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# The role of the mediterranean diet on the development of the metabolic syndrome

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## 1. ABSTRACT

The metabolic syndrome is a health situation of associated conditions, abdominal obesity, dyslipidemia, elevated blood pressure and impaired glucose tolerance with rapidly increasing prevalence. Results from prospective cohort studies, cross-sectional studies and clinical trials indicate that adherence to the Mediterranean dietary pattern is associated with beneficial effects not only regarding the metabolic syndrome, but also its individual components, in particular waist circumference, triglycerides levels, HDL-cholesterol levels, blood pressure levels and glucose metabolism.

## 2, INTRODUCTION

### 2.1. Metabolic syndrome

The metabolic syndrome is a health situation of associated conditions, abdominal obesity, dyslipidemia, elevated blood pressure and impaired glucose tolerance, that promotes atherosclerosis, first described in 1988, associated with increased risk of mortality, diabetes, cardiovascular and kidney disease (1). Different and confusing definitions of the metabolic syndrome from several investigators and organizations exist (2-4). Nevertheless, all agree that the characteristics of the metabolic syndrome include abdominal obesity, elevated triglycerides levels, decreased HDL-cholesterol levels, elevated blood pressure levels, glucose intolerance, as well as a prothrombotic state, chronic low-grade inflammation, microalbuminuria, and increased uric acid (1, 2, 5, 6).

Prevalence of the metabolic syndrome in various parts of the world, Europe, Asia, Australia, North and South America ranges between 9.6% to 55.7% using the NCEP definition, 13.4% to 70.0% using the WHO definition and 7.4% to 50% using the IDF definition (3, 7). Even though estimates of the prevalence of the metabolic syndrome vary depending on the definition used and the population studied (3, 7, 8), this condition is emerging as a major public health problem, as its prevalence is increasing rapidly, in parallel with the increasing prevalence of obesity and diabetes (9) (Table 1).

### 2.2. Mediterranean diet

The Mediterranean diet, first described in the 1960s by Ancel Keys is one of the most known dietary patterns for its beneficial effects on human health. The Mediterranean dietary pattern focuses on consumption of

**Table 1**. The metabolic syndrome definitions

| | **The National Cholesterol Education Program Adult Treatment Panel III** (ATP III) clinical criteria for defining the metabolic syndrome (presence of three of five factors) (4) | **The International Diabetes Federation** (IDF) definition of metabolic syndrome (abdominal obesity plus two other risk factors) | **The World Health Organization** Criteria (2) |
|---|---|---|---|
| Abdominal obesity | Waist circumference >102 cm in men and >88 cm in women | Waist circumference >94 cm in men and >80 cm in women | Waist to hip ratio >0.90 in men and >0.85 in women and/or BMI >30 kg/m$^2$ |
| Elevated triglycerides | >150 mg/dL | >150 mg/dL | >150 mg/dL |
| Reduced HDL cholesterol | Men: <40 mg/dL Women: <50mg/dL | Men: <40 mg/dL Women: <50mg/dL | Men: <35 mg/dL Women: <39 mg/dL |
| Elevated blood pressure | >130/85 mm Hg | >130/85 mm Hg | >= 140/90 mmHg |
| Elevated fasting glucose | >110 mg/dL | >110 mg/dL | Impaired glucose regulation or diabetes, Insulin resistance, Microalbuminuria |

monounsaturated fatty acids, primarily from olive oil, and is characterized by high consumption of fruits, vegetables, tree nuts, legumes, whole grains, moderate consumption of fish and poultry, a relatively low consumption of red meat, as well as a moderate consumption of alcohol normally with meals. However although the dietary patterns that prevail in the Mediterranean region have many common characteristics, the proportions of macronutrients may vary. Total lipid intake may be high, as in Greece (around 40% of total energy intake), or moderate, as in Italy (around 30% of total energy intake) (10-13).

Adherence to the Mediterranean diet has been suggested to be beneficially associated with mortality from all causes, cardiovascular disease (CVD) and cancer (14), as well as obesity and type 2 diabetes (15, 16). Additionally it is important to mention that the Mediterranean diet may exert positive influence regarding human health and the development of the metabolic syndrome in particular, due to its antioxidant and anti-inflammatory effects (15, 17-20).

## 3. SELECTION OF STUDIES

Original-research studies that were published in English between 2000 and 2009 were selected through a computer-assisted literature search (i.e., Pubmed http://igm.nlm.nih.gov, and Scopus www.scopus.com). Computer searches used combinations of key words relating to disease (metabolic syndrome, waist circumference, blood pressure, HDL-cholesterol, triglycerides, fasting glucose) and Mediterranean diet. In addition, the reference lists of the retrieved articles helped us to find relevant to the present articles that did not allocate through the searching procedure. The following information was presented according to a fixed protocol: design of study (prospective cohort, cross-sectional, clinical trial), sample size, mean age and sex of participants, follow-up duration and degree of adjustment for potential confounders. Thus, 31 studies were selected and discussed; of them 2 were prospective, 15 were cross-sectional, and 14 were clinical trials.

## 4. MEDITERRANEAN DIET AND THE METABOLIC SYNDROME

### 4.1. Prospective studies

According to the SUN prospective cohort with 6 years follow-up, including 2,563 university graduates at low cardiovascular risk, an inverse association has been observed between adherence to the Mediterranean diet and metabolic syndrome incidence (defined by the IDF criteria). In particular adherence to the Mediterranean diet was associated with 80% (95% CI: 0.06-0.63) lower risk of the metabolic syndrome. However regarding the Syndrome's defining criteria only weak associations were observed (21).

### 4.2. Cross-sectional studies

The ATTICA Study, examining 2,282 Greek subjects without any evidence of CVD or diabetes mellitus, showed that individuals with higher adherence to the Mediterranean diet had a 20% lower likelihood (OR 0.81, 95% CI: 0.68-0.976) of having the metabolic syndrome (defined by the NCEP ATP III criteria) (22).

In addition, according to the Nureta PREDIMED Study, that included 808 subjects with prior CVD, participants with the highest adherence to the Mediterranean diet had 56% lower likelihood (OR 0.44, 95% CI: 0.27-0.70) of having the metabolic syndrome (defined by the NCEP ATP III criteria). Furthermore participants closer to the Mediterranean diet had 47% (OR 0.53, 95% CI: 0.31-0.90) and 54% (OR 0.46, 95% CI: 0.28-0.76) lower odds of having low HDL-cholesterol levels and high triglycerides levels respectively, compared to those in the lowest quartile of adherence to the Mediterranean dietary pattern (23).

On the contrary, according to another cross-sectional study performed on 578 subjects from the general population of the Canary Islands, no significant relationship was observed between adherence to the Mediterranean diet and development of the metabolic syndrome (defined by the NCEP ATP III criteria). Regarding the Syndrome's defining criteria, subjects in the third tertile of adherence to the Mediterranean dietary pattern had 70% lower prevalence of having increased blood pressure levels, nevertheless they had 2.5 times more prevalence of the glycemia criterion, compared to the first tertile (24).

Furthermore a study examining the relationship between adherence to the Mediterranean diet and development of the metabolic syndrome (defined by the NCEP ATP III and the IDF criteria), in young Greek male navy recruits, showed that in that sample dietary habits closer to the Mediterranean diet did not predict the presence of metabolic syndrome, possibly because of the

young age of the participants and the overall poor adherence of the sample to the Mediterranean diet (25).

The four cross-sectional studies published, studying the relationship between adherence to the Mediterranean diet and development of the metabolic syndrome have contradictory results as two of them indicate a beneficial effect of the Mediterranean diet and the other two do not show significant associations. Nevertheless it is important to mention that one of the studies that did not support a beneficial effect of the Mediterranean diet was conducted in young adults with poor overall adherence to this dietary pattern and that none of the studies showed a harmful effect of the Mediterranean diet.

### 4.3. Clinical trials

All clinical trials examining the relationship between adherence to the Mediterranean diet and metabolic syndrome indicate the beneficial role of the Mediterranean diet.

According to a randomized trial conducted in Italy, 180 patients with the metabolic syndrome (defined by the NCEP ATP III criteria, 99 men, 81 women) were randomized to either a Mediterranean style diet and were instructed to increase the consumption of whole grains, vegetables, fruits, nuts, and olive oil or to a cardiac-prudent diet with fat intake less than 30%. After a two year intervention period a 48% net reduction in the prevalence of the metabolic syndrome was observed, as only 40 patients in the intervention group still had metabolic syndrome, compared with 78 patients on the control diet. In addition body weight decreased more in the Mediterranean diet group than in the control group, but even after controlling for weight loss, inflammatory markers and insulin resistance declined more in the intervention than in the control group, while endothelial function improved (26).

Additionally the PREDIMED Randomized Trial, including 1,224 high CVD risk patients who were assigned to one of three different dietary patterns, a low fat diet, a Mediterranean diet supplemented with nuts and a Mediterranean diet supplemented with olive oil, showed that both Mediterranean diets were associated with reversion of the metabolic syndrome and especially the diet supplemented with nuts (OR for reversion of the metabolic syndrome: MD+VOO: 1.3 (95% CI: 0.8-2.1), MD+nuts: 1.7 (95% CI: 1.1-2.6) (27).

Furthermore a randomized trial in the USA that enrolled 49 subjects to either a modified Mediterranean-style low glycaemic load diet or a Phytochemical enriched diet, showed the beneficial effects of both diets, however more beneficial results were observed for the participants following the Phytochemical enriched diet. In particular 4 of the 18 subjects (22%) that completed the Mediterranean diet intervention did not meet the metabolic syndrome criteria after 12 weeks of the intervention versus the 9 of the 21 subjects (43%) who followed the Phytochemical enriched diet (28) (Table 2).

## 5. MEDITERRANEAN DIET AND THE COMPONENTS OF THE METABOLIC SYNDROME

### 5.1. Abdominal obesity

Regarding the relationship between adherence to the Mediterranean dietary pattern and waist circumference, results from prospective, cross-sectional studies and clinical trials either show no associations or indicate the beneficial effect of this dietary pattern.

As mentioned above, the SUN prospective cohort showed only weak associations between adherence to the Mediterranean diet and the metabolic syndrome's defining criteria. Regarding waist circumference, even though the trend was statistically significant, the decrease is only 0.5 cm between higher and lower adherence to the diet (21). Moreover results from the ATTICA Study, conducted in 3,042 subjects indicate that participants in the highest tertile of the Mediterranean Diet Score (MedDietScore) had 59% lower odds of having central obesity (OR: 0.41, 95% CI: 0.35-0.47) compared to the lowest tertile, after adjusting for confounding factors (29). According to a cross-sectional association of the EPIC-PANACEA Project, including 497,308 individuals from 10 European countries, higher adherence to the Mediterranean diet was significantly associated with lower waist circumference, for a given BMI, in both men (-0.09 cm; 95% CI: -0.14 to -0.04) and women (-0.06 cm; 95% CI: -0.10 to -0.01) (30). Furthermore a randomized trial that allocated 101 overweight adults to a Mediterranean-style diet or a low-fat diet, showed the superiority of the Mediterranean dietary pattern, with long-term participation and with consequent improvements in weight circumference (-9±7.5 cm, $p<0.001$) (31). Another trial in 77 French Canadian women supports the beneficial role of the Mediterranean diet on the reduction of the waist circumference (week 0: 83.4±10.8 cm, week 12: 82.1±10.2 cm, $p<0.001$) (32). In addition according to a recent randomized trial, 20 obese women were allocated for 2 months to either a hypocaloric Mediterranean diet or Atkins diet. Findings indicate that after 2 months waist circumference was significantly reduced in both groups (Mediterranean diet: baseline: 103±2 cm, 2 months: 97±2 cm, $p<0.05$) (33). Two articles from the PREDIMED randomized trial examining the relationship between adherence to the Mediterranean diet and waist circumference have been published. 774 high cardiovascular risk subjects were assigned to one of three different dietary patterns, a low fat diet, a Mediterranean diet supplemented with nuts and a Mediterranean diet supplemented with olive oil. The results published in 2006 do not show significant associations between adherence to the Mediterranean diet and waist circumference (34). Nevertheless, according to the results published in 2009, carriers of the 12Ala allele assigned to the low fat diet significantly increased their waist circumference, compared with the ProPro carriers. However this increase was not observed among 12Ala carriers allocated to both Mediterranean diet groups, demonstrating the beneficial effect of the Mediterranean diet (35). In a recent trial, 90 subjects with abdominal obesity but without cardiovascular disease or type 2 diabetes were separated into an intervention group following the Mediterranean diet

**Table 2.** A summary of studies that evaluated the effect of the mediterranean diet and the development of the metabolic syndrome

| Study | Country | Year | N | Age range | Men | RR / OR |
|---|---|---|---|---|---|---|
| **Prospective Studies** | | | | | | |
| **SUN Cohort** (21)<br>Prospective – 6 yrs<br>MDS<br>IDF | Spain | 2007 | 2,563 | - | - | MS: 0.20 (95% CI: 0.06-0.63) |
| **Cross-sectional Studies** | | | | | | |
| **ATTICA Study** (22)<br>Cross-sectional<br>NCEP ATP III | Greece | 2004 | 2,282 | >18 | 49% | MS: 0.81 (95% CI: 0.68-0.976) |
| **Nureta PREDIMED** (23)<br>Cross-sectional<br>14 point FFQ<br>NCEP ATP III | Spain | 2009 | 808 (prior CVD) | Mean 67 | 45% | MS: 0.44 (95% CI: 0.27-0.70)<br>HDL: 0.53 (95% CI: 0.31-0.90)<br>TAG: 0.46 (95% CI: 0.28-0.76) |
| **Canarian Nutrition Survey** (24) Cross-sectional<br>10-item score<br>NCEP ATP III | Spain<br>Canary Islands | 2006 | 578 | >18 | 43% | MD adherence was not related to MS prevalence |
| **Navy recruits** (25)<br>Cross-sectional<br>MedDietScore<br>IDF, NCEP ATP III | Greece | 2009 | 832 navy recruits | 17-39 | 100% | MD did not predict the presence of MS |
| **Clinical Trials** | | | | | | |
| **Randomized Trial** (26)<br>Clinical Trial – 2 yrs<br>NCEP ATP III | Italy | 2004 | 180 | Mean 44 | IG 54%<br>CC 56% | 48% net reduction in the prevalence of the Metabolic Syndrome |
| **PREDIMED Randomized Trial** (27)<br>Clinical Trial – 1 yr | Spain | 2008 | 1,224 (high CVD risk) | older | | Reversion of MS:<br>MD+VOO: 1.3 (95% CI: 0.8-2.1)<br>MD+nuts: 1.7 (95% CI: 1.1-2.6) |
| **Randomized Trial** (28)<br>Clinical Trial – 12 weeks<br>(MS+ hypercholesterolemia) | USA | 2008 | 49 (MED arm: 23) | 25-80 | 46% | 22% (4 of the 18 subjects) did not meet the MS criteria after 12 weeks |

according to a specific daily and weekly food plan with close supervision by a dietician and provision of basic foods and a control group simply instructed to follow a Mediterranean-style diet. After two months, body weight and waist circumference were significantly decreased in both groups (waist circumference: intervention group: baseline: 106.1±9.1 cm, 2 months: 103.9±9.3 cm, $p<0.001$, control group: baseline: 106.7±9.5 cm, 2 months: 105.7±10.2 cm, $p=0.007$) (50).

On the other hand it should be mentioned that the Greek arm of the EPIC Study investigating the relationship between adherence to the Mediterranean dietary pattern and obesity, showed that a 2-unit increase of the Mediterranean Diet Score (MDS) was associated with a trivial increase of waist-to-hip ratio in men (0.001) and women (0.004) (36). A cross-sectional study from Italy showed no associations between adherence to the Mediterranean diet and central obesity, as the MDS was not related to the waist-to-hip ratio (37). Additionally according to a randomized trial evaluating the outcomes of a 6-month Mediterranean lifestyle program in 279 post-menopausal women with diabetes, no significant associations were observed as far as waist-to hip ratio is concerned (38). Finally an 8-week randomized trial that allocated 60 participants to either a High Saturated Fat diet, a High MUFA diet or a Mediterranean diet did not show significant decrease of waist circumference after the Mediterranean diet intervention (39) (Table 3).

### 5.2. Triglycerides levels

Studies examining the relationship between adherence to the Mediterranean dietary pattern and triglycerides levels, either support the protective role of this diet or do not show significant results.

According to the results from a subsample of the 1992-1993 Catalan Nutritional Survey in Spain, including 328 individuals aged 18-75 from Catalonia, higher adherence to the Mediterranean diet was associated with lower triglycerides levels (p=0.08) (40). Furthermore, according to the Nureta PREDIMED Study, participants closer to the Mediterranean diet had 54% (OR 0.46, 95% CI: 0.28-0.76) lower odds of having high triglycerides levels, compared to those in the lowest quartile of adherence to the Mediterranean dietary pattern (23). Additionally a 4-week cross-over randomized trial, that allocated 22 participants to a Mediterranean-inspired or a Swedish diet, showed that triglycerides concentrations were decreased by 17% after the Mediterranean-inspired diet, compared to the Swedish diet (41). Results from the PREDIMED randomized trial show that participants allocated to the Mediterranean diet supplemented with nuts had significantly lower triglycerides levels compared to the low fat diet. (MD+VOO: -7.1 mg/dL (95% CI: -18.0, 3.9), MD+nuts: -13.0 mg/dL (95% CI : -23.0, -1.9)) (34). Furthermore according to the Medi-RIVAGE Study, a 3 month clinical trial that allocated 212 volunteers to either a low fat diet or a Mediterranean diet, triglycerides levels were significantly lower after 3 months of compliance to

**Table 3.** A summary of studies that evaluated the effect of the mediterranean diet on abdominal obesity

| Study | Country | Year | N | Age range | Men | Results |
|---|---|---|---|---|---|---|
| **Abdominal Obesity** | | | | | | |
| **SUN Cohort** (21)<br>Prospective – 6 yrs<br>MDS | Spain | 2007 | 2,563 | - | - | MDS, p trend=0.03<br>0-2: 82.5±12 cm<br>3-5: 82.2±12 cm<br>6-9: 82.0±12 cm |
| **ATTICA Study** (29)<br>Cross-sectional<br>MedDietScore | Greece | 2006 | 3,042 | >18 | 50% | Greater MedDietScore<br>WHR (OR, 95% CI)<br>0.41 (0.35-0.47) |
| **EPIC-PANACEA Project** (30) Cross-sectional<br>MDS | Europe (10 countries) | 2009 | 497,308 | 25-70 | 29,3% | MD adherence for a given BMI (95% CI:)<br>men -0.09 (-0.14, -0.04)<br>women -0.06 (-0.10, -0.01) |
| **Randomized Trial** (31)<br>Clinical Trial – 18 months | USA | 2001 | 101 (BMI> 26) | 18-70 | 10% | -9±7.5 cm, p<0.001 |
| **Randomized Trial** (32)<br>Clinical Trial – 12 weeks | Canada | 2003 | 77 | 30-65 | 0% | Week 0: 83.4±10.8 cm<br>Week 12: 82.1±10.2 cm (p<0.001) |
| **Randomized Trial** (33)<br>Clinical Trial – 2 months | Italy | 2009 | 20 (BMI >27) | 30-50 | 0% | Waist (cm), p<0.05<br>Baseline: 103±2<br>2 months: 97±2 |
| **PREDIMED Randomized Trial** (34)<br>Clinical Trial – 3 months | Spain | 2006 | 772 (high CVD risk) | 55-80 | 44% | MD+VOO: -0.82 (-1.8, 0.14)<br>MD+nuts: -0.29 (-0.95, 0.37)<br>Low fat diet: -0.37 (-1.20.0.44) *(95% CI:)* |
| **PREDIMED Randomized Trial** (35)<br>Clinical Trial – 2 yrs | Spain | 2009 | 774 (high CVD risk) | 55-80 | 44% | Control+Ala: 2.366 (p=0.01)<br>MD+VOO: NS (no increase)<br>MD+nuts: NS (no increase) |
| **EPIC Study** (36)<br>MDS | Greece | 2005 | 23,597 | 20-86 | 41% | MDS per 2 units, WHR<br>Men: 0.001 (-0.001, 0.002)<br>Women:0.004(0.003, 0.006) |
| **Cross-sectional Study** (37)<br>MDS | Italy | 2007 | 6,619 | Mean 58 | 47% | Greater MDS<br>WHR<br>Men: β= 0.000<br>Women: β= 0.001 |
| **Mediterranean Lifestyle Program** (38)<br>Clinical Trial – 6 months<br>Post-menopausal women | USA | 2003 | 279<br>DM | <75 | 0% | WHR<br>Baseline: 0.91±0.07<br>6 months: 0.90±0.07<br>p=0.318 |
| **Randomized Trial** (39)<br>Clinical Trial – 8 weeks | Netherlands | 2009 | 60 | 40-65 | 40% | Baseline: 98.8 cm, se: 3.1<br>Intervention: 96.4 cm, se 2.7<br>(Med diet: NS, se=standard error) |

the Mediterranean diet (baseline: 1.6±1.0 mmol/L, 3 months: 1.4±0.9 mmol/L) (42). In addition a clinical trial conducted in Italy in 47 obese women, showed that participants following a moderately hypoenergetic Mediterranean diet and exercise program significantly decreased their triglycerides levels after 2 and 4 months of intervention (baseline: 2.04±0.12 mmol/L, 4 months: 1.98±0.11 mmol/L, p<0.001) (43). An 8-week randomized trial that allocated 60 participants to either a High Saturated Fat diet, a High Monounsatured Fat diet or a Mediterranean diet, showed a significant decrease of triglycerides levels after the Mediterranean diet intervention (baseline: 1.33 mmol/L, standard error 0.17, Intervention: 1.09 mmol/L, standard error 0.13) (39).

There are also studies that do not support the protective role of the Mediterranean diet on triglycerides levels. The SUN Cohort Study examining the relationship between adherence to the Mediterranean diet and triglycerides levels showed no significant associations (21). In addition the ATTICA Study showed that in overweight or obese subjects triglycerides levels did not differ significantly between participants in the highest compared to the lowest tertile of the Mediterranean Diet Score (0.55±0.8 mg/dL, p=0.51) (44). A 12-week clinical trial in 77 French Canadian women does not show significant reduction of triglycerides levels (32). According to a 28-day cross-over randomized trial that allocated 59 subjects either to the Mediterranean diet group or a high carbohydrate diet after a saturated fat phase, no significant differences were observed in triglycerides levels (45). Additionally a randomized trial evaluating the outcomes of a Mediterranean lifestyle program in 279 post-menopausal women with diabetes, showed no significant decrease in triglycerides levels after the 6-month intervention (38). According to another randomized trial from Germany, that examined the effect of a Mediterranean diet with 100 hours of education or a written advice only group in 101 patients with established and treated coronary artery disease, no significant differences in triglycerides levels after the 1-year intervention were observed (46). Furthermore a randomized trial in the USA that enrolled 49 subjects to either a modified Mediterranean-style low glycaemic load diet or a Phytochemical enriched diet, did not show significant associations regarding triglycerides levels after the 12-week intervention (28). In addition a randomized trial in Scotland with a 6-month intervention period and a

**Table 4.** A summary of studies that evaluated the effect of the mediterranean diet on triglycerides levels

| Study | Country | Year | N | Age range | Men | Results |
|---|---|---|---|---|---|---|
| **Triglycerides levels** | | | | | | |
| **1992-1993 Catalan Nutritional Survey** (40)<br>Cross-sectional | Spain | 2006 | 328 | 18-75 | 42% | Higher MDS: Lower TAG (p=0.08) |
| **Nureta PREDIMED** (23)<br>Cross-sectional<br>14 point FFQ | Spain | 2009 | 808<br>(prior CVD) | Mean 67 | 45% | TAG: OR 0.46 (95% CI: 0.28-0.76) |
| **Randomized Trial** (41)<br>4 week- cross-over Trial | Sweden | 2004 | 22 | 30-51 | 54% | Baseline: 1.1±0.1 mmol/L<br>Med Inspired: 1.0±0.1<br>Swedish: 1.2±0.1, (p<0.05) |
| **PREDIMED Randomized Trial** (34)<br>Clinical Trial – 3 months | Spain | 2006 | 772<br>(high CVD risk) | 55-80 | 44% | Vs Low fat diet: (mg/dL)<br>MD+VOO: -7.1 (-18.0, 3.9)<br>MD+nuts: -13.0 (95% CI: -23.0, -1.9) |
| **Medi-RIVAGE Study** (42)<br>Clinical Trial – 3 months | France | 2006 | 212 | 18-70 | - | Baseline: 1.6 mmol/L±1.0<br>3 months: 1.4 mmol/L±0.9 |
| **Randomized Trial** (43)<br>Clinical trial – 4 months | Italy | 2007 | 47<br>obese | 25-70 | 0% | Baseline: 2.04±0.12 mmol/L<br>4 months: 1.98±0.11mmol/L<br>(p<0.001) |
| **Randomized Trial** (39)<br>Clinical Trial – 8 weeks | Netherlands | 2009 | 60 | 40-65 | 40% | Baseline: 1.33 (se 0.17)<br>After intervention (Med diet): 1.09 mmol/L (se 0.13) |
| **SUN Cohort** (21)<br>Prospective – 6 yrs<br>MDS | Spain | 2007 | 2,563 | - | - | MDS, p trend=0.11<br>0-2: 80.0±38 mg/dL<br>3-5: 81.2±47 mg/dL<br>6-9: 78.0±40 mg/dL |
| **ATTICA Study** (44)<br>Cross-sectional<br>MedDietScore | Greece | 2007 | 1,762<br>(BMI >25) | >18 | 60% | Highest vs lowest tertile:<br>0.55±0.8 mg/dL, p=0.51 |
| **Randomized Trial** (32)<br>Clinical Trial – 12 weeks | Canada | 2003 | 77 | 30-65 | 0% | Week 0: 1.20±0.47 mmol/L<br>Week 12: 1.17±0.49 mmol/L, NS |
| **Randomized Trial** (45)<br>Clinical Trial<br>Cross-over, 28 days each | Spain | 2001 | 59 | <30 | 51% | SFA diet: 0.77±0.3 mmol/L<br>Med diet: 0.79±0.3 mmol/L<br>NS |
| **Mediterranean Lifestyle Program** (38)<br>Clinical Trial – 6 months<br>Post-menopausal women | USA | 2003 | 279<br>DM | <75 | 0% | Baseline: 202.38±149.06<br>6 months: 176.82±113.98<br>(mg/dL) p=0.963 |
| **Randomized Trial** (46)<br>Clinical Trial – 1 year | Germany | 2006 | 101<br>CAD | Mean<br>59 | 77% | Baseline:1.47±0.99 mmol/L<br>1 year: 1.45±0.82 mmol/L |
| **Randomized Trial** (28)<br>Clinical Trial – 12 weeks | USA | 2008 | 49<br>(MED arm: 23) | 25-80 | 46% | Baseline: 2.37±0.23<br>12 weeks: 2.09±0.19<br>(mmol/L - NS) |
| **Randomized Trial** (47)<br>Clinical Trial – 6 months<br>3 months follow-up | Scotland | 2008 | 72<br>I : 53<br>C : 19 | 25-55 | 0% | Baseline:1.16mmol/L±0.55<br>6 month: 1.11 mmol/L±0.40<br>9 month: 1.18 mmol/L±0.45 |
| **Randomized Trial** (33)<br>Clinical Trial – 2 months | Italy | 2009 | 20<br>(BMI >27) | 30-50 | 0% | Baseline: 106±16 mg/dL<br>2 months: 98±12, NS |

3-month follow-up period, that allocated 53 women to the Mediterranean diet intervention and 19 women to the control group, showed no significant change in triglycerides levels after the Mediterranean diet intervention (47). According to a recent randomized trial, 20 obese women were allocated for 2 months to either a hypocaloric Mediterranean diet or Atkins diet. Findings indicate that after 2 months triglycerides levels in both groups were not significantly altered (33). Finally a recent trial allocated 90 subjects with abdominal obesity but without cardiovascular disease or type 2 diabetes either to an intervention group following the Mediterranean diet according to a specific food plan with close supervision by a dietician or a control group simply instructed to follow a Mediterranean-style diet. After two months triglycerides levels decreased, although not significantly (50) (Table 4).

### 5.3. HDL-cholesterol levels

Regarding the role of the Mediterranean diet on HDL-cholesterol levels, the majority of studies support the lack of associations, while some show a beneficial effect of this dietary pattern. Only one study showed a significant decrease in HDL-cholesterol levels after the Mediterranean diet intervention.

Results from a subsample of the 1992-1993 Catalan Nutritional Survey in Spain, indicate that higher adherence to the Mediterranean diet was associated with higher HDL-cholesterol levels (p=0.033) (40). According to the ZINCAGE project, that evaluated 957 healthy older subjects from 5 European countries, higher adherence to the Mediterranean diet was associated with significantly higher HDL-cholesterol levels in women (48). Furthermore the Nureta PREDIMED Study, that included 808 subjects with prior CVD, supports the beneficial effect of the Mediterranean diet, as participants closer to the Mediterranean diet had 47% (OR 0.53, 95% CI: 0.31-0.90) lower odds of having low HDL-cholesterol levels, compared to those in the lowest quartile of adherence to the Mediterranean dietary pattern (23). Results from the

PREDIMED randomized trial show that participants allocated to the either a Mediterranean diet supplemented with olive oil or nuts increased significantly their HDL-cholesterol levels compared to the low fat diet (34). In addition a clinical trial conducted in Italy in 47 obese women, showed that participants allocated to a moderately hypoenergetic Mediterranean diet and exercise program significantly increased their HDL-cholesterol levels after 4 months of intervention (43). According to a randomized trial in Scotland with a 6-month intervention period and a 3-month follow-up period, that allocated 53 women to the Mediterranean diet intervention and 19 women to the control group, HDL-cholesterol levels significantly increased in the intervention group (47).

On the other hand the SUN Cohort Study examining the relationship between adherence to the Mediterranean diet and HDL-cholosterol levels showed no significant associations (21). In addition the ATTICA Study showed no associations between adherence to the Mediterranean diet and HDL-cholesterol levels in overweight or obese subjects, (highest vs lowest tertile of the Mediterranean Diet Score: -0.04±0.1 mg/dL, p=0.96) (44). A 12-week clinical trial in 77 French Canadian women does not show an increase of the levels of HDL-cholesterol after the nutritional intervention (32). According to a randomized trial evaluating the outcomes of a 6-month Mediterranean lifestyle program in 279 post-menopausal women with diabetes, HDL-cholesterol was not significantly increased (38). Additionally a 4-week cross-over randomized trial, that allocated 22 participants to a Mediterranean-inspired or a Swedish diet, showed that HDL-cholesterol concentrations were similar after the Mediterranean-inspired diet, compared to the Swedish diet (41). The Medi-RIVAGE Study, a 3 month clinical trial that allocated 212 volunteers to either a low fat diet or a Mediterranean diet, did not show significant changes in HDL-cholesterol levels after 3 months of compliance to the Mediterranean diet (42). According to another randomized trial from Germany, that examined the effect of a Mediterranean diet with 100 hours of education or a written advice only group in 101 patients with established and treated coronary artery disease, no significant differences in HDL-cholesterol levels were observed after the 1-year intervention (46). Furthermore a randomized trial in the USA that enrolled 49 subjects to either a modified Mediterranean-style low glycaemic load diet or a Phytochemical enriched diet, did not show significant associations regarding HDL-cholesterol levels after the 12-week intervention (28). An 8-week randomized trial that allocated 60 participants to either a High Saturated Fat diet, a High MUFA diet or a Mediterranean diet did not show significant increase of HDL-cholesterol after the Mediterranean diet intervention (baseline: 1.35 mmol/L, standard error 0.11, Intervention: 1.39 mmol/L, standard error 0.11) (39). According to a recent randomized trial, 20 obese women were allocated for 2 months to either a hypocaloric Mediterranean diet or Atkins diet. Findings indicate that after 2 months HDL-cholesterol levels in both groups were not significantly altered (33). Finally in a recent trial, 90 subjects with abdominal obesity but without cardiovascular disease or type 2 diabetes were separated into an intervention group following the Mediterranean diet according to a specific food plan with close supervision by a dietician and a control group simply instructed to follow a Mediterranean-style diet. After two months, HDL-cholesterol levels were not significantly different than baseline (50).

Only one study, a 28-day crossover randomized trial that allocated 59 subjects either to the Mediterranean diet group or a high carbohydrate diet after a saturated fat phase, showed that participants that followed the Mediterranean diet had significantly lower HDL-cholesterol levels (45) (Table 5).

**5.4. Blood pressure levels**

The majority of the studies examining the relationship between adherence to the Mediterranean diet and blood pressure levels underline the beneficial role of this dietary pattern.

Two articles from the SUN Cohort Study examining the relationship between adherence to the Mediterranean diet and blood pressure levels have been published. As already mentioned according to the article published in 2007, no significant associations between adherence to the Mediterranean diet and blood pressure levels were observed (21). The other article from the SUN cohort, published in 2008, showed that even though adherence to the Mediterranean diet was not associated with hypertension, the mean levels of systolic and diastolic blood pressure of the participants closer to the Mediterranean diet were lower. In particular, subjects with moderate adherence to the Mediterranean diet had -2.4 mmHg (95% CI: -4.0, -0.8) reduction of systolic blood pressure, while those with high adherence had -3.1 mmHg (-5.4, -0.8). Diastolic blood pressure levels were –1.3 mmHg (95% CI: -2.5, -0.1) in subjects with moderate adherence to the Mediterranean diet and -1.9 mmHg (95% CI: -3.6, -0.1) in subjects with high adherence to the Mediterranean diet (49). In addition according to the ATTICA study, examining 2,282 Greek subjects without any evidence of CVD or diabetes mellitus, individuals with dietary habits closer to the Mediterranean diet had a 26% lower likelihood (p=0.008) of being hypertensive and 36% greater probability of having their blood pressure levels controlled (p=0.021) (50). However another article from the ATTICA Study examining the relationship between adherence to the Mediterranean diet and blood pressure levels in 1,762 overweight or obese subjects, indicated that adherence to this pattern is only modestly associated with systolic blood pressure in overweight subjects (highest vs lowest tertile of the Mediterranean Diet Score: SBP: -0.09±0.1 mmHg, p=0.08, DBP: 0.08±0.2 mmHg, p=0.51) (44). Furthermore according to the Greek arm of the EPIC Study, examining 20,343 subjects without hypertension, adherence to the Mediterranean diet is inversely associated with blood pressure levels (MDS per 3 units: SBP: -0.8 mm Hg, 95% CI: -1.1, -0.4, DBP: -0.2 mmHg, 95% CI: -0.5, -0.0) (51). The Medi-RIVAGE Study, a 3 month clinical trial that allocated 212 volunteers to either a low fat diet or a Mediterranean diet, showed that systolic blood pressure tended to decrease, but diastolic blood pressure

**Table 5**. A summary of studies that evaluated the effect of the Mediterranean diet on HDL-cholesterol levels

| Study | Country | Year | N | Age range | Men | Results |
|---|---|---|---|---|---|---|
| **HDL-cholesterol levels** | | | | | | |
| **1992-1993 Catalan Nutritional Survey** (40)<br>Cross-sectional | Spain | 2006 | 328 | 18-75 | 42% | Higher MDS: Higher HDL (p=0.033) |
| **ZINCAGE Study** (48)<br>Cross-sectional | Europe (5 countries) | 2008 | 957 | >60 | 44% | Females: higher diet score, beta=0.144, p=0.029 |
| **Nureta PREDIMED** (23)<br>Cross-sectional<br>14 point FFQ | Spain | 2009 | 808 (prior CVD) | Mean 67 | 45% | HDL: 0.53 (95% CI: 0.31-0.90) |
| **PREDIMED Randomized Trial** (34)<br>Clinical Trial – 3 months | Spain | 2006 | 772 (high CVD risk) | 55-80 | 44% | Vs Low fat diet:<br>mg/dL (95% CI)<br>MD+VOO: 2.9 (1,7, 4,0)<br>MD+nuts: 1.6 (0.45, 2.7) |
| **Randomized Trial** (43)<br>Clinical trial – 4 months | Italy | 2007 | 47 obese | 25-70 | 0% | Baseline: 55.2±4.2 mg/dL<br>4 months: 56.1±9.4 mg/dL (p<0.002) |
| **Randomized Trial** (47)<br>Clinical Trial – 6 months<br>3 months follow-up | Scotland | 2008 | 72<br>I : 53<br>C : 19 | 25-55 | 0% | Baseline:1.42 mmol/L±0.27<br>6 month: 1.65 mmol/L±0.33<br>9 month: 1.69 mmol/L±0.33 |
| **SUN Cohort** (21)<br>Prospective – 6 yrs, MDS | Spain | 2007 | 2,563 | - | - | MDS, p trend=0.11<br>0-2: 63.8±15 mg/dL<br>3-5: 66.1±19 mg/dL<br>6-9: 64.1±19 mg/dL |
| **ATTICA Study** (44)<br>Cross-sectional<br>MedDietScore | Greece | 2007 | 1,762 (BMI >25) | >18 | 60% | Highest vs lowest tertile:<br>-0.04±0.1, p=0.96 |
| **Randomized Trial** (32)<br>Clinical Trial – 12 weeks | Canada | 2003 | 77 | 30-65 | 0% | Week 0: 1.63±0.41 mmol/L<br>Week 12: 1.61±0.41, NS |
| **Mediterranean Lifestyle Program** (38)<br>Clinical Trial – 6 months<br>Post-menopausal women | USA | 2003 | 279 DM | <75 | 0% | Baseline: 43.12±11.06<br>6 months: 43.49±10.14<br>(mg/dL) p=0.823 |
| **Randomized Trial** (41)<br>4 week- cross-over Trial | Sweden | 2004 | 22 | 30-51 | 54% | Baseline: 1.6±0.1 mmol/L<br>Med Inspired: 1.3±0.1<br>Swedish: 1.3±0.1 (NS) |
| **Medi-RIVAGE Study** (42)<br>Clinical Trial – 3 months | France | 2006 | 212 | 18-70 | - | Baseline: 1.5 mmol/L±0.4<br>3 months: 1.5 mmol/L±0.5 |
| **Randomized Trial** (46)<br>Clinical Trial – 1 year | Germany | 2006 | 101 CAD | Mean 59 | 77% | Baseline:1.40±0.30 mmol/L<br>1 year: 1.45±0.37 mmol/L |
| **Randomized Trial** (28)<br>Clinical Trial – 12 weeks | USA | 2008 | 49 (MED arm: 23) | 25-80 | 46% | Baseline: 1.02±0.05<br>12 weeks: 1.04±0.05 (mmol/L - NS) |
| **Randomized Trial** (39)<br>Clinical Trial – 8 weeks | Netherlands | 2009 | 60 | 40-65 | 40% | Baseline:1.35mmol/L,se 0.11<br>8-weeks : 1.39, se 0.11, NS |
| **Randomized Trial** (33)<br>Clinical Trial – 2 months | Italy | 2009 | 20 (BMI >27) | 30-50 | 0% | Baseline: 58±5 mg/dL<br>2 months: 54±5 mg/dL |
| **Randomized Trial** (45)<br>Clinical Trial<br>Cross-over, 28 days each | Spain | 2001 | 59 | <30 | 51% | SFA diet: 1.12±0.3 mmol/L<br>Med diet: 1.03±0.3 mmol/L<br>p<0.001 |

even though weakly, increased after 3 months of compliance to the Mediterranean diet (42). Results from the PREDIMED randomized trial also support the beneficial role of the Mediterranean diet, as systolic and diastolic blood pressure decreased in patients allocated to both Mediterranean diets compared to the low fat diet (compared to the low fat diet: SBP: MD+VOO: -5.9 mmHg (95% CI: -8.7, -3.1), MD+nuts: -7.1 mmHg (95% CI: -10.0, -4.1), DBP: MD+VOO: -1.6 mmHg (95% CI: -3.0, -0.01), MD+nuts: -2.6 mmHg (95% CI: -4.2, 1.0)) (34). In a recent trial, 90 subjects with abdominal obesity but without cardiovascular disease or type 2 diabetes were separated into an intervention group following the Mediterranean diet according to a specific food plan with close supervision by a dietician and a control group simply instructed to follow a Mediterranean-style diet. After two months the experimental group had improved endothelial function, lower systolic and diastolic blood pressure levels compared to baseline and lower diastolic blood pressure than the control group, showing the beneficial effects of close adherence to the Mediterranean diet on the cardiovascular system (50).

There are also some studies that do not confirm the protective role of the Mediterranean dietary pattern regarding blood pressure levels. A randomized trial evaluating the outcomes of a 6-month Mediterranean lifestyle program in 279 post-menopausal women with diabetes, did not show significant decrease of either systolic or diastolic blood pressure levels (38). Another clinical trial conducted in Italy in 47 obese women, allocated to a moderately hypoenergetic Mediterranean diet and exercise program, does not support a beneficial effect of the intervention on systolic or diastolic blood pressure levels (43). Finally according to a recent randomized trial, allocating 20 obese women for 2 months to either a hypocaloric Mediterranean diet or Atkins diet, systolic and diastolic blood pressure levels were not significantly altered in the Mediterranean diet group (33) (Table 6).

**Table 6**. A summary of studies that evaluated the effect of the mediterranean diet on blood pressure

| Study | Country | Year | N | Age range | Men | Results |
|---|---|---|---|---|---|---|
| **Blood pressure levels** | | | | | | |
| **SUN Cohort** (21)<br>Prospective – 6 yrs<br>MDS | Spain | 2007 | 2,563 | - | - | SBP: MDS, p trend=0.64<br>0-2: 112.5±14 mmHg<br>6-9: 113.3±13 mmHg<br>DBP: MDS, p trend=0.66<br>0-2: 68.9±11mmHg<br>6-9: 69.8±10 mmHg |
| **SUN Cohort** (49)<br>Prospective – 6 yrs<br>MDS | Spain | 2008 | 9,408 | 20-90 | 38% | Hypertension: NS (95% CI)<br>SBP, High adherence:<br>-3.1 mmHg (-5.4, -0.8)<br>DBP, High adherence:<br>-1.9 mmHg (-3.6, -0.1) |
| **ATTICA Study** (50)<br>Cross-sectional | Greece | 2003 | 2,282 | >18 | 49% | Hypertension:<br>0.74 (p=0.008) |
| **ATTICA Study** (44)<br>Cross-sectional<br>MedDietScore | Greece | 2007 | 1,762<br>(BMI >25) | >18 | 60% | Highest vs lowest tertile:<br>SBP: -0.09±0.1, p=0.08<br>DBP: 0.08±0.2, p=0.51 |
| **EPIC Study** (51)<br>MDS | Greece | 2004 | 20,343 | 20-86 | 43% | MDS per 3 units: (95% CI:)<br>SBP: -0.8 (-1.1, -0.4)<br>DBP: -0.2 (-0.5, -0.0) |
| **Medi-RIVAGE Study** (42)<br>Clinical Trial – 3 months | France | 2006 | 212 | 18-70 | - | SBP:<br>Baseline: 128 mmHg ±17<br>3 months: 127 mmHg ±12<br>DBP:<br>Baseline: 78 mmHg ±11<br>3 months: 80 mmHg ±8 |
| **PREDIMED Randomized Trial** (34)<br>Clinical Trial – 3 months | Spain | 2006 | 772<br>(high CVD risk) | 55-80 | 44% | Vs Low fat diet:<br>SBP (95% CI:)<br>MD+VOO: -5.9 (-8.7, -3.1)<br>MD+nuts: -7.1 (-10.0, -4.1)<br>DBP<br>MD+VOO: -1.6 (-3.0, -0.01)<br>MD+nuts: -2.6 (-4.2, 1.0) |
| **Mediterranean Lifestyle Program** (38)<br>Clinical Trial – 6 months<br>Post-menopausal women | USA | 2003 | 279<br>DM | <75 | 0% | SBP (mmHg), p=0.483<br>Baseline: 136.06±13.91<br>6 months: 134.21±14.30<br>DBP (mmHg), p=0.204<br>Baseline: 79.29±9.49<br>6 months: 77.15±8.77 |
| **Randomized Trial** (43)<br>Clinical trial – 4 months | Italy | 2007 | 47<br>obese | 25-70 | 0% | SBP (NS)<br>Baseline: 136.9±13.1 mmHg<br>4 months: 135.4±10.4<br>DBP (NS)<br>Baseline: 84.4±7.1 mmHg<br>4 months: 82.9±5.8 mmHg |
| **Randomized Trial** (33)<br>Clinical Trial – 2 months | Italy | 2009 | 20<br>(BMI >27) | 30-50 | 0% | SBP, NS<br>Baseline: 133±7 mmHg<br>2 months: 125±2 mmHg<br>DBP, NS<br>Baseline: 89±3 mmHg<br>2 months: 84±2 mmHg |

### 5.5. Fasting glucose levels

The majority of the studies indicate that adherence to the Mediterranean diet exerts a protective role for fasting glucose levels and glucose metabolism in general. Nevertheless few studies show insignificant associations.

Three articles from the ATTICA Study examining the relationship between adherence to the Mediterranean dietary pattern and fasting glucose levels or diabetes have been published. The first one published in 2005 shows that a 10-unit increase of the Mediterranean Diet Score was associated with 21% lower odds of diabetes (OR: 0.79, 95% CI: 0.65-0.94) (52). In addition in normoglycemic subjects, a 10-unit increase of the Mediterranean Diet Score was associated with significant reductions of fasting glucose levels (b-coefficient + SE: -1.3±0.04, p=0.005), insulin levels (b-coefficient + SE: -.1±0.001, p=0.004) and HOMA-IR index (b-coefficient + SE: -0.2±0.002, p=0.005) (53). Furthermore when examining the relationship between adherence to the Mediterranean diet and HOMA-IR index in overweight or obese subjects, a trend for lower HOMA-IR was observed for the participants closer to the Mediterranean diet (highest vs lowest tertile of the Mediterranean Diet Score: -0.26±0.2, p=0.09) (44). According to a randomized trial evaluating the outcomes of a Mediterranean lifestyle program in 279 post-menopausal women with diabetes, $HbA_{1c}$ levels were significantly decreased after 6 months of intervention (38). Results from the PREDIMED randomized trial show that participants allocated to either a Mediterranean diet supplemented with olive oil or nuts had significantly lower levels of fasting glucose and insulin, as well as the HOMA-IR index, compared to the low fat diet. (Glucose: MD+VOO: -7.0 mg/dL (95%CI: -13.0, -1.3), MD+nuts: -5.4 mg/dL (95%CI : -10.5, -0.2), Insulin

**Table 7**. A summary of studies that evaluated the effect of the mediterranean diet on fasting glucose levels

| Study | Country | Year | N | Age range | Men | Results |
|---|---|---|---|---|---|---|
| **A. Significant results** | | | | | | |
| **Fasting glucose levels** | | | | | | |
| **ATTICA Study** (52) Cross-sectional MedDietScore | Greece | 2005 | 3,042 | >18 | 50% | MedDietScore, 10 unit increase: DM: 0.79 (95% CI: 0.65-0.94) |
| **ATTICA Study** (53) Cross-sectional MedDietScore | Greece | 2007 | 3,042 | >18 | 50% | In normoglycemic subjects: MedDietScore, 10 unit increase: Glu: -1.3±0.04, p=0.005 INS: -0.1±0.001, p=0.004 HOMA-IR: -0.2±0.002, p=0.005 |
| **ATTICA Study** (44) Cross-sectional MedDietScore | Greece | 2007 | 1,762 (BMI >25) | >18 | 60% | Highest vs lowest tertile: HOMA-R: -0.26±0.2, p=0.09 |
| **Mediterranean Lifestyle Program** (38) Clinical Trial – 6 months Post-menopausal women | USA | 2003 | 279 DM | <75 | 0% | $HbA_{1c}$ (%) Baseline: 7.43±1.30 6 months: 7.07±1.11 p<0.001 |
| **PREDIMED Randomized Trial** (34) Clinical Trial – 3 months | Spain | 2006 | 772 (high CVD risk) | 55-80 | 44% | Vs Low fat diet: Glu MD+VOO: -7.0 (-13.0, -1.3) MD+nuts: -5.4 (-10.5, -0.2) INS and HOMA significantly lower (p<0.001) |
| **Medi-RIVAGE Study** (42) Clinical Trial – 3 months | France | 2006 | 212 | 18-70 | - | Glu Baseline: 5.3 mmol/L±0.6 3 months: 5.1 mmol/L±0.6 INS Baseline: 10.6 mmol/L±5.8 3 months: 8.3 mmol/L±4.4 HOMA score Baseline: 2.5±1.6 3 months: 1.9±1.2 |
| **Randomized Trial** (28) Clinical Trial – 12 weeks | USA | 2008 | 49 (MED arm: 23) | 25-80 | 46% | Baseline: 5.63±0.11 12 weeks: 5.41±0.12 (mmol/L – p<0.05) |
| **Randomized Trial** (33) Clinical Trial – 2 months | Italy | 2009 | 20 (BMI >27) | 30-50 | 0% | Fasting glucose, NS Baseline: 96±5 mg/dL 2 months: 94±4 mg/dL Fasting insulin, p<0.05 Baseline: 19±3 μU/mL 2 months: 15±2 μU/mL |
| **Randomized Trial** (45) Clinical Trial Cross-over, 28 days each | Spain | 2001 | 59 | <30 | 51% | Fasting Glucose, NS SFA diet: 4.89±0.3 mmol/L Med diet: 4.79±0.4 mmol/L Fasting insulin, p<0.001 SFA diet: 32.3±9.3 mmol/L Med diet: 14.7±8.5 mmol/L |
| **B. No associations** | | | | | | |
| **Study** | **Country** | **Year** | **N** | **Age range** | **Men** | **Results** |
| **Fasting glucose levels** | | | | | | |
| **SUN Cohort** (21) Prospective – 6 yrs MDS | Spain | 2007 | 2,563 | - | - | MDS, p trend=0.52 0-2: 86.1±11 mg/dL 3-5: 85.8±11= mg/dL 6-9: 87.3±17 mg/dL |
| **Randomized Trial** (41) 4 week- cross-over Trial | Sweden | 2004 | 22 | 30-51 | 54% | Baseline: 5.2±0.1 mmol/L Med Inspired: 4.9±0.1 Swedish: 4.8±0.1 (NS) |
| **Randomized Trial** (46) Clinical Trial – 1 year | Germany | 2006 | 101 CAD | Mean 59 | 77% | Fasting insulin Baseline:10.5±4.8 mlUl/L 1 year: 11.3±9.3 mlUl/L |
| **Randomized Trial** (43) Clinical trial – 4 months | Italy | 2007 | 47 obese | 25-70 | 0% | Baseline: 92.5±14.5 mg/dL 4 months: 89.4±11.4 (NS) |
| **Randomized Trial** (39) Clinical Trial – 8 weeks | Netherlands | 2009 | 60 | 40-65 | 40% | Fasting glucose: Baseline: 5.42 mmol/L, se 0.10 Intervention: 5.33 mmol/L, se 0.09, (NS) Insulin: Baseline: 46.4 pmol/L, se 5.1 Intervention: 41.3 pmol/L, se 4.8, (NS) HOMA-IR: Baseline: 0.89, se 0.10, Intervention: 0.79, se 0.09, (NS) |

MD+VOO: -16.7 pmol/L (95%CI: -27.1, -0.4), MD+nuts: -20.4 pmol/L (95%CI : -31.9, -9.7), HOMA-IR : MD+VOO: -0.91 (95%CI: -1.4, -0.46), MD+nuts: -1.1 (95%CI : -1.6, -0.55)) (34). According to the Medi-RIVAGE Study, a 3 month clinical trial that allocated 212 volunteers to either a low fat diet or a Mediterranean diet, glucose and insulin levels, as well as the HOMA score were significantly lower after 3 months of compliance to the Mediterranean diet (42). Additionally a randomized trial in the USA that enrolled 49 subjects to either a modified Mediterranean-style low glycaemic load diet or a Phytochemical enriched diet, showed that the Mediterranean diet is beneficial regarding glucose metabolism, as participants allocated to the Mediterranean diet had significantly lower fasting glucose and insulin levels after the 12-week intervention (28). According to a recent randomized trial, examining 20 obese women, allocated to either a hypocaloric Mediterranean diet or Atkins diet for 2 months, showed that fasting glucose levels in both groups were not significantly altered. However in both groups fasting insulin levels were significantly decreased, indicating an improvement in glucose metabolism (33). According to a 28-day cross-over randomized trial that allocated 59 subjects either to the Mediterranean diet group or a high carbohydrate diet after a saturated fat phase, despite the fact that no significant differences were observed in fasting glucose levels, fasting insulin levels were significantly lower in those participants following the Mediterranean diet intervention (45). Finally in a recent trial, 90 subjects with abdominal obesity but without cardiovascular disease or type 2 diabetes were separated into an intervention group following the Mediterranean diet according to a specific daily and weekly food plan with close supervision by a dietician and provision of basic foods and a control group simply instructed to follow a Mediterranean-style diet. After two months, although fasting glucose levels were not significantly different from baseline, insulin levels and HOMA index significantly decreased (50).

As already mentioned there are some studies that showed no significant associations between adherence to the Mediterranean diet and glucose metabolism. The SUN Cohort Study examining the relationship between adherence to the Mediterranean diet and fasting glucose levels showed no significant associations (21). A 4-week cross over randomized trial, that allocated 22 participants to a Mediterranean-inspired or a Swedish diet, showed that glucose concentrations were similar after the Mediterranean-inspired diet, compared to the Swedish diet (41). Furthermore according to another randomized trial from Germany, that examined the effect of a Mediterranean diet with 100 hours of education or a written advice only group in 101 patients with established and treated coronary artery disease, no significant differences in fasting insulin levels after the 1-year intervention were observed (46). A clinical trial conducted in Italy in 47 obese women, showed that participants allocated to a moderately hypoenergetic Mediterranean diet and exercise program had no significant changes of their glucose levels after 4 months of intervention (43). Finally an 8-week randomized trial that allocated 60 participants to either a High Saturated Fat diet, a High MUFA diet or a Mediterranean diet did not show significant decrease of fasting glucose levels, insulin levels or the HOMA-IR index after the Mediterranean diet intervention (39) (Table 7).

## 6. PERSPECTIVE

The prevalence of the metabolic syndrome has increased rapidly during the recent years and based on the current estimations will continue to increase. According to the recent guidelines, lifestyle interventions should be the primary therapy approach for the treatment of the metabolic syndrome (5, 54). Adherence to the Mediterranean diet in particular, seems to offer significant benefits regarding the prevention and treatment not only of the metabolic syndrome as a whole, but also of its components. Therefore efforts should be made in order to increase adherence to the Mediterranean dietary pattern, especially in patients with the metabolic syndrome, as this dietary pattern, apart from its health benefits, is tasty and easy to follow in the long term.

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