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*ADAM17*_i33708A>G polymorphism interacts with dietary n-6 polyunsaturated fatty acids to modulate obesity risk in the Genetics of Lipid Lowering Drugs and Diet Network study

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Abstract

Background and aims—The disintegrin and metalloproteinase ADAM17, also known as tumor necrosis factor alpha converting enzyme, is expressed in adipocytes. Importantly, elevated levels of *ADAM17* expression have been linked to obesity and insulin resistance. Therefore, the aim of this study was to evaluate the association of six *ADAM17* single nucleotide polymorphisms (SNPs) (m1254A>G, i14121C>A, i33708A>G, i48827A>C, i53440C>T, and i62781G>T) with insulin-resistance phenotypes and obesity risk, and their potential interactions with dietary polyunsaturated fatty acids (PUFA).

Methods and results—*ADAM17* SNPs were genotyped in 936 subjects (448 men/488 women) who participated in the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study. Anthropometrical and biochemical measurements were determined by standard procedures. PUFA intake was estimated using a validated questionnaire. G allele carriers at the *ADAM17*_m1254A>G polymorphism exhibited significantly higher risk of obesity (*P*=0.003),

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were shorter (*P*=0.017), had higher insulin (*P*=0.016), and lower HDL-C concentrations (*P*=0.027) than AA subjects. For the *ADAM17*_i33708A>G SNP, homozygotes for the A allele displayed higher risk of obesity (*P*=0.001), were heavier (*P*=0.011), had higher BMI (P=0.005), and higher waist measurements (*P*=0.023) than GG subjects. A significant gene-diet interaction was found (*P*=0.030), in which the deleterious association of the i33708A allele with obesity was observed in subjects with low intakes from (n-6) PUFA (*P*<0.001), whereas no differences in obesity risk were seen among subjects with high (n-6) PUFA intake (*P*>0.5)

Conclusion—These findings support that *ADAM17* (m1254A>G and i33708A>G) SNPs may contribute to obesity risk. For the *ADAM17*_i33708A>G SNP, this risk may be further modulated by (n-6) PUFA intake.

Keywords

gene-diet interaction; obesity; BMI; HDL-cholesterol; insulin concentrations

INTRODUCTION

Prevalence of obesity is steadily increasing among Americans, leading to increased morbidity and mortality due to type 2 diabetes and cardiovascular disease (CVD) (1). An environment characterized by an excessive energy intake and lower physical activity leads to obesity. However, not all people in societies with sedentary lifestyles and abundant food become obese, reinforcing the possibility that variation in genetic susceptibility may influence the risk of obesity. Several family and twin studies have demonstrated that genetic factors contribute 40–70% to the susceptibility variation in obesity (2). Therefore, obesity is a multifactorial disease which occurs as a result of the joint action of genetic and environmental factors, as well as their interaction (3).

Recently, several genome wide association analyses (GWAs) have discovered novel genes for common diseases, including obesity (4,5). Particularly, a disintegrin and metalloproteinase gene (ADAM17), also known as tumor necrosis factor alpha converting enzyme (TACE), has been associated with diabetes and CVD (6). Cleavage by TACE releases the soluble form of tumor necrosis factor, transforming growth factor-α, and other proteins such as the pre-adipocyte factor 1 (Pref-1) from their membrane-bound precursors (a phenomenon named ‘shedding’) (7). TNF-α is overexpressed in the adipose tissue of obese animals and humans, and its secretion from explanted adipose tissue is higher in obese as compared to lean samples (8). Likewise, ADAM17 is overexpressed in adipose tissue of obese mice and mRNA levels show modulation upon development of obesity and during differentiation of pre-adipocytes (9). Furthermore, ADAM17 is responsible for the cleavage that generates the large soluble form of Pref-1, leading to the inhibition of adipocyte differentiation (10).

In humans, only one study has investigated the effects of several *ADAM17* genetic variants on phenotypic traits. Morange et al (11) identified two novel polymorphisms, C-154A and Ser747Leu, associated with TNF-α plasma levels and risk of cardiovascular death, respectively. Likewise, several *TNF* genetic variants have been associated with triglycerides (TG), as well as obesity-related traits, pointing out as an obesity-susceptibility candidate

gene (12–15). Particularly, two TNF genetic variants at positions -308 (G>A) and -238 (G>A) in the 5′ regulatory region of the gene have been related to body fat, insulin resistance, as well as arterial blood pressure (13–15). However, prior studies failed to find an association between these TNF variants and obesity-related traits (16,17).

Because ADAM17 is a pivotal element in TNF-α and Pref-1 shedding, it is likely that this metalloproteinase contributes to obesity and its complications. Although the importance of *TNF* in obesity has been revealed, only one recent study (11) has assessed the effect of five *ADAM17* polymorphisms in patients with coronary artery disease. Moreover, that study did not assess the contribution of dietary factors which may modulate the risk for obesity. Hence, the aims of the present study were first to assess the association of novel polymorphisms in the *ADAM17* gene with anthropometric variables, lipid concentrations and obesity-related phenotypes. Secondly, we investigated whether *ADAM17* SNPs interact with dietary fatty acids to modulate the risk of obesity.

METHODS

Subjects

The study population consisted of 936 subjects (448 men and 488 women, aged 49±16 years) participating in the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study. Participants were recruited from three-generational pedigrees from two National Heart, Lung, and Blood Institute Family Heart Study field centers (Minneapolis, MN, and Salt Lake City, UT) (18). The study population was homogeneous with regard to ethnic background, being all individuals of European origin. The detailed design and methodology of the study has been described previously (19). The protocol was approved by the Institutional Review Boards at the University of Alabama, the University of Minnesota, the University of Utah, and Tufts University. Written informed consent was obtained from each participant.

Data collection

For GOLDN participants, clinical examinations at the baseline visit included anthropometrical and blood pressure (BP) measurements. Weight was measured with a beam balance and height with fixed stadiometer. BMI was calculated as weight, in kilograms, divided by the square of height, in meters. Waist circumference was measured at the umbilicus, whereas hip circumference was taken at the maximum posterior extension of the buttocks, measured in meters. BP was measured twice with an oscillometric device (Dinamap Pro Series 100, GE Medical Systems) while subjects were seated and had rested for five min. Reported systolic and diastolic BP values were the mean of the two measurements. Questionnaires were administered to assess demographic information, medical and medication history.

The habitual dietary food intake was assessed by the Diet History Questionnaire developed by the National Cancer Institute. It consisted of 124 food items and included portion size and dietary supplement questions. Two studies have confirmed its validity (20,21).

Laboratory methods

Blood samples were drawn after fasting overnight. Fasting glucose was measured using the method of a hexokinase-mediated reaction and total cholesterol using a cholesterol esterase cholesterol oxidase reaction on a Hitachi 911 autoanalyzer (Roche Diagnostics). The same reaction was used to measure HDL-C after precipitation of non-HDL cholesterol with magnesium/dextran. Low-density lipoprotein cholesterol (LDL-C) was measured by use of a homogeneous direct method (LDL Direct Liquid Select Cholesterol Reagent; Equal Diagnostics). TGs were measured by glycerol-blanked enzymatic method on the Roche COBAS FARA centrifugal analyzer (Roche Diagnostics). Fasting insulin and total adiponectin values were measured by specific radioimmunoassay kits (Linco Research).

Genetic analyses

DNA was extracted from blood samples and purified using commercial Puregene reagents (Gentra Systems) following the manufacturer's instructions. Six *ADAM17* SNPs (m1254A>G, rs11684747; i14121C>A, rs1880439, i33708A>G, rs10495563; i48827A>C, rs1056204; i53440C>T, rs34367192; i62781G>T, rs4622692) were genotyped. SNPs were selected using two criteria: bioinformatics functional assessment and linkage disequilibrium (LD) structure. Assessing LD structure at the *ADAM17* locus facilitated the selection of tag SNPs representing different LD blocks. Although *ADAM17*_i62781G>T SNP maps to intron 16, just 20 bp upstream of the splice acceptor site of exon 17, this SNP did not map within a poly-pyrimidine tract normally found 20–50 bp upstream of splice acceptors. Intronic SNPs were also analyzed with MAPPER to uncover potential allele-specific transcription factor binding sites (22) and manually checked for altered mRNA splice donor and acceptor sites and transversions affecting the poly-pyrimidine tract near splice acceptors. Genotyping was performed using a TaqMan® assay with allele-specific probes on the ABIPrism 7900 HT Sequence Detection System (Applied Biosystems) according to routine laboratory protocols (19). The description of *ADAM17* SNPs, as well as ABI assay-on-demand ID is available upon request. The pairwise LD between SNPs was estimated as correlation coefficient (r^2) in unrelated subjects using the Helixtree software package (Golden Helix).

Statistical analyses

SPSS software (version 16.0) was used for statistical analyses. A logarithmic transformation was applied to measures of plasma insulin and adiponectin to normalize the distribution of the data. Data are presented as means±SE for continuous variables and as frequencies or percentages for categorical variables. Differences in mean values were assessed by using analysis of variance and unpaired t-tests. Categorical variables were compared by using the Pearson chi-square or the Fisher's exact tests. Potential confounding factors were age, sex, physical activity, smoking habit (current vs. never and past smokers), alcohol consumption (current vs. never and past drinkers), prior coronary heart disease (CHD), diabetes, and family relationships. Obesity was defined as BMI ≥30 kg/m^2. We fitted logistic regression models to estimate the odds ratio (OR) and 95% CI of obesity across *ADAM17* genotypes stratified by dietary polyunsaturated fatty acid (PUFA) intakes (as dichotomous variables based on less than and equal or greater than median intakes) and to control for the effect of

covariates and total energy intake (in kcal). Two-sided *P* values <0.05 were considered statistically significant.

RESULTS

Characteristics of the GOLDN participants and genotype frequencies by sex are shown in Table 1. Although BMI did not differ by sex, average weight was higher in men compared to women. BP, glucose and TG concentrations were higher in men, whereas hip measurements and HDL-C and adiponectin concentrations were higher in women. No significant differences in other variables were observed. For all *ADAM17* polymorphisms, there was no departure from the Hardy-Weinberg equilibrium (*P* >0.05). The pairwise LD for all the six SNPs is presented as correlation coefficients in Supplemental Table 1. Given that two *ADAM17* SNPs (i53440C>T and i33708A>G) were in strong LD (>0.8) with *ADAM17*_ i62781G>T, the latter was excluded from further analyses. Because homozygous minor allele carriers were few, we analyzed two *ADAM17* SNPs (m1254A>G and i14121C>A) using two genotype categories (AA *vs.* AG+GG and AA+AC *vs.* CC, respectively). Other SNPs were analysed using three genotype categories (additive model). Considering the lack of a significant *ADAM17* gene-gender interaction for all variables examined, men and women were pooled together for subsequent analyses.

We examined associations between *ADAM17* SNPs and anthropometric measurements and lipids (Table 2). For the *ADAM17*_m1254A>G SNP, G allele carriers were shorter (1.70±0.01 vs 1.72±0.01 in m; *P*=0.017), and displayed higher insulin concentrations (1.11±0.01 vs. 1.07±0.02 in mU/L; *P*=0.016), and lower HDL-C concentrations (1.19±0.01 vs. 1.24±0.01 in mmol/L; *P*=0.027) than AA subjects (Table 2). As a result, G allele carriers exhibited higher risk of obesity compared with AA subjects (*P*=0.003) (Table 3). For the *ADAM17*_ i14121C>A, minor A allele carriers were taller (1.72±0.01 vs. 1.71±0.01 in m; *P*=0.023) and displayed higher glucose (5.68±0.05 vs. 5.54±0.03 in mmol/L; *P*=0.023), and lower adiponectin concentrations (3.83±0.01 vs. 3.86±0.01 in μg/L; *P*=0.041) than CC subjects. However, no differences in obesity risk were observed between genotypes (*P*>0.8) (Table 3). For the *ADAM17*_i33708A>G SNP, homozygotes for the AA allele were heavier (84±0.8 vs. 79±1.6 in kg; *P*=0.011), and displayed higher BMI (28.7±0.3 vs. 26.9±0.5 in kg/m^2; *P*=0.005), and higher waist measurements (0.97±0.01 vs. 0.93±0.02 in m; *P*=0.023) than GG subjects. Likewise, individuals homozygous for the A allele displayed higher risk of obesity than GG subjects (*P*=0.001) (Table 3). We did not observe any significant association between *ADAM17*_i48827A>C SNP and anthropometric variables or fasting lipids. For *ADAM17*_i53440C>T SNP, homozygotes for the major allele (C) were taller than TT subjects (*P*=0.040) (Table 2).

We next examined whether associations between *ADAM17* SNPs and obesity risk were modified by PUFA intake in this population (Supplemental Table 2). Because there were no significant differences in dietary intake according to genotype groups (data not shown), we investigated whether *ADAM17* gene-PUFA interactions could modulate the observed association with obesity risk. We dichotomized dietary intakes according to the median value for total PUFA, (n-3) PUFA, and (n-6) PUFA. A statistically significant gene-diet interaction was found (*P*=0.026), in which subjects homozygous for the i33708A allele

consuming diets containing low PUFA were associated with a higher risk of obesity than subjects homozygous for the i33708G allele (*P*>0.001), whereas no differences in obesity risk was observed among subjects consuming diets with high PUFA independent of the genotype (P>0.3) (Supplemental Table 2). We further tested if different types of PUFA would have different effects on the association between *ADAM17* SNPs and obesity. A significant gene-diet interaction was observed for (n-6) PUFA (*P*=0.030) in which the deleterious association of the i33708A allele with obesity was observed in subjects with low dietary intake from (n-6) PUFA (*P*>0.001), whereas no effect of this SNP on obesity was seen among subjects with high (n-6) PUFA intake (*P*>0.5) (Figure). No significant gene-diet interactions were found for (n-3) PUFA intake (*P*>0.3) nor other dietary fatty acids (data not shown). No significant gene-PUFA interactions were found for other analyzed *ADAM17* SNPs, regardless of the PUFA family investigated: (n-6) or (n-3) (Supplemental Table 2).

DISCUSSION

In the present study, we observed that two *ADAM17* genetic variants (m1254A>G and i33708A>G) were associated with obesity and insulin resistance-related phenotypes (higher insulin and lower HDL-C concentrations). Interestingly, a significant gene-diet interaction was found in which the deleterious association between the i33708A allele and obesity risk was only seen in those subjects with low intakes from PUFA, particularly from (n-6) PUFA. Overall, these findings suggest that dietary habits may modulate the contributions of *ADAM17* polymorphisms on the genetic susceptibility towards developing obesity.

The current study is the first to examine in a relatively large population the effects of several *ADAM17* genetic variants on insulin-resistance phenotypes and obesity in the context of dietary intake of PUFA. We found that two *ADAM17* genetic variants were significantly (m1254A>G, i33708A>G) associated with obesity, in which carriers of the m1254G allele and homozygotes for the i33708A allele had higher BMI. To date, only one prior study (11) has investigated the effect of five *ADAM17* SNPs in a prospective cohort of patients with coronary artery disease. The authors found that those patients carrying the 747Leu allele exhibited higher risk of cardiovascular death. Moreover, it has been recently described that HDL activates ADAM17-mediated substrate shedding and stimulates TNF-α release (23). This explains the association observed between *ADAM17*_m1254A>G and HDL-C concentrations. Because ADAM17 releases TNF-α from adipocytes (7) and prior data support their role in obesity-related phenotypes (9,11), we hypothesize that *ADAM17* is an obesity-susceptibility candidate gene. Prior evidence supported an association between two *TNF* polymorphisms at positions -308(G>A) and -238 (G>A) with increased anthropometric measurements, insulin resistance, and body fat in several populations (13–15). By contrast, no association between both polymorphisms and obesity was seen in 424 subjects self-referred to the Johns Hopkins Weight Management Center (16) and in 380 healthy subjects (17). Inconsistencies regarding the magnitude and direction of the association between these polymorphisms and obesity-related traits may be due to population-specific differences.

The mechanism by which these *ADAM17* polymorphisms may contribute to the observed associations is unknown. Given that five of the analyzed SNPs map to non-coding regions, the likelihood that these SNPs represent a functional mutation is low. However, the presence

of transcriptional enhancers and other regulatory elements, observed frequently in intronic regions, could explain our findings. In this regard, for the m1254A>G polymorphism, computational analysis by MAPPER indicated a potential allele-specific binding site for the hepatocyte nuclear factor-1 alpha (HNF1A/B) transcription factor, whose motif appears enriched in certain genes involved in insulin sensitivity and development of diabetes (24). Moreover, *ADAM17* _i33708A>G polymorphism has a potential allele-specific binding sites for the hepatocyte nuclear factor-2 (FOXA2) that appears to play a pivotal role as a physiological regulator of adipocyte differentiation and metabolism (25).

Interestingly, Dixon et al (5) reported that the polymorphism *ADAM17*_i62781G>T regulates the expression of *ADAM17* gene. Particularly, the major allele G was associated with a higher expression of *ADAM17*. As mentioned in the results section, the aforementioned SNP was in strong LD with SNP i33708A>G. Therefore, we can speculate that subjects homozygous for the major allele (A) may exhibit higher expression of ADAM17 and accordingly, an increased risk of obesity. In addition to genetic susceptibility, environmental factors such as dietary habits may contribute to the risk of obesity. A growing body of evidence supports the pivotal role that PUFAs play as important regulators of gene expression, particularly of genes involved in lipogenesis, triglyceride synthesis and fatty acid oxidation (26). Moreover, diets lower in PUFA (27) have been associated with an increased risk of obesity through mechanisms involving dyslipidemia, vascular dysfunction and insulin resistance. Although epidemiological evidence supports a protective role against obesity for dietary (n-3) PUFA (27), no significant interactions between obesity and intake of (n-3) PUFA were seen in this study. It has been reported that dietary (n-6) PUFA decreases white adipose tissue mass in rodents through the up-regulation of genes involved in energy-demanding processes like urea synthesis and gluconeogenesis (28). Moreover, Fontaine-Bisson et al (29) found that lean subjects with the -308A allele and the -238GG genotype at the *TNF* gene had higher risk of obesity with lower intakes of (n-6) PUFA. By contrast, a case-control study from the EPIC cohort (30) showed that the risk of being obese was higher for carriers of the -308A allele with large intakes of (n-6) PUFA. The described anti- or pro-adipogenic effect for (n-6) PUFA (31) may explain differences between studies. However, both findings are supportive of a synergistic relationship between genes and diet by which tailored dietary recommendations targeted at reducing the risk of obesity may modulate the genetic expression of several *ADAM17* variants.

Despite the evidence, we should be cautious in the interpretation of our data. The cross-sectional design of this study may weaken or distort any true relationship between *ADAM17* and PUFA intakes. Therefore, large prospective studies with a long period of follow-up are required. Another limitation is that dietary intake was measured within a limited period of time and may not be representative of previous or habitual exposures. Thus, replication and extension of research efforts to other populations and ethnic groups is clearly warranted.

In conclusion, the present study carried out in a White population supports the hypothesis that two *ADAM17* polymorphisms (m1254A>G and i33708A>G) play a pivotal role in obesity. The latest association was particularly evident in subjects with low dietary intake of (n-6) PUFA. Interestingly, this gene-diet interaction offers the potential to identify dietary and other lifestyle changes which, when implemented, may obviate the onset of obesity in

individuals with a specific genetic background. Therefore, our findings have wide-ranging implications for health initiatives targeted at reducing obesity risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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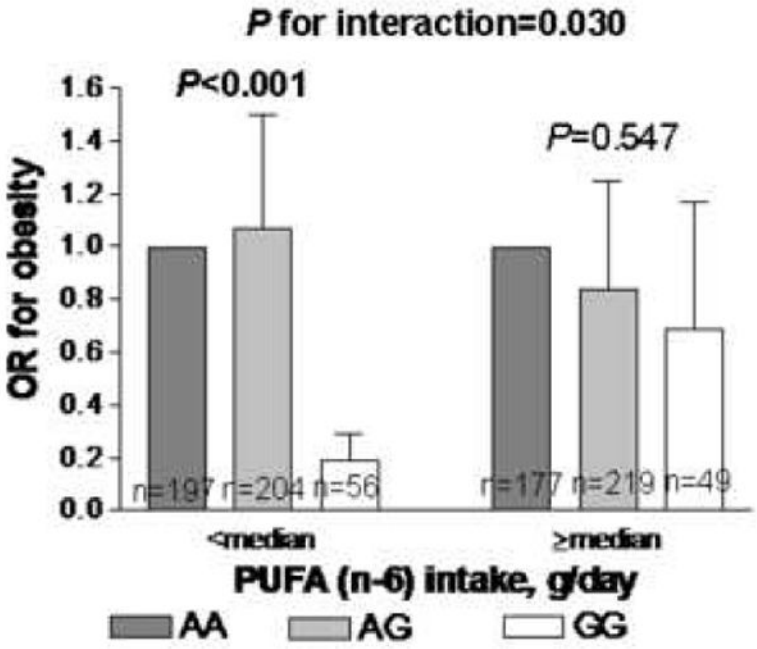

Figure.

OR and 95% CI obesity depending on *ADAM17*_i33708A>G genotypes and (n-6) PUFA intakes.

Table 1

General characteristics of the GOLDN population.

	Men (n=448)	Women (n=488)	*P*
Age, years	49±16.3	49±16.3	0.559
Weight, kg	91±16.0	76±17.7	**<0.001**
Height, m	1.78±0.73	1.65±0.70	**<0.001**
BMI, kg/m^2	28.7±4.7	28.2±6.4	0.159
Waist circumference, m	1.01±0.13	0.93±0.19	**<0.001**
Hip circumference, m	1.06±0.09	1.09±0.15	**0.001**
Current smokers, n (%)	36(8)	38(8)	0.904
Current alcohol drinkers, n (%)	224(50)	255(52)	0.513
Systolic blood pressure, mmHg	119±14.7	113±17.3	**<0.001**
Diastolic blood pressure, mmHg	71±8.7	66±9.1	**<0.001**
Glucose, mmol/L	5.77±1.05	5.39±0.91	**<0.001**
Log (Insulin, mU/L)	1.10±0.21	1.07±0.21	**0.040**
Total cholesterol, mmol/L	4.94±0.95	4.99±1.07	0.449
LDL cholesterol, mmol/L	3.22±0.76	3.12±0.85	0.051
HDL cholesterol, mmol/L	1.07±0.25	1.35±0.36	**<0.001**
Triglycerides, mmol/L	1.68±1.22	1.40±0.93	**<0.001**
Log (adiponectin, μg/L)	3.73±0.24	3.96±0.23	**<0.001**
Obesity, n (%)	149(33)	169(35)	0.679
ADAM17 SNPs, n (%)			
m1254A>G			
AA	287(64)	328(67)	0.335
AG+GG	161(36)	160(33)	
i14121C>A			
AA+AC	131(29)	128(26)	0.307
CC	317(71)	360(74)	
i33708A>G			
AA	179(40)	206(42)	0.732
AG	217(48)	224(46)	
GG	52(12)	58(12)	
i48827A>C			
AA	224(50)	222(46)	0.300
AC	181(40)	208(43)	
CC	43(10)	58(12)	
i53440C>T			
CC	115(26)	115(24)	0.699
CT	227(51)	249(51)	
TT	106(24)	124(25)	
i62781G>T			
GG	134(30)	148(30)	0.369

	Men (n=448)	Women (n=488)	*P*
GT	225(50)	260(53)	
TT	89(20)	80(16)	

All values are means ± SD.

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Table 2

Association between *ADAM17* genetic variants and anthropometric variables and lipids.

Variable	*ADAM17*_m1254A>G			*ADAM17*_i14121C>A			*ADAM17*_i33708A>G			
	AA (n=615)	AG+GG (n=321)	*P**	CC (n=677)	CA+AA (n=259)	*P**	AA (n=385)	AG (n=441)	GG (n=110)	*P*
Weight, kg	83±0.7	84±0.9	0.285	83±0.6	84±1.0	0.300	84±0.8	84±0.8	79±1.6	**0.011**
Height, m	1.72±0.01	1.70±0.01	**0.017**	1.71±0.01	1.72±0.01	**0.023**	1.71±0.01	1.71±0.01	1.71±0.01	0.734
BMI, kg/m^2	28.2±0.2	28.9±0.3	0.051	28.4±0.2	28.5±0.3	0.865	28.7±0.3	28.6±0.3	26.9±0.5	**0.005**
Waist, m	0.96±0.01	0.98±0.01	0.107	0.97±0.01	0.97±0.01	0.592	0.97±0.01	0.98±0.01	0.93±0.02	**0.023**
Hip, m	1.07±0.02	1.08±0.02	0.197	1.08±0.02	1.07±0.02	0.828	1.08±0.01	1.08±0.01	1.05±0.01	0.147
Glucose, mmol/L	5.56±0.03	5.61±0.04	0.342	5.54±0.03	5.68±0.05	**0.023**	5.61±0.04	5.61±0.03	5.44±0.07	0.141
Log (Insulin, mU/L)	1.07±0.01	1.11±0.01	**0.016**	1.08±0.01	1.09±0.01	0.617	1.08±0.01	1.10±0.01	1.06±0.02	0.240
Total cholesterol, mmol/L	4.98±0.03	4.94±0.05	0.483	4.99±0.03	4.94±0.05	0.603	4.96±0.04	4.96±0.04	5.04±0.08	0.620
LDL cholesterol, mmol/L	3.15±0.03	3.19±0.04	0.520	3.17±0.02	3.14±0.04	0.415	3.17±0.03	3.14±0.03	3.25±0.07	0.487
HDL cholesterol, mmol/L	1.24±0.01	1.19±0.01	**0.027**	1.22±0.01	1.22±0.01	0.796	1.22±0.01	1.22±0.01	1.24±0.02	0.627
Triglycerides, mmol/L	1.56±0.05	1.49±0.06	0.401	1.57±0.07	1.52±0.04	0.550	1.52±0.06	1.57±0.05	1.44±0.11	0.711
Log (adiponectin, µg/L)	3.86±0.01	3.85±0.01	0.565	3.86±0.01	3.83±0.01	**0.041**	3.86±0.01	3.85±0.01	3.87±0.02	0.612

Variable	*ADAM17*_i48827A>C				*ADAM17*_i53440C>T			
	AA (n=446)	AC (n=389)	CC (n=101)	*P*	CC (n=230)	CT (n=476)	TT (n=230)	*P*
Weight, Kg	84±0.8	83±0.8	83±1.7	0.909	83±1.1	83±0.8	84±1.1	0.797
Height, m	1.71±0.01	1.71±0.01	1.71±0.01	0.533	1.72±0.01	1.71±0.01	1.70±0.01	**0.040**
BMI, Kg/m^2	28.5±0.3	28.5±0.3	28.4±0.5	0.974	28.1±0.4	28.5±0.3	28.9±0.4	0.292
Waist, m	0.97±0.01	0.96±0.01	0.95±0.02	0.512	0.96±0.01	0.97±0.01	0.97±0.02	0.903
Hip, m	1.08±0.01	1.07±0.01	1.07±0.02	0.661	1.08±0.01	1.07±0.01	1.08±0.02	0.657
Glucose, mmol/L	5.61±0.03	5.54±0.04	5.60±0.08	0.386	5.57±0.05	5.59±0.03	5.56±0.01	0.857
Log (Insulin, mU/L)	1.10±0.01	1.08±0.01	1.06±0.02	0.099	1.09±0.01	1.09±0.01	1.08±0.01	0.796
Total cholesterol, mmol/L	4.94±0.04	5.01±0.04	4.94±0.09	0.534	4.96±0.06	4.96±0.04	4.96±0.06	0.967
LDL cholesterol, mmol/L	3.17±0.03	3.19±0.03	3.09±0.07	0.552	3.16±0.05	3.17±0.03	3.17±0.05	0.980
HDL cholesterol, mmol/L	1.22±0.01	1.22±0.01	1.24±0.03	0.530	1.22±0.02	1.22±0.01	1.19±0.02	0.691
Triglycerides, mmol/L	1.51±0.05	1.56±0.06	1.54±0.12	0.810	1.56±0.08	1.52±0.05	1.53±0.08	0.916
Log (adiponectin, µg/L)	3.84±0.01	3.87±0.01	3.87±0.02	0.111	3.84±0.02	3.85±0.01	3.87±0.02	0.438

Values are mean±SE.

* *P* values are adjusted for age, sex, smoking habit, alcohol consumption, diabetes, coronary heart disease, and family relationships.

Table 3

Odds ratio for obesity depending on *ADAM17* genotypes.

Genotype	OR (95% confidence interval)	*P**	*P** for trend
*ADAM17*_m1254A>G			
AA (n=615)	1 (Reference)	**0.003**	**0.003**
AG+GG (n=321)	1.56 (1.16–2.08)		
*ADAM17*_i14121C>A			
CC (n=677)	1 (Reference)	0.878	0.878
AA+AC (n=259)	0.98 (0.71–1.34)		
*ADAM17*_i33708A>G			
AA (n=385)	1 (Reference)	**<0.001**	**0.001**
AG (n=441)	0.94 (0.55–1.61)	**0.001**	
GG (n=110)	0.37 (0.28–1.72)		
*ADAM17*_i488274A>C			
AA (n=446)	1 (Reference)	0.598	0.426
AC (n=389)	1.16 (0.71–1.89)	0.261	
CC (n=101)	0.88 (0.61–1.61)		
*ADAM17*_i53440C>T			
CC (n=230)	1 (Reference)	**0.018**	0.057
CT (n=476)	1.34 (0.95–1.87)	0.237	
TT (n=230)	1.64 (0.67–1.51)		

* *P* values were adjusted for age, sex, smoking habit, alcohol consumption, diabetes, coronary heart disease, and family relationships.