SUPPLEMENTARY NOTE 1. Look-up of previously identified loci in our data set

To fully explore the efficacy of accounting for smoking in GWAS of adiposity traits, we conducted a look-up in our data of recently published SNP associations with BMI, WHRadjBMI, and WCadjBMI identified in well-powered GWAS meta-analyses that did not account for SMK status\(^1,2\). Although our sample size was as little as one third of previously published GWAS\(^1,2\), the majority of these loci (92% for BMI, 97% for WCadjBMI, and 92% for WHRadjBMI) reached Bonferroni corrected significant for at least one of the three Approaches in the current study.

All previously identified 97 BMI-associated SNPs were nominally significant (P<0.05) in Approach 1 (SNPadjSMK) for BMI including the sex-specific loci, 95 of the 97 for Approach 2 (SNPjoint), and seven for Approach 3 (SNPint). A total of 86 loci reached Bonferroni-corrected significance (P<5.15x10\(^{-4}\)) for Approach 1, 85 for Approach 2, and none for Approach 3. Finally, 41 loci from Approach 1 and 39 of the 97 from Approach 2 reached genome-wide significance (GWS, P<5x10\(^{-8}\)) (Supplementary Table 11). Of the 97 previously identified main effects loci for BMI, 3 of these were genome-wide significant GWS for women-only, 3 for men-only and the remaining in the sex-combined analysis in the previous publication. It is also worth noting that we report results for the All Ancestries meta-analysis, as this was our primary meta-analysis data-set; however, Locke et al. (2015) considered their European-descent only meta-analysis their primary data-set.

Of the 77 previously-identified WCadjBMI loci, 3 of these were GWS for women-only, 3 for men-only and the remaining in the sex-combined analysis as reported in Shungin et al.\(^2\). Of these, 75 were nominally significant for Approach 1 (SNPadjSMK) and Approach 2 (SNPjoint), and 5 for Approach 3 (SNPint). A total of 73 were Bonferroni-corrected significant (P<6.49x10\(^{-4}\)) for Approach 1 and 2; with 41 and 40 reaching GWS, respectively (43 non-overlapping, 56%) (Supplementary Table 12).

Eleven of the 68 previously published WHRadjBMI SNPs were associated in the women-only analyses in the previous investigation\(^2\). Of the 68 variants, 64 were nominally significant for Approach 1 (SNPadjSMK), 59 for Approach 2 (SNPjoint), and 10 for Approach 3 (SNPint). A total of 61 were Bonferroni-corrected significant (P<6.49x10\(^{-4}\)) for Approach 1 and 38 for Approach 2; with 36 and 8 reaching GWS, respectively (36 in total, 53%) (Supplementary Table 13).

In summary, we replicated all previously-identified BMI loci using one or more of our approaches (P<0.05 and concordant direction of effect), but did not replicate all previously-identified loci for WCadjBMI and WHRadjBMI in our current analyses. It is unclear if the lack of replication of previous findings is due to smaller sample size, patterns of linkage disequilibrium in our all ancestries sample, the adjustment of smoking status in the current discovery analysis, or even a combination of these factors.

SUPPLEMENTARY NOTE 2. Summary of literature search on genes nearest to the 21 novel loci and all GxSMK interaction loci.

We used SNIPPER (http://csg.sph.umich.edu/boehnke/snipper/) to identify potential biological functions of genes ±500kb of our novel association signals and those from Approach 3 (SNPint) for further investigation, and present a summary of those findings in this section (Online Methods).

**Body Mass Index (BMI)**
rs2481665 (INADL): There are seven genes within the 500kb region of the lead SNP rs2481665 on chromosome 1. These genes are INADL, L1TD1, KANK4, USP1, DOCK7, TM2D1, and ANGPTL3. The lead SNP is in intron (#15) of the INADL (InaD-Like) gene. INADL encodes the protein Pals1-Associated Tight Junction (PATJ), which helps regulate the formation of tight junctions, and is involved in the processes of cell polarization and directional migration of epithelial cells. A GWAS study (n= 815) designed to identify variants associated with childhood obesity in the Hispanic population, found near genome-wide significant associations between the exonic, non-synonymous SNP rs1056513 in INADL (204 kb downstream from our lead SNP) and the following fat distribution traits: weight [kg] (EAF: [effect allele frequency]: 0.031, p-value: 1.18 x 10^{-07}); BMI [kg/m²] (EAF: 0.021, p-value: 8.34 x 10^{-06}); fat mass [kg] (EAF: 0.035, p-value: 1.59 x 10^{-07}); trunk fat mass [kg] (EAF: 0.035, p-value: 2.36 x 10^{-07}); fat free mass [kg] (EAF: 0.034, p-value: 2.80 x 10^{-07}) and hip circumference (EAF: 0.022, p-value: 2.47 x 10^{-06}). The SNP rs1056513 accounted for 3% of the variance in body weight and body composition. However, this SNP is not in LD with the lead SNP rs2481665 in this study (R^2<0.2).

Farther away is the DOCK7 gene, 326 kb downstream from the lead SNP. This gene encodes a guanine nucleotide exchange factor (GEF) protein that is involved in axon formation and neuronal polarization. GWAS studies have reported the association of variants located near the DOCK7 gene with lipid levels. A GWAS study (n= up to 18,554) conducted with individuals of European ancestry identified the association of rs1213033 with triglycerides (eaf: -0.11, 2 x 10^{-8}). Another GWAS meta-analysis found a genome-wide significant association between rs1168013 and triglycerides in individuals of European ancestry (n=17,723; eaf: 0.035 (0.007), p-value: 6.4 x 10^{-8}). However, authors could not replicate this finding in other study samples consisting of 37,774 Europeans and 9,665 individuals of Indian Asian ethnicity. A GWAS replication study assessing the association between 15 SNPs and blood lipid and lipoprotein concentrations in individuals of Asian descent (n=4638), found a marginal association between the variant rs10889353, located in the intronic region of DOCK7, and triglycerides (eaf: -0.08, p-value: 6.5 x 10^{-04}). None of the variants from the different GWAS studies discussed above are in LD with SNP rs2481665 (R^2<0.2).

TM2D1 is another gene in the 500kb area that is 404 kb upstream from rs2481665. This gene encodes a beta-amylloid peptide-binding protein (BBP), which is involved in neural death and in the decrease of cognitive skills that occurs in Alzheimer’s disease. This protein may be targeted by the beta-amylloid peptide which has been linked to the formation of plaques resulting in neurotoxicity in Alzheimer’s disease. The APP, the precursor of beta-amylloid peptide, is expressed in adipose tissue and its expression is up-regulated in obesity.

ANGPTL3 (Angiopoietin-Like 3) is 469 kb upstream from the lead SNP, and upstream of the DOCK7 gene. ANGPTL3 encodes a protein that plays a role in angiogenesis. This protein is expressed mostly in the liver. Mutations in this gene lead to the disease familial hypobetalipoproteinemia type 2 (FHBL2), which causes low levels of apolipoprotein B (apoB), total cholesterol, low-density lipoprotein (LDL) cholesterol and high density lipoprotein cholesterol. Several genetic association studies suggest that ANGPTL3 has a role in regulating plasma lipoprotein metabolism. A few single-nucleotide polymorphisms, near the ANGPTL3 gene, have been associated with lower triglyceride: rs1213033, rs213192, rs12042319. One of these, rs1213033, is also near the DOCK7 gene.

There are several nearby genes with no documented role in adiposity or related cardiometabolic traits. Including, L1TD1 (Line-1 type transposase domain containing 1) located 66 kb upstream from the lead SNP. L1TD1 encodes the protein ES Cell-Associated Protein 11, a RNA-binding protein that plays a role in maintaining the pluripotency of stem cells, and in the proliferation of cancer cells. Also, KANK4 (KN
motif and ankyrin repeat domains 4) is a gene located 107 kb downstream from our SNP of interest. It encodes the protein Ankyrin Repeat Domain 38, a member of the Kank family of proteins, which are involved in the control of cytoskeleton microfilaments by regulating the polymerization of actin. The Kank gene is a tumor suppressor in renal cell carcinoma\textsuperscript{17}. USP1, 307 kb upstream from rs2481665, encodes a protein that cleaves ubiquitin, a peptide that is added to proteins to signal them for degradation, or modification of their cellular location or enzymatic activity.

The intronic rs2481665 variant does not seem to have a functional role (Score 4 in RegulomeDB\textsuperscript{18}). Two eQTLs were found for rs2481665 (Gene: L1TD1, p-value: 2.1 x 10^{-7}, EAF: -0.73, tissue: brain-cerebellum) and (Gene: INALD, p-value: 4.0 x 10^{-6}, EAF: 0.29, tissue: heart-atrial appendage).

rs10929925 (LOC400940): LOC400940 and SOX11 are the two genes on Chr2 that are within 500 kb of the lead SNP rs10929925. SNP rs10929925 is downstream of LOC400940, the nearest gene, a non-coding RNA gene that remains uncharacterized. The variant is also 314 kb downstream from SOX11, a gene without introns that encodes a transcription factor that is part of the SOX (SRY-related HMG-box) family. This family of transcription factors is involved with processes that regulate embryonic development and cell fate\textsuperscript{19}. One study has proposed that SOX11 has a role in brain development after observing that mutations in the gene may lead to microcephaly, developmental delays and other features found in mild Coffin-Siris Syndrome, a genetic disorder that causes developmental delays\textsuperscript{20}. A recent GWAS meta-analysis study of fat distribution, which included 224,459 individuals of European and non-European ancestry, identified a genome wide significant association (p=4.5 x 10^{-8}) between rs10929925 and hip circumference unadjusted for BMI\textsuperscript{2}. Based on a literature review, the study identified SOX11 as the best candidate gene for rs10929925.\textsuperscript{2}

There is no available information regarding the potential regulatory role of the lead SNP (RegulomeDB\textsuperscript{18}). But there is evidence of an eQTL, although it does not reach 5% FDR (Gene: SOX11, P-value: 8.7 x 10^{-6}, Effect size: 0.39, Tissue: thyroid). In brain tissue, the SNP altered the TATA box motif of the Dlx3 gene a homeodomain gene (HaploReg\textsuperscript{21}).

rs6794880 (SRRM1P2): The 500kb region around the lead SNP, rs6794880, does not show the presence of any protein coding genes. The nearest genomic feature to rs6794880 is SRRM1P2, a pseudogene, named the serine/arginine repetitive matrix 1 pseudogene 2. Upstream rs6794880 is LINCO0971, a long intergenic non-protein coding RNA gene that remains uncharacterized.

There is no evidence that the lead SNP rs6794880 has a functional/regulatory role (Score 6 in RegulomeDB\textsuperscript{18}) in the genome. Additionally, there are no reports of eQTLs for this variant.

rs12629427 (EPHA3): There is only one gene found within 500kb of the peak signal, rs12629427. EPHA3 (EPH receptor A3) is 11kb downstream from rs12629427, and is a member of the ephrin receptor subfamily of the protein-tyrosine kinase family. EPH and EPH-related receptors have been implicated in mediating developmental events, particularly in the nervous system. This gene encodes a protein that binds ephrin-A ligands. EPHA3 has been implicated in the pathogenesis of lung cancer\textsuperscript{22-26}. The SNP rs12629427 has a score of 6 in RegulomeDB\textsuperscript{18} (minimal binding evidence). No significant eQTLs were found for rs12629427 and no GWAS hits were identified within the 1MB region of the lead SNP.

rs2173039 (EPHA3): There is only one gene found within 500kb of rs2173039, which is 14.5kb upstream from EPHA3 (EPH receptor A3). See rs12629427 above.
rs13069244 (CCDC39): A total of 4 genes are found within 500kb of the lead marker, rs13069244. 
CCDC39 (coiled-coil domain containing 39) is located 43.88kb downstream from the lead marker and encodes a protein involved in the motility of cilia and flagella. Defects in this gene cause primary ciliary dyskinesia type 14. Lung disease was worse in those with IDA/CA/MTD ultrastructural defects, most of whom had biallelic mutations in CCDC39\(^27\). FXR1 (fragile X mental retardation, autosomal homolog 1) is located 189kb downstream from rs13069244, and codes for an RNA binding protein that shuttles between the nucleus and cytoplasm, and is associated with polyribosomes, predominantly with the 6OS ribosomal subunit. Deregression of FXR protein 1 by the lipodystrophic lamin A p.R482W mutation elicits a myogenic gene expression program in preadipocytes\(^28\). DNAJC19 (DnaJ (Hsp40) homolog, subfamily C, member 19), located 260kb upstream from our lead marker, encodes a protein involved in the ATP-dependent transport of transit peptide-containing proteins from the inner cell membrane to the mitochondrial matrix. Defects in this gene are a cause of 3-methylglutaconic aciduria type 5 (MGAS), also known as dilated cardiomyopathy with ataxia (DCMA)\(^29-31\). The loss of DNAJC19/PHB complexes affects cardiolipin acylation and leads to the accumulation of cardiolipin species with altered acyl chains\(^32\). There is no evidence that rs13069244 has a functional/regulatory role (RegulomeDB\(^18\) Score 6: minimal binding evidence) in the genome. No GWAS hits were identified within the 1Mb region of rs13069244 and no report of eQTL for the variant.

rs336396 (INPP4B): There are two genes found within 500kb of rs336396. The SNP lies within INPP4B (inositol polyphosphate-4-phosphatase, type II, 105kDa), which encodes inositol polyphosphate 4-phosphatase type II, one of the enzymes involved in phosphatidylinositol signaling pathways. INPP4B has been identified as a tumor suppressor by negatively regulating normal and malignant cell proliferation through regulation of the PI3K/Akt signaling pathway\(^33,34\). Different residues within the catalytic site of INPP4B are responsible for activity with lipid and protein substrates\(^35\). IL15 (interleukin 15) is located 407kb upstream of rs336396. IL15 encodes a cytokine that regulates T and natural killer (NK) cell activation and proliferation. This cytokine may act as an antagonist to IL2, which binds common hematopoietin receptor subunits, and may compete for the same receptor. This cytokine induces the activation of JAK kinases, as well as the phosphorylation and activation of transcription activators STAT3, STAT5, and STAT6. Murine models show that this cytokine may increase expression of apoptosis inhibitor BCL2L1/BCL-x(L), possibly through the transcription activation activity of STAT6, and thus prevent apoptosis. Cigarette smoke compromises IL-15 production – and as a result NK cell function – which could link to the higher incidence of cancers or viral infections observed among smokers\(^36\). A group of SNPs, upstream from IL15, were associated with both smoking status and quantity of cigarette consumption\(^37\). No data was provided for rs336396 by RegulomeDB\(^18\). No GWAS hits were identified within the 1Mb region of rs336396 and no report of an eQTL for the variant.

rs12902602 (CHRNA5-CHRNA3-CHRNB4): A total of 10 genes are found within 500kb of rs12902602. The SNP is located 33.81kb upstream of CHRNB4 (cholinergic receptor, nicotinic beta 4). The CHRNA5-CHRNA3-CHRNB4 gene cluster has consistently been associated with smoking quantity and nicotine dependence\(^38-40\), COPD, lung cancer and peripheral artery disease\(^39,41,42\), and increased risk of death\(^43\). Variants of CHRNA5-CHRNA3-CHRNB4 have also been associated with lower birth weight from smoking mothers\(^44\), and with lower BMI in current adult smokers\(^45,46\), but with lower BMI in never smokers\(^46\). The CHRNA5-CHRNA3-CHRNB4 genes encode the nicotinic acetylcholine receptor (nAChR) subunits α3, α5 and β4 that are expressed in mammalian brain\(^47,48\). GWASs have also identified loci at ADAMTS7 (ADAM metallopeptidase with thrombospondin domain type 1 motif 7), at 84.14 kb downstream from the leader SNP rs12902602, associated with coronary artery disease and its risk factors\(^49-52\).
Waist Circumference adjusted for BMI (WCADJBMI):

rs17396340 (KIF1B). A total of 10 genes are found within 500kb of the lead marker, rs17396340, which is intronic to KIF1B. We highlight four genes in the region here. KIF1B is involved in synaptic vesicle and mitochondrial transport, and may play a critical role in the development of hepatocellular carcinoma. 6PGD codes for an oxidative carboxylase responsible for reduction of 6-phosphogluconate. Cells lacking 6PGD appear to metabolize glucose as an inhibitor to induce senescence. RBP7 is involved in carotenoid metabolism. In avian model organisms, the RBP7 promoter is important in regulating expression of several genes in adipose tissue at later developmental stages. Nicotinamide mononucleotide adenylyltransferase (NMNAT) reversibly catalyzes the important step in the biosynthesis of NAD from ATP and NMN. NAD and NADP are used reversibly in anabolic and catabolic reactions. NAD is necessary for cell survival in oxidative stress and DNA damage. The top SNP, rs17396340, is associated with the expression levels of ARSA (p-value of 6.0e-05) at LCL tissue in Homo sapiens. Human adipocytes express functional DAR (Dopamine receptors) and ARSA, suggesting a regulatory role for peripheral dopamine in adipose functions. It is speculated that the propensity of some DAR-activating antipsychotics to increase weight and alter metabolic homeostasis is due to their direct action on adipose tissue. Our lead SNP is also associated with mean platelet volume. From HaploReg, the lead SNP, rs17396340, is annotated as KIF1B in GENCODE, and is functionally annotated as intronic. This lead SNP is associated with enhancer histone marks in 9 tissues; associated with regulatory motifs at GATA and Hoxa5; and with cis-eQTLs from various tissues (cells transformed fibroblasts, muscle skeletal, lymphoblastoid EUR exonlevel, lymphoblastoid EUR genelevel, and whole blood). The RegulomeDB score for the lead SNP is 4.

rs6743226 (HDLBP). A total of 10 genes are found within 500kb of our lead marker, rs6743226. Three, of biological interest, are mentioned here. Our lead SNP, rs6743226, is intronic to HDLBP, which codes for a protein that binds high density lipoprotein (HDL) that functions to regulate excess cholesterol levels in cells.

STK25 codes for a serine/threonine kinase with important functions in the Golgi apparatus. This gene has been associated with severe hypoxia and pseudohypoparathyroidism, symptoms of which include short stature and obesity. Significantly higher serine/threonine kinase 25 (STK25) levels were observed in the skeletal muscle of type 2 diabetic patients, compared with individuals with normal glucose tolerance. The overexpression of STK25 in conditions of excess dietary fuels associates with a shift in the metabolic balance in peripheral tissues from lipid oxidation to storage, leading to a systemic insulin resistance.

Expression of PAS domain containing serine/threonine kinase (PASK) is regulated by glucose and the encoded protein plays a role in the regulation of insulin gene expression. Down regulation of this gene may play a role in type 2 diabetes. Far2 and Stk25 are candidate genes for the HDL cholesterol locus in mice. The top SNP, rs6743226, is associated with the expression of B-cell CLL/lymphoma 10 (BCL10). The protein encoded by the gene BCL10 contains a caspase recruitment domain (CARD), and induce apoptosis and to activate NF-kappaB MALAT1 and this protein are thought to synergize in the activation of NF-kappaB, and the deregulation of either of them may contribute to the same pathogenetic process that leads to the malignancy.

There is no GWAS signal nearby the lead SNP rs6743226. This lead SNP is associated with enhancer histone marks in 4 tissues; associated with regulatory motifs changed at Goxa and TCF12; and with eQTL from various tissues including adipose subcutaneous, lung, and muscle tissues. The RegulomeDB score for the lead SNP is 6.
rs4378999 (DOCK3): A total of 4 genes are found near our lead marker, rs4378999, DOCK3, MANF, VPRBP, and RBM15B. Our lead variant is intronic to DOCK3 (dedicator of cytokinesis 3), which is highly expressed in the central nervous system and like previously identified obesity related genes, is involved in neurite outgrowth downstream of BDNF-TrkB. MANF (mesencephalic astrocyte-derived neurotrophic factor) is an endoplasmic reticulum protein that acts to protect ER in response to cellular/organismal stress, for example, expression is increased in skeletal muscle of the leg in rats in response to exercise. Further, recent evidence shows that MANF may be an important factor in the protection of pancreatic beta cells and disruption of MANF expression can lead to diabetes. There is very little known about VPRBP, and RBM15B.

Genome-wide association studies have reported the association within 1MB region of lead SNPs for height \((R^2=0.35)\) and melanoma \((R^2=0.48)\). Our lead SNP is associated with regulatory motifs changed at Cdx2, and with eQTL from various tissues including adipose subcutaneous, and muscle skeletal. The lead SNP is associated eQTL in esophagus muscularis tissue based on GTEx lookup. GWAS studies have reported the association within 1Mb of lead SNP for height \((R^2=0.38)\), and fibrinogen \((R^2=0.41)\). The RegulomeDB does not have data for lead SNP rs4378999.

rs7697556 (ADAMTS3): One gene is found within 500kb of our lead marker, rs7697556. ADAM metalloprotease with thrombospondin type 1 motif, 3 (ADAMTS3) is located 80 kb upstream of our variant, rs7697556. While there is no established role for ADAMTS3 in obesity-related traits, there are a number of variants within and near this gene associated with relate anthropometric and cardiometabolic traits, including height, lipid metabolism, and metabolites. From there is no score assigned for our lead SNP in the RegulomeDB.

rs10269774 (CDK6): A total of 10 genes are found within 500 kb of the lead marker, rs10269774. The SNP is located within an intron in cyclin-dependent kinase 6 (CDK6). CDK family members are important regulators of cell cycle progression. GWAS have reported associations between CDK6 variants with height. The CDK6-rs2282978 associated with height is in complete LD with our lead marker (rs10269774: R^2=1, D'=1). Also, GWAS identified associations between CDK6 variants with white blood cell counts and rheumatoid arthritis. CDK6 rs42041 is associated with juvenile idiopathic arthritis (JIA), and patients with JIA are significantly shorter and more often overweight or obese than controls. Research suggests that the microRNA-103a-3p controls proliferation and osteogenic differentiation of human adipose tissue-derived stromal cells by binding to specific target sequences in the CDK6 mRNA 3'-untranslated region. Another study in the human placental transcriptome found that CDK6 mRNA levels correlated with offspring birth weight and birth weight percentiles.

rs10269774 is located in enhancer regions (H3K4Me1 and H3K27ac) with histone modification enrichment in mammary epithelial tissue and lymphoblastoid cell lines. rs10269774 was suggested to have cis-acting associations with five gamma-glutamyltransferase (GGT) family gene expression in lymphoblastoid of Yoruba population \((p=6E-05)\). Elevated serum GGT is associated with waist circumference, BMI, visceral fat area, triglyceride levels, metabolic syndrome, coronary artery calcification, and biomarkers of atherosclerosis, arterial stiffness, incident CVD and death. rs10269774 is located near to several transcription factor binding sites (CTCF, EP300, JUN, POLR2A, FOS, NFIC, and RFX5, among others).

rs9409082 and rs9408815 (TMEM38B): A total of 3 genes are found within 500 kb of the lead markers rs9409082 and rs9408815. At 364 kb downstream of rs9409082 is located TMEM38B (transmembrane
rs6012558 (ARFGEF2): A total of 11 genes are found within 500 kb +/- of our lead SNP, rs6012558, which is 6,989 bp upstream of ARFGEF2 (ADP-ribosylation factor guanine nucleotide-exchange factor 2). ARFGEF2’s primary function involves intracellular trafficking. Our lead variant is 86,866 bp upstream of PREX1 (phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor 1), a gene which encodes a protein involved in intracellular signaling, lipid and protein binding, and regulation of GTPase activity. PREX1 is primarily expressed in the blood leukocytes and brain. Recent mouse models indicate that PREX1 may be important for the regulation of thermogenic potential of brown adipose tissue and white preadipocytes, making this gene very important for energy expenditure. Additionally, rs6012558 is a significant (<5% FDR) cis-acting expression quantitative trait locus (cis-eQTL) for ARFGEF2 (subcutaneous adipose and sigmoid colon tissues), CSE1L (artery, thyroid, subcutaneous adipose, esophagus mucosa, and skeletal muscle tissues), and STAU1 (transformed fibroblast cells) (GTEx). Additional evidence that this variant lies in a potentially important regulatory region includes a RegulomeDB score of 4, it is nearby (<500 kb +/- and R^2>0.7) other variants that rest in active enhancers for ARFGEF2, other cis-eQTLs for ARFGEF2 (monocytes, whole blood, cerebellum, and temporal cortex), DDX27 (monocytes), C2orf199 (monocytes), CSE1L (whole blood), and PREX1 (Cerebellum and Temporal Cortex) (HaploReg and UCSC Browser). Our lead SNP is within 500 kb +/- of several previously identified GWAS SNPs for multiple traits, the nearest of which is rs6012564 associated with tendency toward anger (distance=10kb); however, all of these are in low LD with rs6012558 (R^2<0.3).

rs4141488 (GRIN2A): There are only two genes within 500 kb +/- of our lead SNP, rs4141488, which lies 218 kb downstream of GRIN2A (glutamate receptor, ionotropic, N-methyl D-aspartate 2A). The primary function of GRIN2A is to assist in controlling long-term memory and learning through regulation and efficiency of synaptic transmission. These receptors are essentially the gateway for calcium into post-synaptic cells. Variants in this gene have been associated with various forms of epilepsy, sleep patterns, delayed psychomotor development, speech difficulties, seizures, mental retardation, and various mental disorders, including heroin addiction. The only other gene within 500 kb of rs4141488 is C16orf72; little is known about the function of this gene. While GTEx revealed no significant eQTLs nearby our lead variant, there is some evidence that this locus may lie within an important regulatory region. RegulomeDB provided a score of 5 (minimal binding evidence) for rs4141488. Additionally, HaploReg and UCSC browser show that our lead SNP and variants in high LD...
(R²>0.7) are within active enhancer regions for several tissues, including liver, fetal leg muscle, smooth stomach and intestinal muscle, cortex, and several embryonic and pluripotent cell types; and within altered binding motifs for EWSR1-FLI1, Elf3, STAT, CDP, HNF1, and SOX. Our lead SNP is within 500kb +/- of several previously identified GWAS SNPs for multiple traits, the nearest of which is rs17550532 associated with sudden cardiac arrest. Other associations in this region include behavioral disinhibition, venous thromboembolism, and Transforming Growth Factor-β1; however, all of these are in low LD with rs4141488 (R²<0.4).

rs1545348 (RAI14): Our lead SNP, rs1545348, lies within the intron of RAI14 (Retinoic Acid Induced 14), although very little is known about the function of this gene in humans. There are four additional genes within 500 kb +/- of rs1545348, including RAD1 (RAD1 checkpoint DNA exonuclease) 187 kb upstream. RAD1 encodes a protein involved in stopping the cell cycle in response to DNA damage, as well as recruiting other proteins responsible for DNA repair, including in response to stress caused by cigarette smoke. There is strong evidence of a regulatory role within the region surrounding our lead variant (RegulomeDB score 4, minimal binding evidence). One significant (beta=-0.28, P=5.3E-6) eQTL between rs1545348 and TTC23L was found in sun exposed skin tissue (lower leg) (GTEx). Additionally, HaploReg and the UCSC browser reveal that the region surrounding our lead variant (+/- 500 kb, R²>0.7) harbors marks of open and active chromatin and DNase hypersensitive regions across multiple tissues, including cancer, pluripotent, and normal tissue, brain and adipose tissue among others. Traits with nearby GWAS associations include several metabolite markers and left ventricular mass, although each of these associations are in low LD with rs1545348.

rs6470765 (GSDMC): There are three genes within 500 kb +/- of our lead SNP, rs6470765, which lies within an intron of GSDMC (gasdermin C). There is very little known about the function of GSDMC. Our lead SNP also lies 80 kb downstream of FAM49B (family with sequence similarity 49, member B). Similar to CDK6, a gene nearby another one of our novel variants, rs10269774, FAM49B is a target of BACH1 transcription factor, which is involved in cellular response to oxidative stress and management of the cell cycle. Also, ASAP1 (ArfGAP With SH3 Domain, Ankyrin Repeat And PH Domain 1), a gene located 328 kb upstream of our association signal, may be involved in the differentiation of fibroblasts into adipocytes. There is moderate evidence for the functional role of lead variant in regulation of gene expression (RegulomeDB score of 6: minimal binding evidence). However, the GTEx database indicates that rs6470765 is a significant eQTL for GSDMC in skeletal muscle, sun-exposed skin, and mucous in the esophagus. Furthermore, HaploReg and the UCSC Browser highlight moderate evidence for regulatory elements in high LD >0.9, including DNase hypersensitive regions, and active enhancer and promoter regions in >20 tissue types (e.g. lung, adipose, skeletal muscle, epidermal and esophageal tissues, and many stem/pluripotent cell types). Our lead variant is within several altered binding sites for FOX1, FOX2 and SOX. Last, our lead SNP is in high LD with other potential cis-eQTLs for GSDMC. Nearby associations with other traits include height, hip circumference adjusted for BMI, and inflammatory bowel disorder.

rs6076699 (PRNP): There are seven genes within 500 kb +/- of our lead SNP, rs6076699. The lead SNP is 100kb upstream of PRNP (prion protein) is likely a signaling transducer involved in multiple biological processes related to nervous system, immune system, and general cellular functions. Mutations in the repeat region as well as elsewhere in this gene have been associated with Creutzfeldt-Jakob disease, fatal familial insomnia, Gerstmann-Straussler disease, Huntington disease-like 1, and kuru. Alternate forms of the oligomers have been shown to form in response to oxidative stress caused by copper exposure. Copper is present in cigarette smoke and elevated in serum of smokers, but is not
outside of safe ranges according the U.S. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, and Office on Smoking and Health.147,148 Our lead SNP is 136 kb upstream from a related gene, PRND (prion protein 2), which is biochemically and structurally similar to PRNP.149 Like PRNP, mutations in this gene may also be involved in neurocognitive disorders, although there are only weak associations.150,151 A third prion protein (testes specific, PRNT) is found 145 kb away from our lead SNP; however no much is known about the function of this gene.

Other nearby genes include SLC23A2 (Solute Carrier Family 23 [Ascorbic Acid Transporter], Member 2), ADRA1D (Adrenoceptor Alpha 1D), SMOX (Spermine Oxidase), and RASSF2 (Ras association [RalGDS/AF-6] domain family member 2). SLC23A2 is essential for the uptake and transport of Vitamin C, which is an important nutrient for DNA and cellular repair in response to oxidative stress both directly and through supporting the repair of Vitamin E after exposure to oxidative agents.152-155 Furthermore, this region is associated with success in smoking cessation and is implicated in addictive behaviors in general.156,157 Nearby GWAS-identified associations include preeclampsia, and height.158,159 There is little evidence that our association signal is involved in regulation of gene expression (RegulomeDB score-5: minimal binding evidence).18 While our tag SNP is located within an active enhancer region (open chromatin marks, DNase hypersensitivity, and several transcription factor binding motifs), this activity appears tissue specific (sex-specific tissues and lungs).21,111 There are no other significant regulatory elements in high LD with rs607699.21,73

Waist-to-Hip Ratio adjusted for BMI (WHRadjBMI)
rs670752 (BBX): There are only three genes within 500 kb of our lead SNP, rs670752, which lies within an intron of BBX (Bobby Sox Homolog [Drosophila]). While there is little known about the function of BBX, another nearby intronic variant, rs6437740, has been associated with smoking behavior in a previous GWAS.159 Other nearby genes include CCDC54 (coiled-coil domain containing 54) and CD47 (CD47 molecule). Much is known about the function of CD47 due to mouse models. CD47 encodes a cell surface antigen involved in immune response to bacteria, cell adhesion, inflammatory response, and cell to cell signaling.160-162 CD47 expression is significantly decreased in obese individuals and negatively correlated with BMI, WC, and HIP in RBC.

Conversely, in mouse models, CD47 deficient mice show decreased weight gain on high fat diets, increased energy expenditure, improved glucose profile, and decreased inflammation.164 Our lead SNP, rs670752, has a score of 6 (very little binding evidence) in RegulomeDB and no significant eQTLs were identified in GTEx.73 However, our tag SNP was identified as a significant eQTL for BBX in brain tissue in HaploReg.21 Additionally, multiple SNPs in high LD with rs670752 provide several lines of evidence for nearby regulatory elements (e.g. active promoters, transcription factor binding motifs, strong and poised enhancers), mostly in pluripotent and embryonic cell lines, but also blood cell lines and brain tissue.21,111

rs589428 (EHMT2). A total of seventy-seven genes are found near our lead SNP, rs589428, which is intronic within EHMT2 (Euchromatic Histone-Lysine N-Methyltransferase 2). EHMT2 encodes a histone methyltransferase, a group of genes involved in repression of transcription through the regulation of chromatin state.165 The lead SNP is 302kb downstream of TNF. In patients with end-stage renal disease (ESRD) on long-term hemodialysis (HD), the SNP in the promoter region of the IL-6 and TNF-alpha, and IL-10, show a strong association with indices of comorbidity and function, and biological and nutritional markers.166 TNF-alpha promotes bone loss and inhibits bone formation and has an important role as a mediator of skeletal damage in inflammatory arthritis.167-169 TNF is the master regulator of other inflammatory cytokines and the major cytokine in the pathogenesis of chronic inflammatory disease.171 TNF-alpha exerts an important influence on adipose tissue metabolism and function. It inhibits the
expression of two major adipose tissue differentiation regulators: CCAAT and PPARγ-2. TNF-alpha promoter methylation levels could be involved in the susceptibility to stroke and correlates with increased risk of coronary artery disease. The risk of early childhood wheeze associated with early maternal smoking may be modified by TNF. The lead SNP is also 287kb upstream of NCR3, which is associated with pulmonary function.

The top SNP is 17.5kb upstream of NEU1 (Sialidase 1 (Lysosomal Sialidase)). The activity of NEU1 is higher in epididymal fat and lower in the livers of two strains of obese and diabetic mice. Fluctuations in NEU1 activity might be associated with the pathological status of these tissues in obesity. The lead SNP is 50kb downstream of HSPA1B. Functional HSPA1B variants are associated with lung cancer risk and survival. The top SNP is 65kb upstream of CFB. Increased concentrations of circulating binding factors fH and fB in subjects with altered glucose tolerance could reflect increased SVC-induced activation of the alternative pathway of the complement in omental adipose tissue linked to insulin resistance and metabolic disturbances. The top SNP is 91kb upstream of STK19, which has been reported to be a pleiotropic gene for metabolic syndrome and inflammation and is associated with TG, BMI, WAISt, SBP and inflammatory markers including plasminogen activator inhibitor 1 (PAI-1) and white blood cell count (WBCC). Our top SNP is 102kb upstream of C4A, which was identified as novel potential adipokine candidate regulator of obesity and adipose regions between visceral and subcutaneous adipose tissue. The Top SNP is 102kb upstream of C4B. The carriers of C4B*Q0 (silent allele for the C4B gene) have a substantially increased risk to suffer from myocardial infarction or stroke. Compared to controls, C4B*Q0 carrier frequency was significantly higher at diagnosis in Icelandic smokers with angina pectoris (AP) or acute myocardial infarction (AMI) and Hungarian smokers with severe coronary artery disease, while no such difference was seen in nonsmokers. These findings indicate that C4B*Q0 genotype can be considered as a major covariate of smoking in precipitating the risk for AMI and associated mortality. The top SNP is 150kb upstream of DDAH2 in which SNP rs9267551 may confer increased risk for type 2 diabetes by affecting insulin sensitivity through increased asymmetric dimethylarginine (ADMA) levels.

Our top SNP is 222kb downstream of APOM. The PCSK9 pathway contributes to plasma apoM regulation in humans and the influence of PCSK9 on circulating apoM appears to be modified by adiposity. In addition, APOM expression is related to FEV1/FVC (forced expiratory volume 1/forced vital capacity) ratio and per cent emphysema. The top SNP is 261kb downstream of AGER/RAGE. The lower level of soluble RAGE/AGER is associated with a number of components of metabolic syndrome (central obesity, hypertension, and hyperglycemia). Soluble RAGE is inversely associated with pancreatic cancer risk among Finnish male smokers. The RAGE(2) haplotype is associated with diabetic nephropathy (DN) in type 2 diabetics and with earlier DN onset and, thus, can be regarded a marker for DN. RAGE, via its interaction with ligands, serves as a cofactor exacerbating diabetic vascular disease. Serum endogenous secretory RAGE (esRAGE) levels were inversely correlated with BMI and serum HDL-cholesterol. In healthy subjects plasma levels of sRAGE were negatively correlated with BMI and waist/hip ratio supporting a possible protective role for these proteins before any evidence of diabetic or vascular complications.

The top SNP is 263 downstream of AIF1. The serum AIF-1 concentrations were positively correlated with levels of fasting plasma glucose, hemoglobin A1c, triglycerides, and uric acid, and with WC and BMI, and were inversely correlated with HDL cholesterol levels. Also, the variants in AIF1 show evidence of association with adult obesity in the Greek population. The top SNP is 306 downstream of LTA. SNPs in LTA are associated with chronic kidney disease in Type 2 diabetes. The variability of LT-alpha
genotypes may have potential implications for individual susceptibility to asthma in atopic or in ever-smoking Chinese adults in Hong Kong. The genome-wide association studies have reported the associations within 1Mb of region for age at menopause ($R^2=0.32$), telomere length ($R^2=0.22$), idiopathic membranous nephropathy ($R^2=0.45$), chronic hepatitis B infection ($R^2=0.45$) and phospholipid levels (plasma) ($R^2=0.23$). This lead SNP is associated with regulatory motifs changed at Bcl6b, NF-kappaB, Pou5f1; associated with enhancer histone marks in stomach mucosa, HSMM cell derived skeletal muscle myotubes cell tissue; and in eQTL in various tissues including subcutaneous adipose, visceral omentum, lung and skeletal muscle tissues. The lead SNP is associated with eQTL in tibial artery and blood tissues from GTEx analysis. The RegulomeDB score for the lead SNP is 1f.

rs1856293 (EYA4): A total of nine genes are found near our lead SNP, rs1856293. The lead SNP is 342kb downstream of RPS12. RPS12 is a potential target gene of microRNA-377, which has been consistently upregulated in in vitro diabetic nephropathy (DN) models and in in vivo DN mouse models. If RPS12 is also upregulated in the diabetic milieu, it may contribute to the progression of DN. RPS12 has been reported to be a strong candidate for diabetic nephropathy. In addition, in the study of E3 rats, there were significant positive correlations between TG and the expression of RPS12 gene. The lead SNP is 83kb upstream of EYA4. Serum methylation levels of EYA4 were significant discriminants between stage I colorectal cancer and healthy controls and high methylation of the EYA4 gene is associated with ulcerative colitis with colorectal cancer. The lead SNP is 446kb upstream of VNN1. Alternative splicing in VNN1 is associated with colorectal cancer. The combination of VNN1 and MMP9 may be used as a blood biomarker panel for the discrimination of pancreatic cancer-associated diabetes from type II diabetes. There is no reported GWAS signal in high LD with the lead SNP. This lead SNP is associated with regulatory motifs changed at Esr2, LRH1, Myf_3, Sin3Ak_disc3 and T3R; and associated with enhancer histone marks in ESDR, SKIN and brain tissue. The RegulomeDB score for the lead SNP is 6.

rs2001945 (TRIB1): There are five protein coding genes within 500 kb+/- of our lead SNP, rs2001945, which lies 27 kb downstream from TRIB1. TRIB1 (tribbles pseudokinase 1) encodes a protein involved in ATP binding and the MAPK/ERK1/2 pathway. Very little is known about the function of the other nearby genes, including NSMCE2 (non-SMC element 2, MMS21 homolog), KIAA0196 (strumpellin), SQLE (qualeine epoxidase), and ZNF572 (Zinc Finger Protein S72). GTEx identified no significant eQTLs for our lead SNP; however, RegulomeDB provided a score of 4 (minimal binding evidence). Further, HaploReg UCSC Genome Browser reveal multiple lines of evidence across multiple tissues, including cis-eQTLs between rs2001945 for TRIB1 and NSMCE2 in brain tissue, strong DNase hypersensitivity clusters both at the association peak and across SNPs in high LD with our lead SNP, transcription factor binding motifs, and open chromatin marks primarily in Human Umbilical Vein Endothelial Cells (HUVEC). There are several nearby previously-identified GWAS signals for related cardiometabolic and digestion-related traits, including lipids (e.g. triglycerides, LDL, HDL), adiponectin, liver enzyme levels, gestational age, inflammatory bowel disease, Crohn's disease, and metabolite levels.

rs17065323 (SMIM2): A total of 6 genes are found within 500 kb of the lead marker, rs17065323. The SNP rs17065323, which is located 23.19 kb downstream of the long intergenic non-protein coding RNA 284 (LINC00284, 13q14.11), showed suggestive association with uric acid levels (p=8.7E-6). Variants of the LACC1 (laccase (multicopper oxidoreductase) domain containing 1), at 159.72 downstream of rs17065323, were genome-wide associated with Crohn's disease and a LACC1 mutant showed evidence of association with systemic juvenile idiopathic arthritis. In addition, GWASs have suggested
associations between variants on 13q14 with response to tocilizumab in rheumatoid arthritis (p=2E-7\textsuperscript{25}), antineutrophil cytoplasmic antibody-associated vasculitis (p=3E-6\textsuperscript{26}), and myotrophic lateral sclerosis (p=4E-6, \textsuperscript{27}), as well as SERP2 genotype-carbohydrate interaction influencing fasting insulin and homeostasis model assessment of insulin resistance (p=7E-6 and p=5E-6, respectively \textsuperscript{28}). The nearest protein-coding gene to our tag SNP is SMIM2 (Small Integral Membrane Protein 2), located 89.5 kb upstream; however, very little is known about the function of SMIM2.

rs1049281 (HLA-C): Eighty-six genes are found within 500kb of rs1049281, which lies within the HLA-C gene at 6p21.3. HLA-C encodes an HLA class I heavy chain paralogue found in nearly all cells and important in the function of the immune system. There is strong evidence that our SNP is in a region likely to affect binding activity and gene expression in adipose tissue (RegulomeDB\textsuperscript{18} score 1f). Over 100 alleles of the HLA-C gene have been described, and HLA-C has been associated with risk of various autoimmune diseases which can influence adiposity, including Type I diabetes, celiac disease, and psoriatic arthritis \textsuperscript{229,230}. Our lead SNP is 314569 bp downstream of DPCR1, a gene associated with diffuse panbronchiolitis, a chronic inflammatory lung disease \textsuperscript{231}. A variant near this gene (rs9368649), has been suggestively associated with smoking status (ever smoker) and pack years (P<1.3E-07)\textsuperscript{232}, but not at GWS. This SNP is not in high LD with our lead SNP (R\textsuperscript{2}=0.152, D\textsuperscript{'}=0.902). Our lead SNP is 190789 bp upstream of HCP5, a lncRNA. A variant (rs12175489) near this gene was suggestively associated (p=2.13E-06) with visceral adipose tissue (VAT) in men \textsuperscript{103}, but this variant is also not in high LD with our lead SNP (R\textsuperscript{2}=0.022, D\textsuperscript{'}=0.478). Our lead SNP is 336394bp upstream of AIF1, 310030bp downstream of NCR3, and 341847 upstream of BAT2. Three variants in this region [rs2260000 (R\textsuperscript{2}=0.122, D\textsuperscript{'}=0.526), rs1077393 (R\textsuperscript{2}=0.114, D\textsuperscript{'}=0.434), and rs2844479 (R\textsuperscript{2}=0.100, D\textsuperscript{'}=0.523] have been previously associated with variation in weight\textsuperscript{233}. Another variant near NCR3 (rs2070600) has been previously associated with ever-smoking and lung function, but is not in high LD with our lead SNP (R\textsuperscript{2}=0.137, D\textsuperscript{'}=0.642)\textsuperscript{176,232}. Our lead SNP is 340905bp downstream of VARS2, and a variant near this gene (rs7751505) has been suggestively associated with height change (P<4.05 x 10\textsuperscript{-6}), though it is not in LD with our top SNP (R\textsuperscript{2}=0.054, D\textsuperscript{'}=0.569). Two other variants in the region have been previously associated with extremes of height (p<5E-08), one of which is in strong LD with our lead SNP (rs2247056, 28923bp from rs1049281: R\textsuperscript{2}=0.814, D\textsuperscript{'}=1.000; rs7741091: R\textsuperscript{2}=0.093, D\textsuperscript{'}=0.652)\textsuperscript{77}.

SUPPLEMENTARY NOTE 3. Detailed summary of eQTL methods and results.

eQTL Methods

We used two approaches to systematically explore the role of novel loci in regulating gene expression. First, to gain a general overview of the regulatory role of newly identified GWAS regions, we conducted an eQTL lookup using >50 eQTL studies\textsuperscript{234}, with specific citations for >100 datasets included in the current query: 1) Blood cell related eQTL studies included fresh lymphocytes\textsuperscript{235}, fresh leukocytes\textsuperscript{236}, leukocyte samples in individuals with Celiac disease\textsuperscript{237}, whole blood samples\textsuperscript{73,238-256}, lymphoblastoid cell lines (LCL) derived from asthmatic children\textsuperscript{257,258}, HapMap LCL from 3 populations\textsuperscript{259}, a separate study on HapMap CEU LCL\textsuperscript{260}, additional LCL population samples\textsuperscript{261-267}, neutrophils\textsuperscript{268,269}, CD19+ B cells\textsuperscript{270}, primary PHA-stimulated T cells\textsuperscript{261,264}, CD4+ T cells\textsuperscript{271}, peripheral blood monocytes\textsuperscript{267,270,272-275}, long non-coding RNAs in monocytes\textsuperscript{276} and CD14+ monocytes before and after stimulation with LPS or interferon-gamma\textsuperscript{277}, CD11+ dendritic cells before and after Mycobacterium tuberculosis infection\textsuperscript{278} and a separate study of dendritic cells before or after stimulation with LPS, influenza or interferon-beta\textsuperscript{279}, Micro-RNA QTLs\textsuperscript{280,281}, DNase-I QTLs\textsuperscript{282}, histone acetylation QTLs\textsuperscript{283}, and ribosomal occupancy QTLs\textsuperscript{284} were also queried for LCL. Splicing QTLs\textsuperscript{285} and micro-RNA QTLs\textsuperscript{286} were queried in whole blood. 2) Non-blood cell tissue eQTLs searched included omental and subcutaneous adipose tissues\textsuperscript{73,238,256,263,287}, visceral adipose tissue\textsuperscript{256}, stomach\textsuperscript{287}, endometrial carcinomas\textsuperscript{288}, ER+ and ER- breast cancer tumor
Further mRNA and micro-RNA QTLs were also queried for gluteal and abdominal adipose 313 and liver 314. Methylation QTLs were queried in pancreatic islet cells 315.

Additional eQTL data was integrated from online sources including ScanDB (http://www.scandb.org/newinterface/about.html), the Broad Institute GTEx Portal, and the Pritchard Lab (eQTL.uchicago.edu). Cerebellum, parietal lobe and liver eQTL data were downloaded from ScanDB. Cis-eQTLs were limited to those with P<1.0E-6 and trans-eQTLs with P<5.0E-8. Results for GTEx Analysis V4 for 13 tissues were downloaded from the GTEx Portal and then additionally filtered as described below [www.GTExportal.org]; thyroid, leg skin (sun exposed), tibial nerve, aortic artery, tibial artery, skeletal muscle, esophagus mucosa, esophagus muscularis, lung, heart (left ventricle), stomach, whole blood, and subcutaneous adipose tissue 73]. Splicing QTL (sQTL) results generated with sQTLseeker with false discovery rate P<0.05 were retained. For all gene-level eQTLs, if at least 1 SNP passed the tissue-specific empirical threshold in GTEx 73, the best SNP for that eQTL was always retained. All gene-level eQTL SNPs with P<1.67E-11 were also retained, reflecting a global threshold correction of P=0.05/(30,000 genes X 1,000,000 tests).

Second, since public databases with eQTL data do not have information available on current smoking status, we also conducted an eQTL association analysis using expression results derived from fasting peripheral whole blood collected. Total RNA was isolated from frozen PAXgene blood tubes (PreAnalytiX, Hombrechtikon, Switzerland) and amplified using the WT-Ovation Pico RNA Amplification System (NuGEN, San Carlos, CA) according to the manufacturers’ standard operating procedures. The obtained cDNA was hybridized to the Human Exon 1.0 ST Array (Affymetrix, Inc., Santa Clara, CA). The raw data were quantile-normalized, log2 transformed, followed by summarization using Robust Multi-array Average 327 and further adjusted for technical covariates, including the first principal component of the expression data, batch effect, and the all-probeset-mean residual. Study specific covariates in the association model included blood cell counts and cohort membership.

We evaluated all transcripts +/-1MB around each novel variant in the Framingham Heart Study while accounting for current smoking status, using the following four approaches similar to those used in our primary analyses of our traits:

**Model 1 (adjusted main effect of eQTL):** Expression ~ SNP + SMK + age + age-squared + sex + study specific covariates

**Model 2 (main effect of eQTL stratified by smoking status):** Expression ~ SNP + age + age-squared + sex + study specific covariates

**Model 3 (Interaction effect of eQTL):** Expression ~ SNP + SMK + SNP*SMK + age + age-squared + sex + study specific covariates
Model 4 (Joint effect of eQTL): Expression $\sim$ SNP + SMK + SNP*SMK + age + age-squared + sex + study specific covariates

Significance level was evaluated by FDR < 5% per eQTL analysis and across all loci identified for that model in the primary meta-analysis.

eQTL Results by Trait

Only significant cis-eQTLS in high LD with our novel lead SNPs ($r^2$>0.9, calculated in the CEU+YRI+CHB+JPT 1000 Genomes reference panel), or proxy SNPs, were retained for consideration.

For BMI, three of our seven novel SNPs across six loci that had at least one variant in high LD ($r^2$>0.9) with the tag SNP that is significantly (Online Methods) associated with expression of a gene transcript in the cerebellum and prefrontal cortex, or blood cell types, including EPHA3, TTC14, and INADL. Notably, our lead SNP, rs2481665, is a significant cis-eQTL for INADL, in prefrontal cortex tissue, and for INADL and LITD1 in whole blood after adjusting for SMK (false discovery rate, FDR<5%). For the joint main + interaction effect eQTL analysis, we identified one significant eQTL for a BMI associated variant (rs12902602) for three gene transcripts (PSMA4, CHRNA5, and CTSH).

For WCadjBMI, five of our 12 novel SNPs were in high LD with a cis-eQTL for gene transcripts in the cerebellum, temporal cortex, prefrontal cortex, lymphoblastoid cells, liver, lung, lymph, omental adipose, subcutaneous adipose, Primary PHA-stimulated T cells, skin, and blood cell tissues in publicly available databases. In our cis-eQTL analyses adjusting for SMK, four of our nine novel lead SNPs were significant cis-eQTLS for 14 gene transcripts in 12 genes. Additionally, for the joint main + interaction effect eQTL analysis, we identified that two variants that were associated with the expression of SEPT2, FARP2, PASK, and HDLBP (rs6743226) and KIF1B (rs17396340).

For WHRadjBMI, three of our six novel SNPs were in high LD with a nearby cis-eQTL for gene transcripts in subcutaneous adipose tissue and blood cell types. We identified five novel WHRadjBMI variants near significant cis-eQTLS for 49 gene transcripts after adjusting for SMK, the most significant of which was between our tag SNP rs1049281 and MSH5. Additionally, for the joint main and interaction effect eQTL analysis, we identified two novel WHRadjBMI variants (rs1049281, rs1856293) were associated with 19 gene transcripts.

Across all of our three obesity-related traits, the majority of significant cis-eQTLS from public databases are found in blood cell lines (63% of unique SNP-transcript associations) (Supplementary Table 16). However, as in previous eQTL analyses of obesity-associated variants, we identify cis-eQTLS in brain and adipose tissue. Further analyses are needed to determine if these tissue-specific eQTLS remain significant after accounting for SMK, but our de-novo analysis in whole blood samples from the Framingham Heart Study using models to account for SMK indicate that gene expression may underlie our association signals in some instances and smoking exposure may play a role in influencing these associations (Supplementary Tables 16-18).

SUPPLEMENTARY NOTE 4. Full list of acknowledgments, including study-specific acknowledgements.

Writing and analysis of this study for AEJ were supported by the American Heart Association (13POST16500011) and NIH (2T32HL007055-36), for TOK by the Danish Council for Independent
Research (DFF – 1333-00124 and Sapere Aude program grant DFF – 1331-00730B), and analyses performed by JP were funded through NIH (T32GM074905).

**Study Specific Acknowledgements**

AE: Genotyping was funded by Cavads B.V. Sander W. van der Laan is funded through grants from the Netherlands CardioVascular Research Initiative (“GENIUS”, CVON2011-19), and the Interuniversity Cardiology Institute of the Netherlands (ICIN, 09.001). Sander W. van der Laan and Saskia Haitjema are funded through a grant from FP7 EU project CVgenes@target (HEALTH-F2-2013-601456). Marten A. Siemelink acknowledges funding by the European Union (BiomarCaRE, grant number: HEALTH-2011-278913) and Technology Foundation STW (Stichting voor de Technische Wetenschappen, Project 11679). Claudia Tersteeg, Krista den Ouden, Mirjam B. Smeets, and Loes B. Collé are graciously acknowledged for their work on the DNA extraction. Astrid E.M.W. Willems, Evelyn Velema, Kristy M. J. Vons, Sara Bregman, Timo R. ten Brinke, Sara van Laar, Sander M. van de Weg, Louise M. Catanzariti, Arjan H. Schoneveld, Petra H. Homoed-van der Kraak, Aryan Vink, and Joyce E.P. Vrijenhoek are graciously acknowledged for their past and continuing work on the Athero-Express Biobank Study. We would also like to thank all the (former) employees involved in the Athero-Express Biobank Study of the Departments of Surgery of the St. Antonius Hospital Nieuwegein and University Medical Center Utrecht for their continuing work. Jessica van Setten is graciously acknowledged for her help in the quality assurance and quality control of the genotype data. Lastly, we would like to thank all participants of the Athero-Express Biobank Study. MAS is funded by the European Union (BiomarCaRE, grant number: HEALTH-2011-278913), and the technology foundation “Stichting voor de Technische Wetenschappen” through the Danone partnership program (Project 11679). SWvdL/SH: SWvdL/SH: SWvdL is funded through grants from the Netherlands CardioVascular Research Initiative (“GENIUS”, CVON2011-19) and the Interuniversity Cardiology Institute of the Netherlands (ICIN, 09.001). SWvdL and SH are both funded through the FP7 EU project CVgenes@target (HEALTH-F2-2013-601456).

AGES: The Reykjavik Study cohort originally comprised a random sample of 30,795 men and women born in 1907-1935 and living in Reykjavik in 1967. A total of 19,381 attended, resulting in 71% recruitment rate. Between 2002 and 2006, the AGES-Reykjavik study re-examined 5,764 survivors of the original cohort who had participated before in the Reykjavik Study. [Harris, T. B. et al. (2007). American Journal of Epidemiology, 165(9), 1076-1087. doi:10.1093/aje/kwk115]. This study has been funded by NIH contract N01-AG-1-2100, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament). The study is approved by the Icelandic National Bioethics Committee, VSN: 00-063. The researchers are indebted to the participants for their willingness to participate in the study.

ARIC: The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-C-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, N01-HC-55022, R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research. The project described was supported by Grant Number UL1 RR 025005 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH) and NIH Roadmap for Medical Research, and its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. The authors thank the staff and participants of the ARIC Study for their important contributions.
AUSTWIN: We acknowledge the contributions of many staff in the Genetic Epidemiology Unit, Queensland Institute of Medical Research, in interviewing study participants, sample processing and DNA extraction, and data management. Funding for aspects of this work was provided by the Australian National Health and Medical Research Council (241944, 339462, 389927, 389875, 389891, 389892, 389938, 442915, 442981, 496739, 552485, 552498), the EU 5th Framework Programme GenomeEUTwin Project (QLG2-CT-2002-01254), and the U.S. National Institutes of Health (AA07535, AA10248, AA11998, AA13320, AA13321, AA14041, AA17688, DA12854, MH66206). A portion of the genotyping on which this study was based was carried out at the Center for Inherited Disease Research, Baltimore (CIDR) (Illumina 370K scans on 4300 individuals), through an access award to our late colleague Dr. Richard Todd. Parts of the statistical analyses were carried out on the Genetic Cluster Computer, which is financially supported by the Netherlands Scientific Organization (NWO 480-05-003). R.P.S.M. was, and G.W.M. is, supported by National Health and Medical Research Council (NHMRC) Fellowship Schemes.

BHS: The Busselton Health Study acknowledges the generous support for the 1994/5 follow-up study from Healthway, Western Australia and the numerous Busselton community volunteers who assisted with data collection and the study participants from the Shire of Busselton. The Busselton Health Study is supported by Department of Health and the Office of Science of the Government of Western Australia.

BioMe (MSSM): The Mount Sinai BioMe Biobank is supported by The Andrea and Charles Bronfman Philanthropies.

BLSA: The BLSA was supported by the Intramural Research Program of the NIH, National Institute on Aging.

B58C: We acknowledge use of phenotype and genotype data from the British 1958 Birth Cohort DNA collection, funded by the Medical Research Council grant G0000934 and the Wellcome Trust grant 068545/Z/02. Genotyping for the B58C-WTCCC subset was funded by the Wellcome Trust grant 076113/B/04/Z. The B58C-T1DGC genotyping utilized resources provided by the Type 1 Diabetes Genetics Consortium, a collaborative clinical study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), National Human Genome Research Institute (NHGRI), National Institute of Child Health and Human Development (NICHD), and Juvenile Diabetes Research Foundation International (JDRF) and supported by U01 DK062418. B58C-T1DGC GWAS data were deposited by the Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research (CIMR), University of Cambridge, which is funded by Juvenile Diabetes Research Foundation International, the Wellcome Trust and the National Institute for Health Research Cambridge Biomedical Research Centre; the CIMR is in receipt of a Wellcome Trust Strategic Award (079895). The B58C-GABRIEL genotyping was supported by a contract from the European Commission Framework Programme 6 (018996) and grants from the French Ministry of Research.

CHS: This CHS research was supported by NHLBI contracts HHSN268201200036C, HHSN26820080007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086; and NHLBI grants U01HL080295, R01HL087652, R01HL105756, R01HL103612, R01HL130114, and R01HL120393 with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The
provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center. Subjects for the present study were selected from CHS participants who had donated DNA samples for storage and provided informed consent for participation in DNA studies of cardiovascular-disease-related traits. The content of this work is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

**CLHNS:** The Cebu Longitudinal Health and Nutrition Survey (CLHNS) was supported by National Institutes of Health grants DK078150, TW05596, HL085144 and TW008288 and pilot funds from RR20649, ES10126, and DK56350. We thank the Office of Population Studies Foundation research and data collection teams and the study participants who generously provided their time for this study.

**COLAUS:** The CoLaus study was and is supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation (grants 33CSCO-122661, 33CS30-139468 and 33CS30-148401). The authors thank Vincent Mooser and Dawn Waterworth, Co-PIs of the CoLaus study. Special thanks to Yolande Barreau, Mathieu Firmann, Vladimir Mayor, Anne-Lise Bastian, Binasa Ramic, Martine Morvanille, Martine Baumer, Marcy Sagette, Jeanne Eccokey and Sylvie Mermoud for data collection. SB is supported by the Swiss National Science Foundation (grant 3100AO-116323/1) and the Swiss Institute of Bioinformatics. ZK received financial support from the Leenaards Foundation, the Swiss Institute of Bioinformatics and the Swiss National Science Foundation (31003A-143914, 51RTP0_151019).

**CROATIA-Korcula:** We would like to acknowledge the contributions of the recruitment team in Korcula, the administrative teams in Croatia and Edinburgh and the people of Korcula. The SNP genotyping for the CROATIA-Korcula cohort was performed in Helmholtz Zentrum München, Neuherberg, Germany. The study was financed by the Medical Research Council UK, the Ministry of Science, Education and Sport in the Republic of Croatia (grant number 108-1080315-0302) and the Croatian Science Foundation (grant 8875).

**CROATIA-Vis:** We would like to acknowledge the staff of several institutions in Croatia that supported the field work, including but not limited to The University of Split and Zagreb Medical Schools, Institute for Anthropological Research in Zagreb and Croatian Institute for Public Health. The SNP genotyping for the CROATIA-Vis cohort was performed in the core genotyping laboratory of the Wellcome Trust Clinical Research Facility at the Western General Hospital, Edinburgh, Scotland. This study was supported through grants from the Medical Research Council UK, the Ministry of Science, Education and Sport of the Republic of Croatia (number 108-1080315-0302) and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947).

**DESIR:** This study was supported in part by grants from SFD ("Société Francophone du 358 Diabète"), CPER ("Contrat de Projets État-Région"), and ANR ("Agence Nationale de la 359 Recherche"). The D.E.S.I.R. study has been supported by INSERM contracts with CNAMTS, Lilly, Novartis Pharma and Sanofi-Aventis; by INSERM (Réseaux en Santé Publique, Interactions entre les déterminants de la santé), Cohortes Santé TGIR, the Association Diabète Risque Vasculaire, the Fédération Française de Cardiologie, La Fondation de France, ALFEDIAM, ONIVINS, Ardix Medical, Bayer Diagnostics, Becton Dickinson, Cardionics, Merck Santé, Novo Nordisk, Pierre Fabre, Roche, Topcon.
The DR's EXTRA Study was supported by grants to R. Rauramaa by the Ministry of Education and Culture of Finland (627;2004-2011), Academy of Finland (102318; 12885), Kuopio University Hospital, Finnish Diabetes Association, Finnish Heart Association, Päivikki and Sakari Sohlberg Foundation and by grants from European Commission FP6 Integrated Project (EXGENESIS); LSHM-CT-2004-005272, City of Kuopio and Social Insurance Institution of Finland (4/26/2010).

EGCUT: EGCUT received support from EU FP7 grant Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)-LPC 313010, targeted financing from Estonian Government IUT20-60, IUT24-6, Estonian Research Roadmap through the Estonian Ministry of Education and Research (3.2.0304.11-0312), Center of Excellence in Genomics (EXCEGEN), Development Fund from the University of Tartu (SP1GVARENG). This work was also supported by the US National Institute of Health [R01DK075787].

Ely: We are grateful to all the volunteers and to the staff of St. Mary's Street Surgery, Ely and the study team. The Ely Study was funded by the MRC (MC_U106179471) and Diabetes UK. Genotyping in the Ely and Fenland studies was supported in part by an MRC-GlaxoSmithKline pilot programme grant (G0701863).

EPIC: The EPIC Norfolk diabetes case cohort study is nested within the EPIC Norfolk Study, which is supported by programme grants from the Medical Research Council, and Cancer Research UK and with additional support from the European Union, Stroke Association, British Heart Foundation, Research into Ageing, Department of Health, The Wellcome Trust and the Food Standards Agency. Genotyping was in part supported by the MRC-GSK pilot programme grant. We acknowledge the contribution of the staff and participants of the EPIC-Norfolk Study.

EPIC-Norfolk: The EPIC Norfolk Study is funded by program grants from the Medical Research Council UK and Cancer Research UK, and by additional support from the European Union, Stroke Association, British Heart Foundation, Department of Health, Food Standards Agency, and the Wellcome Trust.

ERF: The ERF study as a part of EUROSPAN (European Special Populations Research Network) was supported by European Commission FP6 STRP grant number 018947 (LSHG-CT-2006-01947) and also received funding from the European Community's Seventh Framework Programme (FP7/2007-2013)/grant agreement HEALTH-F4-2007-201413 by the European Commission under the programme "Quality of Life and Management of the Living Resources" of 5th Framework Programme (no. QLG2-CT-2002-01254). High-throughput analysis of the ERF data was supported by joint grant from Netherlands Organization for Scientific Research and the Russian Foundation for Basic Research (NWO-RFBR 047.017.043). Exome sequencing analysis in ERF was supported by the ZonMw grant (project 91111025). We are grateful to all study participants and their relatives, general practitioners and neurologists for their contributions and to P. Veraart for her help in genealogy, J. Vergeer for the supervision of the laboratory work and P. Snijders for his help in data collection. Najaf Amin is supported by the Netherlands Brain Foundation (project number F2013(1)-28).

FamHS: The Family Heart Study was supported by grant R01-DK-089256 from NIDDK and grant R01HL117078 from NHLBI.

Fenland: The Fenland Study is funded by the Wellcome Trust and the Medical Research Council (MC_U106179471). We are grateful to all the volunteers for their time and help, and to the General Practitioners and practice staff for assistance with recruitment. We thank the Fenland Study...
Investigators, Fenland Study Co-ordination team and the Epidemiology Field, Data and Laboratory teams.

FramHS: This research was conducted in part using data and resources from the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. The analyses reflect intellectual input and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. This work was partially supported by the National Heart, Lung and Blood Institute’s Framingham Heart Study (Contract No. N01-HC-25195 and Contract No. HHSN268201500001I) and its contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278). A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center. This research was partially supported by grant R01-DKO89256 from the National Institute of Diabetes and Digestive and Kidney Diseases (MPIs: I.B. Borecki, L.A. Cupples, K. North).

FUSION: Support for FUSION was provided by NIH grants R01-DKO62370 (to M.B.), R01-DKO72193 (to K.L.M.), and intramural project number 1201-HG000024 (to F.S.C.). Genome-wide genotyping was conducted by the Johns Hopkins University Genetic Resources Core Facility SNP Center at the Center for Inherited Disease Research (CIDR), with support from CIDR NIH contract no. N01-HG-65403.

Gendian: The support of the physicians, the patients, and the staff of the Diabetes Zentrum Mergentheim (Head: Prof. Dr. Thomas Haak), the diabetes outpatient clinic Dr Nusser - Dr Kreisel, the dialysis centers KfH Amberg, KfH Bayreuth, KfH Deggendorf, KfH Donauwörth, KfH Freising, KfH Freyung, KfH Fürth, KfH Hof, KfH Ingolstadt, KfH Kelheim, KfH München Elsenheimerstraße, KfH München-Schwabing, KfH Neumarkt, KfH Neusäß, KfH Oberschleißheim, KfH Passau, KfH Plauen, KfH Regensburg Günststraße, KfH Regensburg Caritas-Krankenhaus, KfH Straubing, KfH Sulzbach-Rosenberg, KfH Weiden, Dialysezentrum Augsburg Dr. Kirschner, Dialysezentrum Bad Alexandersbad, KfH Bamberg, Dialysezentrum Emmering, Dialysezentrum Klinikum Landshut, Dialysezentrum Landshut, Dialysezentrum Pfarrkirchen, Dialysezentrum Schwandorf, Dr. Angela Götz, the medical doctoral student Johanna Christ and the Study Nurse Ingrid Lugauer. The expert technical assistance of Claudia Strohmeier is gratefully acknowledged. Phenotyping was funded by the Dr. Robert Pfleger-Stiftung (Dr Carsten A. Böger), the MSD Stipend Diabetes (Dr Carsten A. Böger) and the University Hospital of Regensburg (intramural grant ReForM A to Dr. A. Götz, ReForM C to Dr. Carsten Böger). Genome-wide genotyping was funded by the KfH Stiftung Präventivmedizin e.V. (Dr. Carsten A. Böger, Dr. Jens Brüning), the Else Kröner-Fresenius-Stiftung (2012_A147 to Dr Carsten A. Böger and Dr Iris M. Heid) and the University Hospital Regina Augustsburg (Dr Carsten A. Böger). Data analysis was funded by the Else Kröner-Fresenius Stiftung (Dr. Iris M. Heid and Dr. Carsten A. Böger: 2012_A147; Dr. Carsten A. Böger and Dr. Bernhard K. Krämer: P48/08//A11/08).

Generation Scotland (GS): We would like to acknowledge the contributions of the families who took part in the Generation Scotland: Scottish Family Health Study, the general practitioners and Scottish School of Primary Care for their help in recruiting them, and the whole Generation Scotland team, which includes academic researchers, IT staff, laboratory technicians, statisticians and research managers. Genotyping was performed at the Wellcome Trust Clinical Research Facility Genetics Core at Western General Hospital, Edinburgh, UK. GS:SFHS is funded by the Scottish Executive Health Department, Chief Scientist Office, grant number CZD/16/6. Exome array genotyping for GS: SFHS was funded by the Medical Research Council UK. MIM is a Wellcome Trust Senior Investigator, and an NIHR Senior Investigator.
GENOA: The Genetic Epidemiology Network of Arteriopathy (GENOA) study is supported by the National Institutes of Health, grant numbers HL054457, HL087660, and HL119443 from National Heart, Lung, Blood Institute. We thank Eric Boerwinkle, PhD from the Human Genetics Center and Institute of Molecular Medicine and Division of Epidemiology, University of Texas Health Science Center, Houston, Texas, USA and Julie Cunningham, PhD from the Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, MN, USA for their help with genotyping.

GLACIER: The GLACIER study was funded by project grants to Paul W. Franks from Novo Nordisk, the Swedish Heart-Lung Foundation, the Swedish Diabetes Association, Pålhlssons Foundation, the Swedish Research Council, Umeå University Career Development Award, and The Heart Foundation of Northern Sweden. Frida Renström was supported by a post-doctoral stipend from the Swedish Heart-Lung Foundation. The investigators thank the staff at the Wellcome Trust Sanger Institute for technical assistance with genotyping (WT098051 to the list of Wellcome Trust funded grants). The investigators are indebted to the study participants who dedicated their time and samples to these studies and the staff at the Umeå Medical Biobank and VIP for biomedical data collection and preparation.

GOOD: Financial support was received from the Swedish Research Council, the Swedish Foundation for Strategic Research, the ALF/LUA research grant in Gothenburg, the Lundberg Foundation, the Torsten and Ragnar Söderberg’s Foundation, the Västra Götaland Foundation, the Göteborg Medical Society, the Novo Nordisk foundation, and the European Commission grant HEALTH-F2-2008-201865-GEFOS. We would like to acknowledge Maria Nethander at the genomics core facility at University of Gothenburg for statistical analyses.

Goya: This study was conducted as part of the activities of the Gene-diet Interactions in Obesity project (GENDINOB, www.gendinob.dk) and the MRC centre for Causal Analyses in Translational Epidemiology (MRC CAiTE). We thank all the participants of the study. TSA was also funded by the GENDINOB project and acknowledges the same.

GxE: Our chief acknowledgement is to the participants in these studies for their willingness to contribute. We also thank Nurses Orgen Brown and Diedre Thomas for assistance with recruitment as well as past and present Laboratory technologists and drivers at TMRU for their invaluable technical assistance. This work was supported by NIH Grants R01HL53353 and R01DK075787.

Health2006: The Health2006 study was financially supported by grants from the Velux Foundation; the Danish Medical Research Council, Danish Agency for Science, Technology and Innovation; the Aase and Ejner Danielsens foundation; ALK-Abello’ A/S (Hørsholm, Denmark), Timber Merchant Vilhelm Bangs Foundation, MEKOS Laboratories (Denmark) and Research Centre for Prevention and Health, the Capital Region of Denmark. The Health2006 was approved by the Ethical Committee of Copenhagen (KA-20060011) and the Danish Data Protection Agency.

HERITAGE: The HERITAGE Family Study is supported by the National Heart, Lung, and Blood Institute Grants HL-45670 and HL118305.

HRS: The HRS is supported by the National Institute on Aging (NIA U01AG009740). The genotyping was funded separately by the National Institute on Aging (RC2 AG036495, RC4 AG039029). Our genotyping was conducted by the NIH Center for Inherited Disease Research (CIDR) at Johns Hopkins University.
Genotyping quality control and final preparation of the data were performed by the Genetics Coordinating Center at the University of Washington.

**HUNT2:** The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology NTNU), Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian Institute of Public Health.

**HYPERGENES:** The study was supported by the European Union (FP7-HEALTH-F4-2007-201550-HYPERGENES, HEALTH-2011.2.4.2-2-EU-MASCARA, HEALTH-F7-305507 HOMAGE and the European Research Council Advanced Researcher Grant-2011-294713-EPLORE); InterOmics project (PB05 MIUR-CNR Italian Flagship Project); The Fonds voor Wetenschappelijk Onderzoek Vlaanderen, Ministry of the Flemish Community, Brussels, Belgium (G.0881.13 and G.088013).

**IMPROVE:** IMPROVE was supported by the European Commission (Contract number: QLG1-CT-2002-00896), the Swedish Heart-Lung Foundation, the Swedish Research Council (projects 8691 and 0593), the Knut and Alice Wallenberg Foundation, the Foundation for Strategic Research, the Stockholm County Council (project 592229), the Strategic Cardiovascular and Diabetes Programmes of Karolinska Institutet and Stockholm County Council, the European Union Framework Programme 7 (FP7/2007-2013) for the Innovative Medicine Initiative under grant agreement n° IMI/115006 (the SUMMIT consortium), the Academy of Finland (Grant #110413), the British Heart Foundation (RG2008/08, RG2008/014) and the Italian Ministry of Health (Ricerca Corrente).

**InCHIANTI:** The InCHIANTI study baseline (1998-2000) was supported as a "targeted project" (ICS110.1/RF97.71) by the Italian Ministry of Health and in part by the U.S. National Institute on Aging (Contracts: 263 MD 9164 and 263 MD 821336).

**Inter99:** The Inter99 study was funded by: Danish Research Councils; The Health Foundation; The Danish Centre for Evaluation and Health Technology Assessment; Copenhagen County; Danish Heart Foundation; Ministry of Health and Prevention; Danish Pharmaceutical Association; Augustinus Foundation; Novo Nordisk; Velux Foundation; Becket Foundation and Ib Henriksens Foundation.

**KORA:** The KORA study was initiated and financed by the Helmholtz Zentrum München – German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF, 01ER1206 and 01ER1507 for IMH) and by the State of Bavaria. Furthermore, KORA research was supported within the Munich Center of Health Sciences (MC-Health), Ludwig-Maximilians-Universität, as part of LMUinnovativ. [PMID: 16032513] [PMID: 16032514]

**Lifelines:** The Lifelines Cohort Study, and generation and management of GWAS genotype data for the Lifelines Cohort Study is supported by the Netherlands Organization of Scientific Research NWO (grant 175.010.2007.006), the Economic Structure Enhancing Fund (FES) of the Dutch government, the Ministry of Economic Affairs, the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the Northern Netherlands Collaboration of Provinces (SNN), the Province of Groningen, University Medical Center Groningen, the University of Groningen, Dutch Kidney Foundation and Dutch Diabetes Research Foundation.

**LOLIPOP:** The LOLIPOP study is supported by the National Institute for Health Research (NIHR) Comprehensive Biomedical Research Centre Imperial College Healthcare NHS Trust, the British Heart Foundation (SP/04/002), the Medical Research Council (G0601966,G0700931), the Wellcome Trust
(084723/Z/08/Z) the NIHR (RP-PG-0407-10371), European Union FP7 (EpiMigrant, 279143) and Action on Hearing Loss (G51). The work was carried out in part at the NIHR/Wellcome Trust Imperial Clinical Research Facility. We thank the participants and research staff who made the study possible.

**LURIC:** We thank the LURIC study team who were either temporarily or permanently involved in patient recruitment as well as sample and data handling, in addition to the laboratory staff at the Ludwigshafen General Hospital and the Universities of Freiburg and Ulm, Germany. This work was supported by the 7th Framework Program (integrated project AtheroRemo, grant agreement number 201668 and RiskyCAD, grant agreement number 305739) of the European Union and by the INTERREG IV Oberrhein Program (Project A28, Genetic mechanisms of cardiovascular diseases) with support from the European Regional Development Fund (ERDF) and the Wissenschaftsoffensive TMO.

**MEC:** The Multiethnic Cohort study (MEC) characterization of epidemiological architecture is funded through the NHGRI PAGE program (U01HG004802 and its NHGRI ARRA supplement). The MEC study is funded through the National Cancer Institute (R37CA54281, R01 CA63, P01CA33619, U01CA136792, and U01CA98758).

**MESA:** MESA and the MESA SHARe project are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, UL1-TR-001079, and UL1-TR-000040. Funding for MESA SHARe genotyping was provided by NHLBI Contract N02-HL-6-4278. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center. The authors thank the MESA participants, as well as the Coordinating Centers, investigators, and study staff for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

**METSIM:** The METSIM study was funded by the Academy of Finland (grants no. 77299 and 124243).

**MRC NSHD:** This work was funded by the Medical Research Council (MC_UU_12019/1), the British Heart Foundation (RG/10/12/28456) and the Wellcome Trust (088869/B/09/Z). We are very grateful to the members of this birth cohort for their continuing interest and participation in the study. We would like to acknowledge the Swallow group, UCL, who performed the DNA extractions (Rousseau, et al 2006). DOI: 10.1111/j.1469-1809.2006.00250.x.

**MrOS Sweden:** This work was supported by the Swedish Research Council, the Swedish Foundation for Strategic Research, The ALF/LUA research grant in Gothenburg, the Lundberg Foundation, the Torsten and Ragnar Söderberg’s Foundation, Magnus Bergvall Foundation, Åke Wiberg Foundation, Tore Nilson Foundation and The Swedish Society for Medical Research.

**NHS:** The study was supported by grants from the National Heart, Lung, and Blood Institute (HL071981, HL034594, HL126024), the National Institute of Diabetes and Digestive and Kidney Diseases (DK091718, DK100383, DK078616), the Boston Obesity Nutrition Research Center (DK46200), and United States – Israel Binational Science Foundation Grant2011036.
This study was funded by the Netherlands Organization for Scientific Research (NWO) and The Netherlands Organisation for Health Research and Development (ZonMW) grants 904-61-090, 985-10-002, 904-61-193, 480-04-004, 400-05-717, Addiction-31160008, Middelgroot-911-09-032, Spinozapremie 56-464-14192, Center for Medical Systems Biology (CSMB, NWO Genomics), NBIC/BioAssist/RK(2008.024), Biobanking and Biomolecular Resources Research Infrastructure (BBMRI – NL, 184.021.007). VU University’s Institute for Health and Care Research (EMGO+) and Neuroscience Campus Amsterdam (NCA); the European Science Foundation (ESF, EU/QLRT-2001-01254), the European Community's Seventh Framework Program (FP7/2007-2013), ENGAGE (HEALTH-F4-2007-201413); the European Research Council (ERC Advanced, 230374, Starting grant 284 167), Rutgers University Cell and DNA Repository (NIMH U24 MH068457-06), the Avera Institute, Sioux Falls, South Dakota (USA) and the National Institutes of Health (NIH, R01D0042157-01A, MH081802, Grand Opportunity grant 1RC2 MH089951). Part of the genotyping and analyses were funded by the Genetic Association Information Network (GAIN) of the Foundation for the National Institutes of Health.

**NFC1966/Oxford Univ:** The Northern Finland Birth Cohort (NFBC) Research program, received financial support from Academy of Finland (1114194, 24300796), NHLBI grant 5R01HL087679 through the STAMPEED program (1R1LM083268-01), ENGAGE project and grant agreement HEALTH-F4-2007-201413, the Medical Research Council (grant G0500539, centre grant G0600705, PrevMetSyn), and the Wellcome Trust (project grant GR069224), UK. The program is currently being funded by the H2020-633595 DynaHEALTH action and Academy of Finland EGEA-project. University of Oxford, UK, was funded by the British Heart Foundation (grant code SP/13/2/30111), the European Commission (ENGAGE: HEALTH-F4-2007-201413), Medical Research Council (G0601261), and the Wellcome Trust (090532, 098381). M.-R.J. received funding from the European Union’s Horizon 2020 research and innovation programme [under grant agreement No 633595].

**ORCADES:** ORCADES was supported by the Chief Scientist Office of the Scottish Government, the Royal Society, the MRC Human Genetics Unit, Arthritis Research UK and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947). DNA extractions were performed at the Wellcome Trust Clinical Research Facility in Edinburgh. We would like to acknowledge the invaluable contributions of Lorraine Anderson and the research nurses in Orkney, the administrative team in Edinburgh and the people of Orkney.

**PIVUS:** PIVUS was supported by Knut and Alice Wallenberg Foundation (Wallenberg Academy Fellow), European Research Council (ERC Starting Grant), Swedish Diabetes Foundation (2013-024), Swedish Research Council (2012-1397, 2012-1727, and 2012-2215), Marianne and Marcus Wallenberg Foundation, County Council of Dalarna, Dalarna University, and Swedish Heart-Lung Foundation (20120197). The computations were performed on resources provided by SNIC through Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX) under Project b2011036. Genotyping was funded by the Wellcome Trust under awards WT064890 and WT086596. Analysis of genetic data was funded by the Wellcome Trust under awards WT098017 and WT090532. We thank the SNP&SEQ Technology Platform in Uppsala (www.genotyping.se) for excellent genotyping. Andrew P Morris is a Wellcome Trust Senior Fellow in Basic Biomedical Science under award WT098017.

**PREVEND:** The PREVEND genetics is supported by the Dutch Kidney Foundation (Grant E033), the EU project grant GENECURE (FP-6 LSHM CT 2006 037697), the National Institutes of Health (grant 2R01LM010098), The Netherlands organization for health research and development (NWO-Groot grant 175.010.2007.006, NWO VENI grant 916.761.70, ZonMw grant 90.700.441), and the Dutch Inter
PROSPER: The PROSPER study was supported by an investigator initiated grant obtained from Bristol-Myers Squibb. Prof. Dr. J. W. Jukema is an Established Clinical Investigator of the Netherlands Heart Foundation (grant 2001 D 032). Support for genotyping was provided by the seventh framework program of the European commission (grant 223004) and by the Netherlands Genomics Initiative (Netherlands Consortium for Healthy Aging grant 050-060-810).

QFS: The Quebec Family Study (QFS) was funded by multiple grants from the Medical Research Council of Canada and the Canadian Institutes for Health Research. This work was supported by a team grant from the Canadian Institutes for Health Research (FR-CN-CCT-83028).

RS1: We thank the Genetic Laboratory of the Department of Internal Medicine of the Erasmus MC and specifically Pascal Arp, Mila Jhamai, Marijn Verkerk, and Carolina Medina-Gomez for their help in creating the GWAS database and the creation and analysis of imputed data. The dedication, commitment, and contribution of inhabitants, general practitioners, and pharmacists of the Ommoord district to the Rotterdam Study are gratefully acknowledged. We also thank the patients participating in the Erasmus Stroke Study.

RS2: The Rotterdam study is supported by the Erasmus MC and Erasmus University Rotterdam; the Netherlands Organisation for Scientific Research; the Netherlands Organisation for Health Research and Development (Zorg onderzoek Nederland Medische Wetenschappen); the Research Institute for Diseases in the Elderly; the Netherlands Genomics Initiative; the Ministry of Education, Culture and Science; the Ministry of Health, Welfare and Sports; the European Commission (Directorate-General XII); and the Municipality of Rotterdam.

RS3: None of the funders had any role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of this article.

SardiNIA: We thank the many individuals who generously participated in this study. This work was supported by Contract NO1-AG-1-2109 from the National Institute of Aging, and in part by a grant from the Italian Ministry of Economy and Finance to the CNR for the Project “FaReBio di Qualità” to F Cucca. The efforts of GR Abecasis were supported in part by contract 263-MA-410953 from the NIA to the University of Michigan and by research grant HG002651 and HL084729 from the NIH.

SCARFSHEEP: The work was supported by the European Commission (LSHM-CT-2007-037273), the Swedish Heart-Lung Foundation, the Swedish Research Council (8691, 09533), the Knut and Alice Wallenberg Foundation, the Foundation for Strategic Research, the Torsten and Ragnar Söderberg Foundation, the Strategic Cardiovascular Programme of Karolinska Institutet and the Stockholm County Council and the Stockholm County Council (560183); the Magnus Bergvall Foundation, Stiftelsen för Gamla Tjänarinnor, and the Tore Nilsson and Fredrik och Ingrid Thurings Foundations.

SHIP: SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (grants no. 01ZZ603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania, and the network ‘Greifswald Approach to Individualized Medicine (GANI_MED)’ funded by the Federal Ministry of Education and Research (grant 03IS2061A). Genom-
wide data have been supported by the Federal Ministry of Education and Research (grant no. 03ZIK012) and a joint grant from Siemens Healthcare, Erlangen, Germany and the Federal State of Mecklenburg-West Pomerania. The University of Greifswald is a member of the Caché Campus program of the InterSystems GmbH.

**SORBS:** This work was supported by grants from the German Research Council (SFB- 1052 “Obesity mechanisms”, SPP 1629 TO 718/2-1), from the German Diabetes Association and from the DHFD (Diabetes Hilfs- und Forschungsfonds DeutschLand). Inga Prokopenko was funded in part through the European Community’s Seventh Framework Programme (FP7/2007-2013), ENGAGE project, grant agreement HEALTH-F4-2007-201413.

**SPT:** Our chief acknowledgement is to the participants in these studies for their willingness to contribute. We also thank Nurses Orgen Brown and Diedre Thomas for assistance with recruitment as well as past and present Laboratory technologists and drivers at TMRU for their invaluable technical assistance. This work was supported by NIH Grants R01HL53353 and R01DK075787.

**THISEAS:** Recruitment for The Hellenic study of Interactions between SNPs and Eating in Atherosclerosis Susceptibility (THISEAS) study was partially funded by a research grant (PENED 2003) from the Greek General Secretory of Research and Technology. We thank all the dieticians and clinicians for their contribution to the project and the Genotyping Facility at the Wellcome Trust Sanger Institute for SNP typing. Analysis was partly supported by BHF grant (Deloukas) RG/14/S/30893 and the Barts Cardiovascular Biomedical Research Unit which is supported and funded by the National Institute for Health Research.

**TRAILS:** TRAILS (TRacking Adolescents’ Individual Lives Survey) is a collaborative project involving various departments of the University Medical Center and University of Groningen, the Erasmus University Medical Center Rotterdam, the University of Utrecht, the Radboud Medical Center Nijmegen, and the Parnassia Bavo group, all in the Netherlands. TRAILS has been financially supported by grants from the Netherlands Organization for Scientific Research NWO (Medical Research Council program grant GB-MW 940-38-011; ZonMW Brainpower grant 100-001-004; ZonMw Risk Behavior and Dependence grant 60-60600-97-118; ZonMw Culture and Health grant 261-98-710; Social Sciences Council medium-sized investment grants GB-MaGW 480-01-006 and GB-MaGW 480-07-001; Social Sciences Council project grants GB-MaGW 452-04-314 and GB-MaGW 452-06-004; NWO large-sized investment grant 175.010.2003.005; NWO Longitudinal Survey and Panel Funding 481-08-013); the Dutch Ministry of Justice (WODC), the European Science Foundation (EuroSTRESS project FP-006), Biobanking and Biomolecular Resources Research Infrastructure BBMRI-NL (CP 32), the participating universities, and Accare Center for Child and Adolescent Psychiatry. We are grateful to all adolescents, their parents and teachers who participated in this research and to everyone who worked on this project and made it possible. Statistical analyses were carried out on the Genetic Cluster Computer (http://www.geneticcluster.org), which is financially supported by the Netherlands Scientific Organization (NWO 480-05-003) along with a supplement from the Dutch Brain Foundation.

**TwinsUK:** The study was funded by the Wellcome Trust; European Community’s Seventh Framework Programme (FP7/2007-2013). The study also receives support from the National Institute for Health Research (NIHR) BioResource Clinical Research Facility and Biomedical Research Centre based at Guy’s and St Thomas’ NHS Foundation Trust and King’s College London. SNP Genotyping was performed by The Wellcome Trust Sanger Institute and National Eye Institute via NIH/CIDR.
UKBB: Dr. Tyrrell is supported by a Diabetes Research and Wellness Foundation Fellowship. Prof. Frayling is supported by the European Research Council grant: 323195-SZ-245 50371-GLUCOSEGENES-FP7-IDEAS-ERC.

WGHS: The WGHS is supported by HL043851 and HL080467 from the National Heart, Lung, and Blood Institute, and CA047988 and UM1CA182913 from the National Cancer Institute (NCI), the Donald W. Reynolds Foundation and the Fondation Leducq, with collaborative scientific support and funding for genotyping provided by Amgen.

WHI: Funding support for the “Epidemiology of putative genetic variants: The Women’s Health Initiative” study is provided through the NHGRI PAGE program (U01HG007376, HG004790, and its NHGRI ARRA supplement). The WHI acknowledgment statement that you have is out of date. The statement should be The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C.

Whitehall: Dr. Kumari’s and Professor Kivimaki’s time on this manuscript was partially supported by the National Heart Lung and Blood Institute (NHLBI: HL36310). The Whitehall-II study has been supported by grants from the Medical Research Council (MRC); British Heart Foundation; Health and Safety Executive; Department of Health; National Institute on Aging (AG13196), US, NIH; Agency for Health Care Policy Research (HS06516); and the John D and Catherine T MacArthur Foundation Research Networks on Successful Midlife Development and Socioeconomic Status and Health.

YFS: The Young Finns Study has been financially supported by the Academy of Finland: grants 286284 (T.L.), 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), and 41071 (Skidi); the Social Insurance Institution of Finland; Kuopio, Tampere and Turku University Hospital Medical Funds (grant X51001 for T.L.); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation of Cardiovascular Research (T.L.); Finnish Cultural Foundation; Tampere Tuberculosis Foundation (T.L.); Emil Aaltonen Foundation (T.L.); and Yrjö Jahnsson Foundation (T.L.). The expert technical assistance in the statistical analyses by Ville Aalto and Irina Lisinen is gratefully acknowledged.

BIBLIOGRAPHY


1667  196. Mak, J.C. et al. Polymorphisms in the IL-4, IL-4 receptor alpha chain, TNF-alpha, and
1668  lymphotoxin-alpha genes and risk of asthma in Hong Kong Chinese adults. Int Arch Allergy
1671  Genet 41, 645-7 (2009).
1672  198. Levy, D. et al. Genome-wide association identifies OBFC1 as a locus involved in human leukocyte
1674  199. Stanescu, H.C. et al. Risk HLA-DQA1 and PLA2R1 alleles in idiopathic membranous
1676  200. Kim, Y.J. et al. A genome-wide association study identified new variants associated with the risk
1678  201. Walt, A.J., Bouwman, D.L., Weaver, D.W. & Sachs, R.J. The impact of technology on the
1681  202. Wang, Q. et al. MicroRNA-377 is up-regulated and can lead to increased fibronectin production
1683  203. McDonough, C.W. et al. A genome-wide association study for diabetic nephropathy genes in
1685  204. Lan, X. et al. Identification of differentially expressed genes related to metabolic syndrome
1687  205. Liu, Y. et al. Serum methylation levels of TAC1. SEPT9 and EYA4 as diagnostic markers for early
1690  4 (EYA4) gene promoter in non-neoplastic mucosa of ulcerative colitis patients with colorectal
1691  cancer: evidence for a field effect. Inflamm Bowel Dis 19, 2079-83 (2013).
1693  135, 2077-84 (2014).
1695  identified by peripheral blood-based gene expression profiles. Am J Gastroenterol 105, 1661-9
1696  (2010).
1697  209. Soubeyrand, S., Naing, T., Martinuk, A. & McPherson, R. ERK1/2 regulates hepatocyte Trib1 in
1701  211. Kim, Y.J. et al. Large-scale genome-wide association studies in East Asians identify new genetic
1705  213. Ko, A. et al. Amerindian-specific regions under positive selection harbour new lipid variants in
1707  214. Kamatani, Y. et al. Genome-wide association study of hematological and biochemical traits in a
1711  216. Aulchenko, Y.S. et al. Loci influencing lipid levels and coronary heart disease risk in 16 European
239. Fehrmann, R.S. et al. Trans-eQTLs reveal that independent genetic variants associated with a complex phenotype converge on intermediate genes, with a major role for the HLA. PLoS Genet 7, e1002197 (2011).


**Supplementary Figure 1.** Summary of overall study design and workflow for meta-analyses. All numbers provided represent the maximum number specific for that trait (BMI-red, WCadjBMI-blue, and WHRadjBMI-green) and strata (EUR-European descent participants, nonEUR-excluding European descent participants). Three studies provided GWAS data for EUR and nonEUR participants.

Phenotypes: BMI, WCadjBMI, WHRadjBMI

For SNPadjSMK, Smoker-only and Nonsmoker-only

---

**HapMap GWAS (EUR)**

# Studies: 39; 37; 36

GC (all SNPs)

**Stage 1 Meta-Analysis (EUR)**

GC (all SNPs)

**MetaboChip GWAS (EUR)**

# Studies: 18; 18; 17

GC (QT SNPs)

**Stage 2 Meta-Analysis (EUR)**

GC (QT SNPs)

**2-file Stage 1 + 2 Meta-Analysis (EUR)**

*Total N*_{EUR} = 210,323; 185,487; 167,884

**HapMap GWAS (NonEUR)**

# Studies: 6; 5; 4

GC (all SNPs)

**Stage 2 Meta-Analysis (NonEUR)**

GC (all SNPs)

**MetaboChip GWAS (NonEUR)**

# Studies: 4; 4; 4

GC (QT SNPs)

**Stage 2 Meta-Analysis (NonEUR)**

*Total N*_{NonEUR} = 30,935; 22,683; 21,283

**2-file Meta-Analysis (EUR + NonEUR)**

*Total N* = 241,258; 208,170; 189,167

Approaches 1-4
Supplementary Figure 2. Summary plots of discovery meta-analysis for Approach 1 primary meta-analyses. (A) Manhattan plot showing the loci identified in Approach 1 in primary meta-analyses, used to identify significant main effects loci (SNPadjSMK), in the primary meta-analyses association \(-\log_{10}P\) values for BMI-red, WCadjBMI-blue, and WHRadjBMI-green; (B) Manhattan plot showing the loci identified in Approach 1 excluding known regions +/- 500 kb and labeled with the nearest gene to the index SNP; (C) QQ-plot showing the Approach 1 P-values as observed against those expected under the null for each phenotypes separately (colored); (D) QQ-plot for Approach 1 after excluding known association regions. *PSMB10 locus is >500 +/- kb from previously identified index SNPs, but is not independent of known GWAS signals.
Supplementary Figure 3. Regional association plot for all loci identified in Approach 1 in primary meta-analyses, used to identify significant interaction (SNPadjSMK), in the primary meta-analyses for A) BMI, B) WCadjBMI, and C) WHRadjBMI, and ordered as they appear in Table 1. LD has been calculated using the combined ancestries from the 1000 Genomes Phase 1 reference panel. For comparison, each plot highlights the p-value for the tag SNP in Approach 1 (P_{adjSMK}), Approach 2 (P_{joint}), Approach 3 (P_{int}), current smokers (P_{SMK}), and in nonsmokers (P_{nonSMK}). EUR-European-only meta-analysis.
A)

BMI: rs10929925 – Approach 1

Position on chr2 (Mb)

Coronary artery calcification

Chronic kidney disease

LINC01248

SOX11

LINC01105

LOC400940

LINC01247

r^2

-\log_{10}(p-value)

Recombination rate (cM/Mb)

P_int

P_joint

P_adjSMK

P_SMK

P_nonSMK
BMI: rs6794880 – Approach 1

- **r^2**
- **Position on chr3 (Mb)**
- **Recombination rate (cM/Mb)**

**Obesity-related traits**

**Brain structure**

- **P_int**
- **P_joint**
- **P_adjSMK**
- **P_SMK**
- **P_nonSMK**
WCadjBMI: rs17396340 – Approach 1

Alcohol dependence (age at onset)
WCadjBMI: rs6743226 – Approach 1
WCadjBMI: rs7697556 – Approach 1

- log10(p-value)

Position on chr4 (Mb)

Lipid metabolism phenotypes

Metabolite levels

HIPadjBMI
Height

ADAMTS3
COX18
ANKRD17

Recombination rate (cM/Mb)
WCadjBMI: rs10269774 – Approach 1

- log10(p-value)

Recombination rate (cM/Mb)

Position on chr7 (Mb)

CYP51A1
ANKB1
GATA1
RBM48
CDK6
SAMD9

LRRD1
KRIT1
PEX1
MGC16142
LOC101927497
FAM133B
FAM133DP

Height
Height
Height
Height
Height

1 GWAS hit omitted
WCadjBMI: rs9409082 – Approach 1

-log10(p-value)

Recombination rate (cM/Mb)

Position on chr9 (Mb)

2 GWAS hits omitted

FKTN
TLR2
TMEM38B
MIR8081
LOC100996590

Menarche (age at onset)
Menarche and menopause (age at onset)
Height

r^2
0.2
0.4
0.6
0.8
1.0

P_{int}
P_{joint}
P_{adjSMK}
P_{SMK}
P_{nonSMK}
WCadjBMI: rs6012558 – Approach 1

- $\log_{10}(p$-value) vs. Recombination rate (cM/Mb)

- $r^2$ colors:
  - 0.2
  - 0.4
  - 0.6
  - 0.8
  - 1.0

Genes:
- PREX1
- ARFGGEF2
- STAUL
- DDX27
- KCNB1
- LOC102723483
- CSE1L
- ZNFX1
- ZFAS1
- SNORD12C
- SNORD12B
- SNORD12

Position on chr20 (Mb):
- 47.2
- 47.4
- 47.6
- 47.8
- 48

Parameters:
- QT interval
- Obesity
  - Height

$P_{int}$, $P_{joint}$, $P_{adjSMK}$, $P_{SMK}$, $P_{nonSMK}$

**Legend:**
- $P_{int}$
- $P_{joint}$
- $P_{adjSMK}$
- $P_{SMK}$
- $P_{nonSMK}$
C)

WHRadjBMI: rs1049281 – Approach 1

Position on chr6 (Mb)

-0.2 -0.4 -0.6 -0.8 -1.0

rs1049281

- log10(p-value)

0 2 4 6 8 10

r²

0.2 0.4 0.6 0.8

Recombination rate (cM/Mb)

0 20 40 60 80 100

Recombination rate

20 GWAS hits omitted

8 genes omitted

Height

Height

Hematology traits

Height

Renal function-related traits (eGRFcrea)

Height

Renal function-related traits (sCR)

Menopause (age at onset)

Position on chr6 (Mb)
**Supplementary Figure 4.** Summary plots of discovery meta-analysis for Approach 2 primary meta-analyses. (A) Manhattan plot showing the loci identified in Approach 2 in primary meta-analyses, used to identify significant joint main+interaction effects loci (SNPjoint), in the primary meta-analyses association –log10P-values for BMI-red, WCadjBMI-blue, and WHRadjBMI-green; (B) Manhattan plot showing the loci identified in Approach 2 excluding known regions +/- 500 kb and labeled with the nearest gene to the index SNP; (C) QQ-plot showing the Approach 2 P-values as observed against those expected under the null for each phenotypes separately (colored); (D) QQ-plot for Approach 2 after excluding known association regions.
Supplementary Figure 5. Regional association plot for all loci identified in Approach 2 in primary meta-analyses, used to identify significant interaction (SNPint), in the primary meta-analyses for A) BMI and B) WCAdjBMI, and ordered as they appear in Table 1. LD has been calculated using the combined ancestries from the 1000 Genomes Phase 1 reference panel. For comparison, each plot highlights the p-value for the tag SNP in Approach 1 ($P_{\text{adjSMK}}$), Approach 2 ($P_{\text{joint}}$), Approach 3 ($P_{\text{int}}$), current smokers ($P_{\text{SMK}}$), and in nonsmokers ($P_{\text{nonSMK}}$). EUR-European-only meta-analysis.
A) BMI: rs10929925 – Approach 2

- Combination rate
- Recombination rate (CM/Mb)

Position on chr2 (Mb)

Diseases:
- Coronary artery calcification
- Chronic kidney disease

Genes:
- LINC01248
- LINC01105
- LOC400940
- SOX11
BMI: rs13069244 – Approach 2
WCadjBMI: rs17396340 – Approach 2

Alcohol dependence (age at onset)
WCadjBMI: rs6743226 – Approach 2

- \log_{10}(p\text{-value})

Position on chr2 (Mb)

Height

Brain structure

KIF1A, C2orf54, SNED1, PASK, ANO7, SEP72, STK25, BOK, ATG4B, NOS3

AGXT, LOC200772, MTERFD2, HDLBP, FARP2, BOK-AS1, DTYMK, GAL3ST2

241.8 242 242.2 242.4 242.6
WCadjBMI: rs7697556 – Approach 2

Position on chr4 (Mb)
Supplementary Figure 6. Regional association plot for all loci identified in Secondary meta-analyses, and ordered as they appear in Tables 2. LD has been calculated using the combined ancestries from the 1000 Genomes Phase 1 reference panel. For comparison, each plot highlights the p-value for the tag SNP in Approach 1 ($P_{\text{adjSMK}}$), Approach 2 ($P_{\text{joint}}$), Approach 3 ($P_{\text{int}}$), current smokers ($P_{\text{SMK}}$), and in nonsmokers ($P_{\text{nonSMK}}$). P-values are shown from the strata in which the signal was identified (e.g. European-only women).
BMI: rs2481665 – Approach 1, EUR, Combined Sexes

6 GWAS hits omitted

- Position on chr1 (Mb)

- Recombination rate (cM/Mb)

- \(-\log(p\text{-value})\)

- \(r^2\) legend:
  - 0.8
  - 0.6
  - 0.4
  - 0.2

Legend:
- \(P_{\text{int}}\)
- \(P_{\text{joint}}\)
- \(P_{\text{adjSMK}}\)
- \(P_{\text{SMK}}\)
- \(P_{\text{nonSMK}}\)
BMI: rs12629427 – Approach 1, EUR Women
B.

WCadjBMI: rs1545348 – Approach 1, EUR Men

- Position on chr5 (Mb)
- Recombination rate (cM/Mb)
- \(-\log_{10}(p\text{-value})\)

- \(p_{\text{int}}\)
- \(p_{\text{joint}}\)
- \(p_{\text{adjSMK}}\)
- \(p_{\text{SMK}}\)
- \(p_{\text{nonSMK}}\)

- Left ventricular mass
- Urinary metabolites (H-NMR features)
- Metabolite levels
C.

WHRadjBMI: rs670752 – Approach 1, All Women
WHRadjBMI: rs1856293 – Approach 2 EUR Combined Sexes
WHRadjBMI: rs2001945 – Approach 1, All Women

- log_{10}(p-value)

Recombination rate (cM/Mb)

Position on chr8 (Mb)

Metabolite levels (Dihydoxy docosatrienoic acid)

Triglycerides–Blood Pressure (TG–BP)

HDL cholesterol

Lipid traits

HDL Cholesterol – Triglycerides (HDL–TG)

LDL cholesterol

ZNF572 → NSMCE2 → TRIB1 → LINC00871

17 GWAS hits omitted
Supplementary Figure 7. Simulation-based estimation of type 1 error using QQ plots. Shown are the QQ plots of simulation results for Approach 1 (adjusted effect), Approach 2 (joint effect), Approach 3 and 4 (interaction effects). The simulation was based on MAF=0.05, 50,000 smokers and 180,000 nonsmokers.
**Supplementary Fig. 8.** Heatmap of $-\log_{10}P$-values for SNPadjSMK, SNPjoint, and SNPint models. We have included each variant identified in the all ancestries analysis which was significant for Approaches 1-3. Strength of color represents the $-\log_{10} P$-value from the all ancestries, combined sexes meta-analysis.
Supplementary Figure 4. Summary plots of discovery meta-analysis for Approach 3 primary meta-analyses. (A) Manhattan plot showing the loci identified in Approach 2 in primary meta-analyses, used to identify significant interaction effects loci (SNPint), in the primary meta-analyses association –log10P-values for BMI-red, WCadjBMI-blue, and WHRadjBMI-green; (B) Manhattan plot showing the loci identified in Approach 2 excluding known regions +/- 500 kb and labeled with the nearest gene to the index SNP; (C) QQ-plot showing the Approach 2 P-values as observed against those expected under the null for each phenotypes separately (colored); (D) QQ-plot for Approach 2 after excluding known association regions.
Supplementary Figure 1. Regional association plot for all loci identified in Approach 3 in primary meta-analyses, used to identify significant interaction (SNPint), in the primary meta-analyses for A) BMI and B) WCadjBMI, and ordered as they appear in Table 3. LD has been calculated using the combined ancestries from the 1000 Genomes Phase 1 reference panel. For comparison, each plot highlights the p-value for the tag SNP in Approach 1 ($P_{\text{adjSMK}}$), Approach 2 ($P_{\text{joint}}$), Approach 3 ($P_{\text{int}}$), current smokers ($P_{\text{SMK}}$), and in nonsmokers ($P_{\text{nonSMK}}$). EUR-European-only meta-analysis.
A) BMI: rs336396 – Approach 3
BMI: rs12902602 – Approach 3

Position on chr15 (Mb)

9 GWAS hits omitted
B) WCadjBMI: rs4141488 – Approach 3

Position on chr16 (Mb)
Supplementary Figure nr. Estimated effects ($\beta \pm 95\%$ CI) per risk allele for A) BMI, B) WCadjBMI, and C) WHRadjBMI for the most significant variant for each locus identified in the primary meta-analyses (combined ancestries and combined sexes) for Approaches 1 (SNPadjSMK), 2 (SNPjoint) and 3 (SNPint). Loci are ordered by greater magnitude of effect in smokers compared to nonsmokers and labeled with the nearest gene.
Supplementary Figure 1n, Estimated effect estimates ($\beta \pm 95\%$ CI) per risk allele for A) BMI, B) WCadjBMI, and C) WHRadjBMI for the most significant variant for each locus identified in the secondary meta-analyses (sex-stratified and European-only analyses) for Approaches 1 (SNPadjSMK), 2 (SNPjoint) and 3 (SNPint). Loci are ordered by greater magnitude of effect in smokers compared to nonsmokers and labeled with the nearest gene.
**Supplementary Figure 13.** Comparison of estimated effect estimates (SE) per risk allele in GIANT only and UKBiobank validation analysis for A) BMI stratified by smoking status, B) BMI adjusted for smoking status, C) WCadjBMI stratified by smoking status, D) WCadjBMI adjusted for smoking status, E) WHRadjBMI stratified by smoking status, and F) WHRadjBMI adjusted for smoking status for each novel and GxSMK SNP in Tables 1-4.