with a null hypothesis that the MD will have no impact on CVD related outcomes of interest. The second hypothesis is that the efficacy of the MD interventions with differ across studies for each of the outcomes in question; some interventions will have significant effect while others will not, allowing researchers to indicate benefit of the MD interventions over the control group. Particularly under multilevel assumptions, the individual Mediterranean diet
comparison groups will significantly differ from one another and will allow researchers to begin to observe dietary dominance of effect. The final hypothesis of this paper is that moderator or predictor variables related to sample characteristics and dietary intervention design will help explain potential sources of heterogeneity in both univariate and multilevel models.

**Methods**

*Literature Search.* Research studies published up until July 17th, 2015 were considered for the study sample. A comprehensive literature search was conducted with the assistance of the University of Connecticut Health Sciences librarian (JL), using a Boolean search approach with appropriate key words and Medical Subject Headings (MeSH). Examples of these search terms include, “Mediterranean diet,” “Mediterranean style diet,” “cardiovascular disease,” “heart disease,” “myocardial infarction,” “heart attack”, “stroke,” and “atherosclerosis.” Seven databases were searched including: PubMed, CINAHL, EMBASE (via Scopus), Academic Search Premier, PsycINFO, Agricola, and CAB direct, suggesting a comprehensive search strategy. Language was not restricted in these searches and translators were used when applicable. Please refer to Appendix 1 to view the comprehensive search details for each database. In addition to computer-assisted programs and electronic data base searches, all studies from Schwingshackl et al\textsuperscript{22} were also screened for inclusion. Please refer to Appendix 2 to review the study screening form used throughout the inclusion process. A list of excluded studies with corresponding reasons for exclusion is available upon request.
Selection Criteria. Original research articles that presented pre- and post- design results regarding MD and CVD related events (specifically, CVD related deaths and or myocardial infarctions) and or MD and at least one inflammatory biomarker of interest (CRP, IL-6, ICAM, VCAM) were included for analysis. Lipid measures were not a direct inclusion criterion rather merely a secondary analysis as the majority of reports reported both measures of inflammation and dyslipidemia. Reports investigating the efficacy of a balanced Mediterranean diet and or an enhanced Mediterranean diet with additional servings of olive oil or nuts on desired outcomes of interest were included for this analysis. Studies that did not provide baseline and post intervention data for CVD related deaths, heart attacks, or inflammatory biomarkers of interest were excluded. In addition, studies that focused only on specific particular components of the MD (such as just seafood, wine only, just olive oil, or nuts only) were excluded from analysis. Reports that failed to report necessary information to calculate effect sizes were also excluded. Relevance of included studies was assessed based on topic, keywords, title, and abstract by two independent researchers (JS and MC) using a hierarchical approach. Researchers consulted an additional third party expert (TBHM) when needed to resolve disagreements regarding inclusion and exclusion criteria. The initial search yielded a total of 1,019 abstracts with relevant key words. After screening, hand searching, and organizing studies, 27 studies with a total of 229 comparisons were included for meta-analytic analysis. These studies met our inclusion criteria and focused on the efficacy of a Mediterranean diet on CVD related deaths, myocardial infarction, and inflammatory biomarkers. Refer to Figure 1 to view a Preferred Reporting Items for Systematic Reviews and Meta-analyses or PRISMA
flow diagram of inclusion and exclusion process. A list of excluded articles with reasoning is available upon request.

*Data extraction.* A team of three Registered Dietitians, a physician, and a Biostatistician developed the comprehensive data extraction form and accompanying protocol originally in July 2014. The protocol included a manual and a data extraction form developed to guide our specific aims and hypotheses as well as to extract or code for information pertaining to sample characteristics including ethnicity, region and gender, intervention characteristics including length, diet type, macronutrient distribution, caloric intake, and participation in dietary counseling, as well as study design characteristics including experimental settings, control group, and number of interventions. The coding form and its manual included a total of 330 descriptive variables and other variables related to the general purpose of evaluating MD efficacy; both documents were initially pilot tested by two independent researchers in July 2014 (JS and MG) before a final review by additional experts (JB, JK, AK, TBHM). The data extraction form was later edited in August 2015 for purposes of the new specific aims and hypotheses of this study and to ensure that researchers obtain necessary information from included studies. Each study was independently reviewed and coded by two independent researchers (JS and MC). Discrepancies were resolved between the two investigators privately or with the help of a third expert when necessary (TBHM). Refer to Appendix 3 to view the comprehensive coding form and corresponding data extraction manual.

*Risk of Bias.* To assess risk of bias within included studies, the Cochrane Collaboration’s risk of bias tool was utilized. With this tool, researchers score items with
either a minus sign ("-") indicating high risk of bias; a plus sign ("+") indicating moderate risk of bias; or a double plus sign ("++") indicating low risk of bias for that parameter in question. Please refer to Figure 14 to review a graphical representation of Cochrane’s risk of bias tool. A total of 8 parameters were assessed addressing quality control issues relating to participant randomization procedures, subject allocation methods, blinding of subjects and personnel, attrition bias, and selective reporting. Methodological quality (MQ) rankings have been identified as an under-analyzed element of the data reported in meta-analyses\textsuperscript{24-26}. In this meta-analysis, MQ ratings calculated using a combined tool based on both Miller\textsuperscript{27} and Jadad’s\textsuperscript{28} methodological quality rating scales. Scores were coded individually and then totaled as separate variables for coding purposes. MQ was introduced as a possible moderator for multilevel analysis.

Effect sizes. Individual effect sizes (ES) were calculated for each intervention with desired outcomes of interest to assess the magnitude of change observed for the Mediterranean dietary intervention. ES were calculated as the standardized mean difference, \(d\)\textsuperscript{38}. The standardized mean change is the difference between the pre-test and post-test means for the sample in question, divided by the pre-test or post-test standard deviation\textsuperscript{40}. This allows for the comparison and or combination of results from several different study designs resulting in the elimination of the need to omit studies based on design differences. Individual effect sizes for each outcome were determined by calculating the standardized mean change for each study sample using data from various sources\textsuperscript{40}. The data extracted for individual effect size analysis could be presented as \textit{means±s.d.}, \textit{t}-\textit{test}, \textit{F}- \textit{ANOVA}, or \textit{mean±s.d.} change, among other units and using the calculator the
different statistical information is transformed in a common metric, $d$, across comparison and studies. Individual effect sizes were calculated using an Excel calculator created by Huedo-Medina et al\textsuperscript{39}. The effect size index, $d_i$, follows a normal distribution from negative infinity to positive infinity, containing zero as the null value\textsuperscript{31}. According to Cohen’s classification, the magnitude of the $d$ value can be interpreted as 0.25 for small effect, 0.5 for median effect, and 0.8 for large effect of outcomes of interest\textsuperscript{31}.

**Statistical Analysis.** All descriptive statistics about the study population were calculated using Excel\textsuperscript{29}. Inter-Rater Reliability (IRR) was conducted for all categorical and continuous variables using IBM SPSS version 22\textsuperscript{30}. Agreement of categorical variables were represented by the Kappa ($\kappa$) coefficient\textsuperscript{31} and Pearson’s correlation coefficient\textsuperscript{32} was used to calculate continuous variable agreement. We tested for publication bias or asymmetries using two inferential tests, Begg\textsuperscript{33} and Egger’s\textsuperscript{34} as well as two graphical tests, the trim-and-fill method\textsuperscript{35} and funnel plots\textsuperscript{36}. Remaining single level and multilevel statistical analyses with introduction of predictor variables was conducted using R version 3.1.2 “Metafor” package\textsuperscript{37}. All code for these analyses can be found in Appendices 4 and 5.

In addition to individual effect sizes, weighted fixed and random overall effect sizes were calculated at univariate and multivariate level\textsuperscript{41}. The fixed effect model assumes that the data is coming from the same population thus only accounting for within study variance\textsuperscript{41}. The random effect model assumes the data originates from multiple study populations thus accounting for both within and between study variance\textsuperscript{41}. Mixed-effects models were run also using different predictors in the model. In addition to a univariate
A multivariate or mixed effect approach was then implemented due to the fact that many studies included in this paper contain multiple dietary interventions as well as primary and secondary endpoints. This type of hierarchy leads to a nested structure within the data set that needs to be accounted for. These four interventions were categorized into: balanced Mediterranean diet (BMD), mixed nut enhanced Mediterranean diet (MDN), olive oil enhanced Mediterranean diet (MDOO), and control. The dietary interventions are clustered within reports resulting in significant dependencies related to the presence of multiple dietary interventions, which needs to be addressed. Ignoring dependencies within a data set can lead to bias within standard errors. This mistake would result in a Type 1 error with an inflated α level. To account for the nested structure and dependencies one
can explore more potential causes of heterogeneity by introducing explanatory or predictor variables to assess their influence on the magnitude of the effect size. In addition, correlations and associations between comparison groups may be observed and evaluated\(^4^5\). When interpreting multilevel results, the test for moderators or QM as along with its corresponding p.value should be noted. The QM is an inference test that helps determine model fit. A p.value of 0.05 or less indicates good model fitness. This value assists researchers in determining if the weighted effect sizes were significant and varied between each dietary comparison group. The individual p.values associated with each dietary comparison should correlate with the QM p.value and represent the significance of variability between dietary interventions within the multilevel model.

**Results**

*Description of Included Studies.* Inter-rater reliability testing resulted in a Kappa (k) coefficient of 0.93 representing a 93% agreement between two independent coders for categorical variables. Pearson’s coefficient of \(r=1\) was obtained for continuous variables. In total, there were 229 separate dietary interventions clustered within the 27 reports included for analysis. A description of included studies can be found in Table 1. Out of 27 reports, only 19% of studies (5) measured cardiovascular disease related deaths and or myocardial infarction. In sum, the studies contained 20,937 participants with an average of mean age (SD) of 54(13.10) years. Participants involved in studies that measured CVD related events totaled 15,974 individuals and had existing CVD risk factors or cardiac complications. Subjects on average mostly male (30.2% or n=6324 were female).
Individuals involved in studies that did not measure CVD events had either CVD risk factors, dyslipidemia, metabolic syndrome, diabetes mellitus, hypertension, obesity or a combination of these diseases. Table 1 describes disease type noted for each specific study. Depiction of baseline health status was provided in all 27 (100%) studies but only described the type of disease and or CVD risk factors as well as serum biomarkers at the beginning of intervention. Medications were not a part of any intervention however, 11 (41%) studies reported continuance of drug regimens when deemed necessary on a per subject basis. In total, 16 (59.3%) interventions allowed current smokers in the studies. Over half of the included studies, 18 reports in total (66.7%) did not specify weight loss as a result of interest; weight loss was not reported in these studies. A total of 20 studies (74.07%) were conducted in Europe, 3 (11.11%) were conducted in the United States, 2 (7.40%) in Australia, 1 (3.7%) in Africa, and 1 (3.7%) in Asia. All reports were published in English. The studies were published between 1994 and 2015 (mean = 2008, SD = 5.29). The average impact factors is 10.93 (SD = 14.25). Both one-on-one intervention and small group intervention levels were measured in 19 (70.3%) of the included studies. The minimum intervention length was 8 weeks and the maximum intervention length was 208 weeks (mean=50.31, SD=58.58). No significant asymmetries were found using either statistical tests or the graphical techniques. A summary of the publication bias results can be found in Table 2.

Univariate Approach

Random Effects. Please refer to Table 3 for an overall summary of univariate results with corresponding Q and I^2 values. Overall the Mediterranean diet had beneficial effects
for 9 out of 10 outcomes of interest. Weighted effect sizes modeled under random effects assumptions attest that the MD had a significant overall effect on total cardiovascular related events ($d_+= -0.37$, 95% CI −0.57 to −0.17), myocardial infarctions ($d_+= -0.32$, 95% CI −0.57 to −0.08), and CVD related death ($d_+= -0.44$, 95% CI −0.78 to −0.089). The Mediterranean diet interventions exerted a favoring response on inflammatory biomarkers CRP ($d_+= -1.02$, 95%CI -1.70 to -0.34) and IL6 ($d_+= -1.48$, 95%CI -2.24to -0.73). Favorable results were also observed for cellular adhesion molecules, ICAM ($d_+= -4.32$ 95%CI -8.37 to -0.26;) and VCAM ($d_+= -1.61$, 95%CI -2.61 to -0.60). Results for lipid disruption indicate beneficial effect on serum lipid markers TG and LDL ($d_+= -0.63$, 95%CI -0.95 to -0.31; $d_+= -1.15$, 95%CI −1.70 to −0.60, respectively). Finally, results for HDL cholesterol ($d_+= 0.15$, 95%CI -0.02 to 0.33) indicate an insignificant effect on this particular serum lipid biomarker.

The ratio of the between-studies variability out of the total variability, $I^2$, was noted to range from 91.21% to 99.97%, indicating that significant variability is present within the models. Please refer to Figures 2-11 to view forest plots for desired outcomes of interest pertaining to CVD related events, inflammation, and dyslipidemia. Significant heterogeneity or variability was found within the study population.

**Mixed-effect Meta-regressions.** Meta-regressions using the moderator variable number of weeks or intervention length were conducted for each of the 7 outcomes of interest. A significant moderating effect by the variable weeks or intervention length, was noted for VCAM ($\beta = -0.0607$, 95% CI -0.1082 to -0.0148) The MD had a greater beneficial effect on serum VCAM levels in longer interventions, In addition, researchers note that the longer subjects adhered to MD interventions, the greater the improvement in HDL.
(\beta=0.0061, \ 95\% \ CI \ 0.001 \ to \ 0.01). \ Intervention \ length \ accounted \ for \ 40.36\% \ of \ heterogeneity \ between \ studies \ for \ the \ variable \ VCAM. \ In \ addition, \ the \ number \ of \ weeks \ explained \ 22.30\% \ of \ heterogeneity \ within \ the \ study \ population \ in \ regards \ to \ MD \ on \ HDL. \ The \ moderator \ weeks \ accounted \ for \ some \ heterogeneity \ within \ the \ study \ population \ for \ both \ VCAM \ and \ HDL.

**Multivariate Approach**

A multilevel technique was used for analysis of both inflammatory biomarkers (k=89) and serum lipid measures (k=112). When applicable, four diet types were accounted for during analysis including a balanced Mediterranean diet (k=73) or BMD, enhanced Mediterranean Diet with mixed nuts (k=23) or MDN, enhanced Mediterranean diet with olive oil (k=24) or MDOO, and a control group (k=81). Results for BMD, MDN, and MDOO only will be discussed in this paper as the specific objectives aim to investigate Mediterranean diet groups only. The multivariate meta-analytic models were conducted for each outcome of interest using sub-groups of weighted effect sizes. Please refer to Tables 5 and 6 for a summary of each multilevel model.

**C-reactive Protein.** The multilevel model for CRP was conducted using 41 comparisons clustered within 17 reports. Overall, the multilevel model revealed that a balanced Mediterranean diet (BMD) and an olive oil-enhanced Mediterranean diet (MDOO) exerted beneficial effects on CRP that were statistically different from the MDN group (d,=\ -4.44, \ 95\%CI=-6.75 \ to \ -2.14; \ d,=\ -8.41, \ 95\%CI=-13.53 \ to \ -3.29 \ respectively). The mixed nut-enhanced Mediterranean diet (MDN) was found to have an non-significant effect when compared to BMD, and MDOO groups (d,=\ -0.22, \ 95\%CI=-2.2 \ to \ 1.76). The multilevel
model for CRP revealed a test of moderator statistic or QM of 25.123 \( (p.value=<.0001) \), suggesting that the efficacy of dietary interventions differed significantly from one another with good model fit. Please refer to Table 5 to review the results of this multilevel model in table format.

*Interleukin-6*. The model for IL6 was conducted with 24 comparisons which were clustered within 10 reports. Overall, the multilevel model revealed that the BMD, MDN, and MDOO exerted beneficial effects that were statistically different from each dietary comparison according to the respective \( p.values \) \( (d_+=13.72, 95\% CI -21.23 \text{ to } -6.23; d_+=3.74, 95\% CI -6.10 \text{ to } -1.38; d_+=2.97, 95\% CI -4.78 \text{ to } -1.15, \text{ respectively}). \) The multilevel model for IL6 resulted in a QM value of 23.2952 \( (p.value=.0001) \), suggesting that the dietary interventions in question differed significantly from one another to some degree with good model fit. Please refer to Table 5 in the appendix to review the results of this multilevel model in table format.

*Intracellular Adhesion Molecule*. The multivariate model for ICAM was conducted with 13 comparisons clustered within 5 reports. Individual \( p.values \) at or above 0.05 confirm that the dietary comparisons did not differ in effect. Overall, the multilevel model revealed that BMD, MDN, and MDOO groups had a non-significant effect for ICAM serum levels under mixed-effect assumptions \( (d_+=2.86, 95\% CI -6.03 \text{ to } 0.31; d_+=2.05, 95\% CI -17.56 \text{ to } 13.46; d_+=1.93, 95\% CI -7.123 \text{ to } 3.26, \text{ respectively}). \) The inferential test for moderators or QM for this multilevel was 6.9250 \( (p.value=0.1399) \) suggesting the fit of this model was not significant. These values correlate with the results as the effect sizes for each dietary
intervention did not result in statistically significant Cis with variability. Please refer to Table 5 in the appendix to view the results for this multilevel model in table format.

**Vascular Cellular Adhesion Molecule.** The multivariate meta-analytic model for VCAM was conducted with 11 comparisons that were clustered within 4 studies. Overall, the multilevel model revealed that MDOO was beneficial in regards to VCAM serum levels ($d_z=-3.31$, $95\% CI$ $–6.48$ to $–0.14$). Both BMD and MDN dietary interventions were both found to have an insignificant effect on VCAM that was not significantly different from the MDOO group ($d_z=-0.36$, $95\% CI$ $–2.57$ to $1.84$; $d_z=-4.19$, $95\% CI$ $–8.63$ to $0.24$, respectively). The multilevel model for VCAM resulted in a QM value of $39.8860$ ($p.value=<.0001$) suggesting good model fit and that at least one of the dietary comparison’s effect differed significantly from the others in question. Please refer to table 5 in the appendix to view results for this multilevel model in table format.

**Triglycerides.** The multivariate model for TG was conducted with 40 comparisons that were clustered within 17 reports. Overall, the multilevel model revealed that beneficial effect on TG by BMD that was significantly different from MDN and MDOO groups ($d_z=-3.0$, $95\% CI$ $–4.91$ to $-1.08$). The enhanced Mediterranean diets with mixed nuts was found to be insignificant under mixed-effect assumptions and did not differ significantly from one another ($d_z=-0.17$, $95\% CI$ $–6.76$ to $6.42$; $d_z=-2.85$, $95\% CI$ $–9.20$ to $3.50$ respectively). The inferential test QM revealed a value of $27.3081$ ($p.value=<.0001$) suggesting good model fit as well as varying effect of dietary comparisons in question. Please refer to table 6 in the appendix to review the corresponding results for the TG model in table format.
Low Density Lipoprotein. The model for LDL was conducted using a total of 34 comparisons clustered within 14 studies. Overall, the multilevel model revealed that the BMD was beneficial for LDL levels and was significantly different when compared to MDN and MDOO groups ($d_+ = -3.46$, 95%CI $-5.53$ to $-1.38$). Both of the enhanced Mediterranean diets were found to have insignificant effect on LDL markers ($d_+ = -3.37$, 95%CI $-7.72$ to $0.98$; $d_+ = -3.5$, 95%CI $-8.34$ to $1.32$, respectively). The inferential test QM resulted in a value of 12.8939 ($p.value = 0.0118$) suggesting decent model fit as well as a varying effect in regards to the dietary comparisons in question, specifically the BMD group. Please refer to table 6 to view the results of this multilevel model in table form.

High Density Lipoprotein. The model for HDL involved 38 comparisons clustered within 16 reports. Overall, the multilevel model revealed that BMD had a significantly different beneficial effect for HDL serum levels when compared to MDN and MDOO groups ($d_+ = 3.03$, 95%CI 1.38 to 4.67). Both enhanced MD groups, MDN and MDOO, revealed insignificant results that did not vary from one another ($d_+ = 3.11$, 95%CI -0.20 to 6.43; $d_+ = -1.58$, 95%CI -4.73 to 1.57, respectively). The inferential test or QM resulted in a value of 18.8379 ($p.value = 0.0008$) suggesting good model fit as well as a varying effect of the dietary interventions in question, specifically the BMD group. Please refer to table 6 in the appendix to view the results for the multilevel HDL model in table format.

Moderator Analysis Using Multivariate Approach

Please refer to Table 7 for complete description of moderator results, including point estimates, 95% confidence intervals, p.values, and corresponding $i^2$ values for each dietary
comparison. $I^2$ results ranged from 89.28% to 99.95% within all multilevel models using moderators. Studies included in this analysis varied in terms of intervention length, mean age, number of female participants, region of study conduction, funding source, participant recruitment locations, level of intervention, and methodological quality. Please refer to Table 9 for a complete list of moderators that produced non-significant results. Refer to Table 10 for a complete list of moderator variables that were unable to be analyzed due to lack of reporting. Additional significant trending associations for each moderator of interest can be observed for all CVD related outcomes. Please refer to Tables 8 through 14 to review important statistics for observed beneficial associations. The effect of the moderator is presented as mods and is considered an unstandardized beta ($\beta$). This value represents the quantity of how the effect size behaves, whether it is increasing or decreasing based on each unit of the moderator variable in question. Individual effect sizes under multivariate assumptions are listed for each diet with the corresponding confidence intervals representing the efficacy of the reference dietary intervention when compared to other dietary comparisons and adjusted for number of weeks. The corresponding $p.value$ represents the significance in variability between the dietary comparison factors.

In regards to design characteristics, intervention length was found to have an overall moderating for the VCAM model, $\beta=-0.06$ (95% CI -0.09 to -0.03) only. In general, BMD group had greater beneficial effects on biomarkers CRP, IL6, and TG in longer interventions when compared to MDN, MDOO, and control groups. Both enhanced Mediterranean diet groups, MDN and MDOO, had an enhanced significant effect on LDL when adjusted for intervention length and compared to BMD and control diets. The longer
the intervention length, the MDN group exerted a greater effect on IL6 in longer interventions while the MDOO group was beneficial for CRP. In addition to number of weeks, region of study conduction was tested for its moderating effect. Studies conducted in Europe measuring LDL had moderating effect $\beta=-2.0057$ (95% CI -3.1102 to -0.9013). Results show that when adjusted for study region, BMD exerted a greater beneficial effect on CRP and TG that differed significantly from the enhanced Mediterranean diet groups. The MDN comparison groups had a statistically different effect on CRP and ICAM when compared to BMD and MDOO groups while MDOO groups were more beneficial for CRP when controlled for study region. In regards to VCAM ($k=11$), all studies were conducted in Europe thus resulting in output error during analysis. Researchers eliminated the piece of code pertaining to factored moderators in order to obtain observable results. Both BMD and MDN had beneficial effects on VCAM when adjusted for study region. Studies recruiting patients from a clinical setting acted as an overall moderating in the IL6 model, $\beta=-3.68$ (95% CI -6.99 to -0.37) only. Effect size of BMD on LDL after adjustment of recruitment location was more beneficial when compared to enhanced Mediterranean diet groups. The efficacy of the MDOO groups on LDL and CRP were influenced by subject recruitment and produced statistically different effects when compared to other Mediterranean diet groups. In regards to ICAM ($k=13$) and VCAM ($k=11$), all subjects were recruited from a clinical setting resulting in errors in analysis output when using the factored moderator code. Beneficial effects were observed for BMD groups on VCAM and for MDN groups on ICAM and VCAM once the factored moderator code was eliminated. Funding source was also tested as a factored moderator for all inflammatory and lipid markers.
Sources of funding varied between each included study with a categorical classification of government source, academic source, private source, or multiple sources. Academic sources of funding had a modulating effect on VCAM, $\beta=-3.57$ ($95\%$ CI -4.67 to -0.47) as well as LDL, $\beta=-2.08$ ($95\%$ CI -3.87 to -0.30). In addition to academic funding sources, a modulating effect was also noted for private funding sources for TG, $\beta=-0.61$ ($95\%$ CI -1.19 to -0.03) and LDL, $\beta=-1.28$ ($95\%$ CI -2.55 to -0.001). Finally, funding from multiple sources was found to have a modulating effect on TG, $\beta=-0.87$ ($95\%$ CI -1.50 to -0.23).

Studies within the included population varied in regards to the level of intervention or supervision provided for subjects participating in the dietary interventions. Responses included one on one, small group interventions, supervised sessions, unsupervised sessions, or incentives. As previously stated in the descriptive results, the majority of studies conducted dietary interventions with small group processes. Due to the categorical nature of this variable, factored moderator analysis was conducted using the same syntax stated above. Under random-effect assumptions, small group intervention level had an overall moderating effect on the inflammatory biomarker, VCAM ($\beta=-2.56$, $95\%$CI -4.71 to -0.42). In regards to the most common intervention level used in the interventions included for VCAM specifically, 82% of dietary interventions were conducted in small groups. The efficacy of the BMD groups on TG and LDL were influenced by small group intervention studies following adjustment. A beneficial effect was also noted for MDN groups on LDL. More intimate group sessions also enhanced the effect of the MDOO interventions on both CRP and LDL.
Within the included study population, researchers noted variance between reports based on randomized control trial methodological quality (MQ). In this meta-analysis, researchers used two measures of methodological quality or risk of bias, previously described in the methods section of this paper. The total score calculated using the scale adapted by a third party expert (TBHM) from Miller and Jadad assessment tools, was introduced as a predictor or moderator variable for each variable in question. Methodological quality was found to not have an overall moderating effect on any of the inflammatory or lipid measures. Overall study MQ was found to have influence on the MDOO groups’ effect on CRP, IL6, and LDL studies after adjustment and comparison to other interventions. In addition, the effect of MDN groups of IL6 and LDL were also affected by overall study MQ after adjustment. The magnitude of effect in regards to the BMD group on IL6 was also found to be affected by study quality.

In regards to population characteristics, multilevel analysis reports that age did not have an overall moderating effect for any of the outcomes of interest. The effect of the balanced Mediterranean diet (BMD) on VCAM was found to have a greater beneficial after adjustment of subject age when compared to other Mediterranean diet groups. The beneficial effect of olive oil-enhanced Mediterranean diet (MDOO) groups was also enhanced by mean age for both CRP and VCAM. The mixed nut-enhanced Mediterranean diet groups (MDN) had statistically different effect on VCAM in older populations when compared to BMD and MDOO groups. In regards to number of female participants, BMD efficacy was significantly different than enhanced groups and influenced by number females reported in the dietary interventions in five out of seven factors. Serum markers
for CRP, IL6, VCAM, TG and LDL had significant effect sizes after adjusting for the number of females. Multilevel analysis reports a greater beneficial effect in female subjects allocated to MDN groups on the following outcomes IL6, ICAM, VCAM, LDL, and HDL. The MDOO group was more beneficial in female participants for CRP, VCAM, LDL, and HDL.

Risk of bias was low for random sequence generation, allocation, blinding, incomplete outcome data, selective reporting, and other potential sources of bias for the many of studies. Low incidence of high risk of bias of included studies. Please refer to Figure 14 for a complete Risk of Bias Summary.

Discussion

The results of this high-quality meta analysis begin to shed light on the benefits of consuming a balanced Mediterranean diet as well as additional dietary enhancement with increased ratios of olive oil or mixed nuts on cardiovascular disease and associated markers of disease severity. The significant heterogeneity observed in this work was partially explained by intervention length, recruitment location, funding source, region of study conduction, and intervention level. In addition, by accounting for each comparison, researchers were able to further explore interesting associations between a balanced Mediterranean diet and two vital components needed to achieve the most balanced form, olive oil and nuts. To our knowledge, this is the first multilevel meta-analysis examining the efficacy of different variations of the Mediterranean diet on CVD, inflammatory biomarkers, and serum lipid measures.
Our findings that a balanced Mediterranean diet pattern as well as enhanced MDs with increased ratio of olive oil and mixed nuts is beneficial in reducing CVD related events and markers of disease severity compliment if not extend previous research efforts. Previously published meta-analyses published on the MD and CVD risk factors report similar beneficial effects on inflammatory biomarkers and serum lipid measures\textsuperscript{22,73,74}. In addition, these studies note similar associations in regards to moderator analysis using intervention length\textsuperscript{73,74}, region of study conduction\textsuperscript{73,74}, and intervention level\textsuperscript{25}. In general, individuals adhering to a Mediterranean diet saw greater beneficial effects when studies were conducted in the Mediterranean basin and with longer duration. In the present meta-analysis, as the majority of studies were conducted in Europe, specifically countries located in the Mediterranean basin, these findings illuminate the possible predictors of Mediterranean diet food quality, food culture, and overall access to traditional food components. Researchers also have considered the baseline health parameters for individuals in the Mediterranean basin. Further investigation is warranted to explore specific cultural food practices and their impact on cardiovascular health. In addition, participants who followed a balanced Mediterranean diet for longer interventions, saw greater reductions in CRP, IL6, and TG. Longer enhanced MD groups had greater effect on LDL for both mixed nuts and olive oil. Longer adherence to healthy dietary patterns may prove to be more beneficial for long term health and maintenance periods. Interestingly, our findings pertaining to intervention level or delivery of educational sessions to promote adequate compliance to dietary therapies, further extend the results of a recent meta-analysis developed by our research team\textsuperscript{25}. While the majority of studies were conducted
using small group proceedings, these findings further extend the existing literature on the importance of more targeted, personal interventions. Small groups may also bring in an additional peer support aspect, as study participants in the same group may be able to provide continued motivation from a more relatable source rather than a principal investigator.

To our knowledge, there is one meta-analysis specifically focusing on a Mediterranean diet pattern, endothelial function, and inflammation. This 2014 meta-analysis by Schwingshackl et al included 17 randomized control trials totaling 2300 subjects. Overall, researchers noted a significant decrease in markers of endothelial dysfunction as well as reductions in specific inflammatory cytokines, CRP and IL6, and intracellular adhesion molecules. Our current findings compliment Schwingshackl et al in that significant reductions were also noted for CRP, IL6, and VCAM specifically.

One notable difference between Schwingshackl et al and this present meta-analysis, is that we considered not only a balanced Mediterranean diet pattern but, additional MD interventions with increased ratios of olive oil and mixed nuts. One interesting recurrent theme worth noting throughout our multilevel results was the effectiveness of the enhanced Mediterranean diet with mixed nuts on interleukin-6 as well as the enhanced Mediterranean diet with olive oil on C-reactive protein. Perhaps these results begin to describe some of the targeted benefits observed for this specific dietary pattern. Thus, the question of interest is if health care professionals could provide a more targeted dietary therapy for these specific inflammatory biomarkers. This association reoccurring theme warrants further investigation into specific nutrient profiles and overall
biochemical composition of these two Mediterranean diet staples. These results may further suggest an underlying biochemical mechanism and or connection between mixed nuts and interleukin 6 as well as for olive oil and c-reactive protein. Clinicians may eventually be able to choose to tailor dietary prescriptions depending on a patient’s specific clinical presentation.

In summary, our research findings suggest a significant cardio-protective effect exerted by the Mediterranean diet that extends beyond a more general view of the dietary pattern. By implementing a multilevel meta-analytic approach, researchers were able to further explore more targeted strategies related to possible clinical predictors. By implementing a multilevel model, notable associations were observed that may provide insight in development of targeted dietary prescriptions for specific inflammatory biomarkers and serum lipid measures. Early detection of rising cellular adhesion molecules may provide insight to the beginning stages of the inflammatory response allowing for more rapid preventative care. In patients with existing complications, targeted dietary therapies using a greater proportion of olive oil may be suitable for patients with chronic systemic inflammation while an increased ratio of mixed nuts, may be more suitable for a localized reaction within the endothelium.

*Practical Application.* The results of this multilevel meta-analysis contribute to the expanding wealth of evidence related to the Mediterranean diet and health, particularly cardiovascular related disease, inflammation, and serum lipid disruption. By attempting moderator analysis with only few variables with an overall effect, this meta-analysis demonstrates the importance of thoroughly reporting design characteristics,
randomization procedures, dietary intervention guidelines, behavioral interventions used, and tools used for compliance. Having more detailed information for extraction would allow for additional moderator analysis with hopes of continued identification of potential predictors that may influence effect size magnitude. This meta-analysis may be influential in various health care fields (medical, nutrition, and dietetics) as the level of intervention had significant influence and associations on many outcomes in question. These findings suggest that small group interventions may prove to be more beneficial and more motivating in regards to health behavior changes. Most studies that involved dietary education, enlisted the help of a Registered Dietitian to carry out dietary comparison instruction. Dietitians should have a primary role in dietary intervention trials as they are considered experts in the field of nutrition and dietetics. In addition, RDs are trained in various counseling techniques and strategies that may be implemented when dietary adherence is poor. These findings extend recent research results concerning Mediterranean diet education delivered in small group interventions. Garcia, et al.\textsuperscript{25} notes in another high quality meta-analysis, that significant beneficial effects were found in studies that focused on small group education and intervention proceedings.

\textit{Study Limitations and Strengths.} This meta-analysis has several limitations and strengths. One limitation would be that the significant heterogeneity between the studies still remains unexplained after both univariate and multilevel analysis. In addition, multiple coded variables did not have enough data reported to utilize in moderator testing. Due to inconsistent reporting, we were unable to control for macronutrient distribution, caloric content, or physical activity level within the models. There is also the potential for
ecological fallacy considering we did not have access to raw study data for this analysis. In that, we should be cautious about translating effect size into individual results. One final note of caution would be the nature of the data, for ICAM and VCAM specifically. Clinical measures for these markers had larger ranges of serum levels reported, which should be considered when interpreting results.

There are multiple strengths for this meta-analysis. In regards to the search strategy implemented, our research team used a comprehensive literature search within seven electronic databases. A comprehensive coding form and manual was revised specifically for this paper and used for data extraction that resulted in 93% agreement between two independent researchers. Lastly, we performed a meta-analysis at two levels: univariate and multivariate. To our knowledge, this is the first meta-analysis to account for dependencies within the dataset to further explore dietary dominance and significant associations with population characteristics across the current literature on this topic.

*Future Research Directions.* To our knowledge, this meta-analysis is the first to implement a multilevel technique to further investigate dietary dominance within the included sample. Researchers were able to observe some significant associations in regards to a balanced Mediterranean diet and enhanced Mediterranean diets with greater proportions of nuts or olive oil. In this analysis, mean differences are correlated due to the repeated use of sample information from the control group\textsuperscript{46}. In order to further investigate dietary dominance, researchers have determined that the next logical step in this ongoing meta-analytic project would be a network meta-analysis\textsuperscript{47}. Only conducted in few reports
and criticized for complexity, a network meta-analysis (NMA) allows for synthesis of both direct and indirect evidence observed within a network of trials with three or more comparison groups\textsuperscript{47}. A NMA allows researchers to simultaneously compare multiple treatment groups within a single statistical model\textsuperscript{47}. We feel that a NMA would be a vital statistical model to include within the developing wealth of research pertaining to the Mediterranean diet considering many studies are conducted with multiple dietary interventions. By using a network meta-analytic model, researchers would be able to rank treatment options from most beneficial to least beneficial thus providing more targeted results per outcome of interest.

**Conclusion**

The results of the present meta-analysis suggest that adherence to the overall Mediterranean diet as well as enhanced MD varieties, can have significant beneficial effects on cardiovascular disease related events, inflammatory biomarkers, and dyslipidemia. More high-quality intervention studies are needed to evaluate the relationship between the traditional MD and the specific roles of olive oil and mixed nut varieties play within this promising dietary pattern, food culture, and lifestyle. This high quality meta-analysis on the effect of the TMD and enhanced varieties on CVD related events, inflammatory biomarkers, and dyslipidemia markers contributes to the expanding wealth of research in favor of the Mediterranean dietary pattern effects on cardiovascular disease related outcomes.
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Figure 1. PRISMA Figure Outlining the Process of Study Identification, Screening, Eligibility, and Inclusion

Records identified through electronic database searches after removing duplicates (k=1019)
- PubMed (k=568)
- EMBASE via Scopus (k=149)
- Academic Search Premier: (k=208)
- CINAHL (k=40)
- Agricola (k=40)
- PsycINFO (k=14)
- CAB Direct (k=423)

Records screened (k=1019)
- Duplicate screening (JS and MC)

Records excluded by title and abstract (k=953)

Full text reports assessed for eligibility (k=66)

Full text reports excluded, with reasons (k=40)
- Used the same database as other sources (k=7)
- Did not report data on an outcome of interest (k=2)
- Did not provide sufficient evidence to calculate effect sizes (k=8)
- Not on the Traditional Mediterranean Diet (k=9)

Reports included in the analysis (k=27)
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<th>Recruit</th>
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<td>Estruch, et al (2009)&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Spain</td>
<td>772</td>
<td>56</td>
<td>68.9</td>
<td>DM, CVDRF</td>
<td>PREDI MED</td>
<td>MDN,MDOO</td>
<td>12</td>
<td>LFD</td>
<td>CVDRF Inflam</td>
</tr>
<tr>
<td>Estruch, et al (2006)&lt;sup&gt;59&lt;/sup&gt;</td>
<td>Spain</td>
<td>772</td>
<td>56</td>
<td>68.9</td>
<td>DM, CVDRF</td>
<td>PREDI MED</td>
<td>MDN,MDOO</td>
<td>12</td>
<td>LFD</td>
<td>CVDRF Inflam</td>
</tr>
<tr>
<td>Estruch, et al (2013)&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Spain</td>
<td>4282</td>
<td>57.5</td>
<td>67</td>
<td>DM, CVDRF</td>
<td>PREDI MED</td>
<td>MDN,MDOO</td>
<td>104</td>
<td>LFD</td>
<td>Events</td>
</tr>
<tr>
<td>Authors</td>
<td>Country</td>
<td>Sample Size</td>
<td>Gender</td>
<td>Healthy</td>
<td>T2DM, CVDRF</td>
<td>CRF (100%)</td>
<td>DM (100%)</td>
<td>Inflam events</td>
<td>Diet</td>
<td>Inflam s.lipids</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------</td>
<td>-------------</td>
<td>--------</td>
<td>---------</td>
<td>-------------</td>
<td>-----------</td>
<td>-----------</td>
<td>---------------</td>
<td>------</td>
<td>----------------</td>
</tr>
<tr>
<td>Itsiopoulos et al. (2010)</td>
<td>Australia</td>
<td>27</td>
<td>41%</td>
<td>Healthy</td>
<td>Primary Care Center</td>
<td>MDOO, MD</td>
<td>41%</td>
<td>DM (100%)</td>
<td>Regular</td>
<td>Inflam s.lipids</td>
</tr>
<tr>
<td>Konstantinidou et al. (2010)</td>
<td>Spain</td>
<td>90</td>
<td>71%</td>
<td>Healthy</td>
<td>MDOO</td>
<td>12</td>
<td>Regular</td>
<td>S.lipids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martinez et al. (2010)</td>
<td>Spain</td>
<td>7216</td>
<td>NR</td>
<td>Healthy</td>
<td>T2DM, CVDRF</td>
<td>MDOO MDN</td>
<td>51.6</td>
<td>WD</td>
<td>Events</td>
<td></td>
</tr>
<tr>
<td>Mekki et al. (2010)</td>
<td>Algeria</td>
<td>40</td>
<td>45%</td>
<td>Healthy</td>
<td>Hospital</td>
<td>MD</td>
<td>12.9</td>
<td>WD</td>
<td>Inflam s.lipids</td>
<td></td>
</tr>
<tr>
<td>Mena et al. (2009)</td>
<td>Spain</td>
<td>106</td>
<td>43%</td>
<td>Healthy</td>
<td>DM CVDRF</td>
<td>MDOO, MDN</td>
<td>12</td>
<td>LFD</td>
<td>Inflam s.lipids</td>
<td></td>
</tr>
<tr>
<td>Mezzano et al. (2001)</td>
<td>Chile</td>
<td>42</td>
<td>0%</td>
<td>Healthy</td>
<td>University</td>
<td>MD</td>
<td>12.9</td>
<td>WD</td>
<td>Inflam s.lipids</td>
<td></td>
</tr>
<tr>
<td>Michelsen et al. (2005)</td>
<td>Germany</td>
<td>101</td>
<td>23%</td>
<td>CAD (100%)</td>
<td>Clinic</td>
<td>MD</td>
<td>48</td>
<td>Advice</td>
<td>Inflam s.lipids</td>
<td></td>
</tr>
<tr>
<td>Panunzi et al. (2011)</td>
<td>Italy</td>
<td>80</td>
<td>52.5%</td>
<td>Healthy</td>
<td>Community</td>
<td>MD</td>
<td>15</td>
<td>NI</td>
<td>Inflam s.lipids</td>
<td></td>
</tr>
</tbody>
</table>
Note. N, number of participants; recruit, population recruitment; MHC, mild hypercholesteremia; NR, not reported; MD, Mediterranean diet; LFD, low fat diet; s.lipids, serum lipids; inflam, inflammation; BP, blood pressure; Ob, obesity; WT, weight; endoD, endothelial dysfunction; OWT, overweight; PREDIMED, Prevención con Dieta Mediterránea; DM, diabetes mellitus; CVDRF, cardiovascular disease risk factors; MDN, Mediterranean diet enhanced with mixed nuts; MDOO, Mediterranean diet enhanced with olive oil; WC, waist circumference; Ngenom, nutrigenomic; MD, medical doctor; CHD, coronary heart disease; events, CVD related events; comm, community; MetS, metabolic syndrome; vas, vascular; T2DM, type 2 diabetes mellitus; WD, Western Diet; CRF, chronic renal failure; CAD, coronary artery disease; OA, osteoarthritis; NI; no intervention; MDI, Mediterranean diet intervention; MDHI, Mediterranean diet high intervention; MDLI, Mediterranean diet low intervention; NMD, non Mediterranean diet; MyP, My Pyramid dietary guidelines for pregnancy and breastfeeding.

Note on Dietary Assessment column:
- Individual: A dietitian performed a dietary assessment, providing individualized needs for caloric intake and recommendations, for each participant.
- Group: The study provided general dietary recommendations for the participants, such as a range of servings of certain food groups, calories based on gender, as opposed to tailoring diets to individual needs based on weight and height.
- Supervised: Participants consumed foods in a supervised setting, where the researchers had control over participant food choices and quantity of food served.
- Unsupervised: Participants food consumption was unsupervised by researchers, such as eating at home.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Egger’s</th>
<th>Begg’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CVD Events</td>
<td>p=0.0005</td>
<td>p=0.0031</td>
</tr>
<tr>
<td>CRP</td>
<td>p=0.0003</td>
<td>p=0.0031</td>
</tr>
<tr>
<td>IL6</td>
<td>p=0.0003</td>
<td>p=0.0031</td>
</tr>
<tr>
<td>ICAM</td>
<td>p=0.0004</td>
<td>p=0.0031</td>
</tr>
<tr>
<td>VCAM</td>
<td>p=0.0706</td>
<td>p=0.6122</td>
</tr>
<tr>
<td>TG</td>
<td>p=0.4278</td>
<td>p=0.0002</td>
</tr>
<tr>
<td>LDL</td>
<td>p=0.1410</td>
<td>p=0.0026</td>
</tr>
<tr>
<td>HDL</td>
<td>p=0.6078</td>
<td>p=0.0812</td>
</tr>
</tbody>
</table>

**Note:** CVD, cardiovascular disease; CRP, c-reactive protein; IL6, interleukin-6; ICAM, intracellular adhesion molecule; VCAM, vascular cellular adhesion molecule; TG, triglycerides; LDL, low density lipoprotein; HDL, high density lipoprotein.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>k</th>
<th>d+ (95% CI)</th>
<th>Homogeneity of d’s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Random-Effects</td>
<td>Q</td>
</tr>
<tr>
<td>Total Events</td>
<td>11</td>
<td>-0.3740 (-0.5726 to -0.1753)*</td>
<td>207.0914</td>
</tr>
<tr>
<td>MI</td>
<td>6</td>
<td>-0.3236 (-0.5681 to -0.0791)*</td>
<td>67.7760</td>
</tr>
<tr>
<td>CVD Death</td>
<td>5</td>
<td>-0.4365 (-0.7838 to -0.0891)*</td>
<td>139.3040</td>
</tr>
<tr>
<td>CRP</td>
<td>26</td>
<td>-1.0174 (-1.6963 to -0.3385)*</td>
<td>478.1697</td>
</tr>
<tr>
<td>IL6</td>
<td>17</td>
<td>-1.4823 (-2.2389 to -0.7256)*</td>
<td>607.8397</td>
</tr>
<tr>
<td>ICAM</td>
<td>10</td>
<td>-4.3157 (-8.3708 to -0.2606)*</td>
<td>1330.1552</td>
</tr>
<tr>
<td>VCAM</td>
<td>9</td>
<td>-1.6076 (-2.6176 to -0.5976)*</td>
<td>321.7464</td>
</tr>
<tr>
<td>TG</td>
<td>24</td>
<td>-0.6306 (-0.9481 to -0.3130)*</td>
<td>513.2172</td>
</tr>
<tr>
<td>LDL</td>
<td>23</td>
<td>-1.1505 (-1.7021 to -0.5990)*</td>
<td>625.2637</td>
</tr>
</tbody>
</table>

**Note:** MI, myocardial infarction; CVD, cardiovascular disease; CRP, c-reactive protein; IL6, interleukin-6; ICAM, intracellular adhesion molecule; VCAM, vascular cellular adhesion molecule; TG, triglycerides; LDL, low density lipoprotein; HDL, high density lipoprotein; * indicates significant effect; Q represents Cochran’s Q indicating significance of heterogeneity; I² represents the magnitude of heterogeneity; p-value represents the significance of heterogeneity.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>k</th>
<th>Weeks</th>
<th>d+ (95%CI)</th>
<th>R²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCAM</td>
<td>9</td>
<td>12</td>
<td>-1.0507 (-1.9091, -0.1922)*</td>
<td>44.32%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>52</td>
<td>-3.5121 (-5.1715, 1.8526)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>23</td>
<td>8</td>
<td>-1.2384 (-3.3518, 0.8750)</td>
<td>0.00%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>104</td>
<td>0.8898 (-0.0879, 1.8676)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** VCAM, vascular cellular adhesion molecule; k, number of comparisons included in analysis; d+, effect size; * represents significant effect; R² indicates the amount of heterogeneity accounted for; p.value represents significance.
Table 5. Summary of Multilevel Results, Overall Effect Sizes, and QM–Inflammation

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>k</th>
<th>BMD</th>
<th>MDN</th>
<th>MDOO</th>
<th>QM</th>
<th>p. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>41</td>
<td>-4.449</td>
<td>-0.2196</td>
<td>-8.4106</td>
<td>25.1234</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-6.7468</td>
<td>(-2.2006</td>
<td>(-13.5294</td>
<td>(-2.2006</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>to -</td>
<td>to</td>
<td>to -</td>
<td>to</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.1430)*</td>
<td>1.7615)</td>
<td>3.2918)*</td>
<td>1.7615)</td>
<td></td>
</tr>
<tr>
<td>IL6</td>
<td>24</td>
<td>-3.7366</td>
<td>-2.9667</td>
<td>23.2952</td>
<td>.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-6.0974</td>
<td>(-4.7842</td>
<td>(-1.1493)*</td>
<td>(-1.1493)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>to -</td>
<td>to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.3758)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICAM</td>
<td>13</td>
<td>-2.8586</td>
<td>-2.0525</td>
<td>6.9250</td>
<td>.1399</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-6.0310</td>
<td>(-17.5600</td>
<td>(-7.1266</td>
<td>(-3.2617)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>to</td>
<td>to</td>
<td>to</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.3139)</td>
<td>13.4551)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCAM</td>
<td>11</td>
<td>-0.3641</td>
<td>-4.1933</td>
<td>39.8868</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-2.5684</td>
<td>(-8.6259</td>
<td>(-6.4809</td>
<td>(-8.6259</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>to</td>
<td>to</td>
<td>to</td>
<td>to</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.8402)</td>
<td>0.2392)</td>
<td>0.1420)*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: CRP, c-reactive protein; IL6, interleukin-6; ICAM, intracellular adhesion molecule; VCAM; vascular cellular adhesion molecule; *indicates significant results; QM represents test of moderators; p.value represents significance.
Table 6. Summary of Multilevel Results, Overall Effect Sizes, and QM--Lipids

<table>
<thead>
<tr>
<th>Serum Lipid</th>
<th>k</th>
<th>BMD</th>
<th>MDN</th>
<th>MDOO</th>
<th>QM</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>40</td>
<td>-2.9992</td>
<td>-0.1682</td>
<td>-2.8504</td>
<td>27.3081</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-4.9145 to -1.0839)*</td>
<td>(-6.7587 to 6.4222)</td>
<td>(-9.1992 to 3.4985)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>34</td>
<td>-3.4582</td>
<td>-3.3664</td>
<td>-3.5086</td>
<td>12.8939</td>
<td>0.0118</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-5.5324 to -1.3841)*</td>
<td>(-7.7156 to 0.9829)</td>
<td>(-8.3435 to 1.3263)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>38</td>
<td>3.0282</td>
<td>3.1113</td>
<td>-1.5818</td>
<td>18.8379</td>
<td>0.0008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.3819 to 4.6746)*</td>
<td>(-0.2079 to 6.4304)</td>
<td>(-4.7361 to 1.5724)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; *indicates significant results; QM represents test of moderators; p.value represents significance of results.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Moderator</th>
<th>( \beta )</th>
<th>95% CI</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL6</td>
<td>recruitment</td>
<td>-3.6840</td>
<td>(-6.9906 to 0.3774) *</td>
<td>0.0290</td>
</tr>
<tr>
<td>VCAM</td>
<td>weeks</td>
<td>-0.0622</td>
<td>(-0.0948 to 0.0297) *</td>
<td>0.0002</td>
</tr>
<tr>
<td>VCAM</td>
<td>Intervention lvl</td>
<td>-2.5683</td>
<td>(-4.7138 to 0.4229) *</td>
<td>0.0190</td>
</tr>
<tr>
<td>VCAM</td>
<td>fund (aca)</td>
<td>-2.5682</td>
<td>(-4.6663 to 0.4700) *</td>
<td>0.0164</td>
</tr>
<tr>
<td>TG</td>
<td>fund (private)</td>
<td>-0.6100</td>
<td>(-1.1929 to 0.0290) *</td>
<td>0.0403</td>
</tr>
<tr>
<td>TG</td>
<td>fund (multiple)</td>
<td>-0.8664</td>
<td>(-1.5043 to 0.2286) *</td>
<td>0.0078</td>
</tr>
<tr>
<td>LDL</td>
<td>region</td>
<td>-2.0057</td>
<td>(-3.1102 to 0.9013) *</td>
<td>0.0004</td>
</tr>
<tr>
<td>LDL</td>
<td>fund (aca)</td>
<td>-2.0848</td>
<td>(-3.8684 to 0.3011) *</td>
<td>0.0220</td>
</tr>
<tr>
<td>LDL</td>
<td>fund (private)</td>
<td>-1.2758</td>
<td>(-2.5503 to 0.0012) *</td>
<td>0.0498</td>
</tr>
</tbody>
</table>

**Note:** IL6, interleukin-6; VCAM, vascular cellular adhesion molecule; lvl, intervention; LDL, low-density lipoprotein; fund, funding source; aca, academic; \( \beta \), unstandardized beta; *indicates significant results; QM represents test of moderators; p.value represents significance of results.
Table 8. Non-Significant Moderators

<table>
<thead>
<tr>
<th>Non-Significant Moderators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number and proportion of females</td>
</tr>
<tr>
<td>Methodological Quality</td>
</tr>
<tr>
<td>Number of interventions</td>
</tr>
<tr>
<td>Ethnicity estimation</td>
</tr>
<tr>
<td>Proportion of participants with any type of disease</td>
</tr>
<tr>
<td>Number of participants with any type of disease</td>
</tr>
<tr>
<td>Proportion of Participants taking any type of medication</td>
</tr>
<tr>
<td>Number of participants taking any type of medication</td>
</tr>
<tr>
<td>Type of medication use</td>
</tr>
<tr>
<td>Experimental setting</td>
</tr>
<tr>
<td>Length of counseling sessions</td>
</tr>
<tr>
<td>Number of counseling sessions</td>
</tr>
<tr>
<td>Publication year</td>
</tr>
<tr>
<td>Language of publication</td>
</tr>
<tr>
<td>Proportion of carbohydrate intake (&lt;50% of ≥50%)</td>
</tr>
<tr>
<td>Proportion of saturated fat intake (&lt;10% or ≥10%)</td>
</tr>
<tr>
<td>Proportion of total fat intake (&lt;30% or ≥30%)</td>
</tr>
<tr>
<td>Proportion of protein intake (&lt;15% or ≥15%)</td>
</tr>
<tr>
<td>Mean age of sample</td>
</tr>
<tr>
<td>Assessment of dietary compliance</td>
</tr>
<tr>
<td>Participation in dietary counseling</td>
</tr>
<tr>
<td>Population with cardiovascular disease</td>
</tr>
<tr>
<td>Population with Type II Diabetes Mellitus</td>
</tr>
<tr>
<td>Population with Metabolic Syndrome</td>
</tr>
</tbody>
</table>
Table 9. Moderators Unable to be Analyzed due to Lack of Reporting

<table>
<thead>
<tr>
<th>Moderators Unable to be Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of Caucasian, Asian, Hispanic, Caribbean</td>
</tr>
<tr>
<td>Oral contraceptive/hormone replacement therapy use</td>
</tr>
<tr>
<td>Proportion of smokers</td>
</tr>
<tr>
<td>Number of smokers</td>
</tr>
<tr>
<td>Supplement use</td>
</tr>
<tr>
<td>Alcohol intake</td>
</tr>
<tr>
<td>Number of alcoholic drinks per week</td>
</tr>
<tr>
<td>Type of alcohol consumption</td>
</tr>
<tr>
<td>Amount of exercise per week</td>
</tr>
<tr>
<td>Type of exercise</td>
</tr>
<tr>
<td>Was dietary adherence monitored</td>
</tr>
<tr>
<td>Were medications part of the intervention</td>
</tr>
<tr>
<td>Total calories</td>
</tr>
<tr>
<td>Dietary sodium intake</td>
</tr>
<tr>
<td>Dietary potassium intake</td>
</tr>
<tr>
<td>Unsaturated fat intake</td>
</tr>
<tr>
<td>Saturated fat intake</td>
</tr>
<tr>
<td>Cholesterol intake</td>
</tr>
<tr>
<td>Fiber intake</td>
</tr>
<tr>
<td>Servings of vegetables recommended</td>
</tr>
<tr>
<td>Servings of dairy recommended</td>
</tr>
<tr>
<td>Servings of wine recommended</td>
</tr>
<tr>
<td>Servings of fish recommended</td>
</tr>
<tr>
<td>Servings of olive oil recommended</td>
</tr>
</tbody>
</table>
Servings of legumes recommended
Servings of meat recommended
Servings of poultry recommended

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Diet</th>
<th>95% CI</th>
<th>$I^2$</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>BMD</td>
<td>-0.6514 (-1.2934 to -0.0094)*</td>
<td>97.58</td>
<td>0.0467</td>
</tr>
<tr>
<td>CRP</td>
<td>MDOO</td>
<td>-2.1013 (-3.2891 to -0.9135)*</td>
<td>97.58</td>
<td>0.0005</td>
</tr>
<tr>
<td>IL6</td>
<td>BMD</td>
<td>-2.0596 (-3.2698 to -0.8493)*</td>
<td>99.14</td>
<td>0.0009</td>
</tr>
<tr>
<td>IL6</td>
<td>MDN</td>
<td>-1.8007 (-3.5096 to -0.0918)*</td>
<td>99.14</td>
<td>0.0389</td>
</tr>
<tr>
<td>TG</td>
<td>BMD</td>
<td>-2.9992 (-4.9145 to -1.0839)*</td>
<td>92.28</td>
<td>0.0021</td>
</tr>
<tr>
<td>LDL</td>
<td>MDN</td>
<td>-1.2735 (-2.4291 to -0.1179)*</td>
<td>98.03</td>
<td>0.0308</td>
</tr>
<tr>
<td>LDL</td>
<td>MDOO</td>
<td>-1.4883 (-2.6436 to -0.3330)*</td>
<td>98.03</td>
<td>0.0116</td>
</tr>
</tbody>
</table>

Note: CRP, c-reactive protein; IL6, interleukin-6; VCAM, vascular cellular adhesion molecule; TG, triglycerides; LDL, low-density lipoprotein; *indicates significant results; $I^2$ represents the magnitude of heterogeneity; p.value represents significance of difference.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Diet</th>
<th>95% CI</th>
<th>I²</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>BMD</td>
<td>-0.9557 (-1.5542 to -0.3571)*</td>
<td>97.78</td>
<td>0.0018</td>
</tr>
<tr>
<td>CRP</td>
<td>MDOO</td>
<td>-2.4291 (-3.7801 to -1.0782)*</td>
<td>97.78</td>
<td>0.0004</td>
</tr>
<tr>
<td>IL6</td>
<td>BMD</td>
<td>-2.2078 (-3.3139 to -1.1016)*</td>
<td>99.04</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>IL6</td>
<td>MDN</td>
<td>-2.0668 (-3.7244 to -0.4093)*</td>
<td>99.04</td>
<td>0.0145</td>
</tr>
<tr>
<td>ICAM</td>
<td>MDN</td>
<td>-9.9019 (-15.9789 to -3.8248)*</td>
<td>99.92</td>
<td>0.0014</td>
</tr>
<tr>
<td>VCAM</td>
<td>BMD</td>
<td>-1.6574 (-2.7934 to -0.5214)*</td>
<td>98.62</td>
<td>0.0042</td>
</tr>
<tr>
<td>VCAM</td>
<td>MDN</td>
<td>-3.2953 (-5.3489 to -1.2417)*</td>
<td>98.62</td>
<td>0.0017</td>
</tr>
<tr>
<td>VCAM</td>
<td>MDOO</td>
<td>-2.7371 (-4.7556 to -0.7186)*</td>
<td>98.62</td>
<td>0.0079</td>
</tr>
<tr>
<td>TG</td>
<td>BMD</td>
<td>-0.6336 (-0.9348 to -0.3324)*</td>
<td>92.28</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LDL</td>
<td>BMD</td>
<td>-1.0553 (-1.6537 to -0.4569)*</td>
<td>97.56</td>
<td>0.0005</td>
</tr>
<tr>
<td>LDL</td>
<td>MDN</td>
<td>-2.5194 (-3.8455 to -1.1932)*</td>
<td>97.56</td>
<td>0.0002</td>
</tr>
<tr>
<td>LDL</td>
<td>MDOO</td>
<td>-2.7329 (-4.0630 to -1.4028)*</td>
<td>97.56</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HDL</td>
<td>MDN</td>
<td>1.4951 (0.5751 to 2.4151)*</td>
<td>97.56</td>
<td>0.0014</td>
</tr>
<tr>
<td>HDL</td>
<td>MDOO</td>
<td>0.9567 (0.0683 to 1.8452)*</td>
<td>97.56</td>
<td>0.0348</td>
</tr>
</tbody>
</table>

**Note:** CRP, c-reactive protein; IL6, interleukin-6; ICAM, intracellular vascular adhesion molecule; VCAM, vascular cellular adhesion molecule; TG, triglycerides; LDL, low-density lipoprotein; *indicates significant results; p.value represents significance of difference.
**Table 12. Significant Associations – Age**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Diet</th>
<th>95% CI</th>
<th>$I^2$</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>MDOO</td>
<td>-2.9057 (-5.6602 to - 0.1512)*</td>
<td>97.82</td>
<td>0.0387</td>
</tr>
<tr>
<td>VCAM</td>
<td>BMD</td>
<td>-91.6845 (-163.8491* to -19.5199)</td>
<td>99.13</td>
<td>0.0128</td>
</tr>
<tr>
<td>VCAM</td>
<td>MDN</td>
<td>-91.9121 (-163.8968 to -19.9274)*</td>
<td>99.13</td>
<td>0.0123</td>
</tr>
<tr>
<td>VCAM</td>
<td>MDOO</td>
<td>-91.3928 (-163.3769 to -19.4086)*</td>
<td>99.13</td>
<td>0.0128</td>
</tr>
</tbody>
</table>

**Note:** CRP, c-reactive protein; VCAM, vascular cellular adhesion molecule; TG, triglycerides; LDL, low-density lipoprotein; *indicates significant results; $I^2$ represents the magnitude of heterogeneity; p.value represents significance of difference.
### Table 13. Significant Associations – Region

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Diet</th>
<th>95% CI</th>
<th>I²</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>BMD</td>
<td>-2.5260 (-3.8809 to -1.1711)</td>
<td>97.05</td>
<td>0.0003</td>
</tr>
<tr>
<td>CRP</td>
<td>MDN</td>
<td>-2.9090 (-4.7087 to -1.1093)</td>
<td>97.05</td>
<td>0.0015</td>
</tr>
<tr>
<td>CRP</td>
<td>MDOO</td>
<td>-3.9153 (-4.7087 to -1.1093)</td>
<td>97.05</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ICAM</td>
<td>MDN</td>
<td>-11.6377 (-18.3046 to -4.9707)</td>
<td>99.93</td>
<td>0.0006</td>
</tr>
<tr>
<td>VCAM</td>
<td>MDN</td>
<td>-2.0563 (-3.9014 to -0.2112)</td>
<td>99.27</td>
<td>0.0289</td>
</tr>
<tr>
<td>TG</td>
<td>BMD</td>
<td>-1.2591 (-1.9250 to -0.5931)</td>
<td>89.28</td>
<td>0.0002</td>
</tr>
<tr>
<td>TG</td>
<td>MDN</td>
<td>-0.8348 (-1.6619 to -0.0077)</td>
<td>89.28</td>
<td>0.0479</td>
</tr>
<tr>
<td>TG</td>
<td>MDOO</td>
<td>-0.7134 (-1.3673 to -0.0596)</td>
<td>89.28</td>
<td>0.0367</td>
</tr>
<tr>
<td>LDL</td>
<td>BMD</td>
<td>-0.7551 (-1.2870 to -0.2232)</td>
<td>96.88</td>
<td>0.0054</td>
</tr>
<tr>
<td>LDL</td>
<td>MDOO</td>
<td>-1.0078 (-1.9416 to -0.0741)</td>
<td>96.88</td>
<td>0.0344</td>
</tr>
</tbody>
</table>

**Note:** CRP, c-reactive protein; intracellular vascular adhesion molecule; VCAM, vascular cellular adhesion molecule; TG, triglycerides; LDL, low-density lipoprotein; *indicates significant results; I² represents the magnitude of heterogeneity; P.value represents significance of difference.
Table 14. Significant Associations – Population Recruitment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Diet</th>
<th>95% CI</th>
<th>$I^2$</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>MDOO</td>
<td>-2.3576 (-4.1607 to -0.5546)*</td>
<td>97.86</td>
<td>0.0104</td>
</tr>
<tr>
<td>ICAM</td>
<td>MDN</td>
<td>-7.6589 (-13.5122 to -1.8057)*</td>
<td>99.95</td>
<td>0.0103</td>
</tr>
<tr>
<td>VCAM</td>
<td>BMD</td>
<td>-1.5763 (-2.8827 to -0.2700)*</td>
<td>99.27</td>
<td>0.0186</td>
</tr>
<tr>
<td>VCAM</td>
<td>MDN</td>
<td>-2.0563 (-3.9014 to -0.2112)*</td>
<td>99.27</td>
<td>0.0289</td>
</tr>
<tr>
<td>LDL</td>
<td>BMD</td>
<td>-1.0943 (-2.1792 to 0.0095)*</td>
<td>98.10</td>
<td>0.0480</td>
</tr>
<tr>
<td>LDL</td>
<td>MDN</td>
<td>-1.7842 (-3.3721 to 0.1963)*</td>
<td>98.10</td>
<td>0.0276</td>
</tr>
<tr>
<td>LDL</td>
<td>MDOO</td>
<td>-1.9969 (-3.5858 to 0.4080)*</td>
<td>98.10</td>
<td>0.0138</td>
</tr>
</tbody>
</table>

**Note:** CRP, c-reactive protein; intracellular vascular adhesion molecule; VCAM, vascular cellular adhesion molecule; TG, triglycerides; LDL, low-density lipoprotein; *indicates significant results; $I^2$ represents the magnitude of heterogeneity; p.value represents significance of difference.
Table 15. Significant Associations – Intervention Level

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Diet</th>
<th>95% CI</th>
<th>$I^2$</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>MDOO</td>
<td>-2.2663 (-3.5380 to -0.9946)*</td>
<td>97.84</td>
<td>0.0005</td>
</tr>
<tr>
<td>VCAM</td>
<td>MDN</td>
<td>-2.0044 (-3.5135 to -0.4953)*</td>
<td>99.08</td>
<td>0.0092</td>
</tr>
<tr>
<td>TG</td>
<td>BMD</td>
<td>-0.6762 (-1.1267 to -0.2258)*</td>
<td>92.14</td>
<td>0.0033</td>
</tr>
<tr>
<td>LDL</td>
<td>BMD</td>
<td>-1.4003 (-2.4459 to -0.3547)*</td>
<td>98.09</td>
<td>0.0087</td>
</tr>
<tr>
<td>LDL</td>
<td>MDN</td>
<td>-1.7488 (-3.1393 to -0.3582)*</td>
<td>98.09</td>
<td>0.0137</td>
</tr>
<tr>
<td>LDL</td>
<td>MDOO</td>
<td>-1.9578 (-3.3444 to -0.5712)*</td>
<td>98.09</td>
<td>0.0057</td>
</tr>
</tbody>
</table>

**Note:** CRP, c-reactive protein; VCAM, vascular cellular adhesion molecule; TG, triglycerides; LDL, low-density lipoprotein; *indicates significant results; $I^2$ represents the magnitude of heterogeneity; p.value represents significance of difference.
### Table 15. Significant Associations – MQ

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Diet</th>
<th>95% CI</th>
<th>$I^2$</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>MDOO</td>
<td>-2.7137 (-5.3348 to -0.0926)*</td>
<td>97.89</td>
<td>0.0424</td>
</tr>
<tr>
<td>IL6</td>
<td>BMD</td>
<td>-7.8048 (-13.6727 to -1.9369)*</td>
<td>99.22</td>
<td>0.0091</td>
</tr>
<tr>
<td>IL6</td>
<td>MDN</td>
<td>-7.7562 (-13.9929 to -1.5194)*</td>
<td>99.22</td>
<td>0.0148</td>
</tr>
<tr>
<td>IL6</td>
<td>MDOO</td>
<td>-7.0516 (-13.2876 to -0.8156)*</td>
<td>99.22</td>
<td>0.0267</td>
</tr>
<tr>
<td>LDL</td>
<td>MDN</td>
<td>-2.9113 (-5.6745 to -0.1482)*</td>
<td>98.08</td>
<td>0.0389</td>
</tr>
<tr>
<td>LDL</td>
<td>MDOO</td>
<td>-3.1220 (-5.8825 to -0.3616)*</td>
<td>98.08</td>
<td>0.0266</td>
</tr>
</tbody>
</table>

**Note:** CRP, c-reactive protein; IL6, interleukin-6; LDL, low-density lipoprotein; *indicates significant results; $I^2$ represents the magnitude of heterogeneity; p.value represents significance.
**Figure 2. Forest Plot for Total CVD Events**

<table>
<thead>
<tr>
<th>Author(s) and Year</th>
<th>Favors Intervention</th>
<th>Favors Baseline</th>
<th>d[95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Longeiri, et al (MD=N) Deaths1994</td>
<td></td>
<td></td>
<td>-1.01 [ -1.18, -0.84 ]</td>
</tr>
<tr>
<td>De Longeiri, et al (MD+N) M1994</td>
<td></td>
<td></td>
<td>-0.74 [ -0.90, -0.58 ]</td>
</tr>
<tr>
<td>De Longeiri, et al (MD+OD) Deaths1996</td>
<td></td>
<td></td>
<td>-0.70 [ -0.80, -0.60 ]</td>
</tr>
<tr>
<td>De Longeiri, et al (MD+OD) M1996</td>
<td></td>
<td></td>
<td>-0.65 [ -0.80, -0.50 ]</td>
</tr>
<tr>
<td>Estruch, et al (MD=N) Deaths2013</td>
<td></td>
<td></td>
<td>-0.25 [ -0.31, -0.19 ]</td>
</tr>
<tr>
<td>Estruch, et al (MD+OD) Deaths2013</td>
<td></td>
<td></td>
<td>-0.03 [ -0.09, 0.03 ]</td>
</tr>
<tr>
<td>Estruch, et al (MD+N) M2013</td>
<td></td>
<td></td>
<td>-0.15 [ -0.21, -0.09 ]</td>
</tr>
<tr>
<td>Estruch, et al (MD+OD) M2013</td>
<td></td>
<td></td>
<td>-0.20 [ -0.27, -0.14 ]</td>
</tr>
<tr>
<td>Martinez-Gonzalez (MD) MI 2005</td>
<td></td>
<td></td>
<td>-0.22 [ -0.26, -0.17 ]</td>
</tr>
<tr>
<td>Martinez-Gonzalez (MD) Death2009</td>
<td></td>
<td></td>
<td>-0.24 [ -0.29, -0.19 ]</td>
</tr>
<tr>
<td>Tuttle, et al (MD) M2008</td>
<td></td>
<td></td>
<td>0.06 [ 0.23, 0.36 ]</td>
</tr>
</tbody>
</table>

**Note:** Squares represent point estimates for each individual study; extended line shows 95% confidence intervals (CIs); dotted line represents the null value of zero; diamond represents the weighted mean effect size for the outcome.

**Figure 3. Forest Plot for Myocardial Infarction**

<table>
<thead>
<tr>
<th>Author(s) and Year</th>
<th>Favors Intervention</th>
<th>Favors Baseline</th>
<th>d[95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Longeiri, et al (MD+N) M1994</td>
<td></td>
<td></td>
<td>-0.74 [ -0.90, -0.58 ]</td>
</tr>
<tr>
<td>De Longeiri, et al (MD+OD) M1996</td>
<td></td>
<td></td>
<td>-0.69 [ -0.80, -0.50 ]</td>
</tr>
<tr>
<td>Estruch, et al (MD=N) M2013</td>
<td></td>
<td></td>
<td>-0.15 [ -0.21, -0.09 ]</td>
</tr>
<tr>
<td>Estruch, et al (MD+OD) M2013</td>
<td></td>
<td></td>
<td>-0.20 [ -0.27, -0.14 ]</td>
</tr>
<tr>
<td>Martinez-Gonzalez2009</td>
<td></td>
<td></td>
<td>-0.22 [ -0.26, -0.17 ]</td>
</tr>
<tr>
<td>Tuttle, et al2008</td>
<td></td>
<td></td>
<td>0.06 [ 0.23, 0.36 ]</td>
</tr>
</tbody>
</table>

**RE Model**

**Standardized Mean Difference**

-0.37 [ -0.37, -0.18 ]
Note: Squares represent point estimates for each individual study; extended line shows 95% confidence intervals (CIs); dotted line represents the null value of zero; diamond represents the weighted mean effect size for the outcome.

Figure 4. Forest Plot for CVD related Events

<table>
<thead>
<tr>
<th>Author(s) and Year</th>
<th>Favor Intervention</th>
<th>Favor Baseline</th>
<th>d(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Longort et al. [ME=0] Deaths 1994</td>
<td>] ]</td>
<td>] ]</td>
<td>-0.91 [-1.19, -0.64]</td>
</tr>
<tr>
<td>De Longort et al. [ME=0] Deaths 1994</td>
<td>] ]</td>
<td>] ]</td>
<td>-0.70 [-0.86, -0.55]</td>
</tr>
<tr>
<td>Esteban et al. [ME=0] Deaths 2013</td>
<td>]</td>
<td>]</td>
<td>-0.26 [-0.31, -0.14]</td>
</tr>
<tr>
<td>Esteban et al. [ME=0] Deaths 2013</td>
<td>]</td>
<td>]</td>
<td>-0.03 [-0.08, 0.02]</td>
</tr>
<tr>
<td>Martinez-Gonzalez 2013</td>
<td>}</td>
<td>}</td>
<td>-0.46 [-0.73, -0.19]</td>
</tr>
</tbody>
</table>

Note: Squares represent point estimates for each individual study; extended line shows 95% confidence intervals (CIs); dotted line represents the null value of zero; diamond represents the weighted mean effect size for the outcome.

Figure 5. Forest Plot for C-reactive Protein
Note: Squares represent point estimates for each individual study; extended line shows 95% confidence intervals (CIs); dotted line represents the null value of zero; diamond represents the weighted mean effect size for the outcome.

Figure 6. Forest Plot for Interleukin 6

Note: Squares represent point estimates for each individual study; extended line shows 95% confidence intervals (CIs); dotted line represents the null value of zero; diamond represents the weighted mean effect size for the outcome.
**Figure 7. Forest Plot for ICAM**

<table>
<thead>
<tr>
<th>Author(s) and Year</th>
<th>Favors Intervention</th>
<th>Favors Baseline</th>
<th>d[95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casas, et al. 2014</td>
<td></td>
<td></td>
<td>-0.96 [-0.62, -0.07]</td>
</tr>
<tr>
<td>Casas, et al. 2014.1</td>
<td></td>
<td></td>
<td>-1.27 [-1.44, -0.09]</td>
</tr>
<tr>
<td>Correa, et al. 2009</td>
<td></td>
<td></td>
<td>-0.32 [-0.41, -0.23]</td>
</tr>
<tr>
<td>Correa, et al. 2009.1</td>
<td></td>
<td></td>
<td>-0.21 [-0.34, -0.08]</td>
</tr>
<tr>
<td>Estroff, et al. 2009</td>
<td></td>
<td></td>
<td>-0.79 [-0.96, -0.03]</td>
</tr>
<tr>
<td>Estroff, et al. 2010</td>
<td></td>
<td></td>
<td>-0.24 [-0.34, -0.14]</td>
</tr>
<tr>
<td>Meno, et al. 2008</td>
<td></td>
<td></td>
<td>-0.91 [-0.79, -0.07]</td>
</tr>
<tr>
<td>Meno, et al. 2008.1</td>
<td></td>
<td></td>
<td>-2.03 [-3.17, -0.75]</td>
</tr>
<tr>
<td>Yip-Soto, et al. 2012</td>
<td></td>
<td></td>
<td>-0.60 [-0.82, -0.34]</td>
</tr>
<tr>
<td>Yip-Soto, et al. 2012.1</td>
<td></td>
<td></td>
<td>-0.98 [-1.27, -0.67]</td>
</tr>
</tbody>
</table>

**Note:** Squares represent point estimates for each individual study; extended line shows 95% confidence intervals (CIs); dotted line represents the null value of zero; diamond represents the weighted mean effect size for the outcome.

**Figure 8. Forest Plot for VCAM**

<table>
<thead>
<tr>
<th>Author(s) and Year</th>
<th>Favors Intervention</th>
<th>Favors Baseline</th>
<th>d[95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Godi, et al. 2014</td>
<td></td>
<td></td>
<td>0.03 [-0.32, 0.27]</td>
</tr>
<tr>
<td>Godi, et al. 2014.1</td>
<td></td>
<td></td>
<td>0.17 [-0.30, 0.27]</td>
</tr>
<tr>
<td>Correa, et al. 2009</td>
<td></td>
<td></td>
<td>0.05 [-0.43, 0.28]</td>
</tr>
<tr>
<td>Correa, et al. 2009.1</td>
<td></td>
<td></td>
<td>0.08 [-0.39, 0.27]</td>
</tr>
<tr>
<td>Estroff, et al. 2009</td>
<td></td>
<td></td>
<td>0.01 [-0.28, 0.08]</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>0.08 [-0.47, 0.35]</td>
</tr>
<tr>
<td>Meno, et al. 2008</td>
<td></td>
<td></td>
<td>0.25 [-0.27, 0.75]</td>
</tr>
<tr>
<td>Meno, et al. 2008.1</td>
<td></td>
<td></td>
<td>0.20 [-0.53, 0.93]</td>
</tr>
</tbody>
</table>

**Note:** Squares represent point estimates for each individual study; extended line shows 95% confidence intervals (CIs); dotted line represents the null value of zero; diamond represents the weighted mean effect size for the outcome.
**Note**: Squares represent point estimates for each individual study; extended line shows 95% confidence intervals (CIs); dotted line represents the null value of zero; diamond represents the weighted mean effect size for the outcome.

**Figure 9. Forest Plot for TG**

![Forest Plot for TG](image)

**Figure 10. Forest Plot LDL**

![Forest Plot LDL](image)
Note: Squares represent point estimates for each individual study; extended line shows 95% confidence intervals (CIs); dotted line represents the null value of zero; diamond represents the weighted mean effect size for the outcome.

**Figure 11.** Forest Plot HDL

![Forest Plot HDL](image)

Note: Squares represent point estimates for each individual study; extended line shows 95% confidence intervals (CIs); dotted line represents the null value of zero; diamond represents the weighted mean effect size for the outcome.
**Figure 12.** Meta-regression Plot for VCAM -- Weeks

![Meta-regression Plot for VCAM -- Weeks](image)

\[ B = -0.0615, \ p\.value = 0.0098, \ R^2 = 44.32 \]

Note: Number of weeks is on the x-axis; Outcome of interest is on the Y-axis; B is the unstandardized beta represented amount of change in outcome per week of intervention; \( R^2 \) indicates the percentage of variability for by length.

**Figure 13.** Meta-regression Plot for HDL--Weeks

![Meta-regression Plot for HDL--Weeks](image)

\[ B = -0.0615, \ p\.value = 0.0098, \ R^2 = 44.32 \]

Note: Number of weeks is on the x-axis; Outcome of interest is on the Y-axis; B is the unstandardized beta represented amount of change in outcome per week of intervention;
R² indicates the percentage of variability for by length.

**Figure 14.** Risk of Bias Summary
Appendix

Appendix 1. Comprehensive Search Strategy Details

PubMed (1940s to present)
Terms were searched in all fields; however, field labels were used to restrict specific terms/phrases to the Medical Subject Headings [Mesh], publication type [pt] and journal name [ta] fields.


Results: 568

EMBASE (via Scopus) (1823 to present)

Limits: Article, review, conference papers, journals

All terms (unless otherwise noted) were searched in "Article Title, Abstract, Keywords". Because of character restrictions in Scopus, this search was run in parts and assembled using the "Search history".

"Mediterranean diet" OR "Mediterranean diets" OR "Mediterranean dietary" OR "Mediterranean style diet" OR "Mediterranean style diets"

AND

"cardiovascular disease" OR "cardiovascular diseases" OR "heart disease" OR "heart diseases" OR CVD OR CVDs OR hypertension OR hypertensive* OR "high blood pressure" OR "myocardial infarction" OR "myocardial infarct" OR MI OR "heart attack" OR stroke OR "coronary artery disease" OR "coronary arterial disease" OR "coronary heart disease" OR "Cerebrovascular Disorders" OR "cerebrovascular disease" OR "cerebrovascular diseases" OR atherosclerosis OR arteriosclerosis OR "peripheral vascular diseases" OR "peripheral vascular disease" OR "peripheral angiopathy" OR "peripheral angiopathies" OR "peripheral artery disease" OR "peripheral artery diseases" OR "peripheral arterial disease" OR "peripheral arterial diseases" OR "venous thrombosis" OR "venous thromboses" OR "deep vein thrombosis" OR "deep vein thromboses" OR "pulmonary embolism" OR "pulmonary embolisms" OR dyslipidemia OR dyslipidemias OR hypercholesterolemia OR hypercholesterolemias OR "Aortic Valve Stenosis" OR "aortic valve stenoses" OR "aortic stenosis" OR "aortic stenoses" OR aneurysms OR Aneurism OR regurgitation OR prolapse

AND

Option 1: (clinical AND trial)

OR

Option 2: random* OR "therapeutic use"

NOT

(in title) rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "case report" OR comment OR editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "retrospective study" OR "non-randomized"

Results: 149
CINAHL (1981-present)
All terms were searched in all fields (unless otherwise noted)
Excluded: MEDLINE Records
Limited: academic journals, journal article
Due to database limitations, search was run in parts and assembled using the search history.
"Mediterranean diet" OR "Mediterranean diets" OR "Mediterranean dietary" OR "Mediterranean style diet" OR "Mediterranean style diets"
AND
"cardiovascular disease" OR "cardiovascular diseases" OR "heart disease" OR "heart diseases" OR "CVD" OR "CVDs" OR "hypertension" OR "high blood pressure" OR "myocardial infarction" OR "MI" OR "heart attack" OR "stroke" OR "coronary artery disease" OR "coronary heart disease" OR "cerebrovascular disease" OR "atherosclerosis" OR "arteriosclerosis" OR "peripheral vascular disease" OR "peripheral artery disease" OR "deep vein thrombosis" OR "pulmonary embolism" OR "dyslipidemia" OR "hypercholesterolemia" OR "aortic stenosis" OR "Aneurism" OR "regurgitation" OR "prolapse"
AND
Option 1: (clinical AND trial)
OR
Option 2: (MH "Clinical Trials+") OR "clinical trial" OR random* OR (MH "Random Assignment") OR "therapeutic use"
NOT
(in title) rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "case report" OR comment OR editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "retrospective study" OR "non-randomized"

Results: 40

PsycINFO (1872 to present)
Limits: academic journals
Due to database limitations, search was run in parts and assembled using the search history.
"Mediterranean diet" OR "Mediterranean diets" OR "Mediterranean dietary" OR "Mediterranean style diet" OR "Mediterranean style diets"
AND
"cardiovascular disease" OR "cardiovascular diseases" OR "heart disease" OR "heart diseases" OR "CVD" OR "CVDs" OR "hypertension" OR "high blood pressure" OR "myocardial infarction" OR "MI" OR "heart attack" OR "stroke" OR "coronary artery disease" OR "coronary heart disease" OR "cerebrovascular disease" OR "atherosclerosis" OR "arteriosclerosis" OR "peripheral vascular disease" OR "peripheral artery disease" OR "deep vein thrombosis" OR "pulmonary embolism" OR "dyslipidemia" OR "hypercholesterolemia" OR "aortic stenosis" OR "Aneurism" OR "regurgitation" OR "prolapse"
AND
Option 1: (clinical AND trial)
OR
Option 2: (DE "Clinical Trials") OR "clinical trial" OR random* OR (DE "Random Sampling") OR "therapeutic use"
NOT
(in title) rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "case report"
OR comment OR editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "retrospective study" OR "non-randomized"

Results: 14

Academic Search Premier (1980s to present)
Limit: Scholarly (Peer Reviewed) Journals
"Mediterranean diet" OR "Mediterranean diets" OR "Mediterranean dietary" OR "Mediterranean style diet" OR "Mediterranean style diets"
AND
"cardiovascular disease" OR "cardiovascular diseases" OR "heart disease" OR "heart diseases" OR "CVD" OR "CVDs" OR "hypertension" OR "high blood pressure" OR "myocardial infarction" OR "MI" OR "heart attack" OR "stroke" OR "coronary artery disease" OR "coronary heart disease" OR "cerebrovascular disease" OR "atherosclerosis" OR "arteriosclerosis" OR "peripheral vascular disease" OR "peripheral artery disease" OR "deep vein thrombosis" OR "pulmonary embolism" OR "dyslipidemia" OR "hypercholesterolemia" OR "aortic stenosis" OR "Aneurism" OR "regurgitation" OR "prolapse"
AND
Option 1: (clinical AND trial)
OR
Option 2: (random* OR "therapeutic use")
NOT
(in title) rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "case report" OR comment OR editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "retrospective study" OR "non-randomized"

Results: 208

Agricola (1970-present)
Searched in "All Fields"
Limits: academic journals
"Mediterranean diet" OR "Mediterranean diets" OR "Mediterranean dietary" OR "Mediterranean style diet" OR "Mediterranean style diets" AND "cardiovascular disease" OR "cardiovascular diseases" OR "heart disease" OR "heart diseases" OR "CVD" OR "CVDs" OR "hypertension" OR "high blood pressure" OR "myocardial infarction" OR "MI" OR "heart attack" OR "stroke" OR "coronary artery disease" OR "coronary heart disease" OR "cerebrovascular disease" OR "atherosclerosis" OR "arteriosclerosis" OR "peripheral vascular disease" OR "peripheral artery disease" OR "deep vein thrombosis" OR "pulmonary embolism" OR "dyslipidemia" OR "hypercholesterolemia" OR "aortic stenosis" OR "Aneurism" OR "regurgitation" OR "prolapse"
AND Option 1: (clinical AND trial)
OR Option 2: (random* OR "therapeutic use")
NOT (in title) rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "case report" OR comment OR editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "retrospective study" OR "non-randomized"

Results: 40

CAB Direct (1973-present)
Limit to Document Type: Journal article and Evidence based research articles only
"Mediterranean diet" OR "Mediterranean diets" OR "Mediterranean dietary" OR "Mediterranean style diet" OR "Mediterranean style diets" AND "cardiovascular disease" OR "cardiovascular diseases" OR "heart disease" OR "heart diseases" OR "CVD" OR "CVDs" OR "hypertension" OR "high blood pressure" OR "myocardial infarction" OR "MI" OR "heart attack" OR "stroke" OR "coronary artery disease" OR "coronary heart disease" OR "cerebrovascular disease" OR "atherosclerosis" OR "arteriosclerosis" OR "peripheral vascular disease" OR "peripheral artery disease" OR "deep vein thrombosis" OR "pulmonary embolism" OR "dyslipidemia" OR "hypercholesterolemia" OR "aortic stenosis" OR "Aneurism" OR "regurgitation" OR "prolapse"
artery disease" OR "deep vein thrombosis" OR "pulmonary embolism" OR "dyslipidemia" OR "hypercholesterolemia" OR "aortic stenosis" OR "Aneurism" OR "regurgitation" OR "prolapse"
AND
Option 1: (clinical AND trial)
OR
Option 2: (random* OR "therapeutic use")
NOT
(in title) rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "case report" OR comment OR editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "retrospective study" OR "non-randomized"

Results: 0 results

Appendix 2. Screening Form

updated: 9/23/15
Study ID:
Coder: __________

Mediterranean Diet CVD Meta-Analysis Selection Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials MUST match all of these criteria:</td>
<td>Studies CANNOT include any of the following:</td>
</tr>
<tr>
<td>Pre- AND Post-intervention design</td>
<td>Animal Models</td>
</tr>
<tr>
<td>Mediterranean diet (as a whole, for example, not just olive oil) for at least one of the interventions. Can also be described as Mediterranean-style diet, hypocaloric Mediterranean diet, etc.</td>
<td>Surveys</td>
</tr>
<tr>
<td>Cardiovascular disease events (ex: MI, CVD related deaths…etc).</td>
<td>Commentary</td>
</tr>
<tr>
<td></td>
<td>Symposium Sessions</td>
</tr>
<tr>
<td></td>
<td>Research Support</td>
</tr>
<tr>
<td></td>
<td>Letters</td>
</tr>
<tr>
<td></td>
<td>Position Paper/Viewpoint</td>
</tr>
</tbody>
</table>
Inflammatory Biomarkers (CRP, IL6, ICAM, VCAM)

Review [ ]

Guidelines [ ]

Epidemiologic Studies [ ]

Cross-sectional Studies [ ]

Observational Studies [ ]

Olive oil only [ ]

Wine only [ ]

Fish only [ ]

Antioxidants only [ ]


CODER________ Coder (Julia=1, Marisa=2, Other=3)

Study Information
ID _______ Study ID (first 3 letters of 1st author’s last name & unique ID#: Pescatello= PES001),
(Last name, Yr)

PUB_YR _______ Publication year (consider this missing if unpublished)

DATA _______ Estimated year of data collection (earliest date for data collection or manuscript
submission/publication;
if unpublished and date unknown, use year manuscript was acquired; for dissertation or thesis, use year)

LANG _______ Language of report 1=English 2=Spanish 3=Japanese 4=Other, specify:

SOURCE _______ Publication Type 1=journal 2=book 3=thesis/dissertation 4=conference paper 5=
unpublished

SCORE _______ Impact Score of the Journal (use ISI Web of Knowledge journal citation reports)

JOURNAL NAME ________________________________

PUBMED NAME/ ABBR. __________________________

FUNDING SOURCE _______ 1= Gov’t (i.e., CDC, NIH, etc) 2= Academic/University 3= Private 4= Multiple

For all, specify source/grant:

__________________________________________

__________________________________________

82
NOTE_STUDY study notes (make note of multiple arms; ex. MD vs. low fat vs. low carb + MD vs. CONTROL):

Sample Characteristics (proportion: 0.0-1.0) Note: IF ethnicity is reported, ETH_EST will be == 0

ETH Ethnicity reported? 1 = yes; 0 = no

PROP_WH Proportion White; whole #  
PROP_BLK Proportion Black/
PROP_HISP Proportion Latino/Hispanic/ whole #  
PROP_MIX Proportion Mixed

ETH_EST Assumed ethnicity (0= n/a, 1= White, 2= Asian, 3= Black, 4= Unreported, 5= Hispanic/Latino)

NUM_FemCON # of Females in Sample; Proportion
NUM_FemiIN1 # of Females in Sample; Proportion
NUM_FemiIN2 # of Females in Sample; Proportion
NUM_FemiIN3 # of Females in Sample; Proportion

REGION Location of sample (if unreported, use location of first author as estimate of study location)

POP Population 0=not reported 1=school/college 2=community (senior center, flyers, etc.)

NOTE_RECRUIT Notes on recruitment/ sample location

Risk Characteristics- report values of baseline data (check methods or descriptive tables) KEEP DATA SEPARATE FOR GROUPS

TOTAL_POP Reported as total sample? (1=yes, 0=no) *if data is collapsed, not separate for groups, chose YES

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CONTROL/COMPARISON n=_____ (total sample)</th>
<th>IN1 n=_____ (total sample), specify intervention_____</th>
<th>IN2 n=_____ (total sample), specify intervention_____</th>
<th>IN3 n=_____ (total sample), specify intervention_____</th>
</tr>
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<td>Mean age (years)</td>
<td>AGE</td>
<td>AGE</td>
<td>AGE</td>
<td>AGE</td>
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<tr>
<td>SD for age (years)</td>
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<td>AGE_SD</td>
<td>AGE_SD</td>
<td>AGE_SD</td>
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<td>CONTROL/ COMPARISON ( n = ) ___ (total sample)</td>
<td>IN1 ( n = ) ___ (total sample), specify intervention___</td>
<td>IN2 ( n = ) ___ (total sample), specify intervention___</td>
<td>IN3 ( n = ) ___ (total sample), specify intervention___</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------------------</td>
<td>---------------------------------</td>
<td>---------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Known disease/ chronic conditions</td>
<td>DISEASE</td>
<td>DISEASE</td>
<td>DISEASE</td>
<td>DISEASE</td>
</tr>
<tr>
<td>0= Healthy</td>
<td>3= CVD(s) (i.e., CAD, PAD, HF, MI)</td>
<td>4= Stroke</td>
<td>5= Diabetes</td>
<td>6= MetS</td>
</tr>
<tr>
<td>7= Arthritis</td>
<td>8= Dyslipidemia</td>
<td>9= Obesity</td>
<td>10= Other, specify:</td>
<td>11= Multiple, specify #s:</td>
</tr>
<tr>
<td>12= Other</td>
<td>13= Other, specify:</td>
<td>14= Other</td>
<td>15= Other, specify:</td>
<td>16= Other</td>
</tr>
<tr>
<td>If disease: report prop. &amp; number</td>
<td>PROP_DISEASE</td>
<td>PROP_DISEASE</td>
<td>PROP_DISEASE</td>
<td>PROP_DISEASE</td>
</tr>
<tr>
<td>if “healthy” denote 0= n/a; if missing=“.” NumberDisease</td>
<td>NumberDisease</td>
<td>NumberDisease</td>
<td>NumberDisease</td>
<td>NumberDisease</td>
</tr>
<tr>
<td>Medication use</td>
<td>MED</td>
<td>MED</td>
<td>MED</td>
<td>MED</td>
</tr>
<tr>
<td>0=no, 1= yes</td>
<td>PROP_USE</td>
<td>PROP_USE</td>
<td>PROP_USE</td>
<td>PROP_USE</td>
</tr>
<tr>
<td>If yes, report prop. &amp; number; if no meds, use 0=NA (if missing =“.”) NumberMED</td>
<td>NumberMED</td>
<td>NumberMED</td>
<td>NumberMED</td>
<td>NumberMED</td>
</tr>
<tr>
<td>Medication Type</td>
<td>MED_TYPE</td>
<td>MED_TYPE</td>
<td>MED_TYPE</td>
<td>MED_TYPE</td>
</tr>
<tr>
<td>if no meds= 0</td>
<td>MED_TYPE</td>
<td>MED_TYPE</td>
<td>MED_TYPE</td>
<td>MED_TYPE</td>
</tr>
<tr>
<td>1= β Blockers</td>
<td>2= Nitrates</td>
<td>3= Ca(^{2+}) Channel Blockers</td>
<td>4= Angiotension Converting Enzyme (ACE) Inhibitors</td>
<td>5= Diuretics</td>
</tr>
<tr>
<td>6= Vasodilators</td>
<td>7= NSAIDs</td>
<td>8= Aspirin</td>
<td>9= Statins</td>
<td>10=Other, specify:</td>
</tr>
<tr>
<td>11= Multiple, specify:</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>BP Medication use</td>
<td>BPMedUse</td>
<td>BPMedUse</td>
<td>BPMedUse</td>
<td>BPMedUse</td>
</tr>
<tr>
<td>1= yes, 0=no</td>
<td>If unreported = “ “</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>If yes, report prop. &amp; number</td>
<td>BPMedProp</td>
<td>BPMedProp</td>
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<td>BPMedProp</td>
</tr>
<tr>
<td>(if “no”=0, NA; if missing denote=“.”) BPMedNumber</td>
<td>BPMedNumber</td>
<td>BPMedNumber</td>
<td>BPMedNumber</td>
<td>BPMedNumber</td>
</tr>
<tr>
<td>Characteristic</td>
<td>CONTROL/COMPARISON</td>
<td>IN1 $n=____$ (total sample), specify intervention_____</td>
<td>IN2 $n=____$ (total sample), specify intervention_____</td>
<td>IN3 $n=____$ (total sample), specify intervention_____</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>If taking meds, is BP controlled? yes= 1, if SBP≤140 OR DBP≤90 no= 0, SBP&gt;140 OR DBP&gt;90 (*if no BP use == NA)</td>
<td>BPControl</td>
<td>BPControl</td>
<td>BPControl</td>
<td>BPControl</td>
</tr>
<tr>
<td>Oral Contraceptive (0=no, 1= yes) OR Hormone replacement therapy</td>
<td>OC_USE HRT_USE</td>
<td>OC_USE HRT_USE</td>
<td>OC_USE HRT_USE</td>
<td>OC_USE HRT_USE</td>
</tr>
<tr>
<td>Smokers/smokers (≤6 months) (0=no,1=yes; if missing = &quot;.&quot;)</td>
<td>SMOKE SMOKE</td>
<td>SMOKE SMOKE</td>
<td>SMOKE SMOKE</td>
<td>SMOKE SMOKE</td>
</tr>
<tr>
<td>If yes, report smoker prop. &amp; number</td>
<td>PROP_SMOKE NumberSMOKE PROP_SMOKE NumberSMOKE PROP_SMOKE NumberSMOKE PROP_SMOKE NumberSMOKE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutritional Supplements Permitted? (0=no, 1=yes)</td>
<td>SUPP SUPP</td>
<td>SUPP SUPP</td>
<td>SUPP SUPP</td>
<td>SUPP SUPP</td>
</tr>
<tr>
<td>If yes, specify type</td>
<td>TYPE TYPE</td>
<td>TYPE TYPE</td>
<td>TYPE TYPE</td>
<td></td>
</tr>
<tr>
<td>Consume Alcohol? (0=no, 1= yes)</td>
<td>ALC ALC</td>
<td>ALC ALC</td>
<td>ALC ALC</td>
<td></td>
</tr>
<tr>
<td>If yes, how many drinks/week?</td>
<td>AMT AMT</td>
<td>AMT AMT</td>
<td>AMT AMT</td>
<td></td>
</tr>
<tr>
<td>If yes, what type of alcohol?</td>
<td>ALCTYPE ALCTYPE</td>
<td>ALCTYPE ALCTYPE</td>
<td>ALCTYPE ALCTYPE</td>
<td></td>
</tr>
<tr>
<td>Amount of exercise per week (in min)</td>
<td>EX EX</td>
<td>EX EX</td>
<td>EX EX</td>
<td></td>
</tr>
<tr>
<td>Type of exercise (e.g., cardio, strength training)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Methods & Design**

**CON_GRP** _______ Type of control group used

1= random assignment of individuals to conditions including a non-diet control group, specify____________

2= random assignment of individuals to conditions including non-diet control session

3= random assignment of individuals to non-MD condition/diet

4= random assignment of individuals to a non-diet control group

5= other, specify: ______________________________________________________________________________________

**Experiment/ Intervention Conditions**

EXPERIMENT_______ INTERVENTIONS/EXPERIMENTAL CONDITION(S)

1= non-diet control/comparison + 1 intervention 

2= non-diet control/comparison + 2 interventions
3= non-diet control/comparison + 3 interventions
4= diet control/comparison + 1 intervention
5= diet control/comparison + 2 interventions
6= diet control/comparison + 3 interventions
7= crossover design

EXP_SETTING Setting of Intervention(s) 1= hospital 2= clinic 3= academic/research lab 4= fitness center, gym
5= Other, specify: _____________________________ 6= multiple, specify:__________

DIET_MONITOR Was diet adherence monitored? (0= none; 1= yes) If yes, specify:
_______________________________________________________________________________________________

BEHAV_TECH Behavioral technique/monitoring system used? (0=none, 1=yes) If yes, specify-
_______________________________________________________________________________________________
Examples: positive reinforcement/contingency management, exercise & lifestyle information/lectures; PA logs, etc.

INTER_LVL Level of intervention or supervision used in the study
1= primarily 1-on-1 2= small group processes (supervisor & group members) 3= supervised session(s)
4= unsupervised session(s) 5= incentive (payment based on sessions attended)
6= multiply, specify #’s:_____________________________

NOTE_EXP & METHODS Notes related to study design & delivery of intervention:
_______________________________________________________________________________________________
### Diet Intervention Characteristics

<table>
<thead>
<tr>
<th>DIET CHARACTERISTICS</th>
<th>CONTROL/COMPARISON</th>
<th>IN1</th>
<th>IN2</th>
<th>IN3</th>
</tr>
</thead>
<tbody>
<tr>
<td>LENGTH___ (in weeks)</td>
<td>LENGTH___</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WTGain/WTLoss___</td>
<td>WTGain/WTLoss___</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PART_LOST # of drop outs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHERENCE (report %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were medications used as part of the intervention? (0=no, 1=yes)</td>
<td>MEDS___</td>
<td>MEDS___</td>
<td>MEDS___</td>
<td>MEDS___</td>
</tr>
<tr>
<td>If yes, specify</td>
<td>MED__TYPE</td>
<td>MED__TYPE</td>
<td>MED__TYPE</td>
<td>MED__TYPE</td>
</tr>
<tr>
<td>DIET__TYPE</td>
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<td>DIET__TYPE</td>
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<tr>
<td>Provision of Med Diet Foods? (0=no, 1=yes)</td>
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<tr>
<td>If yes, type and amount___</td>
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<tr>
<td>Diet specification reported as a distribution of macronutrients? (0=no, 1=yes)</td>
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<tr>
<td>KCAL_TOTAL_BASE(kcal/day)</td>
<td></td>
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<tr>
<td>KCAL_REPORT Reported kcals per day</td>
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</tbody>
</table>

**Energy restriction (kcal or %)**
<table>
<thead>
<tr>
<th>DIET CHARACTERISTICS</th>
<th>CONTROL/COMPARISON</th>
<th>IN1</th>
<th>IN2</th>
<th>IN3</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCAL_RES (unit= kcal) OR RES_PERCENT (%)</td>
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<tr>
<td>SOD_INTAKE (mg/day)</td>
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<tr>
<td>POT_INTAKE (mg/day)</td>
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<tr>
<td>FAT_INTAKE (g/day)</td>
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<tr>
<td>Unsaturated: FAT_UNSAT</td>
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<tr>
<td>Saturated: FAT_SAT</td>
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<tr>
<td>Cholesterol: FAT_CHOL</td>
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<tr>
<td>Dietary Fiber Intake (g/day)</td>
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<tr>
<td>FIB_INTAKE</td>
<td></td>
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<tr>
<td>Servings/week: Fruit and/or Vegetables VEG_SER</td>
<td></td>
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<tr>
<td>Servings/week: Dairy DAIRY_SER</td>
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<tr>
<td>Servings/week: Wine WINE_SER</td>
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<tr>
<td>Servings/week: Whole Grains GRAIN_SER</td>
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<tr>
<td>Servings/week: Fish FISH_SER</td>
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<tr>
<td>Servings/week: Olive Oil OIL_SER</td>
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<tr>
<td>Servings/week: Nuts NUTS_SER</td>
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<tr>
<td>Servings/week: Legumes LEG_SER</td>
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<tr>
<td>Servings/week: Red/processed meat MEAT_SER</td>
<td></td>
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<td></td>
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<tr>
<td>Servings/week: Poultry POUL_SER</td>
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</tr>
</tbody>
</table>

**Dietary Compliance & Counseling**

<table>
<thead>
<tr>
<th>DI_COMPLIANCE</th>
<th>Was dietary compliance assessed?</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0= No; 1= Yes)</td>
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</tbody>
</table>

If yes, specify:
(1=FFQ, 2=Food journal, 3=phone interviewing, 4=24 hr recall, 5=other, specify ___)

Was diet adherence measured pre, during, or post intervention? (1=pre, 2=during, 3=post, 4=pre, during, and post, 5=pre and post, 6=not reported)

Is a scale used to measure adherence? (0=no, 1=yes)

If yes, specify type of scale used___

<table>
<thead>
<tr>
<th>DI_COUNSELING</th>
<th>Participation in dietary counseling?</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0= no; 1= yes</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>DIET CHARACTERISTICS</td>
<td>CONTROL/COMPARISON</td>
<td>IN1</td>
<td>IN2</td>
<td>IN3</td>
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<td>----------------------</td>
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<tr>
<td>If Dietary Counseling was provided, report:</td>
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<tr>
<td>COUNSEL_HR hours per week</td>
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<tr>
<td>COUNSEL_SESS sessions per week</td>
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<tr>
<td>DIET_TOPIC If Dietary Counseling was provided, briefly state topics covered</td>
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<tr>
<td>QoL Was Quality of Life (QoL) assessed? 0=no, 1=yes, if yes, report tool or scale</td>
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<tr>
<td>NOTE_DIET Report here any notes relevant to the dietary intervention, counseling, implementation, etc.</td>
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<tr>
<td># of follow-ups</td>
<td></td>
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<tr>
<td>Interval of follow-ups</td>
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</tbody>
</table>
MEDITERRANEAN DIET: Meta-Analytic Projects

Standard Operating Procedures (SOP) Coding Form Manual
STUDY ID: create unique study ID using the first three letters of 1st author’s last name, and number to denote if multiple ID exists. For example, author is Pescatello= PES001. The number 001 denotes that it the first article with that study ID.

PUB_YR: Publication year

DATA: Record the earliest date for data collection, manuscript submission or acceptance for publication. If there is a date of manuscript submission/acceptance use the publication date. If it is unpublished and the date is unknown, denote as “.”

LANG: language of report

SCORE: Use the ISI Web of Knowledge journal citation report for score (access through www.lib.uconn.edu)
   • Go to “research assistance”
   • Choose “research databases” – choose database by name & type in “Web of Science”
   • Choose “additional resources” and “journal citation report”
   • Under “select an option” choose “search for a specific journal” and submit
   • Click on “view list of full journal titles;” copy and paste journal name into search
   • Record the number under “Impact Factor”

Note: If the journal is not found on ISI Web of Knowledge, you can check the journal’s home page. If you can find the impact factor score there-use it. Make sure you note in (V8) where information was found; if still unable to retrieve score, denote as “.”

JOURNAL NAME: Record the full name of the journal here (i.e., American Journal of Sports Medicine)

PUBMED NAME: Record the PubMed abbreviated name of the journal here (i.e., Am J Sports Med)

NOTE_STUDY: Record any relevant notes here about above variables.

SAMPLE CHARACTERISTICS: If the following variables are reported in the manuscript, record as a proportion; values range from 0.0-1.0.

ETH: Record the ethnicity/race of subjects as a proportion. For example: If article reports, “subjects were all white men” the PROP_WH would be 1.0 and the remaining ethnicity classifications would be 0.0. However, if 18% is reported for Caucasian (or white) ethnicity, the proportion would be 0.18. If not explicitly stated, denote as MISSING (“.”)

ETH_EST=Ethnicity estimate: when ethnicity is unreported or missing ethnicity will be assumed White if study was performed in Europe, Australia, or New Zealand; Asian if conducted in Asia; and Black if conducted in Africa, Hispanic if conducted in Brazil, Mexico. If location of study is not reported in methods section, use the location of the first author’s affiliation (i.e., the university or clinical institution author is a part of). Note: IF ethnicity is reported (i.e., values were recorded for V9), then ETH_EST will be noted with “0” indicating it is not applicable.
NUM_FemCON, NUM_FemIN1 (all the way to NUM_FemIN3): Record the number of females that were in each of the study groups (i.e., intervention group). If there is only a diet + control design, leave the other variables blank or cross out. However, if multiple interventions exist (i.e., control + >1 diet groups), **include # of females for each of the specific intervention and use all the way to NUM_FemIN3 if needed.**

REGION: Record the region of where the sample came from with one of the 8 codes. If the region is not included in the methods, use the location of the first author’s affiliation (i.e., the university or clinical institution author is a part of).

US_ZIP: If the location is not provided in the article, use the zip code of first author’s affiliation (i.e., the university or clinical institution author is a part of).

POP: If available, report population; 1=school or college OR 2= community. If patients were specifically recruited from a clinical setting or community (i.e., cardiac rehabilitation program, outpatient clinic, senior citizen center, local community center, etc.), make sure to specify. If population is not described, denote missing with “0.” For example, if authors report “15 healthy men and women were recruited for the study,” this would not be describing the population and would be coded as 0.

NOTE_RECRUIT: make any notes on recruitment

**RISK CHARACTERISTICS -report values provided for baseline sample data.** This information is commonly reported in either 1) the methods section (written in text) OR 2) in a baseline/ descriptive table. Be careful to note if the data is reported with SD or SEM. Record data in the way it is presented (mean±SD or mean±SEM) but change on sheet if SEM (just scratch SD and put SEM). If SEM is used, make sure this is very clear!

TOTAL_POP: If information is provided for each intervention group separately and not in aggregate form (i.e., mean of total sample), choose “0= no” and use the existing format on sheet (i.e., enter into separate columns). If reported as total sample (i.e., aggregate form), choose “1= yes” and only use one column to record data. If article has >2 groups and reports data for each intervention (i.e. control group, low, moderate, vigorous intensities) use additional columns in table.

NOTE: For n value, this corresponds to the number in sample you are working with (i.e., either total sample or for the specific intervention group).

**RISK CHARACTERISTIC TABLE:** all values should be recorded as metric (i.e., cm, kg).

Any values that are missing, denote with “.” Use intervention columns to compare multiple groups if there is no true control.

**DISEASE:** If text describes subjects as “healthy,” “normotensive,” or “normal BP,” choose 0= subjects were free of disease(s)/ chronic condition(s). If article has clinical population, you may have more than >1 condition and/ or disease. If all conditions are represented in list, choose 9=multiple and record the specific #s. If there is condition that is not included in the list, choose 8=other and record specifically.

1= Pre-Hypertensive is defined as, SBP 120-139 mmHg Or DBP 80-89 mmHg.
2= Hypertension Stage 1: SBP 140-159 mmHg Or DBP 90-99 mmHg, Stage 2: SBP ≥160 mmHg Or DBP ≥100 mmHg (ACSM’s Guidelines for Exercise Testing and Prescription, 8th Edition).

INFLAMMATION: If authors report that inflammation was measured, denote "1" and specify biomarkers/cytokines. If authors do not report measurement of inflammation, denote "0."

CARDIAC EVENTS MEASURED: If authors report measurement of cardiac events, denote number corresponding with events. Report prop and or number if reported. Record how it is measured if it is not in proportion and number of events.

For BP status, only record hypertension or pre-hypertension here IF author has classified population. DO NOT CLASSIFY BASED ON ORIENTATION BP VALUES. NOTE. If there is no mention about cardiovascular diseases or chronic conditions and they are not described as “healthy” denote missing information with “.” DO NOT ASSUME HEALTHY POPULATION.

MED: If authors report that subjects were not taking any medications, choose “0.” If there is no mention of medication or medication use, code “.” indicating missing information. If article states medication use, continue to fill in PROP_USE and WholeNumberUse. IF the study reports medication use but DOES NOT report number of individuals using medication, report missing with “.” If article states that “medication use and dosage did not change during intervention,” chose 1=yes for medication use. If article states that medication was discontinued 4 weeks prior to intervention (i.e., wash out period), choose 0= no for medication use.

MED_TYPE: if there is no medication use, code 0. If article has clinical population, you may have more than >1 medications. If all medications are represented in list, choose 9=multiple and record the specific #s. If there are medications used that are not included in the list, choose 8=other and record specifically.

BPMedUse: If MED is “yes,” report if BP medication specifically is taken; if MED was “no” code as 0.
If MED was a “yes,” BUT article does not include a list of medications used and you cannot determine if BP agents were included, denote as not reported with “.”
If BPMedUse is “yes,” fill in as much information as possible for BPMedProp, BPMedNumber and BPControl. If subjects are taking BP Meds their BP should be “controlled,” defined as a SBP ≤140 mmHg OR DBP ≤90 mmHg—it does not have to be both, just satisfying either the SBP or DBP cut point.

Oral Contraceptive (OC) or Hormone Replacement Therapy (HRT) use: Report whether Oral contraceptives, birth control, or HRT were taken by female subjects during the study. If yes denote “1.” If no denote “0.” If all men subjects, chose=0.

Lifestyle variables (i.e., smoking years, packs/yr; EtOH or alcohol consumption; caffeine consumption, etc.) are often not reported. Denote missing with “.” and make not of unreported lifestyle data in V79 NOTE_RISK (can record as “lifestyle variables = missing data”).
SMOKING: Report if the study sample included individuals who were currently smoking, or had a history of smoking. If yes denote “1,” if no denote “0;” if unreported or history of smoking is not disclosed in either study eligibility criteria (methods) or baseline data table denote missing “.”.

NUTRITIONAL SUPPLEMENTS Nutritional supplements allowed during intervention (not as part of the intervention). If nutritional supplements were allowed during the intervention, indicate with 1=yes. If nutritional supplements is excluded from the list of “approved” supplements, indicate with 0=no. If there was no mention of nutritional supplements, denote with “.”.

SUPPLEMENT TYPE 1=Fish oil, 2=Vitamin D, 3=MVI, 4=Calcium, 5=Other, specify:_________

ALCOHOL If participants do not drink alcohol, chose 0=no, if no mention of alcohol in the article denote with “.”.

DRINKS/WEEK Report number of drinks/week. If participants do not drink alcohol or alcohol was not mentioned in the article, denote with “.”.

TYPE OF ALCOHOL Indicate which type of alcoholic beverage the participants report to consume. If more than one type chose “4=multiple” and indicate the number associated with the consumed beverage. If participants consume another type of alcohol, chose “5=other” and specify the type of alcohol. If the type of alcohol is not mentioned or participants do not consume alcohol denote with “.”.
1 = Beer
2 = Wine
3 = Liquor
4 = Multiple, specify which numbers apply:________
5 = Other, specify:________

EXERCISE Indicate amount of exercise participants engaged in as min/week. If not reported, denote with “.”.

EXERCISE TYPE 1=cardio, 2=strength training, 3=stretching/yoga, 4=other, specify____

NOTE_RISK: Record any additional information about data in table.

Methods & Design

CON_GRP: describes type of control group used in study.
1= non-diet control group (study includes 2 separate groups of people, comprising a diet group and a control group), specify
2= non-diet control session (study includes same individuals who perform both a diet intervention and a control session; more common in acute exercise)
3= random assignment of individuals to non-MD condition/diet
4= random assignment of individuals to a non-diet control group
5= other, specify- if there was a non-diet control group (or session) used that involved a cognitive task, stress management, coping skills, etc. note it here
EXPERIMENT: describes study design (i.e., parallel or repeated measure or cross-over design). *Independent groups refer to a parallel study design.* For example, there are 3 groups: a control group (non-diet), a Med diet group, and a low-fat diet group. The groups are independent of one another; they stay in the same group for the entire intervention. Independent groups are commonly found in training studies (i.e., chronic exercise). *Non-independent groups refer to a repeated measure or cross-over study design.* For example, there are 3 conditions: a control session (non-diet), a Med diet group, and a low-fat diet group. Each person in the intervention will complete each condition serving as their own control. Non-independent groups are commonly found in acute studies (i.e., a single exercise bout). A crossover design assigns subjects to each intervention group for a period of time (ex: 4 wks crossover design with 3 dietary conditions: non diet (control), Med Diet, and LF group. Each subject will be on each diet for 4 wks with washout period).

EXP_SETTING Indicate setting. 1= hospital, 2=clinic, 3=academic/research lab, 4=fitness center/gym, 5=other, specify, 6=multiple, specify.

DIET MONITOR 0=no, 1=yes. Indicate is diet adherence was assessed using food record, food frequency questionnaire, Med Diet score, etc.

BEHAVIOR 0=no, 1=yes. If yes, specify. (examples: positive reinforcement, contingency management diet logs, motivational interviewing, cognitive dissonance, health belief model, etc.) Not food logs. Only if authors specify certain behavior technique.

INTER_LVL: For acute studies specifically, unless author explicitly states exercise occurred in a group setting/ session- answer 3= supervised. If multiple apply, choose 5= multiple and specify. For primary one-on-one (=1), choose when study explicitly states individual counselling sessions or when exercise sessions are conducted with a personal trainer.

NOTES_EXP & METHODS make any notes pertaining to experiment design and or methods.

LENGTH Report length of intervention in weeks.

WTGain/WTLoss Indicate whether the intervention was intended for weight gain, weight loss, or weight maintenance.

PART_LOST Report the number of participants that dropped out from the study in each group. Add # of dropouts if various numbers are stated for different parts of the intervention.

ADHERENCE (assessment of study completion): Record exercise adherence (i.e., the number of sessions completed during intervention) as a percent value, \( \left( \frac{\text{completed sessions}}{\text{total sessions}} \right) \times 100 \) For control groups, use 100% adherence unless explicitly stated by study that subjects in the control group were lost during the intervention (i.e., due to sickness, moving, etc).

MED_USE Report whether or not medications were used as part of the intervention.
YES_MEDS If medications were used as part of the intervention, specify which medication type(s) was used.

DIET_TYPE Indicate what type of diet the participants in each group followed. If one group followed a low-carb Mediterranean Diet that would fall in the “5=other” category and specify.

PROVISION OF FOODS Were any specific foods provided to the participants? 0=no, 1=yes.

IF yes, Type and Amount Indicate type and amount of foods provided to participants.

DIET_MACROS Was the diet reported as a distribution of macronutrients? 0=n0, 1=yes.

Specify Macro Distribution

KCAL Please indicate total Kcals consumed, Total Kcals the participants were “prescribed”/told to consume each day, and total kcals that participants reported that they consumed. If one of these components is not reported, denote with ".".

ENERGY RESTRICTION If calories were restricted for any group, report the Kcal restricted (kcal deficit per day) and/or the percent that energy was restricted. If not reported, denote with ".".

SOD_INTAKE Report sodium intake in mg/day.

POT_INTAKE Report potassium intake in mg/day.

FAT_INTAKE Report all fat categories in g/day (from narrative).

FIB_INTAKE Report dietary fiber intake in g/day.

SERVINGS/WEEK For the following sections please report # of servings per week of each food. If not reported, denote with ".".

DI_COMPLIANCE Was dietary compliance assessed? 0=no, 1=yes.

SPECIFY COMPLIANCE 0=no, 1=food frequency questionnaire, 2=food journal/diary, 3=phone, 4=24 hr recall, 5=other, specify.

ADHERENCE MEASURED 0=no, 1=pre, 2=during, 3=post, 4=pre, during, and post, 5= pre and post, 6= not reported.

SCALE USED Examples of a scale to measure adherence would be the Mediterranean Diet Score.

SPECIFY SCALE Name of scale used.

DI_COUNSELING Participation in dietary counseling? 0=no, 1=yes.
COUNSEL_HR hours per week

COUNSEL_SESS sessions per week

DIET_TOPIC Topics covered in dietary counseling

QoI Was quality of life assessed? If yes, report tool used to measure.

NOTE_DIE Record any notes pertaining to dietary intervention, counseling.

# FOLLOW UPS Please report the number of follow ups that took place AFTER the intervention period to monitor maintenance/success of participants.

INTERVAL Please report the interval of follow ups, for example, 3months after intervention period.

Appendix 4. Single Variant Syntax in R

library("metafor")

# Pub bias for MD and CVD events
# egger's
regtest(model2, model="lm", data=MedDiet)
# begg's
ranktest(model2, data=MedDiet)
# funnel plot
model2trim=trimfill(model1, data=MedDiet)
funnel(model2trim)

# Pub bias for MD and IL6
# egger's
regtest(model4, model="lm", data=MedDiet)
# begg's
ranktest(model4, data=MedDiet)
# funnel plot
model4trim=trimfill(model4, data=MedDiet)
funnel(model4trim)

# Pub bias for MD and CRP
# egger's
regtest(model6, model="lm", data=MedDiet)
# begg's
ranktest(model6, data=MedDiet)
# funnel plot
model6trim=trimfill(model6, data=MedDiet)
funnel(model6trim)

# Pub bias for MD and ICAM
# egger's
regtest(model8, model="lm", data=MedDiet)
# begg's
ranktest(model8, data=MedDiet)
# funnel plot
model8trim=trimfill(model8, data=MedDiet)
funnel(model8trim)

# Pub bias for MD and VCAM
# egger's
regtest(model10, model="lm", data=MedDiet)
# begg's
ranktest(model10, data=MedDiet)
# funnel plot
model10trim=trimfill(model10, data=MedDiet)
funnel(model10trim)

# Pub bias for MD and TG
# egger's
regtest(model12, model="lm", data=MedDiet)
# begg's
ranktest(model12, data=MedDiet)
# funnel plot
model12trim=trimfill(model12, data=MedDiet)
funnel(model12trim)

# Pub bias for MD and LDL
# egger's
regtest(model14, model="lm", data=MedDiet)
# begg's
ranktest(model14, data=MedDiet)
#funnel plot
model12trim=trimfill(model14, data=MedDiet)
funnel(model14trim)

#Pub bias for MD and HDL
#egger's
regtest(model16,model="lm", data=MedDiet)
#begg's
ranktest(model16, data=MedDiet)
#funnel plot
model16trim=trimfill(model16, data=MedDiet)
funnel(model16trim)

library("metafor")

#Run model for MD and CVD events
model1<-rma(d.ex.,var_d.ex.,subset=(Diet==8&Outcome==8),
data=MedDiet,method="FE")
model1
model2<-rma(d.ex.,var_d.ex.,subset=(Diet==8&Outcome==8),
data=MedDiet,method="REML", slab= paste(Reference, Year, sep=""))
model2

#Run model for MD and IL6
model3<-rma(d.ex.,var_d.ex.,subset=(Diet==1&Outcome==4),
data=MedDiet,method="FE")
model3
model4<-rma(d.ex.,var_d.ex.,subset=(Diet==1&Outcome==4),
data=MedDiet,method="REML", slab= paste(Reference, Year, sep=""))
model4

#Run model for MD and CRP
model5<-rma(d.ex.,var_d.ex.,subset=(Diet==1&Outcome==5),
data=MedDiet,method="FE")
model5
model6<-rma(d.ex.,var_d.ex.,subset=(Diet==1&Outcome==5),
data=MedDiet,method="REML", slab= paste(Reference, Year, sep=""))
model6

#Run model for MD and ICAM
model7 <- rma(d.ex., var_d.ex., subset=(Diet==1&Outcome==6),
  data=MedDiet, method="FE")
model7
model8 <- rma(d.ex., var_d.ex., subset=(Diet==1&Outcome==6),
  data=MedDiet, method="REML", slab= paste(Reference, Year, sep=""))
model8

# Run model for MD and VCAM

model9 <- rma(d.ex., var_d.ex., subset=(Diet==1&Outcome==7),
  data=MedDiet, method="FE")
model9
model10 <- rma(d.ex., var_d.ex., subset=(Diet==1&Outcome==7),
  data=MedDiet, method="REML", slab= paste(Reference, Year, sep=""))
model10

# Run model for MD and TG

model11 <- rma(d.ex., var_d.ex., subset=(Diet==1&Outcome==1),
  data=MedDiet, method="FE")
model11
model12 <- rma(d.ex., var_d.ex., subset=(Diet==1&Outcome==1),
  data=MedDiet, method="REML", slab= paste(Reference, Year, sep=""))
model12

# Run model for MD and LDL

model13 <- rma(d.ex., var_d.ex., subset=(Diet==1&Outcome==2),
  data=MedDiet1, method="FE")
model13
model14 <- rma(d.ex., var_d.ex., subset=(Diet==1&Outcome==2),
  data=MedDiet1, method="REML", slab= paste(Reference, Year, sep=""))
model14

# Run model for MD and HDL

model15 <- rma(d.ex., var_d.ex., subset=(Diet==1&Outcome==3),
  data=MedDiet1, method="FE")
model15
model16 <- rma(d.ex., var_d.ex., subset=(Diet==1&Outcome==3),
  data=MedDiet1, method="REML", slab= paste(Reference, Year, sep=""))
model16
table(MedDiet$Diet)

mean(MedDiet$Weeks)

# re run REML models before making forest plots

model2<-rma(d.ex., var_d.ex., subset=(Diet==8 & Outcome==8),
             data=MedDiet, method="REML", slab= paste(Reference, Year, sep=""))
model2

model4<-rma(d.ex., var_d.ex., subset=(Diet==1 & Outcome==4),
             data=MedDiet, method="REML", slab= paste(Reference, Year, sep=""))
model4

model6<-rma(d.ex., var_d.ex., subset=(Diet==1 & Outcome==5),
             data=MedDiet, method="REML", slab= paste(Reference, Year, sep=""))
model6

model8<-rma(d.ex., var_d.ex., subset=(Diet==1 & Outcome==6),
             data=MedDiet, method="REML", slab= paste(Reference, Year, sep=""))
model8

model10<-rma(d.ex., var_d.ex., subset=(Diet==1 & Outcome==7),
              data=MedDiet, method="REML", slab= paste(Reference, Year, sep=""))
model10

model12<-rma(d.ex., var_d.ex., subset=(Diet==1 & Outcome==1),
              data=MedDiet, method="REML", slab= paste(Reference, Year, sep=""))
model12

model14<-rma(d.ex., var_d.ex., subset=(Diet==1 & Outcome==2),
              data=MedDiet, method="REML", slab= paste(Reference, Year, sep=""))
model14

model16<-rma(d.ex., var_d.ex., subset=(Diet==1 & Outcome==3),
              data=MedDiet, method="REML", slab= paste(Reference, Year, sep=""))
model16

# forest plots
# Forest plot MD and CVD events Combined
par("usr")
forest(model2, xlim=c(-10,10), xlab="Standardized Mean Difference", cex=0.8, efac=2,
col="dark blue", border="black")
op<-par(cex=0.90, font=2, col="black")
# to change the size, font, and color of the plot
op<-par(cex=0.80, font=2, col="dark blue") #to change the size, the font, and the color of the inserted text in the plot
text (-0.10, 14, "Med Diet and CVD Events") #the first number indicates where the title starts and the second number how high in the plot
text(c(-4.3, 4), c("Favors Intervention", "Favors Baseline")) #here the -8 is telling us the position where favors intervention starts and 7 where the position where favors baseline starts, and they both are at the 22 height in the plot, if you count the number of authors are 20, plus the line where RE Model is that is 21 rows, so the labels Author, and Favors are in line 22
text(-9.8, 13, "Author(s) and Year", pos=4)
text(7.5, 13, "d[95%CI]", pos=4)
par(op)

#Forest plot MD and IL6
par("usr")
forest(model4, xlim=c(-29, 5), xlab="Standardized Mean Difference", cex=0.8, efac=2, col="dark blue", border="black")
op<-par(cex=0.70, font=2, col="black")#to change the size, font, and color of the plot
op<-par(cex=0.80, font=2, col="dark blue") #to change the size, the font, and the color of the inserted text in the plot
text (-10, 20, "Med Diet and IL6") #the first number indicates where the title starts and the second number how high in the plot
text(c(-21, 0.3), 19, c("Favors Intervention", "Favors Baseline")) #here the -8 is telling us the position where favors intervention starts and 7 where the position where favors baseline starts, and they both are at the 22 height in the plot, if you count the number of authors are 20, plus the line where RE Model is that is 21 rows, so the labels Author, and Favors are in line 22
text(-28.5, 19, "Author(s) and Year", pos=4)
text(2.5, 19, "d[95%CI]", pos=4)
par(op)

#Forest plot MD and CRP
par("usr")
forest(model6, xlim=c(-15, 8), xlab="Standardized Mean Difference", cex=0.8, efac=2, col="dark blue", border="black")
op<-par(cex=0.70, font=2, col="black")#to change the size, font, and color of the plot
op<-par(cex=0.80, font=2, col="dark blue") #to change the size, the font, and the color of the inserted text in the plot
text (-2, 29, "Med Diet and CRP") #the first number indicates where the title starts and the second number how high in the plot
text(c(-7, 3), 28, c("Favors Intervention", "Favors Baseline")) #here the -8 is telling us the position where favors intervention starts and 7 where the position where favors baseline starts, and they both are at the 22 height in the plot, if you count the number of authors
are 20, plus the line where RE Model is that is 21 rows, so the labels Author, and Favors are in line 22
text(-15,28, "Author(s) and Year", pos=4)
text(8,28, "d[95%CI]", pos=4)
par(op)

#forest plot for Med Diet and ICAM
par("usr")
forest(model8, xlim=c(-13,5), xlab="Standardized Mean Difference", cex=0.8, efac=2,
col="dark blue", border="black")

#forest plot for Med Diet and VCAM
par("usr")
forest(model10, xlim=c(-10,9), xlab="Standardized Mean Difference", cex=0.8, efac=2,
col="dark blue", border="black")

#forest plot for Med Diet and TG
par("usr")
```
forest(model12, xlim=c(-25, 10), xlab="Standardized Mean Difference", cex=0.8, efac=2, col="dark blue", border="black")

op<--par(cex=0.70, font=2, col="black") #to change the size, font, and color of the plot
op<--par(cex=0.80, font=2, col="dark blue") #to change the size, the font, and the color of the inserted text in the plot

text(-5, 27.5, "Med Diet and TG") #the first number indicates where the title starts and the second number how high in the plot
text(c(-15, 3), 27, c("Favors Intervention", "Favors Baseline")) #here the -8 is telling us the position where favors intervention starts and 7 where the position where favors baseline starts, and they both are at the 22 height in the plot, if you count the number of authors are 20, plus the line where RE Model is that is 21 rows, so the labels Author, and Favors are in line 22
text(-24, 27, "Author(s) and Year", pos=4)
text(7.5, 27, "d[95%CI]", pos=4)
par(op)

#forest plot for Med Diet and LDL
par("usr")
forest(model14, xlim=c(-10, 10), xlab="Standardized Mean Difference", cex=0.8, efac=2, col="dark blue", border="black")

op<--par(cex=0.70, font=2, col="black") #to change the size, font, and color of the plot
op<--par(cex=0.80, font=2, col="dark blue") #to change the size, the font, and the color of the inserted text in the plot

text(-0.5, 25.4, "Med Diet and LDL") #the first number indicates where the title starts and the second number how high in the plot
text(c(-4.2, 3), 24, c("Favors Intervention", "Favors Baseline")) #here the -8 is telling us the position where favors intervention starts and 7 where the position where favors baseline starts, and they both are at the 22 height in the plot, if you count the number of authors are 20, plus the line where RE Model is that is 21 rows, so the labels Author, and Favors are in line 22
text(-9.20, 24, "Author(s) and Year", pos=4)
text(7, 24, "d[95%CI]", pos=4)
par(op)

#forest plot for Med Diet and HDL
par("usr")
forest(model16, xlim=c(-10, 10), xlab="Standardized Mean Difference", cex=0.8, efac=2, col="dark blue", border="black")

op<--par(cex=0.70, font=2, col="black") #to change the size, font, and color of the plot
op<--par(cex=0.80, font=2, col="dark blue") #to change the size, the font, and the color of the inserted text in the plot

text(-0.5, 27, "Med Diet and HDL") #the first number indicates where the title starts and the second number how high in the plot
```
text(c(-4,3.8),26,c("Favors Baseline", "Favors Intervention")) #here the -8 is telling us the position where favors intervention starts and 7 where the position where favors baseline starts, and they both are at the 22 height in the plot, if you count the number of authors are 20, plus the line where RE Model is that is 21 rows, so the labels Author, and Favors are in line 22

text(-9.8,26, "Author(s) and Year", pos=4)
text(7.5,26, "d[95%CI]", pos=4)
par(op)

#Regressions

#Regression MD and TG
model181 <- rma(d.ex., var_d.ex., subset=(Diet==1 & Outcome==1), mods=Weeks, data=MedDiet, method="REML", slab= paste(Author, sep =" ", ))
model181pred <- predict(model181, newmods=cbind(seq(0,208,.1)))
wi = MedDiet$w_d.ex.
min= min(wi, na.rm=TRUE)
max= max(wi, na.rm=TRUE)
size= 0.5 + 3.0 * (wi - min(wi))/(max(wi) - min(wi))
dietout1= subset(MedDiet,Diet==1 & Outcome==1) #Here we have to create the subsample we are working on to just plot the observed values of that below
plot(dietout1$Weeks,dietout1$d.ex.,pch= 22, col="black", bg = "white", cex=wi, xlab = "Number of Weeks", ylab = "MD on TG and Effect Size(d)", xlim=c(0, 208), ylim=c(-1.5, 0.5))
lines(seq(0,208,.1), model181pred$pred, col = "dark blue") #Plotting here the regression line and confidence interval of the predictive model
lines(seq(0,208,.1), model181pred$ci.lb, lty = "dashed", col="dark blue")
lines(seq(0,208,.1), model181pred$ci.ub, lty = "dashed", col="dark blue")
summary(model181)

#Regression MD and LDL
model191 <- rma(d.ex., var_d.ex., subset=(Diet==1 & Outcome==2), mods=Weeks, data=MedDiet, method="REML", slab= paste(Author, sep =" ", ))
model191pred <- predict(model191, newmods=cbind(seq(0,208,.1)))
wi = MedDiet$w_d.ex.
min= min(wi, na.rm=TRUE)
max= max(wi, na.rm=TRUE)
size = 0.5 + 3.0 * (wi - min)/(max - min)
dietout1 = subset(MedDiet, Diet==1 & Outcome==2) # Here we have to create the subsample we are working on to just plot the observed values of that below
plot(dietout1$Weeks, dietout1$d.ex., pch= 22, col="black", bg = "black", cex = size, xlab = "Number of Weeks", ylab = "MD on LDL and Effect Size(d)", xlim=c(0, 208), ylim=c(-2.0, 2.0))
summary(model191)

# Regression MD and HDL
model201 <- rma(d.ex., var_d.ex., subset=(Diet==1 & Outcome==3), mods=Weeks, data= MedDiet1, method="REML", slab= paste(Author, sep = ","))
model201pred <- predict(model201, newmods=cbind(seq(0, 208, .1)))
wi = MedDiet1$w_d.ex.
min = min(wi, na.rm=TRUE)
max = max(wi, na.rm=TRUE)
size = 0.5 + 3.0 * (wi - min)/(max - min)
dietout1 = subset(MedDiet1, Diet==1 & Outcome==3) # Here we have to create the subsample we are working on to just plot the observed values of that below
plot(dietout1$Weeks, dietout1$d.ex., pch= 23, col="black", bg = "black", cex = size, xlab = "Number of Weeks", ylab = "MD on HDL and Effect Size(d)", xlim=c(0, 208), ylim=c(-1.0, 2.0))
lines(seq(0, 208, .1), model201pred$pred, col = "dark blue") # Plotting here the regression line and confidence interval of the predictive model
lines(seq(0, 208, .1), model201pred$ci.lb, lty = "dashed", col="dark blue")
lines(seq(0, 208, .1), model201pred$ci.ub, lty = "dashed", col="dark blue")
summary(model201)

# create new variable
minweeks = 8 - MedDiet$Weeks

# Regression MD and HDL minweeks
model32 <- rma(d.ex., var_d.ex., subset=(Diet==1 & Outcome==3), mods=minweeks, data= MedDiet1, method="REML", slab= paste(Author, sep = ","))
model32pred <- predict(model32, newmods=cbind(seq(0, 208, .1)))
wi = MedDiet1$w_d.ex.
min = min(wi, na.rm=TRUE)
max = max(wi, na.rm=TRUE)
size = 0.5 + 3.0 * (wi - min)/(max - min)
dietout1 = subset(MedDiet1, Diet==1 & Outcome==3) #Here we have to create the subsample we are working on to just plot the observed values of that below
plot(dietout1$Weeks, dietout1$d.ex., pch= 23, col="black", bg = "black", cex=size, xlab = "Number of Weeks", ylab = "MD on HDL and Effect Size(d)"; xlim=c(0, 208), ylim=c(-1.0, 2.0))
lines(seq(0,208,.1), model32pred$pred, col = "dark blue") #Plotting here the regression line and confidence interval of the predictive model
lines(seq(0,208,.1), model32pred$ci.lb, lty = "dashed", col="dark blue")
lines(seq(0,208,.1), model32pred$ci.ub, lty = "dashed", col="dark blue")
summary(model32)

#create new variable
maxweeks = 208 - MedDiet$Weeks

#Regression MD and HDL max weeks
model33 <- rma(d.ex., var_d.ex., subset=(Diet==1 & Outcome==3), mods=maxweeks, data= MedDiet, method="REML", slab= paste(Author, sep = ","))
model33pred <- predict(model32, newmods=cbind(seq(0,208,.1)))
wi = MedDiet1$w_d.ex.
min = min(wi, na.rm=TRUE)
max = max(wi, na.rm=TRUE)
size = 0.5 + 3.0 * (wi - min)/(max - min)
dietout1 = subset(MedDiet1, Diet==1 & Outcome==3) #Here we have to create the subsample we are working on to just plot the observed values of that below
plot(dietout1$Weeks, dietout1$d.ex., pch= 23, col="black", bg = "black", cex=size, xlab = "Number of Weeks", ylab = "MD on HDL and Effect Size(d)"; xlim=c(0, 208), ylim=c(-1.0, 2.0))
lines(seq(0,208,.1), model33pred$pred, col = "dark blue") #Plotting here the regression line and confidence interval of the predictive model
lines(seq(0,208,.1), model33pred$ci.lb, lty = "dashed", col="dark blue")
lines(seq(0,208,.1), model33pred$ci.ub, lty = "dashed", col="dark blue")
summary(model33)

#Regression MD and IL6
model211 <- rma(d.ex., var_d.ex., subset=(Diet==1 & Outcome==4), mods=Weeks, data= MedDiet, method="REML", slab= paste(Author, sep = ","))
model211pred <- predict(model211, newmods=cbind(seq(0,208,.1)))
wi = MedDiet$w_d.ex.
min= min(wi, na.rm=TRUE)
max= max(wi, na.rm=TRUE)
size= 0.5 + 3.0 * (wi - min)/(max - min)
dietout1= subset(MedDiet,Diet==1 & Outcome==4) #Here we have to create the
subsample we are working on to just plot the observed values of that below
plot(dietout1$Weeks,dietout1$d.ex.,pch= 22, col="black", bg = "black", cex=size, xlab = "Number of Weeks", ylab = "MD on IL6 and Effect Size(d)")
lines(seq(0,208,.1), model211pred$pred, col = "dark blue")
lines(seq(0,208,.1), model211pred$ci.lb, lty = "dashed", col="dark blue")
lines(seq(0,208,.1), model211pred$ci.ub, lty = "dashed", col="dark blue")
summary(model211)

#Regression MD and CRP
model221<-rma(d.ex.,var_d.ex.,subset=(Diet==1 & Outcome==5), mods=region, data= MedDiet, method="REML", slab= paste(Author, sep =","))
model221pred <- predict(model221, newmods=cbind(seq(0,208,.1)))
wi = MedDiet$w_d.ex.
min= min(wi, na.rm=TRUE)
max= max(wi, na.rm=TRUE)
size= 0.5 + 3.0 * (wi - min)/(max - min)
dietout1= subset(MedDiet,Diet==1 & Outcome==5) #Here we have to create the
subsample we are working on to just plot the observed values of that below
plot(dietout1$region,dietout1$d.ex.,pch= 22, col="black", bg = "black", cex=size, xlab = "Number of Weeks", ylab = "MD on CRP and Effect Size(d)")
lines(seq(0,208,.1), model221pred$pred, col = "dark blue")
lines(seq(0,208,.1), model221pred$ci.lb, lty = "dashed", col="dark blue")
lines(seq(0,208,.1), model221pred$ci.ub, lty = "dashed", col="dark blue")
summary(model221)

#Regression MD and ICAM
model241<-rma(d.ex., var_d.ex., subset=(Diet==1 & Outcome==6), mods=Weeks, data=MedDiet, method="REML", slab= paste(Author, sep =","))
model241pred <- predict(model241, newmods=cbind(seq(0,208,.1)))
wi = MedDiet$w_d.ex.
min= min(wi, na.rm=TRUE)
max= max(wi, na.rm=TRUE)
size= 0.5 + 3.0 * (wi - min)/(max - min)
dietout1= subset(MedDiet,Diet==1 & Outcome==6) #Here we have to create the subsample we are working on to just plot the observed values of that below
plot(dietout1$Weeks,dietout1$d.ex.,pch= 22, col="black", bg = "black", cex=size, xlab = "Number of Weeks", #Plotting here the observed values of the subsample
  ylab = "MD on ICAM and Effect Size(d)",xlim=c(0, 208), ylim=c(-10, 1))
lines(seq(0,208,.1), model241pred$pred, col = "dark blue") #Plotting here the regression line and confidence interval of the predictive model
lines(seq(0,208,.1), model241pred$ci.lb, lty = "dashed", col="dark blue")
lines(seq(0,208,.1), model241pred$ci.ub, lty = "dashed", col="dark blue")
summary(model241)

#Regression MD and VCAM
model261<-rma(d.ex., var_d.ex., subset=(Diet==1 & Outcome==7), mods=Weeks, data=MedDiet, method="REML", slab= paste(Author, sep =","))
model261pred <- predict(model261, newmods=cbind(seq(0,208,.1)))
wi = MedDiet$w_d.ex.
min= min(wi, na.rm=TRUE)
max= max(wi, na.rm=TRUE)
size= 0.5 + 3.0 * (wi - min)/(max - min)
dietout1= subset(MedDiet,Diet==1 & Outcome==7) #Here we have to create the subsample we are working on to just plot the observed values of that below
plot(dietout1$Weeks,dietout1$d.ex.,pch= 23, col="black", bg = "white", cex=size, xlab = "Number of Weeks", #Plotting here the observed values of the subsample
  ylab = "MD on VCAM and Effect Size(d)",xlim=c(0, 208), ylim=c(-10, 1.5))
lines(seq(0,208,.1), model261pred$pred, col = "dark blue") #Plotting here the regression line and confidence interval of the predictive model
lines(seq(0,208,.1), model261pred$ci.lb, lty = "dashed", col="dark blue")
lines(seq(0,208,.1), model261pred$ci.ub, lty = "dashed", col="dark blue")
summary(model261)

#create new variable
maxweeks=52-MedDiet$Weeks
maxweeks
#Regression MD and VCAM maxweeks
model27<-rma(d.ex., var_d.ex., subset=(Diet==1 & Outcome==7), mods=maxweeks, data= MedDiet, method="REML", slab= paste(Author, sep =",",))
model27pred <- predict(model27, newmods=cbind(seq(0,208,.1)))
wi = MedDiet$w_d.ex.
min= min(wi, na.rm=TRUE)
max= max(wi, na.rm=TRUE)
size= 0.5 + 3.0 * (wi - min)/(max - min)
dietout1= subset(MedDiet,Diet==1 & Outcome==7) #Here we have to create the subsample we are working on to just plot the observed values of that below
plot(dietout1$Weeks,dietout1$d.ex.,pch= 23, col="black", bg = "white", cex=size, xlab = "Number of Weeks", ylab = "MD on VCAM and Effect Size(d)",xlim=c(0, 208), ylim=c(-10, 1.5))
lines(seq(0,208,.1), model27pred$pred, col = "dark blue") #Plotting here the regression line and confidence interval of the predictive model
lines(seq(0,208,.1), model27pred$ci.lb, lty = "dashed", col="dark blue")
lines(seq(0,208,.1), model27pred$ci.ub, lty = "dashed", col="dark blue")
summary(model27)

#create new variable
minweeks=12-MedDiet$Weeks
minweeks

#Regression MD and VCAM minweeks
model31<-rma(d.ex., var_d.ex., subset=(Diet==1 & Outcome==7), mods=minweeks, data= MedDiet, method="REML", slab= paste(Author, sep =",",))
model31pred <- predict(model31, newmods=cbind(seq(0,208,.1)))
wi = MedDiet$w_d.ex.
min= min(wi, na.rm=TRUE)
max= max(wi, na.rm=TRUE)
size= 0.5 + 3.0 * (wi - min)/(max - min)
dietout1= subset(MedDiet,Diet==1 & Outcome==7) #Here we have to create the subsample we are working on to just plot the observed values of that below
plot(dietout1$Weeks,dietout1$d.ex.,pch= 23, col="black", bg = "white", cex=size, xlab = "Number of Weeks", ylab = "MD on VCAM and Effect Size(d)",xlim=c(0, 208), ylim=c(-10, 1.5))
lines(seq(0,208,.1), model31pred$pred, col = "dark blue") #Plotting here the regression line and confidence interval of the predictive model
lines(seq(0,208,.1), model31pred$ci.lb, lty = "dashed", col="dark blue")
lines(seq(0,208,.1), model31pred$ci.ub, lty = "dashed", col="dark blue")
summary(model31)
Appendix 5. Multivariate Syntax in R

library(metafor)

#CRP
#Calculate total number of participants (Ni)
creactive$ni <- unlist(lapply(split(creactive, creactive$study), function(x) rep(sum(x$ni1) + x$ni2[1], each = nrow(x))))

#Create Variance-Covariance Matrix for Multiple Comparisons:
calc.creactivev <- function(x) {creactivev <- matrix(1/x$ni2[1] + outer(x$d, x$d, "+")/(2*x$ni[1]), nrow = nrow(x), ncol = nrow(x))
diag(creactivev) <- x$var
creactivev}

creactiveproV <- lapply(split(creactive, creactive$study), calc.creactivev)
creactiveproV <- as.matrix(bdiag(creactiveproV))
creactiveproV

##Calculating the Weighted Mean ES
creactive$diet <- as.factor(creactive$diet)
dcreactive <- rma.mv(d, var, creactiveproV, mods = ~ factor(diet) - 1, random = ~ diet|study, struct="UN", data = creactive, method="ML")
dcreactive

table(creactive$diet)

#moderators
#moderator Weeks
model1 <- rma(d, var, creactiveproV, mods = ~ factor(diet) - 1 + creactive$weeks, data = creactive, method="ML")
summary (model1)

#moderator females
model2 <- rma(d, var, creactiveproV, mods = ~ factor(diet) - 1 + creactive$fem, data = creactive, method="ML")
summary (model2)

#moderator proportion of females
model3<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + creactive$propfem,data = creactive, method="ML")
summary (model3)

#moderator region
model4<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + factor(creactive$region),data = creactive, method="ML")
summary (model4)

#moderator population recruit
model5<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + factor(pop),data = creactive, method="ML")
summary (model5)

#moderator age
model6<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + creactive$age,data = creactive, method="ML")
summary (model6)

#moderator interlvl
model7<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + factor(interlvl),data = creactive, method="ML")
summary (model7)

#moderator mq
model8<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + creactive$mq,data = creactive, method="ML")
summary (model8)

#moderator pub year
model9<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + creactive$Year,data = creactive, method="ML")
summary (model9)

#moderator total n
model10<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + creactive$ni,data = creactive, method="ML")
summary (model10)

#moderator score
model11<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + creactive$score,data = creactive, method="ML")
# moderator number of interventions
model12<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + factor(numinterv),data = creactive, method="ML")
summary (model12)

# moderator funding source
model13<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + factor(fund),data = creactive, method="ML")
summary (model13)

# moderator ethnicity estimate
model14<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + factor(ethest),data = creactive, method="ML")
summary (model14)

# moderator proportion disease
model16<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + creactive$diseaseprop, data = creactive, method="ML")
summary (model16)

# moderator number disease
model17<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + creactive$diseasenum, data = creactive, method="ML")
summary (model17)

# moderator proportion meds
model18<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + creactive$medsprop, data = creactive, method="ML")
summary (model18)

# moderator number meds
model19<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + creactive$medsnum, data = creactive, method="ML")
summary (model19)

# moderator med type
model20<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + factor(medtype), data = creactive, method="ML")
summary (model20)

# moderator experimental setting
model21<-rma(d, var, creactiveproV, mods = ~ factor(diet) - 1 + creactive$experiset, data = creactive, method="ML")
summary (model21)

#moderator length of counseling
model22<-rma(d, var, creactiveproV, mods = ~ factor(diet) - 1 + creactive$counsellength, data = creactive, method="ML")
summary (model22)

#moderator number of counseling sessions
model23<-rma(d, var, creactiveproV, mods = ~ factor(diet) - 1 + creactive$counselnum, data = creactive, method="ML")
summary (model23)

#moderator language of publication
model24<-rma(d, var, creactiveproV, mods = ~ factor(diet) - 1 + creactive$publang, data = creactive, method="ML")
summary (model24)

#moderator proportion of carb
model25<-rma(d, var, creactiveproV, mods = ~ factor(diet) - 1 + creactive$carbprop, data = creactive, method="ML")
summary (model25)

#moderator proportion of sat fat
model26<-rma(d, var, creactiveproV, mods = ~ factor(diet) - 1 + creactive$satfatprop, data = creactive, method="ML")
summary (model26)

#moderator proportion of total fat
model27<-rma(d, var, creactiveproV, mods = ~ factor(diet) - 1 + creactive$totfatprop, data = creactive, method="ML")
summary (model27)

#moderator proportion of protein
model28<-rma(d, var, creactiveproV, mods = ~ factor(diet) - 1 + creactive$protprop, data = creactive, method="ML")
summary (model28)

#moderator assessment of dietary compliance
model29<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + factor(dietcompl), data = creactive, method="ML")
summary (model29)

#moderator participation in dietary counseling
model30<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + creactive$dietcoun, data = creactive, method="ML")
summary (model30)

#moderator proportion of cvd
model31<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + creactive$cvd, data = creactive, method="ML")
summary (model31)

#moderator proportion of DM
model32<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + creactive$dm, data = creactive, method="ML")
summary (model32)

#moderator proportion of MetS
model33<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + creactive$mets, data = creactive, method="ML")
summary (model33)

#moderator proportion of overweight/obesity
model34<-rma(d,var,creactiveproV, mods = ~ factor(diet) - 1 + creactive$obes, data = creactive, method="ML")
summary (model34)

#IL6

#Calculate total number of participants (ni)
interl$ni <- unlist(lapply(split(interl,interl$study), function(x)
rep(sum(x$n1i)+x$n2i[1],each=nrow(x))))

#Create Variance-Covariance Matrix for Multiple Comparisons:
calc.interv <- function(x) {interv<- matrix(1/x$n2i[1] +
outer(x$d,x$d,"**")/(2*x$ni[1]),nrow=nrow(x),ncol=nrow(x))
diag(interv) <- x$var
interv}
interv <- lapply(split(interl,interl$study),calc.interv)
intervV <- as.matrix(bdiag(interv))

##Calculating the Weighted Mean ES
```r
interl$diet <- as.factor(interl$diet)

dinterl <- rma.mv(d, var, interV, mods = ~ factor(diet) - 1, random = ~
diet|study, struct="UN", data = interl, method="ML")
dinterl
table(interl$diet)

#moderators
#moderator Weeks
model35 <- rma(d, var, interV, mods = ~ factor(diet) - 1 + interl$weeks, data = interl,
method="ML")
summary(model35)

#moderator females
model36 <- rma(d, var, interV, mods = ~ factor(diet) - 1 + interl$fem, data = interl,
method="ML")
summary(model36)

#moderator region
model37 <- rma(d, var, interV, mods = ~ factor(diet) - 1 + ~ factor(region), data = interl,
method="ML")
summary(model37)

#moderator population recruit
model38 <- rma(d, var, interV, mods = ~ factor(diet) - 1 + ~ factor(pop), data = interl,
method="ML")
summary(model38)

#moderator age
model39 <- rma(d, var, interV, mods = ~ factor(diet) - 1 + interl$age, data = interl,
method="ML")
summary(model39)

#moderator interlvl
model40 <- rma(d, var, interV, mods = ~ factor(diet) - 1 + ~ factor(interlvl), data = interl,
method="ML")
summary(model40)

#moderator mq
model41 <- rma(d, var, interV, mods = ~ factor(diet) - 1 + interl$mq, data = interl,
method="ML")
summary(model41)
```
#moderator pub year
model42<-rma(d,var,interV, mods = ~ factor(diet) - 1 + interl$Year, data = interl, method="ML")
summary(model42)

#moderator total n
model43<-rma(d,var,interV, mods = ~ factor(diet) - 1 + interl$ni, data = interl, method="ML")
summary(model43)

#moderator score
model44<-rma(d,var,interV, mods = ~ factor(diet) - 1 + interl$score, data = interl, method="ML")
summary(model44)

#moderator funding source
model45<-rma(d,var,interV, mods = ~ factor(diet) - 1 + interl$fund, data = interl, method="ML")
summary(model45)

#moderator number of interventions
model45<-rma(d,var,interV, mods = ~ factor(diet) - 1 + interl$numinterv, data = interl, method="ML")
summary(model45)

#moderator ethnicity estimate
model46<-rma(d,var,interV, mods = ~ factor(diet) - 1 + factor( ethest), data = interl, method="ML")
summary(model46)

#moderator proportion disease
model48<-rma(d,var,interV, mods = ~ factor(diet) - 1 + interl$diseaseprop, data = interl, method="ML")
summary(model48)

#moderator number disease
model49<-rma(d,var,interV, mods = ~ factor(diet) - 1 + interl$diseaseenum, data = interl, method="ML")
summary(model49)

#moderator proportion meds
model50<-rma(d,var,interV, mods = ~ factor(diet) - 1 + interl$medsprop, data = interl, method="ML")
summary(model50)
# moderator number meds
model51<-rma(d, var, interV, mods = ~ factor(diet) - 1 + interl$medsnum, data = interl, method="ML")
summary (model51)

# moderator med type
model52<-rma(d, var, interV, mods = ~ factor(diet) - 1 + factor(medtype), data = interl, method="ML")
summary (model52)

# moderator experimental setting
model53<-rma(d, var, interV, mods = ~ factor(diet) - 1 + interl$experiset, data = interl, method="ML")
summary (model53)

# moderator length of counseling
model54<-rma(d, var, interV, mods = ~ factor(diet) - 1 + interl$counsellength, data = interl, method="ML")
summary (model54)

# moderator number of counseling sessions
model55<-rma(d, var, interV, mods = ~ factor(diet) - 1 + interl$counselnum, data = interl, method="ML")
summary (model55)

# moderator language of publication
model56<-rma(d, var, interV, mods = ~ factor(diet) - 1 + interl$publang, data = interl, method="ML")
summary (model56)

# moderator proportion of carb
model57<-rma(d, var, interV, mods = ~ factor(diet) - 1 + interl$carbprop, data = interl, method="ML")
summary (model57)

# moderator proportion of sat fat
model58<-rma(d, var, interV, mods = ~ factor(diet) - 1 + interl$satfatprop, data = interl, method="ML")
summary (model58)

# moderator proportion of total fat
model59<-rma(d, var, interV, mods = ~ factor(diet) - 1 + interl$totfatprop, data = interl, method="ML")
summary (model59)
#moderator proportion of protein
model60<-rma(d,var,interV, mods = ~ factor(diet) - 1 + interl$protprop, data = interl, method="ML")
summary (model60)

#moderator assessment of dietary compliance
model61<-rma(d,var,interV, mods = ~ factor(diet) - 1 + factor(dietcompl), data = interl, method="ML")
summary (model61)

#moderator participation in dietary counseling
model62<-rma(d,var,interV, mods = ~ factor(diet) - 1 + interl$dietcoun, data = interl, method="ML")
summary (model62)

#moderator proportion of cvd
model63<-rma(d,var,interV, mods = ~ factor(diet) - 1 + interl$cvd, data = interl, method="ML")
summary (model63)

#moderator proportion of DM
model64<-rma(d,var,interV, mods = ~ factor(diet) - 1 + interl$dm, data = interl, method="ML")
summary (model64)

#moderator proportion of MetS
model65<-rma(d,var,interV, mods = ~ factor(diet) - 1 + interl$mets, data = interl, method="ML")
summary (model65)

#moderator proportion of overweight/obesity
model66<-rma(d,var,interV, mods = ~ factor(diet) - 1 + interl$obes, data = interl, method="ML")
summary (model66)

#ICAM

#Calculate total number of participants (Ni)
ICAMdata$ni <- unlist(lapply(split(ICAMdata,ICAMdata$study),function(x) rep(sum(x$n1i)+x$n2i[1],each=nrow(x))))

#Create Variance-Covariance Matrix for Multiple Comparisons:
calc.icamv <- function(x) {
  icamv <- matrix(1/x$n2i[1] +
  outer(x$d, x$d, "*")/(2*x$ni[1]), nrow=nrow(x), ncol=nrow(x))
  diag(icamv) <- x$var
  icamv
}

icamV <- lapply(split(ICAMdata, ICAMdata$study), calc.icamv)
icamV <- as.matrix(bdiag(icamV))
icamV

## Calculating the Weighted Mean ES
ICAMdata$diet <- as.factor(ICAMdata$diet)

dicam <- rma.mv(d, var, icamV, mods = ~ factor(diet) - 1, random = ~
diet|study, struct="UN", data = ICAMdata, method="ML")
dicam
table(ICAMdata$diet)

# moderators
# moderator Weeks
model67 <- rma(d, var, icamV, mods = ~ factor(diet) - 1 + ICAMdata$weeks, data =
  ICAMdata, method="ML")
summary(model67)

# moderator females
model68 <- rma(d, var, icamV, mods = ~ factor(diet) - 1 + ICAMdata$fem, data =
  ICAMdata, method="ML")
summary(model68)

# moderator region
model69 <- rma(d, var, icamV, mods = ~ factor(diet) - 1 + ~ factor(ICAMdata$region), data =
  ICAMdata, method="ML")
summary(model69)

# moderator population recruit
model70 <- rma(d, var, icamV, mods = ~ factor(diet) - 1 + ICAMdata$pop, data =
  ICAMdata, method="ML")
summary(model70)

# moderator age
model71 <- rma(d, var, icamV, mods = ~ factor(diet) - 1 + ICAMdata$age, data =
  ICAMdata, method="ML")
summary(model71)
#moderator intervl
model72<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + ~ factor(intervl),data = ICAMdata, method="ML")
summary (model72)

#moderator mq
model73<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$mq,data = ICAMdata, method="ML")
summary (model73)

#moderator pub year
model74<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$Year,data = ICAMdata, method="ML")
summary (model74)

#moderator total n
model75<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$ni,data = ICAMdata, method="ML")
summary (model75)

#moderator score
model76<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$score,data = ICAMdata, method="ML")
summary (model76)

#moderator funding source
model77<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + factor(fund),data = ICAMdata, method="ML")
summary (model77)

#moderator number of interventions
model78<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + factor(numinterv),data = ICAMdata, method="ML")
summary (model78)

#moderator ethnicity estimate
model80<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + factor(ethest),data = ICAMdata, method="ML")
summary (model80)
#moderator proportion disease
model81<rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$diseaseprop, data = ICAMdata, method="ML")
summary (model81)

#moderator number disease
model82<rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$diseasenum, data = ICAMdata, method="ML")
summary (model82)

#moderator proportion meds
model83<rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$medsprop, data = ICAMdata, method="ML")
summary (model83)

#moderator number meds
model84<rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$medsnum, data = ICAMdata, method="ML")
summary (model84)

#moderator med type
model85<rma(d,var,icamV, mods = ~ factor(diet) - 1 + factor(medtype), data = ICAMdata, method="ML")
summary (model85)

#moderator experimental setting
model86<rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$experiset, data = ICAMdata, method="ML")
summary (model86)

#moderator length of counseling
model87<rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$counsellength, data = ICAMdata, method="ML")
summary (model87)

#moderator number of counseling sessions
model88<rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$counselnum, data = ICAMdata, method="ML")
summary (model88)

#moderator language of publication
model89<rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$publang, data = ICAMdata, method="ML")
summary (model89)
#moderator proportion of carb
model90<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$carbprop, data = ICAMdata, method="ML")
summary (model90)

#moderator proportion of sat fat
model91<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$satfatprop, data = ICAMdata, method="ML")
summary (model91)

#moderator proportion of total fat
model92<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$totfatprop, data = ICAMdata, method="ML")
summary (model92)

#moderator proportion of protein
model93<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$protprop, data = ICAMdata, method="ML")
summary (model93)

#moderator assessment of dietary compliance
model94<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + factor(dietcompl), data = ICAMdata, method="ML")
summary (model94)

#moderator participation in dietary counseling
model95<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$dietcoun, data = ICAMdata, method="ML")
summary (model95)

#moderator proportion of cvd
model96<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$cvd, data = ICAMdata, method="ML")
summary (model96)

#moderator proportion of DM
model97<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$dm, data = ICAMdata, method="ML")
summary (model97)

#moderator proportion of MetS
model98<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$mets, data = ICAMdata, method="ML")
summary (model98)
#moderator proportion of overweight/obesity
model99<-rma(d,var,icamV, mods = ~ factor(diet) - 1 + ICAMdata$obes, data = ICAMdata, method="ML")
summary (model99)

#VCAM

#Calculate total number of participants (Ni)
VCAMdata$ni <-unlist(lapply(split(VCAMdata,VCAMdata$study),function(x)
rep(sum(x$n1i)+x$n2i[1],each=nrow(x))))

#Create Variance-Covariance Matrix for Multiple Comparisons:
calc.vcamv <- function(x) {vcamv<- matrix(1/x$n2i[1] +
outer(x$d,x$d,"*")/(2*x$ni[1]),nrow=nrow(x),ncol=nrow(x))
diag(vcamv) <- x$var
vcamv}
vcamV <- lapply(split(VCAMdata,VCAMdata$study),calc.vcamv)
vcamV <-as.matrix(bdiag(vcamV))
vcamV

##Calculating the Weighted Mean ES
VCAMdata$diet <-as.factor(VCAMdata$diet)
dvcam <- rma.mv(d, var, vcamV, mods = ~ factor(diet) - 1,random = ~
diet|study,struct="UN",data = VCAMdata,method="ML")
dvcam

table(VCAMdata$diet)

#moderators
#moderator Weeks
model100<-rma(d,var,vcamV, mods = ~ factor(diet) - 1 + VCAMdata$weeks,data = VCAMdata, method="ML")
summary (model100)

#moderator females
model101<-rma(d,var,vcamV, mods = ~ factor(diet) - 1 + VCAMdata$fem,data = VCAMdata, method="ML")
summary (model101)

#moderator region
model102<-rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$region, data = VCAMdata, method="ML")
summary (model102)

#moderator population recruit
model103<-rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$pop, data = VCAMdata, method="ML")
summary (model103)

#moderator age
model104<-rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$age, data = VCAMdata, method="ML")
summary (model104)

#moderator interlv1
model105<-rma(d, var, vcamV, mods = ~ factor(diet) - 1 + ~ factor(interlv1), data = VCAMdata, method="ML")
summary (model105)

#moderator mq
model106<-rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$mq, data = VCAMdata, method="ML")
summary (model106)

#moderator pub year
model107<-rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$Year, data = VCAMdata, method="ML")
summary (model107)

#moderator total n
model108<-rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$ni, data = VCAMdata, method="ML")
summary (model108)

#moderator score
model109<-rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$score, data = VCAMdata, method="ML")
summary (model109)

#moderator funding source
model110<-rma(d, var, vcamV, mods = ~ factor(diet) - 1 + factor(fund), data = VCAMdata, method="ML")
summary (model110)
#moderator number of interventions
model111 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + factor(numinterv), data = VCAMdata, method = "ML")
summary (model111)

#moderator ethnicity estimate
model112 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + factor(ethest), data = VCAMdata, method = "ML")
summary (model112)

#moderator proportion disease
model113 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$diseaseprop, data = VCAMdata, method = "ML")
summary (model113)

#moderator number disease
model114 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$diseasenum, data = VCAMdata, method = "ML")
summary (model114)

#moderator proportion meds
model115 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$medsprop, data = VCAMdata, method = "ML")
summary (model115)

#moderator number meds
model116 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$medsnum, data = VCAMdata, method = "ML")
summary (model116)

#moderator med type
model117 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + factor(medtype), data = VCAMdata, method = "ML")
summary (model117)

#moderator experimental setting
model118 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$experiset, data = VCAMdata, method = "ML")
summary (model118)

#moderator length of counseling
model119 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$counsellength, data = VCAMdata, method = "ML")
summary (model119)
#moderator number of counseling sessions
model120 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$counselnum, data = VCAMdata, method="ML")
summary (model120)

#moderator language of publication
model121 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$publang, data = VCAMdata, method="ML")
summary (model121)

#moderator proportion of carb
model122 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$carbprop, data = VCAMdata, method="ML")
summary (model122)

#moderator proportion of sat fat
model123 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$satfatprop, data = VCAMdata, method="ML")
summary (model123)

#moderator proportion of total fat
model124 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$totfatprop, data = VCAMdata, method="ML")
summary (model124)

#moderator proportion of protein
model125 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$protprop, data = VCAMdata, method="ML")
summary (model125)

#moderator assessment of dietary compliance
model126 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + factor(dietcompl), data = VCAMdata, method="ML")
summary (model126)

#moderator participation in dietary counseling
model127 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$dietcoun, data = VCAMdata, method="ML")
summary (model127)

#moderator proportion of cvd
model128 <- rma(d, var, vcamV, mods = ~ factor(diet) - 1 + VCAMdata$cvd, data = VCAMdata, method="ML")
summary (model128)
#moderator proportion of DM
model129<-rma(d,var,vcamV, mods = ~ factor(diet) - 1 + VCAMdata$dm, data = VCAMdata, method="ML")
summary (model129)

#moderator proportion of MetS
model130<-rma(d,var,vcamV, mods = ~ factor(diet) - 1 + VCAMdata$mets, data = VCAMdata, method="ML")
summary (model130)

#moderator proportion of overweight/obesity
model131<-rma(d,var,vcamV, mods = ~ factor(diet) - 1 + VCAMdata$obes, data = VCAMdata, method="ML")
summary (model131)

#TG

#Calculate total number of participants (Ni)
tg$ni <-unlist(lapply(split(tg,tg$study),function(x) rep(sum(x$n1i)+x$n2i[1],each=nrow(x))))

#Create Variance-Covariance Matrix for Multiple Comparisons:
calc.tgv <- function(x) {tgv<- matrix(1/x$n2i[1] + outer(x$d,x$d,"*")/(2*x$ni[1]),nrow=nrow(x),ncol=nrow(x))
diag(tgv) <- x$var
tgv}
tgv <- lapply(split(tg,tg$study),calc.tgv)
tgV <- as.matrix(bdiag(tgv))
tgV

##Calculating the Weighted Mean ES
tg$diet <- as.factor(tg$diet)
dtg <- rma.mv(d, var, tgV, mods = ~ factor(diet) - 1,random = ~ diet|study,struct="UN",data = tg,method="ML")
dtg
table(tg$diet)

# moderators
# moderator Weeks
model132 <- rma(d, var, tgV, mods = ~ factor(diet) - 1 + tg$weeks, data = tg, method = "ML")
summary(model132)

# moderator females
model133 <- rma(d, var, tgV, mods = ~ factor(diet) - 1 + tg$fem, data = tg, method = "ML")
summary(model133)

# moderator region
model134 <- rma(d, var, tgV, mods = ~ factor(diet) - 1 + factor(tg$region), data = tg, method = "ML")
summary(model134)

# moderator population recruit
model135 <- rma(d, var, tgV, mods = ~ factor(diet) - 1 + factor(pop), data = tg, method = "ML")
summary(model135)

# moderator age
model136 <- rma(d, var, tgV, mods = ~ factor(diet) - 1 + tg$age, data = tg, method = "ML")
summary(model136)

# moderator interlvl
model137 <- rma(d, var, tgV, mods = ~ factor(diet) - 1 + factor(interlvl), data = tg, method = "ML")
summary(model137)

# moderator mq
model138 <- rma(d, var, tgV, mods = ~ factor(diet) - 1 + tg$mq, data = tg, method = "ML")
summary(model138)

# moderator pub year
model139 <- rma(d, var, tgV, mods = ~ factor(diet) - 1 + tg$Year, data = tg, method = "ML")
summary(model139)

# moderator total n
model140 <- rma(d, var, tgV, mods = ~ factor(diet) - 1 + tg$ni, data = tg, method = "ML")
summary(model140)
#moderator score
model141<-rma(d, var, tgV, mods = ~ factor(diet) - 1 + tg$score, data = tg, method="ML")
summary (model141)

#moderator funding
model142<-rma(d, var, tgV, mods = ~ factor(diet) - 1 + factor(fund), data = tg, method="ML")
summary (model142)

#moderator number of interventions
model143<-rma(d, var, tgV, mods = ~ factor(diet) - 1 + factor(numinterv), data = tg, method="ML")
summary (model143)

#moderator ethnicity estimate
model144<-rma(d, var, tgV, mods = ~ factor(diet) - 1 + factor(ethest), data = tg, method="ML")
summary (model144)

#moderator proportion disease
model145<-rma(d, var, tgV, mods = ~ factor(diet) - 1 + tg$diseaseprop, data = tg, method="ML")
summary (model145)

#moderator number disease
model146<-rma(d, var, tgV, mods = ~ factor(diet) - 1 + tg$diseasenum, data = tg, method="ML")
summary (model146)

#moderator proportion meds
model147<-rma(d, var, tgV, mods = ~ factor(diet) - 1 + tg$medsprop, data = tg, method="ML")
summary (model147)

#moderator number meds
model148<-rma(d, var, tgV, mods = ~ factor(diet) - 1 + tg$medsnum, data = tg, method="ML")
summary (model148)

#moderator med type
model149<-rma(d, var, tgV, mods = ~ factor(diet) - 1 + factor(medtype), data = tg, method="ML")
summary (model149)
#moderator experimental setting
model150<-rma(d,var,tgV, mods = ~ factor(diet) - 1 + tg$experiset, data =tg, method="ML")
summary (model150)

#moderator length of counseling
model151<-rma(d,var,tgV, mods = ~ factor(diet) - 1 + tg$counsellength, data = tg, method="ML")
summary (model151)

#moderator number of counseling sessions
model152<-rma(d,var,tgV, mods = ~ factor(diet) - 1 + tg$counselnum, data = tg, method="ML")
summary (model152)

#moderator language of publication
model153<-rma(d,var,tgV, mods = ~ factor(diet) - 1 + tg$publang, data = tg, method="ML")
summary (model153)

#moderator proportion of carb
model154<-rma(d,var,tgV, mods = ~ factor(diet) - 1 + tg$carbprop, data = tg, method="ML")
summary (model154)

#moderator proportion of sat fat
model155<-rma(d,var,tgV, mods = ~ factor(diet) - 1 + tg$satfatprop, data = tg, method="ML")
summary (model155)

#moderator proportion of total fat
model156<-rma(d,var,tgV, mods = ~ factor(diet) - 1 + tg$totfatprop, data = tg, method="ML")
summary (model156)

#moderator proportion of protein
model157<-rma(d,var,tgV, mods = ~ factor(diet) - 1 + tg$protprop, data = tg, method="ML")
summary (model157)

#moderator assessment of dietary compliance
model158 <- rma(d, var, tgV, mods = ~ factor(diet) - 1 + factor(dietcompl), data = tg, method = "ML")
summary (model158)

#moderator participation in dietary counseling
model159 <- rma(d, var, tgV, mods = ~ factor(diet) - 1 + tg$dietcoun, data = tg, method = "ML")
summary (model159)

#moderator proportion of cvd
model160 <- rma(d, var, tgV, mods = ~ factor(diet) - 1 + tg$cvd, data = tg, method = "ML")
summary (model160)

#moderator proportion of DM
model161 <- rma(d, var, tgV, mods = ~ factor(diet) - 1 + tg$dm, data = tg, method = "ML")
summary (model161)

#moderator proportion of MetS
model162 <- rma(d, var, tgV, mods = ~ factor(diet) - 1 + tg$mets, data = tg, method = "ML")
summary (model162)

#moderator proportion of overweight/obesity
model163 <- rma(d, var, tgV, mods = ~ factor(diet) - 1 + tg$obes, data = tg, method = "ML")
summary (model163)

#LDL

#Calculate total number of participants (Ni)
LDLdata$n1 <- unlist(lapply(split(LDLdata, LDLdata$study), function(x) rep(sum(x$n1i) + x$n2i[1], each = nrow(x))))

#Create Variance-Covariance Matrix for Multiple Comparisons:
calc.ldlv <- function(x) {
ldlv <- matrix(1/x$n2i[1] + outer(x$d, x$d, "*")/(2*x$ni[1]), nrow = nrow(x), ncol = nrow(x))
diag(ldlv) <- x$var
ldlv}
ldlv <- lapply(split(LDLdata, LDLdata$study), calc.ldlv)
ldev <- as.matrix(bdiag(ldlv))
ldev

###Calculating the Weighted Mean ES
LDLdata$diet <- as.factor(LDLdata$diet)
dldl <- rma.mv(d, var, ld1V, mods = ~ factor(diet) - 1,random = ~ diet|study,struct="UN",data = LDLdata,method="ML")
dldl
table(LDLdata$diet)

#moderators
#moderator Weeks
model164<-rma(d, var, ld1V, mods = ~ factor(diet) - 1 + LDLdata$weeks, data = ldl, method="ML")
summary (model164)

#moderator females
model165<-rma(d, var, ld1V, mods = ~ factor(diet) - 1 + LDLdata$fem, data = ldl, method="ML")
summary (model165)

#moderator region
model166<-rma(d, var, ld1V, mods = ~ factor(diet) - 1 + ~ factor(LDLdata$region), data = ldl, method="ML")
summary (model166)

#moderator population recruit
model167<-rma(d, var, ld1V, mods = ~ factor(diet) - 1 + factor(ldl$pop), data = ldl, method="ML")
summary (model167)

#moderator age
model168<-rma(d, var, ld1V, mods = ~ factor(diet) - 1 + ldl$age, data = ldl, method="ML")
summary (model168)

#moderator interlvl
model169<-rma(d, var, ld1V, mods = ~ factor(diet) - 1 + factor(ldl$interlvl), data = ldl, method="ML")
summary (model169)

#moderator mq
model170<-rma(d, var, ld1V, mods = ~ factor(diet) - 1 + ldl$mq, data = ldl, method="ML")
summary (model170)

#moderator pub year
model171<-rma(d, var, ld1V, mods = ~ factor(diet) - 1 + ldl$Year, data = ldl, method="ML")
summary (model171)

moderator total n
model172 <- rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$ni, data = ldl, method = "ML")
summary (model172)

moderator score
model173 <- rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$score, data = ldl, method = "ML")
summary (model173)

moderator fund
model174 <- rma(d, var, ldlV, mods = ~ factor(diet) - 1 + factor(fund), data = ldl, method = "ML")
summary (model174)

moderator number interventions
model175 <- rma(d, var, ldlV, mods = ~ factor(diet) - 1 + factor(numinterv), data = ldl, method = "ML")
summary (model175)

moderator ethnicity estimate
model176 <- rma(d, var, ldlV, mods = ~ factor(diet) - 1 + factor(ethest), data = ldl, method = "ML")
summary (model176)

moderator proportion disease
model177 <- rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$diseaseprop, data = ldl, method = "ML")
summary (model177)

moderator number disease
model178 <- rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$diseasenum, data = ldl, method = "ML")
summary (model178)

moderator proportion meds
model179 <- rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$medsprop, data = ldl, method = "ML")
summary (model179)

moderator number meds
model180 <- rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$medsnum, data = ldl, method = "ML")

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#moderator med type
model181<-rma(d, var, ldlV, mods = ~ factor(diet) - 1 + factor(medtype), data = ldl, method="ML")
summary (model181)

#moderator experimental setting
model182<-rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$experiset, data = ldl, method="ML")
summary (model182)

#moderator length of counseling
model183<-rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$counsellength, data = ldl, method="ML")
summary (model183)

#moderator number of counseling sessions
model184<-rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$counselnum, data = ldl, method="ML")
summary (model184)

#moderator language of publication
model185<-rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$publang, data = ldl, method="ML")
summary (model185)

#moderator proportion of carb
model186<-rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$carbprop, data = ldl, method="ML")
summary (model186)

#moderator proportion of sat fat
model187<-rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$satfatprop, data = ldl, method="ML")
summary (model187)

#moderator proportion of total fat
model188<-rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$totfatprop, data = ldl, method="ML")
summary (model188)

#moderator proportion of protein
model189 <- rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$protprop, data = ldl, method = "ML")
summary(model189)

# moderator assessment of dietary compliance
model190 <- rma(d, var, ldlV, mods = ~ factor(diet) - 1 + factor(dietcompl), data = ldl, method = "ML")
summary(model190)

# moderator participation in dietary counseling
model191 <- rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$dietcoun, data = ldl, method = "ML")
summary(model191)

# moderator proportion of cvd
model192 <- rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$cvd, data = ldl, method = "ML")
summary(model192)

# moderator proportion of DM
model193 <- rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$dm, data = ldl, method = "ML")
summary(model193)

# moderator proportion of MetS
model194 <- rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$mets, data = ldl, method = "ML")
summary(model194)

# moderator proportion of overweight/obesity
model195 <- rma(d, var, ldlV, mods = ~ factor(diet) - 1 + ldl$obes, data = ldl, method = "ML")
summary(model195)

# HDL

# Calculate total number of participants (Ni)
hdlni <- unlist(lapply(split(hdl, hdl$study), function(x) rep(sum(x$n1i) + x$n2i[1], each = nrow(x))))

calc.hdlv <- function(x) {
  hdlv <- matrix(1/x$n2i[1] + outer(x$d, x$d, ""*/""/(2^x$ni[1]), nrow = nrow(x), ncol = nrow(x))
  diag(hdlv) <- x$var
  hdlv
}

hdInV <- lapply(split(hdl,hdl$study),calc.hdlv)
hdInV <- as.matrix(bdiag(hdInV))

##Calculating the Weighted Mean ES
hdIn$diet <- as.factor(hdIn$diet)

dhdl <- rma.mv(d, var, hdInV, mods = ~ factor(diet) - 1,random = ~
diet|study,struct="UN",data = hdIn,method="ML")
dhdl


#moderators

#moderator Weeks
model196<-rma(d,var,hdInV, mods = ~ factor(diet) - 1 + hdIn$weeks, data = hdIn,
method="ML")
summary (model196)

#moderator females
model197<-rma(d,var,hdInV, mods = ~ factor(diet) - 1 + hdIn$fem,data = hdIn,
method="ML")
summary (model197)

#moderator region
model198<-rma(d,var,hdInV, mods = ~ factor(diet) - 1 + factor(hdIn$region),data = hdIn,
method="ML")
summary (model198)

#moderator population recruit
model199<-rma(d,var,hdInV, mods = ~ factor(diet) - 1 + factor(pop),data = hdIn,
method="ML")
summary (model199)

#moderator age
model200<-rma(d,var,hdInV, mods = ~ factor(diet) - 1 + hdIn$age,data = hdIn,
method="ML")
summary (model201)

#moderator intervl
model202<-rma(d,var,hdInV, mods = ~ factor(diet) - 1 + factor(intervl),data = hdIn,
method="ML")
summary (model202)
#moderator mq
model203<-.rma(d,var,hdlV, mods = ~ factor(diet) - 1 + hdl$mq, data = hdl, method="ML")
summary (model203)

#moderator pub year
model204<-.rma(d,var,hdlV, mods = ~ factor(diet) - 1 + hdl$Year, data = hdl, method="ML")
summary (model204)

#moderator total population
model205<-.rma(d,var,hdlV, mods = ~ factor(diet) - 1 + hdl$ni, data = hdl, method="ML")
summary (model205)

#moderator score
model206<-.rma(d,var,hdlV, mods = ~ factor(diet) - 1 + hdl$score, data = hdl, method="ML")
summary (model206)

#moderator funding source
model207<-.rma(d,var,hdlV, mods = ~ factor(diet) - 1 + factor(fund), data = hdl, method="ML")
summary (model207)

#moderator number of interventions
model208<-.rma(d,var,hdlV, mods = ~ factor(diet) - 1 + factor(numinterv), data = hdl, method="ML")
summary (model208)

#moderator ethnicity estimate
model209<-.rma(d,var,hdlV, mods = ~ factor(diet) - 1 + factor(ethest), data = hdl, method="ML")
summary (model209)

#moderator proportion disease
model210<-.rma(d,var,hdlV, mods = ~ factor(diet) - 1 + hdl$diseaseprop, data = hdl, method="ML")
summary (model210)

#moderator number disease
model211<-.rma(d,var,hdlV, mods = ~ factor(diet) - 1 + hdl$diseasenum, data = hdl, method="ML")
#moderator proportion meds
model212<-rma(d,var,hdlV, mods = ~ factor(diet) - 1 + hdl$medsprop, data = hdl, method="ML")
summary (model212)

#moderator number meds
model213<-rma(d,var,hdlV, mods = ~ factor(diet) - 1 + hdl$medsnum, data = hdl, method="ML")
summary (model213)

#moderator med type
model214<-rma(d,var,hdlV, mods = ~ factor(diet) - 1 + factor(medtype), data = hdl, method="ML")
summary (model214)

#moderator experimental setting
model215<-rma(d,var,hdlV, mods = ~ factor(diet) - 1 + hdl$experiset, data = hdl, method="ML")
summary (model215)

#moderator length of counseling
model216<-rma(d,var,hdlV, mods = ~ factor(diet) - 1 + hdl$counsellength, data = hdl, method="ML")
summary (model216)

#moderator number of counseling sessions
model217<-rma(d,var,hdlV, mods = ~ factor(diet) - 1 + hdl$counselnum, data = hdl, method="ML")
summary (model217)

#moderator language of publication
model218<-rma(d,var,hdlV, mods = ~ factor(diet) - 1 + hdl$publang, data = hdl, method="ML")
summary (model218)

#moderator proportion of carb
model219<-rma(d,var,hdlV, mods = ~ factor(diet) - 1 + hdl$carbprop, data = hdl, method="ML")
summary (model219)

#moderator proportion of sat fat
model220 <- rma(d, var, hdlV, mods = ~ factor(diet) - 1 + hdl$satfatprop, data = hdl, method = "ML")
summary(model220)

# moderator proportion of total fat
model221 <- rma(d, var, hdlV, mods = ~ factor(diet) - 1 + hdl$totfatprop, data = hdl, method = "ML")
summary(model221)

# moderator proportion of protein
model222 <- rma(d, var, hdlV, mods = ~ factor(diet) - 1 + hdl$protprop, data = hdl, method = "ML")
summary(model222)

# moderator assessment of dietary compliance
model223 <- rma(d, var, hdlV, mods = ~ factor(diet) - 1 + factor(dietcompl), data = hdl, method = "ML")
summary(model223)

# moderator participation in dietary counseling
model224 <- rma(d, var, hdlV, mods = ~ factor(diet) - 1 + hdl$dietcoun, data = hdl, method = "ML")
summary(model224)

# moderator proportion of cvd
model225 <- rma(d, var, hdlV, mods = ~ factor(diet) - 1 + hdl$cvd, data = hdl, method = "ML")
summary(model225)

# moderator proportion of DM
model226 <- rma(d, var, hdlV, mods = ~ factor(diet) - 1 + hdl$dm, data = hdl, method = "ML")
summary(model226)

# moderator proportion of MetS
model227 <- rma(d, var, hdlV, mods = ~ factor(diet) - 1 + hdl$mets, data = hdl, method = "ML")
summary(model227)

# moderator proportion of overweight/obesity
model228 <- rma(d, var, hdlV, mods = ~ factor(diet) - 1 + hdl$obes, data = hdl, method = "ML")
summary(model228)