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## ORIGINAL ARTICLE

# Genome-Wide Association Study of the Postprandial Triglyceride Response Yields Common Genetic Variation in *LIPC* (Hepatic Lipase)

Dorina Ibi<sup>1</sup>, MSc; Raymond Noordam<sup>1</sup>, PhD; Jan Bert van Klinken<sup>1</sup>, PhD; Ruifang Li-Gao<sup>1</sup>, PhD; Renée de Mutsert, PhD; Stella Trompet<sup>1</sup>, PhD; Tim Christen<sup>1</sup>, MSc; Lisanne L. Blauw, PhD; Diana van Heemst, PhD; Dennis O. Mook-Kanamori, MD, PhD; Frits R. Rosendaal, MD, PhD; J. Wouter Jukema<sup>1</sup>, MD, PhD; Martijn E.T. Dollé, PhD; Patrick C.N. Rensen<sup>1</sup>, PhD; Ko Willems van Dijk<sup>1</sup>, PhD

**BACKGROUND:** The increase in serum triglyceride (TG) concentrations in response to a meal is considered a risk factor for cardiovascular disease. We aimed to elucidate the genetics of the postprandial TG response through genome-wide association studies (GWAS).

**METHODS:** Participants of the NEO (Netherlands Epidemiology of Obesity) study (n=5630) consumed a liquid mixed meal after an overnight fast. GWAS of fasting and postprandial serum TG at 150 minutes were performed. To identify genetic variation of postprandial TG independent of fasting TG, we calculated the TG response at 150 minutes by the residuals of a nonlinear regression that predicted TG at 150 minutes as a function of fasting TG. Association analyses were adjusted for age, sex, and principal components in a linear regression model. Next, using the identified variants as determinants, we performed linear regression analyses on the residuals of the postprandial response of 149 nuclear magnetic resonance-based metabolite measures.

**RESULTS:** GWAS of fasting TG and postprandial serum TG at 150 minutes resulted in completely overlapping loci, replicating previous GWAS. From GWAS of the TG response, we identified rs7350789-A (allele frequency=0.36), mapping to hepatic lipase (*LIPC*), to be associated with a smaller increase in TG concentrations at 150 minutes ( $\beta=-0.11$ ;  $P$ -value= $5.1 \times 10^{-8}$ ). Rs7350789-A was associated with responses of 33 metabolite measures ( $P$ -value  $< 1.34 \times 10^{-3}$ ), mainly smaller increases of the TG-component in almost all HDL (high-density lipoprotein) subparticles (HDL-TG), a smaller decrease of HDL diameter and smaller increases of most components of VLDL (very low density lipoprotein) subparticles.

**CONCLUSIONS:** GWAS of the TG response identified a variant near *LIPC* as a main contributor to postprandial TG metabolism independent of fasting TG concentrations, resulting in smaller increases of HDL-TG and VLDL subparticles.

**Key Words:** cardiovascular diseases ■ Genome-wide association studies ■ hepatic lipase ■ lipoprotein metabolism ■ metabolites ■ postprandial triglyceride response

It is becoming increasingly clear that both fasting and postprandial (nonfasting) serum triglyceride (TG) concentrations are independent risk factors for developing cardiovascular disease (CVD).<sup>1-4</sup> While clinical TG measures are commonly assessed after an overnight fast, it should be acknowledged that individuals spend most

of the day in a postprandial state because of frequent food intake.<sup>5</sup> The typical eating pattern in Western society consists of 3 relatively regularly scheduled meals per day interspersed with more variable eating events. This eating pattern prevents serum TG to reach fasting levels for most of the day.<sup>6</sup> Therefore, postprandial serum TG

Correspondence to: Dorina Ibi, MSc, Department of Human Genetics, Leiden University Medical Center, S4-P, Postbus 9600, 2300 RC Leiden, the Netherlands. Email d.ibi@lumc.nl

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## Nonstandard Abbreviations and Acronyms

<b>CVD</b>	cardiovascular disease
<b>GWAS</b>	genome-wide association studies
<b>HDL</b>	high-density lipoprotein
<b>HL</b>	hepatic lipase
<b>IDL</b>	intermediate-density lipoprotein
<b>LD</b>	linkage disequilibrium
<b>LDL</b>	low-density lipoprotein
<b>NEO</b>	Netherlands Epidemiology of Obesity
<b>NMR</b>	nuclear magnetic resonance
<b>TRL</b>	TG-rich lipoprotein
<b>VLDL</b>	very low-density lipoprotein

concentrations may provide additional insight in CVD risk and the metabolic capacity of an individual to deal with dietary stimuli.<sup>7–9</sup>

The postprandial state is a dynamic, nonsteady-state condition that is characterized by increased serum levels of TG and TRLs (triglyceride-rich lipoproteins), which mainly include chylomicrons, but also VLDLs (very low-density lipoproteins), and their remnants. Cell culture studies and epidemiological data indicate that TRLs and particularly their remnants exert adverse effects on endothelial cells and may penetrate into the sub-endothelial space to initiate atherosclerotic plaques.<sup>6,10</sup> Large prospective studies have shown that delayed clearance of TRLs and their remnants from the blood stream is associated with atherosclerosis progression and therefore is a risk factor for CVD.<sup>1–3,11</sup> For example, the Copenhagen City Heart Study reported a significant association between higher nonfasting TG concentrations and higher myocardial infarction risk over 31 years of follow-up.<sup>12</sup>

In cohort studies, the postprandial TG response has been shown to be highly variable.<sup>5,6</sup> This interindividual variability is at least partly genetic, although dietary pattern, physical activity, alcohol consumption, age, sex, and insulin sensitivity are more than likely involved.<sup>6,13,14</sup> One cross-sectional study reported that healthy sons of men with established coronary artery disease have higher postprandial serum TG concentrations after consumption of a high-fat meal compared with sons of control subjects without CVD,<sup>14</sup> which suggested that prolonged postprandial hypertriglyceridemia is associated with familial risk for CVD. Multiple genetic variants in the *APOA1/C3/A4/A5* gene cluster have been associated with postprandial lipemia in relatively small studies.<sup>15–17</sup> Thus far, a limited number of genome-wide association studies (GWAS) on postprandial TG concentrations have been performed. These include the HAPI (Heredity and Phenotype Intervention) Heart study in Old Order Amish individuals (n=809), identifying a rare null mutation in

*APOC3*, likely due to a founder effect.<sup>18</sup> In addition, a study embedded in the Genetics of Lipid-Lowering Drugs and Diet Network (GOLDN), consisting of 1715 participants, yielded evidence for association of a variant (rs964184) in the vicinity of the *APOA1/C3/A4/A5* gene cluster. However, this association was attenuated upon additional statistical adjustment for fasting TG.<sup>19</sup>

In the present study, we set out to elucidate the genetics and underlying biology of the postprandial TG response to a liquid mixed meal. To this end, we performed a GWAS and a subsequent in-depth assessment of nuclear magnetic resonance (NMR)-based metabolite responses of the identified genomic loci in 5630 middle-aged individuals of the NEO (Netherlands Epidemiology of Obesity) study.

## METHODS

Complete methods are available in the Data Supplement. The NEO study design was approved by the medical ethics committee of the Leiden University Medical Center, and all participants gave their written informed consent. Because of consent issues, we cannot make the individual data of NEO study participants available to other researchers for purposes of reproducing the results or replicating the procedure. However, a file including GWAS summary statistics can be requested via [k.willems\\_van\\_dijk@lumc.nl](mailto:k.willems_van_dijk@lumc.nl).

## RESULTS

### Population Characteristics

Characteristics of the NEO study population as well as for the separate Leiden and Leiderdorp subcohorts are summarized in Table 1. The mean age in the total population was 56 years, and 48.5% of the population were men. Compared with the Leiderdorp subcohort, participants in the Leiden subcohort were more frequently men (49.9% versus 44.3%), had a higher mean body mass index (31.3 versus 26.3 kg/m<sup>2</sup>), used more frequently lipid-lowering drugs (17.6% versus 10.4%), had higher fasting and postprandial serum TG concentrations (1.34 versus 1.00 mmol/L, respectively, for fasting TG; and 2.01 versus 1.63 mmol/L, respectively, for TG at 150 minutes). Compared with the Leiderdorp subcohort, the median untransformed TG response at 150 minutes was somewhat lower in the Leiden subcohort (0.06 [IQR, –0.18 to 0.30] and –0.03 [IQR, –0.26 to 0.22] mmol/L, respectively, as calculated using the nonlinear prediction model between fasting and postprandial TG levels) but showed overlapping and wide interquartile ranges.

### Genome-Wide Association Analysis

The results for the fasting and postprandial TG GWAS analyses in the total cohort are shown in Figure 1. Genetic

**Table 1. Characteristics of the Total, Leiden, and Leiderdorp Cohorts From the NEO Study**

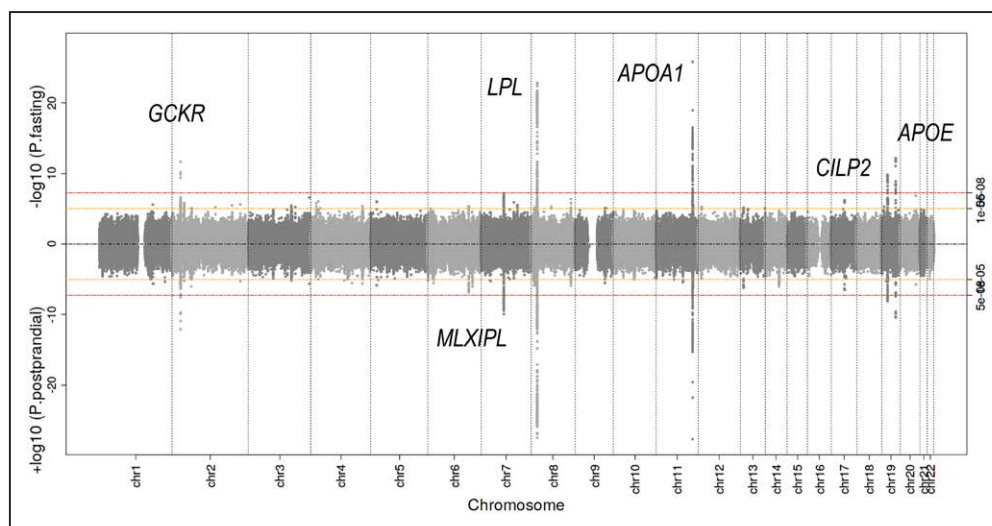
Characteristics	Total Cohort (N=5630)	Leiden Subcohort (N=4192)	Leiderdorp Subcohort (N=1438)
Number of participants	5630	4192	1438
Age, y	56.0 (5.9)	55.9 (5.9)	56.1 (6.0)
Men	48.5%	49.9%	44.3%
BMI, kg/m <sup>2</sup>	30.0 (4.8)	31.2 (4.2)	26.2 (4.5)
Lipid-lowering drug users	15.8%	17.7%	10.4%
Fasting TG, mmol/L	1.25 (0.88–1.77)	1.34 (0.95–1.87)	1.00 (0.71–1.45)
Postprandial TG at 30 min, mmol/L	1.43 (1.04–1.95)	1.51 (1.12–2.06)	1.20 (0.89–1.67)
Postprandial TG_at 150 min, mmol/L	1.91 (1.37–2.64)	2.01 (1.47–2.72)	1.63 (1.14–2.30)
TG response, mmol/L	−0.008 (−0.24–0.24)	−0.03 (−0.26–0.22)	0.06 (−0.18–0.30)

Results are presented as median (inter quartile range) for not normally distributed data, mean (SD), or number (percentage). TG response: residuals at 150 min. BMI indicates body mass index; NEO, Netherlands Epidemiology of Obesity; and TG, triglyceride.

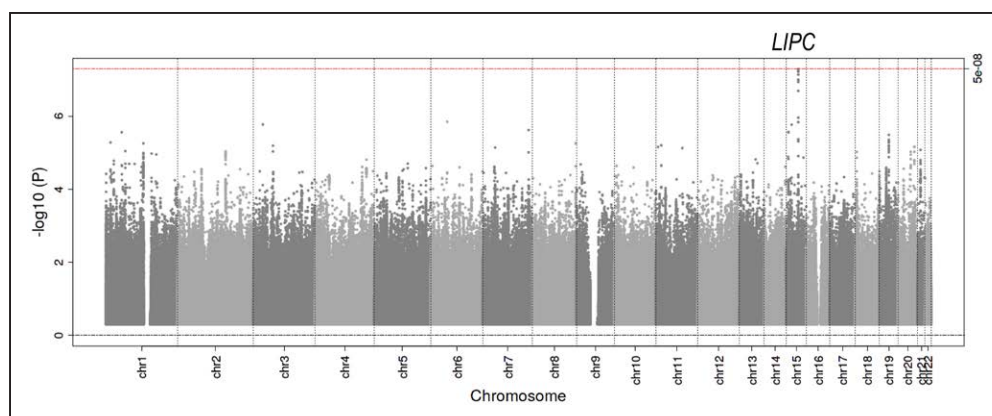
variants mapping to the known TG loci near *APOA1*, *LPL*, *APOE*, *GCKR*, and *CILP2* showed genome-wide significant signals in both fasting and postprandial TG concentrations. Interestingly, the signals in the postprandial analyses completely mirrored the signals of the fasting analyses, although there is some variation in the *P*-values that were reached in the separate analyses. Locus *MLXIPL* on chromosome 7 was borderline significant in the fasting TG GWAS, but achieved a *P*-value of  $1.2 \times 10^{-10}$  in the postprandial TG analyses. However, both effect sizes for rs71556736-T (the top hit in *MLXIPL* locus) were similar (fasting,  $\beta$  [SE]=−0.14 [0.03] SD and postprandial,  $\beta$  [SE]=−0.17 [0.03] SD). The full list with the lead hits for both fasting and postprandial TG is given in Table I in the Data Supplement.

Figure 2 displays the Manhattan plot for the TG response residuals at 150 minutes in the total NEO cohort. On chromosome 15, rs7350789 reached a suggestive *P*-value of  $5.1 \times 10^{-8}$ . In addition to rs7350789, there were 6 independent variants with a suggestive *P*-value ( $P < 5.0 \times 10^{-6}$ , Table II in the Data Supplement), but here we pursued the variant with the strongest

evidence for association, based on the high number of associated variants in strong linkage disequilibrium (LD). None of the loci identified for either fasting and postprandial TG levels showed evidence for association (*P*-values  $> 0.05$ ; Table III in the Data Supplement). The regional association plot is shown in Figure 3A, showing that rs7350789 is 23 kb upstream of the *LIPC*, which encodes HL (hepatic lipase). Rs7350789-A had a per-allele decrease (SE) in TG response residual of −0.11 (0.02) SD (Table 2, Figure 3B). Because the 2 subcohorts from the NEO study had different study characteristics at fasting, analyses on the rs7350789 variant were stratified accordingly. Given the differences in the median postprandial TG response residuals (Table 1), rs7350789-A in the *LIPC* locus still showed an effect in the same direction, although the magnitude of the effect was somewhat smaller in the Leiden subcohort compared with the Leiderdorp subcohort ( $\beta$  [SE]=−0.09 [0.02] SD and  $\beta$  [SE]=−0.15 [0.04] SD, respectively). Adjustment for body mass index and lipid-lowering medication did not change the results ( $\beta$ =−0.11 [0.019] SD and  $\beta$ =−0.11 [0.020] SD), respectively (Table IV in the



**Figure 1. Miami plot showing P-values of the single-nucleotide polymorphism (SNP) associations with fasting TG and postprandial TG.**



**Figure 2. Manhattan plot of the GWAS of postprandial TG residuals at 150 min in the NEO Study.**

x axis shows chromosomal positions. y axis shows  $-\log_{10} P$ -values. The red line indicates the genome-wide significance threshold ( $P=5.0 \times 10^{-8}$ ).

Data Supplement). Furthermore, effect sizes were similar in men and women ( $\beta=-0.11$  [0.030] SD and  $\beta=-0.10$  [0.026] SD, respectively). Rs7350789-A, mapping to *LIPC*, was not associated with either fasting TG levels ( $\beta$  [SE]=0.031 [0.019] SD,  $P$ -value=0.1) or postprandial TG levels ( $\beta$  [SE]=−0.010 [0.019] SD,  $P$ -value=0.6).

### NMR-Based Metabolomics

Based on the single signal of the postprandial residual TG GWAS in the full cohort, we conducted association analyses between rs7350789-A in *LIPC* and residuals of the postprandial response of 149 NMR-based metabolite measures at T=150 (Figure 4, Table V in the Data Supplement). Rs7350789-A was significantly associated with postprandial responses of 33 residuals of metabolite measures ( $P$ -value  $< 1.34 \times 10^{-3}$ ). Overall, the rs7350789-A allele was associated with a smaller increase of the TG-component in almost all HDL (high-density lipoprotein) subparticles (largest effect on HDL-TG,  $P$ -value= $4.5 \times 10^{-7}$ ), a smaller decrease in HDL diameter ( $P$ -value= $2.8 \times 10^{-4}$ ), and a smaller increase of most components of VLDL subparticles (largest effect on VLDL-cholesterol,  $P$ -value= $2.7 \times 10^{-6}$ ). In addition, this variation in the *LIPC* locus was significantly associated with a smaller increase in plasma monounsaturated fatty acids and total fatty acids and a larger decrease of beta-hydroxybutyrate.

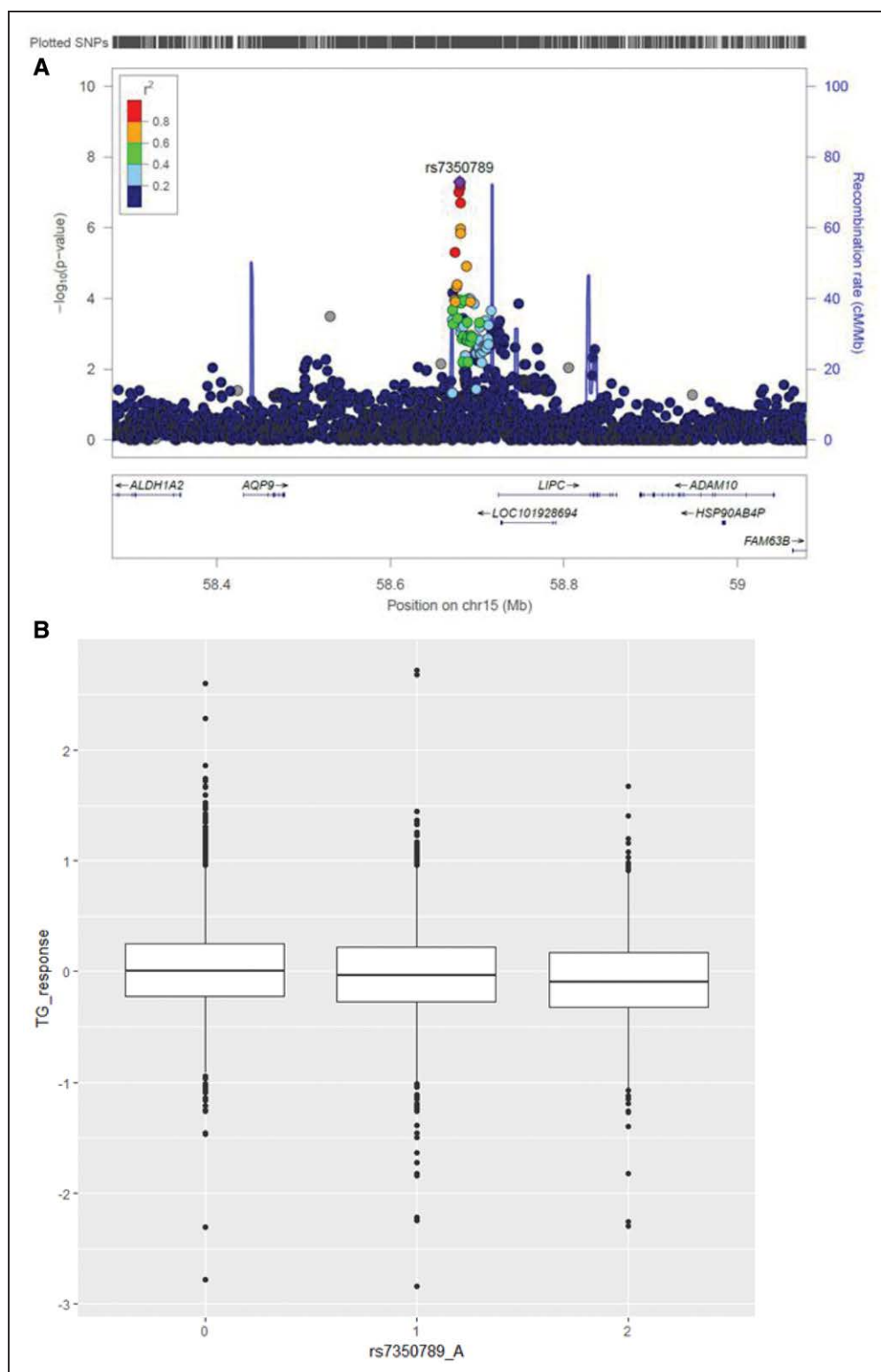
To gain additional insight in the role of rs7350789-A, we performed association analyses of this SNP with fasting and postprandial NMR-based metabolite levels (Figure IIA and IIB and Table VI in the Data Supplement). In the fasting state, rs7350789-A was associated with higher metabolite measures of many components of the larger HDL, LDL (low-density lipoprotein), IDL (intermediate-density lipoprotein), and very small VLDL particles. The strongest associations were observed for the TG-component in LDL and HDL, which were both significantly increased ( $P$ -value= $3.39 \times 10^{-57}$  and  $P$ -value= $1.35 \times 10^{-67}$ , respectively). In addition,

both HDL and LDL diameter were significantly larger ( $P$ -value= $3.21 \times 10^{-36}$  and  $P$ -value= $1.59 \times 10^{-26}$ , respectively), whereas VLDL diameter was significantly smaller ( $P$ -value= $9.49 \times 10^{-09}$ ). Association analyses of rs7350789-A with postprandial NMR-based metabolite levels were remarkably similar to the associations of rs7350789-A with fasting levels.

### DISCUSSION

Our study aimed to identify genes independent of fasting TG concentrations that influence the postprandial TG response. To this end, we performed a GWAS of residuals of the TG response after taking into account the strong nonlinear correlation between fasting and postprandial TG concentrations. We identified rs7350789, mapping to *LIPC* that encodes for HL, to be associated with the residuals of TG response. Association analyses of postprandial metabolite response residuals and rs7350789-A showed that this variation in the *LIPC* locus is significantly associated with 33 metabolite measures: mainly with a smaller increase of the TG-component in almost all HDL subparticles, a smaller decrease of HDL diameter, and a smaller increase of most components of VLDL subparticles at 150 minutes after the meal.

The GWAS of fasting and postprandial TG concentrations in the NEO study revealed overlapping genetic loci, including the previously identified loci near *APOA1*, *LPL*, *APOE*, *GCKR*, and *CILP2*. However, the signals found in the postprandial TG level GWAS resulted in somewhat different  $P$ -values for the various loci as compared with the fasting TG GWAS. Locus *MLXIPL* on chromosome 7 was borderline significant in the fasting TG GWAS but achieved a  $P$ -value of  $1.2 \times 10^{-10}$  in the postprandial TG GWAS. Given the similarity of the effect sizes, the difference in  $P$ -values is likely because of power. In conclusion, the results indicate that the major loci that affect postprandial TG concentrations are the same as



**Figure 3. LIPC and TG response.**

**A**, Regional association plot for *LIPC* on chromosome 15. The purple diamond represents the lead SNP for the locus. **B**, Rs7350789-A genotype specific effects on TG response measured as residuals at 150 min.

those that play a major role in determining fasting TG concentrations.

In previous large-scale GWAS meta-analyses performed by the Global Lipids Genetics Consortium,

rs1532085 near the *LIPC* locus was associated with TG concentrations.<sup>21</sup> Interestingly, this SNP is 3.7 kb upstream from the residual TG response SNP rs7350789 and the LD of rs1532085 and rs7350789 is high

**Table 2. Summary Statistics of the Association of the Suggestive (Borderline) LIPC SNP and TG Response in Response to a Mixed Meal in NEO**

CHR	SNP	Position	Gene	EA/NEA	EAF	Imputation Quality	Total Cohort		Leiden Cohort		Leiderdorp Cohort	
							$\beta^*$ (SE)	P-Value	$\beta^*$ (SE)	P-Value	$\beta^*$ (SE)	P-Value
Suggestive SNP												
15	rs7350789	58679668	LIPC	A/G	0.36	1	-0.11 (0.02)	$5.1 \times 10^{-8}$	-0.09 (0.02)	$9.2 \times 10^{-5}$	-0.15 (0.04)	$5.2 \times 10^{-5}$

Threshold for genome-wide significance is  $5 \times 10^{-8}$ . Threshold for the suggestive signals is  $1 \times 10^{-6}$ . CHR indicates chromosome; EAF, effect allele frequency; (N)EA, (non) effect allele; and SNP, single nucleotide polymorphism.

\*Beta coefficient expressed in SD units.

( $R^2=0.81$ ). However, in our GWAS of fasting and postprandial TG, this *LIPC* SNP was not a significant hit. This is likely because of power problems, because the Global Lipids Genetics Consortium meta-analysis consisted of many tens of thousands of individuals. The effect size of rs7350789-A in the total NEO cohort was  $-0.11$  SD per additional risk allele, indicating a smaller increase of serum TG after a meal in carriers of this allele. Sensitivity analyses stratified by NEO subcohort (Leiden and Leiderdorp) and additional adjustment for body mass index and lipid-lowering medication did not materially change this result. Furthermore, although studies have shown differences in activity of HL in men and women,<sup>22,23</sup> we did not observe differences in the effect size of rs7359789-A on TG response residuals in men and women. These data indicate that although the *P*-value did not reach the genome wide threshold of  $5.0 \times 10^{-8}$ , the association of rs7350789 with the TG response residuals is robust.

As rs7350789 is not in the coding region of a gene, we assessed whether this SNP was in an expression quantitative trait locus for liver gene expression levels. A recent mega-analysis of liver expression quantitative trait locus identified rs11853674-G as an expression quantitative trait locus for *LIPC* with a negative beta ( $\beta$  [SE]= $-0.51$  [0.11]).<sup>24</sup> Rs7350789-A is in moderate LD with rs11853674-G ( $R^2=0.46$ ) and thus associated with decreased expression of *LIPC* and likely reduced hepatic production of HL. In addition, recent genetic association analyses of HL activity showed that rs10468017-T near the *LIPC* gene is associated with decreased HL activity.<sup>25</sup> Rs10468017-T is in strong LD with rs7350789-A ( $R^2=0.74$ ), and this further corroborates that rs7350789-A reduces hepatic production of HL.

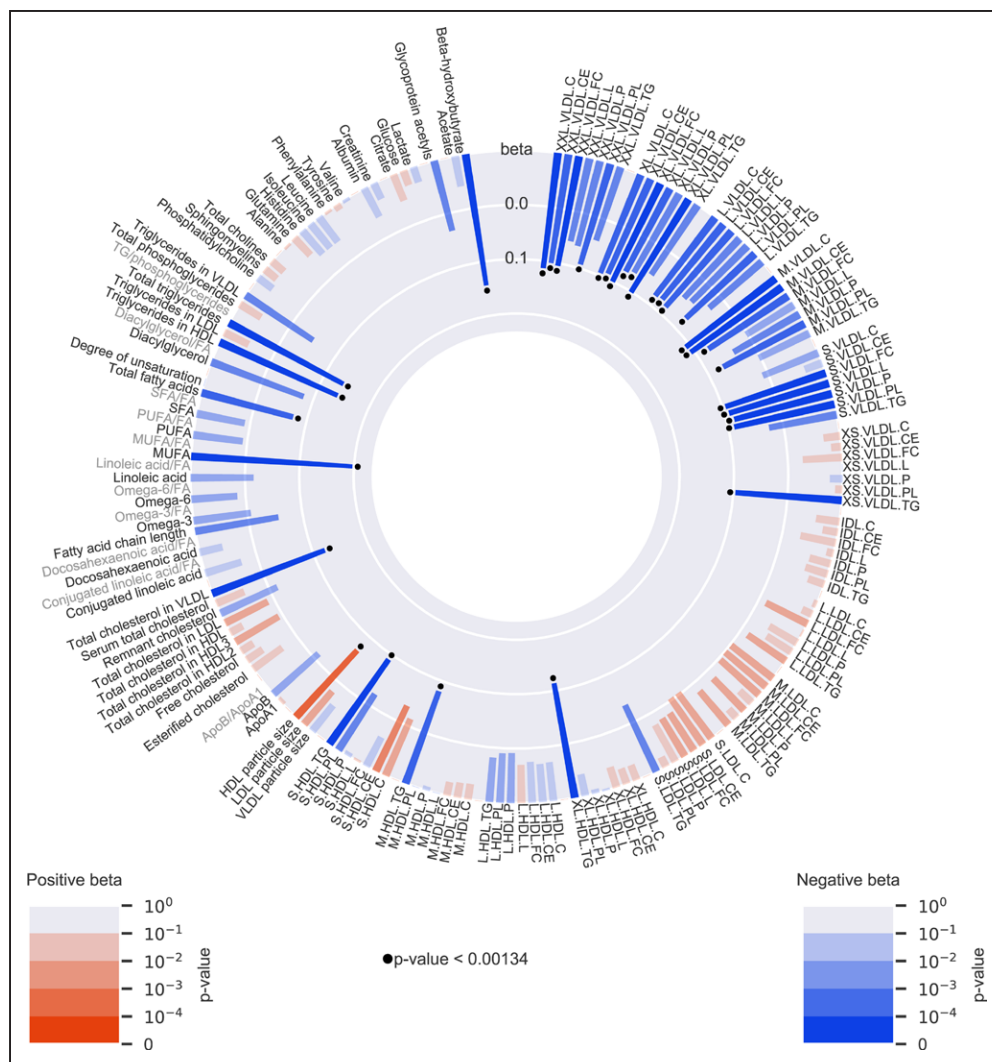
The *LIPC* gene is expressed in the liver, and the majority of the secreted HL is associated with cell surface proteoglycans, which keep HL in an enzymatically inactive form. Cell surface bound HL is exchanged with circulating HDL and under postprandial conditions the HDL-associated HL is presumably activated by changes in the composition of the HDL. The activated HL is thought to hydrolyze TG from chylomicron remnants, IDL and HDL.<sup>26,27</sup> The results from the NMR-analyses showed that in the fasting state, rs7350789-A was not associated with total TG levels, but with the redistribution of TG over the different lipoprotein fractions, mainly

from VLDL particles to the larger HDL, LDL, IDL, and very small VLDL particles (Figure IIA in the Data Supplement), which is concordant with a previous report.<sup>28</sup> This redistribution is nearly identical in the postprandial state (Figure IIB in the Data Supplement), and this likely reflects the lagging effect of the associations in the fasting state. These data indicate that, apparently in the fasting state, lower *LIPC* gene expression is associated with higher TG-content in both HDL and LDL sized particles. Moreover, these data indicate that HL is functional in the fasting state.

As rs7350789-A is also associated with higher plasma levels of HDL particles, this HDL could function as an increased circulating reservoir of liver-derived HL. This increased reservoir of HDL-associated HL is activated after the meal and could explain the smaller than expected increase of TG in HDL particles and smaller than expected increase of the larger VLDL particles. Our results from the NMR-analysis support this role of HL in hydrolyzing TG in HDL particles after a meal, since rs7350789-A is associated with a smaller increase of the postprandial TG concentration in HDL subparticles. The meal thus specifically seems to activate the HDL-TG hydrolysis activity of HDL-associated HL.

In addition, rs7350789-A is associated with a smaller increase of most VLDL subparticles, but not specifically VLDL-TG or IDL-TG. Moreover, no effect was found in the responses of any of the LDL subparticles. These data indicate that in addition to a role for HL in decreasing HDL-TG, HL plays a role in lipoprotein metabolism that is independent of its lipolytic function. In vitro as well in vivo experiments have suggested that HL can act as a bridge between lipoproteins and the cell surface, promoting cellular uptake of lipoproteins and HDL.<sup>29,30</sup> Our NMR data indicate that, independent of lipolytic activity, HL indeed seems to play a role in the clearance of VLDL subparticles irrespective of the particle size. The meal thus seems to uncover a role for HL in whole particle VLDL clearance. Our data indicate that HL has different roles in lipid and lipoprotein metabolism in the fasting versus the postprandial state.

In parallel, rs7350789-A was associated with a smaller than expected decrease of the HDL diameter. Although this effect is very small, apparently, TG-content in HDL particles plays a role in their



**Figure 4. The associations of rs7350789-A and residuals of postprandial NMR-based metabolite measures.**

Bar heights represent the magnitude of the beta coefficient from linear regression, which is expressed in SD (SD) units. Red bars indicate positive betas and blue bars indicate negative betas. The transparency of the bars indicates the level of statistical significance. A  $P$ -value  $< 0.00134$  is regarded statistically significant, as represented by the black dots. Full names for the NMR-based metabolite measures are reported in Blauw et al.<sup>20</sup>

size distribution. Whether this is a direct effect due to changes in HL activity or an indirect effect due to changes in substrate specificity of the HDL particles themselves remains to be determined.

Surprisingly, the association of rs7350789-A with NMR metabolite residuals showed a larger decrease of the postprandial beta-hydroxybutyrate concentration. This ketone body is connected to the oxidation of fatty acids.<sup>31</sup> Possibly, either as a result of the smaller increase of serum HDL-TG or the increased clearance of VLDL-particles, fatty acid oxidation is decreased. The pathophysiological mechanism underlying the association of variation in the *LIPC* locus and beta-hydroxybutyrate remains to be investigated. Other findings of interest for follow-up studies are the associations between the *LIPC* locus and the smaller increase of postprandial monounsaturated fatty acids and total fatty acids levels.

Our results show that carriers of the rs7350789-A allele near *LIPC* have a smaller than expected increase of TG after a meal. However, in the fasting state, the same variant is associated with redistribution of TG from VLDL to HDL and LDL. Since these associations represent both pro- and anti-atherogenic effects, it is difficult to predict the CVD risk in carriers of the rs7350789-A genetic variation. A lookup of rs7350789-A in relation to coronary artery disease in publicly available data of the CARDIoGRAMplusC4D consortium<sup>32</sup> did not reveal evidence for an association ( $\beta$  [SE]=−0.015 [0.009],  $P$ -value=0.12). Given the small absolute effect of rs7350789-A on the postprandial TG response, this may not be surprising. Although our variant has not been associated with CVD risk, recent Mendelian Randomization analyses showed that the LDL TG raising alleles rs1800588-T and rs10468017-T near *LIPC* were

associated with lower HL activity and increased CVD risk in CARDIoGRAMplusC4D.<sup>25</sup> As indicated above, rs10468017 is in LD with our *LIPC* variant rs7350789. Decomposing the Mendelian Randomization analyses revealed that the major contribution of the *LIPC* locus to coronary artery disease risk was contributed by rs1800588, which was not in LD with rs7350789 and thus explains the lack of association of rs7350789 with coronary artery disease (rs10468017-T:  $\beta$  [SE]=−0.015 [0.011], *P*-value=0.15; rs1800588-T:  $\beta$  [SE]=−0.038 [0.011], *P*-value=0.0005).

One of the strengths of the NEO study is the mixed meal-response design that allows for standardized assessment of postprandial meal responses. Many studies that include nonfasting measures have no information on the timing and composition of the last meal before the blood draw. It should be noted, however, that a limitation of the study is that the last postprandial measurement was performed 150 minutes after the meal intake, which may not be the peak of the postprandial TG excursion. Previous research indicated that serum TG may peak up to 3 to 4 hours after meal ingestion.<sup>3,33</sup>

In conclusion, we performed a GWAS to identify loci involved in the TG response following a mixed-meal and to provide insight into postprandial lipoprotein metabolism by a metabolomics analysis, using the identified loci. We identified a variant near *LIPC* as a contributor to postprandial TG and lipoprotein metabolism independent of fasting TG concentrations, mainly affecting HDL and VLDL subparticles. In addition, we showed that the same loci that affect fasting TG concentrations also play a major role in determining postprandial TG concentrations.

## ARTICLE INFORMATION

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### Affiliations

Department of Human Genetics (D.I., J.B.v.K., K.W.v.D.), Division of Gerontology and Geriatrics, Department of Internal Medicine (R.N., D.v.H.), Department of Clinical Epidemiology (R.L.-G., R.d.M., D.O.M.-K., F.R.R.), Department of Cardiology (S.T., J.W.J.), Department of Public Health & Primary Care (D.O.M.-K.), Division of Endocrinology, Department of Internal Medicine (J.B.v.K., L.L.B., P.C.N.R., K.W.v.D.), and Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center (P.C.N.R., K.W.v.D.), National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands (D.I., M.E.T.D.).

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## Disclosures

None.

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