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Original article

Dietary linoleic acid interacts with *FADS1* genetic variability to modulate HDL-cholesterol and obesity-related traits

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SUMMARY

Background & aims: Blood levels of polyunsaturated fatty acids (PUFAs) are under control of endogenous synthesis *via* Δ5- and Δ6-desaturases, encoded by the FADS1 and FADS2 genes, respectively and of diet. Genome-wide associations studies (GWAS) reported associations between polymorphisms in FADS1 −FADS2 and variations in plasma concentrations of PUFAs, HDL- and LDL-cholesterol and triglycerides. However, it is not established whether dietary PUFAs intake modulates these associations. We assessed whether dietary linoleic acid (LA) or α-linolenic acid (ALA) modulate the association between the FADS1 rs174547 polymorphism (a GWAS hit) and lipid and anthropometric phenotypes.

Methods: Dietary intakes of LA and ALA, *FADS1* rs174547 genotypes, lipid and anthropometric variables were determined in three French population-based samples (n = 3069). These samples were stratified according to the median dietary LA (<9.5 and ≥9.5 g/d) and ALA (<0.80 and ≥0.80 g/d) intakes. The meta-analysis was performed using a random-effect.

Results: Our meta-analysis confirmed the association between rs174547 and plasma lipid levels and revealed an association with waist circumference and body mass index. These associations were not modified by dietary ALA intake (all p-interaction > 0.05). In contrast, the associations with HDL-cholesterol levels, waist circumference and BMI were modulated by the dietary intake of LA (p interaction < 0.05). In high LA consumers only, the rs174547 minor allele was significantly associated with lower HDL-cholesterol levels (β = −0.05 mmol/L, p = 0.0002). Furthermore, each copy of the rs174547 minor allele was associated with a 1.58 cm lower waist circumference (p = 0.0005) and a 0.46 kg m^{-2} lower BMI (p = 0.01) in the low LA intake group, but not in the high LA intake group.

Conclusions: The present study suggests that dietary LA intake may modulate the association between the *FADS* gene variants and HDL-cholesterol concentration, waist circumference and BMI. These gene −nutrient interactions, if confirmed, suggest that subjects carrying the rs174547 minor allele might benefit from low dietary LA intakes.

Abbreviations: AA, arachidonic acid; ALA, α-linolenic acid; BMI, body mass index; DGLA, dihomo-γ-linolenic acid; FADS1, fatty acid desaturase 1; GWAS, genome-wide association study; HDL, high-density lipoprotein; LA, linoleic acid; LC-PUFA, long-chain polyunsaturated fatty acid; LD, linkage disequilibrium; LDL, low-density lipoprotein; MET, metabolic equivalent of task; PUFA, polyunsaturated fatty acid.

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1. Introduction

Blood concentrations of long-chain polyunsaturated fatty acids (LC-PUFAs) are determined by dietary intake and by endogenous synthesis *via* the successive elongation and desaturation of the dietary precursors linoleic acid (18:2n-6, LA) and α-linolenic acid (18:3n-3, ALA). Δ5-desaturase and Δ6-desaturase are rate-limiting enzymes involved in the synthesis of LC-PUFAs [1] and are encoded by the *FADS1* and *FADS2* genes, respectively. Dietary PUFAs can modulate the synthesis and metabolism of endogenous LC-PUFAs since LA and ALA are substrates for the same enzymes in the first steps of LC-PUFAs biosynthesis. Accordingly, some studies have shown that (i) the conversion of ALA to eicosapentaenoic acid (20:5n-3, EPA) and docosahexaenoic acid (22:6n-3, DHA) is influenced by dietary n-6 PUFAs and (ii) n-3 supplementation reduces cellular arachidonic acid (20:4n-6, AA) levels [2–4]. Altogether, these data point to possible interaction between dietary intake of PUFAs and capacity for endogenous synthesis of LC-PUFAs.

Many candidate gene [5–7] and genome-wide association studies (GWAS) [8–10] have associated minor alleles of single nucleotide polymorphisms (SNPs) in the *FADS1–FADS2* genes with lower blood concentrations of LC-PUFAs. Minor alleles of SNPs in high linkage disequilibrium (LD) with rs174547 have been consistently associated with higher concentrations of desaturation substrates (such as dietary LA and ALA) and lower concentrations of desaturation products (such as AA, EPA and DHA) [5–10]. It has been concluded from these studies that subjects carrying the *FADS* minor alleles may present a lower desaturase activity. These data are in agreement with GWAS of gene expression, in which the rs174546 minor allele (a proxy of the C allele of rs174547 in the present study) was associated with decreased *FADS1* mRNA expression in lymphoblastoid cells [11] and liver biopsies [12]. Furthermore, recent meta-analyses of GWAS have also reported relationships between *FADS* cluster SNPs (all in strong LD with rs174547) and the plasma levels of triglycerides and total-, HDL- and LDL-cholesterol [12,13].

Although many epidemiological studies have associated the dietary intake of PUFAs with cardiovascular risk factors such as lipids and obesity [reviewed in 14–17], few studies have explored the interaction between dietary PUFAs and *FADS* gene cluster variability on these risk factors [18–20]. Therefore, the aim of our study was to assess whether dietary intake of LA and ALA modified the association between the *FADS1* rs174547 polymorphism and metabolic phenotypes in three French population samples (n = 3069).

2. Methods

2.1. The MONA LISA study

The phenotyping of the subjects from the MONA LISA study has been described previously [21]. The MONA LISA study is a cross-sectional, population-based study performed in the Lille Urban Community (northern France), the Haute-Garonne county (southern France) and the Bas-Rhin county (eastern France). Inhabitants aged 35–74 years were randomly sampled from electoral rolls after stratification by town size, gender and 10-year age groups (n = 4644). The protocol was approved by the local ethics committees and written informed consent was obtained from each participant.

Participants completed a standard questionnaire, and physical measurements were performed by trained nurses. The questionnaire included questions on smoking status, alcohol consumption, physical activity, personal and family medical history, and any current medication use. Individuals were categorized as former or never-smokers and current smokers. Alcohol intake was defined as the total number of milliliters of alcohol per week from beer, wine, cider and spirits. Alcohol habits were classified into four groups with specific cutoffs according to gender. The cutoff levels for women were 0, 1–60, 61–90, >90 g of alcohol per week whereas the cutoff levels for men were 0–100, 101–250, 251–500, >500 g of alcohol per week. Anthropometric measurements were carried out on individuals in light clothing and without shoes. The BMI was calculated according to the Quetelet equation. Waist circumference was measured with a tape measure at midpoint between the lower border of the rib cage and the upper border of the iliac crest. After the subject had fasted for at least 10 h, a 20 ml blood sample was drawn into a disodium ethylene diamine tetra-acetic acid tube. Cholesterol and triglyceride levels were measured using enzyme assays (Olympus). High-density lipoprotein cholesterol was measured after sodium phosphotungstate/magnesium chloride precipitation (Olympus). Plasma LDL-cholesterol was calculated with the Friedewald equation when triglyceride levels were <4.56 mmol/L. Physical activity was defined as previously described [22]. Briefly, the MONICA Optional Study of Physical Activity (MOSPA) questionnaire evaluated physical activity at work, while commuting and during leisure activities. Time spent on doing work-related activities (such as walking, or carrying moderate or heavy loads) and active commuting was evaluated and multiplied by the activity-specific energy expenditure as the metabolic equivalent of task (MET) [23]. Participants also declared their usual leisure-time physical activity by indicating their per week frequency and usual duration. Net physical activity energy expenditure was calculated in MET h/week, as described previously [24] and then categorized into quartiles.

2.2. Dietary intake assessment

Eighty eight percent of the MONA LISA study participants aged between 35 and 64 participated in a dietary assessment (n = 3626, Supplementary Fig. 1). The dietary assessment was carried out in accordance with the EURONUT protocol [25]. Subjects had to record their food consumption for 3 consecutive days and report the nature and the estimated quantity of the drink and food consumed at each intake. One to seven days after completion of the food record, the data were specified during a meeting with a trained dietician with the help of a validated handbook of photographed portions [26]. Mean daily intake (grams per day) from food and supplements was evaluated using the information collected with the 3-day records (available in 3191 individuals, Supplementary Fig. 1) and was converted into nutrient and energy intakes using a French nutrition composition table (The 2008 version of CIQUAL [27] supplemented by the SU.VI.MAX table [28]).

2.3. SNP selection and genotyping

The rs174547 SNP located in the *FADS1* gene was selected because it (i) is consistently associated with PUFAs in GWAS [9,10,29], and (ii) is in perfect LD ($r^2 = 1$) with rs174546, which has been associated with triglycerides, LDL-cholesterol and HDL-cholesterol in GWAS [12,13]. The three population-based samples were genotyped separately using KASPar technology (KBioscience, Hoddesdon, UK). Genotyping was successful in 3069 (96%) of the 3191 individuals with dietary records (Supplementary Fig. 1). Five percent of the samples were randomly selected and genotyped in duplicate, with 100% agreement.

2.4. Statistical analyses

Statistical analyses were performed with SAS software (version 8.02, SAS Institute Inc., Cary, NC, USA). Hardy–Weinberg

equilibrium was evaluated using the χ^2 test (with one degree of freedom). Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as percentages. To obtain a normal data distribution, log transformation was applied for the plasma triglyceride levels and dietary LA and ALA intakes. Then, dietary LA and ALA intakes were classified into two groups (above and below the study's median intake). Lipid (triglycerides, total-, LDL- and HDL-cholesterol) and anthropometric variables (waist and BMI) were compared between genotypes by ANCOVA after adjusting for covariates (General Linear Model procedure). For lipid variables, users of lipid-lowering medication (n = 464) were excluded. Analyses were performed assuming a genetic additive model. The interaction between LA or ALA intake and genotypes on quantitative variables was explored by including interaction terms in the General Linear Model. The adjustment variables were age, gender, center (for combined analysis only), BMI (except for anthropometric variables), alcohol consumption, smoking habit, physical activity, and total energy intake (for gene-diet interactions only). The pooled estimates (beta coefficients ± standard error, SE) were calculated in a random-effect meta-analysis by using the *metafor* package in R [30]. In meta-analysis, the effect of inconsistency across the studies (i.e. heterogeneity) was calculated using Cochrane Q test with 2 degrees of freedom. In sensitivity analyses, under-reporters of energy intake were excluded. These under-reporters were identified as having an energy intake estimated by food records <1.05 times their basal metabolic rate [31] calculated according to the equation of Black and colleagues [32]. The threshold for statistical significance was $p < 0.05$.

3. Results

The characteristics of the three population samples are presented in Supplementary Table 1. The *FADS1* rs174547 genotype distribution was in accordance with Hardy–Weinberg equilibrium in each population sample ($p > 0.46$). Allele frequencies for the rs174547 minor allele ranged from 0.30 to 0.32. The rs174547 minor allele was significantly associated with lower total-, LDL- and HDL-cholesterol concentrations but not with triglycerides concentrations (Table 1). Regarding anthropometric variables, the rs174547 minor allele was associated with a lower waist circumference ($p = 0.003$).

To determine whether dietary PUFA intakes can modify rs174547's impact on lipid-related and anthropometric variables, we performed a gene × diet interaction analysis. Participants were classified into two groups as a function of the median dietary PUFA intake (9.5 and 0.80 g/d for LA and ALA, respectively) in the overall study population. The mean LA and ALA intakes were 6.6 ± 1.9 and 0.59 ± 0.14 g/d in the low-intake groups and 14.1 ± 4.3 and 1.26 ± 0.56 g/d in the high intake groups, respectively. There was no interaction between dietary ALA intake and the *FADS1* rs174547 polymorphism on lipid or anthropometric variables (Table 2). Likewise, there was no significant interaction between LA intake and *FADS1* rs174547 on the plasma levels of triglycerides, total- and LDL-cholesterol (Table 3). Conversely, a significant interaction between LA intake and rs174547 was detected for HDL-cholesterol levels ($p = 0.04$), waist circumference ($p = 0.01$) and BMI ($p = 0.04$). After stratification on LA intake median, the rs174547 minor allele was significantly associated with lower HDL-cholesterol levels ($\beta = -0.05$ mmol/L, $p = 0.0002$) in high LA consumers only (Fig. 1A). When considering anthropometric variables, significant associations were observed only in subjects with a low LA dietary intake. In this subgroup, each copy of the rs174547 minor allele was associated with a 1.58 cm lower waist circumference ($p = 0.0005$, Fig. 1B) and a 0.46 kg m^{-2} lower BMI ($p = 0.01$, Fig. 1C), when compared with the rs174547 major allele.

LA and ALA intakes were correlated ($r = 0.53$; $p < 0.0001$). However, adjustment for ALA intake did not modify the significance of the associations of rs174547 with anthropometric traits (waist and BMI) and HDL-cholesterol in the low- and high LA intake groups, respectively (data not shown). In sensitivity analyses, after excluding under-reporters of energy (17.5% of the sample), the rs174547 minor allele remained significantly associated with waist ($p = 0.0005$) and BMI ($p = 0.03$) in below-median consumers of LA. The association between rs174547 and HDL-cholesterol in the high-intake group also remained significant after excluding under-reporters ($p = 0.0003$).

4. Discussion

In the present study, we (i) confirmed the existence of an association between rs174547 and plasma lipid levels and (ii) detected an association between rs174547 and waist circumference and BMI using three French population samples. Furthermore, we

Table 1
Characteristics of the population sample, as a function of the *FADS1* rs174547 genotypes.

	FADS rs174547 genotypes			p
	TT	TC	CC	
	n = 1459	n = 1326	n = 284	
Age (years)	50.4 (8.4)	50.5 (8.4)	50.7 (8.3)	0.60
Men (%)	52.3	49.9	48.9	0.34
Current smokers (%)	16.3	17.5	18.0	0.61
Physical activity (MET h/week)	49.0 (39.7)	48.5 (39.5)	51.8 (39.5)	0.33
Alcohol consumption (g/week)	125.2 (172.5)	125.1 (170.7)	117.0 (166.9)	0.88
Triglycerides (mmol/L)[a]	1.29 (0.91)	1.35 (1.12)	1.27 (0.70)	0.47
Total-cholesterol (mmol/L)[a]	5.78 (0.98)	5.70 (1.01)	5.52 (0.96)	<0.0001
LDL-cholesterol (mmol/L)[a]	1.50 (0.37)	1.48 (0.37)	1.44 (0.35)	<0.0001
HDL-cholesterol (mmol/L)[a]	3.72 (0.89)	3.63 (0.89)	3.50 (0.85)	0.005
Waist (cm)	90.1 (13.7)	89.0 (13.7)	87.9 (13.1)	0.003
BMI (kg/m^2)	26.4 (4.9)	26.1 (5.0)	26.1 (4.9)	0.07
Total energy intake (kcal/d)	2112 (561)	2086 (616)	2132 (646)	0.47
Usual dietary LA (g/d)	10.3 (4.9)	10.4 (5.2)	10.5 (5.0)	0.38
Usual dietary ALA (g/d)	0.92 (0.49)	0.93 (0.57)	0.93 (0.51)	0.99

Data are means (standard deviation) or frequencies. Triglycerides, LA and ALA were log-transformed. For lipid and anthropometric variables, tests were adjusted for age, gender, center, alcohol and tobacco consumption, physical activity, ±BMI. Otherwise, tests were adjusted for age, gender and center ± calories (for usual dietary intakes of LA and ALA). ALA, α-linolenic acid; BMI, body mass index; HDL, high-density lipoprotein; LA, linoleic acid; LDL, low-density lipoprotein, MET, metabolic equivalent of task.

[a] For lipid traits, users of lipid-lowering medication (n = 464) were excluded.

Table 2
Association between *FADS1* rs174547 and biochemical and anthropometric variables, as a function of dietary ALA intake in the MONA LISA study.

	rs174547	Dietary ALA <0.80 g/d			Dietary ALA ≥0.80 g/d			p interaction
		N	Mean (SD)	p	N	Mean (SD)	p	
Triglycerides (mmol/L)[a]	TT	606	1.30 (0.99)	0.90	619	1.28 (0.74)	0.56	0.68
	TC	572	1.36 (1.07)		551	1.42 (1.21)		
	CC	138	1.22 (0.68)		115	1.30 (0.73)		
Total cholesterol (mmol/L)[a]	TT	606	5.75 (0.98)	0.006	619	5.78 (0.99)	0.0006	0.42
	TC	572	5.71 (0.97)		551	5.66 (1.03)		
	CC	138	5.52 (0.93)		115	5.50 (0.92)		
HDL-cholesterol (mmol/L)[a]	TT	606	1.50 (0.37)	0.09	619	1.49 (0.36)	0.02	0.57
	TC	572	1.49 (0.37)		551	1.43 (0.34)		
	CC	138	1.47 (0.35)		115	1.41 (0.34)		
LDL-cholesterol (mmol/L)[a]	TT	600	3.68 (0.88)	0.01	616	3.72 (0.91)	0.001	0.42
	TC	565	3.61 (0.87)		542	3.60 (0.90)		
	CC	137	3.50 (0.82)		115	3.50 (0.83)		
Waist (cm)	TT	726	89.8 (13.9)	0.02	718	90.5 (13.4)	0.07	0.64
	TC	655	89.1 (14.1)		655	88.9 (13.2)		
	CC	154	85.8 (13.5)		126	90.5 (12.2)		
BMI (kg/m^2)	TT	726	26.5 (5.0)	0.14	719	26.3 (4.8)	0.26	0.76
	TC	656	26.5 (5.2)		656	25.7 (4.7)		
	CC	154	25.7 (4.9)		128	26.5 (4.9)		

Data are means (standard deviation). Tests were adjusted for age, gender, center, total energy intake, alcohol and tobacco consumption, physical activity, ±BMI. Triglycerides were log-transformed. ALA, α-linolenic acid; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a] For lipid traits, users of lipid-lowering medication (n = 464) were excluded.

Table 3
Association between *FADS1* rs174547 and biochemical and anthropometric variables, as a function of dietary LA intake in the MONA LISA study.

	rs174547	Dietary LA < 9.5 g/d			Dietary LA ≥ 9.5 g/d			p interaction
		N	Mean (SD)	p	N	Mean (SD)	p	
Triglycerides (mmol/L)[a]	TT	583	1.31 (1.06)	0.88	619	1.28 (0.74)	0.41	0.53
	TC	584	1.29 (1.03)		551	1.42 (1.21)		
	CC	127	1.25 (0.68)		115	1.30 (0.73)		
Total cholesterol (mmol/L)[a]	TT	583	5.79 (0.97)	0.002	619	5.78 (0.99)	0.0007	0.73
	TC	584	5.75 (0.98)		551	5.66 (1.03)		
	CC	127	5.54 (0.99)		115	5.50 (0.92)		
HDL-cholesterol (mmol/L)[a]	TT	583	1.50 (0.37)	0.39	619	1.49 (0.36)	0.0002	0.04
	TC	584	1.53 (0.39)		551	1.43 (0.34)		
	CC	127	1.48 (0.36)		115	1.41 (0.34)		
LDL-cholesterol (mmol/L)[a]	TT	576	3.71 (0.87)	0.004	616	3.72 (0.91)	0.002	0.87
	TC	577	3.65 (0.88)		542	3.60 (0.90)		
	CC	126	3.50 (0.87)		115	3.50 (0.83)		
Waist (cm)	TT	709	89.7 (13.6)	0.0003	736	90.5 (13.7)	0.70	0.01
	TC	671	87.4 (14.1)		640	90.6 (13.0)		
	CC	143	86.4 (12.9)		137	89.6 (13.2)		
BMI (kg/m^2)	TT	710	26.5 (4.8)	0.01	736	26.4 (5.0)	0.88	0.04
	TC	672	25.9 (5.1)		641	26.3 (4.8)		
	CC	143	25.7 (4.3)		139	26.4 (5.4)		

Data are means (standard deviation). Tests were adjusted for age, gender, center, total energy intake, alcohol and tobacco consumption, physical activity, ±BMI. Triglycerides were log-transformed. BMI, body mass index; HDL, high-density lipoprotein; LA, linoleic acid; LDL, low-density lipoprotein.
[a] For lipid traits, users of lipid-lowering medication (n = 464) were excluded.

observed significant gene-diet effects; dietary LA interacts with the rs174547 SNP to influence HDL-cholesterol levels and obesity-related phenotypes. In carriers of the rs174547 minor allele only, high LA intakes were associated with lower HDL-cholesterol concentrations whereas low LA intakes were associated with lower waist circumference and BMI.

Our results suggest a significant impact of the *FADS1* rs174547C minor allele on plasma lipids and obesity-related traits. Minor alleles of SNPs in high linkage disequilibrium with rs174547 have been consistently associated with higher levels of desaturation substrates (such as LA and ALA) and lower levels of desaturation products (such as AA, eicosapentaenoic acid and docosapentaenoic acid) [7,9,10,29]. It has been concluded from these studies that minor alleles of these SNPs lead to a reduced efficiency of the endogenous desaturation of n-6 and n-3 LC-PUFAs from their precursors (LA and ALA). These data were consistent with GWAS of gene expression, in which the rs174546 minor allele (a proxy of the C allele of rs174547 in the present study) was associated with decreased *FADS1* mRNA expression in lymphoblastoid cells [11] and liver biopsies [12]. In addition, we performed functional assays in order to identify the causal SNP from among the 24 SNPs in strong LD ($r^2 > 0.8$) with rs174547 and that were potentially responsible for the associations observed in population samples. Using luciferase reporter gene assays, we showed that rs174546 may down-regulate *FADS1* expression, at least partly *via* the interaction between its minor allele and miR-149-5p (Personal unpublished data).

In the present sample, we replicated the associations between the *FADS* gene cluster variability and total- and LDL-cholesterol previously reported in GWAS [12,13]. These associations were

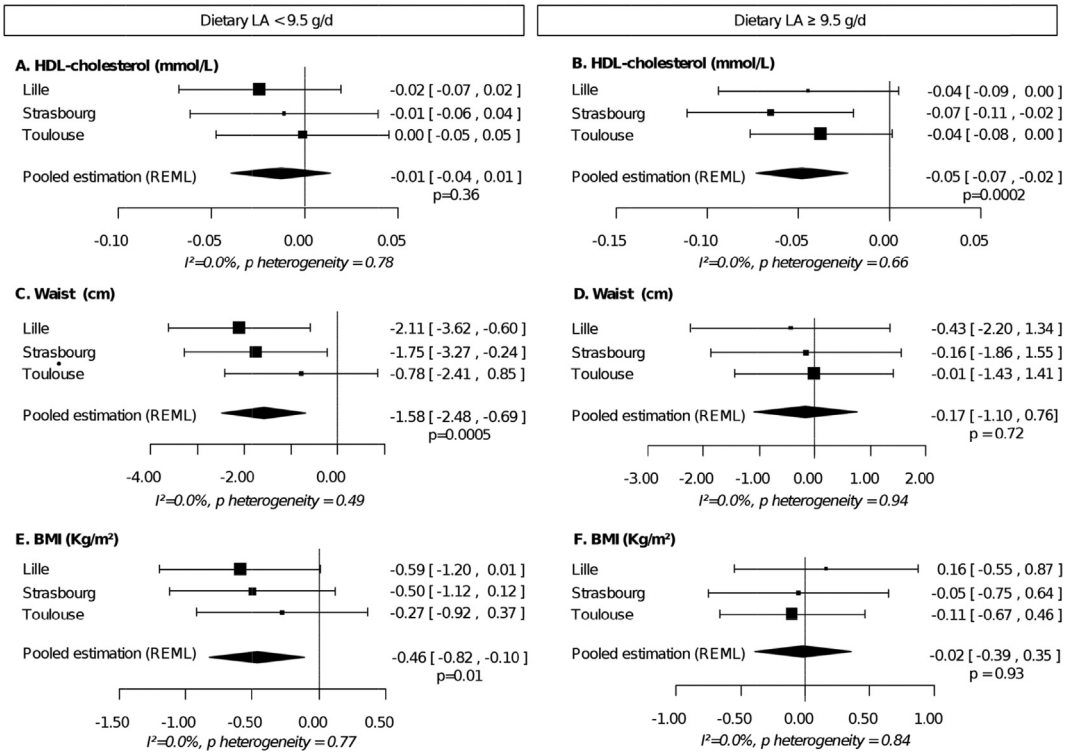

Fig. 1. Population-specific effects of the rs174547 SNP on HDL-cholesterol and obesity-related phenotypes, as a function of dietary LA intake in the MONA LISA study. Population-specific association between rs174547 and (**A, B**) HDL-cholesterol, (**C, D**) waist circumference, and (**E, F**) BMI. The graphs show the population-specific regression coefficients (beta ± standard error), which represent changes in the variable per copy of the rs174547C minor allele. Data are adjusted for age, gender, total energy intake, alcohol consumption, tobacco consumption, and physical activity ± BMI. For HDL-cholesterol, subjects taking lipid-lowering medications were excluded (n = 464).

homogeneous in high and low consumers of LA. In contrast, the *FADS* rs174547 minor allele was associated with lower HDL-cholesterol levels in above-median consumers of LA only. These results are in agreement with another report of an association between the minor allele of rs174546 (a SNP in perfect LD with rs174547 in the present study) and lower HDL concentrations in individuals consuming high levels of n-6 PUFAs (≥5.3% of total energy) [18]. Similarly, Hellstrand et al. reported an association between high dietary ALA/LA and higher HDL concentrations in rs174547C minor allele carriers [20]. In mechanistic terms, a less efficient FADS1 activity (as observed with the rs174547 minor allele) in combination with a high LA intake may result in LA accumulation, which may inhibit the production of n-3 LC-PUFAs [33,34] and consequently may reduce their HDL-cholesterol-raising effects [35–37]. Although functional experiments are required to elucidate the underlying biological mechanism(s), our data suggest that usual intakes of LA may modulate the effects of the FADS genetic variability on HDL-cholesterol concentrations.

Our results showed lower waist circumference and BMI in individuals who both carried the rs174547 C minor allele and consumed less than 9.5 g/day of LA. The biological mechanisms explaining the relationship between PUFAs and obesity are still unknown. However, several studies in animal models [38] and in humans [17,39,40] have reported positive associations between LA intake and AA and adiposity. Furthermore, other studies have suggested that a low FADS1 activity (as observed in rs174547 minor allele carriers) may protect from obesity. For example, it has been shown that *FADS1* KO mice fed with a chow- or high-fat-diet have lower body fat [41]. In addition, the use of a selective inhibitor of the Δ5-desaturase (encoded by FADS1) lowered insulin resistance and reduced body weight in diet-induced obese mice [42]. *FADS1* mRNA expression in circulating monocytes from 1264 subjects was also found to be positively associated with BMI [43]. Collectively, these data suggest that the rs174547 minor allele (which has been associated with a lower desaturase activity) in combination with a low LA intake could result in low AA levels that may protect from obesity. Meta-analyses of GWAS did not report any significant association between *FADS* SNPs and anthropometric phenotypes [44,45]. One possible explanation is that the association may have been masked because dietary LA levels were not taken into account in the analyses. Indeed, GWAS combine population samples with contrasted dietary habits and the lower desaturase activity in subjects carrying the rs174547 minor allele may be compensated by a high LA intake. Gene × diet interaction analyses in other population samples are necessary to validate our findings.

The present study had several strengths and limitations. Our analyses were restricted to the *FADS1* rs174547 polymorphism. However, this SNP shows the strongest associations with blood levels of LC-PUFAs [9,10,29] and tags a cluster of polymorphisms associated with plasma lipid levels in GWAS [12,13]. Therefore, the rs174547 SNP was a logical choice for assessing gene-diet interactions. The strengths of our study include a relatively large sample size and detailed information on dietary intakes based on 3-days records checked by a registered dietitian. However, this short-term diet measurement may not reflect the usual intake and introduce misclassification of PUFA dietary intakes. Lastly, the cross-sectional design of the present study did not allow to assess causality and the observed interactions need to be replicated in well-powered interventional studies.

In conclusion, the present study suggests that the dietary intakes of LA may modulate the impact of the *FADS* gene SNPs on HDL-cholesterol concentration, waist circumference and BMI.

These gene–nutrient interactions, if confirmed, suggest that subjects carrying the rs174547 minor allele might benefit the most from low dietary LA intakes.

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Statement of authorship

JDumont and AM wrote the manuscript; DC, NM, MM, AW, DA, JF, J-BR, PA designed the study; JDumont, LG and BGB performed the statistical analyses; JDallongeville and PA advised on the analysis of data. JDumont was the principal investigator and had primary responsibility for final content.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2017.07.012.

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