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REVIEW ARTICLE

THE MEDITERRANEAN DIET, PART IV: A DIET FOR OBESITY OR FOOD FOR FAT?

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SUMMARY

The rapidly increasing worldwide prevalence of obesity is currently considered a serious health problem that increases the risk for several comorbidities, such as diabetes, cardiovascular disease, hypertension, cancer, osteoarthritis and neuropathological disease. Increasing carbohydrate and/or fat consumption has been established to lead to obesity, and dietary approaches have been suggested to control this epidemic. Epidemiological studies suggest that the Mediterranean diet, rich in vegetal ingredients, fish and olive oil, may reduce the risk for obesity. This diet is an ample source of unsaturated fats and fibers and has a low energy density. Studies have provided evidence that the main component of olive oil (the monounsaturated fatty acid oleic acid) may promote weight loss by biochemical mechanisms, including enhanced β-oxidation and increased channeling of saturated fatty acids into triglyceride pools. By contrast, in the absence of oleic acid, dietary saturated fatty acids give rise to fat storage. This review analyzes the literature that has been published in this field and summarizes experimental and human studies on obesity prevention.

INTRODUCTION

Obesity is a widely prevalent disorder and represents a serious health problem in both developed and developing countries. The World Health Organization (WHO) defines overweight (also called "pre-obese") as a body mass index (BMI; weight in kilograms divided by the square of the height in meters) ≥ 25 and obesity as a BMI ≥ 30, the normal range being 18-24. It states that in 2005, 1.6 billion adults (age 15 years and older) were overweight and that at least 400 million adults were obese. The WHO further projects that by 2015 these numbers will be 2.3 billion and 700 million, respectively (see www.who.int/mediacentre/factsheets). According to a pooling analysis based on representative population samples from 106 countries covering about 88% of the world's population, the absolute numbers for 2030 have been predicted to total 2.16 billion overweight and 1.12 billion obese individuals (1). WHO data also show a considerable geographic variation in the percentage of obese people per country. For instance, in the U.S., this percentage is 35%, in the U.K. 25%, in Finland 15%, in Belgium 12% and in Italy 8% (see, e.g., www.who.int/bmi/index.jsp). The prevelance of overweight among school-age children amounts to 35% in parts of Europe and the estimated burden of pediatric obesity is rising: whereas the annual increase was typically below 0.1% in the 1980s, it was 0.3% in the late 1990s (2). Compared with the data from the 1990 surveys, the worldwide proportion of obese school-age children will almost double by 2010. By that year, 26 million children will be overweight, including 6.4 million in the E.U. The alarming level of this disorder is further illustrated by the fact that in the U.S. the prevalence of obesity in adolescents increased from 5% to 13% in boys and from 5% to 9% in girls between 1966-70 and 1988-91 (3). A health survey completed in 2002 revealed that in China 23% of the population is overweight and in Chinese cities 12% of adults and 8% of children are obese (4). Similar data from other parts of the world have recently been made public (5).

Obesity is associated with an increased risk for a variety of conditions, including cancer, diabetes, hypertension, cardiovascular disease, obstructive sleep apnea syndrome, osteoarthritis, depression and lower scores on measures for quality of life (6). These disorders go hand in hand with increasing healthcare costs. Each year, obesity costs the U.S. economy $150 billion and this number may double every decade, reaching a total expenditure of around $900 billion by 2030 (7). Also in Europe, the obesity-related health economic burden is enormous, reportedly ranging from 0.09% to 0.61% of each country's gross domestic product (8). These data highlight the increasing impact of obesity on general health and that its epidemic proportions require strong health-promoting measures.

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The fact that the prevalence of obesity is increasing so drastically points to environmental factors such as dietary behavior. Increasing consumption of carbohydrates and fat, large portions and units with high energy density have been reported to lead to obesity (9-11) and it is clear that new nutritional strategies are necessary to control this epidemic. In this context, much attention has been paid to Mediterranean dietary patterns, which have been documented to have positive effects on chronic disorders, and it has been pointed out that this diet has beneficial effects on overweight and obesity (12). Historically, the Seven Countries Study (the U.S., Finland, The Netherlands, Italy, Greece, former Yugoslavia and Japan) showed that cardiovascular disease occurs at a lower rate in the olive tree-growing areas around the Mediterranean basin (13).

The supposedly beneficial diet of that region is based on moderate consumption of mostly red wine with meals, which consist mainly of vegetables, legumes, nuts, whole-wheat bread, fresh fruit, fish and poultry rather than red meat, pork and dairy products. Furthermore, the Mediterranean diet contains olive oil as the primary fat source. Although dietary habits in the Mediterranean countries have changed over the past decades, the high consumption of olive oil and vegetal ingredients has remained a main characteristic. It is thought that these dietary components contribute considerably to the lower incidence of chronic disorders and diseases (14). Although vegetal food has a relatively low energy density, the specific use of relatively high amounts of olive oil represents a paradox as far as the prevention of obesity is concerned. It should be noted, however, that olive oil (especially extra-virgin olive oil) is a rich source of the monounsaturated fatty acid (MUFA) oleic acid. There is ample evidence from experimental and human studies that MUFAs promote weight loss due to the fact that they are prone to oxidation, whereas saturated fatty acids (SFAs) can lead to fat storage (15-18). Indeed, an ecological study based on recent data from 168 countries has shown that populations with a lower prevalence of obesity seem to consume a greater amount of MUFAs (19). Although the majority of epidemiological studies found a negative correlation between the Mediterranean diet and the risk of obesity (20-22 and references therein), a few did not find such an association (23, 24). More specifically, the average weight of the participants of the SUN cohort study increased during the 28-month follow-up period (23). The trial participants with a relatively greater adherence to the Mediterranean diet showed a smaller weight increment, although this characteristic was no longer statistically significant after a multivariate adjustment. The objective of this review is to analyze the literature published on the Mediterranean diet and to review experimental studies on obesity prevention and/or weight loss.

EXPERIMENTAL STUDIES

Polyunsaturated fatty acids

Clarke et al. (25) explain that nutrients are an essential component of the environmental factors that interact with hormonal signals to regulate gene expression. These authors emphasize the strong direct influence of fatty acids on the molecular events that govern genetic activity. Ingestion of nutrients rich in ω-3 and ω-6 fatty acids decreases de novo fatty acid biosynthesis by suppressing the expression of genes involved in lipogenic transcription. These polyunsaturated fatty acids (PUFAs), but not SFAs, are present in vegetal food and fish and are able to downregulate the expression of hepatic sterol regulatory element-binding protein (SREBP) gene expression. In cell lines, micromolar concentrations of these fatty acids (predominantly C18:2-C22:6) have been demonstrated to concentration-dependently decrease the transcription of SRE-regulated genes by 20-75% (26). Changes in the levels of intracellular nonesterified fatty acids also correlate well with changes in the expression of peroxisome proliferator-activated receptors PPARα, PPARβ and both isoforms of PPARγ (PPARγ1 and PPARγ2). Although the liver is not a typical organ to store lipids as energy reserves, hepatocytes are strongly involved in de novo lipid biosynthesis. Findings by Schadinger et al. indicate that PPARγ2 is capable of inducing lipid accumulation in hepatocytes by augmenting de novo lipid biosynthesis. This process occurs through direct or indirect activation of SREBP-1 and its downstream targets, the expression of which is increased in hepatocytes expressing PPARγ2 (27). The action of PUFAs inhibits the expression and processing of SREBP-1C, and also of nuclear transcription factor Y, transcription factor Sp1 and upstream stimulatory factors involved in genes encoding lipogenic enzymes (28). In addition, recent experiments by Damiano et al. (29) have shown that inhibition of the gene transcription of the mitochondrial citrate transport protein by PUFAs is mediated by the nuclear level of SREBP-1C protein. The citrate transport protein is important for the transport of acetyl-CoA into the cytosol.

Thus, it is clear that PUFAs, acting as signaling molecules, have biochemical effects on transcription factors in adipocyte differentiation and function. PPARs and SREBPs are considered key players in this field and a pronounced antiadipogenic effect has been demonstrated for ω-3 PUFAs, namely the marine fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). These fatty acids activate a metabolic switch toward lipid catabolism and suppression of lipogenesis. This effect was elucidated by Flachs et al. (30), who in mice found a threefold stimulation of the expression of genes encoding regulatory factors of oxidative lipid metabolism in white fat, coinciding with a reduction of obesity. These findings are consistent with recent results published by Van Schothorst et al. (31), who found increased lipid metabolism in the small intestine of mice based on a molecular response to DHA and EPA. Both peroxisomal and mitochondrial β-oxidation and fatty acid ω-oxidation were increased. Together with the ability of the ω-3-derived compounds resolvin E1 and protectin D1 to alleviate low-grade inflammation of adipose tissue (32), it appears that the DHA/EPA metabolic switch reduces ectopic lipid deposition (33).

Monounsaturated fatty acids

In an excellent review, Bergouignon et al. (34) pursue the metabolic fate of SFAs and MUFAs. They found that the stability of body mass is acutely and tightly controlled by appropriate changes in the oxidation of glucose and amino acids after meals. By contrast, adjustment of fatty acid oxidation may take up to a week, which results in storage of excess dietary fat. The fine tuning of body mass and more specifically the balance between fat storage and fatty acid oxidation is further complicated by the fact that short-chain (C2:0-C4:0) and medium-chain (C6:0-C12:0) fatty acids, as well as unsaturated oleate (18:1) and linoleate (18:2), are more readily oxidized than longer-chain unsaturated fatty acids and SFAs (35). In animal studies this differential oxidation has been shown to influence fat

balance (36) and body mass (37). It has also been demonstrated that diet-induced thermogenesis in rats is lower with long-chain SFA intake than with the intake of plant oils rich in MUFAs, a difference that results in body fat accumulation (38).

Apart from differences in oxidation rates, the metabolic fates in adipose tissues and in muscle also differ between fatty acids. In adipose tissue the MUFA proportion is the highest of the total fatty acid content and relative mobilization increases with increases in the degree of unsaturation, as shown in studies with rat adipocytes (39). Differential incorporation has also been observed in cultured muscle cells; oleate preferentially accumulates in triacylglycerides (TAGs) and its biosynthesis is lower in cells exposed to SFAs than in those exposed to unsaturated fatty acids. In contrast, SFAs preferentially accumulate as diacylglycerides (DAGs). These in vitro results suggest that SFA and MUFA diets can lead to opposite accumulation into DAG and TAG pools. This significant difference in the metabolic fates of fatty acids in cultured cells is also associated with a difference in responsiveness to insulin. It appears that incubation with an excess of oleate induces a high TAG content in cultured muscle cells but no alteration in insulin responsiveness, which may be linked to non-MUFA-induced impairment of insulin action in muscle tissue of rodents (40). In this context, it is interesting to note that improvement of insulin sensitivity has been demonstrated by many experimental studies focusing on high intake of olive oil, of which oleic acid is the major fatty acid component (41). Indeed, recent reports by Pickersgill et al. (42) and Gao et al. (43) have pointed out that human muscle cells coincubated with oleate do not develop palmitate-induced insulin resistance, suggesting a protective effect of oleate. The mechanism behind this important finding was recently further elucidated by Coll et al. (44), who demonstrated that oleate reverses insulin resistance in skeletal muscle cells. The authors explain that MUFAs rather than SFAs stimulate the activity of protein kinase A (PKA) and PPARα, which control the expression of carnitine palmitoyltransferase 1 and peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1-α), transcriptional activators promoting TAG accumulation and mitochondrial β-oxidation, preventing DAG formation. Other experiments have revealed that oleate activates the expression of the genes encoding acyl-CoA desaturase 1 and diacylglycerol *O*-acyltransferase 1. These enzymes increase the desaturation process of palmitate, which facilitates the channeling of palmitate into the TAG pool, thus enhancing β-oxidation of this fatty acid (44). This protective effect of MUFAs is also apparent in their ability to inhibit the cytotoxic actions of palmitate on pancreatic β-cells. It has been demonstrated by Dhayal et al. (45) that palmitate-induced β-cell apoptosis can be inhibited by MUFAs, preferably with a *cis* configuration, oleic acid being the most effective in this respect.

OBESITY, INFLAMMATION AND THE MEDITERRANEAN DIET

Adipocytes secrete free fatty acids, glycerol, proteins and proinflammatory adipokines (46). The latter include the cytokines TNF-α and IL-6. Adipose tissue is also characterized by decreased production of anti-inflammatory adiponectin and, overall, this leads to a state of chronic local or systemic inflammation together with macrophage infiltration in white adipose tissue. The macrophages scavenge abundantly present apoptotic adipocytes (47), but are also responsible for the production of cytokines (48). This provides a mechanistic link between obesity and the development of type 2 diabetes, as TNF-α is known to induce insulin resistance (49). Another biochemical feature is the IL–6-controlled production of C-reactive protein, an important inflammatory biomarker that induces the formation of cytokines related to the vascular system such as vascular cell adhesion protein (VCAM) and intercellular adhesion molecule (ICAM), providing a link between obesity and atherosclerosis (50). Of note is that after weight loss or surgical fat removal, the inflammatory state may be improved, evidenced by a reduction of macrophage infiltration and expression of genes encoding chemoattractants (51).

In their instructive review, Bullo et al. (52) point out that the question of whether the inflammatory state is the cause or the consequence of obesity remains unanswered. Yet there is recent evidence that the expansion of adipose tissue during the development of obesity is associated with low oxygen tension and poor metabolic adaptation to hypoxia. As a result, overexpression of hypoxia-inducible genes may stimulate the release of proinflammatory cytokines (53). In particular, the overexpression of hypoxia-inducible factor 1-α (HIF1-α) in excessive obesity could contribute to macrophage infiltration (53). This inflammatory process gives rise to proinflammatory reactive oxygen and nitrogen species ("oxidative stress"), to which the system reacts by secreting anti-inflammatory cytokines. Under conditions of continuous inflammatory insults, chronic inflammation may develop and proinflammatory cytokines may disturb the cellular redox system, activating nuclear factor NF-kappa-B (NF-κB) and other redox-sensitive transcription factors. In turn, this mechanism may activate proinflammatory effector enzymes such as cyclooxygenase-2 (COX-2). Thus, persisting increased oxidative stress plays a pivotal role in the persistence of inflammation and, eventually, in the creation of comorbidities of obesity.

Adherence to the Mediterranean diet entails a high intake of antioxidant-rich foodstuffs, such as vegetal food (vegetables, legumes, fruits, whole grains and nuts), fish and olive oil (12). There is ample clinical and epidemiological evidence that components of this diet and/or the diet as a whole can modulate the inflammatory response. The bioactive food components of this diet that have been identified as anti-inflammatory compounds include phenolic compounds (predominantly from vegetal food and red wine), ω-3 fatty acids from marine fish and unsaturated fatty acids from olive oil, nuts and vegetal food. With regard to obesity, Schröder (12) suggested that the high antioxidant and anti-inflammatory action of these components has a positive effect on weight loss and the risk for obesity. This protective effect can be boosted by the lower energy density of this diet relative to the diet of Northern Europe and the U.S. In this respect, the relatively high fiber content of vegetables, nuts and whole grains contributes to satiation, which encourages the intake of smaller portions. In addition, the higher oxidation rate of MUFAs in comparison with PUFAs and SFAs may add to the diet's antiobesity action (19, 54, 55). The human studies and epidemiological evidence on these beneficial effects of the Mediterranean diet will be reviewed below.

HUMAN STUDIES

Many clinical studies have focused on oleic acid, one of the major components of the Mediterranean diet. The general outcome is that this fatty acid is oxidized to a higher degree than stearate or palmi-

tate, saturated fatty acids often consumed in the non-Mediterranean diet. Soares et al. (54) examined the influence of the source of dietary fat on postprandial thermogenesis. In 12 postmenopausal women (BMI 21.9-38.3 kg/m^2), it was found that a diet containing olive oil, as opposed to cream, promoted postprandial fat oxidation in obese persons. Previously, the same research group found similar results in men with a large waist circumference (16). In addition, a double-blind trial conducted by Kien et al. (55) in 43 healthy young adults found opposite effects with regard to fat oxidation in diets rich in oleic acid and low in palmitic acid and diets low in oleate and high in palmitate, notably in women (56). Casas-Agustench et al. (57) found a higher postprandial thermogenic response to meals high in PUFAs from walnuts in contrast to a meal high in PUFAs from dairy products. Surprisingly, in this randomized, crossover trial in nonobese men, a clear effect on substrate oxidation or satiety could not be demonstrated.

It is of special interest that Weinbrenner et al. (58) noticed an olive oil-induced modulation of the oxidative/antioxidative status in healthy men on a strict very-low-antioxidant diet, evidenced by decreased plasma levels of oxidized LDL, 8-oxodeoxyguanosine in mitochondrial DNA and urine, as well as malondialdehyde in urine ($P < 0.05$ for linear trend). A later study in 30 healthy volunteers supported this finding, revealing an increased resistance of LDL to oxidation (59), the decrease in oxidative stress being attributed to the phenolic content of olive oil (60). In this context, it is tempting to speculate that phenolic compounds have beneficial effects in fighting obesity. Indeed, in various experimental settings, the inhibition of adipogenesis in adipocytes induced by phenolic compounds has been demonstrated (61-65). It is noteworthy that resveratrol can activate NAD-dependent deacetylase sirtuin-1 (hSIRT1), which protects mammalian organisms from diet-induced obesity (66, 67) through the induction of antioxidant proteins and decreases activation of proinflammatory cytokines such as TNF-α and IL-6 via down-modulation of NF-κB activity (68). However, before resveratrol can be recommended for use in the prevention and treatment of obesity, further studies on this omnipotent bioagent need to establish its safety in the clinical setting (70).

EPIDEMIOLOGICAL STUDIES

Schroder (12), Buckland et al. (71) Moussavi et al. (19) and Bergouignan et al. (34) have reviewed epidemiological studies that have investigated associations between the Mediterranean diet and obesity. A selection of these studies, as well as the most recent findings and general trends, are presented below.

Cross-sectional studies

In the last decade, various cross-sectional studies have observed a beneficial association between BMI and/or obesity and adherence to the Mediterranean-type diet, including those authored by Schroder et al. (20), Shubair et al. (72) and Panagiotakos (21, 73). The most recent studies also demonstrated an inverse relationship between the Mediterranean diet and the risk of obesity. The Predimed group (74) estimated the risk factor in 3,204 asymptomatic high-risk patients and found an odds ratio of 0.67 (95% confidence interval [CI]: 0.53-0.85) for the four clustered risk factors hypertension, diabetes, obesity and dyslipidemia. On a European scale, the diet of a total of 497,308 individuals (70.7% of whom were women) aged 25-70 years from 10 European countries was assessed with country-specific food preference questionnaires and related to BMI and waist circumference. In their report published in 2009, the investigators mention considerable heterogeneity among the various regions but could nevertheless establish a significant association between higher adherence to the Mediterranean diet and a lower waist circumference for a given BMI in both men and women, especially those from the Northern European countries. However, a significant association between the degree of adherence and BMI was not found (75).

Another recently published cross-sectional study, based on a validated food frequency questionnaire, reported on the glycemic load and index and the BMI of 8,195 adults aged 35-74 years. In this study, Mendez et al. (76) demonstrated that a high glycemic load was associated with reduced BMI. Fruits, vegetables and legumes related positively to the glycemic load. These findings confirmed the results of a previous Danish study by Lau et al. (77) and a Japanese study by Murakami et al. (78), although both also found a positive association between glycemic index and BMI. It should be mentioned that the study by Mendez et al. (76), which lacked a follow-up, was a cross-sectional study in which cause and effect were difficult to identify. Moreover, it must be pointed out that the Japanese study comprised women in a very narrow age range (18-20 years), whereas the Danish study focused on carbohydrate intake in relation to insulin resistance and not especially to components of the Mediterranean diet.

Longitudinal studies

Analysis of the EPIC study's Spanish cohort (17,238 women and 10,589 men) over a follow-up period of 3.3 years revealed that a high adherence to the Mediterranean diet was linked to a significantly lower risk for obesity (79). In another study, a 28-month follow-up of the SUN cohort comprising 6,319 participants found a relatively smaller weight increment in individuals with a relatively higher adherence to the Mediterranean diet, although these results did not remain statistically significant after multivariate adjustment. After a follow-up of 1.9-12.5 years (mean 6.5), a significant inverse relationship between the intake of fruit and vegetables and weight change was observed in the European prospective EPIC cohort study including 89,432 men and women from 5 countries (Denmark, Italy, Germany, the Netherlands and the U.K.). The weight change was −14 g/year (95% CI: −19 to −9 g/year) per 100-g intake of fruit and vegetables, which suggests that these components of the Mediterranean diet contribute to a reduced risk for weight gain (80). In the same cohort, the influence of energy-dense food was investigated as well. The researchers could not establish a relationship between this type of food and weight change, but the annual waist circumference change was 0.09 cm (95% CI: 0.01-0.18) per 1 kcal/day. Nonobese participants with a baseline BMI < 25 kg/m^2 were more prone to change in waist circumference (0.17 cm/year; 95% CI: 0.09-0.25). The research group concluded that these findings suggest that lower-energy-dense diets do not prevent weight gain but have a potential beneficial effect on the prevention of abdominal obesity as measured by waist circumference (81). Another analysis of the data revealed that the dietary glycemic index and glycemic load did not affect weight change. However, the glycemic index, but not the glycemic load, was significantly associated with

waist circumference: with every 10-unit increase in the glycemic index, the waist circumference increased by 0.19 cm/year (95% CI: 0.11-0.27) (82). The authors take the view that further studies are needed to confirm the above-mentioned small effects.

These observations on high-density/energy food are interesting, as the Mediterranean diet is characterized by a relatively high content of water and fibers from vegetal food, which adds to the feeling of satiety. This effect diminishes the need for further energy intake (83) and, together with diminished food portion size, can be useful for health-related weight management (84).

Interventional studies

Randomized, controlled, prospective interventional studies looking for a relationship between the Mediterranean diet and weight loss in obese people and/or reduction of risk for obesity are scarce. In their review published in 2008, Buckland et al. (71) mention that only four studies conducted in overweight/obese participants were available. The general outcome of this research was that the Mediterranean diet is effective for losing weight. We identified a few more recent longitudinal interventional studies carried out in obese patients. Among these is a weight loss study by Shai et al. (85). These authors published the results of a 2-year trial in which 322 moderately obese people (BMI 31; 86% male) were randomly assigned to 1 of 3 diets: a low-fat and restricted-calorie diet, a Mediterranean and restricted-calorie diet, or a low-carbohydrate and non-restricted-calorie diet. After 1 year, the mean weight loss was 2.9, 4.4 and 4.7 kg, respectively. At 2 years, 272 participants completed the interventional study and the mean weight loss was 3.3, 4.6 and 5.5 kg, respectively. In addition, the low-carbohydrate diet had the most favorable effect on lipids, whereas the Mediterranean diet had the most favorable effect on glycemic control, as evidenced by fasting plasma glucose and insulin levels among 36 participants with diabetes.

Andreoli et al. (86) studied a group of 47 obese women (aged 39.7 ± 13.2 years; BMI 30.7 ± 6.0 kg/m^2) at baseline, 2 and 4 months. During the trial period, these subjects followed an exercise program on body mass and a moderately hypoenergetic Mediterranean diet. At 2 and 4 months, body weight and BMI decreased significantly ($P < 0.001$), and cardiovascular risk factors including LDL cholesterol and HDL cholesterol improved significantly ($P < 0.001$ and $P < 0.002$, respectively) at 4 months. This combination of exercise and a healthy diet was also effective in a study performed by Caudwell et al. (87) on a group of 58 obese men and women (BMI 31.8 ± 4.5 kg/m^2). After 12 weeks, the researchers found a mean reduction in body weight of 3.3 kg ($P < 0.01$), although large individual variability varying from –14.7 kg to +2.7 kg was observed. This was attributed to differences in energy intake over the intervention period. This research group did not report on possible improvement of cardiovascular risk factors, but beneficial effects in subjects with abdominal obesity were demonstrated in a trial conducted by Rallidis et al. (88). They recruited 90 participants without cardiovascular disease or type 2 diabetes, randomly assigned to the intervention or the control group. Only the subjects in the intervention cohort followed a relevant daily and weekly food plan under close supervision by a dietician. In this group, the provision of basic food led to increased intake of MUFAs, dietary fiber, vitamin C and controlled use of alcohol. As a result of this setup, an increased flow-mediated dilatation (2.05%; 95% CI: 0.97-3.13%) and a decreased diastolic blood pressure (–6.44 mmHg; 95% CI: –8.57 to –4.31) was measured only in the intervention group, indicating that close adherence achieved by close dietetic supervision improves endothelial function in subjects with abdominal obesity. This study shows similarity to an investigation by Corbalan et al. (89), who conducted a trial in 1,406 obese men and women (BMI 31 ± 5 kg; aged 20-65 years) who were submitted to a weight reduction program for 34 weeks. The average weight loss in participants who were able to adhere to the Mediterranean diet pattern over the full intervention period amounted to 7.7 kg. The attrition rate was 4-9%, which was considered low due to dietary/behavioral supervision and the attendance of group therapy.

DISCUSSION AND COMMENTS

The proper way to test the hypothetical efficacy of an intervention is a prospective, randomized study, if possible carried out in a double-blind manner. In this respect, various (obviously unblinded) studies have shown important weight loss in obese participants adhering strictly to a Mediterranean-type diet, already after a few months (71). Indeed, the favorable effect of this diet was recently confirmed in a study conducted over a remarkably long period of 2 years by Shai et al. (85).

Various properties of the Mediterranean diet may explain why it may promote weight loss and/or protect against obesity. Firstly, this diet has a low energy density and represents a low glycemic load because of its relatively high water content. Indeed, high-energy, high-density food is related to weight gain (90-92). Secondly, the high fiber content of vegetal food gives rise to considerable satiation and satiety with smaller portions. Thirdly, the fat composition of the Mediterranean diet is high in ω-3 and MUFAs from vegetal food, fish and olive oil (93). Well known for their antioxidant and anti-inflammatory actions, these components also enhance the protection against obesity and serious diseases such as cancer, cardiovascular disease and type 2 diabetes. Of note is that MUFAs increase fat oxidation and after-meal thermogenesis.

Apart from these aspects, it has also been shown that the Mediterranean diet contributes to a feeling of mental and physical well-being (94, 95). This may increase the daily energy expenditure and encourage preferred physical exercise (96, 97). Indeed, the triangle between nutrition, obesity and physical activity is part of a public health strategy to fight the obesity epidemic exemplified by introducing changes in dietary belief and behavior (school food) and improving physical activity environments for adults of all age groups (98, 99). Against this background, sociodemographic characteristics need to be taken into special account, as the Mediterranean diet is more expensive to follow than a Western dietary pattern (100).

Due to the Mediterranean diet's beneficial health effects, it has been the subject of studies in the field of nutrigenetics and nutrigenomics. As explained by Mutch et al. (101) these scientific disciplines attempt to understand the relationship between diet and health. Whereas nutrigenomics will determine the optimal diet from a series of nutritional alternatives, nutrigenetics may eventually help clinicians to find the optimal individualized diet to help to combat disease. It goes without saying that both fields are closely related. In more biological terms, nutrigenomics starts from the fact that nutrients may

change gene expression and thus the nature of proteins and metabolites in the body. This field may find ways to understand how nutrition influences metabolic pathways and eventually help to modify and prevent diseases for which a genetic predisposition exists (102). At this individual genetic level, polymorphisms of common genes and metabolic changes are the basis of gene–diet interactions. The well-known interindividual differences in response to various nutrients and diets are thought to originate from these interactions. In this respect, various studies have demonstrated that dietary intervention can exhibit interactions with single nucleotide polymorphisms in coding genes involved in lipolytic and adipogenic pathways in adipocytes from obese women (103 and references therein). In this way, genome science may well pave the way to identify nutritional factors that act as agonists or antagonists useful for the management of obesity, in which abnormal lipid metabolism plays a role (104). These research efforts can hopefully lead to tailored diets and help to halt the worldwide spread of obesity and comorbidities.

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DISCLOSURES

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REFERENCES

1. Kelly, T., Yang, W., Chen, C.S., Reynolds, K., He, J. *Global burden of obesity in 2005 and projections to 2030.* Int J Obes (Lond) 2008, 32(9): 1431-7.
2. Jackson-Leach, R., Lobstein, T. *Estimated burden of paediatric obesity and co-morbidities in Europe. Part 1. The increase in the prevalence of child obesity in Europe is itself increasing.* Int J Pediatr Obes 2006, 1(1): 26-32.
3. Kosti, R.I., Panagiotakos, D.B. *The epidemic of obesity in children and adolescents in the world.* Cent Eur J Public Health 2006, 14(4): 151-9.
4. Levine, J.A. *Obesity in China: Causes and solutions*. Chin Med J (Engl) 2008, 121(11): 1043-5.
5. Sarrafzadegan, N., Kelishadi, R., Dana, Siadat Z. et al. *Obesity and cardiometabolic risk factors in a representative population of Iranian adolescents and adults in comparison to a Western population: The Isfahan Healthy Heart Programme.* Public Health Nutr 2009, 13(3): 314-23.
6. Guh, D.P., Zhang, W., Bansback, N., Amarsi, Z., Birmingham, C.L., Anis, A.H. *The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis.* BMC Public Health 2009, 9: 88.
7. Wang, Y., Beydoun, M.A., Liang, L., Caballero, B., Kumanyika, S.K. *Will all Americans become overweight or obese? Estimating the progression and cost of the US obesity epidemic.* Obesity (Silver Spring) 2008, 16(10): 2323-30.
8. Müller-Riemenschneider, F., Reinhold, T., Berghöfer, A., Willich, S.N. *Health-economic burden of obesity in Europe.* Eur J Epidemiol 2008, 23(8): 499-509.
9. Ello-Martin, J.A., Ledikwe, J.H., Rolls, B.J. *The influence of food portion size and energy density on energy intake: Implications for weight management.* Am J Clin Nutr 2005, 82(Suppl. 1): 236S-41S.
10. Cohen, D., Farley, T.A. *Eating as an automatic behavior.* Prev Chronic Dis 2008, 5(1): A23.
11. Bes-Rastrollo, M., Sanchez-Villegas, A., Basterra-Gortari, F.J., Nunez-Cordoba, J.M., Toledo, E., Serrano-Martinez, M. *Prospective study of self-reported usual snacking and weight gain in a Mediterranean cohort: The SUN project.* Clin Nutr 2009, Epub ahead of print.
12. Schröder, H. *Protective mechanisms of the Mediterranean diet in obesity and type 2 diabetes.* J Nutr Biochem 2007, 18(3): 149-60.
13. Keys, A., Menotti, A., Karvonen, M.J. et al. *The diet and 15-year death rate in the seven countries study.* Am J Epidemiol 1986, 124(6): 903-15.
14. Sofi, F., Cesari, F., Abbate, R., Gensini, G.F., Casini, A. *Adherence to Mediterranean diet and health status: Meta-analysis.* BMJ 2008, 337: a1344.
15. Bessesen, D.H., Vensor, S.H., Jackman, M.R. *Trafficking of dietary oleic, linolenic, and stearic acids in fasted or fed lean rats.* Am J Physiol Endocrinol Metab 2000, 278(6): E1124-32.
16. Piers, L.S., Walker, K.Z., Stoney, R.M., Soares, M.J., O'Dea, K. *The influence of the type of dietary fat on postprandial fat oxidation rates: Monounsaturated (olive oil) vs saturated fat (cream).* Int J Obes Relat Metab Disord 2002, 26(6): 814-21.
17. Bergouignan, A., Schoeller, D.A., Normand, S. et al. *Effect of physical inactivity on the oxidation of saturated and monounsaturated dietary fatty acids: Results of a randomized trial.* PLoS Clin Trials 2006, 1(5): e27.
18. Bergouignan, A., Trudel, G., Simon, C. et al. *Physical inactivity differentially alters dietary oleate and palmitate trafficking.* Diabetes 2009, 58(2): 367-76.
19. Moussavi, N., Gavino, V., Receveur, O. *Is obesity related to the type of dietary fatty acids? An ecological study.* Public Health Nutr 2008, 11(11): 1149-55.
20. Schröder, H., Marrugat, J., Vila, J., Covas, M.I., Elosua, R. *Adherence to the traditional Mediterranean diet is inversely associated with body mass index and obesity in a Spanish population.* J Nutr 2004, 134(12): 3355-61.
21. Panagiotakos, D.B., Chrysohoou, C., Pitsavos, C., Stefanadis, C. *Association between the prevalence of obesity and adherence to the Mediterranean diet: The ATTICA study.* Nutrition 2006, 22(5): 449-56.
22. Vioque, J., Weinbrenner, T., Castelló, A., Asensio, L., Garcia de la Hera, M. *Intake of fruits and vegetables in relation to 10-year weight gain among Spanish adults.* Obesity (Silver Spring) 2008, 16(3): 664-70.
23. Sánchez-Villegas, A., Bes-Rastrollo, M., Martínez-González, M.A., Serra-Majem, L. *Adherence to a Mediterranean dietary pattern and weight gain in a follow-up study: The SUN cohort.* Int J Obes (Lond) 2006, 30(2): 350-8.
24. Drichoutis, A.C., Lazaridis, P., Nayga, R.M. Jr. *Can Mediterranean diet really influence obesity? Evidence from propensity score matching.* Eur J Health Econ 2009, 10(4): 371-88.
25. Clarke, S.D., Gasperikova, D., Nelson, C., Lapillonne, A., Heird, W.C. *Fatty acid regulation of gene expression: A genomic explanation for the benefits of the Mediterranean diet.* Ann N Y Acad Sci 2002, 967: 283-98.
26. Worgall, T.S., Sturley, S.L., Seo, T., Osborne, T.F., Deckelbaum, R.J. *Polyunsaturated fatty acids decrease expression of promoters with sterol regulatory elements by decreasing levels of mature sterol regulatory element-binding protein.* J Biol Chem 1998, 273(40): 25537-40.
27. Schadinger, S.E., Bucher, N.L., Schreiber, B.M., Farmer, S.R. *PPARgamma2 regulates lipogenesis and lipid accumulation in steatotic hepatocytes.* Am J Physiol Endocrinol Metab 2005, 288(6): E1195-205.
28. Teran-Garcia, M., Adamson, A.W., Yu, G. et al. *Polyunsaturated fatty acid suppression of fatty acid synthase (FASN): Evidence for dietary modulation of NF-Y binding to the Fasn promoter by SREBP-1c.* Biochem J 2007, 402(3): 591-600.
29. Damiano, F., Gnoni, G.V., Siculella, L. *Functional analysis of rat liver citrate carrier promoter: Differential responsiveness to polyunsaturated fatty acids.* Biochem J 2009, 417(2): 561-71.
30. Flachs, P., Horakova, O., Brauner, P. et al. *Polyunsaturated fatty acids of marine origin upregulate mitochondrial biogenesis and induce beta-oxidation in white fat.* Diabetologia 2005, 48(11): 2365-75.

31. van Schothorst, E.M., Flachs, P., Franssen-van Hal, N.L. et al. *Induction of lipid oxidation by polyunsaturated fatty acids of marine origin in small intestine of mice fed a high-fat diet.* BMC Genomics 2009, 10: 110.
32. González-Périz, A., Horrillo, R., Ferré, N. et al. *Obesity-induced insulin resistance and hepatic steatosis are alleviated by omega-3 fatty acids: A role for resolvins and protectins.* FASEB J 2009, 23(6): 1946-57.
33. Kopecky, J., Rossmeis, I.M., Flachs, P. et al. *n-3 PUFA: Bioavailability and modulation of adipose tissue function.* Proc Nutr Soc 2009, 68(4): 361-9.
34. Bergouignan, A., Momken, I., Schoeller, D.A., Simon, C., Blanc, S. *Metabolic fate of saturated and monounsaturated dietary fats: The Mediterranean diet revisited from epidemiological evidence to cellular mechanisms.* Prog Lipid Res 2009, 48(3-4): 128-47.
35. DeLany, J.P., Windhauser, M.M., Champagne, C.M., Bray, G.A. *Differential oxidation of individual dietary fatty acids in humans.* Am J Clin Nutr 2000, 72(4): 905-11.
36. Leyton, J., Drury, P.J., Crawford, M.A. *Differential oxidation of saturated and unsaturated fatty acids in vivo in the rat.* Br J Nutr 1987, 57(3): 383-93.
37. Storlien, L.H., Hulbert, A.J., Else, P.L. *Polyunsaturated fatty acids, membrane function and metabolic diseases such as diabetes and obesity.* Curr Opin Clin Nutr Metab Care 1998, 1(6): 559-63.
38. Takeuchi, H., Matsuo, T., Tokuyama, K., Shimomura, Y., Suzuki, M. *Diet-induced thermogenesis is lower in rats fed a lard diet than in those fed a high oleic acid safflower oil diet, a safflower oil diet or a linseed oil diet.* J Nutr 1995, 125(4): 920-5.
39. Raclot, T. *Selective mobilization of fatty acids from adipose tissue triacylglycerols.* Prog Lipid Res 2003, 42(4): 257-88.
40. Benoit, S.C., Kemp, C.J., Elias, C.F. et al. *Palmitic acid mediates hypothalamic insulin resistance by altering PKC-theta subcellular localization in rodents.* J Clin Invest 2009, 119(9): 2577-89.
41. Tierney, A.C., Roche, H.M. *The potential role of olive oil-derived MUFA in insulin sensitivity.* Mol Nutr Food Res 2007, 51(10): 1235-48.
42. Pickersgill, L., Litherland, G.J., Greenberg, A.S., Walker, M., Yeaman, S.J. *Key role for ceramides in mediating insulin resistance in human muscle cells.* J Biol Chem 2007, 282(17): 12583-9.
43. Gao, D., Griffiths, H.R., Bailey, C.J. *Oleate protects against palmitate-induced insulin resistance in L6 myotubes.* Br J Nutr 2009, 102(11): 1557-63.
44. Coll, T., Eyre, E., Rodríguez-Calvo, R. et al. *Oleate reverses palmitate-induced insulin resistance and inflammation in skeletal muscle cells.* J Biol Chem 2008, 283(17): 11107-16.
45. Dhayal, S., Welters, H.J., Morgan, N.G. *Structural requirements for the cytoprotective actions of mono-unsaturated fatty acids in the pancreatic beta-cell line, BRIN-BD11.* Br J Pharmacol 2008, 153(8): 1718-27.
46. Ahima, R.S. *Central actions of adipocyte hormones.* Trends Endocrinol Metab 2005, 16(7): 307-13.
47. Cancello, R., Clément, K. *Is obesity an inflammatory illness? Role of low-grade inflammation and macrophage infiltration in human white adipose tissue.* BJOG 2006, 113(10): 1141-7.
48. Weisberg, S.P., McCann, D., Desai, M., Rosenbaum, M., Leibel, R.L., Ferrante, A.W. Jr. *Obesity is associated with macrophage accumulation in adipose tissue.* J Clin Invest 2003, 112(12): 1796-808.
49. Nieto-Vazquez, I., Fernández-Veledo, S., Krämer, D.K., Vila-Bedmar, R., Garcia-Guerra, L., Lorenzo, M. *Insulin resistance associated to obesity: The link TNF-alpha.* Arch Physiol Biochem 2008, 114(3): 183-94.
50. Ridker, P.M. *High-sensitivity C-reactive protein, inflammation, and cardiovascular risk: From concept to clinical practice to clinical benefit.* Am Heart J 2004, 148(Suppl. 1): S19-26.
51. Cancello, R., Henegar, C., Viguerie, N. et al. *Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss.* Diabetes 2005, 54(8): 2277-86.
52. Bulló, M., Casas-Agustench, P., Amigó-Correig, P., Aranceta, J., Salas-Salvadó, J. *Inflammation, obesity and comorbidities: The role of diet.* Public Health Nutr 2007, 10(10A): 1164-72.
53. Stuart Wood, S., de Heredia, F.P., Wang, B., Trayhurn, P. *Cellular hypoxia and adipose tissue dysfunction in obesity.* Proc Nutr Soc 2009, 68(4): 370-7.
54. Soares, M.J., Cummings, S.J., Mamo, J.C., Kenrick, M., Piers, L.S. *The acute effects of olive oil v. cream on postprandial thermogenesis and substrate oxidation in postmenopausal women.* Br J Nutr 2004, 91(2): 245-52.
55. Kien, C.L., Bunn, J.Y., Ugrasbul, F. *Increasing dietary palmitic acid decreases fat oxidation and daily energy expenditure.* Am J Clin Nutr 2005, 82(2): 320-6.
56. Kien, C.L., Bunn, J.Y. *Gender alters the effects of palmitate and oleate on fat oxidation and energy expenditure.* Obesity (Silver Spring) 2008, 16(1): 29-33.
57. Casas-Agustench, P., López-Uriarte, P., Bulló, M., Ros, E., Gómez-Flores, A., Salas-Salvadó, J. *Acute effects of three high-fat meals with different fat saturations on energy expenditure, substrate oxidation and satiety.* Clin Nutr 2009, 28(1): 39-45.
58. Weinbrenner, T., Fitó, M., de la Torre, R. et al. *Olive oils high in phenolic compounds modulate oxidative/antioxidative status in men.* J Nutr 2004, 134(9): 2314-21.
59. Gimeno, E., de la Torre-Carbot, K., Lamuela-Raventós, R.M. *Changes in the phenolic content of low density lipoprotein after olive oil consumption in men. A randomized crossover controlled trial.* Br J Nutr 2007, 98(6): 1243-50.
60. Covas, M.I., Nyyssönen, K., Poulsen, H.E. et al. *The effect of polyphenols in olive oil on heart disease risk factors: A randomized trial.* Ann Intern Med 2006, 145(5): 333-41.
61. Szkudelska, K., Nogowski, L., Szkudelski, T. *Resveratrol, a naturally occurring diphenolic compound, affects lipogenesis, lipolysis and the antilipolytic action of insulin in isolated rat adipocytes.* J Steroid Biochem Mol Biol 2009, 113(1-2): 17-24.
62. Hsu, C.L., Yen, G.C. *Effects of flavonoids and phenolic acids on the inhibition of adipogenesis in 3T3-L1 adipocytes.* J Agric Food Chem 2007, 55(21): 8404-10.
63. Zheng, G., Sayama, K., Okubo, T., Juneja, L.R., Oguni, I. *Anti-obesity effects of three major components of green tea, catechins, caffeine and theanine, in mice.* In Vivo 2004, 18(1): 55-62.
64. Ito, Y., Ichikawa, T., Morohoshi, Y., Nakamura, T., Saegusa, Y., Ishihara, K. *Effect of tea catechins on body fat accumulation in rats fed a normal diet.* Biomed Res 2008, 29(1): 27-32.
65. Zych, M., Folwarczna, J., Trzeciak, H.I. *Natural phenolic acids may increase serum estradiol level in ovariectomized rats.* Acta Biochim Pol 2009, 56(3): 503-7.
66. Yang, J., Kong, X., Martins-Santos, M.E. et al. *Activation of SIRT1 by resveratrol represses transcription of the gene for the cytosolic form of phosphoenolpyruvate carboxykinase (GTP) by deacetylating hepatic nuclear factor 4alpha.* J Biol Chem 2009, 284(40): 27042-53.
67. Zillikens, M.C., van Meurs, J.B., Rivadeneira, F. et al. *SIRT1 genetic variation is related to body mass index and risk of obesity.* Diabetes 2009, 58(12): 2828-34.
68. Pfluger, P.T., Herranz, D., Velasco-Miguel, S., Serrano, M., Tschöp, M.H. *Sirt1 protects against high-fat diet-induced metabolic damage.* Proc Natl Acad Sci U S A 2008, 105(28): 9793-8.

69. Bujanda, L., Hijona, E., Larzabal, M. et al. *Resveratrol inhibits nonalcoholic fatty liver disease in rats.* BMC Gastroenterol 2008, 8: 40.
70. van der Spuy, W.J., Pretorius, E. *Is the use of resveratrol in the treatment and prevention of obesity premature?* Nutr Res Rev 2009, 22(2): 111-7.
71. Buckland, G., Bach, A., Serra-Majem, L. *Obesity and the Mediterranean diet: A systematic review of observational and intervention studies.* Obes Rev 2008, 9(6): 582-93.
72. Shubair, M.M., McColl, R.S., Hanning, R.M. *Mediterranean dietary components and body mass index in adults: The peel nutrition and heart health survey.* Chronic Dis Can 2005 Spring-Summer, 26(2-3): 43-51.
73. Panagiotakos, D.B., Polystipioti, A., Papairakleous, N., Polychronopoulos, E. *Long-term adoption of a Mediterranean diet is associated with a better health status in elderly people; a cross-sectional survey in Cyprus.* Asia Pac J Clin Nutr 2007, 16(2): 331-7.
74. Sánchez-Taínta, A., Estruch, R., Bulló, M. et al. *Adherence to a Mediterranean-type diet and reduced prevalence of clustered cardiovascular risk factors in a cohort of 3,204 high-risk patients.* Eur J Cardiovasc Prev Rehabil 2008, 15(5): 589-93.
75. Romaguera, D., Norat, T., Mouw, T. et al. *Adherence to the Mediterranean diet is associated with lower abdominal adiposity in European men and women.* J Nutr 2009, 139(9): 1728-37.
76. Mendez, M.A., Covas, M.I., Marrugat, J., Vila, J., Schröder, H. *Glycemic load, glycemic index, and body mass index in Spanish adults.* Am J Clin Nutr 2009, 89(1): 316-22.
77. Lau, C., Toft, U., Tetens, I., Richelsen, B., Jørgensen, T., Borch-Johnsen, K., Glümer, C. *Association between dietary glycemic index, glycemic load, and body mass index in the Inter99 study: Is underreporting a problem?* Am J Clin Nutr 2006, 84(3): 641-5.
78. Murakami, K., Sasaki, S., Okubo, H., Takahashi, Y., Hosoi, Y., Itabashi, M. *Dietary fiber intake, dietary glycemic index and load, and body mass index: A cross-sectional study of 3931 Japanese women aged 18-20 years.* Eur J Clin Nutr 2007, 61(8): 986-95.
79. Mendez, M.A., Popkin, B.M., Jakszyn, P. et al. *Adherence to a Mediterranean diet is associated with reduced 3-year incidence of obesity.* J Nutr 2006, 136(11): 2934-8.
80. Buijsse, B., Feskens, E.J., Schulze, M.B. et al. *Fruit and vegetable intakes and subsequent changes in body weight in European populations: Results from the project on Diet, Obesity, and Genes (DiOGenes).* Am J Clin Nutr 2009, 90(1): 202-9.
81. Du, H., van der A, D.L., Ginder, V. et al. *Dietary energy density in relation to subsequent changes of weight and waist circumference in European men and women.* PLoS One 2009, 4(4): e5339.
82. Du, H., van der A, D.L., van Bakel, M.M. et al. *Dietary glycaemic index, glycaemic load and subsequent changes of weight and waist circumference in European men and women.* Int J Obes (Lond) 2009, 33(11):1280-8.
83. Rolls, B.J., Roe, L.S., Meengs, J.S. *Reductions in portion size and energy density of foods are additive and lead to sustained decreases in energy intake.* Am J Clin Nutr 2006, 83(1): 11-7.
84. Ello-Martin, J.A., Ledikwe, J.H., Rolls, B.J. *The influence of food portion size and energy density on energy intake: Implications for weight management.* Am J Clin Nutr 2005, 82(Suppl. 1): 236S-41S.
85. Shai, I., Schwarzfuchs, D., Henkin, Y. et al. *Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet.* N Engl J Med 2008, 359(3): 229-41.
86. Andreoli, A., Lauro, S., Di Daniele, N., Sorge, R., Celi, M., Volpe, S.L. *Effect of a moderately hypoenergetic Mediterranean diet and exercise program on body cell mass and cardiovascular risk factors in obese women.* Eur J Clin Nutr 2008, 62(7): 892-7.
87. King, N., Hopkins, M., Caudwell, P., Stubbs, J., Blundell, J. *Beneficial effects of exercise: Shifting the focus from body weight to other markers of health.* Br J Sports Med 2009, 43(12): 924-7.
88. Rallidis, L.S., Lekakis, J., Kolomvotsou, A. et al. *Close adherence to a Mediterranean diet improves endothelial function in subjects with abdominal obesity.* Am J Clin Nutr 2009, 90(2): 263-8.
89. Corbalán, M.D., Morales, E.M., Canteras, M., Espallardo, A., Hernández, T., Garaulet, M. *Effectiveness of cognitive-behavioral therapy based on the Mediterranean diet for the treatment of obesity.* Nutrition 2009, 25(7-8): 861-9.
90. Ledikwe, J.H., Rolls, B.J., Smiciklas-Wright, H. et al. *Reductions in dietary energy density are associated with weight loss in overweight and obese participants in the PREMIER trial.* Am J Clin Nutr 2007, 85(5): 1212-21.
91. Bes-Rastrollo, M., van Dam, R.M., Martinez-Gonzalez, M.A., Li, T.Y., Sampson, L.L., Hu, F.B. *Prospective study of dietary energy density and weight gain in women.* Am J Clin Nutr 2008, 88(3): 769-77.
92. Savage, J.S., Marini, M., Birch, L.L. *Dietary energy density predicts women's weight change over 6 y.* Am J Clin Nutr 2008, 88(3): 677-84.
93. Bes-Rastrollo, M., Sánchez-Villegas, A., de la Fuente, C., de Irala, J., Martinez, J.A., Martínez-González, M.A. *Olive oil consumption and weight change: The SUN prospective cohort study.* Lipids 2006, 41(3): 249-56.
94. Muñoz, M.A., Fíto, M., Marrugat, J., Covas, M.I., Schröder, H. REGICOR and HERMES investigators. *Adherence to the Mediterranean diet is associated with better mental and physical health.* Br J Nutr 2009, 101(12): 1821-7.
95. Sánchez-Villegas, A., Delgado-Rodríguez, M., Alonso, A., Schlatter, J., Lahortiga, F., Serra Majem, L., Martínez-González, M.A. *Association of the Mediterranean dietary pattern with the incidence of depression: The Seguimiento Universidad de Navarra/University of Navarra follow-up (SUN) cohort.* Arch Gen Psychiatry 2009, 66(10): 1090-8.
96. Pitsavos, C., Panagiotakos, D.B., Tzima, N., Lentzas, Y., Chrysohoou, C., Das, U.N., Stefanadis, C. *Diet, exercise, and C-reactive protein levels in people with abdominal obesity: The ATTICA epidemiological study.* Angiology 2007, 58(2): 225-33.
97. Lazarou, C., Panagiotakos, D.B., Matalas, A.L. *Physical activity mediates the protective effect of the Mediterranean diet on children's obesity status: The CYKIDS study.* Nutrition 2009, 26(1):61-7.
98. Sallis, J.F., Glanz, K. *Physical activity and food environments: Solutions to the obesity epidemic.* Milbank Q 2009, 87(1): 123-54.
99. Story, M., Nanney, M.S., Schwartz, M.B. *Schools and obesity prevention: Creating school environments and policies to promote healthy eating and physical activity.* Milbank Q 2009, 87(1): 71-100.
100. Lopez, C.N., Martinez-Gonzalez, M.A., Sanchez-Villegas, A., Alonso, A., Pimenta, A.M., Bes-Rastrollo, M. *Costs of Mediterranean and western dietary patterns in a Spanish cohort and their relationship with prospective weight change.* J Epidemiol Community Health 2009, 63(11): 920-7.
101. Mutch, D.M., Wahli, W., Williamson, G. *Nutrigenomics and nutrigenetics: The emerging faces of nutrition.* FASEB J 2005, 19(12): 1602-16.
102. Müller, M., Kersten, S. *Nutrigenomics: Goals and strategies.* Nat Rev Genet 2003, 4(4): 315-22.
103. Lau, F.C., Bagchi, M., Sen, C., Roy, S., Bagchi, D. *Nutrigenomic analysis of diet-gene interactions on functional supplements for weight management.* Curr Genomics 2008, 9(4): 239-51.
104. Takahashi, N., Goto, T., Hirai, S., Uemura, T., Kawada, T. *Genome science of lipid metabolism and obesity.* Forum Nutr 2009, 61: 25-38.