Article

Genetic drivers of heterogeneity in type 2 diabetes pathophysiology

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Type 2 diabetes (T2D) is a heterogeneous disease that develops through diverse pathophysiological processes[1,2] and molecular mechanisms that are often specific to cell type[3,4]. Here, to characterize the genetic contribution to these processes across ancestry groups, we aggregate genome-wide association study data from 2,535,601 individuals (39.7% not of European ancestry), including 428,452 cases of T2D. We identify 1,289 independent association signals at genome-wide significance ($P < 5 \times 10^{-8}$) that map to 611 loci, of which 145 loci are, to our knowledge, previously unreported. We define eight non-overlapping clusters of T2D signals that are characterized by distinct profiles of cardiometabolic trait associations. These clusters are differentially enriched for cell-type-specific regions of open chromatin, including pancreatic islets, adipocytes, endothelial cells and enteroendocrine cells. We build cluster-specific partitioned polygenic scores[5] in a further 279,552 individuals of diverse ancestry, including 30,288 cases of T2D, and test their association with T2D-related vascular outcomes. Cluster-specific partitioned polygenic scores are associated with coronary artery disease, peripheral artery disease and end-stage diabetic nephropathy across ancestry groups, highlighting the importance of obesity-related processes in the development of vascular outcomes. Our findings show the value of integrating multi-ancestry genome-wide association study data with single-cell epigenomics to disentangle the aetiological heterogeneity that drives the development and progression of T2D. This might offer a route to optimize global access to genetically informed diabetes care.

Diabetes mellitus is a huge public-health burden, with an estimated prevalence of 537 million adults worldwide in 2021, of whom more than 90% are affected by T2D[6]. The biological processes through which T2D develops are diverse and include impaired insulin secretion and insulin resistance. This aetiological heterogeneity leads to substantial variability in patient phenotypes, including age of disease onset, manifestation of disease complications and response to management strategies[1,2]. Although environment and lifestyle are well-established risk factors for T2D, heritability has been estimated to be 69% amongst individuals of 35–60 years of age[7]. Previous genome-wide association studies (GWASs) of T2D have identified more than 500 risk loci[8,9], which showed variable patterns of association with clinical features mediated by effector genes acting through distinct molecular mechanisms that are often cell-type specific[3,4]. Through the newly established Type 2 Diabetes Global Genomics Initiative, we present findings from a very large meta-analysis of T2D GWAS data, comprising more than 2.5 million individuals of diverse ancestry—an increase of nearly threefold in the effective sample size compared with previous efforts[8,9]. We take advantage of the power afforded by this increased sample size and combine the GWAS data with emerging single-cell functional genomics data derived from disease-relevant tissues to uncover the aetiological heterogeneity of T2D. Furthermore, we construct partitioned polygenic scores (PSs)[5] across multiple ancestry groups, and assess their association with T2D-related macrovascular outcomes and progression to microvascular complications.

Study overview

We assembled GWAS data, including 428,452 cases of T2D and 2,107,149 controls (Supplementary Fig. 1 and Supplementary Tables 1 and 2). We organized these GWASs into six subsets of genetically similar studies, which we refer to as 'ancestry groups' (Extended Data Fig. 1). Specifically, we considered: a European ancestry group (EUR, 60.3% of the effective sample size); an East Asian ancestry group (EAS, 19.8%); an admixed African American group with ancestry predominantly from West Africa and Europe (AFA, 10.5%); an admixed Hispanic group with ancestry predominantly from the Americas, West Africa and Europe (HIS, 5.9%); a South Asian ancestry group (SAS, 3.3%); and a South African ancestry group (SAF, 0.2%). Association analyses accounted for study-level population structure and relatedness, and adjusted for age and sex, where appropriate, and additional study-specific covariates (Supplementary Table 3 and Methods).

Discovery of T2D loci

We aggregated association summary statistics across GWASs through multi-ancestry meta-regression, implemented in MR-MEGA (ref. 10), which allows for allelic effect heterogeneity that is correlated with ancestry. We included three axes of genetic variation as covariates in the meta-regression model that separated GWASs from different ancestry groups (Extended Data Fig. 1 and Methods), which resulted in

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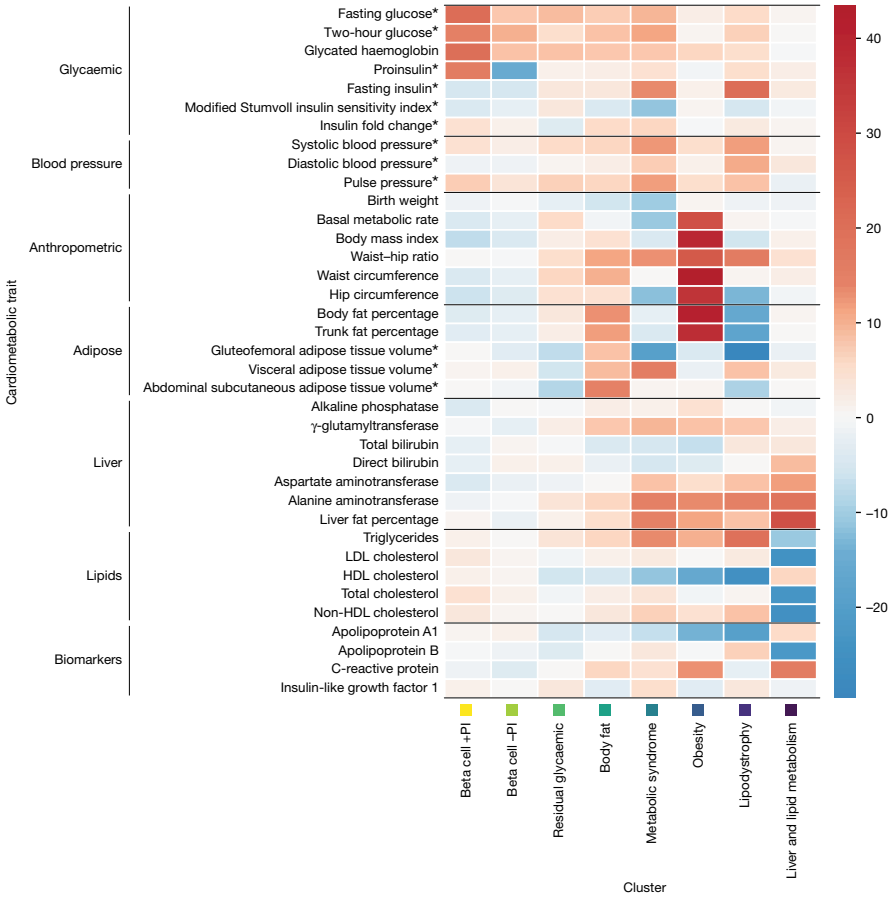

Fig. 1 | Heat map of associations of 37 cardiometabolic phenotypes with 8 mechanistic clusters of index SNVs for T2D association signals. Each column corresponds to a cluster. Each row corresponds to a cardiometabolic phenotype. The 'temperature' of each cell represents the *z*-score (aligned to the T2D risk allele) of association of the phenotype with index SNVs assigned to the cluster. *Phenotype is adjusted for body mass index.

lower genomic control inflation than did a fixed-effects meta-analysis ($\lambda_{GC} = 1.120$ and $\lambda_{GC} = 1.396$, respectively).

The DIAMANTE Consortium previously advocated the use of a multi-ancestry genome-wide significance threshold ($P < 5 \times 10^{-9}$) to define loci, which takes account of the weaker linkage disequilibrium (LD) between single-nucleotide variants (SNVs) expected after multi-ancestry meta-analysis[9]. To gain insight into true positive signals meeting conventional genome-wide significance ($P < 5 \times 10^{-8}$) that would be overlooked at this more stringent threshold, we considered loci reported by the DIAMANTE Consortium, which contributed 39.5% of the effective sample size of the current study. Of 39 loci with association signals meeting $5 \times 10^{-9} \leq P < 5 \times 10^{-8}$ in the DIAMANTE Consortium analysis, 36 (92.3%) attained multi-ancestry genome-wide significance with the larger sample size available to us in the current study (Supplementary Text). We therefore focused our downstream analyses on SNVs that met the conventional genome-wide significance threshold.

We identified a total of 1,289 distinct T2D association signals ($P < 5 \times 10^{-8}$) that were represented by independent ($r^2 < 0.05$) index SNVs (Supplementary Fig. 2, Supplementary Table 4 and Methods). The 1,289 association signals mapped to 611 loci, of which 145 (23.7%) loci have not to our knowledge been previously reported in GWASs of T2D. At association signals that mapped to loci not previously reported for T2D, index SNVs were predominantly common (minor allele frequency (MAF) higher than 5% in at least one ancestry group) with odds ratios (ORs) lower than 1.05 (Supplementary Fig. 3).

Mechanistic clusters of T2D index SNVs

To understand the genetic contribution to phenotypic heterogeneity in T2D, we classified the 1,289 index SNVs according to their profile of associations (aligned to the T2D risk allele) with 37 cardiometabolic phenotypes. These included glycaemic traits, anthropometric measures, body fat and adipose tissue volume, blood pressure, levels of circulating plasma lipids, and biomarkers of liver function and lipid metabolism[11–19] (Supplementary Table 5). We applied an unsupervised 'hard clustering' approach with imputation of missing phenotype associations, which identified eight non-overlapping but exhaustive subsets of index SNVs with similar cardiometabolic profiles (Fig. 1, Table 1, Extended Data Fig. 2, Supplementary Fig. 4, Supplementary Tables 6 and 7 and Methods).

We observed that the cardiometabolic features and loci of five of our identified clusters overlapped with those reported in previous efforts[3,4,20,21], representing beta-cell dysfunction with a positive or negative association with proinsulin (PI), and insulin resistance mediated through obesity, lipodystrophy, and liver and lipid metabolism (Supplementary Table 8). T2D risk alleles at index SNVs in the two beta-cell-dysfunction clusters are associated with increased fasting glucose, two-hour glucose and glycated haemoglobin, and with decreased fasting insulin. Index SNVs in both clusters are also associated with PI, but with opposite directions of effect for the T2D risk allele. The clusters reflecting mechanisms of insulin resistance mediated through obesity, lipodystrophy, and liver and lipid metabolism include index SNVs that are associated with anthropometric measures and levels of

Table 1 | Cardiometabolic profile, example loci and physiological effect of index SNVs at T2D association signals allocated to eight mechanistic clusters

Mechanistic cluster	Cardiometabolic profile	Number of T2D associations	Example loci	Physiological effect	
				Insulin secretion	Insulin sensitivity
Beta cell +PI	+FG*, +2hG*, +HbA1c, +PI*	91	*TCF7L2, KCNQ1, CDKAL1, CDKN2A–CDKN2B, SLC30A8*	–	+
Beta cell –PI	+FG*, +2hG*, +HbA1c, –PI*	89	*CDC123–CAMK1D, HNF1B, KCNJ11–ABCC8, HNF4A, HNF1A*	–	+
Residual glycaemic	+FG*, +HbA1c	389	*GCC1–PAX4–LEP, ANKRD55, GCKR, UBE2E2*	–	–
Body fat	+Body fat, +ASAT*	273	*ZMIZ1, HMGA2, CTBP1*	+	–
Metabolic syndrome	+FG*, +FI*, +WHR, +VAT*, –GFAT*, +TG, –HDL, +BP	166	*IGF2BP2, CCND2, HHEX–IDE, JAZF1, GPSM1*	+	–
Obesity	+BMI, +WHR, +body fat, +BMR, +TG, –HDL	233	*FTO, MC4R, MACF1, TMEM18*	+	–
Lipodystrophy	+FI*, +WHR, –body fat, –GFAT*, +TG, –HDL, +BP	45	*IRS1, GRB14–COBLL1, PPARG*	+	–
Liver and lipid metabolism	–LDL, –TC, +liver fat, +liver biomarkers	3	*TOMM40–APOE–GIPR, TM6SF2, PNPLA3*	–	–

+/–: T2D risk alleles associated with increased or decreased phenotype values.
ASAT, abdominal subcutaneous adipose tissue volume; BMI, body mass index; BMR, basal metabolic rate; BP, blood pressure; FG, fasting glucose; FI, fasting insulin; GFAT, gluteofemoral adipose tissue volume; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PI, proinsulin; TC, total cholesterol; TG, triglycerides; VAT, visceral adipose tissue volume; WHR, waist–hip ratio; 2hG, two-hour glucose.
*Adjusted for BMI.

circulating plasma lipids. T2D risk alleles at index SNVs in the obesity cluster are associated with increased body mass index (BMI), waist–hip ratio (WHR), body fat percentage and basal metabolic rate, and with decreased high-density lipoprotein (HDL) cholesterol. The lipodystrophy cluster comprises index SNVs for which T2D risk alleles are associated with increased fasting insulin, WHR, blood pressure and triglycerides, and with decreased body fat percentage, gluteofemoral adipose tissue (GFAT) volume and HDL cholesterol. T2D risk alleles at index SNVs assigned to the liver and lipid metabolism cluster are associated with increased liver fat and liver-related biomarkers, and with decreased low-density lipoprotein (LDL) cholesterol and total cholesterol.

By increasing the number of index SNVs in the clustering by nearly fourfold relative to previous efforts, we provide a more granular view of the biological processes through which T2D associations affect disease, and highlight three previously unreported clusters of signals with cardiometabolic profiles that are representative of metabolic syndrome, body fat and residual glycaemic effects. We observed significantly weaker allelic effects on T2D in these three clusters than in those previously reported (mean OR of 1.028 versus 1.033, $P = 2.2 \times 10^{-7}$), but there was no noticeable difference in disparity around the centroid between clusters (Extended Data Fig. 3, Supplementary Table 9 and Supplementary Fig. 5). T2D risk alleles at index SNVs assigned to the metabolic syndrome cluster are associated with increased fasting glucose, WHR, triglycerides and blood pressure, and with decreased HDL cholesterol, which together are used to define metabolic syndrome. T2D risk alleles in this cluster are also associated with increased fasting insulin, with accumulations of unhealthy fat depots (increased visceral adipose tissue (VAT) volume and liver fat) and with decreased GFAT volume. Previous investigations have shown that individuals with metabolic syndrome are at increased risk of T2D[22], although Mendelian randomization studies indicate that a causal effect is driven by increased waist circumference and increased fasting glucose[23]. T2D risk alleles at index SNVs assigned to the body fat cluster are associated with increased abdominal subcutaneous adipose tissue volume, VAT volume and body fat percentage. Although the body fat cluster profile of associations with cardiometabolic phenotypes shares these features in common with obesity-mediated insulin resistance, index SNVs in the body fat cluster are not strongly associated with BMI, lipid levels or basal metabolic rate. Previous investigations have highlighted that body fat percentage is predictive of abnormal blood glucose in individuals with a healthy BMI[24]. Finally, T2D risk alleles at index SNVs assigned to the residual glycaemic cluster are most strongly associated with increased fasting glucose and glycated haemoglobin, but, unlike the two beta-cell-dysfunction clusters, are not associated with PI or decreased fasting insulin.

Clustering provides a framework to better understand the diverse physiological processes through which T2D develops and the shared biological pathways that drive genetic correlations with other insulin-resistance-related disorders, including gestational diabetes mellitus (GDM) and polycystic ovary syndrome (PCOS). T2D risk alleles at index SNVs showed a gradient of effects on insulin-related endophenotypes across clusters (Supplementary Text, Extended Data Fig. 4 and Supplementary Tables 10 and 11), representing a cline from insulin production and processing in the two beta-cell-dysfunction clusters through to insulin resistance that was most extreme in the lipodystrophy cluster. Index SNVs in the beta cell +PI cluster showed the strongest associations with GDM, whereas those in the obesity cluster were most strongly associated with PCOS (Supplementary Text, Extended Data Fig. 5 and Supplementary Table 12).

Regulatory processes underlying clusters

To gain insight into tissue-specific regulatory processes underpinning mechanistic clusters, we integrated T2D association signals with assay for transposase-accessible chromatin using sequencing (ATAC-seq) peaks from single-cell atlases of chromatin accessibility (CATLAS and DESCARTES) for 222 cell types derived from 30 human adult and 15 human fetal tissues[25,26] and an additional 106 cell types from the human brain[27] (Fig. 2, Supplementary Tables 13 and 14 and Methods).

We observed significant enrichment for regions of open chromatin in fetal islets and adult neuroendocrine cells in pancreatic islets (alpha, beta, gamma and delta) in the beta cell +PI, beta cell –PI and residual glycaemic clusters. In addition, the residual glycaemic cluster was enriched in fetal and adult pancreatic ductal cells, whereas the beta cell –PI cluster was enriched in adult enterochromaffin cells—a type of enteroendocrine cell that has an essential role in regulating intestinal motility and secretion in the gastrointestinal tract[28]. Enterochromaffin

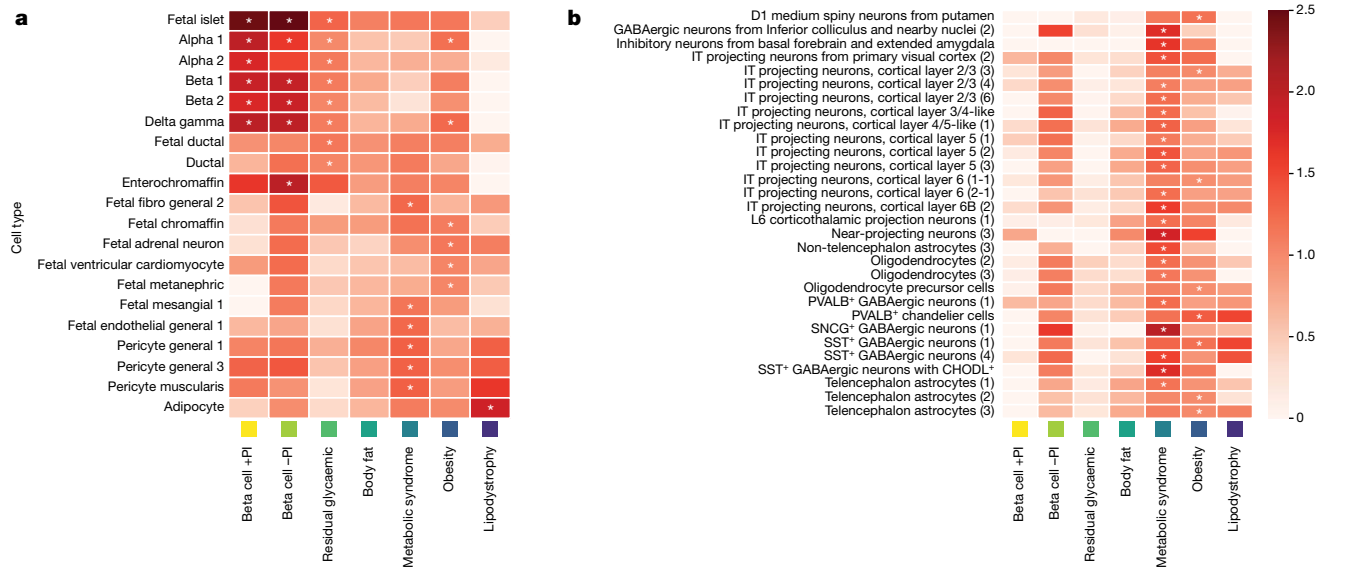

Fig. 2 | Heat map of cluster-specific enrichments of T2D associations for cell-type-specific regions of open chromatin derived from single-cell ATAC-seq peaks in adult and fetal tissue. a, Cell types (222 types) from 30 human adult tissues and 15 human fetal tissues. **b**, Cell types (106 types) from the human brain. In each panel, columns represent mechanistic clusters. Each row represents a cell type that was significantly enriched (Bonferroni correction for the number of cell types) for T2D associations in at least one cluster (indicated by an asterisk). The 'temperature' of each cell defines the magnitude of the log fold enrichment. The liver and lipid metabolism cluster is not presented because it includes only three T2D association signals and the model parameter estimates were unstable.

cells are a major target for glucagon-like peptide 1 (GLP-1) and highly express the GLP-1 receptor, agonists of which are widely used as medications for T2D[29] (Supplementary Text).

The obesity cluster was also significantly enriched for regions of open chromatin in adult pancreatic islets, although not as strongly as were the beta-cell-dysfunction clusters. Enrichment was observed only for alpha, gamma and delta cells, suggesting that there are alternative pathways through which islets affect the development of T2D, other than through the secretion of insulin from beta cells. The obesity cluster was further enriched in fetal adrenal gland cells (chromaffin cells and adrenal neurons), fetal heart cells (ventricular cardiomyocytes) and fetal kidney cells (metanephric cells). Previous studies have reported an enrichment of BMI loci or heritability for epigenomic annotations in pancreatic islets and adrenal gland[30,31], consistent with our findings. In the human brain, the obesity cluster was significantly enriched for regions of open chromatin in cell types including intratelencephalic (IT) projecting neurons, somatostatin-positive (SST^+) GABAergic inhibitory neurons and D1 medium spiny neurons. SST^+ GABAergic neurons exist in the hypothalamus and regulate food intake[32]. D1 medium spiny neurons are a type of GABAergic neuron in the human striatum that expresses D1-type dopamine receptors; these neurons have been implicated in food motivation and the development of diet-induced obesity in mice[33].

The remaining four clusters (lipodystrophy; metabolic syndrome; body fat; and liver and lipid metabolism) were not significantly enriched for regions of open chromatin in pancreatic islets. The lipodystrophy cluster was enriched only in adult adipocytes, which confirms previous reports in bulk adipose tissue[4,20]. Consistent with these results, association signals for WHR, triglycerides and HDL cholesterol, which are strongly affected by index SNVs in the lipodystrophy cluster, have been shown to be enriched in candidate *cis*-regulatory elements in adipocytes[26]. The metabolic syndrome cluster was enriched in cells that reside in the walls of blood vessels (adult pericytes and fetal endothelial cells), fetal kidney cells (mesangial cells) and fetal fibroblasts. Association signals for systolic and diastolic blood pressure, a key component of metabolic syndrome, have been shown to be enriched in candidate *cis*-regulatory elements in these cell types[26]. Endothelial dysfunction is not only a consequence of insulin resistance, but also impairs insulin signalling to further reduce insulin sensitivity, thereby providing a pathophysiological mechanism that links the metabolic and cardiovascular components of metabolic syndrome[34]. In human brain, the metabolic syndrome cluster was significantly enriched for regions of open chromatin in cell types including IT projecting neurons and SST^+ GABAergic inhibitory neurons. IT projecting neurons are a type of glutamatergic excitatory pyramidal neuron in the cerebral cortex, and metabolic syndrome was previously associated with pyramidal neurons and GABAergic neurons in cell-type specificity analyses in a GWAS that examined genetic factors in metabolic syndrome[35]. We observed no significant enrichments in the body fat cluster or in the liver and lipid metabolism cluster.

Ancestry-correlated heterogeneity

Previous multi-ancestry GWASs have shown widespread heterogeneity in allelic effects at T2D association signals across ancestry groups[9,36]. We took advantage of the meta-regression model to partition heterogeneity into an ancestry-correlated component explained by three axes of genetic variation, and a residual component reflecting differences in environmental exposures (that are not correlated with ancestry) and/or study design (Supplementary Table 15). We observed 127 (9.9%) independent T2D association signals with significant evidence for ancestry-correlated heterogeneity ($P_{HET} < 3.9 \times 10^{-5}$, Bonferroni correction for 1,289 signals). We would expect less than one signal to meet this threshold of significance, highlighting that ancestry-correlated heterogeneity is strongly enriched at T2D associations (one-sided binomial test $P < 2.2 \times 10^{-16}$). By contrast, we observed significant evidence of residual heterogeneity at only four (0.3%) association signals (one-sided binomial test $P = 0.031$). These results therefore suggest that differences in allelic effects at index SNVs are more strongly correlated with genetic ancestry than other factors that vary between GWASs.

We next sought to better understand the impact of genetic diversity on differences in allelic effects between GWASs at the 127 association signals with significant evidence of ancestry-correlated heterogeneity (Methods). For 118 (92.9%) signals, allelic effect sizes were most strongly associated with the first two axes of genetic variation, which

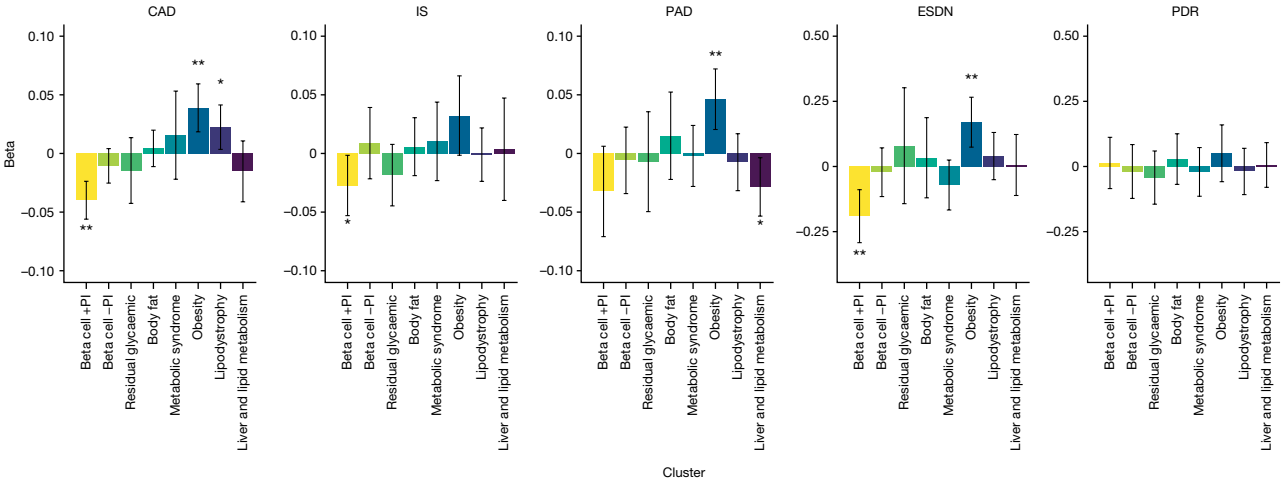

Fig. 3 | Associations of cluster-specific components of the partitioned PS with five T2D-related vascular outcomes in up to 279,552 individuals from multiple ancestry groups. Summaries of the associations of each cluster-specific component of the partitioned PS with CAD, ischaemic stroke (IS), peripheral artery disease (PAD), ESDN and proliferative diabetic retinopathy (PDR). The height of each bar corresponds to the log-odds ratio (beta) per standard deviation of the PS, and the grey bar shows the 95% confidence interval. Analyses of T2D-related macrovascular complications (CAD, PAD and IS) were undertaken in all individuals, with adjustment for T2D status. Analyses of microvascular complications were undertaken in individuals with T2D only. *$P < 0.05$, nominal association; **$P < 0.0063$, Bonferroni correction for eight clusters. Exact P values are provided in Supplementary Table 21.

reflect differences between AFA/EUR and EAS GWASs (AFA–EAS axis), and between AFA/EAS and EUR GWASs (AFA–EUR axis), respectively (Supplementary Text, Extended Data Figs. 1 and 6 and Supplementary Table 16).

We observed significant differences in mean z-scores for association between clusters for both the AFA–EAS axis ($P = 4.1 \times 10^{-6}$) and the AFA–EUR axis ($P = 1.5 \times 10^{-6}$). Index SNVs in the two beta-cell-dysfunction clusters were most positively associated with the AFR–EAS axis, indicating allelic effects on T2D that were greater in EAS GWASs than in AFA and EUR GWASs (Extended Data Fig. 7 and Supplementary Table 17). By contrast, index SNVs in the lipodystrophy and obesity clusters were most positively associated with the AFA–EUR axis, indicating allelic effects on T2D that were greater in EUR GWASs than in EAS and AFA GWASs. These results indicate that ancestry-correlated heterogeneity varies between mechanistic clusters, with allelic effects greatest for EAS GWASs at association signals assigned to clusters acting through beta-cell dysfunction and greatest for EUR GWASs at those assigned to clusters operating through insulin resistance.

Ancestry-correlated heterogeneity in allelic effects between GWASs is not driven by differences in allele frequency between ancestry groups, but can occur because of interaction between index SNVs and environmental and lifestyle factors, if not accounted for in the association analysis[37]. We observed substantial variation in the distribution of study-level mean BMI in T2D cases and controls across ancestry groups (Supplementary Fig. 6). Such variation could affect ancestry-correlated heterogeneity because, when cases and controls are selected from the extremes of the BMI distribution, the magnitude of allelic effect estimates at T2D signals acting through beta-cell dysfunction can be inflated[38]. We therefore extended the MR-MEGA meta-regression model to allow for allelic effect heterogeneity at index SNVs due to mean BMI in T2D cases and controls, in addition to axes of genetic variation (Methods).

After adjustment for study-level mean BMI in cases of T2D and in controls, only 24 association signals retained significant evidence of ancestry-correlated heterogeneity ($P < 3.9 \times 10^{-5}$), compared with 127 signals without adjustment (Supplementary Text and Supplementary Table 18). After adjustment for BMI, significant differences in mean z-scores for association between clusters for the AFA–EUR axis were maintained ($P = 3.2 \times 10^{-5}$ versus $P = 1.5 \times 10^{-6}$ without adjustment), whereas those for the AFA–EAS axis were not ($P = 0.18$ versus $P = 4.1 \times 10^{-6}$ without adjustment). Furthermore, after adjustment for BMI, the two beta-cell-dysfunction clusters were no longer strongly positively associated with the AFA–EAS axis (Extended Data Fig. 7 and Supplementary Table 19). Together, these results suggest that heterogeneity in allelic effects between EAS GWASs and EUR/AFA GWASs, which occur most often at association signals assigned to the beta-cell-dysfunction clusters, can be mostly accounted for by differences in the distributions of mean BMI in T2D cases and in controls between these ancestry groups.

Associations of partitioned PS with outcomes

The major complications in individuals with T2D are macrovascular outcomes including coronary artery disease (CAD), ischaemic stroke and peripheral artery disease, and microvascular outcomes, including end-stage diabetic nephropathy (ESDN) and proliferative diabetic retinopathy. We tested for association of a cluster-specific partitioned PS with these vascular outcomes in up to 279,552 individuals (including 30,288 cases of T2D) across five ancestry groups (AFA, EAS, EUR, HIS and SAS) from the All of Us Research Program, Biobank Japan and the Genes & Health study (Methods). These individuals were not included in the multi-ancestry meta-analysis, thus avoiding potential inflated type I error rates owing to overlap between the discovery and the testing datasets. To maximize sample size, we tested macrovascular outcomes in all individuals, adjusted for T2D status, and microvascular complications only in individuals with T2D (Methods and Supplementary Table 20). To assess the additional information afforded by the partitioned PS over an overall T2D PS, agnostic to cluster membership, we tested for association of each cluster-specific component of the partitioned PS after adjustment for the overall PS. Figure 3 provides an overview of the associations of each cluster-specific component of the partitioned PS with the five vascular outcomes across ancestry groups.

We observed a significant association ($P < 0.0063$, Bonferroni correction for eight clusters) of two components of the partitioned PS with CAD: a negative association with the beta cell +PI cluster (OR = 0.96 per standard deviation of the PS, $P = 1.3 \times 10^{-6}$) and a positive association with the obesity cluster (OR = 1.04, $P = 0.00019$). There was no evidence of heterogeneity in the effects of these two clusters on CAD

across ancestry groups (Supplementary Fig. 7 and Supplementary Table 21). Notably, after adjustment for a CAD PS derived from a previously published multi-ancestry meta-analysis of CAD GWASs[39], the positive CAD association with both components of the partitioned PS remained significant (Extended Data Fig. 8 and Supplementary Table 22): beta cell +PI cluster (OR = 0.96, $P = 4.4 \times 10^{-5}$) and obesity cluster (OR = 1.04, $P = 0.00065$). We also observed a significant positive association of the obesity cluster from the partitioned PS with peripheral artery disease (OR = 1.05, $P = 0.00045$), with no evidence of heterogeneity in effects across ancestry groups (Supplementary Fig. 8 and Supplementary Table 21). Across all three macrovascular outcomes, there was a general trend of negative association with the beta cell +PI cluster and positive association with the obesity cluster, although no cluster-specific components of the partitioned PS attained significance for ischaemic stroke (Supplementary Fig. 9 and Supplementary Table 21). There was no strong association of the overall T2D PS with CAD ($P = 0.17$), ischaemic stroke ($P = 0.022$) or peripheral artery disease ($P = 0.77$) after meta-analysis across ancestry groups. Together, these results highlight the advantages of the partitioned PS over an overall T2D PS for detecting associations with macrovascular outcomes, and provide insight into the biological processes that lead to their development.

We observed significant associations of two components of the partitioned PS with ESDN: a negative association with the beta cell +PI cluster (OR = 0.83, $P = 0.00024$) and a positive association with the obesity cluster (OR = 1.19, $P = 0.00050$). There was no evidence of heterogeneity in the effects of these two clusters across ancestry groups, (Supplementary Fig. 10 and Supplementary Table 21), and the overall PS was not strongly associated with ESDN ($P = 0.048$). By contrast, none of the cluster-specific components of the partitioned PS were associated with proliferative diabetic retinopathy. However, there was a strong positive association of the overall PS with this microvascular outcome (OR = 1.32, $P = 1.1 \times 10^{-9}$), with no evidence of heterogeneity in effects across ancestry groups (Supplementary Fig. 11 and Supplementary Table 21). Together, these results suggest that ESDN is associated with obesity and beta-cell dysfunction with opposite directions of effect, and confirm previous reports that proliferative diabetic retinopathy is driven by hyperglycaemia[40] and therefore strongly associated with the overall burden of T2D risk variants.

Finally, we tested for associations of the cluster-specific components of the partitioned PS and the overall T2D PS with age of onset of T2D (Extended Data Fig. 9 and Methods). The overall PS was strongly associated with an earlier age of onset (1.15 years per standard deviation of the PS, $P = 5.1 \times 10^{-8}$), although the effects were highly heterogeneous across ancestry groups (Supplementary Fig. 12 and Supplementary Table 23). However, even after adjustment for the overall PS, the obesity cluster was significantly associated with an earlier age of onset (0.38 years, $P = 1.4 \times 10^{-7}$), with no evidence of heterogeneity across ancestry groups. These findings highlight the importance of obesity-related processes for the onset of T2D, in addition to the development of vascular complications.

Associations with vascular outcomes in clinical trials

To gain insight into the associations of the obesity and beta cell +PI clusters with a broader range of vascular outcomes, we assessed the performance of the partitioned PS (after adjustment for the overall PS) in prospective GWASs in up to 29,827 EUR individuals with T2D from six clinical trials from the Thrombolysis in Myocardial Infarction (TIMI) Study Group (Methods and Supplementary Table 24). We observed the strongest associations of cluster-specific components of the partitioned PS with risk of hospitalization for heart failure: positive with the obesity cluster (hazard ratio (HR) = 1.15 per standard deviation of the PS, $P = 4.8 \times 10^{-6}$) and negative with the beta cell +PI cluster (HR = 0.90, $P = 0.00092$). Amongst macrovascular outcomes, the beta cell +PI cluster was also negatively associated with cardiovascular death (HR = 0.90, $P = 0.0020$), major cardiovascular events (HR = 0.94, $P = 0.0050$) and myocardial infarction (HR = 0.94, $P = 0.027$). For microvascular outcomes, the two clusters showed associations with opposite directions of effect for albuminuria: obesity cluster (HR = 1.06, $P = 0.012$) and beta cell +PI cluster (HR = 0.95, $P = 0.047$). Across all outcomes, there was a general trend of positive association with the obesity cluster and negative association with the beta cell +PI cluster (Extended Data Fig. 10), consistent with the associations observed from our analyses of retrospective GWASs across ancestry groups.

Discussion

To better understand the aetiological heterogeneity of T2D across diverse populations, we assembled a large collection of T2D GWASs for six ancestry groups through the Type 2 Diabetes Global Genomics Initiative. By increasing the effective sample size by almost threefold compared with previous efforts, we identified a total of 611 loci attaining the conventional threshold of genome-wide significance ($P < 5 \times 10^{-8}$), 145 (23.7%) of which have not to our knowledge been previously reported. This conventional threshold is equivalent to a Bonferroni correction for the effective number of independent SNVs in EUR reference data[41]. Using empirical data from the 1000 Genomes Project, the DIAMANTE Consortium and others have advocated more stringent thresholds for multi-ancestry meta-analysis because the structure of LD is broken down across ancestry groups and the effective number of independent SNVs is increased[9,42]. In fact, our analyses suggest that loci meeting conventional genome-wide significance are unlikely to be false positive association signals, but instead are driven by index SNVs that have modest effects that require larger sample sizes to meet more stringent thresholds. We therefore recommend the use of this conventional threshold but advocate careful review of reported signals to ensure that associations are not driven by single studies or poorly imputed variants to protect against false positives.

Multi-ancestry meta-regression maximizes power to detect associations that are shared across ancestry groups by allowing for heterogeneity in allelic effects at index SNVs. MR-MEGA is not restricted to broad continental ancestry labels that can be used to reinforce the concept of fundamental genetic differences between groups[43], but instead represents ancestry as continuous axes of genetic variation, which better reflect the continuum of human genetic diversity and demographic history[44]. Still, it is important to emphasize that our meta-analysis does not fully capture global genetic diversity, in particular underrepresented populations across Africa, South and Central America, the Middle East and Oceania. For example, 98.2% of the total effective sample size of individuals with the highest proportion of ancestry from Africa are African Americans. The ancestry of these individuals represents a cline of admixture that is predominantly from West Africa and is therefore not representative of other regions in Africa, where the level of genetic variation is equivalent to the differences observed between other continental groups[43]. Bolstering GWAS collections in these underrepresented populations remains an urgent priority for the human genetics research community and highlights the need for careful interpretation of results that does not generalize findings across ancestry groups that are sensitive to biased representation.

Within the landscape of the genetic architecture of T2D, we identified eight clusters of index SNVs with distinct profiles of associations with 37 cardiometabolic phenotypes, which defined pathophysiology-relevant groupings. The addition of previously unreported T2D signals identified through the multi-ancestry meta-analysis helped define three clusters that were not detected in previous clustering efforts[3,4,20,21], with cardiometabolic profiles that are consistent with residual glycaemic effects, accumulations of body fat and metabolic syndrome. These previous efforts have implemented 'soft clustering' approaches, such as Bayesian non-negative matrix factorization, that generate weights

for cluster membership for each index SNV[4]. The assignment of index SNVs to clusters is then determined given a threshold weight for cluster membership, allowing for the possibility that a T2D association signal affects disease through multiple pathophysiological pathways. However, depending on the threshold for cluster membership, some index SNVs will be unassigned. Bayesian non-negative matrix factorization also considers positive and negative associations with the same phenotype as independent variables, and most clustering methods cannot directly accommodate missing phenotype associations. To address these potential limitations, we implemented methodology that jointly conducts *k*-means clustering of index SNVs with powerful iterative multiple imputation of missing phenotype associations. In this 'hard clustering' approach, each index SNV is assigned to exactly one cluster. This has the potential disadvantage, therefore, that index SNVs with outlying or intermediate profiles of trait associations are 'forced' into a cluster that does not fit well. However, the previously unreported clusters that we identified in our hard clustering were not noticeably more disparate than the clusters reported previously, suggesting that we have not introduced substantial noise by forcing all SNVs into exactly one cluster. Ultimately, the choice of clustering approach may depend on the objectives of any downstream investigations.

Our analyses highlighted a significant excess of T2D association signals with ancestry-correlated heterogeneity, which is driven mainly by differences in allelic effects between AFA, EAS and EUR GWASs. The two beta-cell-dysfunction clusters are most strongly associated with the AFA–EAS axis, in which effects are typically larger in EAS GWASs than in those for other ancestry groups. These two clusters are also most strongly associated with reduced insulin secretion and lower insulin resistance. By contrast, the lipodystrophy and obesity clusters, which are characterized by reduced insulin sensitivity and higher insulin resistance, are most strongly associated with the AFA–EUR axis, in which effects are typically larger in EUR than in other ancestry groups. These observations are consistent with studies reporting differences in the pathogenesis of T2D between ancestry groups, whereby T2D is initiated mainly through increased insulin resistance in EUR individuals, but is characterized by reduced insulin secretion with lower insulin resistance in EAS individuals[45,46]. We have shown that most signals with ancestry-correlated heterogeneity can be explained by differences in the distribution of BMI in T2D cases and controls between ancestry groups. Furthermore, after adjustment for study-level mean BMI, we observe no difference in allelic effects between clusters along the AFA–EAS axis. This is consistent with previous studies that reported that body composition is the main determinant of variation in T2D pathogenesis between EAS and EUR individuals, because insulin sensitivity and beta-cell response are similar in the two ancestry groups after accounting for differences in BMI[45,47].

We reveal—across multiple ancestry groups—significant associations of vascular outcomes with cluster-specific components of the partitioned PS after adjustment for the overall PS, which suggests that disease trajectories are associated with genetic burden in certain biological pathways that are consistent across diverse populations. Although the effect sizes of the cluster-specific components of the partitioned PS were small, they motivate future work to strengthen these effects through the identification of further T2D associations in larger sample sizes. Through integration with single-cell chromatin accessibility data across diverse cell types, they also enhance understanding of key biological processes driving heterogeneity in the clinical features of T2D phenotypes. For example, the obesity-cluster-specific component of the PS was positively associated with CAD and ESDN, and included index SNVs that were enriched for regions of open chromatin in fetal ventricular cardiomyocytes, fetal adrenal neuron, adult chromaffin cells in the adrenal gland and fetal metanephric cells. These findings are in line with the reported enrichments of CAD association signals for transcriptomic and epigenomic annotations in bulk tissues including the aorta and arteries, the heart and the adrenal gland[39,48,49], and of renal function association signals in kidney-tissue-specific regulatory annotations[50]. Together, these findings provide a clear link to shared biological mechanisms that drive the development of T2D and other vascular diseases.

In conclusion, our findings show the value of integrating multi-ancestry GWASs of T2D and cardiometabolic traits with single-cell epigenomics across diverse tissues to disentangle the aetiological heterogeneity driving the development and progression of T2D across population groups. Improved understanding of the varied pathophysiological processes that link T2D to vascular outcomes could offer a route to genetically informed diabetes care and global opportunities for the clinical translation of findings from T2D GWASs.

Online content

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Methods

Study-level analyses

Within each study, we assigned individuals to ancestry groups using self-report and genetic background (Supplementary Tables 1 and 2). Any individuals not assigned to an ancestry group were excluded as population outliers. Within each ancestry group-specific GWAS, we conducted quality control of genotype data and imputed up to reference panels from the Trans-Omics for Precision Medicine Program[51], Haplotype Reference Consortium[52], 1000 Genomes Project (phase 1, March 2012 release; phase 3, October 2014 release)[53,54], or population-specific whole-genome sequencing[55–61] (Supplementary Table 3). Studies imputed to reference panels mapped to GRCh38 (hg38) were lifted back to hg19 using the UCSC LiftOver tool (https://genome.ucsc.edu/cgi-bin/hgLiftOver). We excluded SNVs with poor imputation quality and/or minor allele count (MAC) < 5 (Supplementary Table 3).

Within each ancestry group-specific GWAS, we tested for association of each SNV with T2D through generalized linear (mixed) modelling, under an additive dosage of the minor allele, with adjustment for age and sex (where appropriate), and additional study-specific covariates (Supplementary Table 3). We used different strategies to account for population stratification and/or kinship: (i) exclude closely related individuals and adjust for principal components derived from a genetic relatedness matrix (GRM) as additional covariates; or (ii) incorporate a random effect for the GRM (Supplementary Table 3). Allelic effects and corresponding standard errors that were estimated from a linear mixed model were converted to the log-odds scale[62]. We corrected study-level association summary statistics for residual structure by the LD-score regression intercept[63] (Supplementary Table 3) using an LD reference that we derived from ancestry-matched haplotypes from continental groups in the 1000 Genomes Project (phase 3, October 2014 release)[54]. We matched AFA GWASs to the 'African' continental group and HIS GWASs to the 'American' continental group.

Multi-ancestry meta-analyses

We analysed autosomal bi-allelic SNVs that overlap reference panels from the 1000 Genomes Project (phase 3, October 2014 release)[54] and the Haplotype Reference Consortium[52]. We considered SNVs with MAF > 0.5% in at least one of the five continental groups in the 1000 Genomes Project (phase 3, October 2014 release)[54]. We excluded SNVs that differed in allele frequency by more than 20% when comparing reference panels in the same subsets of haplotypes.

We used meta-regression, implemented in MR-MEGA[10], to aggregate association summary statistics across GWASs. MR-MEGA models allelic effect heterogeneity that is correlated with genetic ancestry by including axes of genetic variation as covariates in the meta-regression model to capture diversity between GWASs. We used SNVs reported in all studies to construct a distance matrix of differences in mean effect allele frequency between each pair of GWASs. We implemented multi-dimensional scaling of the distance matrix to obtain three principal components that represent axes of genetic variation to separate GWASs across ancestry groups (Extended Data Fig. 1).

For each SNV, we aggregated inverse-variance weighted allelic effects across GWASs through linear regression, including three axes of genetic variation as covariates. We tested for: (i) association with T2D allowing for ancestry-correlated allelic effect heterogeneity between GWASs; (ii) ancestry-correlated allelic effect heterogeneity between GWASs (defined by the axes of genetic variation); and (iii) residual allelic effect heterogeneity between GWASs. MR-MEGA is a meta-regression approach, and therefore does not produce an allelic effect estimate because this is allowed to vary with the axes of genetic variation. Consequently, we also aggregated association summary statistics across GWASs through fixed-effects meta-analysis (inverse-variance weighting of allelic effects) using METAL[64]. To assess the extent of residual structure between GWASs, we calculated the genomic control inflation factor[65] for the multi-ancestry meta-regression and the fixed-effects meta-analysis. We considered only those SNVs reported in at least five GWASs for downstream interrogation.

Defining T2D signals and loci

We identified all SNVs attaining genome-wide significance ($P < 5 \times 10^{-8}$) for association with T2D from the multi-ancestry meta-regression. Clumps were formed around index variants, which were selected using a greedy algorithm in PLINK v.1.9 (ref. 66), after ranking SNVs by ascending P value. SNVs less than 5 Mb from an index SNV were assigned to the clump if $r^2 > 0.05$ in at least one of the five continental groups from the 1000 Genomes Project (phase 3, October 2014 release)[54]. Index SNVs separated by less than 1 Mb were assigned to the same locus. Each locus was then defined as mapping 500 kb up- and downstream of index SNVs contained within it. We considered the locus to have been previously reported if it contained variants discovered in published large-scale T2D GWASs at genome-wide significance.

Ancestry-group-specific meta-analyses

We aggregated association summary statistics across GWASs from the same ancestry group through fixed-effects meta-analysis (inverse-variance weighting of allelic effects) using METAL[64]. We estimated the mean effect allele frequency across GWASs from each ancestry group, weighted by the effective sample size of the study. We generated forest plots of association summary statistics of index SNVs across ancestry groups using the R package meta (https://cran.r-project.org/package=meta/).

Defining clusters of T2D index SNVs with distinct cardiometabolic profiles

We considered cardiometabolic-related quantitative phenotypes that are used to define T2D status and/or are associated with risk of T2D or complications. We excluded phenotypes for which GWAS summary statistics were available only after imputation to reference panels from the International HapMap Project[67] because they did not provide sufficient coverage of SNVs included in the multi-ancestry meta-analysis. We considered the largest available GWAS meta-analysis (ancestry-specific or multi-ancestry) that provided the following association summary statistics for each SNV: effect allele, other allele, allelic effect and corresponding standard error (Supplementary Table 5). We re-aligned the effect estimate to the T2D risk allele from the fixed-effects multi-ancestry meta-analysis, denoted β_{ij} for the jth index SNV and the ith phenotype. We then calculated a sample size corrected z-score, given by $Z_{ij} = \beta_{ij} / (\sqrt{N_i} s_{ij})$, where s_{ij} is the standard error of the effect estimate of the jth index SNV and the ith phenotype, and N_i is the maximum sample size reported for the ith phenotype. Where association summary statistics were not reported, the z-score was set as 'missing'.

We conducted k-means clustering of index SNVs with imputation of missing z-scores using the R package ClustImpute (https://cran.r-project.org/package=ClustImpute). For a pre-defined number of clusters, ClustImpute replaces missing z-scores at random from the marginal distribution for the phenotype in the first iteration and performs k-means clustering. In subsequent iterations, missing z-scores are updated, conditional on the current cluster assignment, so that correlations between phenotypes are considered. At each iteration, penalizing weights are imposed on imputed values and successively decreased (to zero) as the missing data imputation improves. Finally, we determined the 'optimal' number of clusters according to the majority rule across 27 indices of cluster performance[68], implemented in the R package NbClust (https://cran.r-project.org/package=NbClust).

We tested for association of the ith phenotype with index SNVs across clusters in a linear regression model, given by $E(Z_{ij}) = \sum_k \gamma_{ik} C_{jk}$, where C_{jk} is an indicator variable that takes the value 1 if the jth index SNV was assigned to the kth cluster and 0 otherwise. The strength or direction of the association of each phenotype with each cluster was then

presented in a heat map, in which the 'temperature' was defined by the direction of the regression coefficient γ_{ik} and the corresponding $-\log_{10}$ P value. Regression models were fitted using the glm function in R.

We extracted cardiometabolic phenotype z-scores from the final imputed dataset from ClustImpute. We calculated the Euclidean distance between the jth SNV and kth cluster centroid as

$$\delta_{jk} = \sqrt{\sum_i (Z_{ij} - \mu_{ik})^2},$$

where Z_{ij} and μ_{ik} are the z-score of the jth SNV and the location of the kth cluster centroid for the ith cardiometabolic phenotype. To assess cluster disparity, we also performed principal components analysis of cardiometabolic phenotype z-scores from the final imputed dataset using the R package factoextra (https://cran.r-project.org/package=factoextra).

Cluster-specific associations of index SNVs with T2D

We tested for association of T2D with index SNVs across clusters in a linear regression model, given by $E(\beta_j) = \sum_k \gamma_k C_{jk}$, where C_{jk} is an indicator variable that takes the value 1 if the jth index SNV was assigned to the kth cluster and 0 otherwise, and weighted by the inverse of the variance of the allelic effect. We tested for heterogeneity in cluster effects on T2D by comparing the deviance of this model with that of $E(\beta_j) = \gamma_0$, again weighted by the inverse of the variance of the allelic effect. To compare associations between previously reported clusters and previously unreported clusters, we replaced C_{jk} with an indicator variable that takes the value 1 if the jth index SNV was assigned to a previously reported cluster and 0 otherwise. Regression models were fitted using the glm function in R.

Enrichment of T2D associations for cell-type-specific regions of open chromatin within clusters

For each T2D association signal, we defined 'null' SNVs that mapped within 50 kb of the index SNV and were not in LD ($r^2 > 0.05$) with the index SNV in any of the five continental groups from the 1000 Genomes Project (phase 3, October 2014 release)[54]. We defined an indicator variable, Y_j, taking the value 1 if the jth SNV is an index SNV and 0 if the jth SNV is a null SNV. We mapped index SNVs and null SNVs to genic regions defined by the Ensembl Project (release 104)[69], including protein-coding exons, and 3′ UTRs and 5′ UTRs. We defined indicator variables, G_j^{EXON}, G_j^{3UTR} and G_j^{5UTR}, which each take the value 1 if the jth SNV mapped to the respective genic annotation and 0 otherwise. We also mapped index SNVs and null SNVs to ATAC-seq peaks from single-cell atlases of chromatin accessibility (CATLAS and DESCARTES) for: 222 cell types derived from 30 human adult and 15 human fetal tissues[25,26]; and 106 cell types derived from human brain[27]. We defined an indicator variable, X_{ij}, that takes the value 1 if the jth SNV mapped to an ATAC-seq peak for the ith cell type and 0 otherwise.

Within each cluster, we modelled enrichment of T2D associations for ATAC-seq peaks in the ith cell type, after accounting for genic annotations, in a Firth bias-reduced logistic regression, given by

$$f^{-1}(Y_j) = \alpha_0 + \alpha_{\text{EXON}} G_j^{\text{EXON}} + \alpha_{\text{3UTR}} G_j^{\text{3UTR}} + \alpha_{\text{5UTR}} G_j^{\text{5UTR}} + \theta_i X_{ij},$$

where f is the logit link function. In this expression, α_0 is an intercept, α_{EXON}, α_{3UTR} and α_{5UTR} are log fold enrichments of genic annotations, and θ_i is the log fold enrichment of ATAC-seq peaks in the ith cell type. We conducted a test of enrichment of the ith cell type by comparing the deviances of models in which $\theta_i = 0$ and θ_i is unconstrained. We identified cell types with significant evidence of enrichment ($P < 0.00023$, Bonferroni correction for 222 cell types in adult and fetal tissues; $P < 0.00047$, Bonferroni correction for 106 cell types in the brain). All models were fitted using the R package logistf (https://cran.r-project.org/package=logistf).

Contribution of each axis of genetic variation to ancestry-correlated heterogeneity

For each index SNV, we calculated a z-score (beta/SE) for association with each axis of variation by aligning the effect from the meta-regression model to the T2D risk allele. For each index SNV, we identified the axis of genetic variation with the strongest association (greatest magnitude z-score).

Differences in ancestry-correlated heterogeneity between mechanistic clusters

We tested for differences in z-scores (beta/SE) for association of index SNVs in each cluster with the ith axis of genetic variation by comparing two linear models by ANOVA: (i) $f^{-1}(Z_{ij}) = \tau_{0i}$; and (ii) $f^{-1}(Z_{ij}) = \sum_k \tau_{ki} C_{jk}$. In these expressions: f is the identity link function; Z_{ij} is the z-score for the jth index SNV; C_{jk} is an indicator variable that takes the value 1 if the jth index SNV was assigned to the kth cluster and 0 otherwise; and τ_{0i} and τ_{ki} are regression coefficients. Regression models were fitted using the glm function in R.

Effect of BMI on ancestry-correlated and residual heterogeneity in allelic effects between GWASs

For each index SNV, we aggregated inverse-variance weighted allelic effects across GWASs by linear regression, implemented in MR-MEGA[10], including as covariates: (i) three axes of genetic variation; (ii) mean BMI in controls; and (iii) mean BMI in T2D cases. After adjustment for BMI, we tested for: (i) ancestry-correlated allelic effect heterogeneity between GWASs; and (ii) residual allelic effect heterogeneity between GWASs. After adjustment, as outlined above, we re-assessed: (i) the contribution of each axis of genetic variation to ancestry-correlated heterogeneity; and (ii) the difference in ancestry-correlated heterogeneity between mechanistic clusters.

Cluster-specific partitioned PS analyses of vascular outcomes and age of T2D onset

We tested for association of cluster-specific components of the partitioned PS and an overall PS with T2D-related macrovascular outcomes (CAD, ischaemic stroke and peripheral artery disease), microvascular complications (ESDN and proliferative diabetic retinopathy) and age of T2D onset in participants from the All of Us Research Program (AoURP; AFA, EUR and HIS ancestry groups), Biobank Japan (BBJ; EAS ancestry group), and Genes & Health (G&H; SAS ancestry group). Cohort descriptions and details of sequencing and genotyping, quality control and phenotype derivation are provided in the Supplementary Methods.

We conducted analyses separately for each ancestry group in AoURP, BBJ and G&H. For each ancestry, we performed analyses for macrovascular outcomes using all individuals, irrespective of T2D status, and for microvascular complications in individuals with T2D only. For each analysis, we calculated the overall PS and cluster-specific partitioned PS for each individual, with each index SNV weighted by the allelic log-OR from the ancestry-specific meta-analyses. We did not include index SNVs with MAF < 1% in the PS. We also excluded index SNVs with poor imputation quality ($r^2 < 0.7$) in BBJ and G&H, and those with extreme deviation from Hardy–Weinberg equilibrium ($P < 10^{-6}$) in AoURP. We standardized the overall PS and each cluster-specific component of the partitioned PS to have mean zero and unit variance. We tested for association with each vascular outcome through generalized linear regression and with age of T2D onset through linear regression. For each outcome, we considered a model including the overall PS and then each cluster-specific component the partitioned PS adjusted for the overall PS. All association analyses were conducted using the glm function in R.

We adjusted association analyses with vascular outcomes for age, sex and the first 20 principal components. In BBJ, we also adjusted for recruitment phase and status of the registered common diseases

(other than T2D) to account for ascertainment. We further adjusted analyses of macrovascular outcomes for T2D status. We also further adjusted analyses of microvascular complications for duration of T2D. In AoURP, we defined age as age at last hospital visit. In BBJ, we defined age as age at first record. In G&H, we defined age as age at diagnosis for T2D cases and age at last follow-up for controls. For CAD, we also conducted sensitivity analyses by including, as an additional covariate, a CAD PS from the largest published multi-ancestry CAD GWAS[39]. The PS was constructed from index SNVs for 241 conditionally independent CAD associations, weighted by the multi-ancestry allelic log-OR (ancestry-specific effects were not available), and standardized to have mean zero and unit variance. We adjusted association analyses with age of T2D onset for sex and the first 20 principal components. In BBJ, we also adjusted for recruitment phase and status of the registered common diseases (other than T2D) to account for ascertainment.

For each outcome, we aggregated association summary statistics from each cluster-specific component of the partitioned PS and the overall PS across ancestries through random-effects meta-analyses. All meta-analyses were conducted using the R package meta (https://cran.r-project.org/package=meta).

Cluster-specific partitioned PS analyses of clinical outcomes

We tested for association of cardiovascular and kidney-related clinical outcomes in EUR individuals with T2D in prospective GWASs from six clinical trials from the Thrombolysis in Myocardial Infarction (TIMI) Study Group (https://timi.org/). Trial descriptions and details of genotyping and quality control are provided in the Supplementary Methods.

Within each trial, we calculated the overall PS and cluster-specific components of the partitioned PS for each individual, with each index SNV weighted by the allelic log-OR from the European ancestry-specific meta-analysis. We standardized the overall PS and each cluster-specific component of the partitioned PS to have mean zero and unit variance. Data from the six trials were subsequently pooled, and we considered the following clinical outcomes in patients with T2D only: myocardial infarction, ischaemic stroke, cardiovascular death, hospitalization for heart failure, atrial fibrillation, acute limb ischaemia, peripheral revascularization, end-stage renal disease or renal death and albuminuria. We tested for association of each cluster-specific component of the partitioned PS with each clinical outcome under a Cox proportional hazards model, including age, sex, the first ten principal components and the overall PS as covariates. All association analyses were conducted using the coxph function with Efron ties handling from the R package survival (https://cran.r-project.org/package=survival).

Ethics statement

Study-level ethics statements are provided in the Supplementary Note.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Genome-wide association summary statistics from the multi-ancestry meta-analysis and ancestry-specific meta-analyses reported in this study are available through the DIAGRAM Consortium website (http://www.diagram-consortium.org/downloads.html).

Code availability

Analyses were conducted using publicly available software: the UCSC LiftOver tool (https://genome.ucsc.edu/cgi-bin/hgLiftOver), MR-MEGA v.0.2 (https://genomics.ut.ee/en/tools), METAL v.2011-03-25 (https://genome.sph.umich.edu/wiki/METAL), PLINK v.1.9 (https://www.cog-genomics.org/plink/1.9/), Beagle 4.1 (https://faculty.washington.edu/browning/beagle/b4_1.html), SNPTEST v.2.5.6 (https://www.well.ox.ac.uk/~gav/snptest/), GWAMA v.2.2.2 (https://genomics.ut.ee/en/tools), EIGENSOFT v.7.2.1 (https://www.hsph.harvard.edu/alkes-price/software/), PLINK v.2.0 (https://www.cog-genomics.org/plink/2.0/), SHAPEIT4 (https://odelaneau.github.io/shapeit4/), Minimac4 (https://genome.sph.umich.edu/wiki/Minimac4), KING v.2.3 (https://www.kingrelatedness.com/) and EAGLE v.2.4 (https://alkesgroup.broadinstitute.org/Eagle/#Xeagle2). Analyses were also conducted using the following R packages: meta (https://cran.r-project.org/package=meta), ClustImpute (https://cran.r-project.org/package=ClustImpute), NbClust (https://cran.r-project.org/package=NbClust), factoextra (https://cran.r-project.org/package=factoextra) and logistf (https://cran.r-project.org/package=logistf).

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Additional information

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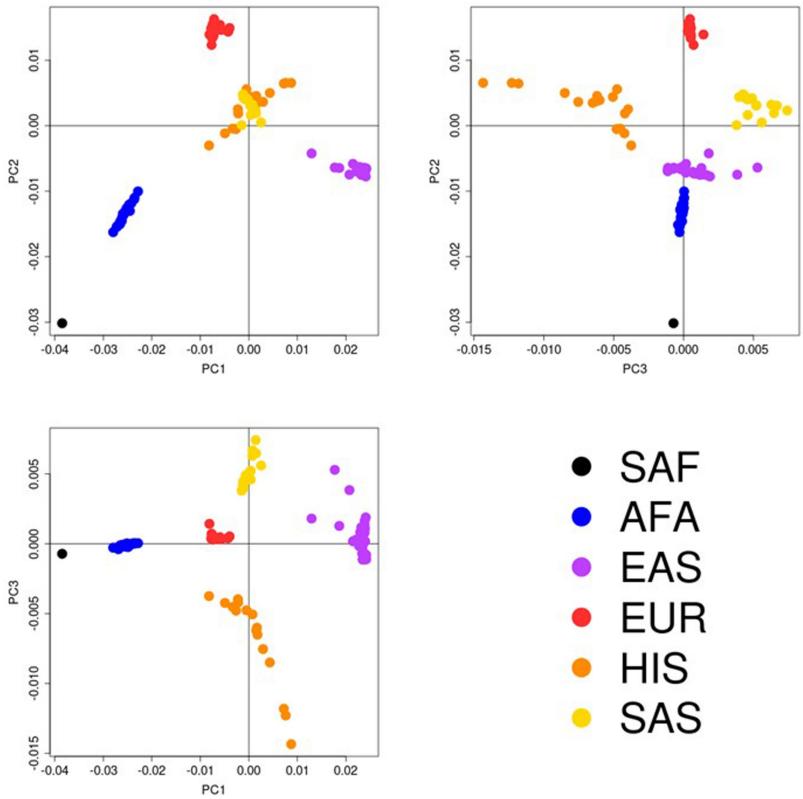
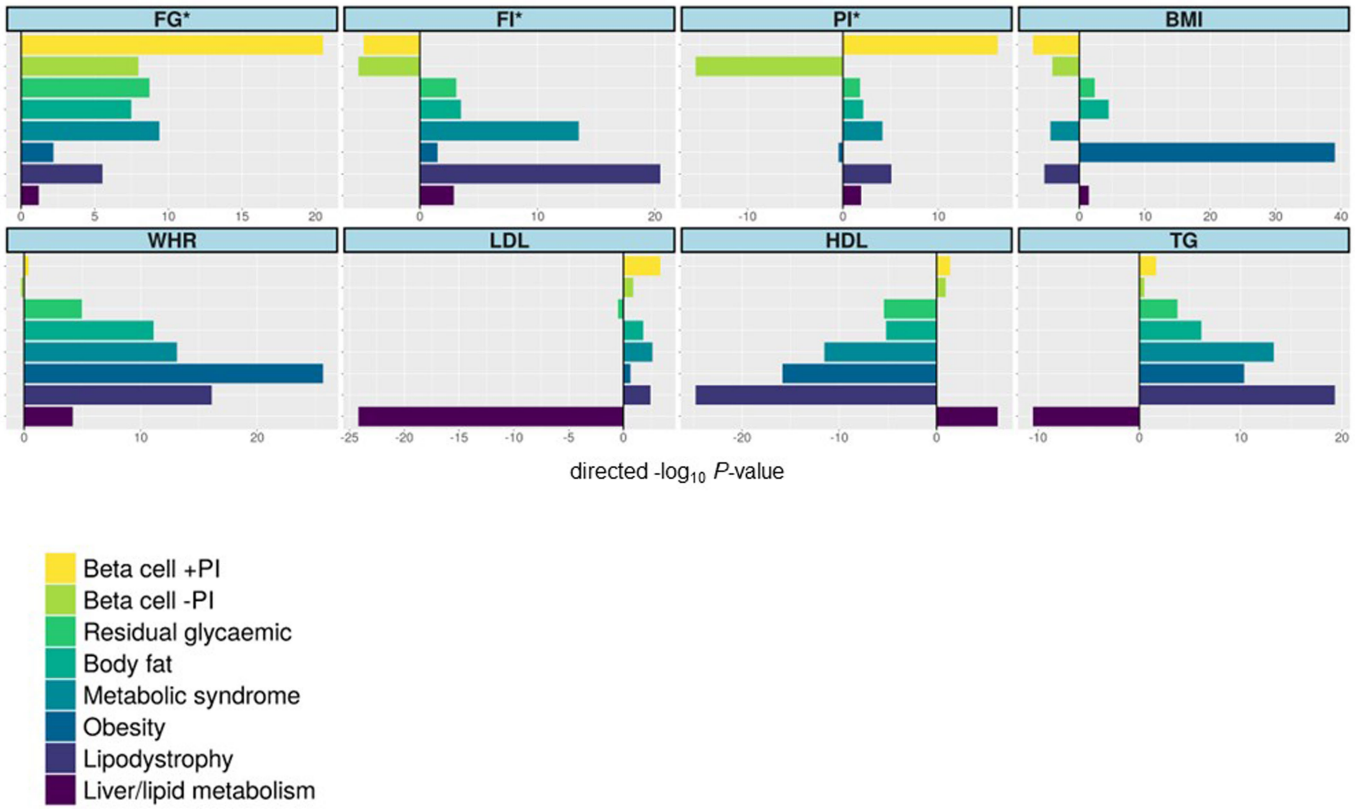
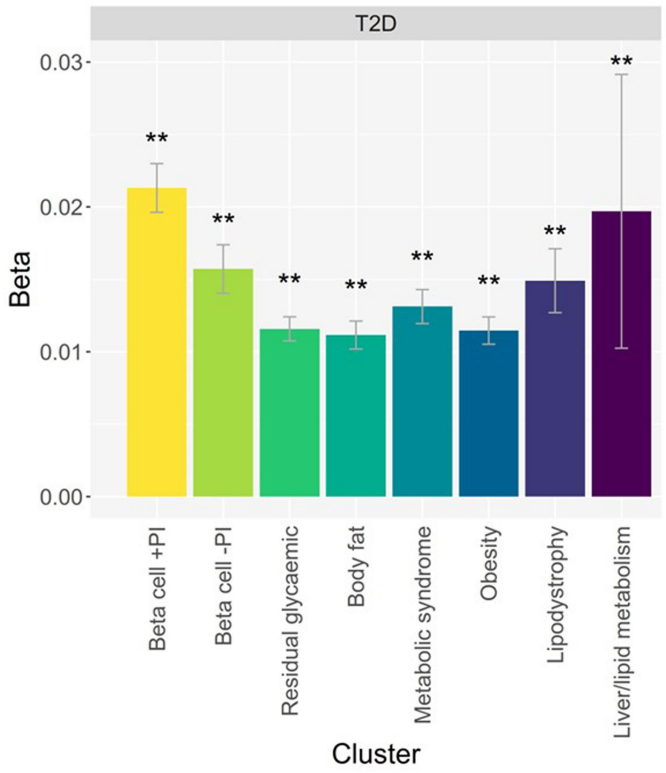


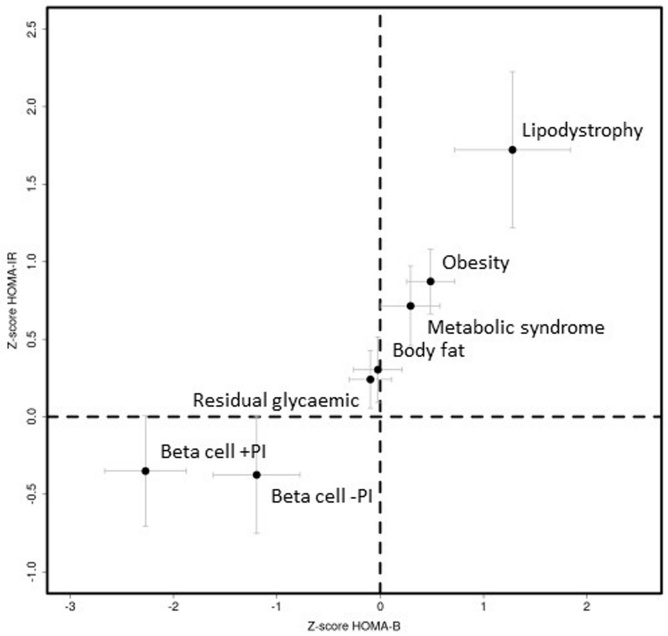
Extended Data Fig. 1 | Axes of genetic variation separating GWASs of T2D across ancestry groups. We used SNVs that were reported in all studies to construct a distance matrix of mean effect allele frequency differences between each pair of GWASs. We implemented multi-dimensional scaling of the distance matrix to principal components that represent axes of genetic variation. The first three axes of genetic variation (PC1, PC2 and PC3) from multi-dimensional scaling of the Euclidean distance matrix between populations are sufficient to separate GWASs from six ancestry groups: African American (AFA), East Asian (EAS), European (EUR), Hispanic (HIS), South African (SAF), and South Asian (SAS). Variance explained by each axis: PC1 90.7%; PC2 6.5%; PC3 1.0%.

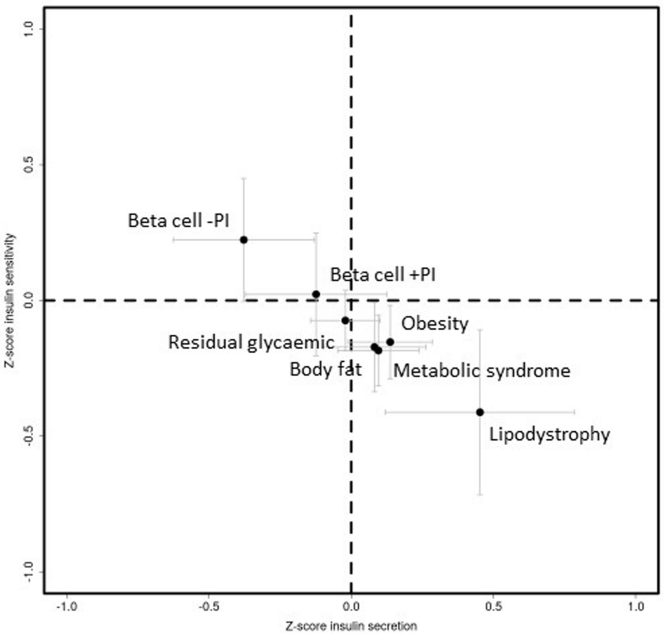


Extended Data Fig. 2 | Cluster-specific associations of index SNVs with defining cardiometabolic phenotypes. Each bar presents the $-\log_{10} P$ value for association, with effect direction aligned to the T2D risk allele. FG: fasting glucose. FI: fasting insulin. PI: proinsulin. BMI: body mass index. WHR: waist–hip ratio. LDL: low-density lipoprotein cholesterol. HDL: high-density lipoprotein cholesterol. TG: triglycerides. *Trait adjusted for BMI.

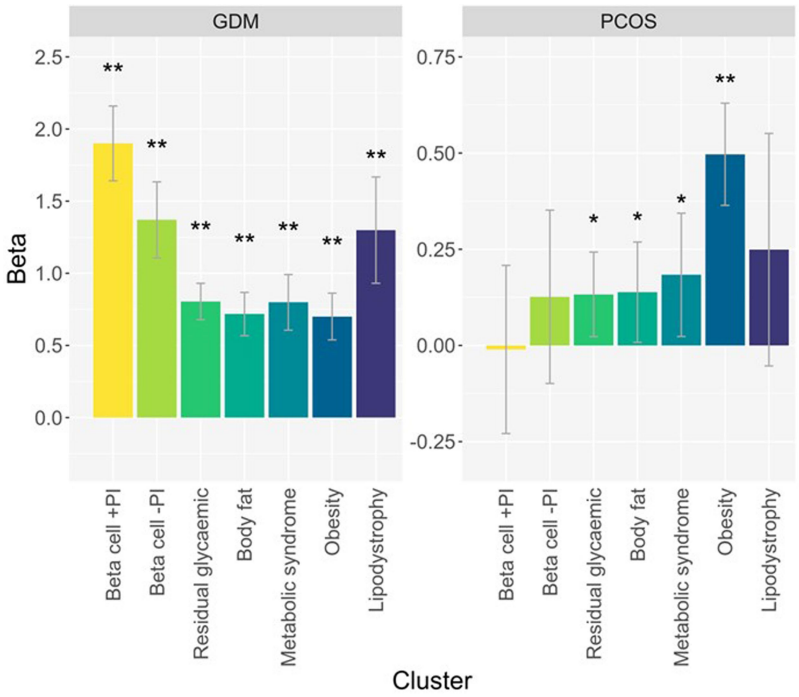


Extended Data Fig. 3 | Cluster-specific associations of index SNVs with T2D. The height of each bar corresponds to the log-odds ratio (beta), and the grey bar shows the 95% confidence interval. *$P < 0.05$, nominal association. **$P < 0.0063$, Bonferroni correction for eight clusters. Exact P values are presented in Supplementary Table 9.

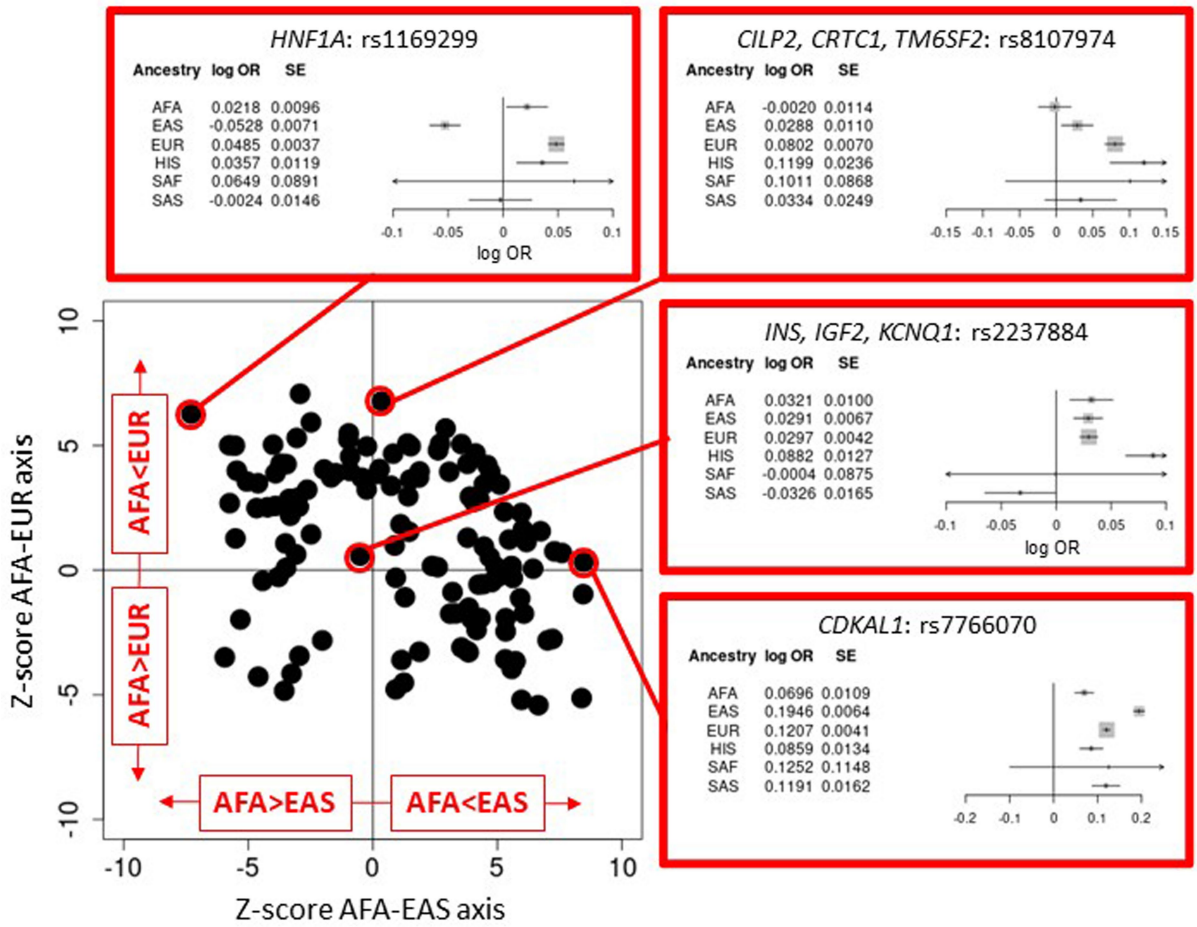




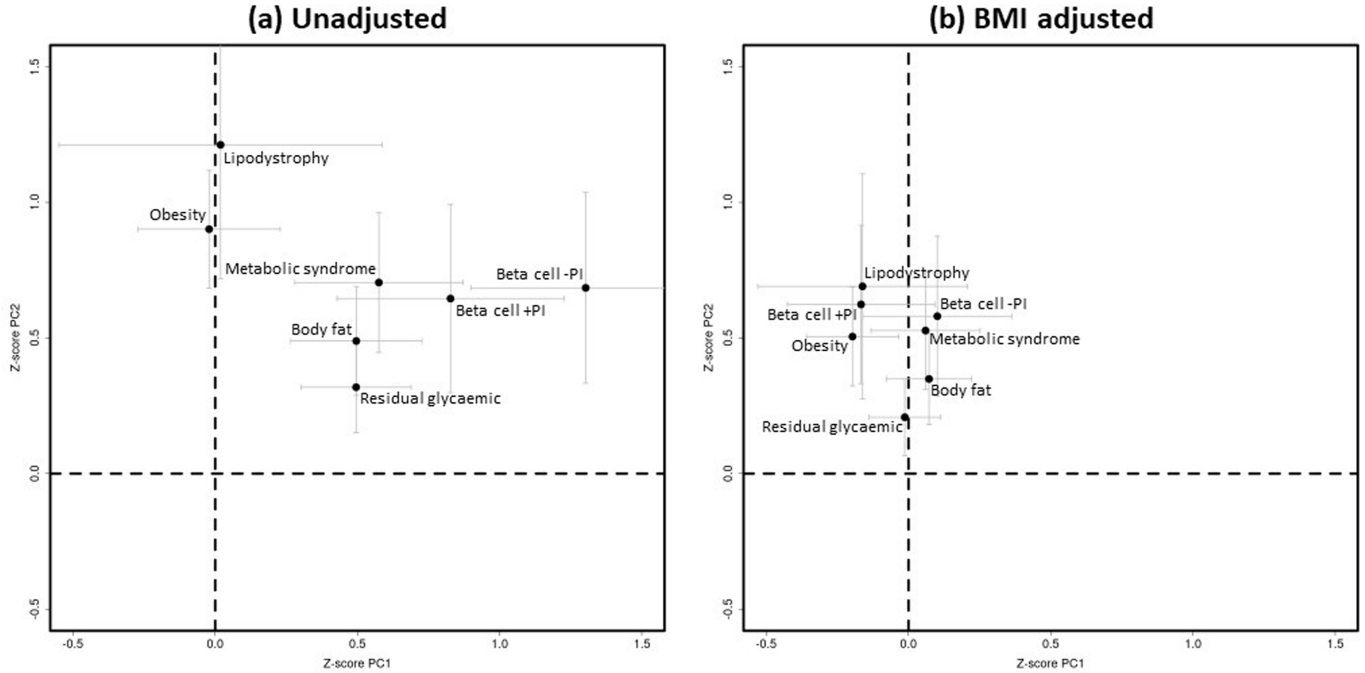
Extended Data Fig. 4 | Cluster-specific associations of T2D risk alleles at index SNVs with insulin-related endophenotypes. Measures of insulin secretion and insulin sensitivity were derived from hyperinsulinaemic-euglycaemic clamp assessments and oral glucose tolerance tests in up to 1,316 Mexican American participants without diabetes. Homeostatic model assessment measures of beta-cell function (HOMA-B) and insulin resistance (HOMA-IR) were obtained from 36,466 non-diabetic individuals of European ancestry. Each point corresponds to the cluster-specific mean *z*-score for each trait, and grey bars represent 95% confidence intervals. The liver and lipid metabolism cluster has been removed for ease of presentation.



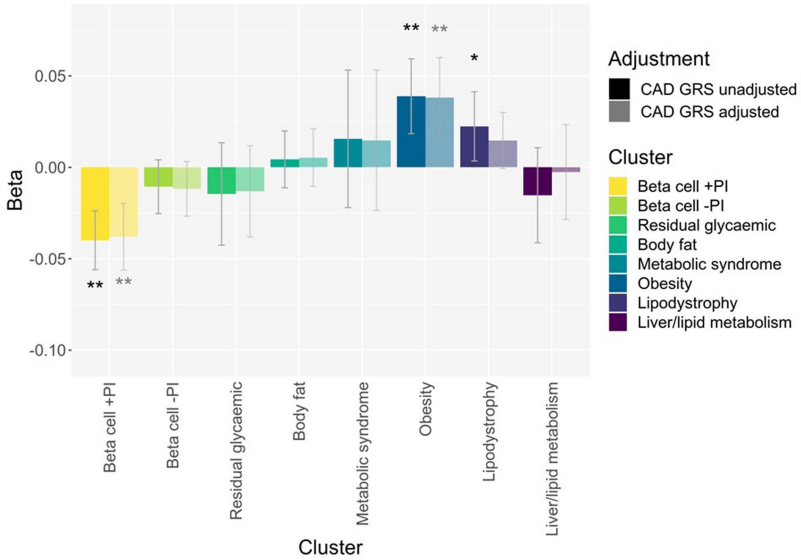
Extended Data Fig. 5 | Cluster-specific associations of T2D risk alleles at index SNVs with insulin-resistance-related disorders. Association with gestational diabetes mellitus (GDM) was assessed in 5,485 cases and 347,856 female controls of diverse ancestry. Association with polycystic ovary syndrome (PCOS) was assessed in 10,074 cases and 103,164 female controls of European ancestry. The height of each bar corresponds to the mean *z*-score, and the grey bar shows the 95% confidence interval. The liver and lipid metabolism cluster has been removed for ease of presentation. *$P < 0.05$, nominal association. **$P < 0.0063$, Bonferroni correction for eight clusters. Exact *P* values are presented in Supplementary Table 12.



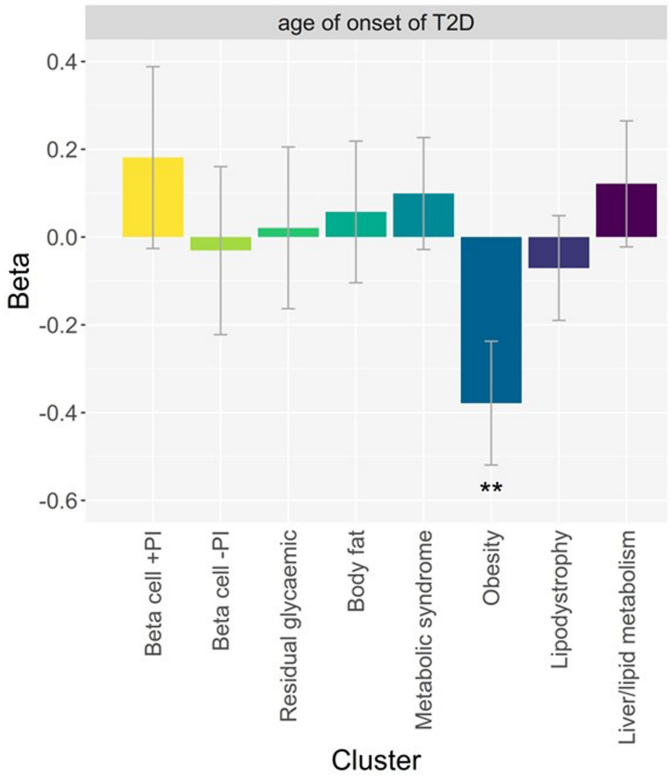
Extended Data Fig. 6 | Ancestry-correlated heterogeneity is driven by differences in allelic effect sizes between AFA, EAS and EUR ancestry groups. In the scatter plot, index SNVs with significant evidence ($P_{HET} < 3.9 \times 10^{-5}$, Bonferroni correction for 1,289 signals) for ancestry-correlated heterogeneity are plotted according to their association (*z*-score) with the first two axes of genetic variation. The first axis represents differences in allelic effect sizes between AFA/EUR GWASs and EAS GWASs (AFA–EAS axis), whilst the second axis represents differences in effect size between AFA/EAS GWASs and EUR GWASs (AFA–EUR axis). The forest plots present examples of ancestry-correlated heterogeneity at index SNVs. In each forest plot, the allelic log-odds ratio (OR) from each ancestry group-specific fixed-effects meta-analysis is given by the black tick mark, the 95% confidence interval is given by the horizontal line, and the weight (inverse-variance) of each ancestry group by the grey box. AFA: African American ancestry group. EAS: East Asian ancestry group. EUR: European ancestry group. HIS: Hispanic ancestry group. SAF: South African ancestry group. SAS: South Asian ancestry group.



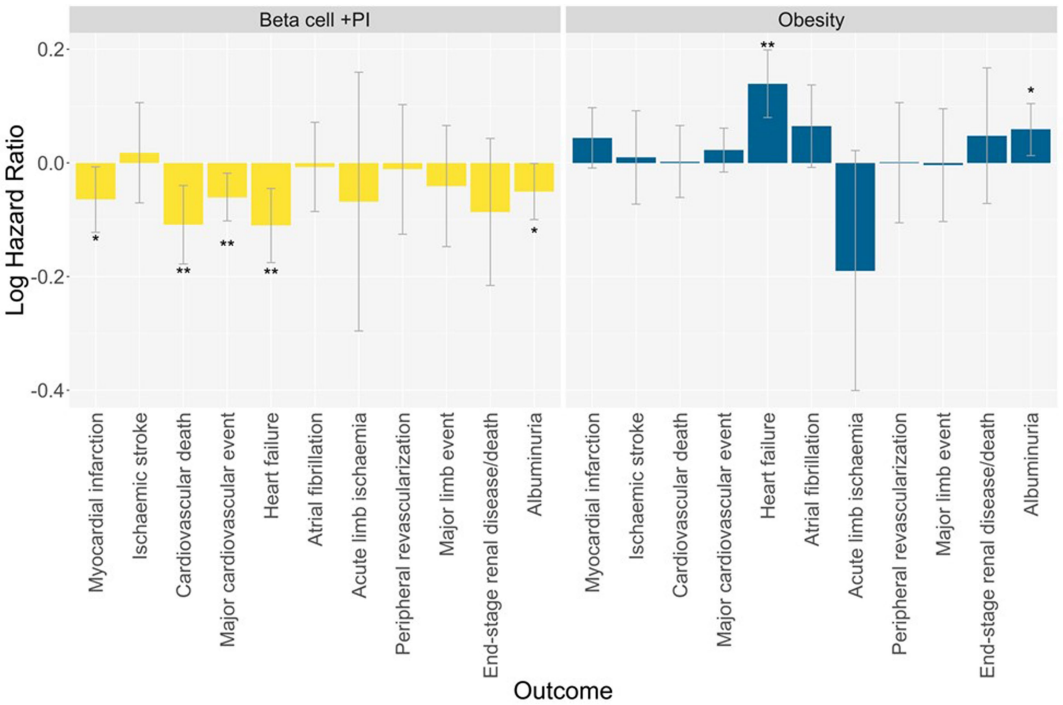
Extended Data Fig. 7 | Cluster-specific associations of index SNVs with the first two axes of genetic variation in T2D cases and controls. a, Unadjusted for BMI. **b**, Adjusted for study-level mean BMI. Each point corresponds to a cluster, plotted according to the mean *z*-score for association with the first two axes of genetic variation (PC1 and PC2) on the *x* axis and *y* axis, respectively. Grey bars correspond to 95% confidence intervals. The liver and lipid metabolism cluster has been removed for ease of presentation.



Extended Data Fig. 8 | Associations of cluster-specific components of the partitioned PS with CAD in up to 279,552 individuals across diverse ancestry groups. The panel summarizes the associations of each cluster-specific component of the partitioned PS with CAD, with and without adjustment for a previously published multi-ancestry CAD PS. The height of each bar corresponds to the log-OR (beta) per standard deviation of the PS, and the grey bar shows the 95% confidence interval. Analyses were undertaken in all individuals, with adjustment for T2D status. *$P < 0.05$, nominal association. **$P < 0.0063$, Bonferroni correction for eight clusters. Exact P values are presented in Supplementary Tables 21 and 22.



Extended Data Fig. 9 | Associations of cluster-specific components of the partitioned PS with T2D age of onset in up to 30,288 individuals across diverse ancestry groups. The panel summarizes the associations of each cluster-specific component of the partitioned PS with age of onset. The height of each bar corresponds to years (beta) per standard deviation of the PS, and the grey bar shows the 95% confidence interval. A negative effect corresponds to earlier age of onset. *$P < 0.05$, nominal association. **$P < 0.0063$, Bonferroni correction for eight clusters. Exact P values are presented in Supplementary Table 23.



Extended Data Fig. 10 | Associations of the beta cell +PI and obesity cluster-specific components of the partitioned PS with vascular outcomes in up to 29,827 EUR individuals with T2D from six clinical trials from the TIMI Study Group. Major cardiovascular event is defined as myocardial infarction, ischaemic stroke, or cardiovascular death. Major limb event is defined as acute limb ischaemia or peripheral revascularization. The height of each bar corresponds to the log-hazard ratio per standard deviation of the PS, and the grey bar shows the 95% confidence interval. *$P < 0.05$, nominal association. **$P < 0.0063$, Bonferroni correction for eight clusters. Exact P values are presented in Supplementary Table 24.

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Software and code

Policy information about availability of computer code

Data collection	No software were used for data collection.
Data analysis	Analyses were conducted using publicly available software: UCSC liftOver tool (https://genome.ucsc.edu/cgi-bin/hgLiftOver), MR-MEGA v0.2 (https://genomics.ut.ee/en/tools), METAL v2011-03-25 (https://genome.sph.umich.edu/wiki/METAL), PLINKv1.9 (https://www.cog-genomics.org/plink/1.9/), Beagle 4.1 (https://faculty.washington.edu/browning/beagle/b4_1.html), SNPTEST v2.5.6 (https://www.well.ox.ac.uk/~gav/snptest/), GWAMA v2.2.2 (https://genomics.ut.ee/en/tools), EIGENSOFT v7.2.1 (https://www.hsph.harvard.edu/alkes-price/software/), PLINKv2.0 (https://www.cog-genomics.org/plink/2.0/), SHAPEIT4 (https://odelaneau.github.io/shapeit4/), Minimac4 (https://genome.sph.umich.edu/wiki/Minimac4), KING v2.3 (https://www.kingrelatedness.com/), and EAGLE v2.4 (https://alkesgroup.broadinstitute.org/Eagle/#Xeagle2). Analyses were also conducted using the following R packages: meta (https://cran.r-project.org/package=meta), ClustImpute (https://cran.r-project.org/package=ClustImpute), NbClust (https://cran.r-project.org/package=NbClust), factoextra (https://cran.r-project.org/package=factoextra), and logistf (https://cran.r-project.org/package=logistf).

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- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Data availability. Genome-wide association summary statistics from the multi-ancestry meta-analysis and ancestry-specific meta-analyses reported in this study are available through the DIAGRAM Consortium website (http://www.diagram-consortium.org/downloads.html).

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	The numbers of males and females for each contributing study are reported in Supplementary Table 3. Sex-stratified analyses were not conducted.
Population characteristics	Characteristics are presented for each contributing study in Supplementary Table 3.
Recruitment	Ascertainment of type 2 diabetes cases and controls for each contributing study are presented in Supplementary Table 1.
Ethics oversight	All human research was approved within each contributing study by the relevant institutional review boards and conducted according to the Declaration of Helsinki. All participants provided written informed consent. Ethics statements from each contributing study are provided in the Supplementary Note.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Our discovery GWAS meta-analysis and polygenic score test GWAS brought together the largest sample size of type 2 diabetes cases and (population) controls that was available to the Type 2 Diabetes Global Genomics Initiative. Discovery GWAS meta-analysis. With our sample size of 428,452 T2D cases and 2,107,149 controls, at a genome-wide significance threshold ($p<5x10-8$), under an additive genetic model of homogeneous effects across ancestry groups, we had ≥80% power to detect association of SNVs with MAF ≥5% and OR ≥1.035 or MAF ≥0.5% and OR ≥1.107. Polygenic score test GWAS. We aggregated 30,288 T2D cases and 249,264 controls from the All of Us Research Program, Biobank Japan, and Genes & Health, who were not included as part of the discovery meta-analysis. We also consider 29,827 individuals with T2D from six clinical trials from the Thrombolysis in Myocardial Infarction (TIMI) Study Group.
Data exclusions	Within each contributing study, individuals were excluded on the basis of well-established individual and variant quality control (QC) procedures to remove poor quality genotypes, samples and SNVs. These QC procedures are described in Supplementary Table 3 for each study.
Replication	We did not conduct a formal replication analysis since we had already brought together all GWAS data available to the Type 2 Diabetes Global Genomics Initiative. The polygenic score test GWAS were not used to replicate association signals from the discovery meta-analysis because sample overlap can lead to increased false positive error rates in polygenic score analyses. All reported association signals from the discovery meta-analysis were checked to confirm that effects were not driven by false positives in single studies.
Randomization	Randomization was not performed. Within each study, covariates were adjusted for to account for potential confounding. Covariate adjustments are reported in Supplementary Table 3.
Blinding	Group allocation was not relevant to this study, so blinding was not necessary.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

nature portfolio

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Supplementary information

Genetic drivers of heterogeneity in type 2 diabetes pathophysiology

In the format provided by the authors and unedited

Genetic drivers of heterogeneity in type 2 diabetes pathophysiology

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SUPPLEMENTARY INFORMATION

Supplementary Note

Supplementary Figures

Supplementary Text

Summary of loci identified through recent large-scale multi-ancestry meta-analyses. Two recent partially overlapping multi-ancestry meta-analyses of T2D GWAS together account for 69.3% of the total effective sample size of the multi-ancestry meta-regression undertaken by the T2D Global Genomics Initiative (**Supplementary Figure 1**). First, the meta-analysis of GWAS from the Million Veteran Program[1], which includes 228,499 T2D cases and 1,178,783 controls. Second, the meta-analysis of GWAS from the DIAMANTE Consortium[2], which includes 180,834 cases and 1,159,055 controls. We aimed to provide a comprehensive overview of the genetic contribution to T2D by summarising loci reported in these multi-ancestry GWAS meta-analyses at the conventional genome-wide significance threshold ($P<5x10^{-8}$) and a more stringent multi-ancestry genome-wide significance threshold ($P<5x10^{-9}$) proposed by the DIAMANTE Consortium. We aggregated loci reported in each of the three meta-analyses, ensuring no overlap between adjacent loci. Taken together, the three studies report 636 non-overlapping loci spanning 835.5Mb, of which 536 (84.3%) meet stringent multi-ancestry genome-wide significance in at least one of the multi-ancestry meta-analyses (**Supplementary Table 25**).

We investigated the likelihood that loci reported at the conventional genome-wide significance threshold by the DIAMANTE Consortium meet the more stringent multi-ancestry threshold in the larger sample size afforded by the T2D Global Genomics Initiative. We focussed on comparing results from these two efforts because both used the same meta-regression approach (MR-MEGA) to aggregate association summary statistics across GWAS. Of 39 loci with association signals meeting $5x10^{-9}\leq P<5x10^{-8}$ reported by the DIAMANTE Consortium, 36 (92.3%) attained multi-ancestry genome-wide significance in the T2D Global Genomics Initiative (**Supplementary Table 25**). Of the three loci that did not meet the more stringent threshold, the signal at the *RASA1* locus was marginally more strongly associated (lead SNV rs11953892, $P=1.6x10^{-8}$ versus $P=1.9x10^{-8}$) in the T2D Global Genomics Initiative meta-analysis than in the DIAMANTE Consortium meta-analysis. However, association signals at the two remaining loci were weaker in the T2D Global Genomics Initiative than in the DIAMANTE Consortium, despite the increase in sample size. At the locus encompassing *CCDC39* and *FXR1*, the association signal was nominally significant in the Million Veteran Program (lead SNV rs4854992, $P=0.0081$) with the same direction of effect as in the DIAMANTE Consortium meta-analysis. However, at the *CFAP6* locus, there was no association in the Million Veteran Program (lead SNV rs7261425, $P=0.13$).

Taken together, these results indicate that index SNVs attaining the conventional threshold of $P<5x10^{-8}$ are unlikely to be false positive association signals but have modest effects that require larger sample sizes to meet multi-ancestry genome-wide significance.

Clusters are differentially associated with insulin-related endophenotypes. We assessed the association of index SNVs with insulin-related endophenotypes that were not used for clustering and derived from: hyperinsulinemic-euglycemic clamp assessments and oral glucose tolerance tests (OGTT) in up to 1,316 Mexican American participants without diabetes from the GUARDIAN Consortium[3]; and homeostatic model assessment measures of beta-cell function (HOMA-B) and insulin resistance (HOMA-IR) in up to 36,466 non-diabetic EUR individuals from MAGIC[4] (**Supplementary Methods**). We observed significant heterogeneity in the effects of T2D risk alleles at index SNVs between clusters on HOMA-B ($P_{HET}<2.2x10^{-16}$), HOMA-IR ($P_{HET}=4.1x10^{-15}$), insulin secretion (OGTT-derived area under the

curve for insulin normalised for glucose from baseline to 30 minutes, P_{HET}=0.0026), and insulin sensitivity (clamp-derived glucose infusion rate, P_{HET}=0.026). T2D risk alleles at index SNVs showed a gradient of effects on these correlated measures across clusters (**Extended Data Figure 4, Supplementary Tables 10 and 11**), representing a cline from insulin production and processing in the two beta-cell dysfunction clusters (increased insulin sensitivity; decreased insulin secretion, HOMA-B, and HOMA-IR) through to insulin resistance (decreased insulin sensitivity; increased insulin secretion, HOMA-B, and HOMA-IR) that was most extreme in the lipodystrophy cluster.

Clusters are differentially associated with insulin resistance-related disorders. To understand the shared biological pathways driving genetic correlations with gestational diabetes mellitus (GDM) and polycystic ovary syndrome (PCOS), we extracted association summary statistics for each T2D index SNV from the largest available published GWAS for both disorders[5,6] (**Supplementary Methods**). We observed significant heterogeneity in the effects of T2D risk alleles at index SNVs between clusters for both disorders (**Extended Data Figure 5, Supplementary Table 12**): GDM (P_{HET}=7.0x10^{-16}) and PCOS (P_{HET}=0.00022). Index SNVs in the beta-cell +PI cluster demonstrated the strongest associations with GDM. This cluster includes T2D index SNVs that overlap with association signals previously reported for GDM, mapping to/near *MTNR1B*, *CDKAL1*, *TCF7L2*, and *CDKN2A-CDKN2B*, consistent with hyperglycaemia due to beta-cell dysfunction on a background of pregnancy-induced physiologic insulin resistance[7]. In contrast, PCOS is most strongly associated with index SNVs in the obesity cluster, consistent with previous Mendelian randomization studies that report a strong causal effect of higher BMI on increased PCOS risk[8].

Cluster-specific associations of index SNVs with circulating GLP-1 concentrations. The beta-cell -PI cluster was enriched in adult enterochromaffin cells, a type of enteroendocrine cell that plays an essential role in regulating intestinal motility and secretion in the gastrointestinal tract[9]. Enterochromaffin cells are a major target for GLP-1 and highly express GLP-1 receptor, whose agonists are widely used as medications for T2D[10]. Between clusters, we compared the associations of index SNVs with 2-hour and fasting circulating GLP-1 concentrations in up to 3,514 EUR individuals from the Malmo Diet and Cancer Study[11] and the PPP-Botnia Study[12] (**Supplementary Methods**). Whilst differences in the effects of index SNVs on these measures were not significant between clusters (P>0.05), T2D risk alleles for index SNVs in the beta-cell -PI cluster showed a trend of association with decreased 2-hour GLP-1, whilst those in other clusters showed a trend of association with increased fasting GLP-1 (**Supplementary Figure 13**). Additional analyses in GLP-1 GWAS with larger sample sizes will be required to validate this finding.

T2D association signals are differentially enriched for ancestry-correlated heterogeneity across mechanistic clusters. To understand better the impact of genetic diversity on differences in allelic effects between GWAS at T2D association signals, we assessed the contribution of each of the three axes of genetic variation to heterogeneity (**Methods**). For 118 (92.9%) of the 127 association signals with significant evidence of ancestry-correlated heterogeneity, allelic effect sizes were most strongly associated with the first two axes of genetic variation (**Extended Data Figure 1, Supplementary Table 16**). This may simply reflect greater power to detect heterogeneity because these two axes separate GWAS from the three ancestry groups (AFA, EAS, and EUR) that make the largest contributions to the

effective sample size of the multi-ancestry meta-analysis. The magnitude and direction of the association of index SNVs with these two axes reflected differences in allelic effect size between AFA/EUR and EAS GWAS on the AFA-EAS axis, and AFA/EAS and EUR GWAS on the AFA-EUR axis (**Extended Data Figure 6**). For example, the T2D association signal indexed by rs7766070 at the *CDKAL1* locus was positively associated with the AFA-EAS axis (P=4.2x10^{-14}), but not the AFA-EUR axis (P=0.74) and is therefore characterised by a larger allelic effect in EAS GWAS than in AFA and EUR GWAS. On the other hand, at the locus encompassing *CILP2*, *CRTC1*, and *TM6SF2*, the T2D association signal indexed by rs8107974 has a larger allelic effect in EUR GWAS than in AFA and EAS GWAS, consistent with a positive association with the AFA-EUR axis (P=3.7x10^{-10}), but not the AFA-EAS axis (P=0.72).

The most significant evidence of ancestry-correlated heterogeneity was observed for the T2D association signal at the *HNF1A* locus indexed by rs1169299 (P_{HET}=4.8x10^{-35}). This index SNV was negatively associated with the AFA-EAS axis (P_{HET}=2.7x10^{-11}), and positively associated with the AFA-EUR axis (P_{HET}=4.6x10^{-9}), corresponding to an AFA allelic effect (OR=1.02) that was intermediate between the EAS and EUR allelic effects (OR=0.95 and OR=1.05, respectively). In contrast, the association signal indexed by rs2237884, at the locus encompassing *INS*, *IGF2*, and *KCNQ1*, was not associated with either the AFA-EAS axis (P_{HET}=0.61) or AFA-EUR axis (P_{HET}=0.56), indicating no difference in allelic effects between AFA, EAS, and EUR GWAS (OR=1.03 for all three ancestry groups). Instead, the heterogeneity for this signal was driven by association with the third axis of genetic variation (P_{HET}=2.8x10^{-8}), which separates HIS and SAS GWAS (OR=1.09 and OR=0.97, respectively).

We investigated whether the observed ancestry-correlated differences in allelic effects on T2D between ancestry groups varied across mechanistic clusters. To do this, we compared the magnitude and direction of association of index SNVs in each cluster with the first three axes of genetic variation (**Methods**). We observed significant differences in mean Z-scores for association between clusters for both the AFA-EAS axis (P=4.1x10^{-6}) and the AFA-EUR axis (P=1.5x10^{-6}), but not for the HIS-SAS axis (P=0.17), reflecting at least in part differences in sample size and therefore statistical power. Index SNVs in the two beta-cell clusters were most positively associated with the AFR-EAS axis, indicating allelic effects on T2D that were greater in EAS than in AFA and EUR GWAS (**Extended Data Figure 7, Supplementary Table 17**). In contrast, index SNVs in the lipodystrophy and obesity clusters were most positively associated with the AFA-EUR axis, indicating allelic effects on T2D that were greater in EUR GWAS than in EAS/AFA GWAS.

Impact of BMI on ancestry-correlated heterogeneity between GWAS. To investigate the impact of ancestry-correlated heterogeneity in allelic effects between GWAS, we extended the MR-MEGA meta-regression model to account for mean BMI in T2D cases and controls, in addition to axes of genetic variation (**Methods**). After adjustment for study-level mean BMI in T2D cases and in controls, only 24 association signals retained significant evidence of ancestry-correlated heterogeneity (P<3.9x10^{-5}), compared with 127 signals without adjustment (**Supplementary Table 18**). For example, at the *HNF1A* locus, the ancestry-correlated heterogeneity at the T2D association indexed by rs1169299 was attenuated after BMI adjustment (P=0.00016 versus P=4.8x10^{-35} without adjustment), which is consistent with the assignment of this signal to the beta-cell -PI cluster. In contrast, at the association signal indexed by rs2237884, at the locus encompassing *INS*, *IGF2*, and *KCNQ1*, which was assigned to the body fat cluster, ancestry-correlated heterogeneity was not meaningfully impacted by BMI adjustment (P=5.0x10^{-7} versus P=2.7x10^{-7} without adjustment). After

adjustment for BMI, significant differences in mean Z-scores for association between clusters for the AFA-EUR axis were maintained (P=3.2x10^{-5} versus P=1.5x10^{-6} without adjustment), whilst those for the AFA-EAS axis were not (P=0.18 versus P=4.1x10^{-6} without adjustment). Furthermore, after adjustment for BMI, the two beta-cell clusters were no longer strongly positively associated with the AFA-EAS axis (**Extended Data Figure 7, Supplementary Table 19**).

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Supplementary Methods

Cluster-specific associations of index SNVs with insulin-related endophenotypes and insulin resistance-related disorders. We extracted association summary statistics for measures of glucose homeostasis derived from hyperinsulinemic-euglycemic clamp assessments and oral glucose tolerance tests (OGTT) performed by the GUARDIAN Consortium[1], which were obtained from GWAS undertaken in up to 1,316 non-diabetic Mexican American participants from the Mexican American Coronary Artery Disease (MACAD) study[2] and the Hypertension and Insulin Resistance (HTN-IR) study[3]. The measures used were: insulin sensitivity (clamp-derived glucose infusion rate in 1,316 participants from MACAD and HTN-IR); insulin clearance (clamp-derived metabolic clearance rate of insulin in 1,261 participants from MACAD and HTN-IR); and insulin secretion (OGTT-derived area under the curve for insulin normalised for glucose from baseline to 30 minutes in 513 participants from MACAD). We also extracted association summary statistics for homeostatic model assessment measures of beta-cell function (HOMA-B) and insulin resistance (HOMA-IR) from published GWAS meta-analyses of up to 36,466 non-diabetic European ancestry individuals from MAGIC[4]. We also extracted association summary statistics for insulin resistance-related disorders from published GWAS meta-analyses of: (i) 5,485 GDM cases and 347,856 female controls of diverse ancestry from the GenDIP Consortium[5]; and (ii) 10,074 PCOS cases and 103,164 female controls of European ancestry[6].

For each endophenotype/disorder, we aligned the effect estimate to the T2D risk allele from the fixed-effects multi-ancestry meta-analysis, denoted β_j for the jth index SNV. We then calculated the Z-score, given by $Z_j = \beta_j / s_j$, where s_j is the standard error of the effect estimate of the jth index SNV. We tested for association of each endophenotype with index SNVs across clusters in a linear regression model, given by $E(Z_j) = \sum_k \gamma_k C_{jk}$, where C_{jk} is an indicator variable that takes the value "1" if the jth index SNV was assigned to the kth cluster and "0" otherwise. We tested for heterogeneity in cluster effects on each endophenotype by comparing the deviance of this model with that of $E(Z_j) = \gamma_0$. Regression models were fitted using the glm function in R.

Cluster-specific associations of index SNVs with circulating GLP-1 concentrations. The Malmo Diet and Cancer Study (MDCS) is a prospective population-based cohort study that includes 31088 men and women aged 44 to 74 who completed a baseline examination between 1991 and 1996 and lived in Malmo[7]. A random subset was invited to a reinvestigation starting in 2007, where GLP-1 was measured[8]. Individuals with diabetes were excluded from the analysis. An overnight fast was followed by the administration of 75g OGTT for diabetes free individuals. Blood samples were analyzed for GLP-1 concentrations at 0 and 120 minutes. Total plasma GLP-1 concentrations, including intact GLP-1 and the metabolite GLP-1 9-36 amide, were determined radioimmunologically with an in-house anti-serum (no. 89390; sensitivity <1 pmol/l)[9,10].

The Prevalence, Prediction and Prevention of type 2 diabetes (PPP)-Botnia Study is a population-related study that began in 2004 in Finland. Participants were randomly selected from the National Finnish Population Registry, representing 6%-7% of the 18-75 age population. Of the original 5,208 participants, 3,850 (77%) attended the first follow-up study in 2011-2015, where GLP-1 was measured[11]. A 75g OGTT was conducted after overnight 10-12 hours fasting with blood samples drawn at 0, 30, and 120 minutes. GLP-1 was measured at 0 and 120 minutes. GLP-1 was measured using GLP-1 (total) radioimmunoassay (GLP1T-

36HK, EMD Millipore) with high specificity to GLP-1 (GLP-2, glucagon, and exendin <0.2%). The range was 3–333 pmol/l. Serum insulin was measured by an AutoDelfia fluoroimmunometric assay (B080-101, PerkinElmer)[11].

MDCS was genotyped at the Broad genotyping facility using the Infinium OmniExpressExome v1.0 B Beadchip array (Illumina). PPP-Botnia genotyping was performed on a FinnGen ThermoFisher Axiom custom array[12] at the Thermo Fisher genotyping service facility in San Diego. Standard quality control filters were applied to filter SNvs and samples before imputation. SNVs were excluded for monomorphism, low call rate, or Hardy-Weinberg deviation. Samples with duplications or low call rates, unexpected relatives, sex mismatches, heterozygosity outliers, ancestral outliers (non-EUR) were excluded. For MDCS, genotype imputation for autosomal chromosomes was performed using the Haplotype Reference Consortium version 1.0.3 on the Michigan Server. For PPP-Botnia, genotype imputation was carried out using the population-specific SISu v3 reference panel[12] with Beagle 4.1[13]. In both studies, GLP-1 hormone levels were log-transformed before analysis. SNPTEST v.2.5.6[14] was used for genome-wide association analyses, using frequentist score method adjusted for age, sex and first four principal components. The results were filtered based on MAF >0.01, Hardy-Weinberg equilibrium $P>5x10^{-7}$, and imputation info >0.4. A fixed effect meta-analysis (inverse-variance weighting) was performed using GWAMA[15]. The final analysis included 3,514 individuals with fasting GLP-1 and 3,511 individuals with 2-hour GLP-1.

All of Us Research Program (AoURP) cohort description, sequencing, quality control, and phenotype derivation. We considered participants with whole-genome sequencing (WGS) and electronic health record (EHR) data from the AoURP Controlled Tier Dataset v7[16,17]. Details of the generation and quality control of the genomic data can be found in the AoURP Genomic Quality Report release C2022Q4R9 (https://support.researchallofus.org/hc/en-us/article_attachments/17973653017236). Briefly, we used computed genetic ancestries and removed related individuals in the maximal independent set (kinship score >0.1). To reduce the computational burden of the WGS dataset, we considered only high-quality SNVs (as defined in the AoURP Genomic Quality Report release C2022Q4R9) with MAF >1% or MAC >100 in at least one of the computed genetic ancestries. To correct for population structure, within each computed genetic ancestry, we derived principal components using the smartpca function from EIGENSOFT v7.2.1 with the “fastmode” option enabled[18]. In the principal component calculations, we excluded SNVs that were not present in the 1000 Genomes Project (phase 3, October 2014 release) reference panel[19]. We also excluded SNVs with MAF <1%, that deviated from Hardy-Weinberg equilibrium ($P<10^{-6}$), or were located in the major histocompatibility complex and regions of high LD. Subsequently, we extracted autosomal LD-pruned SNVs ($r^2<0.05$) using PLINK v2.0[20]. Cases of T2D, T2D-related macrovascular outcomes, and microvascular complications were derived from the combination of diagnosis codes (ICD-9-CM and ICD-10-CM), drug exposures, and LOINC codes for laboratory test results, extracted from EHR data. Age of T2D onset was defined by age at the first diagnosis code or age at the first drug exposure code.

Derivation of T2D cases and controls. For T2D cases, we used a previously developed method (https://phekb.org/phenotype/type-2-diabetes-mellitus). Briefly, we considered participants as T2D cases if they fit the following criteria: (a) at least one T2D diagnosis code and at least one drug exposure for T2D medications, unless at least one type 1 diabetes (T1D) diagnosis code; (b) at least one T2D diagnosis code, at least two drug exposures for

T1D and T2D medications with a T2D drug exposure occurring at least one day before T1D drug exposure, unless at least one T1D diagnosis code; (c) at least two T2D diagnosis codes and at least one drug exposure for T1D medication, unless at least one T1D diagnosis code; or (d) at least one drug exposure for T2D medications and at least one abnormal laboratory test result (random glucose, fasting glucose, or HbA1c), unless at least one T1D diagnosis codes. For controls, we considered those participants that were free of all diabetes diagnosis codes, including T2D, T1D, and other forms of diabetes. Additionally, we excluded participants that matched criteria (d) from the T2D definition. Age of T2D onset was defined by age at the first diagnosis code under criteria (a-c), and by age at the first drug exposure code under criteria (d).

For T2D, we used diagnosis codes 250.00, 250.02, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92 from ICD-9-CM and E11.00, E11.01, E11.21, E11.29, E11.311, E11.319, E11.36, E11.39, E11.40, E11.51, E11.618, E11.620, E11.621, E11.622, E11.628, E11.630, E11.638, E11.641, E11.649, E11.65, E11.69, E11.8, E11.9 from ICD-10-CM. For T2D drug exposures, we used the following medications: acarbose, acetohexamide, albiglutide, alogliptin, canagliflozin, chlorpropamide, colesevelam, dapagliflozin, dulaglutide, empagliflozin, exenatide, glimepiride, glipizide, glyburide, linagliptin, liraglutide, lixisenatide, metformin, miglitol, nateglinide, pioglitazone, repaglinide, rosiglitazone, saxagliptin, semaglutide, sitagliptin, tolazamide, and troglitazone. Finally, we considered the following abnormal lab results: random glucose (LOINC codes: 2339-0, 2345-7) > 200mg/dl, fasting glucose (LOINC code: 1558-6) ≥ 125mg/dl, and HbA1c (LOINC codes: 4548-4, 17856-6, 4549-2, 17855-8) ≥ 6.5%. For T1D, we used diagnosis codes 250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93 from ICD-9-CM and E10.10, E10.11, E10.21, E10.29, E10.311, E10.319, E10.36, E10.39, E10.40, E10.51, E10.618, E10.620, E10.621, E10.622, E10.628, E10.630, E10.638, E10.641, E10.649, E10.65, E10.69, E10.8, E10.9 from ICD-10-CM. For T1D drug exposures, we used the following medications: insulin, insulin NPH, insulin aspart, insulin degludec, insulin detemir, insulin glargine, insulin glulisine, insulin lispro, pramlintide. For other forms of diabetes, we used diagnosis codes 249*, 648.0*, 648.8* in ICD-9-CM and E08*, E09*, E13*, O24* in ICD-10-CM.

Derivation of cases and controls for T2D-related clinical outcomes. For each T2D-related clinical outcome, we used previously-defined ICD-9-CM and ICD-10-CM diagnosis codes from EHR data to identify cases and controls[21-24]. For macrovascular outcomes (CAD, ischemic stroke, and peripheral artery disease), we defined cases and controls as participants with and without, respectively, the relevant diagnosis codes, irrespective of T2D status. For CAD, we used 410*, 411*, 412*, 413* in ICD-9-CM and I20*, I21*, I22*, I23*, I24*, I25* in ICD-10-CM. For ischemic stroke, we used 433*, 434* in ICD-9-CM and I63* in ICD-10-CM. For peripheral artery disease, we used 4400, 4402, 4438, 4439 in ICD-9-CM and I70.0, I70.00, I70.01, I70.2, I70.20, I70.21, I70.8, I70.80, I70.9, I70.90, I73.8, I73.9 in ICD-10-CM. For microvascular complications (ESDN and proliferative diabetic retinopathy), we considered only T2D cases. ESDN cases were defined with relevant diagnosis codes for both diabetic nephropathy and end-stage kidney disease (ESKD), and ESDN controls were defined as being free of any diagnosis code for diabetic nephropathy, defined using the AoURP cohort builder. For ESKD, we used 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.6 in ICD-9-CM and I12.0, I13.11, I13.2, N18.6 in ICD-10-CM. For DN, we used E11.21 in ICD-10-CM. Proliferative diabetic retinopathy cases were defined with

relevant diagnosis codes. Proliferative diabetic retinopathy controls were defined as being free of any diagnosis code for diabetic retinopathy. For proliferative diabetic retinopathy, we used 362.02 in ICD-9-CM and E08.35*, E09.35*, E10.35*, E11.35*, E13.35* in ICD-10-CM. For diabetic retinopathy, we used 362.0* in ICD-9-CM and E08.31*, E08.32*, E08.33*, E08.34*, E08.35*, E09.31*, E09.32*, E09.33*, E09.34*, E09.35*, E10.31*, E10.32*, E10.33*, E10.34*, E10.35*, E11.31*, E11.32*, E11.33*, E11.34*, E11.35*, E13.31*, E13.32*, E13.33*, E13.34*, E13.35* in ICD-10-CM.

Biobank Japan (BBJ) cohort description, genotyping, quality control, and phenotype derivation. BBJ is a multi-institutional hospital-based registry that comprises DNA and medical records from individuals of Japanese ancestry[25,26]. The first BBJ cohort comprises approximately 200,000 participants with at least one of 47 common diseases collected between 2003 and 2007. The second BBJ cohort comprises approximately 67,000 participants with at least one of 38 common diseases collected between 2013 and 2017. Physicians of 66 cooperating hospitals determined the eligibility of cases. Only those individuals who were not included in the multi-ancestry meta-analysis were considered for testing of the partitioned GRS.

Genomic DNA was prepared following standard protocols from peripheral blood samples and genotyped using the Illumina Asian Screening Array, following the manufacturer's instructions. We excluded individuals with call rate <98% and outliers from the cluster of East Asian populations based on principal component analysis with reference individuals from Phase II HapMap[27]. We excluded SNVs with call rate <99%, MAC <5, exact Hardy-Weinberg equilibrium $P<10^{-10}$, and >5% difference in MAF when compared with Japanese whole-genome sequence data[28,29] and the Tohoku Medical Megabank Project[30]. After quality control, we performed pre-phasing using SHAPEIT4[31]. Phased haplotypes were imputed to the combined reference panel of 1000 Genomes Project Phase 3 and Japanese whole-genome sequencing data from 1,037 individuals[28,29] using Minimac4[32]. We subsequently excluded individuals with a mismatch between inferred genetic sex and sex registered in clinical information, who were not in a set of unrelated individuals defined by using PLINK with KING-cutoff <0.09375, or were outliers of heterozygosity rates (more than 5 SD from the mean). To correct for population structure, we derived principal components using PLINKv2.0[20], calculated from a set of autosomal LD-pruned SNVs ($r^2<0.1$) with MAF ≥0.5% after excluding the major histocompatibility complex region.

We selected participants of at least 18 years of age for PS analyses. We defined T2D cases as participants with a diagnosis of T2D, made by physicians at participating hospitals, but not type 1 diabetes, mitochondrial diabetes, maturity-onset diabetes of the young, or any other type of diabetes[33]. We extracted cases of microvascular complications from medical records in which diagnosis was made by physicians at participating hospitals. We defined controls for microvascular complications as T2D cases without any diagnosis of diabetic nephropathy or diabetic retinopathy. We defined CAD as a composite of stable angina, unstable angina, and myocardial infarction. These conditions, in addition to ischemic stroke and peripheral artery disease, were diagnosed by physicians at collaborating hospitals based on general medical practices following relevant guidelines. Age of T2D onset was defined from a questionnaire of medical history.

Genes & Health (G&H) cohort description, genotyping, quality control, and phenotype derivation. G&H is a UK-based cohort of British Pakistani and Bangladeshi individuals

recruited and consented for lifelong electronic health record access and genetic analysis[34]. Medical records are linked to ICD-10-CM, OPCS and SNOMED diagnosis and procedural codes across inpatient and hospital settings as well as clinical laboratory measurements, and a baseline questionnaire containing demographic information. Individuals were genotyped using the Illumina Infinium Global Screening Array. Full details of quality control have been reported previously[35]. KING was used to calculate kinship metrics[36] and individuals with at least second-degree relatedness were subsequently removed. Ancestry outliers based on principal component analysis were also excluded. Individuals were imputed to the TOPMed r2 reference panel[37]. Cases of T2D, T2D-related macrovascular outcomes, and microvascular complications were derived from the combination of diagnosis codes (ICD-10-CM), drug exposures, and laboratory test results, extracted from EHR data. Age of T2D onset was defined as the date a diagnosis was made (ICD-10-CM), or a medication was prescribed, or an abnormal laboratory test was recorded, whichever occurred first.

Derivation of T2D cases and controls. We considered participants as T2D cases if they fit the following criteria: (a) at least one T2D diagnosis code and at least one drug exposure for T2D medications, unless at least one type 1 diabetes (T1D) diagnosis code; (b) at least one T2D diagnosis code, at least two drug exposures for T1D and T2D medications with a T2D drug exposure occurring at least one day before T1D drug exposure, unless at least one T1D diagnosis code; (c) at least two T2D diagnosis codes and at least one drug exposure for T1D medication, unless at least one T1D diagnosis code; or (d) at least one drug exposures for T2D medications and at least one abnormal laboratory test result (random glucose, fasting glucose, or HbA1c), unless at least one T1D diagnosis codes. For controls, we considered those participants that were free of all diabetes diagnosis codes, including T2D, T1D, and other forms of diabetes. Additionally, we excluded participants that matched criteria (d) from the T2D definition.

For T2D, we used diagnosis codes E11.00, E11.01, E11.21, E11.29, E11.311, E11.319, E11.36, E11.39, E11.40, E11.51, E11.618, E11.620, E11.621, E11.622, E11.628, E11.630, E11.638, E11.641, E11.649, E11.65, E11.69, E11.8, E11.9 from ICD-10-CM. For T2D drug exposures, we used the following medications: acarbose, acetohexamide, albiglutide, alogliptin, canagliflozin, chlorpropamide, colesevelam, dapagliflozin, dulaglutide, empagliflozin, exenatide, glimepiride, glipizide, glyburide, linagliptin, liraglutide, lixisenatide, metformin, miglitol, nateglinide, pioglitazone, repaglinide, rosiglitazone, saxagliptin, semaglutide, sitagliptin, tolazamide, and troglitazone. Finally, we considered the following abnormal lab results: random glucose > 200mg/dl, fasting glucose ≥ 125mg/dl, and HbA1c ≥ 6.5%. For T1D, we used diagnosis codes E10.10, E10.11, E10.21, E10.29, E10.311, E10.319, E10.36, E10.39, E10.40, E10.51, E10.618, E10.620, E10.621, E10.622, E10.628, E10.630, E10.638, E10.641, E10.649, E10.65, E10.69, E10.8, E10.9 from ICD-10-CM. For T1D drug exposures, we used the following medications: insulin, insulin NPH, insulin aspart, insulin degludec, insulin detemir, insulin glargine, insulin glulisine, insulin lispro, pramlintide. For other forms of diabetes, we used diagnosis codes E08*, E09*, E13*, O24* in ICD-10-CM.

Derivation of cases and controls for T2D-related clinical outcomes. For macrovascular outcomes (CAD, ischemic stroke, and peripheral artery disease), we defined cases and controls as participants with and without, respectively, the relevant diagnosis codes, irrespective of T2D status. For CAD, we used I20*, I21*, I22*, I23*, I24*, I25* in ICD-10-CM. For ischemic stroke, we used I63* in ICD-10-CM. For peripheral artery disease, we used I70.0, I70.00, I70.01, I70.2, I70.20, I70.21, I70.8, I70.80, I70.9, I70.90, I73.8, I73.9 in ICD-10-CM. For microvascular complications (ESDN and proliferative diabetic retinopathy), we

considered only T2D cases. ESDN cases were defined with relevant diagnosis codes for both diabetic nephropathy and end-stage kidney disease (ESKD), and ESDN controls were defined as being free of any diagnosis code for diabetic nephropathy. For ESKD, we used I12.0, I13.11, I13.2, N18.6 in ICD-10-CM. For DN, we used E11.21 in ICD-10-CM. Proliferative diabetic retinopathy cases were defined with relevant diagnosis codes. Proliferative diabetic retinopathy controls were defined as being free of any diagnosis code for diabetic retinopathy. For proliferative diabetic retinopathy, we used E08.35*, E09.35*, E10.35*, E11.35*, E13.35* in ICD-10-CM. For diabetic retinopathy, we used E08.31*, E08.32*, E08.33*, E08.34*, E08.35*, E09.31*, E09.32*, E09.33*, E09.34*, E09.35*, E10.31*, E10.32*, E10.33*, E10.34*, E10.35*, E11.31*, E11.32*, E11.33*, E11.34*, E11.35*, E13.31*, E13.32*, E13.33*, E13.34*, E13.35* in ICD-10-CM. No cases with proliferative diabetic retinopathy were identified in the G&H cohort.

Clinical trials from the Thrombolysis in Myocardial Infarction (TIMI) Study. ENGAGE AF-TIMI 48 was a 3-arm trial comparing two doses of the Factor Xa inhibitor edoxaban to warfarin in patients with atrial fibrillation and CHADS2 risk score of 2 or higher, where co-morbidities included diabetes (38%), stroke (28%), and heart failure (57%). SOLID-TIMI 52 was a trial of the lipoprotein-associated phospholipase A2 inhibitor darapladib versus placebo in patients with recent acute coronary syndrome on optimal background medical therapy, where co-morbidities included hypertension (73%), hyperlipidemia (64%), and diabetes (35%). SAVOR-TIMI 53 was a trial of the DPP4 inhibitor saxagliptin in patients with T2D, where co-morbidities included atherosclerosis (78%) and hypertension (81%). PEGASUS-TIMI 54 was a trial of the antiplatelet drug ticagrelor in patients with prior myocardial infarction, where co-morbidities included smoking (17%), hypertension (78%), diabetes (32%), prior percutaneous coronary intervention (83%), and prior coronary artery bypass graft (5%). FOURIER-TIMI 59 was a trial of the PCSK9 inhibitor evolocumab in patients with myocardial infarction, stroke, or peripheral artery disease, where co-morbidities included hypertension (80%), diabetes (37%), and prior myocardial infarction (81%). DECLARE-TIMI 58 was a trial of the SGLT-2 inhibitor dapaglifozin in patients with T2D, where co-morbidities included established atherosclerotic cardiovascular disease (40%) or multiple risk factors for atherosclerotic cardiovascular disease (60%).

Genotyping was performed on the Infinium Global Array chip (FOURIER-TIMI 59), Affymetrix Biobank Array (SOLID-TIMI 52), Infinium Global Screening Array MD (DECLARE-TIMI 58) and Illumina Multi-Ethnic Genotyping Array (ENGAGE AF-TIMI 48, PEGASUS-TIMI 54 and SAVOR-TIMI 53). PLINK v2.0[20] was used for pre-imputation quality control, which included mapping to hg38 coordinates, removing SNVs and individuals with missingness >0.2 (first round) and >0.02 (second round), removing individuals with sex discrepancies based on X-chromosome F-values (<0.2 for females and >0.8 for males) and heterozygosity more than 3 SD from the mean, and removing SNVs with MAF <1% and extreme deviation from Hardy-Weinberg equilibrium ($P<10^{-6}$). Imputation was performed on the Michigan Imputation Server using Eagle v2.4[38] for phasing and Minimac4[32] on TOPMed Freeze 5 reference panel[37] with imputation quality filter $r^2>0.3$. Cryptic relatedness was assessed using identity by descent, and a pi-hat threshold of 0.2 was used to identify related samples. EUR individuals were identified using the 1000 Genomes phase 3 v5 reference panel and the ADMIXTURE tool[39] (cutoff for European ancestry was set at 0.8) and were retained for analysis.

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Ethics statements

Anti-aging study cohort (AASC). The ethics committees of Ehime University Graduate School of Medicine approved all study procedures. Written informed consent was obtained from all participants.

All Of Us Research Program (AOURP). All research was conducted under the guidelines defined by the All of Us Ethical Conduct of Research Policy.

Atherosclerosis Risk in Communities (ARIC). Institutional Review Board approvals were obtained at all study sites: National Heart, Lung, and Blood Institute, University of North Carolina at Chapel Hill, Wake Forest Baptist Medical Center, University of Mississippi Medical Center, University of Minnesota, and Johns Hopkins University. All participants provided written informed consent.

Biobank Japan (BBJ). All participants provided written informed consent as approved by the ethical committees of the RIKEN Yokohama Institute and the Institute of Medical Science, the University of Tokyo. Ethical approvals of AMED GRIFIN Diabetes Initiative Japan were gained from the Ethics Committees of Osaka University and the University of Tokyo.

Beijing Eye Study (BES). Approval was obtained from the Medical Ethics Committee of the Beijing Tongren Hospital. All participants gave written informed consent.

BioMe Biobank (BIOME). Approval was obtained from the Institutional Review Board at the Icahn School of Medicine at Mount Sinai. All participants provided written informed consent for genomic data sharing.

Vanderbilt University Medical Center's BioVU (BIOVU). Analyses of DIAMANTE data at Vanderbilt University Medical Center are approved under IRB #190891 and analysis of BioVU data are approved under IRBs #210163 and #171279. In all three cases, the data analyzed received non-human subject determinations.

Bangladesh Population Cohort (BPC). The conduct of the BPC was reviewed and approved by Ethical Committees of the Bangladesh Medical Research Council and Institutional Review Boards of the University of Chicago.

Cardiometabolic Genome Epidemiology (CAGE-AMAGASKI and CAKE-GWAS). Approval was obtained from the Institutional Review Boards at the National Center for Global Health and Medicine. All participants provided written informed consent.

Cardiometabolic Genome Epidemiology (CAGE-KING). Approval was obtained from the ethics committees of Aichi Gakuin University, Jichi Medical University, Nagoya University and Kyushu University. All participants provided written informed consent.

Coronary Artery Risk Development in Young Adults (CARDIA). Participating centers (Northwestern University, University of Alabama Birmingham, University of Minnesota, and

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Cleveland Family Study (CFS). Approval was obtained from the Institutional Review Board of Mass General Brigham (formerly Partners HealthCare). Written informed consent was obtained from all participants.

China Health and Nutrition Survey (CHNS). Approval was obtained from the Institutional review Boards at the University of North Carolina at Chapel Hill, the Chinese National Human Genome Center at Shanghai, and the Institute of Nutrition and Food Safety at the China Centers for Disease Control. All participants provided written informed consent.

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Cebu Longitudinal Health and Nutrition Survey (CLHNS). Written informed consent was obtained from all participants. Study protocols were approved by the University of North Carolina Institutional review Board for the Protection of Human Subjects.

Diabetic Cohort and Singapore Prospective Study Program (DC/SP2). Study protocols were approved by the Singapore General Hospital Ethics Committee, and National University of Singapore Institutional Review Board. All participants provided written informed consent.

Durban Diabetes Study and Durban Diabetes Case Control (DDS/DCC). Approvals were granted by the Biomedical Research Ethics Committee at the University of KwaZulu-Natal and the UK National Research Ethics Service. All participants provided written informed consent.

deCODE genetics (DECODE). The study was approved by the Icelandic National Bioethics Committee (approval no. VSN-16-112) after evaluation by the Icelandic Data Protection Authority. We obtained written informed consent for all participants in this study who donated samples. All data processing complies with the Icelandic Data Protection Authority (no. PV_2017060950ÞS).

Diabetes Gene Discovery Group (DGDG). All participants signed informed consent, and the protocol was approved by the French ethics committee.

Diabetes Genetics Initiative (DGI). The study was approved by the Ethics Committees of the Helsinki University Hospital, Helsinki, Finland, and Lund University, Sweden.

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Electronic Medical Records and Genomics Network (EMERGE). Approval was obtained from the Institutional Review Boards at Boston Children's Hospital, Children's Hospital of Philadelphia, Cincinnati Children's Hospital Medical Center, Essentia Institute of Rural Health, Geisinger Clinic, Group Health Cooperative, Marshfield Clinic Research Foundation, Mayo Clinic, Icahn School of Medicine at Mount Sinai, Northwestern University, Pennsylvania State University, Vanderbilt University Medical Center, and University of Washington. All participants provided written informed consent.

European Prospective Investigation into Cancer and Nutrition (EPIC-INTERACT). The EPIC-InterAct study was approved by the local ethics committee in the participating countries and the Internal Review Board of the International Agency for Research on Cancer. All participants gave written informed consent. The study was coordinated by the Medical Research Council Epidemiology Unit at the University of Cambridge.

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German Chronic Kidney Disease (GCKD). All participants provided written informed consent. The study was registered in the national registry for clinical studies (DRKS 00003971) and was approved by local ethics committees.

Genetic Study of Atherosclerosis Risk (GENESTAR). Approval was obtained from the Johns Hopkins Medicine Institutional Review Board. All participants gave written informed consent.

Genetic Epidemiology Network of Arteriosclerosis (GENOA). Approval was granted by Institutional Review Boards of the University of Michigan, University of Mississippi Medical Center and Mayo Clinic. Written informed consent was obtained from all participants.

Resource for Genetic Epidemiology on Adult Heath and Aging (GERA). The Institutional Review Boards for Human Subjects Research of both Kaiser Permanente Medical Care Plan (Northern California Region) and the University of California at San Francisco approved the project.

Genetics of Diabetes and Audit Research in Tayside Scotland (GODARTS). Approval was obtained from the Tayside Medical Ethics Committee. Informed consent was obtained for all participants.

Genetics of Latinos Diabetic Retinopathy (GOLDR). Approval was granted by the Institutional Review Board of the Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center.

Genetic Overlap Between Metabolic and Psychiatric Traits and Teens of Attica: Genes and Environment (GOMAP-TEENAGE). Ethical permission for TEENAGE was obtained from the Bioethics Committee of Harokopio University, Athens. Ethical permission for GOMAP was obtained from the Dromokaiteio Scientific Committee, Dromokaiteio Management Committee, Dafni Scientific Committee, Eginitio Scientific Committee and Harokopio Ethics Committee. All participants of GOMAP-TEENAGE gave written informed consent.

Genomic Research Cohort for CCMB Diabetes Study (GRCCDS). Ethics committees of CSIR-Centre for Cellular and Molecular Biology and KEM Hospital and Research Centre approved the project.

Health, Aging and Body Composition Study (HABC). The Institutional Review Boards at the University of Memphis and the University of Pittsburgh granted approval to conduct the Health ABC Study, and all participants provided written informed consent.

Healthy Aging in Neighborhoods of Diversity Across the Life Span Study (HANDLS). Approval was granted by the National Institutes of Health Institutional Review Board (study number 09AGN248). All participants provided written informed consent.

Hispanic Community Health Study/Study of Latinos (HCHS/SOL). Approval was obtained from Institutional Review Boards at the University of North Carolina at Chapel Hill, Albert Einstein College of Medicine, University of Illinois at Chicago, University of Miami, and San Diego State University. All participants provided written informed consent.

Hong Kong Diabetes Registry (HKDR). Approval was obtained from the Chinese University of Hong Kong Clinical Research Ethics Committee.

Health Professionals' Follow-Up Study (HPFS). Approval was obtained from the Human Research Committee at the Brigham and Women's Hospital. All participants provided written informed consent**.**

Mexican American Hypertension and Insulin Resistance (HTNIR). Approval was granted by Human Subjects Protection Institutional Review Boards at the University of California at Los Angeles, University of Southern California, Lundquist/LABioMed/Harbor-UCLA and Cedars-Sinai Medical Center.

Howard University Family Study (HUFS). All human participants from the HUFS included in the analyses of this manuscript provided written informed consent prior to enrollment. The HUFS study was approved by the Institutional Review Board at Howard University.

Indian Diabetes Consortium (INDICO). Approval was obtained by the Human Ethics Committees of All India Institute of Medical Sciences, New Delhi and CSIR-Institute of Genomics and Integrative Biology, New Delhi, India, and was conducted in accordance with the principles of Helsinki Declarations. Informed written consent was obtained from all of participants.

INTERHEART (INTERHEART). All study participants consented to analysis of blood samples. Approval was granted by the Hamilton Integrated Research Ethics Board, at McMaster University, Hamilton, Canada.

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Collaborative Health Research in the Region of Augsburg (KORA). Approval was granted by the Ethics Committee of the Medical Association of Bavaria (number 06068). All participants provided informed consent.

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Mexico City (MC). Approval was obtained from Institutional Review Boards at the Ethics and Scientific Commission members and the AUTHORIZATION is issued with registration number R-2011-785-018 and the Conacyt SALUD-2010-02-150352. In Canada, approval was obtained from the Research Ethics Board from the University of Toronto (Protocol 15770).

Malmo Diet and Cancer Study (MDCS). The study protocol for MDC was sanctioned by the Ethics Review Committee of Lund University (approval numbers 532/2006, 51-90). All participants provided their written consent.

Multi-Ethnic Study of Atherosclerosis (MESA). Approval was obtained from Institutional Review Boards at the University of Washington, Wake Forest School of Medicine, Northwestern University, University of Minnesota, Columbia University, Johns Hopkins University, Cedars-Sinai Medical Center, and the University of California at Los Angeles.

Metabolic Syndrome in Men (METSIM). Approval was granted by the Ethics Committee of the University of Kuopio and the Kuopio University Hospital. All participants gave written informed consent.

Mass General Brigham Biobank (MGB). The MGB Biobank protocol and informed consent documents are reviewed annually by the Partners-MGB Institutional Review Board (#2009P002312). All patients who participate in the MGB Biobank are consented for their samples to be linked to their identified clinical information. They have also consented for their information to be used for a broad range of research and for their deidentified information to be shared outside of MGB.

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Singapore Chinese Eye Study (SCES). The study adhered to the Declaration of Helsinki. Ethical approval was obtained from the SingHealth Institutional Review Board and National University of Singapore Institutional Review Board. Written informed consent was obtained from all participants.

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UK Biobank (UKBB). Approval was obtained from the North West Centre for Research Ethics Committee (11/NW/0382).

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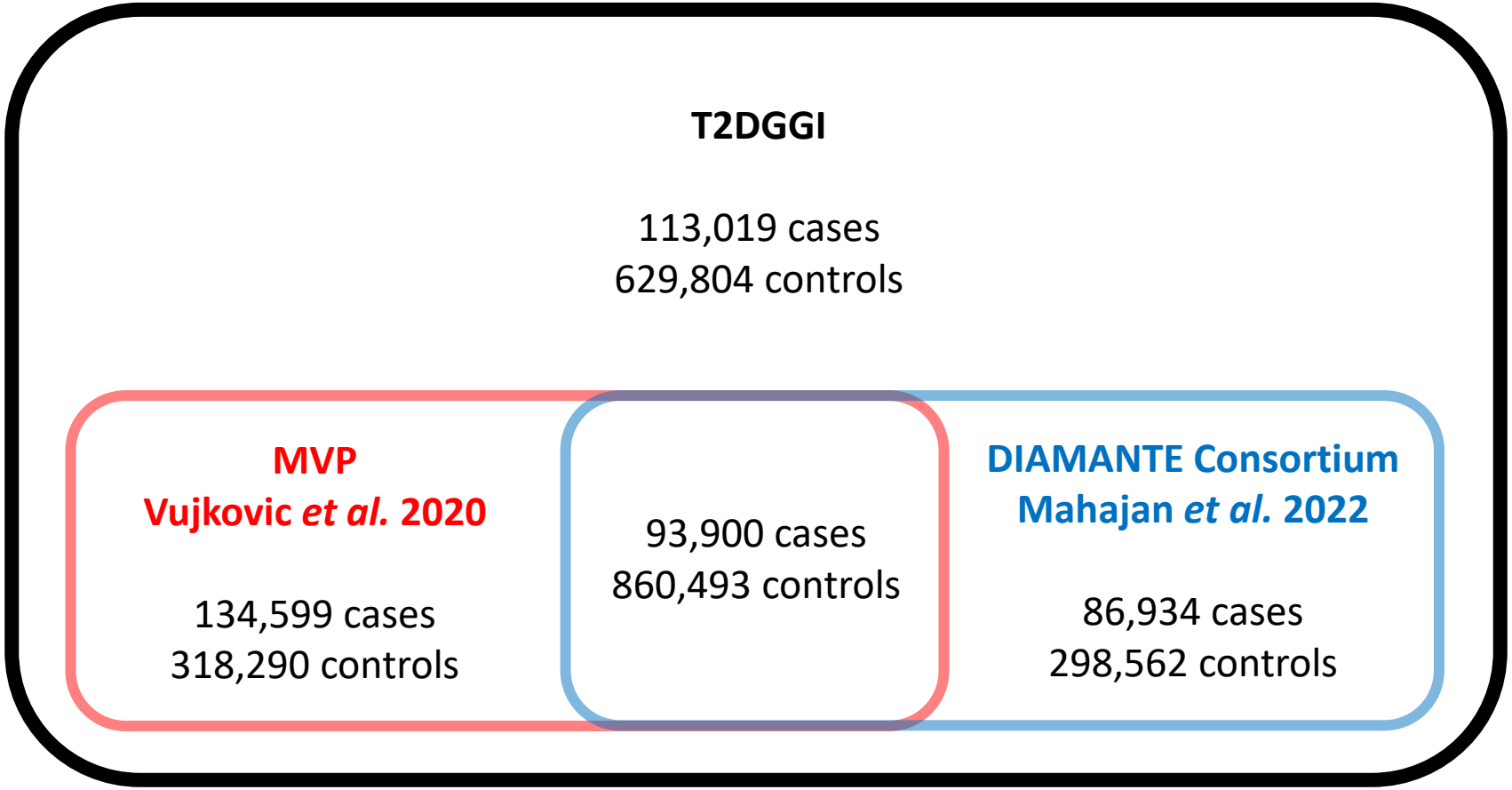
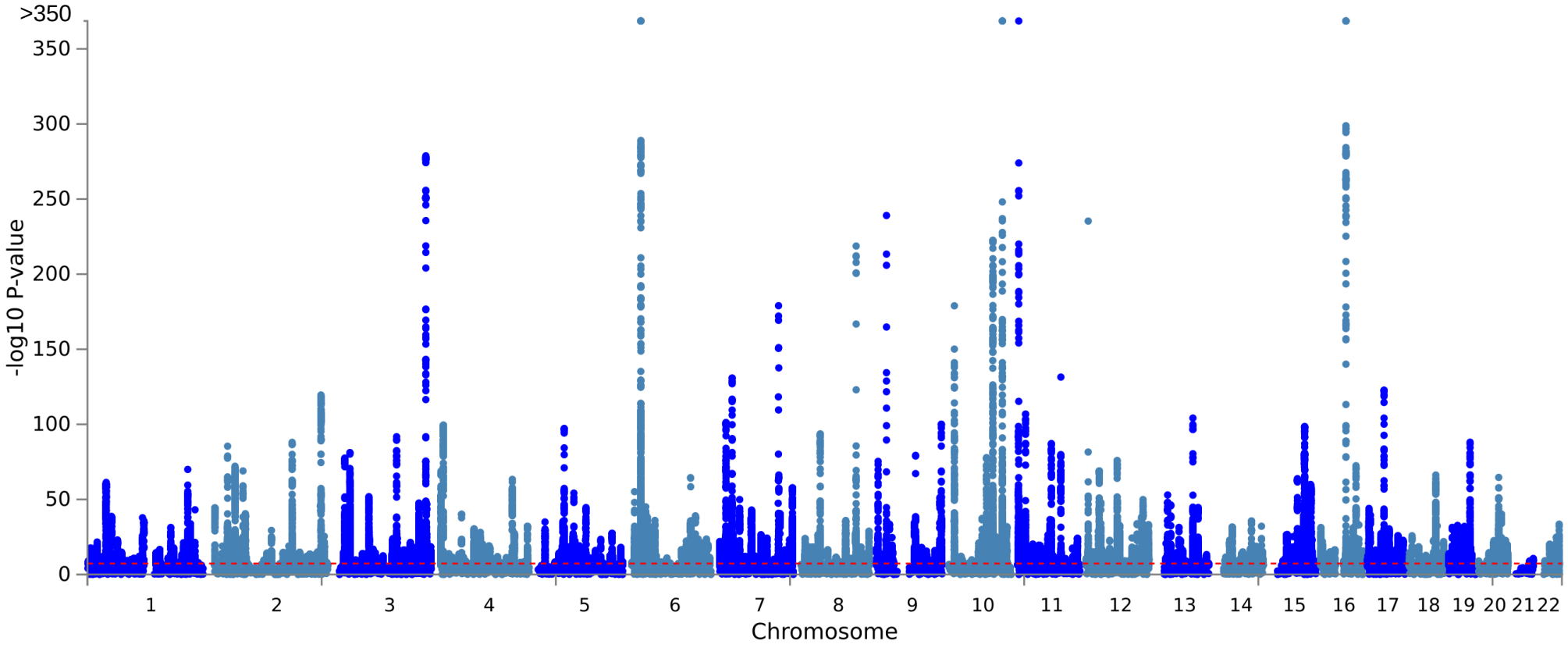
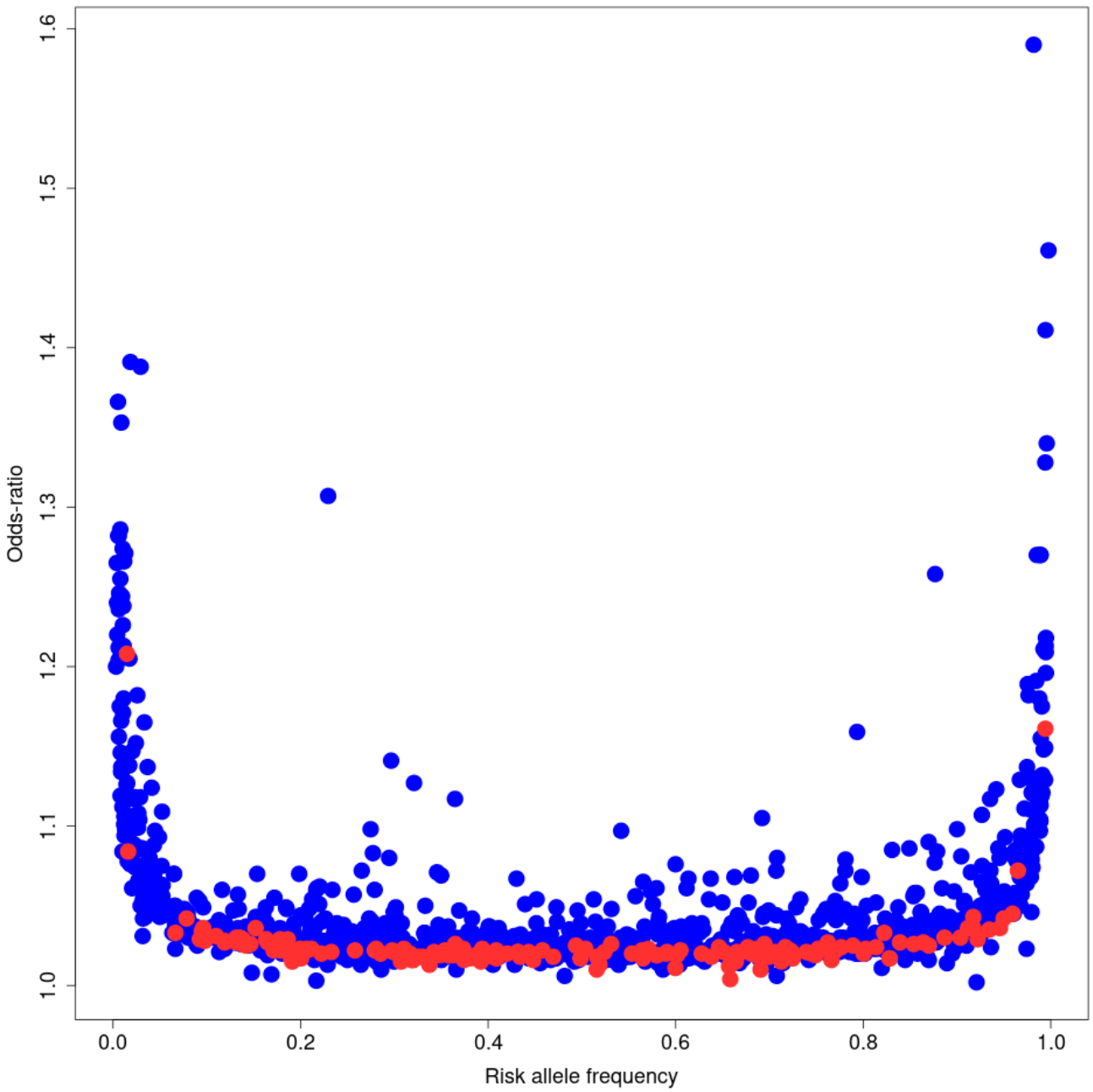
Supplementary Figure 1. Overlap of samples contributing to recent multi-ancestry T2D GWAS meta-analyses. The Type 2 Diabetes Global Genomics Initiative (T2DGGI) includes 428,452 cases and 2,107,149 controls, of which 315,433 cases and 1,477,345 controls have contributed to previous multi-ancestry investigations of the genetic contribution to T2D from the Million Veterans Program (MVP) and the DIAMANTE Consortium.

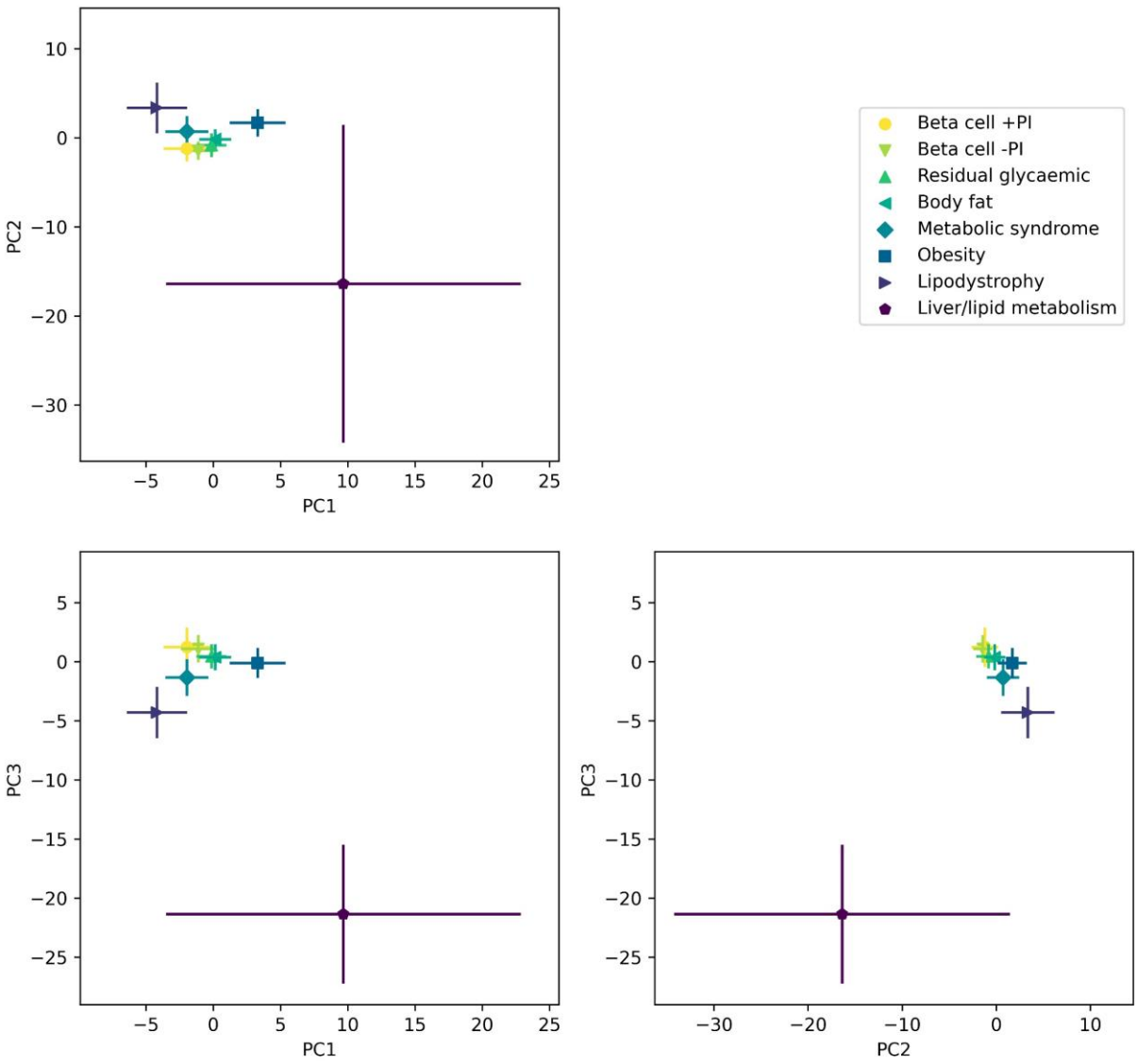




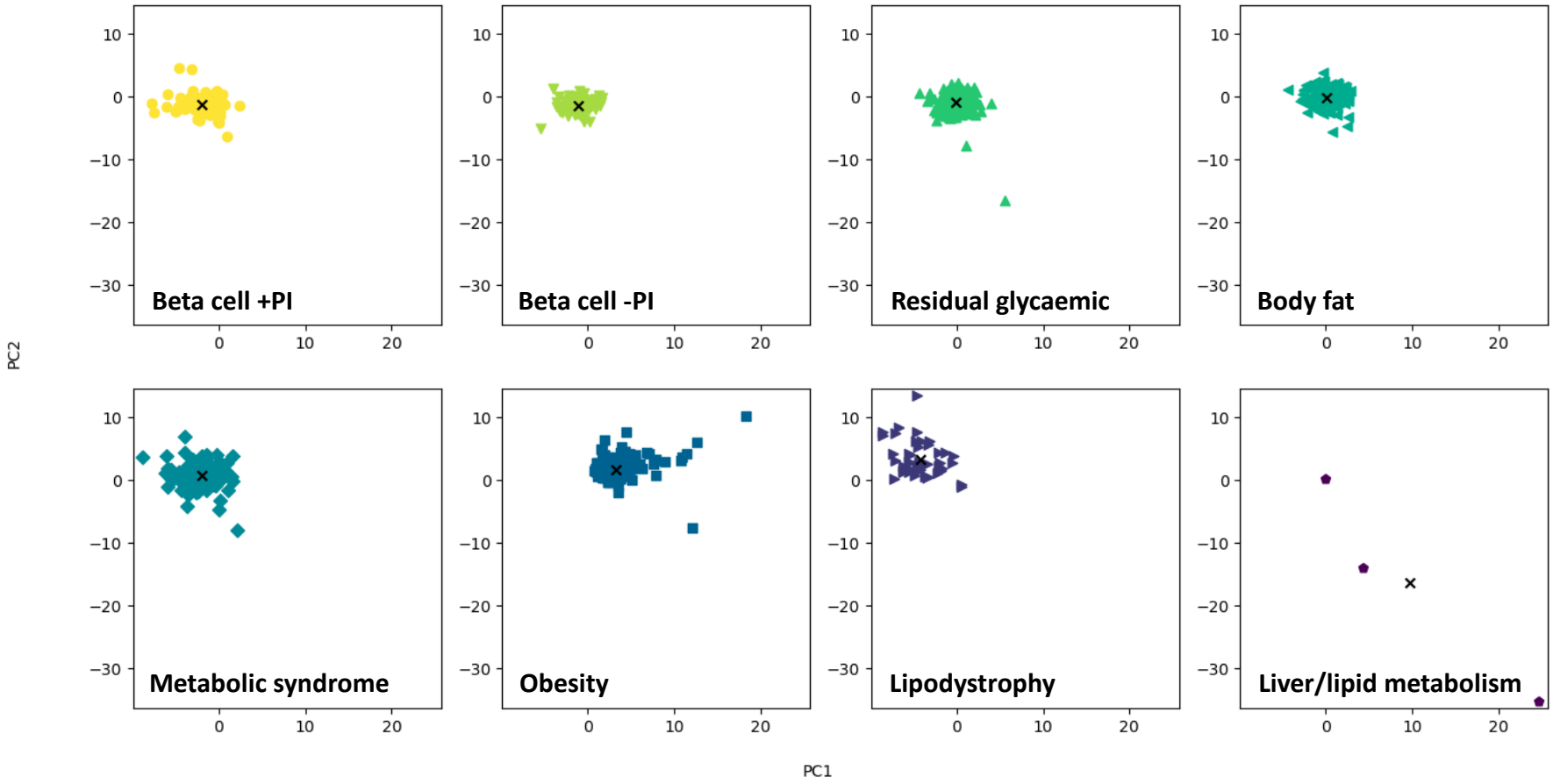
Supplementary Figure 2. Manhattan plot of genome-wide T2D association from multi-ancestry meta-regression (MR-MEGA) of up to 428,452 T2D cases and 2,107,149 controls across multiple ancestry groups. Each point represents a SNV passing quality control in the multi-ancestry meta-regression, plotted with their association p-value (on a -$\log_{10}$ scale, truncated at 300) as a function of genomic position (NCBI build 37). Genome-wide significance ($P<5x10^{-8}$) is highlighted by the dashed horizontal red line.



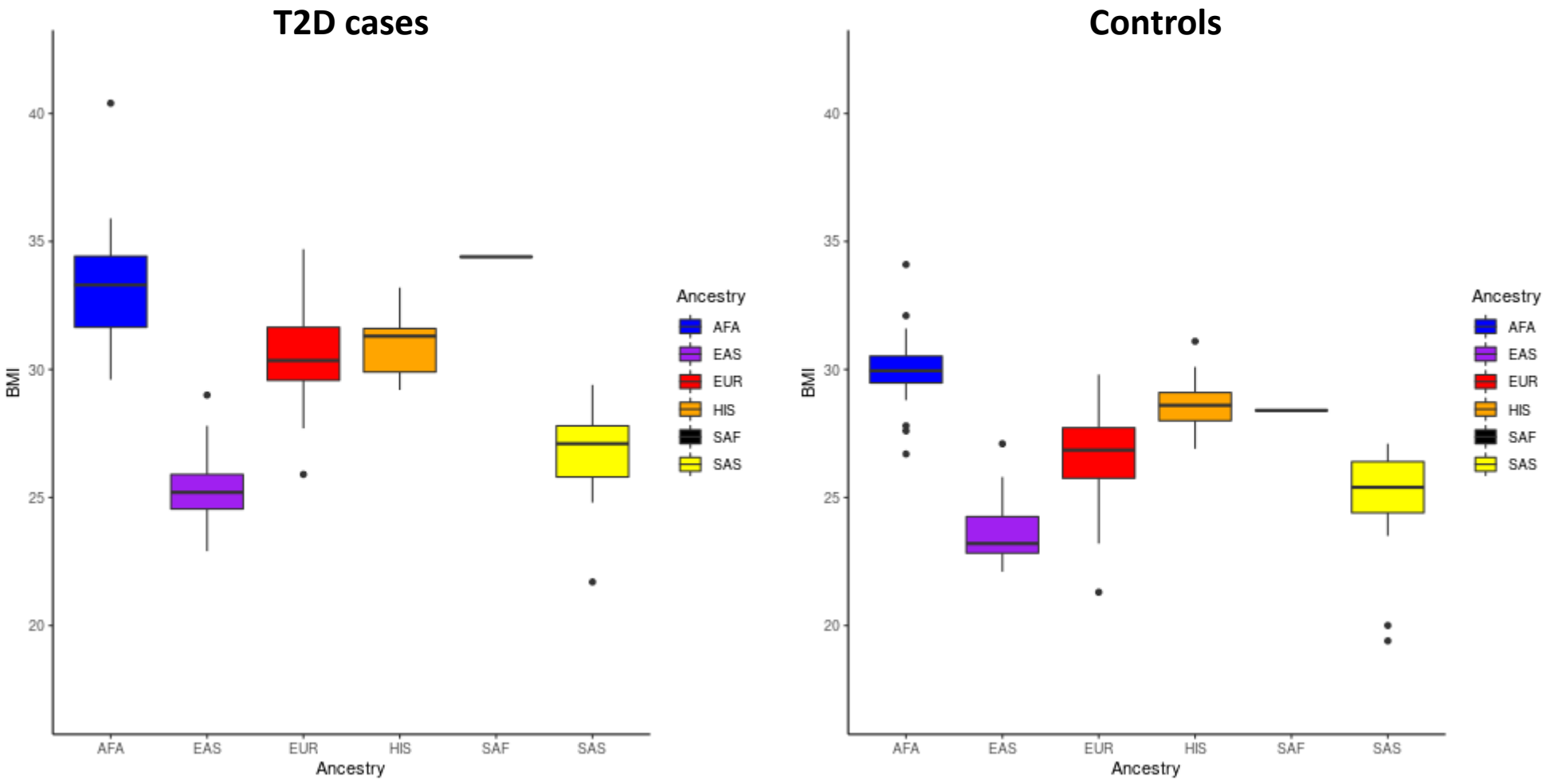
Supplementary Figure 3. Distribution of risk allele frequency and odds-ratio at index SNVs for distinct T2D association signals. Each point corresponds to an index SNV, plotted according to the mean risk allele frequency across GWAS (on the x-axis) and the odds-ratio from fixed-effects meta-analysis (on the y-axis). Index SNVs highlighted in blue map to previously reported loci for T2D susceptibility. Index SNVs highlighted in red do not map to previously reported loci for T2D susceptibility.



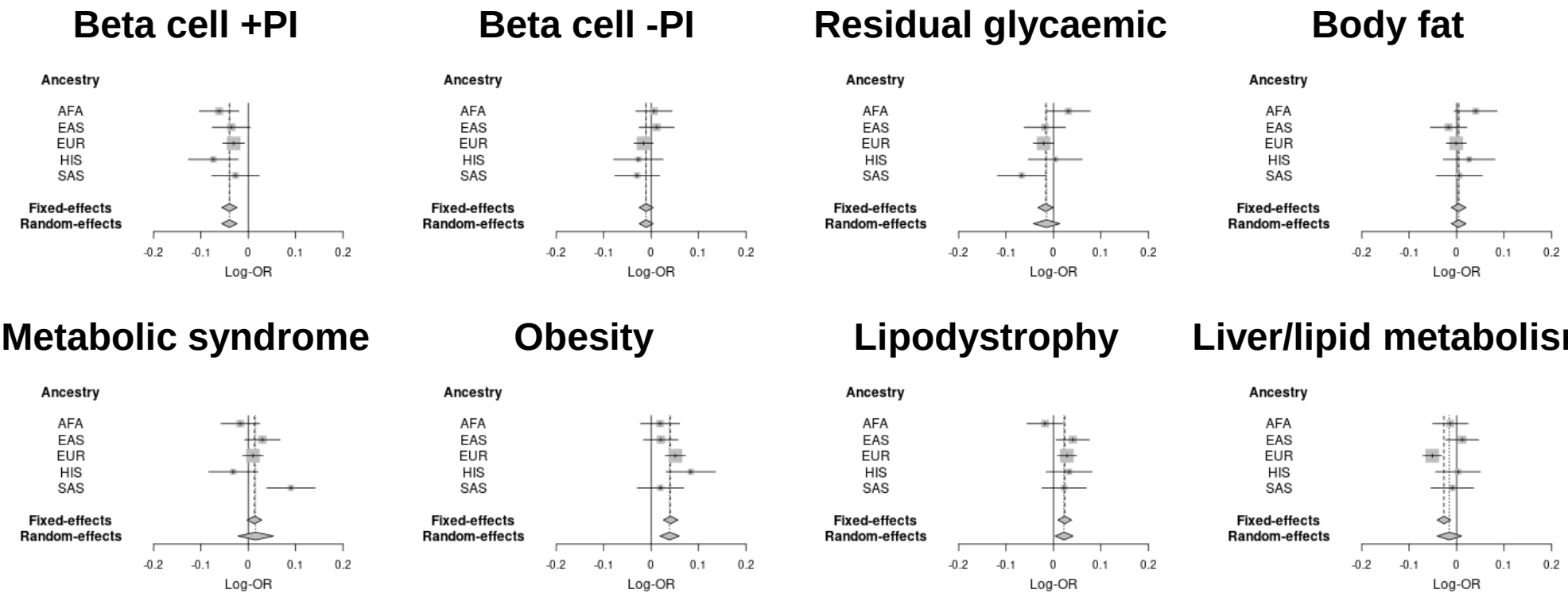
Supplementary Figure 4. Distribution of clusters of SNVs on the first three principal components derived from 37 cardiometabolic traits. The principal components analysis was conducted on the final imputed dataset obtained from K-means clustering with ClustImpute. Each point corresponds to the mean values of the first three principal components for SNVs assigned to the cluster. The bars correspond to +/- standard deviation. The percentage of variance explained by each principal component (PC) was: 16.7% by PC 1, 12.6% by PC 2, and 10.5% by PC 3.

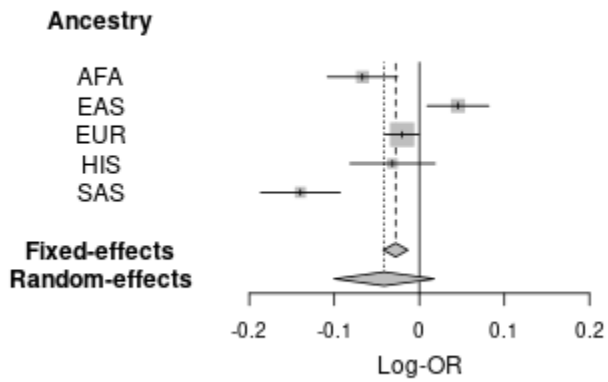


Supplementary Figure 5. Distribution of clusters of SNVs on the first two principal components derived from 37 cardiometabolic traits. The principal components analysis was conducted on the final imputed dataset obtained from K-means clustering with ClustImpute. The "X" corresponds to the cluster centroid. The percentage of variance explained by each principal component (PC) was: 16.7% by PC 1 and 12.6% by PC 2.

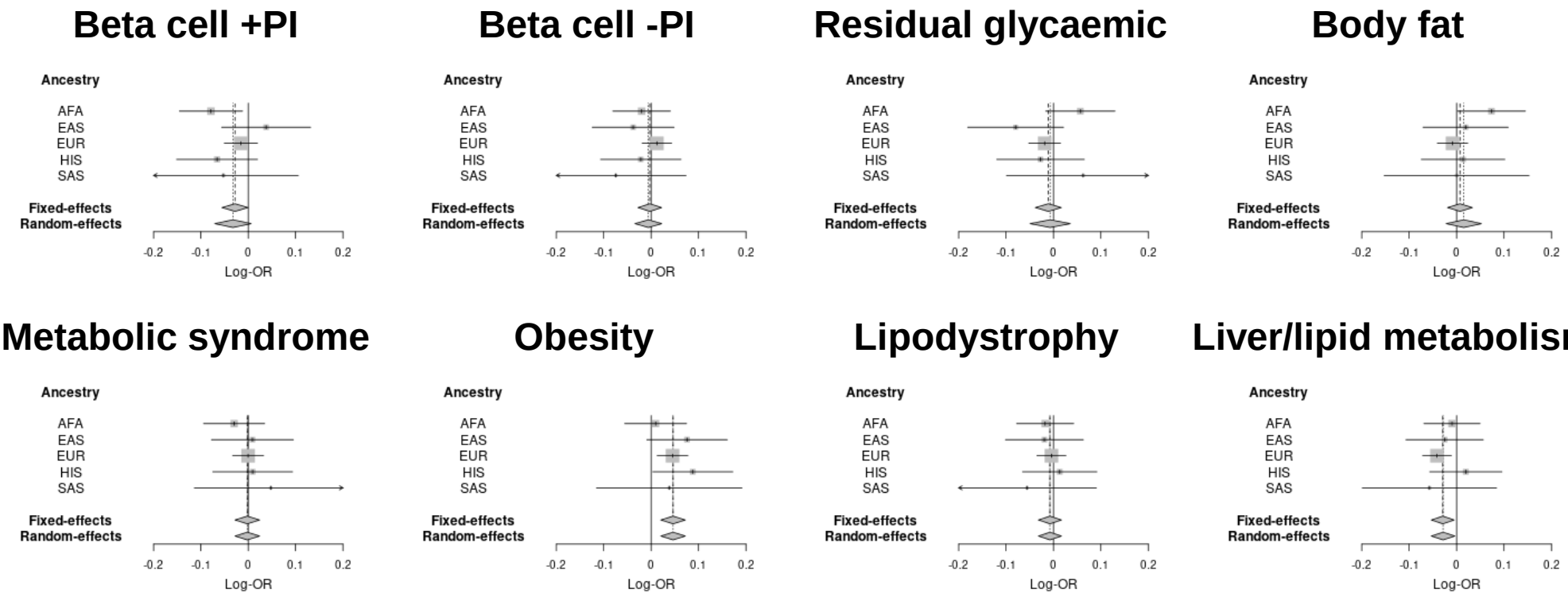


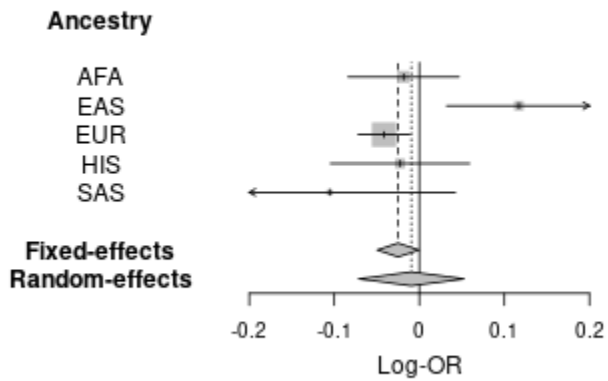
Supplementary Figure 6. Distribution of study-level mean BMI in T2D cases and controls across ancestry groups. Each box and whisker plot presents the median (back horizontal line), upper and lower quartiles (extremes of coloured boxes), minimum and maximum (excluding outliers, extremes of black vertical line), and outliers (more than 1.5x inter-quartile range, black dots). AFA: African American ancestry group (n=25 GWAS). EAS: East Asian ancestry group (n=40 GWAS). EUR: European ancestry group (n=36 GWAS). HIS: Hispanic ancestry group (n=17 GWAS). SAF: South African ancestry group (n=1 GWAS). SAS: South Asian ancestry group (n=17 GWAS).





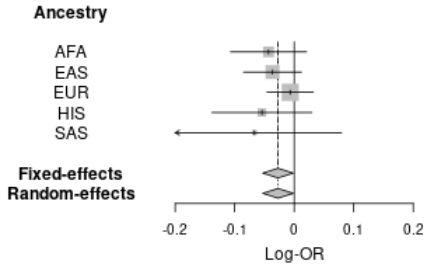
Supplementary Figure 7. Association of overall T2D PS and cluster-specific components of partitioned PS with CAD across multiple ancestry groups. In each forest plot, the log-odds ratio (log-OR) of the standardised PS for each ancestry is presented, together with the 95% confidence interval (horizontal bar) and weight (inverse variance, size of grey box). The grey diamonds correspond to the fixed- and random-effects estimates of the log-OR of the PS across ancestry groups (upper/lower points of diamond) and corresponding 95% confidence interval (left/right points of diamond). The cluster-specific components of the partitioned PS are adjusted for the overall T2D PS. Analyses were conducted in all individuals with adjustment for T2D status. AFA: African American ancestry group (3,537 cases and 40,932 controls). EAS: East Asian ancestry group (4,078 cases and 58,904 controls). EUR: European ancestry group (13,602 cases and 96,793 controls). HIS: Hispanic ancestry group (2,171 cases and 31,612 controls). SAS: South Asian ancestry group (2,398 cases and 25,525 controls).





Supplementary Figure 8. Association of overall T2D PS and cluster-specific components of partitioned PS with peripheral artery disease across multiple ancestry groups. In each forest plot, the log-odds ratio (log-OR) of the standardised PS for each ancestry is presented, together with the 95% confidence interval (horizontal bar) and weight (inverse variance, size of grey box). The grey diamonds correspond to the fixed- and random-effects estimates of the log-OR of the PS across ancestry groups (upper/lower points of diamond) and corresponding 95% confidence interval (left/right points of diamond). The cluster-specific components of the partitioned PS are adjusted for the overall T2D PS. Analyses were conducted in all individuals with adjustment for T2D status. AFA: African American ancestry group (1,241 cases and 43,228 controls). EAS: East Asian ancestry group (615 cases and 62,367 controls). EUR: European ancestry group (4,847 cases and 105,548 controls). HIS: Hispanic ancestry group (723 cases and 33,060 controls). SAS: South Asian ancestry group (199 cases and 27,724 controls).

Beta cell +PI



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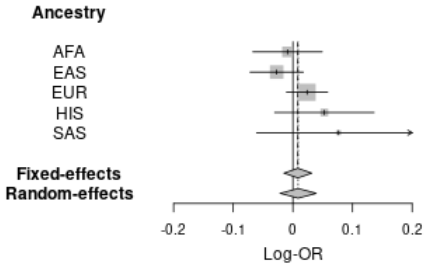
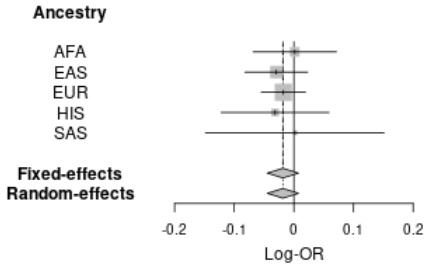
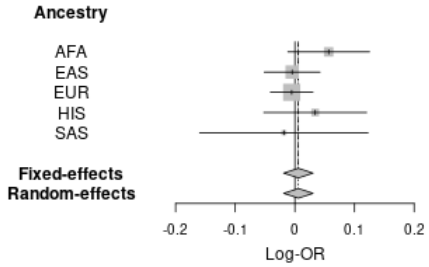


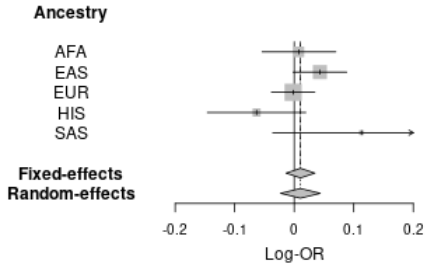
Residual glycaemic



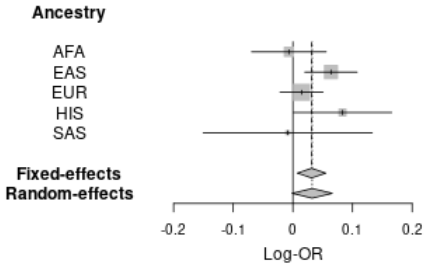
Body fat



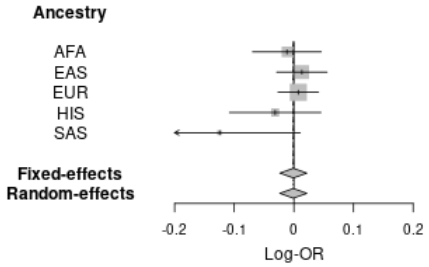
Metabolic syndrome



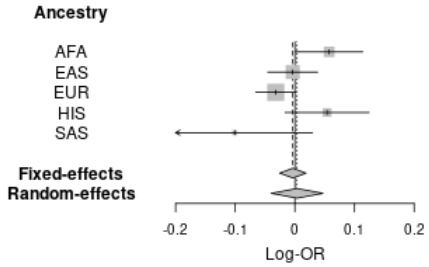
Obesity



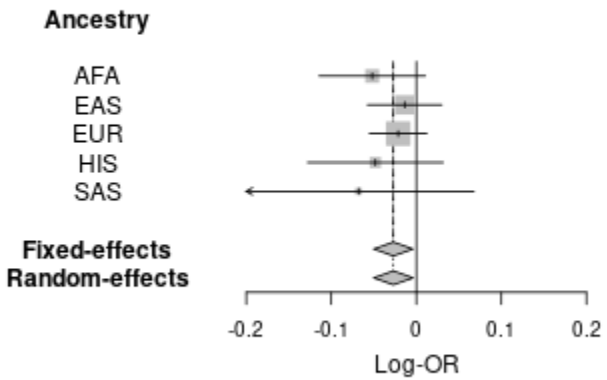
Lipodystrophy



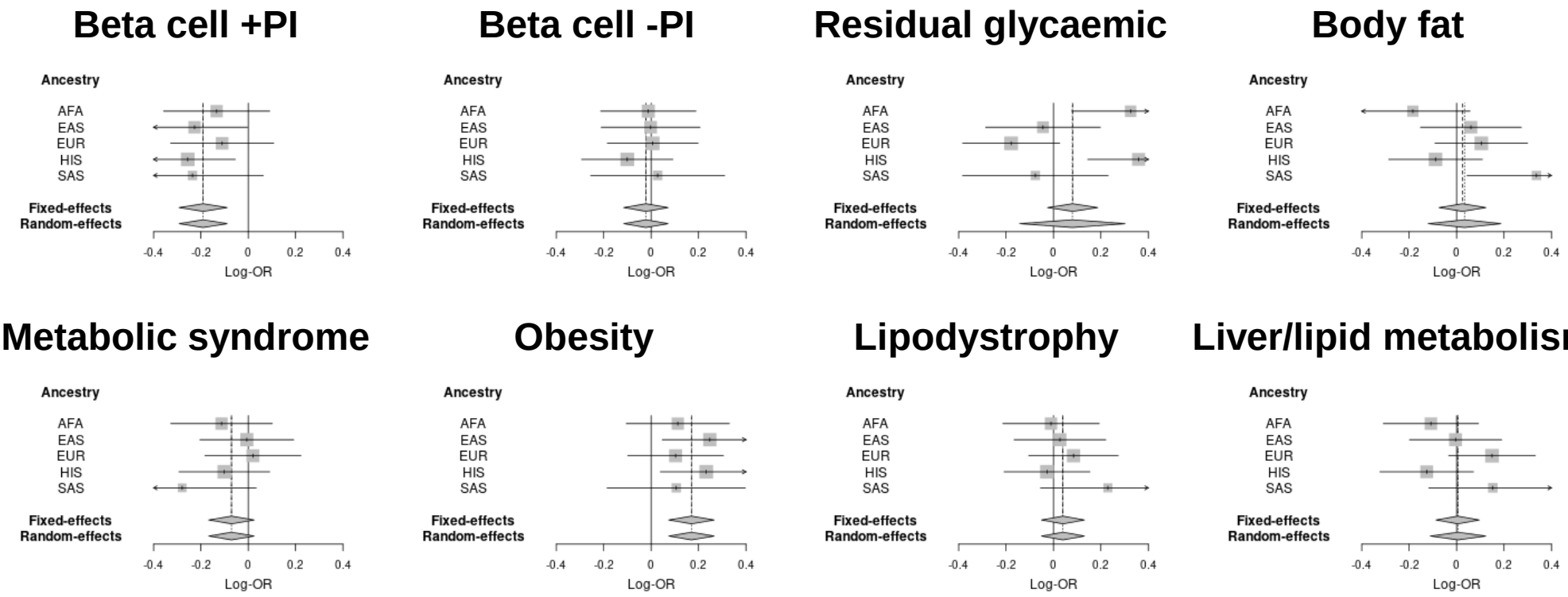
Liver/lipid metabolism

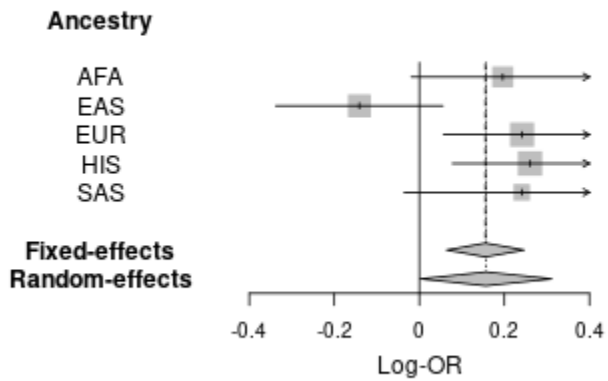


Overall

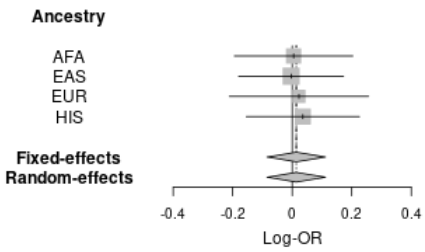


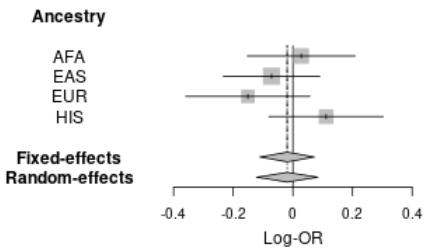
Supplementary Figure 9. Association of overall T2D PS and cluster-specific components of partitioned PS with ischemic stroke across multiple ancestry groups. In each forest plot, the log-odds ratio (log-OR) of the standardised PS for each ancestry is presented, together with the 95% confidence interval (horizontal bar) and weight (inverse variance, size of grey box). The grey diamonds correspond to the fixed- and random-effects estimates of the log-OR of the PS across ancestry groups (upper/lower points of diamond) and corresponding 95% confidence interval (left/right points of diamond). The cluster-specific components of the partitioned PS are adjusted for the overall T2D PS. Analyses were conducted in all individuals with adjustment for T2D status. AFA: African American ancestry group (1,241 cases and 43,228 controls). EAS: East Asian ancestry group (2,396 cases and 60,586 controls). EUR: European ancestry group (3,782 cases and 106,613 controls). HIS: Hispanic ancestry group (722 cases and 33,061 controls). SAS: South Asian ancestry group (230 cases and 27,693 controls).

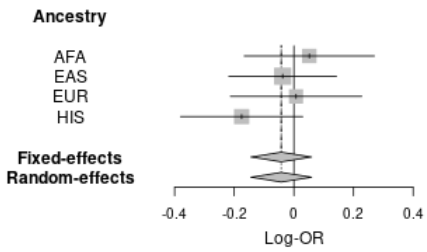


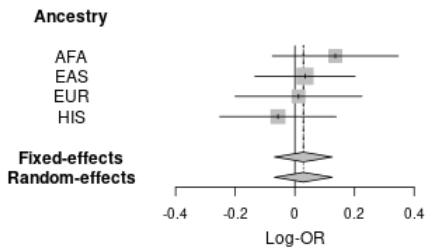


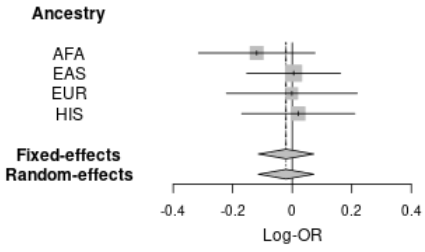
Supplementary Figure 10. Association of overall T2D PS and cluster-specific components of partitioned PS with ESDN across multiple ancestry groups. In each forest plot, the log-odds ratio (log-OR) of the standardised PS for each ancestry is presented, together with the 95% confidence interval (horizontal bar) and weight (inverse variance, size of grey box). The grey diamonds correspond to the fixed- and random-effects estimates of the log-OR of the PS across ancestry groups (upper/lower points of diamond) and corresponding 95% confidence interval (left/right points of diamond). The cluster-specific components of the partitioned PS are adjusted for the overall T2D PS. Analyses were conducted in individuals with T2D only. AFA: African American ancestry group (105 cases and 5,330 controls). EAS: East Asian ancestry group (133 cases and 3,155 controls). EUR: European ancestry group (116 cases and 9,538 controls). HIS: Hispanic ancestry group (141 cases and 3,695 controls). SAS: South Asian ancestry group (56 cases and 8,019 controls).

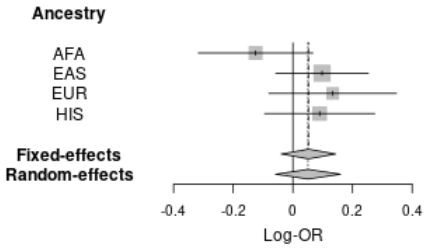


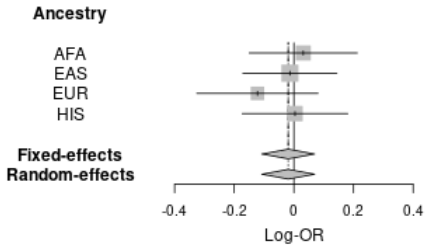


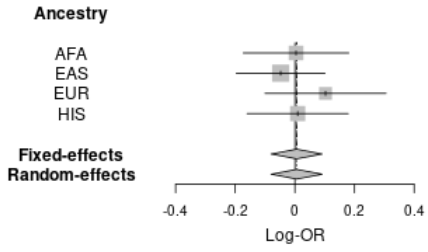


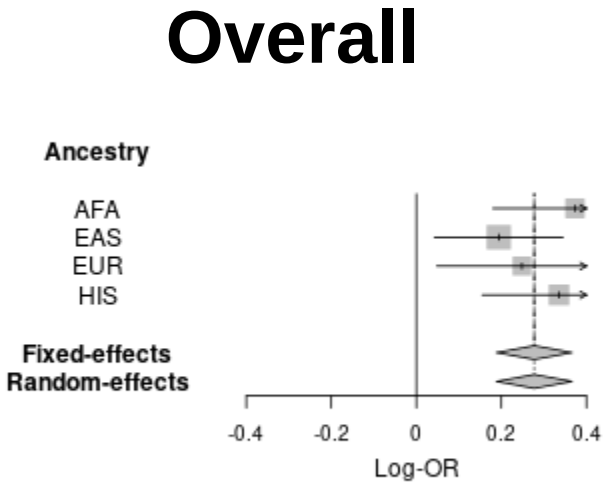




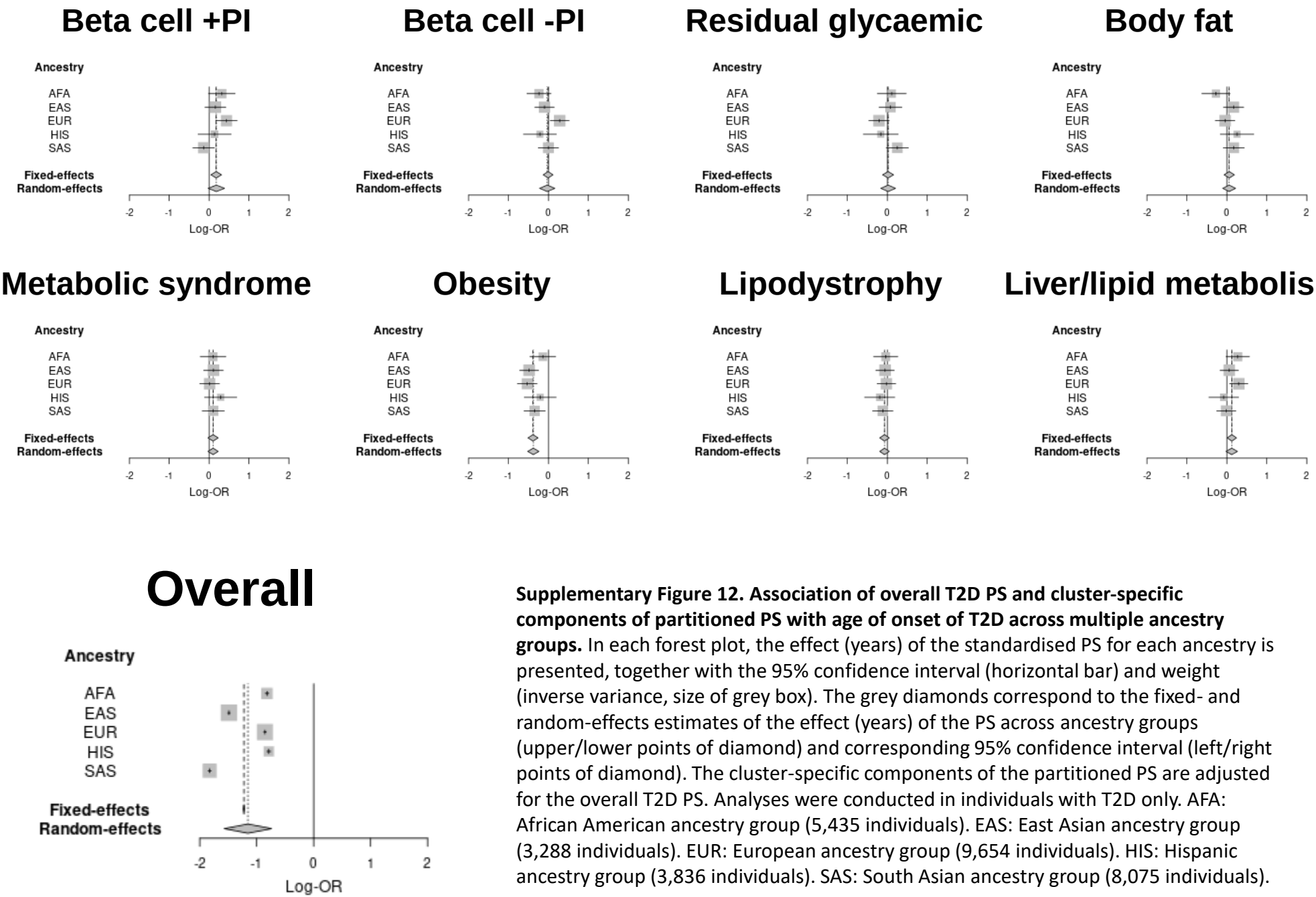




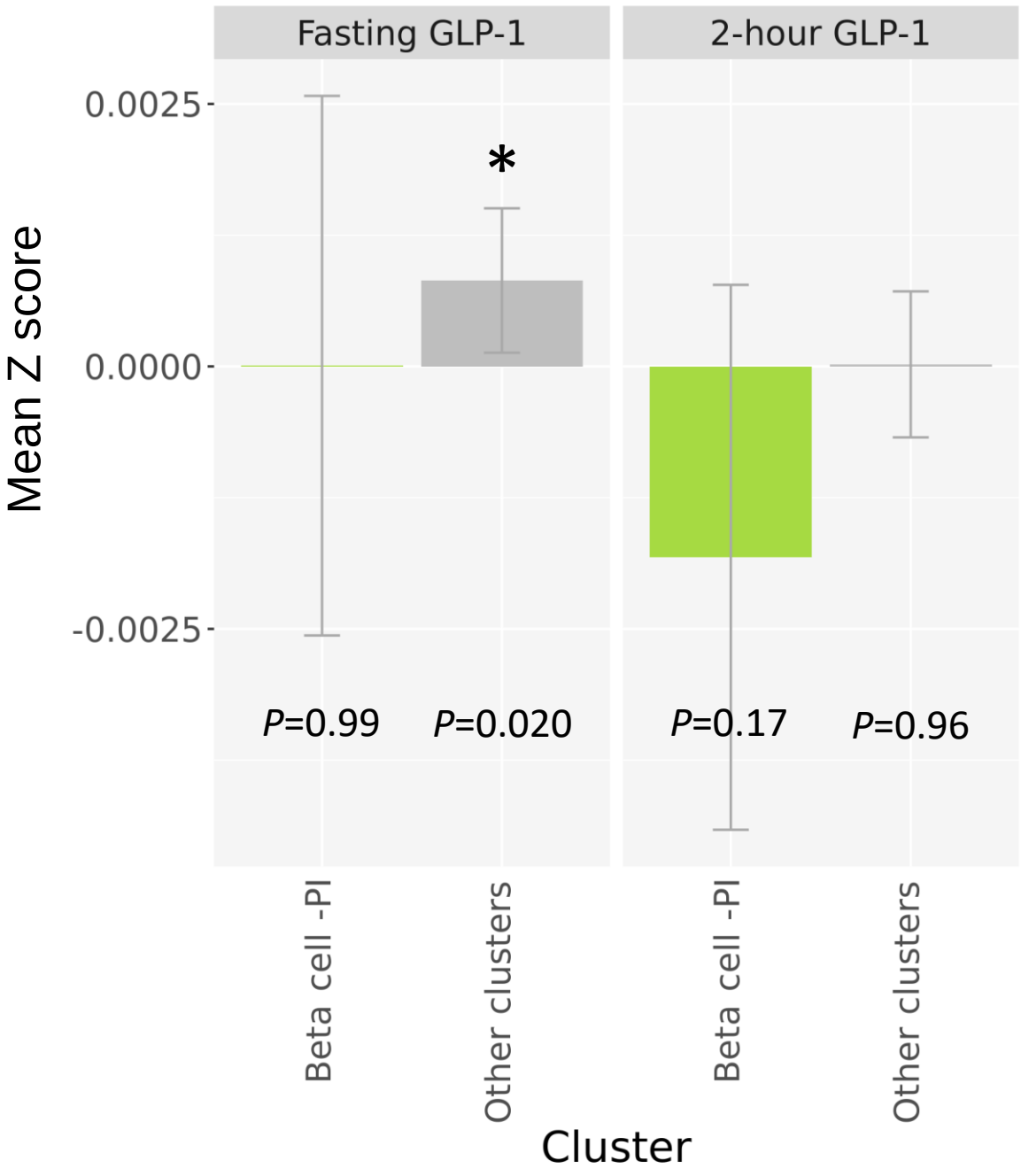




Supplementary Figure 11. Association of overall T2D PS and cluster-specific components of partitioned PS with end stage diabetic retinopathy across multiple ancestry groups. In each forest plot, the log-odds ratio (log-OR) of the standardised PS for each ancestry is presented, together with the 95% confidence interval (horizontal bar) and weight (inverse variance, size of grey box). The grey diamonds correspond to the fixed- and random-effects estimates of the log-OR of the PS across ancestry groups (upper/lower points of diamond) and corresponding 95% confidence interval (left/right points of diamond). The cluster-specific components of the partitioned PS are adjusted for the overall T2D PS. Analyses were conducted in individuals with T2D only. AFA: African American ancestry group (132 cases and 5,072 controls). EAS: East Asian ancestry group (196 cases and 3,461 controls). EUR: European ancestry group (100 cases and 9,417 controls). HIS: Hispanic ancestry group (146 cases and 3,441 controls).



Supplementary Figure 12. Association of overall T2D PS and cluster-specific components of partitioned PS with age of onset of T2D across multiple ancestry groups. In each forest plot, the effect (years) of the standardised PS for each ancestry is presented, together with the 95% confidence interval (horizontal bar) and weight (inverse variance, size of grey box). The grey diamonds correspond to the fixed- and random-effects estimates of the effect (years) of the PS across ancestry groups (upper/lower points of diamond) and corresponding 95% confidence interval (left/right points of diamond). The cluster-specific components of the partitioned PS are adjusted for the overall T2D PS. Analyses were conducted in individuals with T2D only. AFA: African American ancestry group (5,435 individuals). EAS: East Asian ancestry group (3,288 individuals). EUR: European ancestry group (9,654 individuals). HIS: Hispanic ancestry group (3,836 individuals). SAS: South Asian ancestry group (8,075 individuals).



Supplementary Figure 13. Cluster-specific associations of T2D risk alleles at index SNVs with circulating GLP-1 concentrations. Association was assessed in 3,514 individuals of European ancestry from the Malmo Diet and Cancer Study and the PPP-Botnia Study. The height of each bar corresponds to the mean Z-score, and the grey line shows the 95% confidence interval. The liver/lipid metabolism cluster has been removed for ease of presentation. *P<0.05, nominal association.