

Carotid intima-media thickness in UK Biobank: Identification of novel genome-wide loci, sex-specific effects and genetic correlations with obesity and glucometabolic traits.

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Abstract

Objectives: Atherosclerosis is the underlying cause of most cardiovascular disease, but mechanisms underlying atherosclerosis are incompletely understood. Ultra-sound measurement of the carotid artery intima-media thickness (cIMT) can be used to measure vascular remodelling, which is indicative of atherosclerosis. Genome-wide association studies have identified a number of genetic loci associated with cIMT, but heterogeneity of measurements collected by many small cohorts have been a major limitation in these efforts. Here we conducted genome-wide association analyses in UK Biobank (N=22,179), the largest single study with consistent cIMT measurements.

Approach and results: We used BOLT-LMM to run linear regression of cIMT in UK Biobank, adjusted for age, sex, genotyping platform and population structure. In white British participants, we identified 4 novel loci associated with cIMT and replicated most previously reported loci. In the first sex-specific analyses of cIMT, we identified a female-specific locus on Chromosome 5, associated with cIMT in women only and highlight *VCAN* as a good candidate gene at this locus. Genetic correlations with body-mass index and glucometabolic traits were also observed.

Conclusion: These findings replicate previously reported associations, highlight novel biology and provide new directions for investigating the sex differences observed in cardiovascular disease presentation and progression.

Introduction

Atherosclerosis is the underlying cause of the majority of cardiovascular events (CVE) and is characterised by vascular remodelling, incorporation of lipids into the vessel wall and subsequent inflammation^{1,2}. Atherosclerosis is a systemic process

which precedes clinical presentation of cardiovascular events such as stroke by decades. Indeed, evidence of vascular remodelling indicative of atherosclerosis has been observed as early as in adolescent age groups ³.

Atherosclerosis can be non-invasively assessed by ultrasound measurement of the carotid artery vessel wall, specifically the intima-media thickness (cIMT). In some cases, cIMT assessment is used for monitoring after CVE such as stroke, but could also be useful for screening individuals at high risk of CVE. Currently use is limited as it requires specialist equipment and training, and high-quality data analysis is laborious. Measurement of cIMT has been performed for research purposes, predominantly in cohorts recruited for the study of cardiovascular disease. Whilst undeniably useful, the use of clinical cohorts does not cover the whole spectrum of atherosclerotic burden in the population.

Genetic analyses of clinical cohorts have begun to identify single nucleotide polymorphisms (SNPs) associated with increased cIMT ⁴⁻⁷, which paves the way for better understanding of processes leading to cardiovascular events. A limitation for these studies (N~68,000) has been heterogeneity in recruitment and ultrasound methodology, which could lead to failure to detect some true genetic effects. In this respect, UK Biobank provides an unprecedented opportunity to analyse IMT measurements in a very large cohort (N~22,000) with consistent recruitment and standardised cIMT measurements, analysis and quality control.

We therefore set out primarily to identify genetic variants associated with cIMT in a large general population cohort. A secondary aim was to investigate the possibility of sex-specific genetic effects on IMT. Here we report the replication of previously reported associations, highlight novel biology and provide new directions for

investigating the sex differences observed in cardiovascular disease presentation and progression.

Methods

Study population

The UK Biobank study (UKB) has been described in detail previously^{8,9}. In brief, UKB recruited ~500,000 participants from the UK between 2006 and 2010.

Participants attended one of the 22 recruitment centres across the UK where they provided a blood sample for DNA extraction and biomarker analysis, and completed questionnaires covering a wide range of medical, social and lifestyle information. All participants provided informed consent and the study was conducted in accordance with the Helsinki Declaration. Generic approval was granted by the NHS National Research Ethics Service (approval letter dated 13 May 2016, Ref 16/NW/0274) and the study conducted under UK Biobank projects #7155 (PI Jill Pell) and #6553 (PI Daniel Smith).

Phenotyping

Starting in 2014, participants were invited to participate in a follow-up and imaging assessment, including ultrasound imaging of the carotid arteries. cIMT phenotyping began in 2015, in a pilot phase, where 2,272 individuals were imaged at 18 centres (with 8 centres accounting for 98% of the sample) with extensive manual quality control being conducted. Subsequently, manual quality control was deemed unnecessary and all centres began recruiting and recording automated measurements (with 10 centres accounting for 93% of the sample). Details of the protocol are available at <https://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=101>. In

[brief](#), ultrasound measurements were recorded at 2 angles on each of the left and right carotid artery with automated software recording images and measurements of mean and maximum intima-media (UKB data fields 22670-22681). Recruitment for imaging is ongoing, but to date (2019), 25,769 individuals have ultrasound measurements of the cIMT. The average of 4 measures (2 for each of the left and right carotid arteries) was calculated for the mean (IMTmean) and for maximum IMT (IMTmax), the largest of the 4 measures was used. Where more than one value was missing due to poor quality of the image, the participant was excluded from analyses. Values were expressed in mm and natural log transformed for normality prior to analysis.

In the follow-up assessment, anthropometric measures, lifestyle variables, medication and disease history was again recorded including: age, weight, waist circumference, hip circumference, waist:hip ratio (WHR), body-mass index (BMI), systolic and diastolic blood pressure (SBP and DBP respectively), hypertension (defined as $SBP \geq 140\text{mmHg}$ and/or $DBP \geq 90\text{mmHg}$ and/or anti-hypertensive medication), probable type 2 diabetes (T2D, coding as per Eastwood et al ¹⁰), ischemic heart disease (ISH, defined as heart attack or angina). Corrected SBP and DBP, reflecting probable untreated levels, were calculated as per Ehret et al ¹¹. These contemporary values were used in the analysis of cIMT.

Genotyping

DNA was extracted from blood samples provided by participants, using standard protocols. Details of the UKB genotyping and imputation procedures have been described previously ^{12, 13}. Briefly, the full genetic data release (March 2018) was used for this study. Genotyping, pre-imputation quality control, imputation and post-

imputation quality control were conducted centrally by UKB, according to standard procedures.

Statistical analyses

Descriptive statistics and Spearman's rank correlations were conducted using Stata. Only individuals of white British ancestry were included in the GWAS to maximise homogeneity. BOLT-LMM was used to conduct genetic association analyses, to calculate heritability estimates and estimates of λ_{GC} . IMTmean and IMTmax values were natural logarithm-transformed for normality and genetic association analyses were conducted, adjusted for age, sex and genotyping array (primary analysis) or age and genotyping array (secondary analyses). SNPs were excluded if minor allele frequency <0.01 , Hardy-Weinberg equilibrium $p < 1 \times 10^{-6}$ or imputation score <0.3 . Genome-wide significance was set at $p < 5 \times 10^{-8}$, with suggestive evidence of association being set at $p < 1 \times 10^{-5}$. After quality control there were 22,179 participants with IMT and genetic data for analysis.

Genetic association results were visualised using FUMA¹⁴ and LocusZoom¹⁵.

Linkage disequilibrium and genetic correlations

Linkage disequilibrium (LD) between analysed SNPs in each GWAS-significant locus was calculated and visualised in a random subset of 10000 white British individuals (or 5000 individuals where the locus is computationally too large with 10000 individuals) included in the cIMT subset, using Haploview (default settings)¹⁶.

Genetic correlations between IMTmean and IMTmax and relevant cardiometabolic traits were calculated, using previously published summary statistics and LD score regression¹⁷. IMT summary statistics were provided by the CHARGE consortium (<http://www.chargeconsortium.com/>). Data on glycaemic traits were contributed by

MAGIC investigators and were downloaded from www.magicinvestigators.org. Type 2 diabetes (T2D) data were contributed by the DIAGRAM consortium (<http://diagram-consortium.org/downloads.html>). Summary statistics for lipid traits were downloaded from the Global Lipids Genetics Consortium website (<http://lipidgenetics.org/>). Data on anthropometric traits were downloaded from the GIANT consortium website (http://portals.broadinstitute.org/collaboration/giant/index.php/Main_Page). Coronary artery disease data were downloaded from the CARDIoGRAMplusC4D consortium (<http://www.cardiogramplusc4d.org/>). Blood pressure data were provided by the International Consortium for Blood Pressure genetics (https://www.ncbi.nlm.nih.gov/projects/gap/cgibin/study.cgi?study_id=phs000585.v1.p1).

Data-mining

The GWAS catalogue (<https://www.ebi.ac.uk/gwas/>, accessed 20190717) was used to identify previously reported associations with significant loci. All SNPs with at least suggestive evidence of association ($p < 1 \times 10^{-5}$) within significantly associated loci were assessed for deleterious effect using the Ensemble variant effect predictor (VEP) ¹⁸. GWAS-significant SNPs and those predicted by VEP to have at least moderate impact were assessed for effects on genotype expression patterns of nearby genes using the Genotype Tissue Expression project (GTEx) ¹⁹. Functions of highlighted genes were explored using the NCBI Gene platform (<https://www.ncbi.nlm.nih.gov/gene/>, accessed 20190717) and literature identified using NCBI PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>, accessed 20190717).

Results

Demographic characteristics of the UKB cIMT subset are presented in Table 1. The UKB cIMT subset consist of 48.3% men. Women were slightly younger (average 54.6 years versus 56.0 years) and were healthier (average BMI 26.1 kg/m² and SBP 132 mmHg, % with hypertension 37.0%) and smoked less (% smokers 30.4) compared to men (average 56.0 years, BMI 27.1 kg/m², 140 mmHg, % hypertension 54.0, smokers 36.0). Values for both IMT_{mean} and IMT_{max} were lower in women than in men. Measurements of IMT_{mean} and IMT_{max} were highly correlated (Spearman's Rho=0.865, p<0.0001 (full cIMT subset), Rho=0.868 p<0.0001 (men) and Rho=0.852 p<0.0001 (women)). IMT_{mean} and IMT_{max} were significantly and positively associated with classical risk factors including increasing age, obesity, and blood pressure (Table 2).

Primary analysis: SNPs associated with IMT_{mean} and IMT_{max}

Manhattan and QQ plots of the GWAS results are presented in Figure 1. There was some evidence of inflation for both IMT_{mean} and IMT_{max} (λ_{GC} =1.15 and 1.10, respectively), however this is likely due to polygenicity rather than population structure (LDSR intercept (standard error) = 1.03 (0.03) for both phenotypes).

GWAS-significant evidence of association with IMT_{mean} was observed for 176 SNPs in 8 loci (Figure 1A) and 76 SNPs in 3 loci demonstrated GWAS-significant evidence of association with IMT_{max} (Figure1B). The lead SNP for each locus is provided in Table 3. As BOLT-LMM includes neighbouring SNPs in the model (essentially conditioning on other SNPs in the region), each locus reported here is independent and contains only a single signal. Effect sizes of all lead SNPs were comparable with those previously reported (Beta 0.0091-0.441) ⁶.

Of the 8 loci significantly associated with IMTmean identified here, four are novel (Chr7, lead SNP rs342988; Chr8 (124.6Mb), rs34557926; Chr11, rs2019090; Chr19 (41.3Mb), rs111689747; Figure 2A-D) and 4 have previously been reported (Figure 2E-H).

In the previously reported loci, on Chr5 there is only one SNP, rs758080886, which reaches GWAS-significant evidence for association with IMTmean which is located 3417b from the previously reported lead SNP rs224904⁶. rs758080886 is not available in the reference panel used by LocusZoom¹⁵ and is therefore not plotted, hence this region is represented by the previously reported SNP, rs224904. The LD between rs75808088 and rs224904 is moderate ($r^2=0.44$) therefore rs224904 is not a good proxy, however this is the same for all SNPs in the locus (SFigure A). On Chr8, rs2912062 is 738b from the previously reported lead, rs2912063, and in high LD ($r^2=0.98$), demonstrating that these SNPs represent the same signal. On Chr16, the lead SNP, rs561732, is 22.3kb from the previously reported lead, rs844396, with moderate LD ($r^2=0.66$). The Chr19 lead here, rs1065853 is 1.15kb from the reported rs7412, but with almost complete LD ($r^2=0.99$). The novel Chr19 locus is ~4Mb from this signal, and whilst long-range LD is possible, the calculated LD between rs111689747 and rs1065853 or rs7412 does not support this possibility ($r^2=0$).

There were three GW-significant loci for IMTmax. Of these, two overlap with those for IMTmean: the lead SNPs for IMTmean and IMTmax on Chr7 (rs342988 and rs11762074 respectively) are 26.9kb apart with LD of $r^2=0.77$. For Chr19, the locus not only overlaps, but the lead SNP is the same for both traits. The Chr11 for IMTmax (20.5Mb) is distinct from that for IMTmean (103.6Mb) (Figure 2I).

When considering SNPs significantly associated with IMTmean, the direction of effects on IMTmax are consistent with those for IMTmean, and the magnitude is similar (Table 1). The same is true for the Chr11 IMTmax SNP, rs11025608, which shows a similar effect size and direction in IMTmean (beta -0.008, se 0.002, $p=1.6 \times 10^{-6}$). Therefore further analyses focused on IMTmean, for more robust comparisons with previous studies.

UKB IMT GWAS and the CHARGE consortium IMT GWAS meta-analysis

The largest GWAS meta-analysis of IMTmean previously published⁶ included 68,962 individuals from 30 studies with a variety of recruitment strategies, inclusion criteria and measurements of cIMT. The range of average ages was 37.7-78.8 years and average IMTmean 0.50-1.13mm. The single largest study within the meta-analysis included 8,663 individuals (approximately evenly split between men and women). That meta-analysis reported 11 robustly associated loci⁶, of which nine lead SNPs were available in UKB (Table 2). Seven of these demonstrated significant ($p<0.05$) associations with IMTmean, with consistent effect directions when compared to the previous report⁶ (Table 2). One SNP demonstrated a non-significant association and one demonstrated a significant association but inconsistent direction (Table 2).

Conversely, of the lead SNPs reported here for UKB, 10 were available in the CHARGE meta-analysis (Table 3). Of these, nine were significant ($p<0.05$) with consistent effect directions to those reported in UKB. One lead SNP was not significant. Effects sizes were generally 2-3-fold larger in UKB than in the CHARGE meta-analysis.

Secondary analyses: sex-specific genetic effects on IMT

Sex-specific analyses suggest that the genetic variants associated with IMTmean in men and women is distinctly different (Figure 3): In men-only analyses (Figure 3A), three GWAS-significant loci were identified on Chr7 (rs35099106), Chr8 (6.4Mb, rs2912063) and Chr19 (rs1065853), all of which overlap with those identified in the primary (sex-combined) analysis (Table 3 and Figure 4). The Chr7 lead SNP is in strong LD with that for IMTmax (rs11762074, $r^2=0.97$) but only moderate LD with the sex-combined IMTmean lead SNP (rs342988, $r^2=0.64$). The lead SNPs on Chr8 and 19 are consistent with either the primary analysis or with previously reported lead SNPs.

In analysis of women (Figure 3B), only a locus on Chr5 was GWAS-significant (Table 3 and Figure 4). The lead SNP for this locus, rs309563, is ~1.2Mb from, and demonstrated no LD with, the lead sex-combined SNP for IMTmean ($r^2=0$) or the previously reported lead SNP for this locus (rs224904, $r^2=0$, SFigure A), suggesting that it is a separate locus.

Effect directions for SNPs with suggestive evidence of association were consistent between men and women, however in men, the SNPs associated with cIMT in women demonstrated 3-6 fold smaller (non-significant) effect sizes (STable 4). In contrast, for the SNPs associated with cIMT in men, effect sizes were halved in women, with at least nominal significance being observed for most SNPs, and suggested significance noted for the Chr19/APOE locus.

Genetic correlations with cardiovascular phenotypes and risk factors

UKB IMTmean and IMTmax GWAS demonstrated significant genetic correlations with the CHARGE GWAS IMTmean meta-analyses ($r_g=0.77-0.82$, Table 4)^{4, 6}. As

the individuals included in the IMTmean and IMTmax analyses overlap completely was not possible to compare these analyses. Significant positive genetic correlations were observed between IMTmean and total obesity (BMI), type 2 diabetes (T2D), fasting glucose and insulin (Table 4). For IMTmax, positive correlations with total and central obesity (BMI and WHRadjBMI), T2D, fasting glucose and rheumatoid arthritis were observed. It was surprising to note that a significant positive association with high density lipoprotein (HDL) and a significant negative association with fasting insulin was observed. The significance of these findings is unclear.

In men, similar to the sex-combined results, IMTmean was positively genetically correlated with the CHARGE IMTmean meta-analyses, total obesity, fasting glucose and fasting insulin. In women, only the genetic correlations with the CHARGE meta-analyses survive FDR correction (STable 5).

Datamining

The GWAS catalogue was explored (using lead SNPs and locus positions, as per Table 3) to identify previous associations with the cIMT-associated loci (STable 6). Chr7 and Chr8 (6.4Mb) have previously been associated with diastolic blood pressure (DBP), whilst Chr11, Chr13 and both Chr19 loci have previously been associated with coronary artery disease and/or pulse pressure or cIMT.

Atherosclerosis is considered a condition requiring both fatty deposits and inflammation in the vascular wall. Therefore it was interesting to note the reported associations of Chr8 (6.4Mb) and Chr11 with immune response or immune components as well as the Chr19 (45Mb) locus with lipid (and other biomarker) levels and Chr7 with fatty liver disease. The Chr19 locus includes the apolipoprotein gene cluster (including *APOE*), which has been the focus of much research into lipid

levels, cardiovascular disease and Alzheimer's disease. In contrast, previous associations at the Chr5, Chr8 (124Mb) and Chr16 loci have no obvious relevance to cIMT. For the vast majority of previous associations with relevant traits, the effects on cIMT were in the expected direction: the alleles associated with increased DBP, systolic blood pressure (SBP), pulse pressure, total cholesterol, low-density lipoprotein (LDL), apolipoprotein E (APOE) and lipoprotein A (LP(a)) levels and lipoprotein phospholipase A2 activity were associated with increased cIMT, as were the alleles associated with decreased HDL levels. The only unexpected finding was that the rs7412 allele associated with decreasing triglyceride (TG) levels was associated with increased cIMT, however the authors suggest that the skewed distribution of lipids in those homozygous for this allele might cause inflation of test statistics²⁰ and that this should be considered when interpreting results.

Of SNPs within significantly associated loci showing at least suggestive evidence of association with IMTmean, 13 SNPs were predicted¹⁸ to have functional or coding effects (STable 7). Lead SNPs and those predicted by VEP to have functional or coding effects were assessed for evidence of genotype-specific effects on gene expression levels (eQTLs) in the GTEx dataset (STable 8). Only rs2019090 on Chr11 demonstrated eQTLs in a tissue of obvious relevance, namely the aorta, where the cIMT-increasing allele was associated with increased *RP11-563P16.1* levels. Lack of knowledge about this genes role precludes interpretation of this finding.

Candidate genes

Of the genes highlighted by eQTL analysis (though in a tissue of unclear relevance), *APOE* (Chr19) has been widely studied in cardiovascular (and other, notably

Alzheimer's) diseases ²¹, whilst the function of *MCPH1-AS1(CTD-2541M15.3)* (Chr8) is thought to be as a regulator of *MCPH1*, a DNA damage response gene with no obvious role in vessel wall biology. Similarly, *CBFA2T3* (Chr16) has documented roles in cancer biology as a transcriptional repressor but again there is no obvious role in vascular biology.

Only *VCAN* (Chr5, women-only locus) is potentially an interesting candidate gene. Its encoded product, versican, is a chondroitin sulphate proteoglycan present in the adventitia and intima of normal blood vessels (reviewed in ²²). Versican protein levels have been shown to increase dramatically during progression of vascular diseases including atherosclerosis ²². Versican exists as a variety of protein isoforms of different sizes, due to alternative splicing, a variety of post-translational modifications and proteolytic cleavage ²². The diverse effects of versican in vascular pathology are likely determined by the balance of different sized isoforms and partners in complexes ²²: larger molecules are better able to bind and thus retain LDL in the vessel wall; loss of the largest versican isoform has been observed in aortic aneurysms; various cytokines promote different sized versican entities or versican degradation; smaller versican isoforms could act directly as mitogens for arterial smooth muscle cells; and the smallest isoform of versican influences elastic fibre formation and therefore vessel function. Therefore, it is interesting to note that the lead SNP for the women-only locus is an eQTL for a versican antisense molecule, *VSCAN1-AS1*, in testes, suggesting yet another mechanism regulating versican expression, although the role of versican in the testes is unknown. Full understanding of versican biology is required before the impact of this SNP is predictable.

Discussion

Here we present results from a GWAS of the largest single study of IMT to date, and the first sex-specific analysis of IMT. We identified 10 loci (4 of which were novel) associated with cIMT and one locus specific for IMTmean women. We also found genetic correlations with obesity, glucometabolic and lipid traits, which suggest differences between sexes.

Many studies have reported the utility of cIMT measurements as predictors of CVD (reviewed by Katakami et al ²³), although whether predictive power is independent of traditional risk factors is still unclear. A large part of the discrepancies in the literature is likely due to the different protocols used (which part of the carotid artery is measured, whether plaque is included or not, whether mean (IMTmean) or maximum (IMTmax) values are used) in the analyses. Indeed it has been reported that IMTmean and IMTmax differ in their predictive value ²³. Therefore the partial overlap in loci associated with IMTmean and IMTmax is of interest. For the most part, SNPs influencing one phenotype also influence the other, but the relative importance of each locus (and/or mechanism) differs. This hints at differences in biology between the 2 measures, which is perhaps not surprising: overall increases in vascular wall thickness could indicate general vascular dysfunction, which is a component of high blood pressure for example. Local increases in vascular wall thickness are likely indicative of plaque formation, which precede vessel occlusion and ischemic events.

Sex-specific differences in cardiovascular disease are well established, therefore the distinctly different IMTmean GWAS results for men compared to women were intriguing. The existence of a women-only locus, whereas the men-only analysis largely resembled the sex-combined analysis, is unexpected. It suggests that the

sex-combined results could be “driven” by the men. This is unlikely given the fairly balanced sex distribution of the sample (48% men vs 52% women), however the larger variability in measures in men compared to women could cause this effect. It has been observed that sex-differences in IMT measures can be attributed to sex-differences in risk factors such as BMI and blood pressure ²⁴. Despite UKB being approximately 20 years older than the subjects in that study, similar sex differences in risk factors are observed here. It is also worth noting that menopause status is associated both with cIMT measures and cardiovascular risk factors ^{25, 26}.

Menopause status was not considered in the study, as direction of effect is unclear. However this factor would be worth considering for future studies of sex differences.

Another noteworthy finding is the stronger effect of APOE rs7412 in men compared to women (Beta=0.027 vs 0.016 respectively). To our knowledge this is the first demonstration of a sex effect of APOE variation in a cardiovascular disease phenotype, which is of value when considering the relatively nascent concept of an ageing, sex and APOE triad ²⁷. Sex-specific differences in APOE-e genotypes associations with Alzheimer’s disease (AD) have been noted (summarised by Fisher et al ²⁸), with female carriers of APOE-e3/e4 demonstrating increased risk of AD and faster decline than their male counterparts. Indeed this finding (a variant that increases risk of atherosclerosis for men and AD for women) supports the hypothesis that women have higher rates for AD than men, at least partly because men with CVD die earlier than women, therefore in the at-risk age-range for AD, men have lower CVD risk than women ²⁸.

In line with known epidemiology and previous genetic findings ²⁹, the genetic correlations between IMTmean or IMTmax and obesity and glucometabolic traits are unsurprising. The lack of genetic correlations with lipid traits is unexpected, but may

reflect the relative health, adherence to statin therapy or healthy diet of the general population sample of UKB.

In comparison with the CHARGE consortium IMT meta-analysis, this study was smaller (22,000 vs 68,000) but used a phenotype that was recorded in a consistent manner in all individuals, reducing heterogeneity in measurements. This is likely the reason for identifying loci not reported by CHARGE as well as the larger effect sizes reported here, and is in line with previous observations (for example the C4D³⁰ and CARDIoGRAM findings³¹).

It should be noted that there is some evidence of inflation of the GWAS statistics, for which there are a number of possible explanations. Polygenicity is an obvious explanation and highly plausible, as it is observed most complex traits. Whilst the pilot phase cIMT data (N~2500) underwent manual QC procedures, the full IMT dataset (N~22,000) did not. Comparisons between the QCed and non-QCed data in the pilot study show very high correlation (IMTmean $\rho=1.0$, IMTmax $\rho=0.98$), however the possibility of noise in measurements cannot be excluded. Despite this limitation, the consistent effect sizes and directions of most previous IMT loci suggests that this study is valid.

In conclusion, we have conducted a GWAS of cIMT (mean and maximum measures) in the largest single study sample to date, in which we identified four novel loci and validated 7 of 11 previously reported loci. We also report the first sex-specific analysis of IMT, in which we identified a novel women-only locus. Genetic correlations with obesity and glucometabolic traits were observed, and VACN was highlighted as a plausible candidate gene in the women-only locus. Overall, our findings represent an important stimulus for the further elucidation of mechanisms of

vascular pathology, particularly differences between men and women and could contribute to stratified medicine approaches.

Data availability

GWAS summary statistics are available upon request, to the corresponding author. Raw data and coding can be requested via UK Biobank directly.

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Disclosures

The authors have no conflicts of interest to declare.

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Figure Legends

Figure 1: QQ and Manhattan plots of results of the GWAS of A) IMTmean and B) IMTmax.

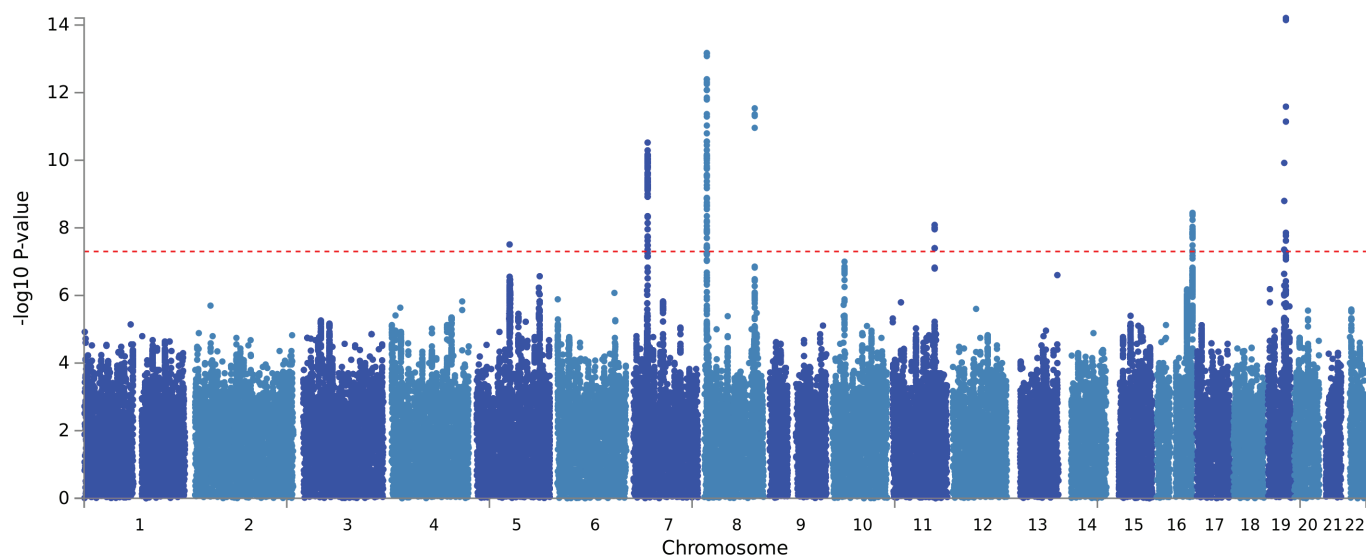
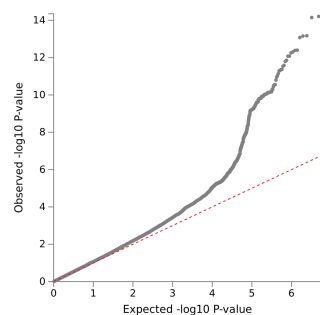
Figure 2: Regional plots for novel IMTmean-associated loci on A) Chr7 (rs342988), B) Chr8 (rs34557926), C) Chr11 (rs2019090), D) Chr19 (rs111689747) and known IMTmean-associated loci on E) Chr5 (rs224904, instead of lead SNP rs758080886), F), Chr8 (rs2912062), G) Chr16 (rs561732), H) Chr19 (rs1065853) as well as the novel locus for IMTmax on Chr11 (rs11025608). The lead SNP is indicated by a purple diamond. LD (r^2) between other SNPs and the lead SNP is indicated by colour. Grey indicates LD is not known.

Figure 3: QQ and Manhattan plots of results of the GWAS of IMTmean in A) men only and B) women only.

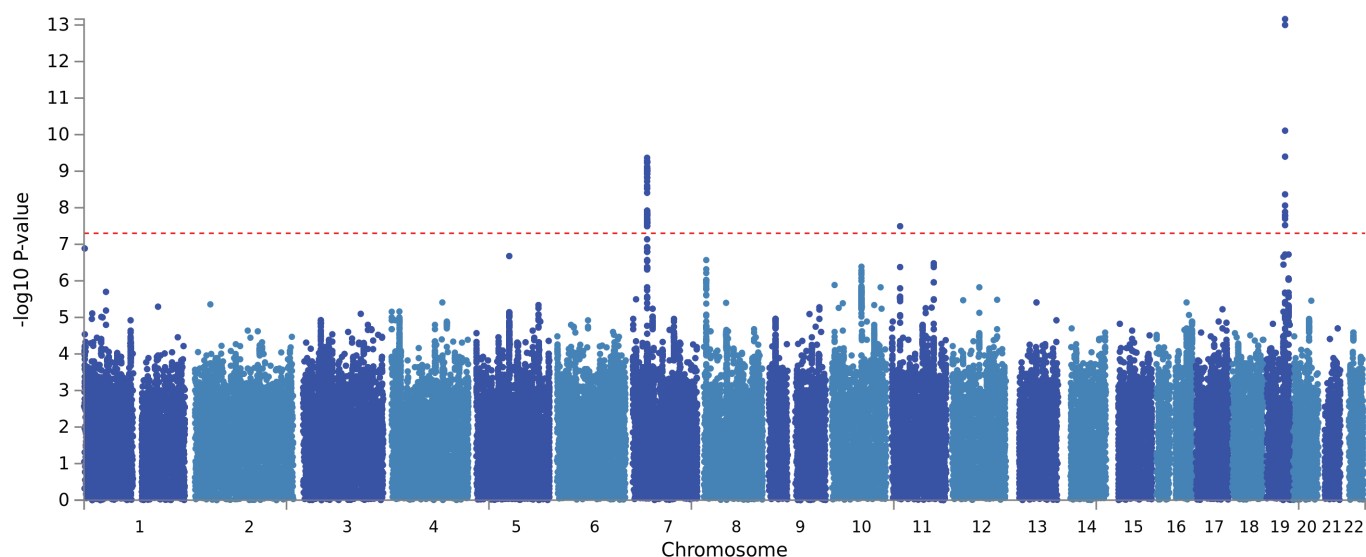
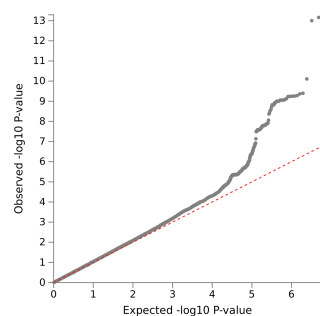
Figure 4: Regional plots for sex-specific IMTmean-associated loci. Men-only loci on A) Chr7 (rs35099106), B) Chr8 (rs2912063), C) Chr19 (rs1065853) and the women-only locus on D) Chr5 (rs309563). The lead SNP is indicated by a purple diamond.

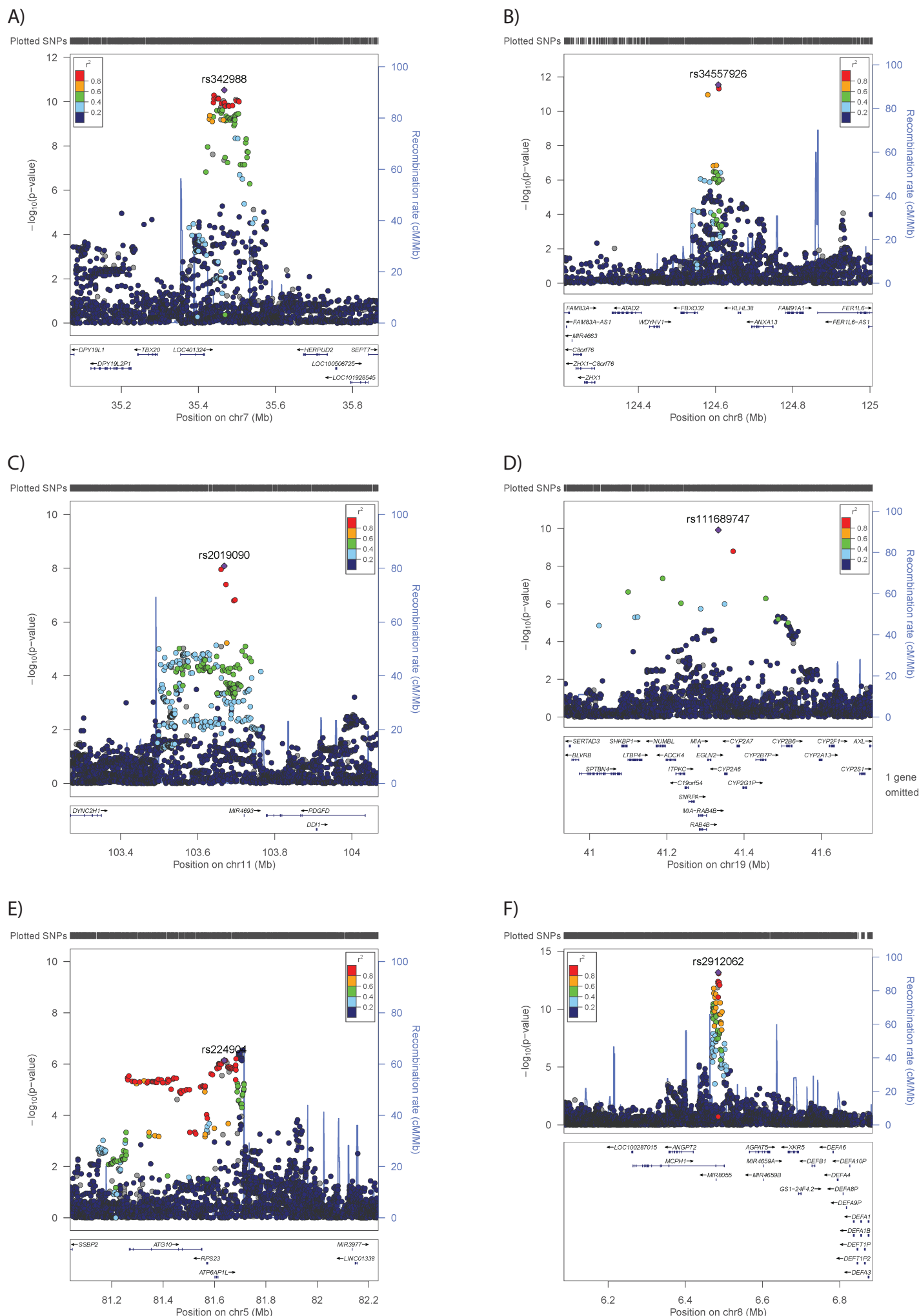
LD (r^2) between other SNPs and the lead SNP is indicated by colour. Grey indicates LD is not known.

A)

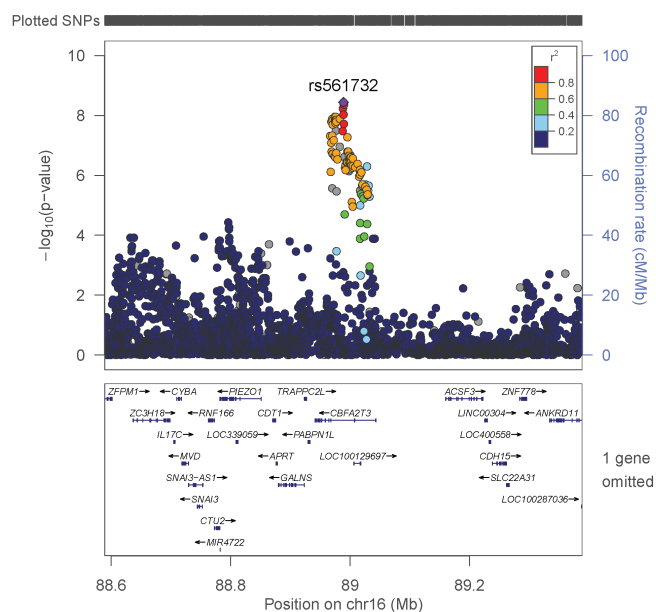


B)

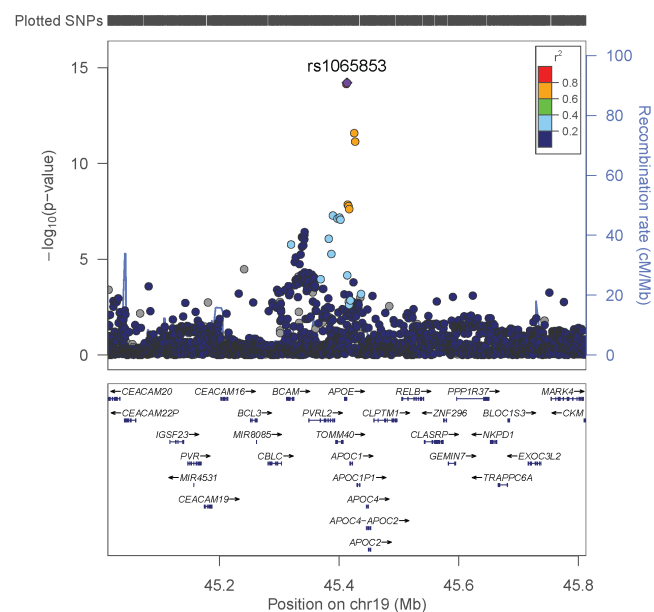




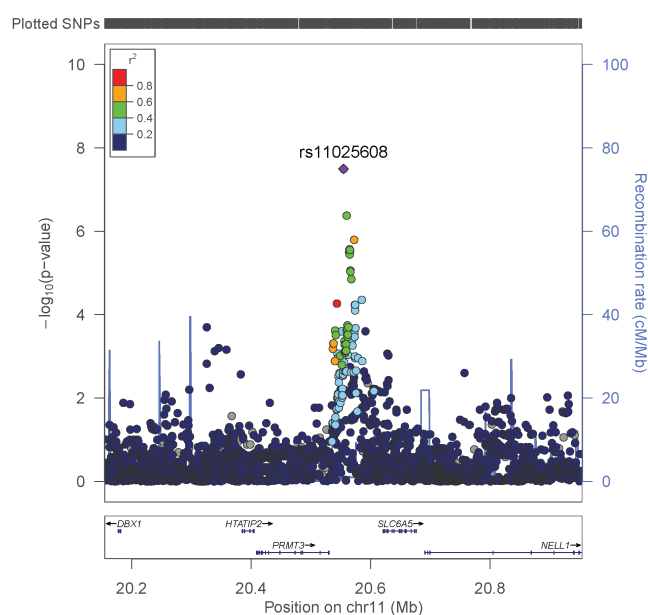
G)



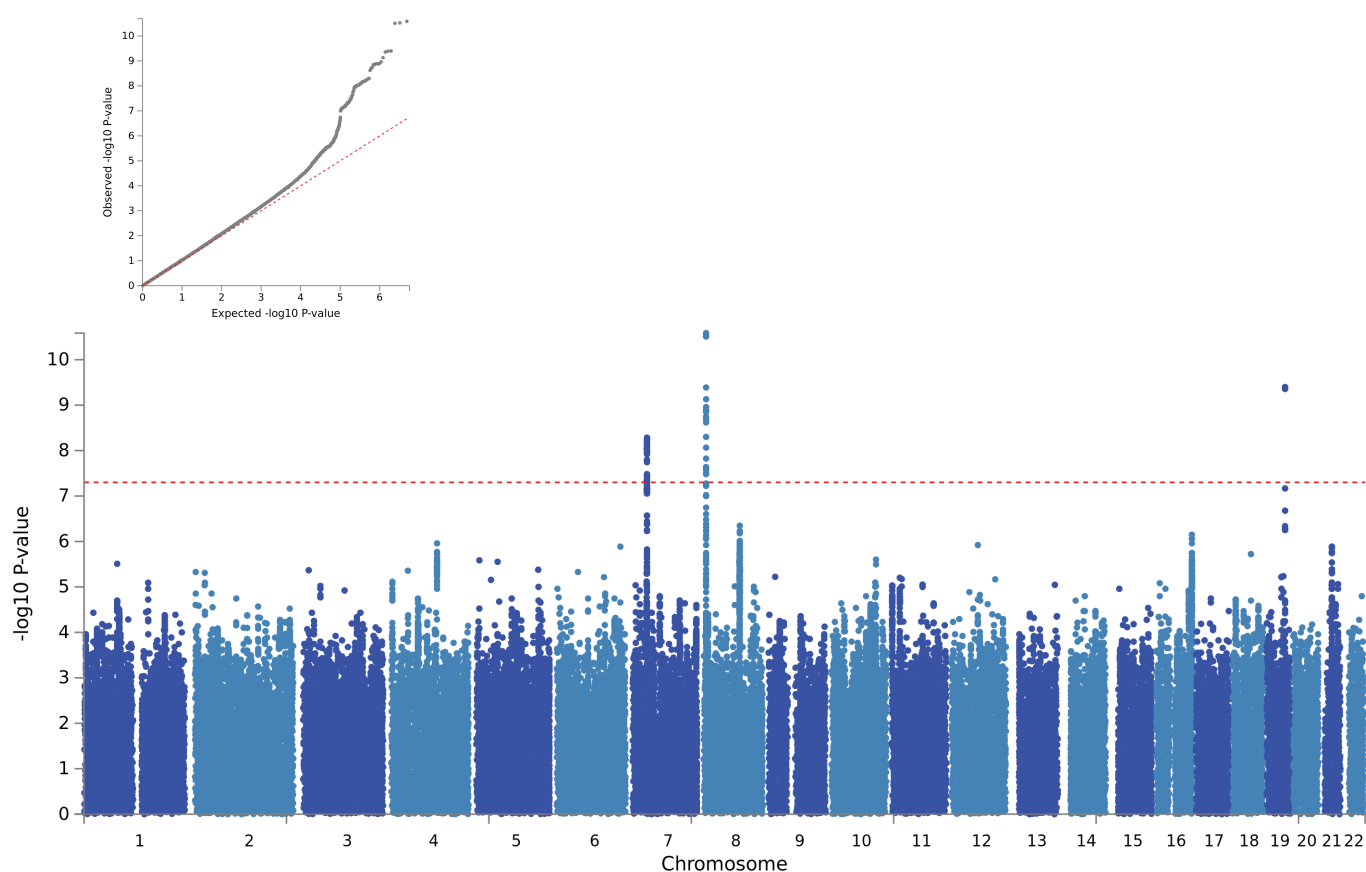
H)



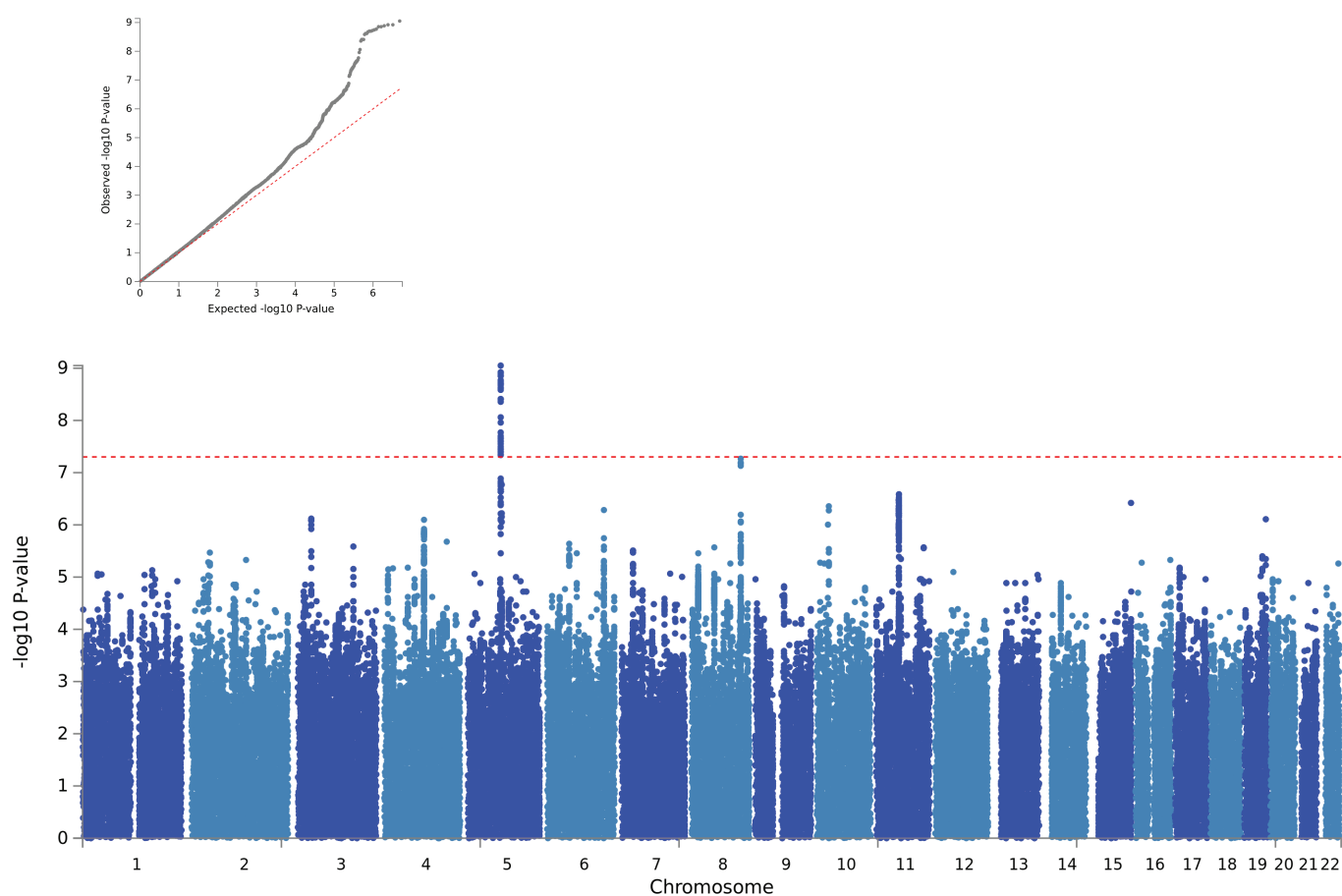
I)



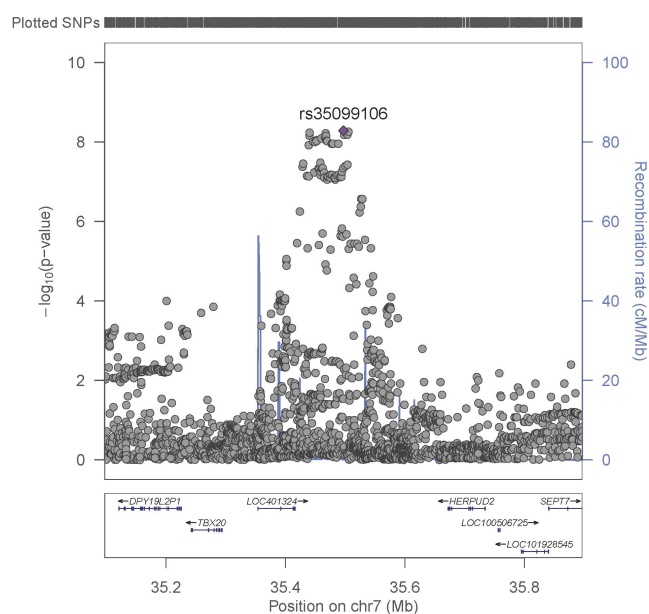
A)



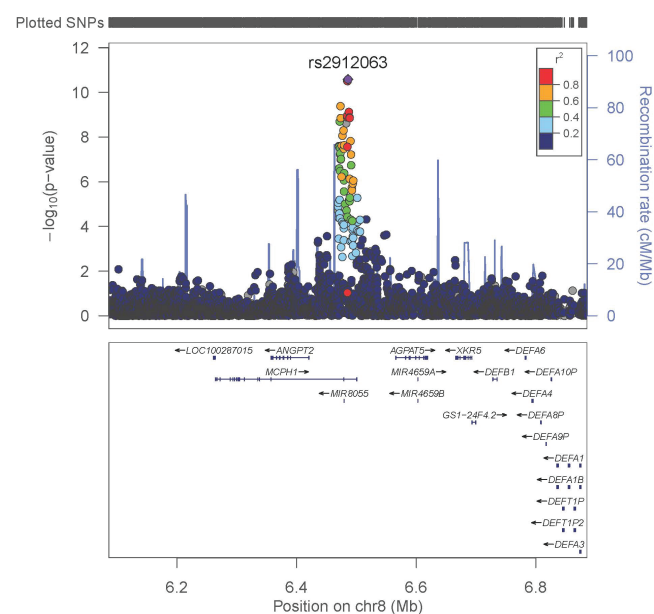
B)



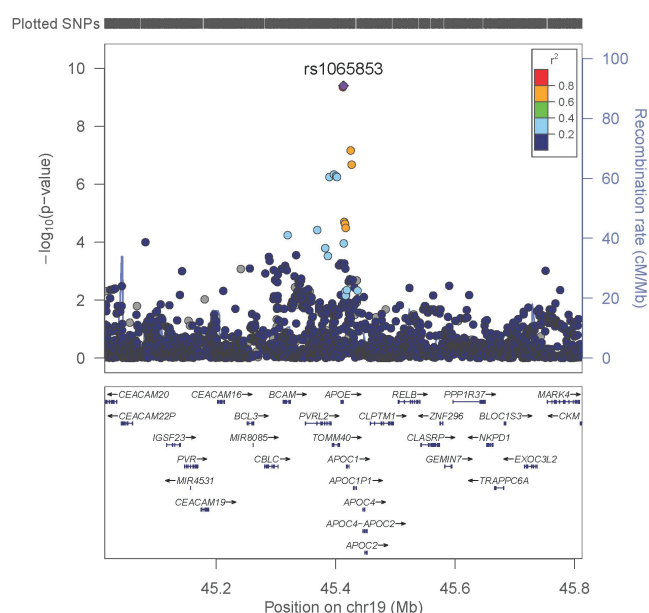
A)



B)



C)



D)

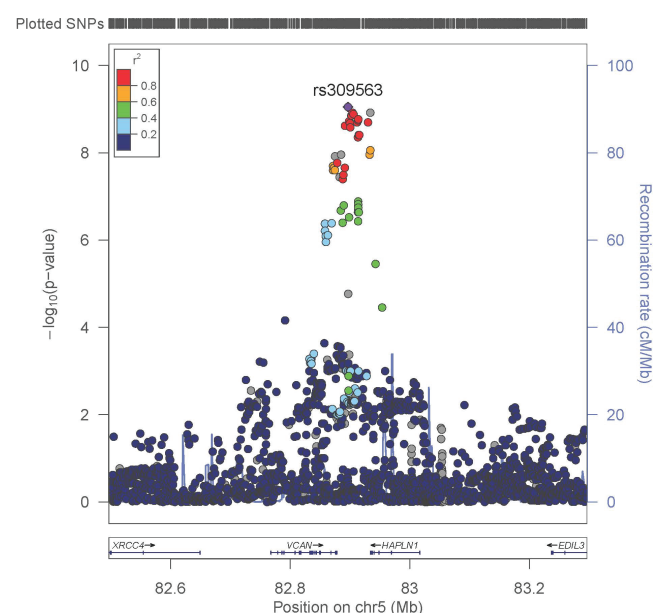


Table 1: Demographics of the UKB cohort with cIMT measures

	Men	Women	all
N (%)	10708 (48.3)	11471 (51.7)	22179
Age (years)	63.9 (7.6)	62.4 (7.3)	63.1 (7.5)
Weight (Kg)	83.8 (13.2)	69.2 (13.9)	76.2 (15.0)
Waist (cm)	94.0 (10.4)	82.6 (11.5)	88.1 (12.4)
Hip (cm)	101.2 (7.2)	101.4 (9.8)	101.3 (8.6)
WHR	0.93 (0.06)	0.81 (0.07)	0.87 (0.09)
BMI (kg/m ²)	27.0 (3.8)	26.1 (4.7)	26.5 (4.3)
SBP (mmHg)	141 (17)	134 (18)	137 (18)
DBP (mmHg)	80 (10)	77 (10)	79 (10)
Corrected SBP (mmHg)*	145 (19)	137 (20)	141 (10)
Corrected DBP (mmHg)*	83 (11)	79 (11)	81 (11)
IMTmean (mm)	0.706 (0.135)	0.658 (0.109)	0.682 (0.125)
IMTmax(mm)	0.952 (0.216)	0.875 (1.86)	0.912 (0.204)
N hypertension	7320 (69.0)	6121 (53.8)	13441 (61.2)
N on BP medication	3026 (28.4)	1973 (17.3)	4999 (22.7)
N on lipid lowering medication	3255 (34.5)	1681 (17.7)	3255 (34.5)
N probable t2d	614 (5.7)	325 (2.8)	939 (4.2)
N ISH	275 (2.6)	97 (0.9)	372 (1.7)
n current smoking	444 (4.2)	356 (3.1)	800 (3.6)

Where: * adjusted for blood pressure medication as per Ehret et al, T2D, type 2 diabetes;
ISH, ischemic heart disease

Table 2: Correlations between cIMT and classical cvd risk factors

	men				women				all			
	IMTmean		IMTmax		IMTmean		IMTmax		IMTmean		IMTmax	
	rho	p	rho	p	rho	p	rho	p	rho	p	rho	p
Age (years)	0.385	<0.0001	0.320	<0.0001	0.465	<0.0001	0.397	<0.0001	0.433	<0.0001	0.369	<0.0001
Weight (Kg)	0.062	<0.0001	0.117	<0.0001	0.057	<0.0001	0.121	<0.0001	0.147	<0.0001	0.204	<0.0001
Waist (cm)	0.109	<0.0001	0.169	<0.0001	0.105	<0.0001	0.176	<0.0001	0.179	<0.0001	0.243	<0.0001
Hip (cm)	0.073	<0.0001	0.122	<0.0001	0.075	<0.0001	0.134	<0.0001	0.078	<0.0001	0.130	<0.0001
WHR	0.100	<0.0001	0.150	<0.0001	0.087	<0.0001	0.140	<0.0001	0.190	<0.0001	0.236	<0.0001
BMI (kg/m2)	0.089	<0.0001	0.152	<0.0001	0.073	<0.0001	0.148	<0.0001	0.105	<0.0001	0.174	<0.0001
SBP (mmHg)	-0.030	0.0054	0.001	0.9306	0.025	0.0145	0.051	<0.0001	0.083	<0.0001	0.117	<0.0001
DBP (mmHg)	0.237	<0.0001	0.216	<0.0001	0.324	<0.0001	0.297	<0.0001	0.320	<0.0001	0.308	<0.0001
Corrected SBP (mmHg)*	0.021	0.0534	0.055	<0.0001	0.071	<0.0001	0.099	<0.0001	0.030	<0.0001	0.061	<0.0001
Corrected DBP (mmHg)*	0.250	<0.0001	0.239	<0.0001	0.333	<0.0001	0.313	<0.0001	0.306	<0.0001	0.286	<0.0001

Table 3: lead SNPs in loci associated with cIMT

Analysis	SNP	CHR	locus*	Genes under the locus	A1	A0	A1 freq	beta	se	chi- 2	P	GWAS SNPs in locus
IMTmean sex combined	rs758080886	5		<i>ATG10, RPS23, ATP6AP1L</i>	CA	C	0.15	0.013	0.002	30.6	3.10E-08	1
	rs342988 ^{a, d}	7	35423859- 35528567	<i>LOC401324</i>	C	T	0.28	0.011	0.002	44.2	3.00E-11	78
	rs2912062 ^b	8	6470650- 6494850	<i>MCPH1, MIR8055</i>	C	G	0.71	0.012	0.002	56.2	6.70E-14	56
	rs34557926 ^d	8	124579985- 124608614	<i>FBXO23, KLHL38, ANAXA13</i>	C	T	0.64	- 0.011	0.002	48.8	2.90E-12	4
	rs2019090 ^d	11	103660567- 103673294	<i>MIR4693</i>	A	T	0.29	0.009	0.002	33.2	8.20E-09	5
	rs561732	16	88966667- 88989862	<i>CBFA2T3, LOC100129697, TRAPPC2L</i>	T	C	0.65	0.009	0.002	34.8	3.60E-09	22
	rs111689747 ^d	19	41188985- 41371458	<i>CYP2A6, CYP2A7, CYP2G1PCYP2B7P, CYP2B6, SNRPA, MIA, EGLN2, RAB4B, MIA-RAB4B, RAB4B-EGLN2, C19ORF54, ITPKC, ADCK4, NUMBL, LTBP4, SHKBP1, SPTBN4</i>	G	A	0.99	- 0.044	0.007	41.5	1.20E-10	3
	rs1065853 ^c	19	45412079- 45426792	<i>BCAM, PVRL2, TOMM40, APOE, APOC1, APOC1P1, APOC4- APOA2, APOC2, CLPTM1, APOC4, RELB</i>	G	T	0.92	0.021	0.003	60.8	6.20E-15	7
IMTmax sex combined	rs11762074 ^a	7	35428513- 35505204	<i>LOC401324</i>	T	C	0.77	- 0.014	0.002	39	4.30E-10	63
	rs11025608 ^d	11		<i>PRMT3, SLC6A5</i>	G	T	0.44	- 0.010	0.002	30.6	3.20E-08	1

	rs1065853 ^c	19	45389596-45426792	BCAM, PVRL2, TOMM40, APOE, APOC1, APOC1P1, APOC4-APOA2, APOC2, CLPTM1, APOC4, RELB	G	T	0.92	0.026	0.003	56.1	6.90E-14	11
IMTmean Men	rs35099106 ^a	7	35428513-35505204	LOC401324	C	CT	0.24	0.016	0.003	34.1	5.20E-09	38
	rs2912063 ^b	8	6470650-6490544	MCPH1, MIR8055	A	G	0.71	0.017	0.003	44.5	2.60E-11	24
	rs1065853 ^c	19	45412079-45413233	BCAM, PVRL2, TOMM40, APOE, APOC1, APOC1P1, APOC4-APOA2, APOC2, CLPTM1, APOC4, RELB	G	T	0.92	0.027	0.004	39.1	4.00E-10	2
IMTmean Women	rs309563 ^d	5	82870033-82933913	VCAN, HAPLN1	A	T	0.66	-0.01	0.002	37.6	8.90E-10	37

Where: *, region bordered by gwas-significant SNPs; a, LD between rs342988, rs11762074 and rs35099106 suggests that these SNPs represent 1 signal; b, LD between rs2912062 and rs2912063 indicate that these SNPs are proxies; c, consistent lead SNP convincingly demonstrates that the same locus is being identified; d, novel locus.

Table4: Genetic correlations between IMTmean, IMTmax and cardiometabolic traits and risk factors

p2	IMTmean					IMTmax				
	rg	se	z	p	FDR-p	rg	se	z	p	FDR-p
CHARGE IMTmean 2018	0.82	0.07	11.1601	6.39E-29	1.53E-27	0.79	0.09	8.56	1.16E-17	2.79E-16
CHARGE IMTmean 2011	0.77	0.08	9.7403	2.03E-22	2.44E-21	0.74	0.10	7.6706	1.71E-14	2.05E-13
BMI	0.13	0.03	3.8486	1.19E-04	9.50E-04	0.22	0.04	4.9424	7.72E-07	6.17E-06
Fasting Glucose	0.26	0.07	3.73	1.91E-04	1.15E-03	0.50	0.14	3.6953	2.20E-04	1.32E-03
Fasting Insulin	0.30	0.10	3.0553	2.25E-03	1.08E-02	-0.17	0.05	-3.5411	3.99E-04	1.91E-03
Type 2 Diabetes	0.21	0.08	2.8074	4.99E-03	2.00E-02	0.28	0.09	3.2499	1.15E-03	4.62E-03
HDL	-0.09	0.04	-2.3216	2.03E-02	6.94E-02	0.17	0.06	2.823	4.76E-03	1.63E-02
WHR adjBMI	0.10	0.05	2.0435	4.10E-02	1.23E-01	0.24	0.09	2.7267	6.40E-03	1.92E-02
Rheumatoid arthritis	0.11	0.06	1.7488	8.03E-02	2.14E-01	0.31	0.12	2.5252	1.16E-02	3.08E-02
Smoking onset	-0.15	0.15	-0.977	3.29E-01	5.63E-01	-0.09	0.08	-1.0276	3.04E-01	5.21E-01
Fasting Proinsulin	0.13	0.14	0.9269	3.54E-01	5.66E-01	-0.08	0.08	-0.9862	3.24E-01	5.18E-01
DBP	0.02	0.02	1.1779	2.39E-01	5.73E-01	0.10	0.05	1.9659	4.93E-02	1.18E-01
Cholesterol	-0.06	0.06	-0.9904	3.22E-01	5.94E-01	-0.07	0.06	-1.1716	2.41E-01	4.46E-01
Triglycerides	0.03	0.04	0.8345	4.04E-01	6.06E-01	-0.15	0.17	-0.8927	3.72E-01	5.58E-01
SBP	0.02	0.02	0.7862	4.32E-01	6.10E-01	0.06	0.08	0.8107	4.18E-01	5.89E-01
Fasting Insulin adjBMI	0.10	0.10	1.001	3.17E-01	6.34E-01	0.10	0.08	1.3348	1.82E-01	3.64E-01
Ever Smoker	0.06	0.06	1.0029	3.16E-01	6.89E-01	0.18	0.13	1.3399	1.80E-01	3.93E-01
Ulcerative Collitis	-0.05	0.08	-0.6214	5.34E-01	7.12E-01	0.02	0.02	0.7077	4.79E-01	6.39E-01
Cigarettes per day	0.05	0.11	0.465	6.42E-01	8.11E-01	0.10	0.17	0.5961	5.51E-01	6.96E-01
LDL	-0.01	0.05	-0.2795	7.80E-01	8.14E-01	0.01	0.02	0.4633	6.43E-01	6.71E-01
Irritable Bowel Disorder	-0.02	0.05	-0.3614	7.18E-01	8.20E-01	0.08	0.15	0.5662	5.71E-01	6.53E-01
Cardiovascular disease	-0.07	0.21	-0.307	7.59E-01	8.28E-01	-0.03	0.07	-0.5171	6.05E-01	6.60E-01
Crohns Disease	0.02	0.06	0.3635	7.16E-01	8.60E-01	-0.16	0.29	-0.574	5.66E-01	6.79E-01
2hr Glucose	-0.02	0.12	-0.1734	8.62E-01	8.62E-01	-0.01	0.06	-0.1364	8.92E-01	8.92E-01

Supplementary Table 1: Comparison of GWAS significant SNPs for IMTmean on IMTmax

CHR	BP	SNP	A1	A0	A1freq	Beta	IMTmean		Beta	IMTmax	
							se	P		se	P
5	81634499	rs758080886	CA	C	0.15	0.013	0.002	3.10E-08	0.015	0.003	2.10E-07
5	81616381	rs420800	G	A	0.95	-0.017	0.003	4.30E-08	-0.018	0.004	9.20E-06
5	81618075	rs224803	C	T	0.95	-0.017	0.003	4.80E-08	-0.018	0.004	1.00E-05
5	81683739	rs224805	A	G	0.05	0.017	0.003	4.10E-08	0.017	0.004	2.50E-05
5	81699253	rs224960	A	G	0.52	0.008	0.001	4.90E-08	0.008	0.002	8.00E-06
7	35423859	rs2541899	C	T	0.24	0.009	0.002	2.20E-08	0.009	0.002	1.70E-05
7	35428513	rs12155459	A	T	0.77	-0.011	0.002	2.40E-10	-0.013	0.002	2.80E-09
7	35429465	rs11766731	G	T	0.77	-0.011	0.002	1.60E-10	-0.013	0.002	1.90E-09
7	35435835	rs2541905	T	C	0.23	0.011	0.002	4.60E-10	0.013	0.002	2.50E-09
7	35436932	rs70981917	C	CT	0.43	0.008	0.001	9.70E-09	0.009	0.002	2.70E-06
7	35438779	rs2013385	A	G	0.32	0.009	0.002	5.10E-10	0.011	0.002	2.00E-08
7	35438831	rs741408	T	C	0.23	0.011	0.002	3.80E-11	0.013	0.002	7.50E-10
7	35440055	rs2592856	C	T	0.23	0.011	0.002	2.60E-11	0.013	0.002	5.50E-10
7	35440155	rs11762074	T	C	0.77	-0.011	0.002	1.80E-11	-0.014	0.002	4.30E-10
7	35446189	rs2592855	T	C	0.23	0.011	0.002	2.40E-11	0.013	0.002	5.20E-10
7	35448018	rs2250212	A	G	0.32	0.010	0.002	3.10E-10	0.011	0.002	1.20E-08
7	35449334	rs998652	A	G	0.23	0.011	0.002	2.60E-11	0.013	0.002	5.70E-10
7	35451830	rs17765314	G	A	0.77	-0.011	0.002	2.50E-11	-0.013	0.002	5.70E-10
7	35451910	rs2592851	T	C	0.23	0.011	0.002	2.50E-11	0.013	0.002	5.60E-10
7	35452092	rs1362655	G	A	0.23	0.011	0.002	2.60E-11	0.013	0.002	5.90E-10
7	35455088	rs2592850	T	A	0.32	0.010	0.002	2.80E-10	0.011	0.002	1.30E-08
7	35456691	rs2592849	A	T	0.32	0.010	0.002	3.20E-10	0.011	0.002	1.40E-08
7	35457954	7:35457954_AT_A	AT	A	0.32	0.009	0.002	5.50E-10	0.012	0.002	3.90E-09
7	35458137	rs140476889	A	AAAAC	0.32	0.010	0.002	2.90E-10	0.011	0.002	1.20E-08
7	35458551	rs200832044	GT	G	0.32	0.009	0.002	9.00E-10	0.011	0.002	3.20E-08
7	35458934	rs342976	T	C	0.32	0.009	0.002	4.40E-10	0.011	0.002	1.90E-08
7	35459888	rs342977	G	A	0.23	0.011	0.002	4.40E-11	0.013	0.002	1.10E-09
7	35460547	rs342979	C	T	0.32	0.009	0.002	3.90E-10	0.011	0.002	1.60E-08

7	35461538	rs342981	G	A	0.32	0.010	0.002	3.30E-10	0.011	0.002	1.60E-08
7	35461715	rs2551797	T	C	0.32	0.010	0.002	3.30E-10	0.011	0.002	1.60E-08
7	35462145	rs342982	G	T	0.32	0.010	0.002	3.20E-10	0.011	0.002	1.60E-08
7	35464620	rs34502079	A	AT	0.33	0.010	0.002	8.30E-11	0.012	0.002	3.00E-09
7	35464784	rs342983	T	G	0.27	0.010	0.002	1.70E-10	0.012	0.002	3.20E-08
7	35466464	rs342986	G	A	0.23	0.011	0.002	3.90E-11	0.013	0.002	1.00E-09
7	35466658	rs35361607	A	AC	0.37	0.008	0.001	2.80E-08	0.009	0.002	1.80E-06
7	35466755	rs342987	T	G	0.23	0.011	0.002	3.70E-11	0.013	0.002	1.00E-09
7	35467026	rs342988	C	T	0.28	0.011	0.002	8.90E-12	0.013	0.002	8.80E-10
7	35467677	7:35467677_TAA_T	TAA	T	0.24	0.011	0.002	3.80E-11	0.013	0.002	1.00E-09
7	35467896	rs342989	A	G	0.23	0.011	0.002	3.60E-11	0.013	0.002	9.80E-10
7	35468763	rs17697812	T	C	0.77	-0.011	0.002	4.90E-11	-0.013	0.002	1.20E-09
7	35469045	rs342990	G	T	0.38	0.008	0.001	2.80E-08	0.009	0.002	8.50E-07
7	35469691	rs342991	G	T	0.32	0.009	0.002	8.20E-10	0.011	0.002	2.60E-08
7	35469835	rs342992	C	T	0.23	0.011	0.002	4.90E-11	0.013	0.002	1.20E-09
7	35469898	rs342993	G	A	0.32	0.009	0.002	7.20E-10	0.011	0.002	2.50E-08
7	35471979	rs342996	G	C	0.33	0.009	0.002	6.00E-10	0.011	0.002	2.10E-08
7	35474622	rs342997	T	C	0.32	0.009	0.002	7.20E-10	0.011	0.002	2.60E-08
7	35475980	rs342998	T	C	0.32	0.009	0.002	7.20E-10	0.011	0.002	2.60E-08
7	35477175	rs343000	C	T	0.23	0.011	0.002	5.60E-11	0.013	0.002	1.50E-09
7	35478327	rs343001	C	G	0.32	0.009	0.002	7.30E-10	0.011	0.002	2.60E-08
7	35478515	rs343002	T	C	0.23	0.011	0.002	5.60E-11	0.013	0.002	1.50E-09
7	35479439	rs343003	C	T	0.23	0.011	0.002	5.90E-11	0.013	0.002	1.50E-09
7	35481642	rs343004	C	A	0.32	0.009	0.002	9.00E-10	0.011	0.002	3.00E-08
7	35482940	rs343005	G	T	0.32	0.009	0.002	8.70E-10	0.011	0.002	2.60E-08
7	35483018	rs343006	C	A	0.32	0.009	0.002	9.10E-10	0.011	0.002	2.60E-08
7	35483055	rs343007	G	T	0.32	0.009	0.002	8.00E-10	0.011	0.002	2.60E-08
7	35485648	rs343010	C	A	0.32	0.009	0.002	7.50E-10	0.011	0.002	2.60E-08
7	35487040	7:35487040_CT_C	CT	C	0.29	0.011	0.002	3.20E-09	0.013	0.002	1.60E-08
7	35488349	rs343011	T	G	0.23	0.011	0.002	5.50E-11	0.013	0.002	1.50E-09
7	35488769	rs343012	C	A	0.32	0.009	0.002	7.40E-10	0.011	0.002	2.70E-08

7	35491532	rs343016	G	C	0.32	0.009	0.002	8.00E-10	0.011	0.002	2.60E-08
7	35492168	rs343019	G	C	0.41	0.009	0.001	7.10E-10	0.010	0.002	1.60E-07
7	35493178	rs343020	T	C	0.32	0.009	0.002	8.20E-10	0.011	0.002	2.40E-08
7	35493309	rs343021	T	C	0.32	0.009	0.002	8.10E-10	0.011	0.002	2.40E-08
7	35493603	rs343022	C	T	0.32	0.009	0.002	8.70E-10	0.011	0.002	2.20E-08
7	35494013	rs343024	C	G	0.41	0.009	0.001	5.80E-10	0.010	0.002	1.20E-07
7	35494243	rs777980	G	A	0.32	0.009	0.002	6.10E-10	0.011	0.002	1.70E-08
7	35494556	rs702843	G	C	0.41	0.009	0.001	3.90E-10	0.010	0.002	7.30E-08
7	35495599	rs343025	T	A	0.37	0.009	0.001	5.00E-09	0.010	0.002	2.80E-07
7	35496678	rs343026	T	G	0.32	0.009	0.002	5.20E-10	0.011	0.002	1.50E-08
7	35497055	rs35099106	C	CT	0.23	0.011	0.002	3.70E-11	0.013	0.002	8.70E-10
7	35498200	rs343029	A	G	0.23	0.011	0.002	3.50E-11	0.013	0.002	8.90E-10
7	35500493	rs343031	G	A	0.32	0.009	0.002	5.00E-10	0.011	0.002	1.50E-08
7	35501883	rs343034	C	T	0.37	0.009	0.001	5.20E-09	0.010	0.002	2.70E-07
7	35503445	rs343036	G	C	0.23	0.011	0.002	3.50E-11	0.013	0.002	8.70E-10
7	35503600	rs343037	G	T	0.23	0.011	0.002	3.60E-11	0.013	0.002	8.70E-10
7	35503696	rs343038	G	C	0.32	0.009	0.002	4.70E-10	0.011	0.002	1.40E-08
7	35505204	rs343039	C	T	0.23	0.011	0.002	3.90E-11	0.013	0.002	7.90E-10
7	35508859	rs343044	A	G	0.20	0.010	0.002	3.60E-08	0.012	0.002	4.30E-07
7	35509024	rs343045	C	A	0.20	0.010	0.002	3.60E-08	0.012	0.002	4.40E-07
7	35515295	rs343048	G	A	0.20	0.010	0.002	3.30E-08	0.012	0.002	4.20E-07
7	35519519	rs343052	G	T	0.20	0.010	0.002	3.50E-08	0.012	0.002	4.20E-07
7	35522553	rs343053	A	G	0.17	0.011	0.002	4.30E-09	0.012	0.002	4.60E-07
7	35523883	rs343055	G	A	0.17	0.011	0.002	3.50E-09	0.013	0.002	2.90E-07
7	35526022	rs1646989	T	G	0.20	0.010	0.002	1.50E-08	0.012	0.002	1.60E-07
7	35526024	rs1646988	T	A	0.20	0.010	0.002	1.50E-08	0.012	0.002	1.60E-07
7	35526390	rs343056	A	G	0.20	0.010	0.002	7.00E-09	0.012	0.002	1.30E-07
7	35528567	rs11766156	G	C	0.80	-0.010	0.002	7.40E-09	-0.012	0.002	1.20E-07
7	35532991	rs73087411	C	T	0.82	-0.010	0.002	4.60E-08	-0.011	0.002	2.80E-06
8	6470650	rs3020257	C	A	0.76	0.010	0.002	6.60E-10	0.009	0.002	8.10E-05
8	6471126	rs2980664	G	A	0.76	0.011	0.002	2.50E-10	0.009	0.002	2.60E-05

8	6471182	rs3020258	C	T	0.78	0.010	0.002	2.00E-09	0.009	0.002	9.60E-05
8	6471995	rs2959802	G	A	0.42	-0.008	0.001	3.30E-08	-0.007	0.002	9.20E-05
8	6472105	rs2959801	G	A	0.69	0.010	0.002	2.00E-10	0.009	0.002	9.10E-06
8	6472603	rs11137038	G	A	0.64	0.010	0.001	6.30E-11	0.008	0.002	2.00E-05
8	6472721	rs12543564	T	C	0.67	0.009	0.002	1.30E-08	0.009	0.002	1.70E-05
8	6472795	rs3020259	C	A	0.65	0.009	0.001	2.30E-10	0.008	0.002	2.10E-05
8	6473118	rs11998083	C	T	0.64	0.010	0.001	4.50E-11	0.008	0.002	1.30E-05
8	6473356	rs1256	C	G	0.70	0.010	0.002	1.80E-11	0.010	0.002	1.20E-06
8	6473715	rs2959799	A	G	0.63	0.010	0.001	1.10E-10	0.008	0.002	1.80E-05
8	6473746	rs2959798	A	G	0.63	0.009	0.001	1.20E-10	0.008	0.002	1.80E-05
8	6473758	rs2454517	A	G	0.70	0.010	0.002	4.30E-11	0.010	0.002	2.40E-06
8	6474136	rs2936501	A	G	0.63	0.009	0.001	1.60E-10	0.008	0.002	1.70E-05
8	6475113	rs2515557	G	A	0.70	0.009	0.002	3.90E-08	0.008	0.002	6.60E-05
8	6475489	rs2980662	G	C	0.69	0.009	0.002	2.60E-09	0.009	0.002	1.90E-05
8	6476626	rs7005662	C	T	0.72	0.010	0.002	1.50E-10	0.010	0.002	2.50E-06
8	6478481	rs2253560	G	A	0.72	0.010	0.002	7.80E-11	0.009	0.002	4.20E-06
8	6478960	rs11137040	C	G	0.71	0.010	0.002	7.90E-10	0.009	0.002	2.70E-05
8	6479178	rs2912016	C	A	0.65	0.009	0.001	6.70E-10	0.008	0.002	4.70E-05
8	6479282	rs11137041	G	T	0.65	0.009	0.001	2.20E-09	0.008	0.002	7.30E-05
8	6479432	rs2515559	A	G	0.72	0.010	0.002	5.10E-10	0.009	0.002	8.40E-06
8	6479497	rs2011423	G	A	0.67	0.009	0.002	1.40E-09	0.008	0.002	4.10E-05
8	6483059	rs201338894	ATAAAT	A	0.73	0.011	0.002	9.30E-12	0.010	0.002	1.70E-06
8	6483482	rs2912057	C	T	0.60	0.008	0.001	2.60E-08	0.008	0.002	4.10E-05
8	6484505	8:6484505_CA_C	CA	C	0.72	0.011	0.002	3.10E-12	0.010	0.002	9.40E-07
8	6484510	rs2454524	A	C	0.72	0.011	0.002	3.10E-12	0.010	0.002	9.50E-07
8	6484530	rs2246801	C	T	0.72	0.011	0.002	4.50E-12	0.010	0.002	1.10E-06
8	6484635	rs2278147	C	A	0.71	0.011	0.002	4.10E-13	0.010	0.002	6.10E-07
8	6484982	rs2448611	C	T	0.70	0.010	0.002	1.50E-10	0.010	0.002	1.30E-06
8	6485295	rs2912062	C	G	0.70	0.011	0.002	2.70E-13	0.010	0.002	2.70E-07
8	6486033	rs2912063	A	G	0.71	0.011	0.002	4.20E-13	0.010	0.002	4.80E-07
8	6487449	rs3020263	G	A	0.72	0.011	0.002	4.40E-12	0.010	0.002	1.00E-06

8	6487727	rs2936511	C	G	0.63	0.008	0.001	2.20E-08	0.007	0.002	5.30E-04
8	6488317	rs569123053	A	C	0.80	0.011	0.002	2.70E-09	0.010	0.002	6.50E-05
8	6488505	rs2911968	T	C	0.62	0.008	0.001	2.30E-08	0.007	0.002	4.20E-04
8	6488577	rs3020264	G	A	0.72	0.011	0.002	5.80E-12	0.010	0.002	1.40E-06
8	6488710	rs2912064	C	T	0.65	0.009	0.001	2.60E-10	0.008	0.002	1.10E-04
8	6488787	rs1974946	G	A	0.72	0.011	0.002	5.70E-12	0.010	0.002	1.60E-06
8	6488921	rs3020265	G	A	0.63	0.008	0.001	1.60E-08	0.007	0.002	3.30E-04
8	6488990	8:6488990_CA_C	CA	C	0.62	0.008	0.001	2.40E-08	0.007	0.002	3.60E-04
8	6490200	rs2433143	C	T	0.73	0.010	0.002	6.50E-11	0.009	0.002	3.40E-05
8	6490544	8:6490544_TA_T	TA	T	0.70	0.010	0.002	2.00E-11	0.008	0.002	3.90E-05
8	6490975	rs2515561	G	A	0.66	0.009	0.001	6.70E-10	0.007	0.002	2.60E-04
8	6491181	rs1834451	T	C	0.61	0.009	0.001	1.60E-09	0.007	0.002	2.70E-04
8	6492014	8:6492014_CTG_C	CTG	C	0.67	0.008	0.002	1.90E-08	0.006	0.002	9.60E-04
8	6492391	rs2980655	A	T	0.67	0.009	0.002	6.70E-09	0.007	0.002	4.70E-04
8	6492498	rs3020266	G	A	0.67	0.009	0.002	8.20E-09	0.007	0.002	5.20E-04
8	6492792	8:6492792_AC_A	AC	A	0.66	0.009	0.002	1.10E-08	0.007	0.002	5.00E-04
8	6493910	rs2042670	A	C	0.66	0.008	0.001	1.40E-08	0.006	0.002	1.80E-03
8	6494850	rs2515563	G	C	0.69	0.010	0.002	2.50E-10	0.008	0.002	9.50E-05
8	124579985	rs6470156	G	A	0.73	-0.011	0.002	5.30E-13	-0.009	0.002	2.10E-05
8	124594184	rs13270370	G	A	0.55	-0.008	0.001	2.40E-08	-0.006	0.002	2.60E-03
8	124594923	rs11776999	G	A	0.80	-0.010	0.002	3.50E-08	-0.008	0.002	5.40E-04
8	124599786	rs13251106	C	T	0.80	-0.010	0.002	3.60E-08	-0.008	0.002	5.60E-04
8	124601535	rs12547541	G	A	0.80	-0.010	0.002	3.70E-08	-0.008	0.002	5.50E-04
8	124602054	rs35534969	A	C	0.55	-0.008	0.001	2.20E-08	-0.006	0.002	2.40E-03
8	124607159	rs34557926	C	T	0.64	-0.011	0.001	1.40E-13	-0.008	0.002	2.60E-05
8	124608162	rs2891781	C	T	0.64	-0.011	0.001	2.70E-13	-0.008	0.002	3.90E-05
8	124608614	rs7006122	T	G	0.64	-0.011	0.001	3.10E-13	-0.008	0.002	4.50E-05
10	30138169	rs7912501	A	G	0.30	0.009	0.002	2.40E-08	0.007	0.002	1.20E-03
10	30138411	rs6481643	T	C	0.30	0.009	0.002	2.20E-08	0.007	0.002	1.20E-03
10	30144471	rs10763762	T	C	0.30	0.008	0.002	4.80E-08	0.006	0.002	1.60E-03
10	30161168	rs1929257	A	G	0.31	0.009	0.002	6.00E-09	0.007	0.002	5.70E-04

10	30162423	rs2150562	A	G	0.31	0.009	0.002	8.70E-09	0.007	0.002	5.60E-04
10	30163133	rs777393148	TC	T	0.31	0.008	0.002	3.30E-08	0.007	0.002	1.00E-03
10	30165983	rs7096778	T	C	0.41	0.008	0.001	1.60E-08	0.007	0.002	1.40E-04
10	30166035	rs7078837	C	A	0.41	0.008	0.001	1.40E-08	0.007	0.002	1.10E-04
10	30166547	rs10826719	G	A	0.41	0.008	0.001	1.70E-08	0.007	0.002	1.30E-04
10	30167009	rs1571759	T	C	0.41	0.008	0.001	1.30E-08	0.007	0.002	1.20E-04
10	30167754	rs10740811	G	A	0.41	0.008	0.001	1.10E-08	0.007	0.002	8.50E-05
10	30168031	rs2369339	T	C	0.32	0.009	0.002	5.10E-09	0.007	0.002	2.60E-04
10	30168699	rs2202	C	T	0.32	0.009	0.002	8.80E-09	0.007	0.002	2.80E-04
10	30169653	rs10763764	A	T	0.42	0.008	0.001	1.10E-08	0.007	0.002	8.60E-05
10	30170487	rs914279	T	G	0.42	0.008	0.001	6.80E-09	0.007	0.002	7.00E-05
11	103660567	rs974819	T	C	0.29	0.010	0.002	5.60E-10	0.010	0.002	3.70E-07
11	103668962	rs2019090	A	T	0.29	0.010	0.002	3.70E-10	0.010	0.002	3.30E-07
11	103669291	rs796784254	T	TTATTGAA	0.29	0.010	0.002	5.80E-10	0.010	0.002	4.20E-07
11	103673277	rs2128739	A	C	0.28	0.009	0.002	2.20E-09	0.010	0.002	1.10E-06
11	103673294	rs2839812	T	A	0.28	0.009	0.002	2.20E-09	0.010	0.002	1.10E-06
11	103693627	rs11226029	G	A	0.29	0.009	0.002	1.10E-08	0.009	0.002	3.30E-06
11	103696851	rs1384705	C	T	0.29	0.009	0.002	1.30E-08	0.009	0.002	3.20E-06
13	111049623	rs9515203	T	C	0.74	-0.009	0.002	1.10E-08	-0.009	0.002	1.20E-05
16	88966667	rs844396	C	T	0.68	0.008	0.002	4.50E-08	0.009	0.002	1.40E-05
16	88968540	rs564669	T	C	0.62	0.008	0.001	4.30E-08	0.008	0.002	2.70E-05
16	88969969	rs865102	A	G	0.65	0.008	0.001	9.10E-09	0.008	0.002	1.30E-05
16	88970040	rs4995274	T	C	0.65	0.008	0.001	3.20E-08	0.008	0.002	2.90E-05
16	88970776	rs475796	C	G	0.65	0.008	0.001	1.00E-08	0.008	0.002	1.40E-05
16	88970818	rs561795	A	G	0.65	0.008	0.001	1.30E-08	0.008	0.002	1.30E-05
16	88972554	rs488251	G	A	0.68	0.008	0.002	3.30E-08	0.008	0.002	4.00E-05
16	88974516	rs548591	A	G	0.62	0.008	0.001	1.80E-08	0.008	0.002	1.60E-05
16	88974860	rs533406	A	G	0.62	0.008	0.001	2.70E-08	0.008	0.002	2.40E-05
16	88975447	rs8058234	C	G	0.62	0.008	0.001	3.20E-08	0.008	0.002	4.10E-05
16	88975910	rs7405380	G	C	0.62	0.008	0.001	2.20E-08	0.008	0.002	3.80E-05
16	88975954	rs7404039	A	G	0.62	0.008	0.001	2.70E-08	0.008	0.002	5.20E-05

16	88976477	rs1673931	T	C	0.62	0.008	0.001	2.30E-08	0.008	0.002	3.50E-05
16	88976968	rs529900	G	C	0.62	0.008	0.001	2.50E-08	0.008	0.002	3.90E-05
16	88982789	rs12444726	G	T	0.63	0.008	0.001	4.70E-08	0.007	0.002	2.90E-04
16	88987861	rs1673932	T	C	0.63	0.008	0.001	3.50E-08	0.008	0.002	5.30E-05
16	88988989	rs561732	T	C	0.65	0.008	0.001	4.70E-08	0.008	0.002	3.80E-05
19	41188985	rs113228202	G	A	0.99	-0.036	0.007	3.40E-08	-0.034	0.008	6.70E-05
19	41333152	rs111689747	G	A	0.99	-0.040	0.006	7.10E-10	-0.044	0.008	2.20E-07
19	41371458	rs111240159	C	T	0.99	-0.037	0.006	4.00E-09	-0.041	0.008	3.60E-07
19	45337737	rs11667253	C	T	0.30	-0.009	0.002	2.70E-08	-0.009	0.002	1.10E-05
19	45338220	rs4369782	A	G	0.30	-0.009	0.002	2.90E-08	-0.009	0.002	9.60E-06
19	45338493	rs4605275	T	C	0.30	-0.009	0.002	3.40E-08	-0.009	0.002	9.20E-06
19	45341948	rs10407439	A	G	0.30	-0.009	0.002	2.30E-08	-0.009	0.002	9.90E-06
19	45342241	rs4239533	A	G	0.30	-0.009	0.002	1.80E-08	-0.009	0.002	8.50E-06
19	45397229	rs1160983	G	A	0.97	0.023	0.004	4.70E-08	0.030	0.005	1.70E-08
19	45412079	rs7412	C	T	0.92	0.021	0.003	2.10E-15	0.025	0.003	1.00E-13
19	45413233	rs1065853	G	T	0.92	0.021	0.003	1.60E-15	0.026	0.003	6.90E-14
19	45414399	rs72654473	C	A	0.90	0.013	0.002	2.40E-08	0.017	0.003	8.70E-09
19	45415640	rs445925	G	A	0.89	0.013	0.002	3.20E-08	0.017	0.003	1.30E-08
19	45416831	rs390082	T	G	0.89	0.013	0.002	4.10E-08	0.017	0.003	2.00E-08
19	45425178	rs190712692	G	A	0.95	0.023	0.003	1.30E-12	0.028	0.004	7.80E-11
19	45426792	rs141622900	G	A	0.95	0.023	0.003	1.90E-12	0.026	0.004	4.00E-10

Supplementary Table 2: Effects of previously reported IMT loci in the UKB GWAS

SNP	Genomic region	Nearest Coding Gene	Alleles Effect/ Other	Effect allele frequency	Franceschini		Alleles Effect/ Other	UKB			
					Beta (SE)	p-value		A1 freq	beta	P	Consistent
rs201648240	chr1:208953176		D/I	0.83	-0.0062 (0.0011)	3.6×10^{-9}					
rs224904	chr5:81637916	<i>ATP6AP1L</i>	C/G	0.95	-0.0088 (0.0016)	5.1×10^{-8}	G/C	0.05	0.0163	7.20E-07	y
rs6907215	chr6:143608968	<i>AIG1</i>	T/C	0.6	-0.0040 (0.0007)	4.7×10^{-8}	C/T	0.40	0.0060	6.80E-05	Y
rs13225723	chr7:106416467	<i>PIK3CG</i>	A/G	0.22	0.0052 (0.0009)	3.2×10^{-9}	G/A	0.89	-0.0097	0.0004	y
rs2912063	chr8:6486033	<i>MCPH1</i>	A/G	0.71	0.0045 (0.0008)	8.9×10^{-9}	A/G	0.71	0.0122	8.3E-14	y
rs11785239	chr8:8205010	<i>SGK223</i>	T/C	0.65	-0.0043 (0.0008)	8.7×10^{-9}	C/T	0.37	-0.0045	0.0033	n
rs11196033	chr10:114410998	<i>VTI1A</i>	A/C	0.48	0.0042 (0.0008)	3.9×10^{-8}	C/A	0.49	0.0011	0.4500	n
rs844396	chr16:88966667	<i>CBFA2T3</i>	T/C	0.3	-0.0051 (0.0009)	6.0×10^{-9}	C/T	0.68	0.0086	4.80E-08	y
rs148147734 ^a	8:123401537-indel	<i>ZHX2</i>	-/G	0.54	0.0050 (0.0007)	3×10^{-11}	G/A	0.54	0.0015	3.70E-05	y
rs200482500	8:10606223-indel	<i>PINX1</i>	-/GTACC	0.52	0.0056 (0.0008)	7×10^{-12}					
rs7412	19:45412079	<i>APOE</i>	T/C	0.08	-0.0119 (0.0015)	1×10^{-14}	C/T		0.0214	7.1E-15	y

^aPublished cIMT SNP in LD with our most significant SNP: rs11781551 ($r^2 = 0.95$ with rs148147734)

Supplemental Table 3: Effects of GWAS-significant loci reported here in the CHARGE meta-analysis of IMT.

Analysis	SNP	CHR	BP	UKB				Franceschini et al							
				A1	A1 freq	beta	p bolt Imm inf	A1	Freq	Beta	Meta P	Het ISq	Het Df	Het PVal	Consistent
IMTmean	rs758080886	5	81 634 499	CA	0.15	0.013	3.10E-08								
sex combined	rs342988 ^{a, d}	7	35 467 026	C	0.28	0.011	3.00E-11	T	0.75	-0.003	1.53E-04	7.4	27	0.3533	y
	rs2912062 ^b	8	6 485 295	C	0.71	0.012	6.70E-14	C	0.70	0.004	5.53E-08	2.6	28	0.4260	y
	rs34557926 ^d	8	124 607 159	C	0.64	-0.011	2.90E-12	T	0.38	0.004	3.45E-06	0	27	0.7801	y
	rs2019090 ^d	11	103 668 962	A	0.29	0.009	8.20E-09	A	0.28	0.002	0.0046	25.3	29	0.1048	y
	rs561732	16	88 988 989	T	0.65	0.009	3.60E-09	T	0.67	0.004	1.95E-06	56.9	18	0.0012	y
	rs111689747 ^d	19	41 333 152	G	0.99	-0.044	1.20E-10								
	rs1065853 ^c	19	45 413 233	G	0.92	0.021	6.20E-15								
IMTmax sex combined	rs11762074 ^a	7	35 440 155	T	0.77	-0.014	4.30E-10	T	0.79	-0.004	5.94E-07	27.6	29	0.0829	y
	rs11025608 ^d	11	20 554 790	G	0.44	-0.010	3.20E-08	T	0.57	-0.001	0.1911	32.1	26	0.0566	N
	rs1065853 ^c	19	45 413 233	G	0.92	0.026	6.90E-14								
IMTmean Men	rs35099106 ^a	7	35 497 055	C	0.24	0.016	5.20E-09	C	0.21	0.005	3.65E-07	37.5	25	0.0290	y
	rs2912063 ^b	8	6 486 033	A	0.71	0.017	2.60E-11	A	0.71	0.005	8.96E-09	9	27	0.3292	y
	rs1065853 ^c	19	45 413 233	G	0.92	0.027	4.00E-10								
IMTmean Women	rs309563 ^d	5	82 896 644	A	0.66	-0.012	8.90E-10	A	0.66	-0.003	1.10E-05	13.5	28	0.2591	y

Where: *, region bordered by gwas-significant SNPs; a, LD between rs342988, rs11762074 and rs35099106 suggests that these SNPs represent 1 signal; b, LD between rs2912063 and rs2912063 indicate that these SNPs are proxies; c, consistent lead SNP convincingly demonstrates that the same locus is being identified; d, novel locus.

Supplementary Table 4: Comparison of GWAS significant SNPs for IMTmean in men and women

CHR	BP	SNP	ALLELE1	ALLELE0	A1F	women			P	men		
						BETA	SE			BETA	SE	P
5	82870033	5:82870033	TC	T	0.65	-0.011	0.002	3.50E-08	0.66	-0.002	0.002	4.80E-01
5	82871546	rs309581	T	C	0.65	-0.011	0.002	2.00E-08	0.66	-0.002	0.002	4.90E-01
5	82871657	rs309580	A	T	0.65	-0.011	0.002	2.50E-08	0.66	-0.002	0.002	4.40E-01
5	82873262	rs309579	G	T	0.65	-0.011	0.002	2.20E-08	0.66	-0.002	0.002	4.00E-01
5	82874549	rs309578	G	A	0.65	-0.011	0.002	2.50E-08	0.66	-0.002	0.002	4.40E-01
5	82874942	rs309577	T	A	0.65	-0.011	0.002	1.20E-08	0.65	-0.002	0.002	3.30E-01
5	82878519	rs178024	G	A	0.65	-0.011	0.002	1.70E-08	0.66	-0.003	0.002	2.40E-01
5	82882637	rs10646744	G	GAAAA	0.64	-0.011	0.002	3.60E-08	0.64	-0.002	0.002	3.20E-01
5	82884891	rs310520	T	A	0.65	-0.011	0.002	1.10E-08	0.66	-0.003	0.002	2.50E-01
5	82885467	5:82885467	ACTCT	A	0.65	-0.011	0.002	4.50E-08	0.65	-0.002	0.002	3.20E-01
5	82886448	5:82886448	AAAC	A	0.65	-0.011	0.002	4.60E-08	0.65	-0.002	0.002	3.20E-01
5	82887835	rs4260646	A	G	0.65	-0.011	0.002	4.00E-08	0.65	-0.002	0.002	3.90E-01
5	82887839	rs3864259	C	T	0.65	-0.011	0.002	4.00E-08	0.65	-0.002	0.002	3.80E-01
5	82888812	rs310498	T	C	0.64	-0.011	0.002	3.20E-08	0.65	-0.003	0.002	2.80E-01
5	82890586	rs753731735	ATCAG	A	0.66	-0.011	0.002	2.80E-08	0.66	-0.003	0.002	1.70E-01
5	82891343	rs310502	A	T	0.65	-0.011	0.002	2.20E-08	0.65	-0.003	0.002	2.30E-01
5	82891552	rs310503	G	T	0.66	-0.012	0.002	2.40E-09	0.66	-0.003	0.002	1.80E-01
5	82896644	rs309563	A	T	0.66	-0.012	0.002	8.90E-10	0.66	-0.003	0.003	2.30E-01
5	82898246	rs309570	T	G	0.66	-0.012	0.002	1.90E-09	0.67	-0.003	0.002	2.00E-01
5	82899830	rs309574	C	T	0.66	-0.012	0.002	2.10E-09	0.67	-0.003	0.002	2.00E-01
5	82900450	rs309575	C	A	0.66	-0.012	0.002	2.60E-09	0.67	-0.003	0.002	1.90E-01
5	82902032	rs1673051	G	A	0.66	-0.012	0.002	1.40E-09	0.67	-0.003	0.002	2.90E-01
5	82902267	rs12153581	A	T	0.66	-0.012	0.002	1.40E-09	0.67	-0.003	0.002	2.90E-01
5	82904002	rs617228	C	G	0.66	-0.012	0.002	1.20E-09	0.67	-0.003	0.002	2.90E-01
5	82905733	rs471580	C	T	0.66	-0.012	0.002	1.30E-09	0.67	-0.003	0.002	3.00E-01
5	82909489	rs796444361	AC	A	0.64	-0.012	0.002	2.40E-09	0.65	-0.002	0.003	4.30E-01
5	82911748	rs492356	C	G	0.66	-0.012	0.002	2.00E-09	0.66	-0.002	0.002	3.20E-01
5	82913284	rs567721	C	G	0.65	-0.011	0.002	4.40E-09	0.65	-0.002	0.002	4.50E-01

5	82913361	rs566799	G	A	0.66	-0.012	0.002	1.80E-09	0.66	-0.002	0.002	3.40E-01
5	82913780	rs651198	T	G	0.66	-0.012	0.002	1.70E-09	0.66	-0.002	0.002	3.40E-01
5	82914527	rs336946	C	G	0.65	-0.012	0.002	3.90E-09	0.65	-0.002	0.002	4.50E-01
5	82915184	rs336943	C	T	0.65	-0.012	0.002	3.90E-09	0.65	-0.002	0.002	4.50E-01
5	82915497	rs336942	A	G	0.65	-0.012	0.002	3.90E-09	0.65	-0.002	0.002	4.40E-01
5	82929987	rs9784716	C	A	0.67	-0.012	0.002	2.00E-09	0.67	-0.003	0.002	2.70E-01
5	82932634	rs12189364	C	T	0.67	-0.011	0.002	1.10E-08	0.68	-0.003	0.003	1.90E-01
5	82933835	rs71709944	C	CT	0.69	-0.013	0.002	1.20E-09	0.69	-0.002	0.003	3.60E-01
5	82933913	rs17206069	G	A	0.67	-0.011	0.002	8.70E-09	0.68	-0.003	0.003	1.90E-01
7	35428513	rs12155459	A	T	0.77	-0.007	0.002	3.30E-03	0.77	-0.015	0.003	4.20E-08
7	35429465	rs11766731	G	T	0.77	-0.007	0.002	2.80E-03	0.77	-0.015	0.003	3.50E-08
7	35438831	rs741408	T	C	0.23	0.007	0.002	1.70E-03	0.23	0.016	0.003	1.20E-08
7	35440055	rs2592856	C	T	0.23	0.007	0.002	1.80E-03	0.23	0.016	0.003	6.90E-09
7	35440155	rs11762074	T	C	0.77	-0.007	0.002	1.50E-03	0.77	-0.016	0.003	5.80E-09
7	35446189	rs2592855	T	C	0.23	0.007	0.002	1.30E-03	0.23	0.016	0.003	9.70E-09
7	35449334	rs998652	A	G	0.23	0.007	0.002	1.40E-03	0.23	0.016	0.003	1.00E-08
7	35451830	rs17765314	G	A	0.77	-0.007	0.002	1.40E-03	0.77	-0.016	0.003	9.10E-09
7	35451910	rs2592851	T	C	0.23	0.007	0.002	1.40E-03	0.23	0.016	0.003	9.00E-09
7	35452092	rs1362655	G	A	0.23	0.007	0.002	1.40E-03	0.23	0.016	0.003	9.40E-09
7	35455088	rs2592850	T	A	0.32	0.007	0.002	4.50E-04	0.32	0.014	0.003	4.60E-08
7	35456691	rs2592849	A	T	0.32	0.007	0.002	4.70E-04	0.32	0.014	0.003	4.70E-08
7	35457954	7:35457954	AT	A	0.32	0.007	0.002	8.40E-04	0.32	0.014	0.003	1.60E-08
7	35458137	rs140476889	A	AAAAC	0.32	0.007	0.002	4.70E-04	0.32	0.014	0.003	3.30E-08
7	35459888	rs342977	G	A	0.23	0.007	0.002	2.40E-03	0.23	0.016	0.003	8.10E-09
7	35460547	rs342979	C	T	0.32	0.007	0.002	5.20E-04	0.32	0.014	0.003	4.70E-08
7	35461538	rs342981	G	A	0.32	0.007	0.002	4.70E-04	0.32	0.014	0.003	4.60E-08
7	35461715	rs2551797	T	C	0.32	0.007	0.002	4.80E-04	0.32	0.014	0.002	4.70E-08
7	35462145	rs342982	G	T	0.32	0.007	0.002	4.80E-04	0.32	0.014	0.003	4.50E-08
7	35466464	rs342986	G	A	0.23	0.007	0.002	2.30E-03	0.23	0.016	0.003	7.90E-09
7	35466755	rs342987	T	G	0.23	0.007	0.002	2.30E-03	0.23	0.016	0.003	7.50E-09
7	35467026	rs342988	C	T	0.28	0.007	0.002	7.40E-04	0.28	0.015	0.003	6.00E-09

7	35467677	7:35467677	TAA	T	0.24	0.007	0.002	1.50E-03	0.24	0.016	0.003	1.80E-08
7	35467896	rs342989	A	G	0.23	0.007	0.002	2.40E-03	0.23	0.016	0.003	7.00E-09
7	35468763	rs17697812	T	C	0.77	-0.007	0.002	2.60E-03	0.77	-0.016	0.003	9.30E-09
7	35469835	rs342992	C	T	0.23	0.007	0.002	2.60E-03	0.23	0.016	0.003	9.50E-09
7	35477175	rs343000	C	T	0.23	0.007	0.002	2.40E-03	0.23	0.016	0.003	1.10E-08
7	35478515	rs343002	T	C	0.23	0.007	0.002	2.40E-03	0.23	0.016	0.003	1.10E-08
7	35479439	rs343003	C	T	0.23	0.007	0.002	2.40E-03	0.23	0.016	0.003	1.10E-08
7	35488349	rs343011	T	G	0.23	0.007	0.002	2.30E-03	0.23	0.016	0.003	1.10E-08
7	35496678	rs343026	T	G	0.32	0.007	0.002	7.70E-04	0.32	0.014	0.003	4.50E-08
7	35497055	rs35099106	C	CT	0.23	0.007	0.002	2.50E-03	0.24	0.016	0.003	5.20E-09
7	35498200	rs343029	A	G	0.23	0.007	0.002	2.20E-03	0.23	0.016	0.003	6.60E-09
7	35500493	rs343031	G	A	0.32	0.007	0.002	7.70E-04	0.32	0.014	0.003	4.00E-08
7	35503445	rs343036	G	C	0.23	0.007	0.002	2.20E-03	0.23	0.016	0.003	6.40E-09
7	35503600	rs343037	G	T	0.23	0.007	0.002	2.20E-03	0.23	0.016	0.003	6.50E-09
7	35503696	rs343038	G	C	0.32	0.007	0.002	8.10E-04	0.32	0.014	0.003	3.70E-08
7	35505204	rs343039	C	T	0.23	0.007	0.002	2.60E-03	0.23	0.016	0.003	5.50E-09
8	6470650	rs3020257	C	A	0.76	0.007	0.002	9.90E-04	0.76	0.016	0.003	2.50E-08
8	6471126	rs2980664	G	A	0.76	0.008	0.002	4.80E-04	0.76	0.015	0.003	2.70E-08
8	6472105	rs2959801	G	A	0.69	0.006	0.002	1.50E-03	0.69	0.015	0.003	2.00E-09
8	6472603	rs11137038	G	A	0.64	0.007	0.002	2.80E-04	0.64	0.014	0.002	3.20E-08
8	6473356	rs1256	C	G	0.70	0.007	0.002	3.40E-04	0.70	0.016	0.003	4.10E-10
8	6473758	rs2454517	A	G	0.70	0.007	0.002	3.10E-04	0.70	0.016	0.003	1.40E-09
8	6475489	rs2980662	G	C	0.68	0.007	0.002	8.80E-04	0.69	0.014	0.003	2.40E-08
8	6476626	rs7005662	C	T	0.72	0.008	0.002	1.70E-04	0.73	0.015	0.003	8.60E-09
8	6478481	rs2253560	G	A	0.72	0.008	0.002	1.80E-04	0.73	0.015	0.003	5.00E-09
8	6478960	rs11137040	C	G	0.70	0.007	0.002	3.40E-04	0.71	0.014	0.003	3.30E-08
8	6479432	rs2515559	A	G	0.72	0.008	0.002	2.60E-04	0.72	0.015	0.003	2.30E-08
8	6483059	rs201338894	ATAAAT	A	0.72	0.008	0.002	1.10E-04	0.73	0.016	0.003	2.40E-09
8	6484505	8:6484505	CA	C	0.72	0.008	0.002	6.60E-05	0.73	0.016	0.003	1.30E-09
8	6484510	rs2454524	A	C	0.72	0.008	0.002	6.70E-05	0.73	0.016	0.003	1.30E-09
8	6484530	rs2246801	C	T	0.72	0.008	0.002	8.60E-05	0.72	0.016	0.003	1.10E-09

8	6484635	rs2278147	C	A	0.71	0.008	0.002	1.90E-04	0.71	0.017	0.003	3.00E-11
8	6484982	rs2448611	C	T	0.87	0.001	0.003	8.30E-01	0.70	0.015	0.003	2.70E-08
8	6485295	rs2912062	C	G	0.70	0.008	0.002	1.60E-04	0.71	0.017	0.003	3.10E-11
8	6486033	rs2912063	A	G	0.71	0.008	0.002	2.20E-04	0.71	0.017	0.003	2.60E-11
8	6487449	rs3020263	G	A	0.72	0.008	0.002	1.00E-04	0.72	0.016	0.003	7.40E-10
8	6488577	rs3020264	G	A	0.72	0.008	0.002	1.10E-04	0.72	0.016	0.003	1.30E-09
8	6488787	rs1974946	G	A	0.72	0.008	0.002	1.10E-04	0.72	0.016	0.003	1.40E-09
8	6490200	rs2433143	C	T	0.73	0.008	0.002	2.80E-04	0.73	0.015	0.003	1.50E-08
8	6490544	8:6490544	TA	T	0.70	0.007	0.002	7.00E-04	0.71	0.016	0.003	1.80E-09
19	45412079	rs7412	C	T	0.92	0.016	0.003	4.40E-06	0.92	0.027	0.004	4.40E-10
19	45413233	rs1065853	G	T	0.92	0.016	0.003	4.00E-06	0.92	0.027	0.004	4.00E-10

Supplemental Table 5: Genetic correlations with IMTmean by sex

Phenotype	men					women				
	rg	se	z	p	FDR-P	rg	se	z	p	FDR-P
CHARGE IMTmean 2011	0.88	0.11	7.87	3.57E-15	8.21E-14	0.71	0.10	7.45	9.14E-14	2.1E-12
CHARGE IMTmean 2018	0.86	0.12	6.88	6.06E-12	6.97E-11	0.70	0.10	6.87	6.48E-12	7.46E-11
BMI	0.18	0.05	3.66	2.48E-04	1.90E-03	0.21	0.09	2.47	1.35E-02	1.04E-01
Fasting Glucose	0.23	0.09	2.74	6.22E-03	3.57E-02	-0.12	0.05	-2.36	1.84E-02	1.06E-01
Fasting Insulin	0.31	0.11	2.71	6.70E-03	3.08E-02	0.23	0.10	2.36	1.84E-02	8.45E-02
Type 2 Diabetes	0.26	0.11	2.45	1.42E-02	5.46E-02	0.10	0.05	2.11	3.52E-02	1.35E-01
Rheumatoid arthritis	0.21	0.09	2.33	1.96E-02	6.43E-02	0.18	0.10	1.74	8.23E-02	2.70E-01
Ever Smoker	0.19	0.10	1.97	4.87E-02	1.40E-01	-0.10	0.07	-1.52	1.29E-01	3.70E-01
WHR adjBMI	0.12	0.07	1.75	8.08E-02	2.06E-01	0.03	0.02	1.36	1.74E-01	4.44E-01
Smoking onset	-0.36	0.22	-1.63	1.03E-01	2.37E-01	0.08	0.06	1.24	2.14E-01	4.93E-01
Fasting Proinsulin	0.28	0.18	1.57	1.18E-01	2.46E-01	0.03	0.02	1.06	2.88E-01	6.02E-01
HDL	-0.06	0.04	-1.28	2.00E-01	3.83E-01	-0.09	0.09	-1.04	3.00E-01	5.74E-01
Fasting Insulin adjBMI	0.10	0.11	0.90	3.69E-01	6.53E-01	-0.05	0.06	-0.86	3.89E-01	6.87E-01
Ulcerative Collitis	-0.08	0.10	-0.75	4.56E-01	7.49E-01	0.03	0.05	0.59	5.56E-01	9.13E-01
2hr Glucose	-0.10	0.14	-0.72	4.72E-01	7.24E-01	0.07	0.13	0.55	5.81E-01	8.91E-01
Triglycerides	0.04	0.06	0.69	4.88E-01	7.02E-01	0.07	0.13	0.53	5.95E-01	8.55E-01
Irritable Bowel Disorder	-0.03	0.08	-0.41	6.85E-01	9.27E-01	-0.04	0.09	-0.49	6.28E-01	8.49E-01
DBP	0.01	0.03	0.38	7.06E-01	9.02E-01	0.07	0.16	0.46	6.46E-01	8.25E-01
Cigarettes per day	0.05	0.14	0.33	7.38E-01	8.93E-01	-0.03	0.07	-0.45	6.52E-01	7.89E-01
LDL	0.02	0.06	0.30	7.66E-01	8.81E-01	-0.12	0.27	-0.43	6.67E-01	7.67E-01
Cholesterol	-0.02	0.07	-0.27	7.86E-01	8.61E-01	0.04	0.10	0.40	6.87E-01	7.52E-01
Cardiovascular disease	-0.05	0.30	-0.16	8.72E-01	9.11E-01	-0.02	0.08	-0.26	7.96E-01	8.33E-01
SBP	0.00	0.03	-0.05	9.56E-01	9.56E-01	-0.01	0.17	-0.04	9.69E-01	9.69E-01

Supplemental Table 6: Previous associations with SNPs in GWAS-significant loci

Chr	BP	SNP	RA	RAF	OR	Beta	P-value	Mapped gene	P-value annotation	GWAS catalogue accession	A1	beta	p_bolt_lmm_inf	direction
5	81696676	rs446064					9 x 10 ⁻²⁹	<i>SSBP2</i>	Adolescent idiopathic scoliosis	GCST006287				
7	35428286	rs342989	A	0.23		0.163	3 x 10 ⁻¹⁵	<i>AC007652.1</i> , <i>AC009531.1</i>	Diastolic blood pressure	GCST006627	A	0.01	3.6E-11	consistent
7	35435712	rs2541918	T	0.68		0.157	8 x 10 ⁻⁷	<i>AC007652.1</i> , <i>AC009531.1</i>	Diastolic blood pressure	GCST004280	A	0.01	8.7E-08	consistent
7	35506177	rs11763856	T	0.04		3.055	1 x 10 ⁻⁸	<i>AC007652.1</i>	PR interval	GCST007226	C	-0.02	0.00022	
7	35506177	rs11763856	T	0.03		3.100	4 x 10 ⁻¹⁰	<i>AC007652.1</i>	PR interval	GCST007045	C	-0.02	0.00022	
7	35515178	rs343064	A	0.40		1.310	3 x 10 ⁻⁸	<i>HERPUD2</i> , <i>AC007652.1</i>	Non-alcoholic fatty liver disease histology (Fibrosis)	GCST000765	C	0.00	0.96	
8	6493731	rs17077154	G	0.07		0.302	8 x 10 ⁻⁶	<i>MCPH1</i>	Cytomegalovirus antibody response	GCST001272				
8	6494184	rs141416541	T	0.03		0.451	4 x 10 ⁻⁷	<i>MCPH1</i>	Diastolic blood pressure	GCST004280	C	0.01	0.0019	consistent
11	103718366	rs1917445					6 x 10 ⁻⁷	<i>AP002989.1</i>	Neutrophil count	GCST001059	C	0.01	2.6E-06	
11	103789839	rs974819	T	0.31		0.067	6 x 10 ⁻²⁹	<i>AP002989.1</i>	Coronary artery disease	GCST005196	T	0.01	5.6E-10	consistent
11	103789839	rs974819	T	0.31		0.061	1 x 10 ⁻²⁸	<i>AP002989.1</i>	Coronary artery disease	GCST005195	T	0.01	5.6E-10	consistent
11	103789839	rs974819	T	0.32	1.07		2 x 10 ⁻⁹	<i>AP002989.1</i>	Coronary heart disease	GCST000999	T	0.01	5.6E-10	consistent
11	103798234	rs2019090	A	0.36	1.07		4 x 10 ⁻⁹	<i>AP002989.1</i>	Myocardial infarction	GCST003117	A	0.01	3.7E-10	consistent

13	110397276	rs9515203	T	0.74		0.068	6 x 10 ⁻²⁴	COL4A2	Coronary artery disease	GCST005194	T	-0.01	1.1E-08	consistent
13	110397276	rs9515203	T	0.74		0.068	6 x 10 ⁻²⁴	COL4A2	Coronary artery disease	GCST005196	T	-0.01	1.1E-08	consistent
13	110397276	rs9515203	T	0.74		0.060	4 x 10 ⁻²³	COL4A2	Coronary artery disease	GCST005195	T	-0.01	1.1E-08	consistent
19	41319286	rs73045269	T	0.15		0.070	1 x 10 ⁻¹⁴	CCDC97, TGFB1	Coronary artery disease	GCST005194	C	0.00	0.99	
19	41326326	rs12980942	A	0.16		0.061	7 x 10 ⁻¹⁵	TGFB1	Coronary artery disease	GCST005196	G	0.00	0.29	
19	41345604	rs4803455	A	0.49		0.054	4 x 10 ⁻¹⁷	TGFB1	Coronary artery disease	GCST005194	C	0.00	0.19	
19	41345604	rs4803455	A	0.50		0.048	2 x 10 ⁻¹⁷	TGFB1	Coronary artery disease	GCST005195	C	0.00	0.19	
19	41345604	rs4803455	A	0.50		0.162	8 x 10 ⁻¹¹	TGFB1	Pulse pressure	GCST007269	C	0.00	0.19	
19	41346870	rs2288874	T	0.42		0.053	4 x 10 ⁻¹⁶	TGFB1	Coronary artery disease	GCST005196	T	0.00	0.11	
19	41348629	rs8108632	T	0.48	1.05		4 x 10 ⁻⁸	TGFB1	Coronary artery disease (broad definition)	GCST004787	T	0.00	0.2	
19	41353016	rs1800470	A	0.62		0.259	5 x 10 ⁻²⁶	TGFB1, AC011462.1, TMEM91	Blood protein levels (TGFB1)	GCST006585	G	0.00	0.33	
19	41355454	rs4803457	T			0.149	2 x 10 ⁻⁸	B9D2, TMEM91, AC011462.1	Pulse pressure	GCST007096	T	0.00	0.32	
19	44908822	rs7412	C	0.93	2.07		1 x 10 ⁻⁷	APOE	Alzheimer's disease (females)	GCST007600	C	0.02	2.1E-15	
19	44908822	rs7412	C	0.93	2.21		4 x 10 ⁻¹³	APOE	Alzheimer's disease	GCST007600	C	0.02	2.1E-15	
19	44908822	rs7412			2.31		3 x 10 ⁻¹⁰⁵	APOE	Alzheimer's disease (late onset)	GCST005549	C	0.02	2.1E-15	

19	44908822	rs7412				2 x 10 ⁻⁷⁶	APOE	Alzheimer's disease or family history of Alzheimer's disease	GCST005922	C	0.02	2.1E-15	
19	44908822	rs7412	T	0.08	21.200	1 x 10 ⁻⁹⁹	APOE	Alzheimer's disease or family history of Alzheimer's disease	GCST007320	C	0.02	2.1E-15	
19	44908822	rs7412	C	0.94	0.795	3 x 10 ⁻⁵⁶	APOE	Blood protein levels (APOE)	GCST006585	C	0.02	2.1E-15	consistent
19	44908822	rs7412				3 x 10 ⁻⁶³	APOE	Cardiovascular disease	GCST007072	C	0.02	2.1E-15	
19	44908822	rs7412			11.960	9 x 10 ⁻¹⁹	APOE	Cardiovascular risk factors (LDL-cholesterol)	GCST004704	C	0.02	2.1E-15	
19	44908822	rs7412	T	0.08	0.012	1 x 10 ⁻¹⁴	APOE	Carotid intima media thickness	GCST007436	C	0.02	2.1E-15	consistent
19	44908822	rs7412	C	0.93	0.413	239	APOE	Cholesterol, total	GCST002896	C	0.02	2.1E-15	consistent
19	44908822	rs7412	T	0.08	0.420	5 x 10 ⁻⁹⁴	APOE	Cholesterol, total	GCST004209	C	0.02	2.1E-15	consistent
19	44908822	rs7412	T	0.08	0.160	3 x 10 ⁻³⁹	APOE	Coronary artery disease	GCST005194	C	0.02	2.1E-15	consistent
19	44908822	rs7412	T	0.08	0.160	3 x 10 ⁻³⁹	APOE	Coronary artery disease	GCST005196	C	0.02	2.1E-15	consistent
19	44908822	rs7412	T	0.08	0.137	2 x 10 ⁻³⁵	APOE	Coronary artery disease	GCST005195	C	0.02	2.1E-15	consistent
19	44908822	rs7412	C	0.92	1.15	2 x 10 ⁻¹⁹	APOE	Coronary artery disease (broad definition)	GCST004787	C	0.02	2.1E-15	consistent

19	44908822	rs7412				9 x 10 ⁻⁶²	APOE	Family history of Alzheimer's disease	GCST005921	C	0.02	2.1E-15	
19	44908822	rs7412	T	0.08	0.156	6 x 10 ⁻¹⁴	APOE	HDL cholesterol	GCST004207	C	0.02	2.1E-15	consistent
19	44908822	rs7412	C	0.92	0.079	5 x 10 ⁻²⁹	APOE	High density lipoprotein cholesterol levels	GCST007140	C	0.02	2.1E-15	consistent
19	44908822	rs7412	C	0.95	0.152	2 x 10 ⁻⁷	APOE	High density lipoprotein cholesterol levels	GCST007140	C	0.02	2.1E-15	consistent
19	44908822	rs7412	C		0.085	2 x 10 ⁻³⁶	APOE	High density lipoprotein cholesterol levels	GCST007140	C	0.02	2.1E-15	consistent
19	44908822	rs7412				9 x 10 ⁻¹⁶	APOE	Ideal cardiovascular health (clinical and behavioural)	GCST003278	C	0.02	2.1E-15	
19	44908822	rs7412		0.10	12.300	2 x 10 ⁻⁹	APOE	LDL cholesterol	GCST001645	C	0.02	2.1E-15	
19	44908822	rs7412	T		0.313	7 x 10 ⁻¹⁵	APOE	LDL cholesterol levels	GCST004243	C	0.02	2.1E-15	consistent
19	44908822	rs7412	T	0.07	0.590	2 x 10 ⁻²⁸⁶	APOE	LDL cholesterol levels (Trans-ethnic initial)	GCST004233	C	0.02	2.1E-15	consistent
19	44908822	rs7412			0.750	3 x 10 ⁻⁵⁸	APOE	Lipid metabolism phenotypes (L-LDL-FC)	GCST001392	C	0.02	2.1E-15	
19	44908822	rs7412	T	0.12	0.480	3 x 10 ⁻⁵³	APOE	Lipid traits (LDL-C)	GCST002174	C	0.02	2.1E-15	consistent
19	44908822	rs7412	T	0.12	0.090	2 x 10 ⁻³⁰	APOE	Lipid traits (TC)	GCST002174	C	0.02	2.1E-15	consistent
19	44908822	rs7412	T		3.340	3 x 10 ⁻¹⁰	APOE	Lipoprotein (a) levels	GCST004398	C	0.02	2.1E-15	
19	44908822	rs7412	T	0.06	17.110	8 x 10 ⁻⁷⁸	APOE	Lipoprotein phospholipase	GCST004963	C	0.02	2.1E-15	consistent

19	44908822	rs7412	T		2.780	3 x 10 ⁻⁹	APOE	A2 activity in cardiovascular disease Lipoprotein(a) levels adjusted for apolipoprotein(a) isoforms	GCST004399	C	0.02	2.1E-15	consistent
19	44908822	rs7412	T	0.06	0.040	2 x 10 ⁻²⁷	APOE	Lipoprotein-associated phospholipase A2 activity change in response to darapladib treatment in cardiovascular disease	GCST004966	C	0.02	2.1E-15	consistent
19	44908822	rs7412	T	0.08	0.419	3 x 10 ⁻¹⁹	APOE	Low density lipoprotein cholesterol levels	GCST004541	C	0.02	2.1E-15	consistent
19	44908822	rs7412	C	0.92	0.493	1 x 10 ⁻³⁰⁰	APOE	Low density lipoprotein cholesterol levels (EA)	GCST007141	C	0.02	2.1E-15	consistent
19	44908822	rs7412	C	0.95	0.574	9 x 10 ⁻⁵⁹	APOE	Low density lipoprotein cholesterol levels (Hispanic)	GCST007141	C	0.02	2.1E-15	consistent
19	44908822	rs7412	C	0.89	0.522	2 x 10 ⁻³⁶	APOE	Low density lipoprotein cholesterol levels (AA)	GCST007141	C	0.02	2.1E-15	consistent

19	44908822	rs7412	C		0.498	1 x 10-300	APOE	Low density lipoprotein cholesterol levels	GCST007141	C	0.02	2.1E-15	consistent
19	44908822	rs7412	T	0.06	-0.59	2 x 10-120	APOE	Metabolite levels (Free cholesterol in large LDL)	GCST003665	C	0.02	2.1E-15	consistent
19	44908822	rs7412	T	0.08	0.3826	4 x 10-10	APOE	Pulse pressure	GCST004278	C	0.02	2.1E-15	consistent
19	44908822	rs7412		0.08	0.3753	5 x 10-31	APOE	Pulse pressure	GCST006629	C	0.02	2.1E-15	
19	44908822	rs7412	T	0.08	-0.361	4 x 10-24	APOE	Pulse pressure	GCST007269	C	0.02	2.1E-15	consistent
19	44908822	rs7412			-6.2	2 x 10-47	APOE	Response to statins (baseline LDL-C)	GCST001408	C	0.02	2.1E-15	
19	44908822	rs7412	T	0.08	-0.326	2 x 10-11	APOE	Systolic blood pressure	GCST007267	C	0.02	2.1E-15	consistent
19	44908822	rs7412				4 x 10-21	APOE	Systolic blood pressure	GCST007087	C	0.02	2.1E-15	
19	44908822	rs7412	T	0.08	-0.27	1 x 10-8	APOE	Total cholesterol levels	GCST004548	C	0.02	2.1E-15	consistent
19	44908822	rs7412	T	0.07	-0.374	8 x 10-315	APOE	Total cholesterol levels (Trans-ethnic initial)	GCST004235	C	0.02	2.1E-15	consistent
19	44908822	rs7412	C	0.92	0.342	1 x 10-300	APOE	Total cholesterol levels (EA)	GCST007143	C	0.02	2.1E-15	consistent
19	44908822	rs7412	C	0.95	0.411	3 x 10-31	APOE	Total cholesterol levels (Hispanic)	GCST007143	C	0.02	2.1E-15	consistent
19	44908822	rs7412	C	0.89	0.381	3 x 10-20	APOE	Total cholesterol levels (AA)	GCST007143	C	0.02	2.1E-15	consistent
19	44908822	rs7412	C		0.348	1 x 10-300	APOE	Total cholesterol levels	GCST007143	C	0.02	2.1E-15	consistent
19	44908822	rs7412	C	0.92	-0.09	5 x 10-31	APOE	Triglycerides (EA)	GCST007142	C	0.02	2.1E-15	inconsistent
19	44908822	rs7412	C		-0.087	2 x 10-32	APOE	Triglycerides	GCST007142	C	0.02	2.1E-15	inconsistent

19	44909976	rs1065853	T	0.08	-0.72	2 x 10 ⁻⁵⁸	AC011481.3	Blood protein levels ((isoform E3), APOE)	GCST005806	G	0.02	1.6E-15	consistent
19	44909976	rs1065853			-0.642	1 x 10 ⁻⁶²	AC011481.3	Free cholesterol levels in large LDL	GCST005485	G	0.02	1.6E-15	
19	44909976	rs1065853	G	0.93	-0.603	5 x 10 ⁻³²⁴	AC011481.3	LDL cholesterol	GCST002898	G	0.02	1.6E-15	consistent
19	44909976	rs1065853	T		-0.162	3 x 10 ⁻⁵⁴	AC011481.3	Low density lipoprotein cholesterol levels	GCST007442	G	0.02	1.6E-15	consistent
19	44909976	rs1065853			-0.399	4 x 10 ⁻²⁵	AC011481.3	Serum total cholesterol levels	GCST005448	G	0.02	1.6E-15	
19	44909976	rs1065853	T	0.06	13.125	2 x 10 ⁻²⁶	AC011481.3	Total cholesterol levels	GCST007441	G	0.02	1.6E-15	consistent
19	44909976	rs1065853			-0.573	5 x 10 ⁻⁵⁰	AC011481.3	Total cholesterol levels in LDL	GCST005447	G	0.02	1.6E-15	

Supplemental Table 7: predicted functional, coding or loss of function variants

SNP	chr	pos	Allele	Consequence	IMPACT	SYMBOL	SIFT	PolyPhen
rs6658335	1	1707555	T	missense_variant	MODERATE	<i>CDK11A</i>	tolerated_low_confidence(0.06)	benign(0.007)
rs2912010	8	6621465	T	synonymous_variant	LOW	<i>MCPH1</i>	-	-
rs1057090	8	6621521	A	missense_variant	MODERATE	<i>MCPH1</i>	tolerated(0.08)	benign(0.129)
rs1057090	8	6621521	G	missense_variant	MODERATE	<i>MCPH1</i>	deleterious(0.02)	benign(0.025)
rs1057090	8	6621521	T	missense_variant	MODERATE	<i>MCPH1</i>	tolerated(1)	benign(0)
rs2912016	8	6621657	A	synonymous_variant	LOW	<i>MCPH1</i>	-	-
rs2912057	8	6625961	G	missense_variant	MODERATE	<i>MCPH1</i>	-	-
rs2912057	8	6625961	G	missense_variant	MODERATE	<i>MCPH1</i>	-	-
rs11558719	10	72213199	T	missense_variant	MODERATE	<i>ASCC1</i>	tolerated(0.21)	benign(0.203)
rs28375406	16	88930433	G	missense_variant	MODERATE	<i>LOC105371409</i>	-	-
rs12924185	16	88950476	T	missense_variant	MODERATE	<i>LOC100129697</i>	tolerated_low_confidence(0.07)	unknown(0)
rs1160983	19	44893972	A	synonymous_variant	LOW	<i>TOMM40</i>	-	-
rs7412	19	44908822	T	missense_variant	MODERATE	<i>APOE</i>	deleterious(0)	probably_damaging(1)

Supplemental Table 8: EQTLs identified in GTEx

	SNP Id	Chr	Pos	A1	A2	Gene Symbol	Gencode Id	P-Value	NES	Tissue
lead	rs309563	5	82896644	A	T	<i>VCAN-AS1</i>	ENSG00000249835.2	4.60E-06	-0.2	Testis
VEP	rs1057090	8	6479042	C	T	<i>MCPH1-AS1</i>	ENSG00000271743.1	5.20E-06	-0.44	Testis
VEP	rs1057090	8	6479042	C	T	<i>MCPH1-AS1</i>	ENSG00000271743.1	2.70E-05	-0.26	Thyroid
VEP	rs2912010	8	6478986	C	T	<i>MCPH1-AS1</i>	ENSG00000271743.1	8.30E-06	-0.28	Nerve - Tibial
VEP	rs2912010	8	6478986	C	T	<i>MCPH1-AS1</i>	ENSG00000271743.1	8.00E-06	-0.43	Testis
VEP	rs2912016	8	6479178	C	A	<i>MCPH1-AS1</i>	ENSG00000271743.1	3.90E-06	-0.37	Colon - Transverse
VEP	rs2912016	8	6479178	C	A	<i>MCPH1-AS1</i>	ENSG00000271743.1	1.30E-05	-0.3	Esophagus - Muscularis
VEP	rs2912016	8	6479178	C	A	<i>MCPH1-AS1</i>	ENSG00000271743.1	4.30E-09	-0.37	Nerve - Tibial
VEP	rs2912016	8	6479178	C	A	<i>MCPH1-AS1</i>	ENSG00000271743.1	3.10E-06	-0.58	Prostate
VEP	rs2912016	8	6479178	C	A	<i>MCPH1-AS1</i>	ENSG00000271743.1	3.90E-06	-0.46	Stomach
VEP	rs2912016	8	6479178	C	A	<i>MCPH1-AS1</i>	ENSG00000271743.1	2.80E-06	-0.47	Testis
VEP	rs2912016	8	6479178	C	A	<i>MCPH1-AS1</i>	ENSG00000271743.1	1.00E-07	-0.33	Thyroid
VEP	rs2912057	8	6483482	C	T	<i>MCPH1-AS1</i>	ENSG00000271743.1	2.30E-05	-0.26	Nerve - Tibial
lead	rs2912062	8	6485295	C	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	3.10E-06	-0.52	Brain - Cortex
lead	rs2912062	8	6485295	C	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	7.70E-07	-0.46	Brain - Nucleus accumbens (basal ganglia)
lead	rs2912062	8	6485295	C	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	1.20E-06	-0.65	Cells - EBV-transformed lymphocytes
lead	rs2912062	8	6485295	C	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	5.40E-11	-0.55	Colon - Transverse
lead	rs2912062	8	6485295	C	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	1.60E-06	-0.35	Esophagus - Muscularis
lead	rs2912062	8	6485295	C	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	8.70E-11	-0.43	Nerve - Tibial
lead	rs2912062	8	6485295	C	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	2.70E-06	-0.58	Ovary
lead	rs2912062	8	6485295	C	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	2.10E-06	-0.48	Stomach
lead	rs2912062	8	6485295	C	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	4.80E-08	-0.55	Testis
lead	rs2912062	8	6485295	C	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	2.40E-07	-0.34	Thyroid
lead	rs2912063	8	6486033	A	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	4.60E-06	-0.51	Brain - Cortex

lead	rs2912063	8	6486033	A	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	2.00E-06	-0.44	Brain - Nucleus accumbens (basal ganglia)
lead	rs2912063	8	6486033	A	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	8.40E-11	-0.55	Colon - Transverse
lead	rs2912063	8	6486033	A	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	3.80E-07	-0.37	Esophagus - Muscularis
lead	rs2912063	8	6486033	A	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	6.20E-10	-0.41	Nerve - Tibial
lead	rs2912063	8	6486033	A	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	2.90E-06	-0.59	Ovary
lead	rs2912063	8	6486033	A	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	1.20E-06	-0.5	Stomach
lead	rs2912063	8	6486033	A	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	1.10E-07	-0.54	Testis
lead	rs2912063	8	6486033	A	G	<i>MCPH1-AS1</i>	ENSG00000271743.1	3.30E-07	-0.34	Thyroid
lead	rs2019090	11	103668962	A	T	<i>RP11-563P16.1</i>	ENSG00000254987.1	3.70E-05	-0.3	Artery - Aorta
lead	rs561732	16	88988989	T	C	<i>CBFA2T3</i>	ENSG00000129993.10	7.10E-15	-0.47	Pancreas
lead	rs561732	16	88988989	T	C	<i>CBFA2T3</i>	ENSG00000129993.10	1.90E-05	-0.17	Thyroid
VEP	rs28375406	16	88996841	A	G	<i>CBFA2T3</i>	ENSG00000129993.10	2.90E-10	-0.39	Pancreas
VEP	rs28375406	16	88996841	A	G	<i>CBFA2T3</i>	ENSG00000129993.10	1.50E-05	-0.17	Thyroid
VEP	rs7412	19	45412079	C	T	<i>APOE</i>	ENSG00000130203.5	2.20E-05	-0.29	Skin - Not Sun Exposed (Suprapubic)

Where: CTD-2541M15.3 also known as MCPH1-AS1