Title: Interplay of physical activity and genetic variants of the endothelial lipase on cardiovascular disease risk factors

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Keywords: LIPG, cardiovascular disease, genetic susceptibility, adolescents, physical activity

Running head: LIPG polymorphisms and CVD risk factors
Author contributions

JMP, IL, AIR, LC, LB, NM, MGG, YM, CPL, LAM, AM, MJC, DST and JRR designed the study; DST performed all analyses; DST and JRR wrote the initial draft and all co-authors significantly contributed to the final version.

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Acknowledgments

The HELENA Study received funding from via contract FOOD-CT-2005-007034 within the European Community Sixth RTD Framework Programme. The study was also supported by the Spanish Ministry of Education (FPU13/03410; FPU16/02127), via Redes Temáticas de Investigación Cooperativa RETIC grant (Red SAMID RD16/0022), by the University of Granada Plan Propio de Investigación 2016 (Excellence actions: Unit of Excellence on Exercise and Health [UCEES]), by the European Regional Development Fund (ERDF), by the Junta de Andalucía, Consejería de Conocimiento, Investigación y Universidades (ref. SOMM17/6107/UGR), and by grants from the Public University of Navarra, “Ayudas a Grupos de Investigación (2019)”. We wish to thank Rosa Maria Torres, Petra Pickert, and Anke Berchtold for their contribution to laboratory work.

Conflict of Interest
The authors declare no competing interests. The content of this article reflects only the authors’ views, and the European Community is not liable for any use that may be made of the information contained therein.

**Category of study:** Clinical research article.

**Consent Statement:** The subjects and their parents/guardians were fully informed regarding the aims and methods of the study, including the inclusion criteria, and provided informed written consent for their data to be analysed.

**Impact:**

- Using gene-phenotype and gene*environment analyses, we detected associations between the Endothelial lipase gene and cardiovascular risk factors, along with interactions with physical activity.

- This study shows that physical activity may modulate the influence of *LIPG* gene on cardiovascular risk in adolescents.

- These results bring insights about the mechanisms by which physical activity positively influences CVD in adolescents.
Abstract

Background: To study the association of endothelial lipase gene (*LIPG*) polymorphisms with cardiovascular disease (CVD) risk factors in adolescents and their interaction with physical activity.

Methods: Six polymorphisms of *LIPG* were genotyped in 1057 European adolescents (12-18 years old) enrolled in the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) Study. CVD risk factors related to lipid profile, blood pressure, adiposity and glucose regulation were recorded. Physical activity was objectively measured by accelerometry.

Results: The major C allele of rs2000813, the minor T allele of rs2276269, and the minor G allele of rs9951026 were associated with lower levels of several CVD risk factors related to lipid profile. We also found a significant association of the TTACA *LIPG* haplotype (rs2000812, rs2000813, rs8093249, rs2276269 and rs9951026) with higher concentrations of low-density cholesterol and apolipoproteinB. Finally, the interaction between physical activity and the polymorphisms rs2000813, rs2276269 and rs9951026 had a significant influence on several CVD risk factors.

Conclusions: *LIPG* polymorphisms were significantly associated with CVD risk factors in European adolescents. Interestingly, alleles of these polymorphisms were associated with a better cardiovascular profile in physically active adolescents only. High physical activity may reduce the development of CVD, modulating its genetic risk.
Introduction

Cardiovascular disease (CVD) is the result of a complex interplay between genetic and environmental factors. Several genes and polymorphisms have been associated with susceptibility to CVD by influencing risk factors such as blood pressure, and high-density and low-density cholesterol (HDL-C and LDL-C, respectively) and triglyceride (TG) levels (1). The influence of a number of genetic variants on stroke (2,3) and myocardial infarction (1,4–6) has also been reported. The development of CVD therefore appears to have a polygenic basis (7).

Physical activity plays a key role in the prevention and treatment of CVD (8,9). Regular physical activity provides a wide range of health benefits in the general population, including the improvement of blood pressure, sensitivity to insulin and tolerance to glucose (beneficial in diabetes), and increased HDL-C levels plus reduced TG, LDL-C and total cholesterol (TC) levels (improved lipid profile). Together these all reduce the overall risk of developing CVD (8). Current evidence suggests that moderate-intensity physical activity reduces the incidence of all-cause mortality, and especially death associated with coronary artery disease (CAD) (8). The results of several cross-sectional and interventional studies also suggest that the genetic predisposition to CVD risk factors is lowered by moderate levels of physical activity in adults (10,11) and adolescents (12–14).

The endothelial lipase (LIPG) is a member of the TG lipase family with only a minor role as triglyceride lipase, acting primarily as a phospholipase (15). LIPG favours the internalization of HDL-C, LDL-C and very low-density cholesterol (VLDL-C), being especially relevant for HDL-C metabolism. Therefore, LIPG influences the levels of lipoprotein in plasma and facilitates the release of lipid precursors (fatty acids) inside the cell (16). In addition, this lipase could favour
atherogenesis by its pro-inflammatory effect via reduction of HDL-C (anti-inflammatory lipid) or the production of inflammatory markers like pro-inflammatory cytokines (16,17). Accordingly, several genetic association studies have assessed the association between polymorphisms of LIPG and plasma lipids (6,18,19), along with its interaction with physical activity (10,20). Given the role of LIPG in the clearance of plasma lipids, polymorphisms of LIPG may influence the CVD risk factors affecting adolescents.

The Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study (www.helenastudy.com) was designed to provide reliable data on nutrition and health-related phenotypes in a relatively large sample of European adolescents from nine countries. The data for this cohort includes information on 6 SNPs of the LIPG gene, as well as CVD risk factors. The aim of the present study was to assess the association between 6 LIPG polymorphisms and CVD risk factors in this population. The influence of the interaction between physical activity and LIPG polymorphisms on CVD risk factors was also examined.

Methods

Participants

A total of 3865 subjects (12-18 years-old) from 10 cities in nine European countries (Austria, Belgium, France, Germany, Greece, Hungary, Italy, Spain, and Sweden) were enrolled in the HELENA study. All were randomly selected from public and private schools in each city between October 2006 and December 2007. Blood samples for genetic and clinical biochemistry analyses were obtained from one-third of the subjects (N=1155), which were randomly selected. The data for 1057 (552 girls) of these subjects with information on LIPG polymorphisms and CVD risk
factors were examined for the present study. The selected subjects did not differ respect to the rest of the cohort in terms of age, sex or BMI (p>0.1 in all cases; p-values obtained with Kruskal-Wallis tests between groups). Within this sample, physical activity data were also available for 698 subjects. The subjects and their parents/guardians were fully informed regarding the aims and methods of the study, including the inclusion criteria (21,22), and provided informed written consent for their data to be analysed. The study was conducted according to the ethical guidelines of the Declaration of Helsinki (Edinburgh 2000 revision), the Good Clinical Practice guidelines, and adhering to the laws on clinical research in humans of all the participating countries. The human research committees of each involved centre approved the protocol followed (23).

Assessment of cardiovascular risk factors

Thirty ml of venous blood were extracted between 8 and 10 am, 10 h after the last meal consumed (fasting conditions). Stability of samples had been tested before (24). The CVD risk factors analysed included serum TC, HDL-C, LDL-C, apolipoproteinA1 (ApoA1), apolipoproteinB (ApoB), TG and glucose, all determined using the enzymatic methods of the Dimension RxL clinical chemistry system (Dade Behring, Schwalbach, Germany). Insulin was measured by solid-phase, two-site, chemiluminescent, immunometric assay using an Immulite 2000 analyzer (DPC Biermann GmbH, Bad Nauheim, Germany). Leptin concentrations were measured in duplicate using the RayBio® Human Leptin ELISA Kit. The homeostatic model assessment (HOMA) index - an indicator of insulin resistance - was calculated as ([glycaemia X insulin]/22.5). The quantitative insulin sensitivity check index (QUICKI) was also determined, as 1/[log(insulin) + log(glycaemia)]. Blood pressure
was measured in the extended right arm using an OMRON M6 automatic oscillometric device. The subjects sat quietly for 5 min before taking two measurements 5 min apart. The mean (in mmHg) was used in all analyses.

Anthropometric measurements were made in triplicate according to standardised techniques (25). Weight was measured to the nearest 0.1 kg using a SECA 861 electronic scale (Seca Deutschland, Hamburg, Germany), height to the nearest 0.1 cm using a SECA 225 stadiometer, and the skinfold thicknesses on the left side at the triceps and subscapularis to the nearest 0.2 mm using a Holtain Caliper (Holtain Ltd, Crymmych, Wales). A CVD risk score was computed from the mean of the standardized values [(value-mean)/standard deviation] of the following variables: TC/HDL, TG, HOMA, systolic blood pressure, and triceps and subscapular skinfolds, as done previously in other pediatric cohorts (26,27).

Assessment of physical activity

Physical activity was assessed over seven consecutive days using a GT1M uniaxial accelerometer (ActiGraph, Pensacola, FL) attached to the lower back (28). Adolescents were instructed to wear the accelerometer during all time spent awake, removing it only during water-based activities. At least three days of recording for a minimum of 8 h per day were required for data to be used in analyses (28). The time-sampling interval (epoch) was set at 15 s. The time engaged in at least moderate physical activity (≥3 metabolic equivalents) was calculated based on a standardized cut-off of 2000 counts/min or more. Moderate to vigorous physical activity (MVPA) was dichotomized into <60 min/day (inactive adolescents) and ≥60 min/day (active adolescents).
Genotyping

Blood for DNA extraction was collected in EDTA K3 tubes, stored at the Analytical Laboratory at the University of Bonn and then sent to the Genomic Analysis Laboratory at the Institut Pasteur de Lille (Lille, France). DNA was extracted from white blood cells with the Puregene kit (Qiagen, Courtaboeuf, France) and stored at -20 °C. In the context of the HELENA study, polymorphism selection was performed using previous literature and/or HapMap (tag SNPs with $r^2$ higher than 0.8) as previously described (29,30). In the specific case of LIPG polymorphisms, the selection was based on previous literature of LIPG SNPs. Samples were genotyped by using an Illumina System (Illumina, Inc, San Diego, California) and the software used was GoldenGate (Inc., San Francisco, California). High rate of genotyping success was performed (≥99.8%) and each polymorphism respected the Hardy-Weinberg equilibrium (p≥0.05 in all cases; Table 1). Several polymorphisms of the LIPG gene showed linkage disequilibrium between them (Figure 1).

Statistical analysis

Deviations from the Hardy-Weinberg equilibrium (HWE) were determined using an exact test with significance set at p<0.01 (31). Associations between genetic markers and CVD risk factors were assessed via linear regression models. Five genetic models (dominant, recessive, additive, codominant and overdominant) were contemplated in all analyses. The adjustment variables were body mass index (BMI; calculated as weight [in kg] divided by height in m²), age, sex and centre. The influence of the interaction between physical activity and polymorphisms on CVD risk factors was also examined using the same models.
For each polymorphism, p values were computed using the likelihood ratio test (LRT) comparing a model with the polymorphism/the interaction term, and a null model without the term of interest. Associations in which any combination of genotype and/or level of physical activity was represented by fewer than 10 subjects were discarded. All analyses were performed using R software (32). The associations between all SNPs and phenotypes under a given heritage model were contemplated as the family test, i.e., the number of tests was equal to the number of SNPs analysed. Significant genotype-phenotype associations were selected for interaction and haplotype analysis. Given the exploratory nature of these analyses, and the reduced number of independent markers (these were in linkage disequilibrium; Figure 1), the Bonferroni correction was deemed too stringent (33). Instead, an exploratory selection of associations was undertaken using an approach that controls for the expected proportion of false positives (false discovery rate [FDR]) (34,35). Associations with a FDR lower than 0.1 were used in the interaction and haplotype analyses.

Linkage disequilibrium between polymorphisms and haplotype block structures was examined using Haploview v.4.2 software (http://www.broad.mit.edu/mpg/haploview), haplo.stats software (36), and the “SNPassoc” R package (31). First, haplotype blocks were generated by the four-gamete rule algorithm (37) (Figure 1). For each block, it was determined whether the frequencies of haplotypes deviated from the expected under linkage equilibrium. Finally, the association between haplotypes and phenotypes was assessed using a permutation procedure. Only additive and dominant models were contemplated given the low frequency of some haplotypes. For significant associations, regressions between haplotypes and phenotypes were performed to search for significant differences between haplotype levels. Again, the FDR was calculated, using p values
to spot differences between the reference (the most common) and other haplotypes. In the interaction analyses, a correction for multiple comparisons was made using the FDR (threshold 0.05). Note that no LIPG polymorphism was significantly associated with the time spent in moderate to vigorous physical activity (p>0.13 in all cases; p-value obtained by comparing linear models with and without each polymorphism as predictor and including physical activity as response variable, i.e., nested models).

Results

Values of the CVD risk factors considered are shown across the whole cohort in Table 2, but also stratified according to CVD risk, using the median of CVD risk score as cut-off. Adolescents under lower CVD risk showed better lipid profile, lower adiposity, better glucose regulation and lower blood pressure, which is congruent with the calculation of CVD risk.

Association between LIPG polymorphisms and CVD risk factors

The exploratory analysis suggested that three of the six SNPs examined (rs2000813, rs2276269 and rs9951026) were associated with CVD risk factors (see Figure 2 for significant associations under additive model; see Supplementary Appendix S1-2 for significant associations across all models). P values for all markers and heritage models are shown in the Supplementary Appendix S3-20.

The major C allele of rs2000813 was associated with lower TC (p=0.00168; FDR=0.0101), lower LDL-C (p=0.00031; FDR=0.0019), lower TC/HDL ratio (p=0.01209; FDR=0.0725), lower LDL-C/HDL-C ratio (p=0.00485; FDR=0.029), lower ApoB (p=0.00054; FDR=0.0033), and lower ApoB/ApoA1 ratio (p=0.00236; FDR=0.0141). Similarly, an association of the minor T allele of rs2276269 was
observed with lower LDL-C/HDL-C and ApoB/ApoA1 ratios (P=0.04784 and 0.03044; FDR=0.0957 and 0.0609, respectively). Finally, an association was observed between the minor G allele of rs9951026 and lower LDL-C (P=0.03287; FDR=0.0986), along with lower LDL-C/HDL-C and lower ApoB/ApoA1 ratios (P=0.02961 and 0.01989; FDR=0.0888 and 0.0597, respectively).

**Association between LIPG polymorphism haplotypes and CVD risk factors**

*LIPG* block 1 contains rs2000812, rs2000813, rs8093249, rs2276269 and rs9951026 (Figure 1). The TTACA haplotype of *LIPG* was significantly associated with higher LDL-C under the dominant model (global p=0.0116) than were haplotypes TCATG (difference between groups 0.05; 95%CI=0.01-0.08; p=0.0112; FDR=0.02), TCACA (difference between groups 0.07; 95%CI=0.02-0.11; p=0.0059; FDR=0.02) or CCATG (difference between groups 0.05; 95%CI=0.01-0.09; p=0.0120; FDR=0.02). The same pattern was seen under the additive model: the TTACA haplotype was associated with higher LDL-C (global p=0.0181) than was the TCATG (difference between groups 0.04; 95%CI=0.01-0.07; p=0.0089; FDR=0.0154), TCACA (difference between groups 0.07; 95%CI=0.02-0.11; p=0.0020; FDR=0.0101) or CCATG haplotype (difference between groups 0.05; 95%CI=0.01-0.08; p=0.0092; FDR=0.0154).

Finally, the TTACA haplotype was significantly associated with higher ApoB values under the additive model (global p=0.043) than was the TCATG (difference between groups 0.04; 95%CI=0.01-0.07; p=0.0084; FDR=0.0211), TCACA (difference between groups 0.06; 95%CI=0.02-0.09; p=0.0064; FDR=0.0211) or CCATG haplotype (difference between groups 0.04; 95%CI=0.01-0.07; p=0.0171; FDR=0.0285).
Interaction between LIPG polymorphisms, physical activity and CVD risk factors

The alleles of rs2000813, rs2276269 and rs9951026 were associated with a lower cardiovascular risk only in the active adolescents (i.e., those who practiced ≥60 min/day of moderate to vigorous physical activity; see Figure 3 for significant interactions under additive models; see Supplementary Appendix 21 for significant interactions across all models).

The major C allele of rs2000813 was associated with lower LDL-C levels only in those individuals performing moderate/high levels of physical activity (p=0.035417; FDR=0.035417). Similarly, active subjects carrying the minor T allele of rs2276269 showed lower LDL-C/HDL-C values (p=0.006504; FDR=0.022013), and lower ApoB/ApoA1 ratios (p=0.014327; FDR=0.035817). Finally, active subjects carrying the minor G allele of rs9951026 showed lower values of LDL-C (p=0.023001; FDR=0.035417), LDL-C/HDL-C (p=0.011235; FDR=0.022013), and ApoB/ApoA1 (p=0.007245; FDR=0.035817).

Discussion

Our preliminary analyses showed associations between the C, T and G alleles of LIPG rs2000813, rs2276269 and rs9951026, respectively, and a better cardiovascular profile (lower TC, LDL-C, TC/HDL-C, LDL-C/HDL-C, ApoB/ApoA1 and ApoB values) in European adolescents. In addition, the LIPG haplotype block TTACA (rs2000812, rs2000813, rs8093249, rs2276269 and rs9951026) was significantly associated with higher levels of LDL-C and ApoB. Importantly, physical activity modulated the influence of LIPG polymorphisms on CVD risk factors; the alleles of
rs2000813, rs2276269 and rs9951026 polymorphisms were associated with a better cardiovascular profile only in physically active adolescents.

Previous studies have shown significant associations between lipid profile and some of the polymorphisms analysed in the present study in adults. Halverstadt et al. (20) found higher levels of some HDL-C fractions for carriers of the CC genotype of rs2000813. Moreover, Liu et al. (38) reported an association between this polymorphism and higher HDL-C in two ethnic Chinese groups, but for the genotype TT. They also showed an association between rs2000813 genotype and ApoB levels in one of the groups. A similar pattern was found by Hutter et al. (19) in Japanese Americans, an haplotype constituted by rs2000813 T and rs3813082 C alleles was associated with higher HDL-C and ApoA1, along with lower LDL-C and ApoB. Paradis et al. (39) reported the same pattern, with higher HDL-C values related to the rs2000813 T allele in white women. Similarly, Elnaggar et al. (6) showed that T carriers had higher values of HDL-C and lower risk of CAD in a Egyptian cohort, being the T allele a protective factor for CAD independently of plasma lipids. Mank-Seymour et al. (18) also detected a relationship between HDL-C and one of the polymorphism considered in this study, as white carriers of the TT allele of rs2276269 had lower HDL-C levels. Finally, other studies have failed to detect any association between lipid profile and LIPG polymorphisms analysed in the present study. For example, Smith et al. (10) found no association between either rs2000813 or rs6507931 polymorphisms with HDL-C or LDL-C when interaction with lifestyle was not considered. Other studies have found no differences between genotypes of rs2000813 and LDL-C levels (6,20,39). Similarly, DeLemos et al. (40) found no differences in the genotype frequencies of rs2000813 between white individuals with high HDL-C levels and normal level controls. The same lack of significance was
reported by Yamakawa-Kobayashi et al. (41) for rs2000813 in a cohort of Japanese schoolchildren. To our knowledge, there is no previous evidence relating the rs9951026 polymorphism to plasma lipoprotein levels in European adolescents or any other population. There is an important inconsistence between studies about the influence of \textit{LIPG} on lipid profile, including the present study. Although we found associations between \textit{LIPG} polymorphisms and ratios including HDL-C or ApoA1, no significant association was found for these variables in isolation. In addition, we found a strong link between \textit{LIPG}, LDL-C and ApoB as previous studies, but in opposite sense. In our study, T allele of rs2000813 was associated with higher LDL-C. Variation between study results can be caused by several factors. For example, the measurement of variables differed between studies, with some of them estimating LDL-C through the Friedewald's formula (42) instead of using direct measurements like in the present study. In addition, the existence of false positives/negatives in these studies cannot be disregarded, although the present showed strong significant associations for LDL-C and ApoB even after applying stringent corrections for multiple comparison (see Methods section). Other relevant factors for explaining this variability could be differences in population-dependent penetrance and allele frequencies, subject age, ethnicity and sample size.

Exercise can affect lipid profile (43), but its effect varies among individuals (44), suggesting the existence of heritable differences in the response to physical activity. In the present work, carriers of certain genotypes of the rs2000813, rs2276269 and rs9951026 polymorphisms showed a better lipid profile under moderate/high levels of physical activity. Halverstad et al. (20) showed the interaction between physical activity and rs2000813 to significantly influence HDL-C levels, reporting higher levels of HDL-C in CC compared to CT-TT genotypes under
the training intervention. Interestingly, CT-TT carriers showed a better lipid profile than the CC carriers before the training intervention, suggesting that these genotypes may be protective under sedentary conditions. This might an additional factor to explain the discrepancy among studies assessing the association between \textit{LIPG} polymorphism and HDL-C levels without contemplating physical activity, as a given genotype could be protective or not depending on the level of physical activity. Smith et al. (10) also found a significant interaction between \textit{LIPG} and physical activity. Women spending \(\geq 2.6\) h/day of on-screen time and who carried the TT genotype of the rs6507931 polymorphism had lower total HDL-C and higher small LDL-C, suggesting a worse lipid profile compared to the CT-CC genotypes. In contrast with rs6507931, no association was found for the rs2000813 polymorphism in that study. Our results follow the inconsistency of previous studies, as we found an interaction between \textit{LIPG} rs2000813 polymorphism and physical activity on LDL-C and related ratios, while no significant interaction was found for rs6507931 or HDL-C.

Discrepancies between these studies could be due to the method used for monitoring study variables. Halverstadt et al. (20) estimated LDL-C instead of using direct measurements, which was the approach followed in the present study and by Smith et al. (10). In addition, the monitoring of physical activity differs between studies. In contrast with Halverstadt et al. (20) and the present study, Smith et al. (10) did not objectively measure physical activity; rather, they used the time spent in front of screens as a proxy of activity level. These factors, along with differences in the sample characteristics could explain the observed discrepancies.

Endothelial lipase is involved in the metabolism of plasma lipoproteins such as LDL-C, VLDL-C, and HDL-C (16). This is congruent with the association detected between \textit{LIPG} polymorphism and plasma lipoproteins. LIPG is also involved in the
uptake of ApoA1 and ApoB (constituents of HDL-C and LDL-C particles respectively) in mice, via heparin sulphate proteoglycans that bind to LIPG in the cell membrane (45,46). Accordingly, in the present work, significant associations were found between LIPG polymorphisms and ApoB levels, and the ApoB/ApoA1 ratio. In contrast with other lipases of its family, LIPG has only minor triglyceride lipase activity (16), which agrees with the lack of significance of any association with TG reported here or in previous studies (20,38,47).

The interaction between physical activity and LIPG could be explained by blood pressure. Regular physical activity is known to reduce the blood pressure (8,48), which in turn could affect LIPG production via endothelial shear stress. Support for this hypothesis comes from evidence showing that LIPG mRNA increases under fluid shear stress in cultured endothelial cells and in hypertensive animals (49,50). Another cause could be inflammation, as long-term inflammation impairs the effects of exercise (e.g., increased anabolic resistance under low-grade chronic inflammation in elderly (51)). LIPG has been positively associated with inflammation (52,53), thus polymorphisms that reduce the functionality of this lipase might generate a more favourable environment for the development of beneficial effects of exercise. Lower LIPG activity might reduce inflammation via a reduction in HDL-hydrolysis (HDL-C has anti-inflammatory activity) (16), but this would not fully explain our results given the lack of associations between LIPG and HDL-C. However, LIPG can also influence inflammation through facilitation of monocyte-endothelial adhesion and reduction of pro-inflammatory cytokines production (16,17,54). Given the lack of data in plasma for endothelial lipase in the present study, possible mechanisms of action can only be hypothesised. Further research is needed to elucidate the enzymatic mechanism of action and impact on plasma lipids.
The present study has some limitations. Firstly, it is observational in design, so no cause-effect relationships can be established. The results should be tested in future experimental studies looking for causal correlations between *LIPG* polymorphisms, CVD risk factors and physical activity, along with their impact on hard endpoints like myocardial infarction to quantify their clinical relevance. In addition, these associations could be modified by gene-gene and other gene-environment interactions. Finally, no information is available regarding patterns of relatedness between subjects, and the ethnic origins of the sample members are unknown. Our results should be considered carefully; studies with larger sample size could help to further confirm the role of *LIPG* gene on the development of CVD and its interaction with physical activity.

In summary, an association was found between *LIPG* polymorphisms and CVD risk in European adolescents. The results also suggest that the influence of the rs2000813, rs2276269 and rs9951026 polymorphisms on the lipid profile can be modulated by physical activity. *LIPG* polymorphisms were only associated with a better cardiovascular profile in those individuals meeting the recommendations of daily physical activity. Therefore, increased physical activity may modulate the genetic risk of CVD development.
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**Figure legends**

**Figure 1.** Block 1 *LIPG* polymorphisms, which contains rs2000812, rs2000813, rs8093249, rs2276269 and rs9951026 according to the obtained genotyping data. Box numbers refer to linkage disequilibrium (D’) between SNPs, while boxes with no number indicate 100% correlation (D’ = 1). Logarithm of odds (LOD) score $\geq 2$ and D’ = 1 shown as dark gray. See Haploview documentation about the standard colour scheme for further details (https://www.broadinstitute.org/haploview/ld-display).

**Figure 2.** Significant associations (FDR<0.1) between *LIPG* polymorphisms and CVD risk factors under additive model. The P value and false positive discovery rate (FDR) are shown for each association. Values are adjusted for body mass index, centre, sex, and age.

**Figure 3.** Significant interactions (FDR<0.05) between the studied SNPs and level of physical activity under additive model. The P value and false positive discovery rate (FDR) are shown for each association. Values are adjusted for body mass index, centre, sex, and age. Abbreviations: PA = physical activity.
