Effect of the Mediterranean diet on lipid and lipoprotein profile: is it influenced by the family history of dyslipidemia?

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Abstract

Background: A large inter-individual variability in the lipid-lipoprotein response to Mediterranean diet (MedDiet) has been highlighted in clinical studies. This variability may be attributed to multiple factors, including inherited genetic susceptibilities to dyslipidemia. The aim of the present study was to examine whether family history of dyslipidemia influences the lipid-lipoprotein response to the MedDiet. Design and Methods: We recruited 36 individuals with a positive family history of dyslipidemia (i.e. having at least one first-degree relative with a diagnosis of dyslipidemia) and 28 individuals with a negative family history of dyslipidemia, aged between 24-53 years, who had slightly elevated LDL-C concentrations (3.4-4.9 mmol/l) or total cholesterol to HDL-C ratio ≥5.0. Variables related to the lipid-lipoprotein profile were measured before and after a 4-week isocaloric MedDiet during which all foods and drinks were provided to participants. Results: A group by time interaction was noted for plasma total cholesterol concentrations (P=0.03), subjects with a negative family history of dyslipidemia having greater decreases than those with a positive family history of dyslipidemia (respectively -11.3% vs. -5.1%). Decreases in LDL-C, HDL-C, total cholesterol to HDL-C ratio, LDL-C to HDL-C ratio, apolipoprotein (apo) B, apo A-1, apo A-2 and apo B to apo A-1 ratio were also noted, with no difference between groups (P for group by time interaction≥0.11). No change was observed for triglyceride (TG) concentrations and TG to HDL-C ratio. Conclusions: Results highlight that inherited susceptibilities to dyslipidemia may explain at least in part the heterogeneity in the cholesterol-lowering effects of the MedDiet. (Abstract wordcount: 249 words)

Keywords: Family history; lipid-lipoprotein profile; Mediterranean diet; Cholesterol; Sex

Introduction

The adoption of healthy dietary habits plays a key role in primary prevention of cardiovascular diseases (CVD), still one of the leading causes of disability and mortality worldwide [1]. In this regard, cardiovascular benefits of the traditional Mediterranean diet (MedDiet) have been well-explored in the past, and there are now strong evidence supporting the usefulness of this dietary food pattern to reduce the incidence of major cardiovascular events in both men and women [2, 3]. This cardioprotective role of the MedDiet is, at least in part, explained by its beneficial impact on the plasma lipid and lipoprotein profile. In fact, adherence to the MedDiet has been associated with lipid-lipoprotein improvements, such as reduced levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein (apo) B and triglycerides (TG) and a decreased total cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio [4-7].

Even if the MedDiet is now recognized as having lipid-lowering effects, a large inter-individual variability in the plasma lipid-lipoprotein response has been highlighted in clinical studies [8]. This heterogeneity in response to diet has also been noted by our research group. In fact, mildly hypercholesterolemic subjects exposed to a 4-week fully-controlled MedDiet experienced changes in total cholesterol ranging from -34% to +15% and changes in LDL-C ranging from -46% to +23% [6]. This phenomenon emphasizes the clinical need to get a better understanding of the determinants of this inter-individual variability which, as a consequence, will help health care providers to better identify

individuals who may be more prone to reduce their risk of CVD by adopting this healthy food pattern.

The individual's genetic background remains one of the leading predictors suggested to explain the inter-individual variability in response to diet. Compared to genetic testing, self-reported family history of dyslipidemia is a simple and inexpensive approach which is frequently used for assessing inherited susceptibilities to dyslipidemia in clinical settings [9-12]. In addition to environmental factors, individuals with a family history of dyslipidemia share genetic susceptibilities to dyslipidemia [10], which could impede the lipid-lowering effect of the diet in these individuals. However this hypothesis has never been tested before. The objective of the present study was therefore to examine whether family history of dyslipidemia influences the lipid-lipoprotein profile response to the MedDiet in a sample characterized by a slightly deteriorated lipid-lipoprotein profile. Because higher baseline lipid-lipoprotein values [7, 13] and the fact that being a male [14] have been previously shown to potentially enhance the lipid-lipoprotein response to dietary modifications, we also explored whether the family history of dyslipidemia influences the impact of these clinical predictors on the lipid-lipoprotein response to the MedDiet.

Methods

Subjects

Subjects of the present study were men and premenopausal women, aged between 24-53 years, recruited from the Quebec City metropolitan area (Canada). To participate in the trial, subjects had to be characterized by a slightly elevated LDL-C concentrations (between 3.4 and 4.9 mmol/l) or total cholesterol to HDL-C ratio ≥5.0 [15]. Moreover, they had to have at least one of the four following CVD risk factors: waist circumference > 94 cm in men and > 80 cm in women [16]; TG > 1.7 mmol/l; fasting glycemia between 6.1 and 6.9 mmol/l and/or blood pressure levels ≥ 130 / 85 mm Hg. Accordingly, participants included in the present study are those in whom the adoption of healthy dietary habits is strongly recommended in primary prevention of CVD in order to avoid the need of lipid-lowering medication later in life. The exclusion criteria were as follows: significant body weight change (>2.5 kg) in the three months before the study, cardiovascular events or a diagnosis of type 1 or 2 diabetes in the past, endocrine disorders, use of medication that could affect dependent variables under study (namely lipid-lowering, hypoglycemic and insulin sensitizers medication), smoking, pregnancy and use of systemic hormonal contraceptives. The present study was conducted according to the guidelines laid down in the Helsinki Declaration of 1964. All subjects signed an informed consent form before their inclusion in the study, which has been approved by the Laval University Research Ethics Committee (#2007-180; October 4, 2007). The present study was initially designed to directly

document sex differences in the impact of a MedDiet on lipid-lipoprotein concentrations [6]. Therefore, results presented here are part of secondary analyses of a previously published study.

Study design

The study design has been previously described in detail [6]. Briefly, the study protocol consisted of a 4-week run-in period, immediately followed by a 4-week fully-controlled MedDiet phase. The 4-week run-in period preceded the feeding phase in order to minimize the intra- and inter-variability in dietary intakes before the consumption of the MedDiet. During this run-in period, subjects received personalized recommendations by a registered dietitian in order to follow the health recommendations of the Canada's Food Guide [17].

During the 4-week fully-controlled feeding phase, subjects were assigned to an experimental diet formulated to be concordant with the characteristics of the traditional MedDiet [18]. A 7-day cyclic menu was used and repeated for 4 weeks. The percentages of energy derived from lipids, carbohydrates, proteins and alcohol were respectively of 32% (6.7% saturated fatty acids (SFA), 18.1% monounsaturated fatty acids (MUFA) and 4.7% polyunsaturated fatty acids (PUFA)), 46%, 17% and 5%. More details about the composition of the MedDiet have been previously reported [6]. Vitamin and mineral supplements as well as natural health products were forbidden. Subjects were instructed to consume only the provided foods and drinks, which corresponded to 100% of their estimated energy needs. Energy needs were established by averaging energy requirements

estimated by a validated FFQ [19] administered at the beginning of the run-in period and energy needs as determined by the Harris-Benedict formula. On weekdays, subjects came to the Clinical Investigation Unit to consume their noon meal under the supervision of at least one member of the research team, at which time they picked up their evening meal and next day's packaged breakfast. Weekend meals were prepared, packaged and provided at Friday's visits. The compliance of subjects was closely monitored with a daily checklist in which participants noted foods consumed and, if needed, the amount of foods not consumed. On each weekday, body weight was measured immediately before lunch. To maintain constant weight, caloric intake was increased or decreased by 250 kcal/day if a subject lost or gained greater than 1 kg and maintained that body weight for at least 3 days.

Family history of dyslipidemia

At screening, subjects were asked to report whether one first-degree relative (i.e. father, mother, and siblings) had in the past a diagnosis of dyslipidemia (hypercholesterolemia and/or hypertriglyceridemia). If subjects were not aware or not sure of their family history of dyslipidemia, they were asked to contact the study coordinator in the next few days after being informed. If at least one first-degree relative was identified by subjects as having been diagnosed with dyslipidemia, subjects were considered as having a positive family history of dyslipidemia. Otherwise, subjects were classified in the group with a negative family history of dyslipidemia.

Anthropometric measurements

Body weight, height, BMI, and waist circumference were measured using standardized methods [20].

Physical activity participation

Daily energy expenditure from physical activity participation was determined during the fourth week of both the run-in period and the MedDiet phase using a validated 3-day activity diary record developed by Bouchard et al. [21], as previously described [22]. Mean daily energy expenditure from activities with an energy cost higher than 1.2 kcal·kg^{-1}·15 min^{-1} (>4.8 METs) are reported in the present study. Subjects were instructed to maintain stable physical activity participation during the whole study protocol.

Dietary assessment

Dietary intakes were assessed for each participant using a quantitative food frequency questionnaire (FFQ), which has been previously validated in French Canadian men and women [19]. The FFQ which was administrated by a registered dietitian inquired on food habits during the last month just before the controlled MedDiet phase (i.e. during the entire 4-week run-in period). More precisely, participants were asked to report their frequency of intake for each food group included in the FFQ (91 food groups and 33 subquestions) in terms of day, week or month. Thereafter, examples of portion size were provided to participants in order to have a better estimation of the real portion size consumed. A

Mediterranean score (MedScore) derived from the FFQ was calculated as described by

Goulet and colleagues [13]. The MedScore can vary between zero and forty-four points. A

MedScore of forty-four would imply a food pattern which is perfectly concordant with the

traditional MedDiet.

Lipid-lipoprotein profile

Blood samples were collected from an antecubital vein into vacutainer tubes after a 12-h

overnight fast. Total plasma cholesterol, TG and HDL-C concentrations were measured

using commercial reagents on a Modular P chemistry analyzer (Roche Diagnostics,

Mannheim, Germany). Apo B was measured by immunoturbidimetry (Roche Diagnostics,

Mannheim, Germany). LDL-C was obtained by the equation of Friedewald and colleagues

[23]. Plasma apo A-1 and apo A-2 concentrations were measured by immunonephelometry.

Statistical analyses

Data were collected before (i.e. immediately after the run-in period, referred as baseline

values) and after the controlled MedDiet phase. Data were analyzed by using SAS

statistical package version 9.2 (SAS Institute Inc., Cary, NC, USA). Statistical significance

was defined as $P \leq 0.05$ (two-sided). Variables with a skewed distribution were transformed

prior to statistical analysis. Differences in characteristics and dietary intakes before the

controlled MedDiet phase between subjects with a negative family history of dyslipidemia

and those with a positive family history of dyslipidemia were assessed using the General

Linear Model (GLM) procedure. Chi-square test was used in order to investigate difference in the proportion of men/women between groups. MIXED procedures for repeated measurements were used to assess main effects of time (i.e. baseline vs. post-intervention values), group (i.e. subjects with a positive vs. subjects with a negative family history of dyslipidemia) and time by group interaction on lipid-lipoprotein profile. Tukey-Kramer adjusted P-values were used to determine the precise location of differences when a significant main effect was detected by the MIXED analysis. As initial baseline lipid-lipoprotein values and sex may influence lipid-lipoprotein response to diet, MIXED procedures were also used to investigate whether the family history of dyslipidemia influenced the response over time in a different manner according to baseline value or sex.

Although the controlled MedDiet phase aimed at being isocaloric, both groups experienced a small but significant weight loss (-1.4±0.3 kg or 1.5% in subjects with a negative family history of dyslipidemia, P<0.0001 and -0.5±0.1 kg or 0.6% of initial body weight in subjects with a positive family history of dyslipidemia, P=0.004; P for group difference=0.004). Despite this body weight loss, waist circumference did not significantly change during the MedDiet phase (-1.0±0.6 cm or 0.9% in subjects with a negative family history of dyslipidemia, P=0.09 and +0.2±0.3 cm or 0.2% of initial waist circumference in subjects with a positive family history of dyslipidemia, P=0.52). As body weight loss has been shown to improve lipid-lipoprotein profile, all analyses linked to lipid-lipoprotein response are presented with adjustments for body weight change occurring during the controlled MedDiet phase.

Results

One hundred and forty-four individuals volunteered to the study and 75 subjects met the inclusion criteria. Among this initial group, five subjects dropped out during the run-in period for personal reasons. Therefore, 70 participants underwent the controlled feeding intervention. Of them, five subjects were not able to provide information about their family history of dyslipidemia and were therefore excluded from analyses of the present study. In total, 29 subjects with a negative family history of dyslipidemia and 36 with a positive family history of dyslipidemia completed the controlled MedDiet phase. One subject with a negative family history of dyslipidemia had an illness which led to a significant reduction in food intake during several days just before the end of the controlled feeding phase and was excluded from our analyses. Therefore data in the present article are from the remaining 28 subjects with a negative family history of dyslipidemia and 36 with a positive family history of dyslipidemia.

Baseline characteristics

No difference was found between subjects with a negative and those with a positive family history of dyslipidemia for the mean age and fasting glucose (Table 1). However, there were a lower proportion of men in the group with a positive family history of dyslipidemia compared to the group with a negative family history. Moreover, subjects with a positive family history of dyslipidemia had lower body weight, BMI and waist circumference mean values than individuals with a negative family history of dyslipidemia. These differences in

anthropometric variables remained significant even after adjustment for differences in the proportion of men/women between groups, except for body weight, for which only a trend was observed after adjustments (body weight, P=0.08, BMI, P=0.03 and waist circumference, P=0.002). Baseline body weight, BMI and waist circumference were not significantly associated with changes in lipid-lipoprotein concentrations during the MedDiet phase (-0.20>r<0.15, P≥0.12 for body weight; -0.17>r<0.23, P≥0.07 for BMI; -0.20>r<0.16, P≥0.12 for waist circumference).

For dietary intakes, no significant difference between groups was observed for energy intake, MUFA to SFA ratio and fiber intake (Table 2). Moreover, there was no significant difference for macronutrient intakes, except for the proportion of energy derived from carbohydrates, subjects with a positive family history consuming a higher proportion of carbohydrates than those with a negative family history. Finally, as suggested by the MedScore, subjects with a positive family history of dyslipidemia had prior to the intervention a dietary pattern which was more concordant with MedDiet principles than those with a negative family history. There was no difference between groups for any variable of the lipid-lipoprotein profile at baseline (all variables, P>0.11) (Table 3).

Energy expenditure from physical activity was similar between groups during the run-in period (4.27±1.01 kcal/kg*day for individuals with a negative family history of dyslipidemia and 2.38±0.51 kcal/kg*day for subjects with a positive family history of dyslipidemia; P for group difference=0.23) and the MedDiet phase (2.84±0.99 kcal/kg*day

for individuals with a negative family history of dyslipidemia and 2.07±0.53 kcal/kg*day for subjects with a positive family history of dyslipidemia; P for group difference=0.61).

Effects of the MedDiet according to the family history of dyslipidemia

Greater decreases in LDL-C, HDL-C, total cholesterol to HDL-C ratio, LDL-C to HDL-C ratio, apo B, apo A-1, apo A-2 were observed in individuals with a negative family history of dyslipidemia compared to those with a positive family history; however these differences between groups reached statistical significance only for total cholesterol as suggested by the group by time interaction (subjects with a negative family history of dyslipidemia, P<0.0001 and subject with a positive family history of dyslipidemia, P=0.03; Table 3). Decreases in LDL-C, HDL-C, total cholesterol to HDL-C ratio, LDL-C to HDL-C ratio, apo B, apo A-1, apo A-2 and apo B to apo A-1 ratio were noted in response to the MedDiet, as suggested by significant time effects for these variables. No change was observed for TG concentrations and TG to HDL-C ratio.

To verify whether baseline value interacts with the family history of dyslipidemia to modulate respective lipid-lipoprotein response, two subgroups were formed according to the baseline value of each variable, individuals with a baseline value lower than the median of the whole sample were considered as having "low" baseline values and individuals with a baseline value higher than the median value were identified as having "high" baseline values. For total cholesterol, a group by time interaction was found for both individuals with "low" baseline values (P=0.04) and those with "high" baseline values (P=0.01; median

of the whole sample for total cholesterol = 5.44 mmol/l), subjects with a negative family history of dyslipidemia exhibiting more pronounced decreases in total cholesterol than individuals with a positive family history (respectively -6.9% vs. -0.3% for individuals with "low" baseline values and -16.5% vs. -7.9% for individuals with "high" baseline values) (Figure 1). Moreover, a group by time interaction was found for subjects with a "low" baseline LDL-C value (< 3.39 mmol/l; P=0.0003), subjects with a negative family history of dyslipidemia having a significant decrease in LDL-C (-11.1%, P=0.001) while those with a positive family history experienced a non-significant increase (+4.2%, P=0.40) (Figure 1). On the other hand, subjects with "high" baseline LDL-C value ($\geq$ 3.39 mmol/l) experienced a significant decrease in LDL-C regardless of the family history of dyslipidemia (-12.4%, P=0.02 for individuals with a negative family history and -11.0%, P=0.005 for those with a positive family history, P for group by time interaction=0.73). For all other variables related to the lipid-lipoprotein profile, no group by time interaction was noted, irrespective of baseline value. Except for apo B to apo A-1 ratio, significant negative associations between baseline values and changes in respective lipid-lipoprotein variable was found (r $\leq$-0.40, P $\leq$0.001 for all), i.e. individuals with higher baseline value having more important decreases than subjects with lower baseline values.

Analysis by sex revealed that for men, individuals with a negative family history of dyslipidemia decreased their HDL-C (-8.0%, P=0.04) whereas men with a positive family history experienced no significant change in response to the MedDiet (-0.1%, P=0.97; group by time interaction effect P=0.07) (Figure 2). In women, a tendency toward a group

by time interaction was also observed for HDL-C (P=0.09) but in contrast to men, a trend

toward a decrease was found in women with a positive family history (-4.9%, P=0.06)

while no significant change was noted in women with a negative family history of

dyslipidemia (+1.3%, P=1.00). A group by time interaction was also observed for apo A-1

in men (P=0.02) but not in women (P=0.34). In men, decreases were noted in subjects with

a negative family history of dyslipidemia while those with a positive family history

experienced no change (respectively, -8.8%, P<0.0001 and -2.8%, P=0.51). In women, no

difference was found between groups, both having non-significant decreases in apo A-1

concentrations (-1.1%, P=0.97 for women with a negative family history and -4.2%,

P=0.08, for women with a positive family history). In contrast, a group by time interaction

was found for apo A-2 in women (P=0.047) but not in men (P=0.19). In women, a decrease

was noted in subjects with a positive family history of dyslipidemia (-5.9%, P=0.02)

whereas no change was observed in those with a negative family history (+1.2%, P=0.97).

In men, decreases in apo A-2 concentrations were found, regardless of the family history of

dyslipidemia (-9.8%, P=0.0002 for men with a negative family history and -5.9%, P=0.08,

for men with a positive family history). A group by time interaction was also noted for total

cholesterol to HDL-C ratio in women (P=0.03) but not in men (P=0.94). In women, a

tendency for a decrease was noted for those with a negative history while women with a

positive family history had a non-significant increase (respectively -9.4%, P=0.09 and

+0.6%, P=0.99). Finally, a group by time interaction was noted for LDL-C to HDL-C ratio

in women (P=0.02) but not in men (P=0.27). More precisely in women, those with a

negative family history experienced a tendency toward a decrease for this ratio (-11.7%,

P=0.097) while women with a positive family history had a non-significant increase (+2.0, P=0.91). In men, LDL-C to HDL-C ratio decreased irrespective of the family history of dyslipidemia, however this decrease reached statistical significance only in men with a positive family history (-6.0%, P=0.33 for men with a negative family history and -10.8%, P=0.02, for men with a positive family history).

Adjustments for the MedScore as well as energy, carbohydrate, SFA and PUFA intakes before the controlled MedDiet phase did not influence results obtained (not shown), suggesting that differences observed between groups for dietary intakes at baseline do not explain differences in the response between individuals with a negative and those with a positive family history of dyslipidemia.

Discussion

These results highlight that inherited susceptibilities to dyslipidemia, as assessed by the family history of dyslipidemia, may explain at least in part the heterogeneity in the plasma lipid-lipoprotein response to the MedDiet, a food pattern well-documented for its cardioprotective effects and now widely recommended in CVD prevention [24]. In fact, results showed that individuals characterized by a positive family history of dyslipidemia experienced limited improvements in lipid-lipoprotein concentrations in response of the consumption of the MedDiet compared to those with a negative family history, and more especially for improvements related to total cholesterol. Moreover, results also suggest that the family history of dyslipidemia may interact with baseline lipid values that are at least partly inherited as well as with sex to modulate the lipid-lipoprotein response.

There is growing interest in identifying factors responsible for inter-individual variability in lipid-lipoprotein response to dietary modifications. Among others, a favorable genetic background seems to be needed to achieve full benefits [8]. Our results suggest that family history of dyslipidemia may be one easily documented and inexpensive indicator of an unfavorable genetic background in clinical settings. In fact, in this study, baseline characteristics of participants underlined that genetic-related resistance of the lipid-lipoprotein profile in individuals with a positive family history of dyslipidemia. Indeed, despite the fact that these individuals consumed a diet more closely in agreements with the MedDiet principles before the feeding phase, they had a lipid-lipoprotein profile which was

not more favorable than the one found in those with a negative family history of dyslipidemia. Moreover, our results showed that the consumption of the MedDiet leads to greater decreases in cholesterol concentrations in individuals with a negative family history of dyslipidemia compared to those with a positive family history of dyslipidemia. This difference in cholesterol-lowering effects does not seem to be due to differences in baseline dietary intakes since adjustments did not change results obtained.

Differences in anthropometric characteristics between individuals with a positive vs. a negative family history of dyslipidemia were observed at baseline. In fact, individuals with a negative family history of dyslipidemia had higher body weight, BMI and waist circumference than those with a positive history. One may assume that these baseline differences may have a significant impact on results observed. However, analyses showed that baseline body weight, BMI and waist circumference were not associated with changes in lipid-lipoprotein concentrations during the MedDiet phase. Moreover, in a previous paper from our research team, results showed that individuals with abdominal obesity (waist circumference >102 cm in men and >88 cm in women) had similar lipid-lipoprotein benefits from the MedDiet than those with no abdominal obesity [25]. These results suggest that it is unlikely that differences observed between individuals with a positive history vs. those with a negative history of dyslipidemia are mainly due to baseline differences in anthropometric characteristics.

Although greater improvements in lipid-lipoprotein profile were observed in individuals with a negative family history of dyslipidemia, and more especially for total cholesterol, it is imperative to underline that both individuals with a negative and a positive family history of dyslipidemia benefited from the MedDiet. In fact, results from the current study indicate that, regardless of their family history, clinically significant improvements in lipid profile can be achieved by the consumption of a MedDiet. These results are relevant since our sample included individuals at risk of CVD in whom primary prevention should be started through the adoption of healthy dietary habits in order to prevent the need of lipid-lowering medications later in life. However, because previous studies such as ours have shown that, in some individuals, the consumption of the MedDiet has no effect on the lipid-lipoprotein profile, these results suggest that other factors than the family history of dyslipidemia may contribute to the heterogeneity of lipid-lipoprotein response to the MedDiet.

In the literature, baseline values of lipid-lipoprotein variables have been demonstrated as influencing the response to diet modifications [26], and more precisely in response to the MedDiet [7, 13]. Among others, Goulet and collaborators have reported decreases in LDL-C concentrations in response to a 12-week nutritional intervention promoting the MedDiet in women with baseline LDL-C ≥3.3 mmol/l, but not in women with lower baseline LDL-C values [13]. In the present study, negative associations between baseline values and changes in respective lipid-lipoprotein variable were found, i.e. individuals with higher baseline values having greater decreases in response to the MedDiet than those with lower baseline values. However, our results bring additional information, suggesting that the

family history of dyslipidemia may modulate the impact of the baseline value on lipid-lipoprotein response to the MedDiet. In fact, individuals with "high" baseline concentrations of LDL-C (i.e. ≥ 3.39 mmol/l) experienced decreases in LDL-C in response to the MedDiet, irrespective of their family history of dyslipidemia. However, among individuals with lower baseline LDL-C values (i.e. <3.39 mmol/l), only subjects with a negative family history of dyslipidemia experienced decreases in LDL-C concentrations. Previous studies on statin therapy have pointed out that the reduction in major vascular events is directly proportional to the absolute LDL-C reduction achieved. Even if LDL-C is lower than 2.0 mmol/l, further benefit may be obtained with LDL-C reduction [27]. Hence, the genetic-related resistance to the MedDiet observed in this study in individuals with a positive family history of dyslipidemia and LDL-C baseline values lower than 3.39 mmol/l may represent a disadvantage for these individuals in an effort to reduce their CVD risk. Other studies are needed to confirm the present findings.

Results also suggest that family history of dyslipidemia may affect differently lipid-lipoprotein response to the MedDiet in men and in women. In fact, a different impact of the family history of dyslipidemia was noted in men and women for HDL-C, apo A-1, apo A-2, total cholesterol to HDL-C ratio and LDL-C to HDL-C ratio responses, all variables related to HDL particles. HDL-C is influenced by both environmental factors (e.g. dietary patterns, alcohol consumption, and physical activity participation) and genetic factors [28]. Genetic studies have highlighted that HDL have the highest heritability of lipid subfractions, with around 45% of HDL-C concentrations determined by the individual's genetic background

[29, 30]. Moreover, some previous studies have observed the existence of different gene-diet interactions between men and women for HDL-C levels [31, 32]. Taken together, these results highlight the importance of analyzing men and women separately for genetic-diet interactions related to plasma HDL-C concentrations.

Due to the highly nutritional controlled nature of this intervention, we were limited to a relatively small sample size, which may be viewed as a limitation. However, this controlled environment allowed evaluating directly the impact of the inherited susceptibilities to dyslipidemia on the plasma lipid-lipoprotein response with a maximum control on confounding variables, thereby reducing variability attributable to these confounders and therefore, the number of participants required. Nevertheless, results from this study need to be confirmed. Another limitation is that the family history of dyslipidemia was reported by participants and therefore a possible misclassification may have occurred. However, the accuracy of parental history reports of high blood cholesterol by offspring reporters has been previously highlighted. Indeed, Murabito et al. have reported that, compared to medical records, offspring parental history reports of high blood cholesterol had positive predictive values of 78% for father and 88% for mother [12]. No difference was found between male and female reporters. Moreover, as previously discussed, in the present study, despite healthier characteristics of individuals with a positive family history of dyslipidemia, these individuals had a similar lipid-lipoprotein profile compared to individuals with a negative family history at baseline, suggesting inherited genetic susceptibilities to dyslipidemia in these individuals.

In summary, the short-term consumption of a MedDiet is successful for lowering plasma lipids and lipoproteins, regardless of the family history of dyslipidemia. However, these lipid-lowering effects of the MedDiet are more pronounced in those with no inherited susceptibilities to dyslipidemia, and more especially for total cholesterol levels. Moreover, these results emphasize the importance of considering other confounding variables which may also interfere in the link between inherited susceptibilities to dyslipidemia and lipid-lipoprotein response, such as baseline lipid-lipoprotein value and sex. Since this is the first study to document whether family history of dyslipidemia influences lipid-lipoprotein response to the MedDiet, other studies exploring this research question and investigating mechanisms behind the limited cholesterol lowering effect of the MedDiet in individuals with a positive family history of dyslipidemia are needed. However, these findings provide useful clinical information, which, along with further studies aiming at identifying factors responsible for the heterogeneity in response to healthy food patterns, will help personalizing dietary recommendations in order to improve lipid-lipoprotein profile, thereby reducing more efficiently CVD risk.

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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Figure 1. Total cholesterol and LDL-C response to the Mediterranean diet according to the family

history of dyslipidemia in both individuals with low and high baseline values

FHD-: with a negative family history; FHD+: with a positive family history
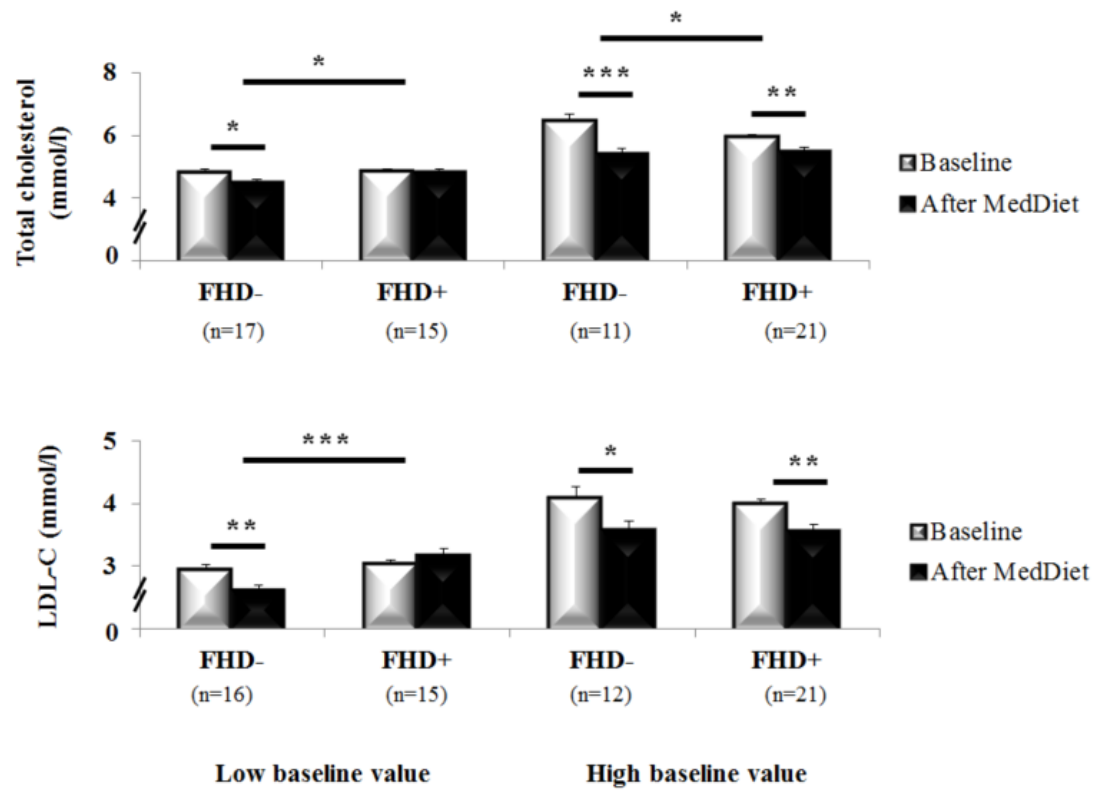
* P<0.05, ** P<0.01, *** P<0.001

Figure 2. Lipid-lipoprotein response to the Mediterranean diet according to the family history of dyslipidemia in men and women separately

FHD-: with a negative family history; FHD+: with a positive family history

Men FHD-, n=20; Men FHD+, n=16; women FHD-, n=8; women FHD+, n=20

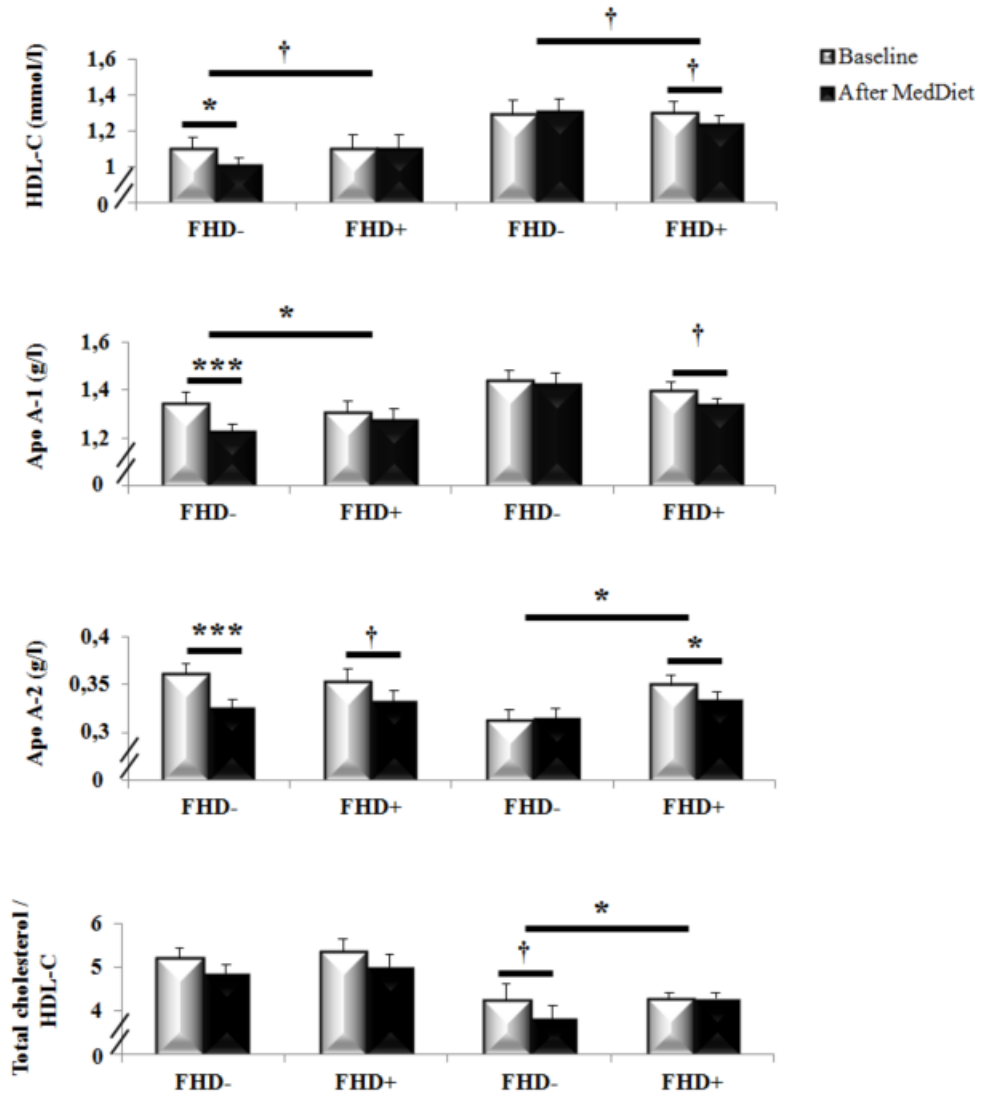† P<0.10, * P<0.05, ** P<0.01, *** P<0.001

Table 1. Characteristics before the 4-week fully-controlled Mediterranean diet phase according to the family history of dyslipidemia

Variables	Negative family history (n=28)		Positive family history (n=36)		Difference between groups
	Mean	SEM	Mean	SEM	P-value
Men (n, (%))	20 (71.4)		16 (44.4)		0.03
Age (years)	43.0	1.5	41.0	1.2	0.29
Body weight (kg)	91.7	3.3	81.6	2.3	0.01
BMI (kg/m^2) [a]	30.6	0.8	28.5	0.7	0.03
Waist circumference (cm)	105.3	2.2	95.7	1.5	0.0004
Fasting glucose (mmol/l)	5.91	0.10	5.73	0.09	0.17

[a] Analysis was performed on transformed values

Table 2: Dietary intakes before the 4-week controlled Mediterranean diet phase according to the family history of dyslipidemia [a]

Variables	Negative family history (n=28)		Positive family history (n=36)		Difference between groups
	Mean	SEM	Mean	SEM	P-value
Energy (kCal)	2878	163	2519	87	0.06
Carbohydrate (% of total energy)	43.7	1.3	47.2	1.0	0.03
Protein (% of total energy)	18.0	0.7	17.2	0.5	0.29
Fat (% of total energy) [b]	34.8	1.0	33.2	1.1	0.23
SFA (% of total energy)	11.5	0.5	10.5	0.4	0.09
MUFA (% of total energy) [b]	14.4	0.5	14.5	0.8	0.50
PUFA (% of total energy) [b]	6.0	0.3	5.5	0.2	0.07
Alcohol (% of total energy) [b]	3.4	0.6	2.3	0.3	0.17
MUFA to SFA ratio [b]	1.28	0.04	1.43	0.09	0.27
Total fibers (g) [b]	28.4	1.6	29.9	1.6	0.49
MedScore (arbitrary units)	22.8	1.0	26.9	0.8	0.002

SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; MedScore, mediterranean score.

[a] Data represent dietary intakes during the run-in period.

[b] Analysis was performed on transformed values.

Table 3: Effects of the 4-week controlled Mediterranean diet on the lipid-lipoprotein profile in subjects with a positive and those with a negative family history

Variables	Negative family history (n=28)			Positive family history (n=36)			P-value		
	Pre-intervention	Post-intervention	Δ %	Pre-intervention	Post-intervention	Δ %	Time	Group	Group* time
TG (mmol/l) [b]	1.90 ± 0.25	1.56 ± 0.12	-18.0	1.46 ± 0.10	1.38 ± 0.08	-5.8	0.09	0.51	0.46
Total cholesterol (mmol/l)	5.46 ± 0.19	4.84 ± 0.14	-11.3	5.48 ± 0.11	5.20 ± 0.11	-5.1	<0.0001	0.50	0.03
LDL-C (mmol/l)	3.43 ± 0.14	3.03 ± 0.12	-11.8	3.59 ± 0.10	3.39 ± 0.09	-5.6	<0.0001	0.10	0.11
HDL-C (mmol/l)	1.15 ± 0.06	1.10 ± 0.05	-5.0	1.21 ± 0.05	1.18 ± 0.05	-2.9	0.008	0.75	0.50
TG / HDL-C [b]	1.81 ± 0.24	1.54 ± 0.14	-15.1	1.33 ± 0.12	1.28 ± 0.10	-4.0	0.19	0.44	0.41
Total cholesterol / HDL-C ratio	4.93 ± 0.21	4.57 ± 0.18	-7.2	4.75 ± 0.18	4.60 ± 0.16	-3.0	0.001	0.67	0.16
LDL-C / HDL-C ratio	3.10 ± 0.15	2.87 ± 0.14	-7.4	3.14 ± 0.14	2.99 ± 0.12	-4.6	0.003	0.35	0.48
Apo B (g/l)	1.12 ± 0.04	1.00 ± 0.03	-10.5	1.07 ± 0.03	1.00 ± 0.03	-7.0	<0.0001	0.87	0.28
Apo A-1 (g/l)	1.37 ± 0.04	1.28 ± 0.03	-6.5	1.36 ± 0.03	1.31 ± 0.03	-3.6	<0.0001	0.78	0.14
Apo A-2 (g/l)	0.35 ± 0.01	0.32 ± 0.01	-7.0	0.35 ± 0.01	0.33 ± 0.01	-5.2	<0.0001	0.46	0.43
Apo B / Apo A-1	0.83 ± 0.03	0.79 ± 0.03	-3.8	0.80 ± 0.03	0.77 ± 0.03	-3.8	0.03	0.98	0.96

of dyslipidemia [a]

Δ %, percentage of change; BMI, body mass index; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; Apo, apolipoprotein.

[a] All analyses are adjusted for weight change during the MedDiet phase. Pre-intervention values represent those collected after the run-in period, and therefore immediately before the 4-week MedDiet phase. Post-intervention values are those collected after the MedDiet phase.

[b] Analysis was performed on transformed values.