

Serum Lipid Levels, Body Mass Index, and Their Role in Coronary Artery Calcification A Polygenic Analysis

Jessica van Setten, PhD; Ivana Išgum, PhD*; Sonali Pechlivanis, PhD*; Vinicius Tragante, PhD; Pim A. de Jong, MD, PhD; Joanna Smolonska, PhD; Mathieu Platteel, BSc, Per Hoffmann, PhD; Matthijs Oudkerk, MD, PhD; Harry J. de Koning, MD, PhD; Markus M. Nöthen, MD; Susanne Moebus, PhD; Raimund Erbel, MD; Karl-Heinz Jöckel, PhD; Max A. Viergever, PhD; Willem P.Th.M. Mali, MD, PhD; Paul I.W. de Bakker, PhD

Background—Coronary artery calcification (CAC) is widely regarded as a cumulative lifetime measure of atherosclerosis, but it remains unclear what is the relationship between calcification and traditional risk factors for coronary artery disease (CAD) and myocardial infarction (MI). This study characterizes the genetic architecture of CAC by evaluating the overall impact of common alleles associated with CAD/MI and its traditional risk factors.

Methods and Results—On the basis of summary-association results from the CARDIoGRAMplusC4D study of CAD/MI, we calculated polygenic risk scores in 2599 participants of the Dutch and Belgian Lung Cancer Screening (NELSON) trial, in whom quantitative CAC levels (Agatston scores) were determined from chest computerized tomographic imaging data. The most significant polygenic model explained $\approx 14\%$ of the observed CAC variance ($P=1.6 \times 10^{-11}$), which points to a residual effect because of many as yet unknown loci that overlap between CAD/MI and CAC. In addition, we constructed risk scores based on published single-nucleotide polymorphism associations for traditional cardiovascular risk factors and tested these scores for association with CAC. We found nominally significant associations for genetic risk scores of low-density lipoprotein-cholesterol, total cholesterol, and body mass index, which were successfully replicated in 2182 individuals of the Heinz Nixdorf Recall Study.

Conclusions—Pervasive polygenic sharing between CAC and CAD/MI suggests that a substantial fraction of the heritable risk for CAD/MI is mediated through arterial calcification. We also provide evidence that genetic variants associated with serum lipid levels and body mass index influence CAC levels. (*Circ Cardiovasc Genet.* 2015;8:327-333. DOI: 10.1161/CIRCGENETICS.114.000496.)

Key Words: coronary artery disease ■ genome-wide association study ■ myocardial infarction

Over the past few years, several collaborative genome-wide association studies (GWAS) have identified many loci associated with coronary artery disease (CAD) and myocardial infarction (MI).^{1,2} The CARDIoGRAMplusC4D Consortium reported 46 loci at genome-wide significance in an association analysis of as many as 64 000 cases and 131 000 controls, where the lead variants at these loci collectively explain 10.6% of CAD heritability.² In parallel, several studies have also focused on the genetic basis of

known CAD risk factors, including circulating lipid levels,^{3,4} hypertension,⁵⁻⁷ type 2 diabetes mellitus (T2D),⁸ body mass index (BMI),^{9,10} and arterial calcification,¹¹⁻¹³ altogether pinpointing hundreds of loci across the genome. An important question now is to what extent the identified genetic variants overlap across traits and which biological mechanisms are shared.

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From the Department of Medical Genetics, Center for Molecular Medicine (J.v.S., P.I.W.d.B.), Image Sciences Institute (I.I., M.A.V.), Department of Cardiology (V.T.); Department of Radiology (P.A.d.J.), Department of Epidemiology, Julius Center for Health Sciences and Primary Care (P.I.W.d.B.), University Medical Center Utrecht, Utrecht, The Netherlands; Institute for Medical Informatics, Biometry and Epidemiology (S.P., S.M.), Clinic of Cardiology, West-German Heart Centre (R.E.), University Hospital Essen, Essen, Germany; Department of Genetics (J.S., M.P.), Department of Epidemiology (J.S.), University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; Institute of Human Genetics (P.F., M.M.N.), Department of Genomics, Life and Brain Center (P.F., M.M.N.), University of Bonn, Bonn, Germany; Division of Medical Genetics, University Hospital and Department of Biomedicine, University of Basel, Basel, Switzerland (P.F.); Department of Radiology-Radiodiagnostics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands (M.O.); and Department of Public Health, Erasmus Medical Center, Rotterdam, The Netherlands (H.J.d.K.).

*Drs Išgum and Pechlivanis contributed equally to this work.

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Correspondence to Paul de Bakker, PhD, University Medical Center Utrecht, Stratum, 1.305, PO Box 85090, 3508 AB Utrecht, The Netherlands. E-mail pdebakker@umcutrecht.nl

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In this study, we focus on coronary artery calcification (CAC), a strong and independent risk factor for cardiovascular events.^{14–18} To date, only 2 loci (*CDKN2A/CDKN2B* and *PHACTR1*) have been consistently associated with CAC at genome-wide significance in 3 independent studies, and these loci are also linked to CAD and MI risk.^{2,11–13} Going beyond these 2 *bona fide* loci, we and others have demonstrated a significant concordance in direction of effect for 25 single-nucleotide polymorphisms (SNPs) associated with CAD/MI^{11,13} (identified by the initial CARDIoGRAM Study¹). It was subsequently suggested that there is a strong causal overlap between vascular calcification and cardiovascular events, even though the associated SNPs discovered to date explain only a modest fraction of the heritability of CAC, CAD, or MI.¹⁹

Here, we test the hypothesis that CAD/MI SNPs associated below genome-wide significance influence the degree of calcification in the coronary arteries beyond the overlapping associations already identified. Because power is limited to detect small effects for single SNPs, we evaluated the collective—polygenic—impact of SNPs published by the CARDIoGRAMplusC4D consortium² on CAC. We also investigated whether SNPs associated with serum lipid levels, T1D, T2D, height, BMI, and blood pressure have a measurable influence on CAC levels.

Materials and Methods

Cohort Characteristics

Details on sample collection, genotyping, and measurement of phenotypes were described elsewhere.¹³ In brief, the Dutch and Belgian Lung Cancer Screening trial (NELSON trial) was designed to study the early detection of lung cancer in an at-risk population. The study was approved by the Ministry of Health of the Netherlands, and written informed consent was obtained from all participants. Low-dose, non-ECG synchronized, non-contrast-enhanced baseline chest computerized tomographies were available for all participants. We used a computer-aided detection system for automatic identification and quantification of CAC.²⁰ Scores were manually inspected and corrected when needed. CAC burden was expressed in terms of Agatston scores.²¹ All individuals were male smokers or former smokers.

Genotype Data and SNP Imputation

Genome-wide SNP genotype data were collected in 3082 participants on the Illumina Human610-Quad BeadChip, and quality control was performed to remove low-quality SNPs and samples.¹³ After extensive quality control of the data (including principal components analysis), we kept 2599 samples for all downstream analyses. We performed imputation of untyped SNPs with Minimac,²² splitting all samples into random batches of ~500 individuals. As reference panel, we used the 998 phased haplotypes from the Genome of the Netherlands Project release 4 encompassing 19 763 454 SNPs.²³

Association Testing Framework

We used a linear regression model to test genetic risk scores for association to the log-transformed Agatston scores ($\ln[\text{Agatston score}+1]$), including as covariates the first principal component of the genotype data (which was the only statistically significant component at univariate $P<0.05$), age, and smoking history (in pack years). The baseline model included only these 3 covariates. In the 3-SNP model, we included the risk alleles of 3 SNPs (rs4977574 at 9p21, rs3825807 at *ADAMTS7*, and rs12526453 at *PHACTR1*) as independent terms in the regression model. These 3 SNPs reach genome-wide significance in a combined analysis of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium,¹¹ the Heinz

Nixdorf Recall Study,¹² and the NELSON trial.¹³ The 45-SNP model includes the risk alleles of all 45 CAD/MI-associated SNPs identified by the CARDIoGRAMplusC4D Study² as independent terms in the regression model. Of the 46 associations originally reported by CARDIoGRAMplusC4D, one SNP, rs6903956 at *C6orf105*, was not included because this SNP was identified in the Han Chinese population²⁴ and has not been replicated in Europeans to date. Statistical software R 3.0.2 was used for the analysis. To calculate the explained variance of the 3 CAC SNPs and 45 CAD/MI SNPs, we subtracted the variance explained by the baseline model from that explained by the 3-SNP and 45-SNP models, respectively.

Polygenic Risk Scores for CAD/MI

We calculated polygenic risk scores for all individuals in the NELSON trial using publicly available association results for 79 128 SNPs from the CARDIoGRAMplusC4D consortium.² We extracted all SNPs that were present in both the CARDIoGRAMplusC4D data and our NELSON GWAS data. After removing A/T and C/G SNPs we used PLINK²⁵ to prune remaining SNPs based on linkage disequilibrium (LD), preferentially keeping SNPs with lower P values in the CARDIoGRAMplusC4D results and leaving no pairs of SNPs with $r^2>0.05$. We calculated multiple polygenic scores based on SNPs with P values reported by the CARDIoGRAMplusC4D consortium² that reached a predefined threshold ($<5\times10^{-7}$, $<5\times10^{-6}$, $<5\times10^{-5}$, $<5\times10^{-4}$, <0.05 , <0.1 , <0.2 , <0.3 , <0.4 , and <0.5).²⁶ This resulted in 11 polygenic models containing between 39 and 15 475 SNPs. Allelic dosages for the risk alleles for all SNPs were calculated from the posterior probabilities provided by the imputation software Minimac,²² as follows:

$$\text{Dosage}(A \text{ allele}) = 2 \times P(AA \text{ genotype}) + P(AB \text{ genotype}),$$

where A is the risk allele and B is the alternative allele. We calculated the genetic risk score using the following formula:

$$\text{Genetic risk score} = \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_n x_n, \text{ where } \beta_i$$

is the natural log of the reported odds ratio for CAD/MI, and x_i is the estimated allele dosage (between 0 and 2) in a given individual for the i th SNP. The genetic risk score was then divided by the total number of SNPs in the model to account for missing data, and added as a single term to the regression model. We corrected for the effects of the 45 SNPs associated with CAD/MI by adding them as covariates to the regression model. We subtracted the explained variance of the 45-SNP model to estimate the explained variance because of the polygenic signal.

We partitioned the polygenic scores by chromosome and tested each separately for association to CAC levels using linear regression and including the same covariates as for the 12 polygenic models listed above.²⁷ This allowed us to test whether there was a relation between the explained variance and chromosome size for each chromosome. Under a polygenic model, the assumption is that larger chromosomes explain more of the trait than smaller ones. We used a binomial test to assess whether effect directions across a set of SNPs are more concordant than expected by chance.

We evaluated whether the variance explained per chromosome could be explained by particular gene sets from Kyoto Encyclopedia of Genes and Genomes (KEGG), Gene Ontology, Biocarta, Reactome, canonical, and chemical pathways, all obtained from the Molecular Signatures Database (MSigDB).²⁸ We mapped SNPs to genes using GENCODE annotations,²⁹ and selected only pathways with ≥ 50 genes. For each gene set, we tested for an association between the number of genes per chromosome and the explained trait variance.

Polygenic Risk Scores for Traditional Risk Factors

We tested 9 polygenic risk score models on the basis of known SNP associations for circulating lipids (high-density lipoprotein [HDL]-cholesterol, low-density lipoprotein [LDL]-cholesterol, triglycerides, and total cholesterol),⁴ T2D,⁸ height,³⁰ BMI,⁹ and T1D^{31–33} and

a combined set of blood pressure SNPs as described by Van't Hof et al.^{5-7,34} For each individual, we calculated the polygenic risk score by summing up the number of risk alleles of the trait-associated SNPs, weighted by the reported effect size of each SNP and dividing this by the total number of included SNPs (similar to CAD/MI as described above). We used linear regression to test this genetic risk score for association to CAC, using the same covariates as the baseline regression model described above. We subtracted the explained variance of the baseline model to estimate the explained variance because of the polygenic signal. We claimed statistical significance after multiple testing correction ($P < 0.0056$ for 9 independent polygenic risk score models tested to achieve a type 1 error of 5%).

Replication in the Heinz Nixdorf Recall Study

We replicated polygenic models in the Heinz Nixdorf Recall Study. Study rationale, study design, and methods have been described previously.^{12,35} The study was approved by the local ethics committees, and informed consent was obtained from all participants. CAC levels were assessed by nonenhanced electron-beam computerized tomography (C-150 scanner; GE Imatron, San Francisco, CA). Individuals were genotyped using 3 different genotyping chips: Illumina HumanOmni1-Quad, Illumina HumanOmni1S, and Illumina HumanOmniExpress. After extensive quality control, 2182 samples were included in downstream analyses. SNPs were imputed with IMPUTE version 2.1.1²² using the 1000 Genomes Project (release 2012) as a reference panel. Using SNPTEST version 2.1.1,³⁶ scores were tested for association with log-transformed Agatston scores ($\ln[\text{Agatston score} + 1]$) using a linear regression model correcting for age and sex. We report 1-sided P values because these tests are based on hypotheses with a prespecified effect of direction. We claimed statistical significance after correcting for the number of independent tests performed in the replication data set.

Results

CAC Variance Explained by Known Genetic Risk Factors

First, we assessed the explained variance of CAC by a baseline model containing only age, smoking (pack years), and the first principal component to correct for population structure within the Netherlands as covariates. This baseline model explained 8.3% of the phenotypic variance (Figure 1). Next, we tested

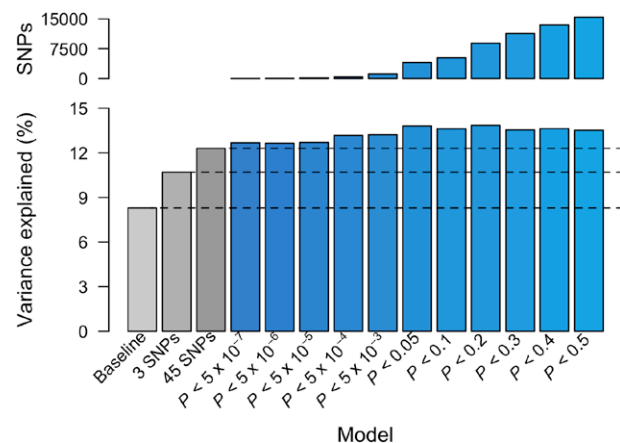


Figure 1. Phenotypic variance explained by baseline (age, smoking history, and the first principal component), 3 coronary artery calcification (CAC) risk single-nucleotide polymorphisms (SNPs), 45 coronary artery disease (CAD)/myocardial infarction (MI) risk SNPs, and 12 polygenic models containing SNPs based on CAD/MI P values. Dashed lines show the variance explained by the baseline model, 3 known CAC risk SNPs, and 45 known CAD/MI risk SNPs. The polygenic models are adjusted for the effects of the 45 CAD/MI SNPs.

the additional variance explained by the collective effect of 3 SNPs (at 9p21, *PHACTR1*, and *ADAMTS7*) associated with CAD/MI and with CAC. This 3-SNP model explained an additional 2.4% of the variance of the CAC phenotype (Figure 1). To test whether other published CAD/MI risk SNPs are also associated with CAC, we included 45 established CAD/MI risk SNPs in the model.² The total variance explained by this 45-SNP model was 12.3%, of which 4% could be attributed to the 45 SNPs associated with CAD/MI risk (Figure 1). Association results for the 45 SNPs with CAC are shown in Table I in the Data Supplement.

CAC Variance Explained by Polygenic Effects

To characterize the impact of CAD-/MI-associated SNPs that never reached genome-wide significance in the CARDIoGRAMplusC4D study, we created 11 polygenic models and tested each for association with CAC, while adjusting for the collective effects of the 45 known CAD/MI risk alleles. All models were significantly associated with CAC with P -values ranging from 10^{-3} to 10^{-11} (Table II in the Data Supplement). The most significant model ($P = 1.6 \times 10^{-11}$) was for the 8918 SNPs with $P < 0.2$ in CARDIoGRAMplusC4D, explaining an additional 1.5% of the observed CAC variance (Figure 1).

To test whether these polygenic associations are evenly distributed over the genome, we partitioned all SNPs with $P < 0.2$ in the CARDIoGRAMplusC4D analysis for each chromosome separately, again adjusting for the effects of the 45 CAD/MI SNPs, and estimated the explained variance of CAC for each chromosome. The correlation between the explained variance per chromosome and chromosome number is significant ($r^2 = 0.39$; $P = 0.0019$; Figure 2). We obtained similar results for the relation between explained variance and SNPs on each chromosome after LD pruning ($r^2 = 0.45$, $P = 0.0006$; Table III in the Data Supplement), and explained variance and physical chromosome length ($r^2 = 0.45$, $P = 0.0006$).

Chromosomes 2 and 6 explained more of the variance than expected on the basis of their physical size or number of SNPs. For both chromosomes, we observed an excess of SNPs with concordant direction of effects between CAD/MI and CAC (binomial $P = 1.5 \times 10^{-5}$ for chromosome 2 and $P = 1.5 \times 10^{-3}$ for

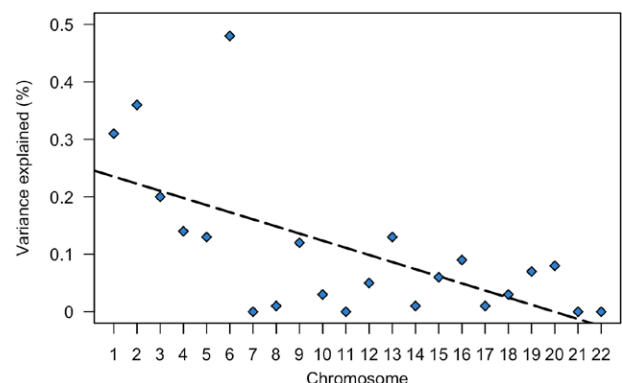


Figure 2. Variance explained for each chromosome. The numbers are based on the polygenic model containing single-nucleotide polymorphisms (SNPs) with coronary artery disease (CAD)/myocardial infarction (MI) $P < 0.2$, adjusting for the effects of the 45 CAD/MI SNPs. The correlation between variance explained and chromosome number ($r^2 = 0.39$) is significant ($P = 0.0019$).

chromosome 6). Removing the extended major histocompatibility complex region (chromosome 6, 26–34 Mb) did not influence the results. We did not observe any evidence for certain pathways or gene sets related to cardiovascular disease overrepresented on these 2 chromosomes (data not shown).

Influence of Traditional Risk Factors on CAC

Finally, we evaluated whether there was a shared genetic basis between CAC and 7 traits involving traditional cardiovascular risk factors that influence risk for CAD and MI. To this end, we tested polygenic risk score models for HDL-cholesterol, LDL-cholesterol, triglycerides, total cholesterol, height, BMI, blood pressure, T1D, and T2D; all based on validated SNP associations from the GWAS literature (Table). The model containing LDL-cholesterol SNPs was significantly associated with CAC ($P=0.002$) and another 3 models (BMI, T2D, and total cholesterol) were associated with CAC at nominal significance ($P<0.05$). We attempted to replicate the findings for these 4 genetic risk score models in the Heinz Nixdorf Recall Study assuming consistent effect directions (Table). We observed significant replication evidence for the model for LDL-cholesterol ($P=0.0097$), total cholesterol ($P=0.0063$), and BMI ($P=0.0018$). This suggests that alleles that increase LDL or total cholesterol levels or BMI will collectively tend to increase levels of CAC, even though their overall quantitative contribution is modest ($<1\%$ variance explained). Summary statistics for the individual SNPs are shown in Table IV in the Data Supplement. The association signal for the T2D-based model (which was nominally significant in the NELSON trial) seemed to be predominantly driven by a single SNP (rs944801) at the pleiotropic 9p21 locus.

Discussion

The 3 loci that have been associated with CAC thus far (*CDKN2A/B* at 9p21, *PHACTR1*, and *ADAMTS7*) were first discovered for their association with CAD and MI. This

observation motivated us to test the hypothesis that other loci associated with CAD/MI might also influence CAC. Because single-variant association testing has limited power to detect modest effects, we adopted a polygenic approach by aggregating the effects of $\leq 15\,000$ independent SNPs into a single genetic risk score and then tested each for association with CAC. The polygenic score is based on the assumption that markers act additively; that is, gene–gene interactions (epistasis) are ignored in these models. Our results demonstrate that there is at least a polygenic component with alleles acting additively, and its quantitative contribution may represent a lower bound estimate if we assume a non-negligible contribution because of epistatic effects.

In our data, the 3 known CAC SNP associations found by recent GWAS explained 2.4% of the phenotypic variance, and the 45 CAD/MI risk SNPs identified by the CARDIoGRAMplusC4D study accounted for an additional 4%. Accounting for the effects of these 45 SNPs, the most significant polygenic model was based on 8918 SNPs with $P<0.2$ in the CARDIoGRAMplusC4D study, and collectively, these SNPs explained another 1.5% of the observed CAC variance, indicating nontrivial genetic overlap between CAC and CAD/MI. This number is likely an underestimate because causal variants are only poorly tagged by the sparse set of 8918 unlinked SNPs throughout the genome. In addition, it should be noted that the MetaboChIP is biased toward gene regions prioritized by early GWAS of cardiometabolic traits.³⁷ That is to say, other (unsuspected) gene regions may also play a role. The relative contributions of the 3-SNP, 45-SNP, and polygenic models to the variance explained are consistent with the expectation that variants with stronger effects were the first ones to be identified in discovery GWAS. These common variants will consequently explain a correspondingly larger fraction of the phenotypic variance. The effect size and variance explained for individual variants captured by the polygenic

Table. Influence of Genetic Risk Scores for Various Traits on Quantitative Coronary Artery Calcification Levels

Genetic Risk Score		NELSON Study (n=2599)			Heinz Nixdorf Recall Study (n=2182)		
Trait	No. of SNPs	PValue	Effect Direction	Explained Variance, %	PValue (1-Sided)	Effect Direction	Explained Variance, %
LDL-cholesterol	56	1.6×10^{-3}	+	0.25	9.7×10^{-3}	+	0.21
Body mass index	31	8.5×10^{-3}	+	0.25	1.8×10^{-3}	+	0.33
Type 2 diabetes mellitus	55	2.6×10^{-2}	+	0.18	2.4×10^{-2}	+	0.15
Total cholesterol	72	4.0×10^{-2}	+	0.15	6.3×10^{-3}	+	0.24
Height	173	0.228	...	—	—	...	—
Type 1 diabetes mellitus	34	0.829	...	—	—	...	—
HDL-cholesterol	71	0.912	...	—	—	...	—
Blood pressure	38	0.928	...	—	—	...	—
Triglycerides	40	0.939	...	—	—	...	—

Genetic risk scores are based on bona fide SNP associations for the traits listed. Results are sorted by decreasing significance in the NELSON Study. The explained variance and effect direction are only given for traits that are nominally significant in the NELSON Study. Nominally, significant models were replicated in the Heinz Nixdorf Recall Study. Results of the NELSON Study are corrected for age, smoking history (in pack years), and the first principal component of the genotype data. Results of the Heinz Nixdorf Recall Study are corrected for age and sex. HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein; NELSON Study, the Dutch and Belgian Lung Cancer Screening Study; SNP, single-nucleotide polymorphism.

association signal will be much lower, but they may still give important insights into the underlying biology.

Considering the phenotypic heterogeneity among the many CAD/MI studies that were part of the CARDiOGRAMplusC4D study, it is not straightforward to interpret the magnitude of effect of the SNPs because they may not necessarily reflect the true impact on the CAC phenotype. We, therefore, expect that the estimated variance explained in our analysis is probably not that precise although the qualitative result should be robust. Indeed, ignoring the effect sizes for the CAD/MI-associated SNPs (as weights in the polygenic score) produced essentially identical results (data not shown). These observations are consistent with the notion that the effect sizes of the individual SNPs underlying the polygenic association are small and hard to detect individually at the genome-wide significance level. An important result is that the cumulative effects on CAC seem to be distributed all over the genome, again consistent with a polygenic architecture.

To investigate the role of traditional risk factors on CAC, we tested genetic risk scores based on validated SNPs associated with LDL-cholesterol, HDL-cholesterol, triglycerides, total cholesterol, height, BMI, blood pressure, T1D, and T2D. Of these, we found statistically significant positive associations for LDL-cholesterol, total cholesterol, and BMI. One interpretation of these results is that certain genes underlying these traits have pleiotropic effects on CAC.

Previous observational studies have demonstrated the relationship between LDL and total cholesterol levels and CAC levels.^{38,39} Our results confirm that common SNPs associated with LDL and total cholesterol affect calcification levels and are in agreement with findings from a similar genetic risk score analysis in 1987 elderly individuals from the Rotterdam Study.⁴⁰ We did not observe a significant association for the HDL-cholesterol genetic risk score, which is consistent with recent evidence that genes influencing HDL-cholesterol may not have a significant impact on MI risk.⁴¹ This finding appears at odds, however, with recent results from the Diabetes Heart Study where HDL-based genetic risk scores were found to be (inversely) associated with CAC.⁴² With respect to the impact of obesity on CAC, several studies have described (positive) associations between CAC and BMI (or obesity), which is consistent with our results.^{43–45}

We did not observe an association for the genetic risk scores for triglycerides and hypertension, which is perhaps somewhat more surprising given their established causal role in cardiovascular disease.^{46,47} On the basis of these observations, we found that increasing blood pressure or triglyceride levels are likely to exert their harmful effects on cardiovascular disease with no direct effect on calcification.

It is interesting to speculate whether LDL and total cholesterol and BMI may have a direct impact on CAC levels in the sense that their effects on CAD/MI risk are (partially) mediated through CAC, but we caution that our study was not designed to make such causal inferences. Even so, the results presented here are consistent with genes having a direct (that is, pleiotropic) effect on calcification or an indirect effect on calcification because of, for example, LDL-cholesterol.

In this study, we characterized the genetic architecture of CAC in relation to CAD and MI and traditional risk factors. First, we identified a polygenic model based on common SNPs associated with CAD/MI that could explain up to 13.9% of the observed CAC variance. This suggests that a substantial fraction of the genetic risk for CAD/MI is mediated through CAC. Second, polygenic models based on published risk alleles for traditional cardiovascular risk factors showed that SNPs associated with LDL-cholesterol, total cholesterol, and BMI may also be involved in the cause of CAC. Further insight into the underlying CAC mechanisms may lead us toward novel treatment opportunities for CAD/MI beyond traditional risk factor management. Collaborative GWAS of larger sample sizes will remain a useful activity as they continue to identify novel loci, especially for imaging-based traits where sample numbers have not been as large as compared with other traits. Such a strategy will likely lead to a better understanding of the underlying processes of arterial calcification and its role in CAD and MI.

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Disclosures

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References

1. Schunkert H, König IR, Kathiresan S, Reilly MP, Assimes TL, Holm H, et al.; Cardiogenics; CARDiOGRAM Consortium. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet.* 2011;43:333–338. doi: 10.1038/ng.784.

2. Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, et al. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet*. 2013;45:25–33.
3. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, et al. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature*. 2010;466:707–713. doi: 10.1038/nature09270.
4. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, et al.; Global Lipids Genetics Consortium. Discovery and refinement of loci associated with lipid levels. *Nat Genet*. 2013;45:1274–1283. doi: 10.1038/ng.2797.
5. Newton-Cheh C, Johnson T, Gateva V, Tobin MD, Bochud M, Coin L, et al.; Wellcome Trust Case Control Consortium. Genome-wide association study identifies eight loci associated with blood pressure. *Nat Genet*. 2009;41:666–676. doi: 10.1038/ng.361.
6. Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, Chasman DI, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature*. 2011;478:103–109.
7. Wain LV, Verwoert GC, O'Reilly PF, Shi G, Johnson T, Johnson AD, et al.; LifeLines Cohort Study; EchoGen consortium; AortaGen Consortium; CHARGE Consortium Heart Failure Working Group; KidneyGen consortium; CKDGen consortium; Cardiogenics consortium; CardioGram. Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure. *Nat Genet*. 2011;43:1005–1011. doi: 10.1038/ng.922.
8. Morris AP, Voight BF, Teslovich TM, Ferreira T, Segrè AV, Steinthorsdottir V, et al.; Wellcome Trust Case Control Consortium; Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) Investigators; Genetic Investigation of ANthropometric Traits (GIANT) Consortium; Asian Genetic Epidemiology Network–Type 2 Diabetes (AGEN-T2D) Consortium; South Asian Type 2 Diabetes (SAT2D) Consortium; Diabetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat Genet*. 2012;44:981–990. doi: 10.1038/ng.2383.
9. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al.; MAGIC; Procardis Consortium. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. 2010;42:937–948. doi: 10.1038/ng.686.
10. Berndt SI, Gustafsson S, Mägi R, Ganna A, Wheeler E, Feitosa MF, et al. Genome-wide meta-analysis identifies 11 new loci for anthropometric traits and provides insights into genetic architecture. *Nat Genet*. 2013;45:501–512. doi: 10.1038/ng.2606.
11. O'Donnell CJ, Kavousi M, Smith AV, Kardia SL, Feitosa MF, Hwang SJ, et al.; CARDIOGRAM Consortium. Genome-wide association study for coronary artery calcification with follow-up in myocardial infarction. *Circulation*. 2011;124:2855–2864. doi: 10.1161/CIRCULATIONAHA.110.974899.
12. Pechlivanis S, Mühleisen TW, Möhlenkamp S, Schädendorf D, Erbel R, Jöckel KH, et al.; Heinz Nixdorf Recall Study Investigative Group. Risk loci for coronary artery calcification replicated at 9p21 and 6q24 in the Heinz Nixdorf Recall Study. *BMC Med Genet*. 2013;14:23. doi: 10.1186/1471-2350-14-23.
13. van Setten J, Isgum I, Smolonska J, Ripke S, de Jong PA, Oudkerk M, et al. Genome-wide association study of coronary and aortic calcification implicates risk loci for coronary artery disease and myocardial infarction. *Atherosclerosis*. 2013;228:400–405. doi: 10.1016/j.atherosclerosis.2013.02.039.
14. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA*. 2004;291:210–215. doi: 10.1001/jama.291.2.210.
15. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. *J Am Coll Cardiol*. 2005;46:158–165. doi: 10.1016/j.jacc.2005.02.088.
16. Vliegenthart R, Oudkerk M, Hofman A, Oei HH, van Dijk W, van Rooij FJ, et al. Coronary calcification improves cardiovascular risk prediction in the elderly. *Circulation*. 2005;112:572–577. doi: 10.1161/CIRCULATIONAHA.104.488916.
17. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med*. 2008;358:1336–1345. doi: 10.1056/NEJMoa072100.
18. Polonsky TS, McClelland RL, Jorgensen NW, Bild DE, Burke GL, Guerci AD, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. *JAMA*. 2010;303:1610–1616. doi: 10.1001/jama.2010.461.
19. Aherrahrou Z, Schunkert H. Genetics of atherosclerosis and vascular calcification go hand-in-hand. *Atherosclerosis*. 2013;228:325–326. doi: 10.1016/j.atherosclerosis.2012.10.029.
20. Isgum I, Prokop M, Niemeijer M, Viergever MA, van Ginneken B. Automatic coronary calcium scoring in low-dose chest computed tomography. *IEEE Trans Med Imaging*. 2012;31:2322–2334. doi: 10.1109/TMI.2012.2216889.
21. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990;15:827–832.
22. Howie B, Fuchsberger C, Stephens M, Marchini J, Abecasis GR. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. *Nat Genet*. 2012;44:955–959. doi: 10.1038/ng.2354.
23. Francioli LC, Menelaou A, Pulit SL, van Dijk F, Francesco Palamara P, Elbers CC, et al. Whole-genome sequence variation, population structure and demographic history of the dutch population. *Nat Genet*. 2014;46:818–825.
24. Wang F, Xu CQ, He Q, Cai JP, Li XC, Wang D, et al. Genome-wide association identifies a susceptibility locus for coronary artery disease in the Chinese Han population. *Nat Genet*. 2011;43:345–349. doi: 10.1038/ng.783.
25. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 2007;81:559–575. doi: 10.1086/519795.
26. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. 2009;460:748–752.
27. Yang J, Manolio TA, Pasquale LR, Boerwinkle E, Caporaso N, Cunningham JM, et al. Genome partitioning of genetic variation for complex traits using common SNPs. *Nat Genet*. 2011;43:519–525. doi: 10.1038/ng.823.
28. Subramanian A, Tamayo P, Mootha VK, Mukherjee S, Ebert BL, Gillette MA, et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci U S A*. 2005;102:15545–15550. doi: 10.1073/pnas.0506580102.
29. Harrow J, Frankish A, Gonzalez JM, Tapanari E, Diekhans M, Kokocinski F, et al. GENCODE: the reference human genome annotation for The ENCODE Project. *Genome Res*. 2012;22:1760–1774. doi: 10.1101/gr.135350.111.
30. Lango Allen H, Estrada K, Lettre G, Berndt SI, Weedon MN, Rivadeneira F, et al. Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature*. 2010;467:832–838. doi: 10.1038/nature09410.
31. Barrett JC, Clayton DG, Concannon P, Akolkar B, Cooper JD, Erlich HA, et al.; Type 1 Diabetes Genetics Consortium. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. *Nat Genet*. 2009;41:703–707. doi: 10.1038/ng.381.
32. Wallace C, Smyth DJ, Maisuria-Armer M, Walker NM, Todd JA, Clayton DG. The imprinted DLK1-MEG3 gene region on chromosome 14q32.2 alters susceptibility to type 1 diabetes. *Nat Genet*. 2010;42:68–71. doi: 10.1038/ng.493.
33. Bradfield JP, Qu HQ, Wang K, Zhang H, Sleiman PM, Kim CE, et al. A genome-wide meta-analysis of six type 1 diabetes cohorts identifies multiple associated loci. *PLoS Genet*. 2011;7:e1002293. doi: 10.1371/journal.pgen.1002293.
34. van't Hof FN, Ruigrok YM, Baas AF, Kiemeny LA, Vermeulen SH, Uitterlinden AG, et al. Impact of inherited genetic variants associated with lipid profile, hypertension, and coronary artery disease on the risk of intracranial and abdominal aortic aneurysms. *Circ Cardiovasc Genet*. 2013;6:264–270.
35. Schmermund A, Möhlenkamp S, Stang A, Grönemeyer D, Seibel R, Hirche H, et al. Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the Heinz Nixdorf RECALL Study. Risk Factors, Evaluation of Coronary Calcium and Lifestyle. *Am Heart J*. 2002;144:212–218.
36. Marchini J, Howie B, Myers S, McVean G, Donnelly P. A new multipoint method for genome-wide association studies by imputation of genotypes. *Nat Genet*. 2007;39:906–913. doi: 10.1038/ng2088.
37. Voight BF, Kang HM, Ding J, Palmer CD, Sidore C, Chines PS, et al. The metabochip, a custom genotyping array for genetic studies of metabolic, cardiovascular, and anthropometric traits. *PLoS Genet*. 2012;8:e1002793. doi: 10.1371/journal.pgen.1002793.

38. Allison MA, Wright M, Tiefenbrun J. The predictive power of low-density lipoprotein cholesterol for coronary calcification. *Int J Cardiol*. 2003;90:281–289.
39. Orakzai SH, Nasir K, Blaha M, Blumenthal RS, Raggi P. Non-HDL cholesterol is strongly associated with coronary artery calcification in asymptomatic individuals. *Atherosclerosis*. 2009;202:289–295. doi: 10.1016/j.atherosclerosis.2008.03.014.
40. Bos D, Ikram MA, Isaacs A, Verhaaren BF, Hofman A, van Duijn CM, et al. Genetic loci for coronary calcification and serum lipids relate to aortic and carotid calcification. *Circ Cardiovasc Genet*. 2013;6:47–53. doi: 10.1161/CIRCGENETICS.112.963934.
41. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet*. 2012;380:572–580. doi: 10.1016/S0140-6736(12)60312-2.
42. Raffield LM, Cox AJ, Hsu FC, Ng MC, Langefeld CD, Carr JJ, et al. Impact of HDL genetic risk scores on coronary artery calcified plaque and mortality in individuals with type 2 diabetes from the Diabetes Heart Study. *Cardiovasc Diabetol*. 2013;12:95. doi: 10.1186/1475-2840-12-95.
43. Rhee EJ, Seo MH, Kim JD, Jeon WS, Park SE, Park CY, et al. Metabolic health is more closely associated with coronary artery calcification than obesity. *PLoS One*. 2013;8:e74564. doi: 10.1371/journal.pone.0074564.
44. Chang Y, Kim BK, Yun KE, Cho J, Zhang Y, Rampal S, et al. Metabolically-healthy obesity and coronary artery calcification. *J Am Coll Cardiol*. 2014;63:2679–2686. doi: 10.1016/j.jacc.2014.03.042.
45. Lee SY, Chang HJ, Sung J, Kim KJ, Shin S, Cho IJ, et al. The impact of obesity on subclinical coronary atherosclerosis according to the risk of cardiovascular disease. *Obesity (Silver Spring)*. 2014;22:1762–1768. doi: 10.1002/oby.20760.
46. Do R, Willer CJ, Schmidt EM, Sengupta S, Gao C, Peloso GM, et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat Genet*. 2013;45:1345–1352. doi: 10.1038/ng.2795.
47. Lieb W, Jansen H, Loley C, Pencina MJ, Nelson CP, Newton-Cheh C, et al.; CARDIoGRAM. Genetic predisposition to higher blood pressure increases coronary artery disease risk. *Hypertension*. 2013;61:995–1001. doi: 10.1161/HYPERTENSIONAHA.111.00275.

CLINICAL PERSPECTIVE

Understanding the root causes for cardiovascular disease and associated risk factors is a key priority for biomedical research. Calcification of the coronary arteries is a strong and independent risk factor for cardiovascular events including myocardial infarction. In this study, we analyzed the genetic architecture of coronary calcification in relation to genetic associations for coronary artery disease and traditional risk factors including low-density lipoprotein-cholesterol, type 2 diabetes mellitus, blood pressure, and obesity. Our analyses underscore a substantial genetic overlap between quantitative calcification levels (measured by computed tomography) and coronary artery disease (including myocardial infarction), reinforcing the notion that calcification plays a causal role in myocardial infarction. In addition, we tested if bona fide single-nucleotide polymorphisms associated with traditional risk factors were also associated with coronary calcification, and found that variants influencing low-density lipoprotein and total cholesterol levels, body mass index, and type 2 diabetes mellitus risk also have an effect on coronary calcification. This finding is consistent with the notion that at least some of the adverse effects of these risk factors may be mediated through calcification.

Serum Lipid Levels, Body Mass Index, and Their Role in Coronary Artery Calcification: A Polygenic Analysis

Jessica van Setten, Ivana Isgum, Sonali Pechlivanis, Vinicius Tragante, Pim A. de Jong, Joanna Smolonska, Mathieu Platteel, Per Hoffmann, Matthijs Oudkerk, Harry J. de Koning, Markus M. Nöthen, Susanne Moebus, Raimund Erbel, Karl-Heinz Jöckel, Max A. Viergever, Willem P.Th.M. Mali and Paul I.W. de Bakker

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SUPPLEMENTAL MATERIAL

Supplementary Table 1: The CARDIoGRAMplusC4D consortium described 45 CAD/MI risk SNPs. This table shows the association results of these SNPs with Agatston score in the NELSON study.

SNP	Chr	Position	Coded allele	Non-coded allele	Coded-allele frequency	Beta	Standard error	P-value
rs11206510	1	55496039	T	C	0.8091	-0.0311	0.1032	0.7629
rs17114036	1	56962821	A	G	0.9119	0.0532	0.1292	0.6805
rs599839	1	109822166	A	G	0.7574	0.1094	0.0908	0.2283
rs4845625	1	154422067	C	T	0.5580	0.0121	0.0769	0.8753
rs17465637	1	222823529	C	A	0.7380	0.2067	0.0827	0.0125
rs515135	2	21286057	C	T	0.8316	-0.0310	0.0979	0.7516
rs6544713	2	44073881	C	T	0.7021	-0.1152	0.0819	0.1598
rs1561198	2	85809989	C	T	0.5346	-0.2231	0.0737	0.0025
rs2252641	2	145801461	T	C	0.5576	-0.0269	0.0760	0.7232
rs6725887	2	203745885	T	C	0.8684	-0.0244	0.1094	0.8236
rs9818870	3	138122122	C	T	0.8307	-0.0496	0.1001	0.6201
rs1878406	4	148393664	C	T	0.8629	-0.2440	0.1069	0.0226
rs7692387	4	156635309	G	A	0.8105	0.0349	0.0964	0.7175
rs273909	5	131667353	A	G	0.8823	0.0873	0.1157	0.4506
rs12526453	6	12927544	C	G	0.6536	0.2420	0.0781	0.0020
rs17609940	6	35034800	G	C	0.7903	0.0054	0.0904	0.9526
rs10947789	6	39174922	T	C	0.7690	-0.0821	0.0887	0.3547
rs12190287	6	134214525	C	G	0.6377	0.0603	0.0843	0.4743
rs2048327	6	160863532	T	C	0.6224	-0.0542	0.0759	0.4754
rs4252120	6	161143608	T	C	0.6934	-0.0689	0.0815	0.3985
rs2023938	7	19036775	T	C	0.8985	-0.0132	0.1220	0.9136
rs12539895	7	107091849	C	A	0.7922	-0.0431	0.0907	0.6345
rs11556924	7	129663496	C	T	0.5745	0.0886	0.0829	0.2851
rs264	8	19813180	G	A	0.8541	0.1683	0.1047	0.1082
rs2954029	8	126490972	A	T	0.5227	-0.0187	0.0739	0.8008
rs3217992	9	22003223	C	T	0.6441	-0.3487	0.0766	5.6 x 10 ⁻⁶
rs579459	9	136154168	T	C	0.8008	-0.1172	0.0930	0.2077
rs2505083	10	30335122	T	C	0.5739	-0.1001	0.0792	0.2064
rs2047009	10	44539913	G	T	0.5425	0.0923	0.0742	0.2135
rs11203042	10	90989109	C	T	0.5468	-0.0213	0.0863	0.8052
rs12413409	10	104719096	G	A	0.9236	0.0072	0.1400	0.9591
rs974819	11	103660567	C	T	0.7094	-0.1339	0.0827	0.1057
rs964184	11	116648917	C	G	0.8644	-0.2244	0.1119	0.0449
rs3184504	12	111884608	C	T	0.5277	-0.1225	0.0792	0.1222

rs9319428	13	28973621	G	A	0.6861	-0.0490	0.0787	0.5342
rs9515203	13	111049623	T	C	0.7263	0.1015	0.0914	0.2670
rs2895811	14	100133942	T	C	0.5443	-0.0944	0.0746	0.2055
rs3825807	15	79089111	A	G	0.5575	0.3656	0.0805	5.8×10^{-6}
rs17514846	15	91416550	C	A	0.5324	0.0313	0.0730	0.6678
rs216172	17	2126504	G	C	0.6424	-0.0814	0.0767	0.2887
rs12936587	17	17543722	G	A	0.5320	0.1430	0.0751	0.0571
rs46522	17	46988597	T	C	0.5292	0.0517	0.0733	0.4810
rs1122608	19	11163601	G	T	0.7492	0.0186	0.0851	0.8270
rs2075650	19	45395619	A	G	0.8541	-0.2485	0.1024	0.0153
rs9982601	21	35599128	C	T	0.8563	-0.1911	0.1109	0.0850

Supplementary Table 2: Influence of polygenic risk score calculated from CAD/MI associated SNPs on quantitative coronary artery calcification levels in the NELSON Cohort Study. The threshold refers to the *P*-value below which SNPs from the CARDIoGRAMplusC4D study are included in the model. The models are adjusted for age, smoking history (in pack years), the first principal component of the genotype data, and 45 known CAD/MI risk SNPs.

Threshold	# SNPs	<i>P</i> -value	Explained variance (%)
$P < 5 \times 10^{-7}$	7	8.0×10^{-4}	0.38
$P < 5 \times 10^{-6}$	42	1.4×10^{-3}	0.35
$P < 5 \times 10^{-5}$	136	6.0×10^{-4}	0.40
$P < 5 \times 10^{-4}$	376	3.8×10^{-7}	0.88
$P < 5 \times 10^{-3}$	1148	1.9×10^{-7}	0.92
$P < 0.05$	4043	2.8×10^{-11}	1.50
$P < 0.1$	5217	4.2×10^{-10}	1.32
$P < 0.2$	8896	1.6×10^{-11}	1.54
$P < 0.3$	11343	1.5×10^{-9}	1.24
$P < 0.4$	13483	3.8×10^{-10}	1.33
$P < 0.5$	15431	2.1×10^{-9}	1.22

Supplementary Table 3: Explained CAC variance per chromosome based on the model with all CAD/MI associated SNPs with $P < 0.2$ in the CARDiOGRAMplusC4D study. The explained variance correlates significantly with the number of SNPs that overlap between the CARDiOGRAMplusC4D and NELSON Studies, after removal of A/T and C/G SNPs and after LD pruning (leaving no SNP pairs with $r^2 > 0.05$).

Chromosome	Number of SNPs on chromosome (LD pruned)	Explained variance (%)	P-value
1	732	0.31	0.0028
2	735	0.36	0.0012
3	578	0.20	0.0156
4	523	0.14	0.0450
5	553	0.13	0.0490
6	603	0.48	0.0002
7	512	0.00	0.7904
8	463	0.01	0.4852
9	423	0.12	0.0598
10	506	0.03	0.3450
11	488	0.00	0.8618
12	478	0.05	0.2402
13	306	0.13	0.0514
14	269	0.01	0.5393
15	307	0.06	0.1928
16	300	0.09	0.1015
17	258	0.01	0.5424
18	249	0.03	0.3569
19	162	0.07	0.1367
20	227	0.08	0.1223
21	134	0.00	0.7953
22	112	0.00	0.6988

Supplementary Table 4: Association results for CAC levels in the NELSON Cohort Study and the Heinz Nixdorf Recall Study for validated SNPs associated with nine traits/diseases.

Supplementary Table 4a: Total cholesterol

SNP	Chr	Position	TC increasing allele	Other allele	NELSON Cohort Study		Heinz Nixdorf Recall Study	
					Beta	P-value	Beta	P-value
rs1077514	1	23766233	T	C	0.0773	0.4578	0.1371	0.1413
rs12027135	1	25775733	T (major)	A	0.0411	0.5922	-0.1081	0.0987
rs2479409	1	55504650	G	A	0.2226	0.0169	0.1520	0.0283
rs2131925	1	63025942	T	G	-0.0775	0.3282	0.1255	0.0741
rs7515577	1	93009438	A	C	-0.0218	0.8086	0.0374	0.6447
rs629301	1	109818306	T	G	0.1073	0.2335	0.0919	0.2492
rs2642442	1	220973563	T	C	0.0183	0.8295	0.1111	0.1254
rs514230	1	234858597	T (major)	A	0.1549	0.0408	-0.0201	0.7541
rs1367117	2	21263900	A	G	0.0124	0.8785	0.0973	0.1693
rs1260326	2	27730940	T	C	0.0025	0.9740	0.0235	0.7192
rs4299376	2	44072576	G	T	0.1050	0.1999	0.0752	0.2907
rs10490626	2	118835841	G	A	-0.1821	0.2283	0.1911	0.1321
rs2030746	2	121309488	T	C	-0.0765	0.3511	-0.0084	0.8998
rs7570971	2	135837906	A	C	-0.0690	0.3861	-0.0321	0.6387
rs2287623	2	169830155	G	A	0.0168	0.8238	0.0293	0.6660
rs11694172	2	203532304	G	A	-0.0095	0.9126	0.0634	0.3929
rs11563251	2	234679384	T	C	0.0078	0.9539	0.0666	0.5534
rs2290159	3	12628920	G (major)	C	0.0553	0.5497	0.1495	0.0965
rs7640978	3	32533010	C	T	0.1823	0.2185	0.2007	0.1064
rs13315871	3	58381287	G	A	-0.2045	0.1231	-0.2246	0.1841
rs6831256	4	3473139	G	A	0.0705	0.3525	0.0493	0.4577
rs12916	5	74656539	C	T	-0.0075	0.9205	-0.0188	0.7787
rs4530754	5	122855416	A	G	0.0736	0.3182	-0.0491	0.4734
rs6882076	5	156390297	C	T	0.0171	0.8226	0.0899	0.1773
rs3757354	6	16127407	C	T	-0.1745	0.0722	-0.0078	0.9203
rs1800562	6	26093141	G	A	0.2797	0.0727	0.9462	0.1191
rs3177928	6	32412435	A	G	0.2301	0.0227	0.1167	0.2105
rs2814982	6	34546560	C	T	-0.1978	0.1042	-0.1406	0.1701
rs2758886	6	39250837	A	G	-0.1040	0.2086	0.0328	0.6695
rs9488822	6	116312893	T (minor)	A	-0.0142	0.8600	0.0596	0.4278
rs9376090	6	135411228	T	C	-0.0163	0.8497	0.0412	0.5734
rs1564348	6	160578860	C	T	-0.0681	0.5133	0.1214	0.1676
rs1997243	7	1083777	G	A	0.1483	0.1230	-0.2110	0.2332
rs12670798	7	21607352	C	T	0.1179	0.1692	-0.0453	0.6215
rs4722551	7	25991826	C	T	0.0574	0.6200	0.0607	0.4931
rs2072183	7	44579180	C (minor)	G	-0.0870	0.4099	0.1072	0.1810
rs9987289	8	9183358	G	A	0.1782	0.1749	0.1600	0.1704
rs1495741	8	18272881	G	A	0.0776	0.3619	-0.1288	0.0958

rs10102164	8	55421614	A	G	0.0673	0.4769	0.0442	0.5930
rs2081687	8	59388565	T	C	0.0536	0.4928	-0.0646	0.3419
rs2954029	8	126490972	A (major)	T	-0.0187	0.8008	-0.0301	0.6531
rs11136341	8	145043543	G	A	0.1068	0.2112	-0.0902	0.2591
rs3780181	9	2640759	A	G	0.0239	0.8701	-0.0406	0.7503
rs581080	9	15305378	C (major)	G	0.0281	0.7634	-0.1023	0.2937
rs1883025	9	107664301	C	T	-0.0578	0.4997	-0.0958	0.2097
rs9411489	9	136155000	T	C	0.1065	0.2681	0.2313	0.0036
rs10904908	10	17260290	G	A	0.0039	0.9616	0.1614	0.0225
rs970548	10	46013277	C	A	0.1517	0.0780	0.0974	0.2219
rs2255141	10	113933886	A	G	0.0288	0.7261	0.0696	0.2966
rs10128711	11	18632984	C	T	-0.0134	0.8988	0.0597	0.4308
rs174546	11	61569830	C	T	-0.0793	0.3184	-0.0671	0.3385
rs964184	11	116648917	G (major)	C	-0.2244	0.0449	-0.1670	0.3009
rs11603023	11	118486067	T	C	0.0716	0.3431	0.0585	0.3776
rs7941030	11	122522375	C	T	0.0734	0.3443	0.0972	0.1459
rs11220462	11	126243952	A	G	-0.0657	0.5365	-0.1392	0.1835
rs4883201	12	9082581	A	G	-0.1531	0.2229	-0.0227	0.8673
rs11065987	12	112072424	A	G	-0.1456	0.0516	0.0363	0.5850
rs1169288	12	121416650	C	A	0.0827	0.3168	-0.0540	0.4262
rs1532085	15	58683366	A	G	0.0574	0.4504	0.0574	0.3944
rs3764261	16	56993324	A	C	-0.0244	0.7555	0.0641	0.3558
rs2000999	16	72108093	A	G	-0.0686	0.4613	-0.0009	0.9909
rs314253	17	7091650	T	C	0.0351	0.6767	0.1183	0.0811
rs7206971	17	45425115	A	G	-0.1011	0.1987	0.0207	0.7511
rs7241918	18	47160953	T	G	0.2210	0.0252	0.0424	0.6275
rs6511720	19	11202306	G	T	0.1458	0.2110	0.1350	0.1880
rs10401969	19	19407718	T	C	-0.1576	0.2565	0.0438	0.7302
rs4420638	19	45422946	G	A	0.2707	0.0211	-0.0241	0.7815
rs492602	19	49206417	G	A	-0.0171	0.8211	-0.0409	0.5330
rs2277862	20	34152782	C	T	0.0890	0.4197	-0.0583	0.5187
rs2902940	20	39091487	A	G	0.1415	0.0768	0.0870	0.2315
rs6029526	20	39672618	A (minor)	T	0.0452	0.5466	-0.0394	0.5784
rs1800961	20	43042364	C	T	-0.2096	0.3560	-0.1490	0.4757
rs138777	22	35711098	A	G	-0.0433	0.5751	-0.1134	0.1097
rs4253772	22	46627603	T	C	-0.0170	0.8915	-0.0510	0.6343

Supplementary Table 4b: Type 2 diabetes

SNP	Chr	Position	T2D increasing allele	Other allele	NELSON Cohort Study		Heinz Nixdorf Recall Study	
					Beta	P-value	Beta	P-value
rs10923931	1	120517959	T	G	-0.0318	0.8150	0.1318	0.2157
rs2075423	1	214154719	G	T	0.0568	0.4828	0.0381	0.5943
rs780094	2	27741237	C	T	0.0170	0.8256	-0.0326	0.6199
rs10203174	2	43690030	C	T	0.1327	0.2518	-0.0549	0.5786
rs243088	2	60568745	T (minor)	A	-0.1471	0.0455	0.0375	0.5600
rs7593730	2	161171454	C	T	0.1491	0.1026	-0.0751	0.3734

rs13389219	2	165528876	C	T	0.0817	0.2905	0.0415	0.5532
rs2943640	2	227093585	C	A	-0.0566	0.4643	-0.0028	0.9690
rs1801282	3	12393125	C (major)	G	0.2789	0.0089	0.0326	0.7205
rs1496653	3	23454790	A	G	-0.0630	0.4830	0.0615	0.4567
rs6795735	3	64705365	C	T	-0.1045	0.1689	0.0007	0.9914
rs11717195	3	123082398	T	C	-0.1005	0.2234	-0.0732	0.3489
rs4402960	3	185511687	T	G	0.1503	0.0666	0.0824	0.2435
rs4458523	4	6289986	G	T	-0.0620	0.4183	-0.0349	0.6021
rs459193	5	55806751	G	A	-0.0686	0.4313	0.0253	0.7834
rs6878122	5	76427311	G	A	0.0112	0.8932	-0.0061	0.9308
rs7756992	6	20679709	G	A	0.1401	0.0939	0.1708	0.0177
rs17168486	7	14898282	T	C	-0.1046	0.2938	-0.0563	0.5138
rs849135	7	28196413	G	A	0.0429	0.5717	0.0491	0.4475
rs10278336	7	44245363	A	G	0.1506	0.0610	-0.1772	0.0076
rs13233731	7	130437689	G	A	-0.0743	0.3133	0.2269	0.0007
rs516946	8	41519248	C	T	0.1164	0.1846	-0.0498	0.5059
rs7845219	8	95937502	T	C	-0.0115	0.8759	0.0645	0.3182
rs3802177	8	118185025	G	A	-0.0083	0.9162	0.0037	0.9591
rs10758593	9	4292083	A	G	-0.0409	0.5883	-0.0179	0.7978
rs944801	9	22051670	C (major)	G	0.3498	2.4×10^{-6}	0.1754	0.0080
rs10811661	9	22134094	T	C	0.0097	0.9195	-0.1343	0.1516
rs17791513	9	81905590	A	G	0.1978	0.1410	-0.2417	0.0580
rs2796441	9	84308948	G	A	0.0270	0.7361	0.0472	0.4838
rs11257655	10	12307894	T	C	0.0066	0.9426	0.1236	0.1326
rs12571751	10	80942631	A	G	0.1316	0.0779	0.0028	0.9664
rs1111875	10	94462882	C	T	0.0640	0.4086	0.0521	0.4319
rs7903146	10	114758349	T	C	-0.0440	0.6197	0.1213	0.0984
rs231361	11	2691500	A	G	0.0024	0.9778	0.0808	0.3039
rs163184	11	2847069	G	T	-0.0916	0.4364	0.1026	0.1113
rs5215	11	17408630	C	T	0.0335	0.6654	-0.0247	0.7127
rs1552224	11	72433098	A	C	0.1162	0.2341	-0.0070	0.9365
rs10830963	11	92708710	G (minor)	C	-0.0500	0.6165	0.0601	0.4061
rs11063069	12	4374373	G	A	0.0973	0.3787	0.0084	0.9159
rs10842994	12	27965150	C	T	0.0041	0.9710	0.0462	0.5706
rs2261181	12	66212318	T	C	-0.1271	0.3390	0.0070	0.9509
rs7955901	12	71433293	C	T	0.0113	0.8800	0.0437	0.5074
rs12427353	12	121426901	G (major)	C	-0.1009	0.2870	-0.0053	0.9521
rs1359790	13	80717156	G	A	-0.0674	0.4100	-0.0283	0.7364
rs4502156	15	62383155	T	C	-0.0298	0.6875	-0.0543	0.4204
rs7177055	15	77832762	A	G	-0.0371	0.6516	-0.0570	0.4246
rs11634397	15	80432222	G	A	-0.0925	0.2421	0.0348	0.6183
rs12899811	15	91544076	G	A	0.0266	0.7363	0.0310	0.6621
rs9936385	16	53819169	C	T	0.1121	0.1403	0.1247	0.0613
rs7202877	16	75247245	T	G	-0.0453	0.7425	0.0683	0.5143
rs11651052	17	36102381	A	G	0.1083	0.1553	-0.0127	0.8453
rs12970134	18	57884750	A	G	-0.1501	0.0645	0.0529	0.4661
rs10401969	19	19407718	C	T	0.1576	0.2565	-0.0438	0.7302
rs8108269	19	46158513	G	T	-0.1060	0.2383	-0.0515	0.4638
rs4812829	20	42989267	A	G	0.0814	0.3881	-0.1127	0.1678

Supplementary Table 4c: BMI

SNP	Chr	Position	BMI increasing allele	Other allele	NELSON Cohort Study		Heinz Nixdorf Recall Study	
					Beta	P-value	Beta	P-value
rs2815752	1	72812440	A	G	0.0039	0.9583	0.0233	0.7294
rs1514175	1	74991644	A	G	0.0197	0.7909	0.0599	0.3754
rs1555543	1	96944797	C	A	0.0221	0.7746	0.0660	0.3107
rs543874	1	177889480	G	A	0.1755	0.0557	0.0086	0.9195
rs2867125	2	622827	C	T	0.1991	0.0590	0.0509	0.5414
rs713586	2	25158008	C	T	0.0458	0.5385	0.1194	0.0832
rs887912	2	59302877	T	C	0.0663	0.4106	0.0343	0.6752
rs2890652	2	142959931	C	T	0.0098	0.9186	0.0495	0.5547
rs13078807	3	85884150	G	A	-0.0400	0.6632	-0.0728	0.3853
rs9816226	3	185834499	T (major)	A	-0.0599	0.5352	0.1659	0.4136
rs10938397	4	45182527	G	A	0.0214	0.7981	0.1833	0.0052
rs13107325	4	103188709	T	C	0.2081	0.3427	0.1803	0.1668
rs2112347	5	75015242	T	G	0.2401	0.0497	0.0977	0.1588
rs206936	6	34302869	G	A	0.0097	0.9184	0.1264	0.1210
rs987237	6	50803050	G	A	-0.0412	0.6704	0.1964	0.0189
rs10968576	9	28414339	G	A	0.0732	0.3656	-0.1442	0.0413
rs4929949	11	8604593	C	T	-0.0144	0.8453	0.0838	0.2113
rs10767664	11	27725986	A (major)	T	0.0838	0.3554	-0.0033	0.9682
rs3817334	11	47650993	T	C	0.0007	0.9922	0.0494	0.4613
rs7138803	12	50247468	A	G	0.0828	0.2738	0.0927	0.1678
rs4771122	13	28020180	G	A	-0.0851	0.3205	-0.3916	0.0141
rs11847697	14	30515112	T	C	0.1385	0.4723	-0.5090	0.1984
rs10150332	14	79936964	C	T	0.0154	0.8628	0.1500	0.0556
rs2241423	15	68086838	G	A	0.1158	0.1868	0.0343	0.6557
rs12444979	16	19933600	C	T	0.0608	0.5782	-0.1051	0.2611
rs7359397	16	28885659	T	C	-0.0328	0.6625	0.0682	0.3116
rs1558902	16	53803574	A (minor)	T	-0.1139	0.1363	0.1399	0.0342
rs571312	18	57839769	A	C	-0.1151	0.1724	0.0052	0.9451
rs29941	19	34309532	G	A	0.0303	0.7005	-0.0099	0.8888
rs2287019	19	46202172	C	T	0.0720	0.4807	0.0019	0.9814
rs3810291	19	47569003	A	G	0.0264	0.7948	0.0021	0.9763

Supplementary Table 4d: LDL-cholesterol

SNP	Chr	Position	LDL increasing allele	Other allele	NELSON Cohort Study		Heinz Nixdorf Recall Study	
					Beta	P-value	Beta	P-value
rs12027135	1	25775733	A (major)	T	0.0411	0.5922	-0.1081	0.0987
rs12748152	1	27138393	T	C	-0.0683	0.6055	0.0161	0.8917
rs2479409	1	55504650	G	A	0.2226	0.0169	0.1520	0.0283
rs2131925	1	63025942	T	G	-0.0775	0.3282	0.1255	0.0741
rs629301	1	109818306	T	G	0.1073	0.2335	0.0919	0.2492

rs267733	1	150958836	A	G	-0.2589	0.0083	0.0297	0.7377
rs2642442	1	220973563	T	C	0.0183	0.8295	0.1111	0.1254
rs514230	1	234858597	A (major)	T	0.1549	0.0408	-0.0201	0.7541
rs1367117	2	21263900	A	G	0.0124	0.8785	0.0973	0.1693
rs4299376	2	44072576	G	T	0.1050	0.1999	0.0752	0.2907
rs2710642	2	63149557	A	G	-0.0144	0.8570	-0.0531	0.4901
rs10490626	2	118835841	G	A	-0.1821	0.2283	0.1911	0.1321
rs2030746	2	121309488	T	C	-0.0765	0.3511	-0.0084	0.8998
rs1250229	2	216304384	C	T	-0.1231	0.1617	-0.0372	0.7245
rs11563251	2	234679384	T	C	0.0078	0.9539	0.0666	0.5534
rs7640978	3	32533010	C	T	0.1823	0.2185	0.2007	0.1064
rs17404153	3	132163200	G	T	0.0022	0.9848	0.0448	0.6648
rs6831256	4	3473139	G	A	-0.0705	0.3525	0.0493	0.4577
rs12916	5	74656539	C	T	-0.0075	0.9205	-0.0188	0.7787
rs4530754	5	122855416	A	G	-0.0736	0.3182	-0.0491	0.4734
rs6882076	5	156390297	C	T	0.0171	0.8226	0.0899	0.1773
rs3757354	6	16127407	C	T	-0.1745	0.0722	-0.0078	0.9203
rs1800562	6	26093141	G	A	0.2797	0.0727	0.9462	0.1191
rs3177928	6	32412435	A	G	0.2301	0.0227	0.1167	0.2105
rs9488822	6	116312893	T (minor)	A	-0.0142	0.8600	0.0596	0.4278
rs1564348	6	160578860	C	T	-0.0681	0.5133	0.1214	0.1676
rs12670798	7	21607352	C	T	0.1179	0.1692	-0.0453	0.6215
rs4722551	7	25991826	C	T	0.0574	0.6200	0.0607	0.4931
rs2072183	7	44579180	C (minor)	G	-0.0870	0.4099	0.1072	0.1810
rs9987289	8	9183358	G	A	0.1782	0.1749	0.1600	0.1704
rs10102164	8	55421614	A	G	0.0673	0.4769	0.0442	0.5930
rs2081687	8	59388565	T	C	0.0536	0.4928	-0.0646	0.3419
rs2954029	8	126490972	A (major)	T	-0.0187	0.8008	-0.0301	0.6531
rs11136341	8	145043543	G	A	0.1068	0.2112	-0.0902	0.2591
rs3780181	9	2640759	A	G	-0.0239	0.8701	-0.0406	0.7503
rs635634	9	136155000	T	C	0.1065	0.2681	0.2313	0.0036
rs2255141	10	113933886	A	G	-0.0288	0.7261	0.0696	0.2966
rs174546	11	61569830	C	T	-0.0793	0.3184	-0.0671	0.3385
rs964184	11	116648917	G (minor)	C	-0.2244	0.0449	0.1670	0.3009
rs11220462	11	126243952	A	G	-0.0657	0.5365	-0.1392	0.1835
rs11065987	12	112072424	A	G	0.1456	0.0516	0.0363	0.5850
rs1169288	12	121416650	C	A	0.0827	0.3168	-0.0540	0.4262
rs4942486	13	32953388	T	C	0.0077	0.9162	0.1018	0.1224
rs8017377	14	24883887	A	G	0.0841	0.2660	0.0234	0.7175
rs3764261	16	56993324	C	A	0.0244	0.7555	-0.0641	0.3558
rs2000999	16	72108093	A	G	-0.0686	0.4613	-0.0009	0.9909
rs314253	17	7091650	T	C	0.0351	0.6767	0.1183	0.0811
rs7206971	17	45425115	A	G	-0.1011	0.1987	0.0207	0.7511
rs1801689	17	64210580	C	A	-0.2442	0.3826	0.1574	0.3802
rs6511720	19	11202306	G	T	0.1458	0.2110	0.1350	0.1880
rs10401969	19	19407718	T	C	-0.1576	0.2565	0.0438	0.7302

rs4420638	19	45422946	G	A	0.2707	0.0211	-0.0241	0.7815
rs364585	20	12962718	G	A	0.0426	0.5731	-0.0209	0.7576
rs2328223	20	17845921	C	A	-0.0519	0.5851	-0.0590	0.4686
rs2902940	20	39091487	A	G	-0.1415	0.0768	0.0870	0.2315
rs6029526	20	39672618	A (minor)	T	-0.0452	0.5466	-0.0394	0.5784
rs5763662	22	30378703	T	C	0.1923	0.5232	0.2990	0.1772
rs4253772	22	46627603	T	C	-0.0170	0.8915	-0.0510	0.6343

Supplementary Table 4e: Triglycerides

SNP	Chr	Position	TG increasing allele	Other allele	NELSON Cohort Study		Heinz Nixdorf Recall Study	
					Beta	P-value	Beta	P-value
rs12748152	1	27138393	T	C	-0.0683	0.6055	0.0161	0.8917
rs2131925	1	63025942	T	G	-0.0775	0.3282	0.1255	0.0741
rs4846914	1	230295691	G	A	-0.1386	0.1027	0.0215	0.7519
rs1260326	2	27730940	T	C	0.0025	0.9740	0.0235	0.7192
rs2972146	2	227100698	T	G	-0.0578	0.4525	0.0717	0.4214
rs645040	3	135926622	T	G	-0.0204	0.8228	0.1193	0.1503
rs6831256	4	3473139	G	A	0.0705	0.3525	0.0493	0.4577
rs442177	4	88030261	T	G	0.0007	0.9925	0.0704	0.3082
rs9686661	5	55861786	T	C	0.0508	0.6201	0.0383	0.6404
rs6882076	5	156390297	C	T	0.0171	0.8226	0.0899	0.1773
rs998584	6	43757896	A	C	0.2931	0.0209	0.0138	0.8482
rs1936800	6	127436064	T	C	0.0162	0.8277	-0.0276	0.6783
rs4722551	7	25991826	C	T	0.0574	0.6200	0.0607	0.4931
rs13238203	7	72129667	C	T	-0.1526	0.5782	-0.4639	0.0981
rs17145738	7	72982874	C	T	0.1951	0.0799	-0.0678	0.4965
rs38855	7	116358044	A	G	-0.0175	0.8152	0.0218	0.7415
rs11776767	8	10683929	C (minor)	G	0.0559	0.4756	-0.0777	0.3374
rs1495741	8	18272881	G	A	0.0776	0.3619	-0.1288	0.0958
rs12678919	8	19844222	A	G	0.2480	0.0395	-0.0522	0.6430
rs2954029	8	126490972	A (major)	T	-0.0187	0.8008	-0.0301	0.6531
rs1832007	10	5254847	A	G	0.0073	0.9433	0.0305	0.7585
rs10761731	10	65027610	A (major)	T	-0.1864	0.0169	0.0664	0.3976
rs2068888	10	94839642	G	A	0.1734	0.0201	0.0013	0.9838
rs174546	11	61569830	T	C	0.0793	0.3184	0.0671	0.3385
rs964184	11	116648917	G (major)	C	-0.2244	0.0449	-0.1670	0.3009
rs11613352	12	57792580	C	T	-0.0403	0.6351	0.0066	0.9292
rs4765127	12	124460167	G	T	-0.0002	0.9980	0.1684	0.0159
rs2412710	15	42683787	A	G	-0.3012	0.2917	-0.7519	0.0503
rs2929282	15	44245931	T (minor)	A	-0.0122	0.9478	0.1931	0.6315
rs1532085	15	58683366	A	G	0.0574	0.4504	0.0574	0.3944
rs3198697	16	15129940	C	T	-0.0650	0.5132	-0.1336	0.0450
rs11649653	16	30918487	C (major)	G	-0.0867	0.3043	0.0174	0.7951
rs1121980	16	53809247	A	G	0.1000	0.1842	0.1292	0.0500
rs3764261	16	56993324	C	A	0.0244	0.7555	-0.0641	0.3558

rs8077889	17	41878166	C	A	0.1262	0.1765	0.1347	0.0986
rs7248104	19	7224431	G	A	0.0401	0.5975	-0.0693	0.3036
rs10401969	19	19407718	T	C	-0.1576	0.2565	0.0438	0.7302
rs731839	19	33899065	G	A	0.0255	0.7450	0.0786	0.2629
rs6065906	20	44554015	C	T	0.0995	0.3065	0.0902	0.6451
rs5756931	22	38546033	T	C	-0.0101	0.9011	0.0022	0.9740

Supplementary Table 4f: Type 1 diabetes

SNP	Chr	Position	T1D increasing allele	Other allele	NELSON Cohort Study		Heinz Nixdorf Recall Study	
					Beta	P-value	Beta	P-value
rs2476601	1	114377568	A	G	0.1235	0.3023	-0.1668	0.1327
rs3024505	1	206939904	A	G	0.0751	0.4509	-0.1320	0.1438
rs478222	2	25301755	A (major)	T	0.0523	0.4817	-0.1104	0.1058
rs1990760	2	163124051	T	C	-0.1354	0.0810	-0.0436	0.5190
rs3087243	2	204738919	G	A	-0.0751	0.3182	0.1042	0.1168
rs10517086	4	26085511	A	G	0.0542	0.5051	-0.0470	0.5092
rs17388568	4	123329362	A	G	0.0847	0.2905	0.0143	0.8398
rs9268645	6	32408527	G (major)	C	-0.0846	0.2585	0.0222	0.7442
rs11755527	6	90958231	G (minor)	C	-0.0243	0.7422	0.0415	0.5346
rs9388489	6	126698719	G	A	0.0437	0.5574	0.0200	0.7591
rs924043	6	170379025	C	T	0.0254	0.8118	0.0259	0.8577
rs7804356	7	26891665	C	T	-0.1321	0.1572	-0.1019	0.2711
rs10272724	7	50477213	T	C	-0.0134	0.8717	0.0590	0.4380
rs10758593	9	4292083	A	G	-0.0409	0.5883	-0.0179	0.7978
rs12722495	10	6097283	T	C	0.0239	0.8478	0.1259	0.4962
rs10509540	10	90023033	C	T	-0.0727	0.4088	-0.0029	0.9687
rs4763879	12	9910164	A	G	-0.0312	0.6858	0.0534	0.4316
rs2292239	12	56482180	T	G	0.0144	0.8543	0.1428	0.0424
rs3184504	12	111884608	T	C	0.1225	0.1222	-0.0103	0.8758
rs9585056	13	100081766	C	T	0.0412	0.6346	0.1162	0.1237
rs1465788	14	69263599	T	C	0.0949	0.2634	0.0665	0.3681
rs4900384	14	98498951	G	A	-0.1096	0.1776	0.0359	0.6291
rs941576	14	101306045	A	G	-0.0307	0.7279	-0.0166	0.7984
rs3825932	15	79235446	T	C	0.0463	0.5575	-0.1017	0.1473
rs12708716	16	11179873	A	G	0.0105	0.8941	0.0012	0.9862
rs4788084	16	28539848	T	C	-0.0120	0.8748	-0.0254	0.7510
rs7202877	16	75247245	G	T	0.0453	0.7425	-0.0683	0.5143
rs2290400	17	38066240	T	C	-0.0204	0.7852	0.0884	0.1744
rs763361	18	67531642	T	C	-0.0848	0.2519	0.0014	0.9826
rs2304256	19	10475652	C	A	-0.0392	0.6328	0.0457	0.5218
rs425105	19	47208481	C	T	0.0267	0.7903	0.1253	0.1691
rs2281808	20	1610551	T	C	0.0578	0.4710	0.0282	0.6893
rs11203203	21	43836186	A	G	-0.0313	0.6815	-0.0114	0.8683
rs5753037	22	30581722	T	C	0.0032	0.9666	0.0366	0.5894
rs229541	22	37591318	A	G	-0.0456	0.5499	0.0366	0.5819

Supplementary Table 4g: Blood pressure

SNP	Chr	Position	BP increasing allele	Other allele	NELSON Cohort Study		Heinz Nixdorf Recall Study	
					Beta	P-value	Beta	P-value
rs17367504	1	11862778	A	G	0.1927	0.0539	0.0358	0.6954
rs2932538	1	113216543	G	A	0.0550	0.5117	0.1409	0.0569
rs13002573	2	164915208	A	G	0.1688	0.0541	-0.0326	0.7222
rs1446468	2	164963486	C	T	0.0145	0.8507	0.0323	0.6582
rs13082711	3	27537909	C	T	0.0130	0.8821	0.0012	0.9875
rs3774372	3	41877414	C	T	-0.1556	0.1375	0.0598	0.5044
rs319690	3	47927484	T	C	-0.1851	0.0221	0.0234	0.7844
rs419076	3	169100886	T	C	-0.0029	0.9685	0.0588	0.4106
rs871606	4	54799245	T	C	0.0935	0.5528	-0.1044	0.3584
rs1458038	4	81164723	T	C	0.0413	0.6365	0.1640	0.0196
rs13107325	4	103188709	C	T	-0.2081	0.3427	-0.1803	0.1668
rs13139571	4	156645513	C	A	0.0681	0.4469	0.0169	0.8270
rs1173771	5	32815028	G	A	-0.0138	0.8619	0.0881	0.2070
rs11953630	5	157845402	C	T	-0.0083	0.9147	-0.0267	0.7528
rs1799945	6	26091179	G (minor)	C	0.0417	0.6968	0.0726	0.4298
rs805303	6	31616366	G	A	0.0999	0.1848	-0.0414	0.5422
rs17477177	7	106411858	C	T	-0.0375	0.6852	0.0650	0.4140
rs2071518	8	120435812	T	C	-0.1334	0.1334	0.0417	0.5772
rs4373814	10	18419972	G (minor)	C	0.0127	0.8695	-0.1090	0.1219
rs1813353	10	18707448	T	C	0.0338	0.6694	-0.0400	0.5574
rs4590817	10	63467553	G (major)	C	-0.1158	0.2718	-0.1323	0.1339
rs932764	10	95895940	G	A	-0.2311	0.0018	0.0957	0.1716
rs11191548	10	104846178	T	C	0.0383	0.7859	-0.0824	0.4436
rs2782980	10	115781527	C	T	-0.0244	0.7677	-0.0824	0.2464
rs7129220	11	10350538	A	G	-0.0821	0.5249	-0.1169	0.5179
rs381815	11	16902268	T	C	0.0176	0.8376	0.0949	0.1956
rs633185	11	100593538	G	C	-0.0030	0.9710	0.1754	0.0655
rs11222084	11	130273230	T (minor)	A	-0.0662	0.4414	0.0124	0.8446
rs17249754	12	90060586	G	A	-0.1870	0.0646	-0.1861	0.0486
rs3184504	12	111884608	T	C	0.1225	0.1222	-0.0103	0.8758
rs10850411	12	115387796	T	C	0.0752	0.3552	0.0632	0.3780
rs1378942	15	75077367	C	A	-0.1407	0.0730	-0.0255	0.7242
rs2521501	15	91437388	T (minor)	A	0.0315	0.7117	-0.0314	0.6783
rs12946454	17	43208121	T (minor)	A	-0.0492	0.5584	0.0713	0.4029
rs17608766	17	45013271	C	T	0.0326	0.7616	-0.1703	0.0781
rs12940887	17	47402807	T	C	0.0917	0.2338	0.0473	0.4795
rs1327235	20	10969030	G	A	0.0528	0.4808	0.0702	0.2969
rs6015450	20	57751117	G	A	0.0846	0.4402	-0.4593	0.0330

Supplementary Table 4h: HDL-cholesterol

SNP	Chr	Position	HDL increasing allele	Other allele	NELSON Cohort Study		Heinz Nixdorf Recall Study	
					Beta	P-value	Beta	P-value
rs12748152	1	27138393	C	T	0.0683	0.6055	-0.0161	0.8917
rs4660293	1	40028180	A	G	0.0178	0.8295	0.0297	0.6945
rs12145743	1	156700651	G	T	0.0862	0.2733	-0.0071	0.9162
rs4650994	1	178515312	G	A	-0.0611	0.4117	-0.0875	0.1775
rs1689800	1	182168885	A	G	0.0565	0.4638	0.0788	0.2555
rs4846914	1	230295691	A	G	0.1386	0.1027	-0.0215	0.7519
rs12328675	2	165540800	C	T	-0.1873	0.1082	-0.0164	0.8621
rs1047891	2	211540507	C	A	0.2249	0.0120	0.0109	0.8749
rs2972146	2	227100698	G	T	0.0578	0.4525	-0.0717	0.4214
rs2606736	3	11400249	C	T	-0.0078	0.9201	0.0061	0.9275
rs2290547	3	47061183	G	A	0.1276	0.2125	0.0132	0.8845
rs2013208	3	50129399	T	C	-0.2057	0.0056	-0.0178	0.7888
rs13326165	3	52532118	A	G	-0.1225	0.1842	-0.0390	0.6804
rs6805251	3	119560606	T	C	-0.0029	0.9703	-0.0751	0.2910
rs17404153	3	132163200	G	T	0.0022	0.9848	0.0448	0.6648
rs10019888	4	26062990	A	G	-0.0786	0.4589	-0.1522	0.0813
rs3822072	4	89741269	G	A	0.0821	0.2795	0.1555	0.0272
rs2602836	4	100014805	A	G	-0.0406	0.5908	-	-
rs13107325	4	103188709	C	T	-0.2081	0.3427	-0.1803	0.1668
rs6450176	5	53298025	G	A	0.1191	0.1660	-0.0145	0.8494
rs998584	6	43757896	C	A	-0.2931	0.0209	-0.0138	0.8482
rs1936800	6	127436064	C	T	-0.0162	0.8277	0.0276	0.6783
rs605066	6	139829666	T	C	0.0470	0.5513	-0.0559	0.4233
rs702485	7	6449272	G	A	0.0138	0.8533	-0.1658	0.0110
rs4142995	7	17919258	G	T	-0.0071	0.9259	-0.0200	0.7797
rs4917014	7	50305863	G	T	-0.0364	0.7110	-0.0738	0.2877
rs17145738	7	72982874	T	C	-0.1951	0.0799	0.0678	0.4965
rs4731702	7	130433384	T	C	0.0751	0.3112	-0.1570	0.0218
rs17173637	7	150529449	T	C	-0.1417	0.2393	-0.1704	0.1101
rs9987289	8	9183358	G	A	0.1782	0.1749	0.1600	0.1704
rs12678919	8	19844222	G	A	-0.2480	0.0395	0.0522	0.6430
rs2293889	8	116599199	G	T	-0.0569	0.4465	-0.0835	0.2185
rs2954029	8	126490972	T (minor)	A	0.0187	0.8008	0.0301	0.6531
rs581080	9	15305378	C (major)	G	0.0281	0.7634	-0.1023	0.2937
rs1883025	9	107664301	C	T	-0.0578	0.4997	-0.0958	0.2097
rs970548	10	46013277	C	A	0.1517	0.0780	0.0974	0.2219
rs2923084	11	10388782	A	G	-0.1222	0.2106	0.0477	0.5710
rs3136441	11	46743247	C	T	-0.0254	0.8181	0.1640	0.0792
rs11246602	11	51512090	C	T	0.0217	0.8349	-0.0400	0.7474
rs174546	11	61569830	C	T	-0.0793	0.3184	-0.0671	0.3385
rs12801636	11	65391317	A	G	0.0472	0.5917	-0.0096	0.9038
rs499974	11	75455021	C	A	-0.0795	0.4277	-0.0041	0.9614

rs964184	11	116648917	C (minor)	G	0.2244	0.0449	0.1670	0.3009
rs7941030	11	122522375	C	T	0.0734	0.3443	0.0972	0.1459
rs7134375	12	20473758	A	C	-0.0044	0.9529	-0.0409	0.5432
rs11613352	12	57792580	T	C	0.0403	0.6351	-0.0066	0.9292
rs7134594	12	110000193	T	C	0.0919	0.2174	-0.0067	0.9190
rs4759375	12	123796238	T	C	-0.0140	0.9290	-0.0773	0.4732
rs4765127	12	124460167	T	G	0.0002	0.9980	-0.1684	0.0159
rs838880	12	125261593	C	T	-0.0406	0.6060	-0.0486	0.5260
rs4983559	14	105277209	G	A	-0.0448	0.5621	0.0525	0.4291
rs1532085	15	58683366	A	G	0.0574	0.4504	0.0574	0.3944
rs2652834	15	63396867	G	A	0.0367	0.6980	0.0359	0.6895
rs1121980	16	53809247	G	A	-0.1000	0.1842	-0.1292	0.0500
rs3764261	16	56993324	A	C	-0.0244	0.7555	0.0641	0.3558
rs16942887	16	67928042	A	G	0.0533	0.6255	-0.0896	0.3465
rs2925979	16	81534790	C	T	-0.0330	0.7009	0.0234	0.7392
rs11869286	17	37813856	C (major)	G	-0.1011	0.1880	-0.0944	0.1751
rs4148008	17	66875294	C (major)	G	-0.1544	0.0503	0.0261	0.7205
rs4129767	17	76403984	A	G	-0.1004	0.1758	-0.0186	0.7866
rs7241918	18	47160953	T	G	0.2210	0.0252	0.0424	0.6275
rs12967135	18	57849023	G	A	0.1255	0.1363	-0.0049	0.9491
rs7255436	19	8433196	A	C	0.0985	0.1821	-0.0534	0.4226
rs737337	19	11347493	T	C	0.0325	0.8309	-0.0286	0.8051
rs731839	19	33899065	A	G	-0.0255	0.7450	-0.0786	0.2629
rs4420638	19	45422946	A	G	-0.2707	0.0211	0.0241	0.7815
rs17695224	19	52324216	G	A	0.0178	0.8307	0.1342	0.0670
rs386000	19	54792761	C (minor)	G	0.0601	0.6612	-0.0904	0.2839
rs1800961	20	43042364	C	T	-0.2096	0.3560	-0.1490	0.4757
rs6065906	20	44554015	T	C	-0.0995	0.3065	-0.0902	0.6451
rs181362	22	21932068	C	T	0.0922	0.3397	0.0420	0.6128

Supplementary Table 4i: Height

SNP	Chr	Position	Height increasing allele	Other allele	NELSON Cohort Study		Heinz Nixdorf Recall Study	
					Beta	P-value	Beta	P-value
rs425277	1	2069172	T	C	-0.0918	0.2745	0.1096	0.1319
rs2284746	1	17306675	C (major)	G	0.0033	0.9678	-0.0790	0.2423
rs1738475	1	23536891	C (major)	G	-0.0162	0.8339	0.0921	0.1799
rs4601530	1	25044111	C	T	-0.1378	0.1084	-0.0761	0.3106
rs7532866	1	26741544	A	G	0.1437	0.0820	0.0175	0.8079
rs2154319	1	41745770	C	T	0.2397	0.0095	-0.0655	0.5156
rs17391694	1	78623626	T	C	0.1605	0.1865	0.1387	0.2710
rs6699417	1	89123443	T	C	-0.0519	0.4948	0.0002	0.9978
rs10874746	1	93323971	C	T	-0.0699	0.3790	0.0856	0.2227
rs9428104	1	118855587	G	A	-0.0758	0.4093	0.0157	0.8368
rs11205277	1	149892872	G	A	-0.0332	0.6614	-0.0015	0.9815
rs17346452	1	172053287	C	T	-0.0842	0.3011	-0.1569	0.0346
rs1325598	1	176792249	G	A	0.1494	0.0417	-0.1032	0.1300

rs1046934	1	184023529	C	A	-0.0282	0.7144	0.0161	0.8146
rs10863936	1	212237798	G	A	-0.0072	0.9225	0.0290	0.6625
rs6684205	1	218609702	G	A	-0.0492	0.5548	0.0069	0.9255
rs11118346	1	219743719	C	T	0.0151	0.8403	-0.1118	0.0870
rs10799445	1	227911883	A	C	-0.0256	0.7719	-0.0226	0.7773
rs4665736	2	25187599	T	C	-0.0508	0.4999	0.0183	0.7889
rs6714546	2	33361425	G	A	-0.1081	0.1931	-0.1267	0.0896
rs17511102	2	37960613	A (minor)	T	0.0095	0.9424	-0.2623	0.0261
rs2341459	2	44768202	T	C	-0.0355	0.6721	-0.0385	0.6062
rs12474201	2	46921285	A	G	0.1105	0.1525	-0.0732	0.3017
rs3791675	2	56111309	C	T	-0.0274	0.7403	-0.0053	0.9411
rs11684404	2	88924622	C	T	-0.0024	0.9752	0.0846	0.2304
rs7567288	2	134434824	C	T	0.0107	0.9065	-0.0718	0.4068
rs7567851	2	178684720	C (minor)	G	0.1406	0.3107	-0.0206	0.8088
rs1351164	2	218271898	T	C	-0.1268	0.1994	0.1995	0.1646
rs12470505	2	219908369	T	G	-0.0107	0.9351	0.0777	0.4682
rs2629046	2	225047744	T	C	0.0252	0.7609	0.0168	0.7964
rs2580816	2	232797966	C	T	-0.1878	0.0570	0.1435	0.0922
rs12694997	2	242262986	G	A	-0.0743	0.4036	0.0574	0.4597
rs2597513	3	13555836	C	T	-0.0572	0.6236	0.0632	0.5521
rs13088462	3	51071713	C	T	0.1394	0.3713	0.0841	0.5558
rs2336725	3	53118739	C	T	-0.0211	0.7764	0.0045	0.9439
rs9835332	3	56667682	C (major)	G	-0.1011	0.1810	-0.0636	0.3470
rs17806888	3	67416322	T	C	0.1266	0.3131	0.1144	0.2499
rs9863706	3	72437413	C	T	0.0484	0.5852	-0.0310	0.6950
rs6439167	3	129050756	C	T	-0.0746	0.4047	0.0067	0.9310
rs9844666	3	135974216	G	A	-0.0189	0.8276	-0.0216	0.7759
rs724016	3	141105570	G	A	0.0295	0.6942	0.0102	0.8773
rs572169	3	172165727	T	C	0.0709	0.3793	-0.0227	0.7468
rs720390	3	185548683	A	G	0.1696	0.0324	0.0357	0.5892
rs2247341	4	1701317	A	G	-0.0768	0.3337	0.0223	0.7477
rs6449353	4	18033488	T	C	-0.0762	0.4948	0.0803	0.4882
rs17081935	4	57823476	T	C	0.0611	0.5271	0.0340	0.6538
rs7697556	4	73515313	T	C	-0.1209	0.1075	-0.0265	0.6782
rs788867	4	82150006	G	T	0.0933	0.2486	-0.0500	0.4700
rs10010325	4	106106353	A	C	0.1848	0.0123	0.0019	0.9773
rs7689420	4	145568352	C	T	-0.1829	0.0786	0.0504	0.5797
rs955748	4	184215675	G	A	0.0352	0.6818	0.0396	0.6116
rs1173727	5	32830521	T	C	0.0083	0.9159	-0.0820	0.2485
rs11958779	5	55001899	G	A	-0.0581	0.4541	-0.0843	0.3209
rs10037512	5	88354675	T	C	-0.0129	0.8611	-0.0229	0.7273
rs13177718	5	108113344	C	T	-0.1209	0.4072	0.0498	0.6998
rs1582931	5	122657199	G	A	-0.1139	0.1348	-0.0246	0.7360
rs274546	5	131699867	G	A	0.0125	0.8694	-0.0159	0.8131
rs526896	5	134356705	T	G	0.0261	0.7686	0.0168	0.8236
rs4282339	5	168256240	G	A	0.0052	0.9562	0.0740	0.3736
rs12153391	5	171203438	C	A	-0.0252	0.7848	-0.0732	0.3122
rs889014	5	172984114	C	T	0.0561	0.4823	-0.0438	0.5166
rs422421	5	176517326	C	T	0.3300	0.0116	0.3434	0.0223

rs6879260	5	179731014	C	T	-0.1108	0.1506	-0.0290	0.6805
rs3812163	6	7725760	A (minor)	T	-0.0310	0.6831	0.0287	0.6815
rs1047014	6	19841493	C	T	0.0417	0.6407	0.0040	0.9674
rs806794	6	26200677	A	G	-0.1055	0.2039	0.0672	0.3474
rs3129109	6	29084232	C	T	-0.0453	0.5525	-0.0247	0.7077
rs2256183	6	31380529	A	G	-0.1204	0.1010	-0.1474	0.0550
rs2780226	6	34199092	C	T	-0.0728	0.6181	0.4250	0.0077
rs6457821	6	35402805	C	A	0.4242	0.0763	-0.1101	0.6349
rs9472414	6	44946506	A (major)	T	-0.0591	0.5314	-0.0407	0.6126
rs9360921	6	76265642	G	T	0.0444	0.7175	-0.0966	0.3476
rs310405	6	81800362	A	G	-0.0852	0.2570	-0.0197	0.7610
rs7759938	6	105378954	C	T	0.0030	0.9694	-0.0511	0.4741
rs1046943	6	109783941	A	G	0.0634	0.3939	0.0112	0.8673
rs961764	6	117522156	C (major)	G	-0.0680	0.3748	0.0483	0.4769
rs1490384	6	126851160	T	C	0.1168	0.1161	-0.0499	0.4501
rs6569648	6	130349119	C	T	0.0484	0.5856	-0.0110	0.8818
rs7763064	6	142797289	G	A	-0.0389	0.6333	-0.0141	0.8581
rs543650	6	152110943	G	T	0.0632	0.4505	0.0188	0.7785
rs9456307	6	158929442	A (major)	T	0.2278	0.1589	-0.1385	0.3709
rs798489	7	2801803	C	T	-0.0711	0.4231	-0.0005	0.9944
rs4470914	7	19616522	T	C	-0.1873	0.0518	-0.0248	0.7853
rs12534093	7	23502974	A (major)	T	-0.0697	0.4370	0.0703	0.3919
rs1708299	7	28189946	A	G	0.0146	0.8562	-0.0722	0.3289
rs6959212	7	38128326	C	T	0.0476	0.5623	0.0561	0.4277
rs42235	7	92248076	T	C	-0.0437	0.6088	-0.0692	0.3250
rs822552	7	148650634	C (minor)	G	-0.1286	0.1559	-0.0218	0.8165
rs1013209	8	24116304	C	T	0.0959	0.2804	-0.0882	0.2437
rs7460090	8	57194163	T	C	-0.3430	0.0090	0.0298	0.7783
rs6473015	8	78178485	C	A	0.0055	0.9450	0.0308	0.6607
rs6470764	8	130725665	C	T	-0.0170	0.8568	0.1012	0.2316
rs12680655	8	135637337	C (minor)	G	-0.0710	0.3574	-0.0198	0.7716
rs7864648	9	16368732	T	G	0.0588	0.5171	0.0168	0.8088
rs11144688	9	78542286	G	A	-0.0503	0.7266	-0.0105	0.9210
rs7853377	9	86552205	G	A	-0.1390	0.1143	0.0513	0.5109
rs8181166	9	89116628	C (major)	G	-0.1173	0.1174	-0.1233	0.0689
rs2778031	9	90835726	T	C	0.1000	0.2294	0.1173	0.1921
rs9969804	9	95429120	A	C	-0.0694	0.3486	0.1103	0.0924
rs1257763	9	96893945	A	G	0.1835	0.3007	-0.1774	0.3172
rs473902	9	98256235	T	G	-0.2164	0.1879	0.0121	0.9362
rs7027110	9	109599046	A	G	0.1093	0.2150	-0.2257	0.0048
rs1468758	9	113807082	C	T	-0.1103	0.2263	0.0260	0.7287
rs751543	9	119122342	T	C	0.0030	0.9742	-0.0535	0.4566
rs7466269	9	133464084	A	G	-0.0457	0.5537	-0.1223	0.0805
rs7849585	9	139111870	T	G	-0.1318	0.1108	-0.1292	0.0667
rs7909670	10	12918764	C	T	-0.1016	0.1844	-0.0590	0.3680
rs2145998	10	81121696	A (major)	T	0.0528	0.4836	0.0279	0.6729
rs11599750	10	101805442	C	T	-0.0670	0.4064	0.0229	0.7352
rs2237886	11	2810731	T	C	0.0683	0.6050	-0.0240	0.8272
rs7926971	11	12698040	G	A	0.1043	0.1625	-0.1068	0.1202

rs1330	11	17316029	T	C	0.0015	0.9850	0.0007	0.9924
rs1814175	11	49559172	T	C	0.0354	0.6355	0.0905	0.1775
rs3782089	11	65336819	C	T	0.0820	0.5727	0.0573	0.7866
rs7112925	11	66826160	C	T	0.1002	0.2747	-0.0967	0.1586
rs634552	11	75282052	T	G	-0.1855	0.0884	-0.5943	0.0716
rs494459	11	118574675	T	C	0.0323	0.6716	-0.0825	0.2150
rs654723	11	128586155	A	C	0.0818	0.3326	0.0065	0.9195
rs2856321	12	11855773	G	A	-0.1061	0.1666	-0.1213	0.0723
rs10770705	12	20857467	A	C	0.0396	0.6105	0.0986	0.1757
rs2638953	12	28534415	C (major)	G	0.0233	0.7697	0.1006	0.1559
rs2066807	12	56740682	C (minor)	G	0.1619	0.2466	-0.1109	0.3712
rs1351394	12	66351826	T	C	0.0820	0.2688	0.0673	0.3026
rs10748128	12	69827658	T	G	0.0081	0.9173	-0.0192	0.7820
rs11107116	12	93978504	T	G	0.1504	0.0864	-0.1119	0.1668
rs7971536	12	102373788	A (major)	T	0.0472	0.5504	-0.0520	0.4389
rs11830103	12	123823546	G	A	-0.0603	0.5103	-0.0570	0.4780
rs7332115	13	33147548	G	T	0.0180	0.8144	0.0958	0.1565
rs3118905	13	51105334	G	A	0.1026	0.2297	-0.0128	0.8710
rs7319045	13	92024574	A	G	0.0373	0.6254	0.0228	0.7615
rs1950500	14	24830850	T	C	-0.0677	0.4206	0.0327	0.6454
rs2093210	14	60957279	C	T	-0.0975	0.2012	0.0002	0.9976
rs1570106	14	68813115	C	T	0.1081	0.2530	-0.0498	0.5777
rs862034	14	74990746	G	A	0.0752	0.3403	0.1494	0.0300
rs7155279	14	92485881	G	T	-0.0432	0.5638	-0.0096	0.9068
rs16964211	15	51530495	G	A	0.0200	0.9028	0.0034	0.9872
rs7178424	15	62380259	C	T	-0.0370	0.6171	-0.0964	0.1466
rs10152591	15	70048157	A	C	0.0440	0.7224	0.0145	0.8973
rs12902421	15	72161403	C	T	0.2069	0.3762	0.6068	0.0425
rs5742915	15	74336633	C	T	0.1447	0.0719	-0.0500	0.4501
rs11259936	15	84580582	C	A	0.0002	0.9981	-0.0371	0.5666
rs16942341	15	89388905	C	T	0.1123	0.6539	-0.7415	0.3549
rs2871865	15	99194896	C (major)	G	-0.0575	0.6915	0.1060	0.3823
rs4965598	15	100759614	C	T	-0.0337	0.6781	-0.0688	0.4773
rs11648796	16	792190	G	A	-0.0843	0.4599	0.1454	0.3289
rs26868	16	2249376	A (minor)	T	0.0732	0.3572	-0.0853	0.1980
rs8052560	16	88777242	A	C	-0.1880	0.0917	0.0336	0.6707
rs4640244	17	21284223	A	G	-0.1415	0.0620	0.0061	0.9263
rs3110496	17	27917771	G	A	0.0271	0.7441	0.0290	0.6912
rs3764419	17	29164023	C	A	-0.0706	0.3654	0.0001	0.9988
rs17780086	17	30343282	A	G	-0.0370	0.7303	-0.0108	0.9082
rs1043515	17	36922196	G	A	0.0181	0.8094	-0.0600	0.3559
rs4986172	17	43216281	C	T	-0.0662	0.4079	-0.0833	0.2301
rs4605213	17	49244747	C (minor)	G	-0.0754	0.4092	-0.0295	0.7016
rs227724	17	54778817	A (minor)	T	0.1295	0.1036	-0.0550	0.4349
rs2079795	17	59496649	T	C	-0.0743	0.3370	0.0113	0.8708
rs2665838	17	61966465	C (minor)	G	-0.0363	0.6552	-0.2132	0.0067
rs11867479	17	68090207	T	C	-0.0257	0.7490	-0.0294	0.6658
rs4800452	18	20727611	T	C	0.0976	0.3027	0.0505	0.5360
rs9967417	18	46959500	C (minor)	G	-0.0343	0.6559	0.0427	0.5509

rs17782313	18	57851097	C	T	-0.1267	0.1321	0.0127	0.8664
rs12982744	19	2177193	C (minor)	G	0.1444	0.0631	0.0069	0.9202
rs7507204	19	3428834	C (minor)	G	-0.0153	0.8600	0.0606	0.5749
rs891088	19	7184762	G	A	0.0579	0.4861	-0.1044	0.1639
rs4072910	19	8644031	C (major)	G	0.0254	0.8013	-0.0610	0.3623
rs2279008	19	17283303	T	C	0.0314	0.7165	0.0263	0.7266
rs17318596	19	41937095	A	G	-0.0657	0.3886	0.0919	0.1664
rs1741344	20	4101800	C	T	0.0432	0.5791	0.0071	0.9153
rs2145272	20	6626218	G	A	-0.0003	0.9964	0.0349	0.6136
rs7274811	20	32333181	G	T	-0.0501	0.5885	-0.1202	0.1217
rs143384	20	34025756	G	A	0.0391	0.6174	-0.1331	0.0437
rs237743	20	47903019	A	G	0.0377	0.6666	0.0400	0.5874
rs2834442	21	35690786	A (major)	T	-0.0490	0.5181	-0.0771	0.2742