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Plant Oils and Cardiometabolic Risk Factors: The Role of Genetics

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Abstract

More than 25 years have passed since Ancel Keys and others observed that high intake of monounsaturated fatty acids, especially as supplied by plants (eg, olive oil) was associated with lower cardiovascular and overall mortality. About 15 years later, advances in genotyping technologies began to facilitate widespread study of relationships between dietary fats and genetic variants, illuminating the role of genetic variation in modulating human responses to fatty acids. More recently, microarray technologies evaluate the ways in which minor, bioactive compounds in plant oils (including olive, thyme, lemongrass, clove, eucalyptus, and others) alter gene expression to mediate anti-inflammatory and antioxidant effects. Results from a range of diverse technologies and approaches are coalescing to improve understanding of the role of the genome in shaping our responses to plant oils, and to clarify the genetic mechanisms underlying the cardioprotective benefits we derive from a wide range of plant oil constituents.

Keywords

Plant oils; Olive oil; Essential oils; Fatty acids; Single nucleotide polymorphisms; Nutrient–gene interactions; Cardiovascular disease; Gene expression; Obesity; Insulin resistance; Inflammation; Lipids; Cardiometabolic risk factors; Genetics; Phenotypes

Introduction

Recognition of the relationships between plant oils and risk factors for cardiovascular disease (CVD) is longstanding, with many studies focused on fatty acids as the predominant and active compounds in modulating risk. The seminal work of Keys et al. [1] documented differences in mortality, including CVD deaths, that were strongly related to fatty acid intake (eg, SFA [saturated fatty acids] vs MUFA [monounsaturated fatty acids]). That study also reported that olive oil consumption was protective [1]. Recently, growing identification of bioactive compounds supplied in plant oils has expanded the focus from fatty acids to the study of whole oils and their minor compounds. The best characterized oil is olive oil, which in its less processed (extra virgin) form supplies polyphenolic compounds that improve lipid and oxidative stress biomarkers in a dose-dependent manner [2]. However, understanding of which oil constituents mediate health benefits for olive or other plant oils remains incomplete, and genetics represents an important avenue through which the relative roles of both fatty acids and minor oil compounds continue to be investigated.

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The current review considers the relationships between plant oils, genetics, and CVD risk from two angles. The first angle, genetic association and interaction studies, focuses on nutritional modulation of genetically based risk, with a goal of developing targeted, genetically informed dietary recommendations. These studies are both observational and intervention based, and several examine the effect of intake of specific oils, including olive and flaxseed. Others focus on fatty acids, either by type (MUFA vs SFA) or by individual fatty acid (oleic vs linoleic). The second angle considers gene expression studies that aim to identify mechanisms and pathways through which plant oils confer health benefits. These studies generally evaluate the components of a single oil or series of oils, using both in vivo and in vitro approaches. Together, both angles improve understanding of the role in genetics in modulating the benefits attributable to plant oils intake, and in identifying the oil constituents that mediate reduced CVD risk through effects related to body weight, inflammation, glucose metabolism, and lipids.

Olive Oil and Cardiometabolic Risk Factors: The Role of Genotype

Body Weight

Several studies have examined relationships between genetic variants and olive oil for the outcome of body weight using data from the PREDIMED (Prevención con Dieta Mediterránea) study, a multicenter, randomized clinical trial aimed at primary cardiovascular prevention in at-risk individuals [3]. The 3-year intervention consisted of two Mediterranean diets, one supplemented with virgin olive oil and the other with nuts (almonds, walnuts, and hazelnuts), compared with a low-fat control diet. Several studies focus on whether these interventions interact with genetic variants to modulate cardiometabolic risk factors.

One PREDIMED-based study investigated body weight changes in the context of adiponectin variants [4]. Adiponectin is a protein hormone that is produced by the adipose and that has been inversely associated with obesity, insulin resistance, and atherosclerosis [5]. In an evaluation of three adiponectin variants (rs822395, rs2241766, rs1501299), no genotypic differences were detected for weight change in the population as a whole. However, higher weight gain was observed in men who were homozygous recessive (TT) for rs1501299. For the same variant, a marginally significant interaction between genotype and diet was detected, indicating that the genetic association may be modulated by dietary factors. In the case of rs1501299, the nut-supplemented Mediterranean diet was protective against the weight gain associated with TT genotype in men. Whether the beneficial effects associated with nuts are attributable to nut oils or to other constituents of the nuts (eg, fiber) is unclear.

In a second PREDIMED-based study using a subset of the overall study ($n=737$), Razquin et al. [6] investigated weight gain in the context of *IL-6*, which encodes the inflammatory cytokine interleukin (IL)-6 [6]. Inflammation is an important component of both obesity and atherosclerosis. This study detected an interaction between diet and *IL-6*-174G/C (rs1800795) genotype, in that homozygous minor allele carriers lost more weight compared with homozygous major and heterozygous subjects only in the diet supplemented with virgin olive oil. The authors note that in spite of the higher total fat content of the olive oil-supplemented diet relative to the low-fat diet, the low-fat diet contained a high proportion of SFA. Differences in SFA content, as opposed to specific olive oil components, may therefore be contributing to the observed genotype-based differences.

Inflammatory Markers

In a third study using PREDIMED data, Corella et al. [7] evaluated two variants, one of which was the same *IL-6* variant explored above (rs1800795), as well as the

COX-2-735G>C variant (rs20417) for the inflammatory molecules IL-6, CRP (C-reactive protein), ICAM-1 (soluble intercellular adhesion molecule 1) and VCAM-1 (vascular adhesion molecule 1) [7]. The *COX*-variant was associated with lower serum IL-6 and ICAM-1. The *IL-6* variant was associated with higher ICAM-1 and higher IL-6 (the latter in men only). Although no statistical interactions were detected between the genetic variants and the interventions, indicating that diet did not modulate the effect of genotype, both forms of the Mediterranean diets (supplemented with nuts or with olive oil) were associated with lower inflammatory biomarkers (IL-6, ICAM-1, VCAM-1) compared with the low-fat diet. In addition, the olive oil-supplemented diet reduced CRP compared with the low-fat diet.

Insulin Resistance

In light of the well-established connections between diabetes and CVD risk, several groups have investigated interactions between olive oil and genetic variants linked to impaired glucose metabolism. In a cross-sectional study based in southern Spain ($n=1,226$), Morcillo et al. [8] examined the role of cooking oil in modulating differences based on *FABP2* Ala54Thr genotype for glucose phenotypes. This variant has been associated with higher insulin and insulin resistance in some, but not all studies [9]. In the current study, the investigators compared olive oil with sunflower oil or a sunflower/olive oil mixture. An interaction between the type of cooking oil and *FABP2* Ala54Thr genotype was detected for the outcome of insulin resistance. Specifically, minor allele carriers exhibited higher insulin resistance only if they also consumed sunflower or a sunflower mixture rather than olive oil. Insulin resistance did not differ by genotype in those consuming olive oil, suggesting that olive oil ameliorated the genetic risk associated with *FABP2* genotype.

Although the study's cross-sectional design introduces limitations, its results are strengthened by the gas chromatographic analysis of the oils consumed in a subset of individuals ($n=538$) and analysis of serum phospholipids fatty acids in these individuals. Linoleic acid content was used to categorize the oils as olive oil (<25% linoleic acid), sunflower oil (>50% linoleic acid), and intermediate oils (>25% but <50% linoleic acid). Expected serum fatty acids of individuals consuming each of the three types of oils were confirmed by analysis, with lower stearic and linoleic acid and higher oleic acid concentration in olive oil consumers compared with sunflower oil consumers. Although supportive of a beneficial effect of olive oil compared with linoleic-based oils, the study cannot differentiate between benefits provided by the fatty acids (eg, oleic vs linoleic) versus other compounds that are specific to olive oil.

Another study [10] conducted in a subset of the same population ($n=538$, aged 18–65 years) evaluated dietary MUFA intake rather than oil type. However, in light of the study location (Malaga in southern Spain), the primary source of MUFA was olive oil. This study evaluated *PPARG* (peroxisome proliferator activated receptor) Pro12Ala, which has been variably associated with metabolic outcomes [11]. In this study, an interaction between MUFA intake and the *PPARG* Pro12Ala variant was detected for insulin resistance, but only in obese individuals. Specifically, obese individuals consuming low intakes of MUFA and carrying the Ala-12 allele exhibited higher insulin resistance. Several limitations should be noted, including a cross-sectional design and a relatively small population that was stratified by obese status, further reducing the size of the groups compared. In addition, both age and gender have been shown to modify the relationships between the *PPARG* Pro12Ala variant, dietary fat type (SFA vs unsaturated), and adiposity traits [12]. The current study includes individuals over a wide age range as well as individuals of both genders, which could confound results.

A third study examining genetic interactions for glucose-related traits investigated relationships between diet and a *SCARB1* variant. The *SCARB1* (scavenger receptor class B type 1 protein) was originally recognized as a high-density lipoprotein receptor, and relationships between *SCARB1* locus and glucose metabolism had not been previously reported. In the current study, investigators used a randomized crossover design to evaluate relationships between three diets and a *SCARB1* exon 1 variant for the outcome of insulin sensitivity [13]. Macronutrient compositions for the three diets were as follows: 1) SFA diet, 38% fat, 20% SFA; 2) MUFA diet, 38% fat, 22% MUFA (80% of which was supplied by virgin olive oil); and 3) CHO (carbohydrate) diet, 30% fat, 55% CHO. In this study, carriers of the minor alleles exhibited greater insulin sensitivity compared with homozygous major subjects only in the high MUFA diet. Interestingly, a tendency for increased insulin sensitivity was observed in the high CHO diet, possibly suggesting that the replacement of SFA provided by both MUFA and CHO diets played a role in the improved insulin responses. Although olive oil was an important dietary component, whether dietary fatty acids or other olive oil components conferred the observed benefits is unclear.

Lipids

Although a growing number of recent studies are focused on olive oil–gene interactions for nonlipid risk factors, one study examined the effect on lipids of adding olive oil to a fat-free food. In a crossover intervention study of mildly hypercholesterolemic children ($n=36$), individuals were randomly assigned to drink skim milk or skim milk augmented with olive oil [14]. Concentrations of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), or apolipoprotein A-1 (APOA1) were compared according to *CETP*Taq 1B (rs708272) genotype. This *CETP* variant has been linked to lipid concentrations in several studies, and with protection against acute coronary syndrome reported for healthy weight individuals with the B2B2 genotype compared with other genotypes [15]. The current study confirmed an association of the B2 allele with higher HDL-C compared with B1 carriers. In addition, although olive oil–supplemented skim milk increased HDL-C and APOA1 protein independently of genotype, the increase in HDL-C was greater in B1 homozygotes compared with B2 carriers. In addition, the decrease in the LDL/HDL ratio was greater in B1 homozygotes. The significance of the study is that the increased MUFA intake supplied by the olive oil–supplemented milk (~9 g/d) ameliorated the genetic risk associated with B1 homozygote genotype. Although responses to full-fat milk were not evaluated, the results imply that substituting olive oil–supplemented milk for whole milk or skim milk would provide the dual benefits of reducing SFA (and potentially LDL-C) while also preserving HDL-C. This study does not rule out the possibility that other high MUFA oils could provide similar benefits.

Other Plant Oils: Role of Genotype

Gene–diet interaction studies for plant oils other than olive oil are limited. Nelson et al. [16] conducted an 8-week intervention with flaxseed oil (supplying 5% of total energy as ALA [alpha linolenic acid]) to individuals ($n=57$ overweight or obese) genotyped for two adiponectin variants (rs2241766 and rs1501299) [16]. Independently of genotype, no changes in body mass index (BMI) or glucose-related outcomes were detected. Plasma adiponectin concentrations decreased with ALA supplementation to a greater extent in rs1501299 minor allele carriers and homozygous major carriers for rs2241766. Whether the changes in adiponectin concentration are clinically significant or whether these results from overweight individuals are generalizable to other groups is unclear.

Relationships between ALA as supplied by flaxseed oil have also been evaluated for plasma lipids and inflammatory markers [17]. An intervention was conducted in dyslipidemic Greek men ($n=50$) who received 8.1 g of ALA daily for 12 weeks, and biomarkers were evaluated

based on apolipoprotein E (*APOE*) genotype. Relationships between *APOE* genotype and LDL-C have been recognized for many years [18], but *APOE* has more recently been associated with inflammation [19]. In the current study, relationships between *APOE* genotype ($\epsilon 2/\epsilon 3$ [$n=7$], $\epsilon 3/\epsilon 3$ [$n=33$], and $\epsilon 3/\epsilon 4$ [$n=10$]) and responses to flaxseed oil were evaluated. In the overall group and also in $\epsilon 3/\epsilon 3$, HDL-C decreased. Inflammatory markers SAA (serum amyloid A), CRP (C-reactive protein), MCSF (macrophage colony stimulating factor), and IL-6 also decreased with flaxseed supplementation in the combined group, and SAA and MCSF decreased in the $\epsilon 3/\epsilon 3$ and $\epsilon 3/\epsilon 4$ groups. In summary, although changes in lipids were not detected, except for a reduction in HDL-C, favorable changes in inflammatory biomarkers were detected in most groups. This study was the first to report differential responses to ALA based on *APOE* genotype. The study authors noted that the ALA intake was greater than that obtainable through dietary sources, and that the small dyslipidemic sample may not have been representative of other groups.

Olive Oil and Cardiometabolic Risk Factors: Role of Gene Expression

Genetic association and interaction studies are valuable from the perspective of informing dietary recommendations but are unable to distinguish which constituents of given oil are conferring benefits. Gene expression studies offer a more mechanistic analysis of how plant oil constituents protect health. Several approaches are commonly used. With in vivo dietary interventions, individuals consume the oil, and gene expression is then evaluated using cells derived from the individuals. In contrast, in vitro approaches expose cells to extracts or specific components derived from the oil to determine which substances alter gene expression. As was observed in genetic association and interaction studies, most gene expression studies for plant oils have investigated olive oil.

Gene expression studies range from those involving many genes to targeted analysis of a few genes or pathways. Khymenets et al. [20] explored the effects of consuming a fixed dose (22 g or 25 mL) of virgin olive oil daily for 3 weeks ($n=10$). Of 23 candidate genes evaluated, 10 were upregulated in peripheral blood mononuclear cells at the end of the intervention compared with baseline. These genes encode the proteins ADAM17 (a membrane-anchored metalloprotease that interacts with HDL), ALDH1A1 (aldehyde dehydrogenase), BIRC1 (an apoptosis regulator that functions in innate immunity), ERCC5 and XRCC5 (both participate in DNA repair), LIAS (mitochondrial protein, involved in lipoic acid synthesis), OGT (encodes DNA repair protein O-linked N-acetylglucosamine transferase), PPARBP (peroxisome proliferator-activator receptor binding protein), TNFSF10 (from the tumor necrosis factor superfamily of cytokines), and USP48 (ubiquitin proteasome system). Although the upregulated genes suggest potentially plausible hypotheses by which olive oil constituents may modulate atherogenic risk, the study has some limitations and should be considered exploratory. Of the small sample, five individuals were smokers. In addition, the diet was uncontrolled, allowing for additional confounders. However, strengths of the study include an olive oil intake that is close to that consumed in a traditional Mediterranean diet, and its advice to participants to exclude consumption of other high-phenolic foods that might confound the results.

A subsequent intervention extended this work to test the hypotheses that polyphenols are the bioactive compounds in olive oil that regulate genes involved in atherosclerosis [21•]. The study consisted of a 3-month Mediterranean diet intervention ($n=90$) that was supplemented by virgin olive oil (which preserves polyphenol content) or with “washed” olive oil, in which polyphenols were removed. Both Mediterranean diets improved plasma lipids, glucose, and CRP compared with the control diet. However, the inflammatory and oxidative stress biomarkers IFN- γ (interferon- γ), F2 α -isoprostanes, and s-P-selectin decreased only in the virgin olive oil group. Interestingly, treatment with virgin olive oil was also

accompanied by downregulation of genes encoding IFN- γ , ADRB2 (adrenergic β 2 receptor), and ARHGAP15 (RhoGTPase activating protein 15), with a tendency for downregulation of IL7R (IL-7 receptor). These genes are involved in lipid metabolism, inflammation, and oxidative stress, supporting the hypothesis that olive oil polyphenols modify gene expression to reduce atherosclerosis-related biomarkers. Although these results are intriguing, particularly because they are based on in vivo methods, they would be greatly strengthened by confirmation in additional human interventions.

While the two studies described above evaluated chronic olive oil intake, others have examined the in vitro effects of particular olive oil constituents on gene expression in human cells. One relatively early study examined the phenolic secoiridoid oleuropein aglycone (OleA) and hydroxytyrosol, a phenol with strong antioxidant properties [22]. Using human umbilical vein endothelial cells, investigators demonstrated that physiologically based concentrations of OleA and hydroxytyrosol inhibited expression of VCAM-1, which recruits inflammatory cells into atherosclerotic lesions [23]. In phenol-exposed cells, reductions of mRNA and protein concentrations of VCAM-1 were correlated, suggesting similar protective mechanisms for both OleA and hydroxytyrosol.

Other groups have looked specifically at inflammatory cells and their products. Monocytes produce metalloproteinases (MMP) that may contribute to atherosclerotic plaque progression and rupture [24]. Using THP cells (a monocyte-like cell line) Dell'Agli et al. [25•] evaluated olive oil phenolic extracts containing the flavenoids apigenin and luteolin and the previously investigated OleA. With in vitro concentrations approximating plasma concentrations based on intake of 30 to 50 g/d of olive oil (20–30 mg of phenols), they determined that phenolic extracts and the specific phenols OleA, apigenin, and luteolin reduced MMP-9 secretion and mRNA. Using the same cell-based models, the researchers also demonstrated that phenolic extract reduction of MMP-9 expression interfered with nuclear factor- κ B (NF- κ B) signaling, supporting a biologically plausible pathway.

Other Plant Oils, Cardiometabolic Protection, and Gene Expression

Although olive oil has been widely explored, gene expression studies using other oils are sparse, with only a single study for most. Oil from wormwood (*Artemisia princeps*), a plant used medicinally and as a flavoring in Korean and Chinese cuisine, provided antiatherosclerotic protection in animals [26]. Chung et al. [27] used an in vitro model to investigate wormwood oil modulation of expression for genes related to cholesterol metabolism [27]. When HepG2 (human liver-derived) cells were incubated with wormwood oils, LDL receptor mRNA and protein were increased, supporting an enhanced capacity for cholesterol uptake and a mechanism for improved lipids. Although expression of HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase expression was unaffected, SREBP-1c (sterol regulatory element binding protein) expression was decreased, with implications for improved triglyceride concentration. The authors note that this oil is a complex mixture of bioactive compounds including 1,8-cinole, trans-caryophyllene, l-limonene, phenol, and camphene, and is cytotoxic at high concentrations. Additional studies are needed to establish its safety and effectiveness in humans.

While some groups focus on a particular oil and its constituents, others examine a few genes in the context of a larger number of plant-derived oils. For example, Hotta et al. [28] had previously demonstrated that *COX-2* expression was regulated by PPAR gamma in macrophages, and that the antioxidant polyphenol resveratrol downregulated *COX-2* through PPAR-dependent mechanisms [29]. They hypothesized that similar mechanisms might underlie *COX-2* regulation by other plant compounds and investigated their hypothesis using U937 cells (from a human leukemic monocyte lymphoma cell line) [30•].

Of a wide range of plant oils including bergamot, castor, clove, cottonseed, croton, eucalyptus, fennel, lavender, lemon, linseed, olive, orange, palm, rose, safflower, sesame, soybean, turpentine, and thyme, those considered “essential oils” (thyme, clove, rose, eucalyptus, fennel, bergamot) suppressed *COX-2* promoter activity, with thyme showing the greatest effects. Although several oils exhibited PPAR-alpha agonist activity, only thyme oil demonstrated both PPAR-alpha and PPAR-gamma activation. Closer examination of thyme oil components revealed that carvacrol, a monoterpene also present in oregano oil, appeared to mediate PPAR downregulation of *COX-2*. While PPAR-gamma does not appear to mediate most of the oil-based suppression of *COX-2*, these findings suggest that many essential oils provide anti-inflammatory effects through regulation of gene expression.

Based on evidence of carvacrol’s activation of PPAR, the same investigators applied similar analytic methods to the essential oil of lemongrass, an herb popular in Southeast Asian foods, and to which anti-inflammatory and analgesic properties have been attributed [31]. In this study, investigators isolated the monoterpene citral, a major constituent of lemongrass oil. They detected activation of PPAR-alpha and PPAR-gamma by lemongrass oil, and further showed that citral acts via PPAR-gamma activation to reduce *COX-2* mRNA, mRNA stability, and *COX-2* protein. Citral exhibited greater PPAR-gamma activation than carvacrol, the compound evaluated in their previous study. The authors note that in vivo studies are needed for confirmation and to establish whether other dietary compounds with known PPAR activity, such as fatty acids, may augment citral’s PPAR activation. Fatty acids and monoterpene phenols found in lemongrass oil might act in concert to provide anti-inflammatory protection.

PPAR are not the only regulators of *COX-2* that appear to be modulated by essential oils. In a study designed to examine anti-inflammatory properties of *Pimpinella* spp, Tabanca et al. [32] evaluated its effects on NF- κ B, a transcriptional regulator of COX-2. Anise seed flavoring is obtained from *Pimpinella anisum* and is cultivated in many regions, including in Europe, Asia, North Africa, and South America. Using human chondrosarcoma cells with extracts from multiple *Pimpinella* spp, 12 oils and 5 of 21 phenylpropanoid compounds tested were demonstrated to downregulate NF- κ B transcription. Again, additional studies are needed to confirm that these in vitro effects can be replicated in an in vivo setting.

Conclusions

Genetics approaches facilitate understanding of which components of plant oils confer health benefits and through which biological pathways. For example, the PREDIMED study, in which unprocessed olive oil or ALA-containing nuts are added to a baseline Mediterranean diet, represents a wealth of data that will be used to investigate how genetic variation shapes the response to diet. Similarly, the comparisons of “washed” (polyphenol-depleted) versus extra virgin olive oils in gene expression studies have been valuable in confirming the role of minor plant components, as are expression data that support modulation of established genetic regulators such as PPAR and targets such as COX-2. Gene expression studies have also suggested mechanisms by which anti-inflammatory and antioxidant oils, supplied in plants ranging from oregano to lemongrass to clove, may reduce cardiometabolic risk.

Although the breadth of data from investigations of genes and plant oils is rapidly expanding, the challenges of translating these data to dietary recommendations are considerable. Studies that shift the focus from well-established, clinically recognized outcomes (eg, lipids) to less clinically quantifiable outcomes (eg, inflammatory and oxidative stress biomarkers) will be more difficult to interpret and apply. Similarly, many recent studies focus on minor plant compounds (eg, oleuropein aglycone, carvacrol, citral)

for which optimal intakes are unknown. Obtaining sufficient quantities of these components to achieve obtain health benefits may require a high level of dietary diversity in which many different plants are consumed as part of an overall healthy diet. Moreover, data on how these newly recognized oil constituents interact with genotype do not yet exist. In spite of these limitations, existing studies reinforce longstanding dietary advice to maintain high intakes of a diverse range of plant-based foods in light of the cardioprotective compounds available only through a wide variety of plant oils.

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suggesting mechanisms underlying anti-inflammatory benefits obtained from a diverse range of plants.

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Table 1

Plant oils and cardiometabolic risk factors: summary of the role of genetics

Gene and/or SNP	Plant oils or oil constituent evaluated	Main findings	Reference
<i>Adiponectin</i> (rs822395, rs2241766, rs1501299)	Olive oil or nuts added to Mediterranean Diet (PREDIMED)	Gene–diet interaction; nut-supplemented diet protective for body weight in rs1501299	Razquin et al. (2010) [4]
<i>IL-6</i> (rs1800795)	Olive oil or nuts added to Mediterranean diet (PREDIMED)	Gene–diet interaction; olive oil-supplemented diet protective for body weight	Razquin et al. (2010) [6]
<i>IL-6</i> (rs1800795) and <i>COX-2</i> (rs20417)	Olive oil or nuts added to Mediterranean diet (PREDIMED)	No gene–diet interaction; both diets lowered plasma IL-6, ICAM-1, VCAM-1	Corella et al. (2010) [7]
<i>FABP2</i> Ala54Thr	Olive oil vs sunflower/sunflower mix	Minor allele associated with insulin resistance only in sunflower/sunflower mix consumers	Morcillo et al. (2007) [8]
<i>PPARG</i> Pro12Ala	Olive oil-supplied MUFA	Gene–diet interaction in obese individuals; low MUFA increased insulin resistance in minor allele carriers	Soriguer et al. (2006) [10]
<i>SCARB1</i> exon 1 (G→A)	Olive oil-supplied MUFA	Gene–diet interaction; minor allele carriers had greater insulin sensitivity only with high MUFA supplied by olive oil	Perez-Martinez et al. (2005) [13]
<i>CETP</i> Taq1B (rs708272)	Olive oil added to skim milk	Improvements in lipids were greater in B1 homozygous subjects who consumed olive oil-supplemented milk	Estevez-Gonzalez et al. (2010) [14]
<i>APOE</i> ^ε 2/ε3/ε4	Flaxseed oil	Changes in HDL-C and inflammatory biomarkers differed by genotype in response to flaxseed oil	Paschos et al. (2005) [17]
<i>ADAM17</i> , <i>ALDH1A1</i> , <i>BIRC1</i> , <i>ERCC5</i> , <i>XRCC</i> , <i>LIAS</i> , <i>OGT</i> , <i>PPARBP</i> , <i>TNFSF10</i> , <i>USP48</i>	Virgin olive oil	Upregulated expression of 10 of 23 genes evaluated	Khymenets et al. (2009) [20]
<i>IFN-γ</i> , <i>ADRB2</i> , <i>ARHGAP15</i>	Virgin olive oil vs polyphenol-depleted olive oil	Downregulation of genes involved in lipid metabolism, inflammation, and oxidative stress only with virgin olive oil	Konstantinidou et al. (2010) [21•]
<i>VCAM-1</i>	Phenols oleuropein, aglycone, and hydrotyrosol	Phenols reduced mRNA and protein	Carluccio et al. (2003) [22]
<i>MMP-9</i>	Phenols oleuropein, aglycone, apigenin, and luteolin	Phenols reduced MMP-9 mRNA and secretion through interference with NF-κβ	Dell'Agli et al. (2010) [25•]
<i>SREBP-1c</i> , <i>LDLR</i>	Wormwood oil	LDL receptor mRNA and protein increased, SREBP-1c expression decreased	Chung et al. (2007) [26]
<i>COX-2</i> , <i>PPARG</i>	Essential oils (thyme, clove, rose, eucalyptus, fennel, bergamot)	Essential oils reduced COX-2 promoter activity; several oils acted via PPAR-α, and thyme oil component carvacrol was mediated via PPAR-γ	Hotta et al. (2010) [30•]
<i>COX-2</i> , <i>PPARG</i> , <i>PPARα</i>	Lemongrass oil	Oil component citral reduced COX-2 mRNA, mRNA stability, and protein via PPAR activation	Katsukawa et al. (2010) [31]
<i>NF-κβ</i>	Anise seed oil (<i>Pimpinella</i> spp)	<i>Pimpinella</i> oils and phenylpropanoid compounds downregulate NF-κβ transcription	Tabanca et al. (2007) [32]