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The trans-ancestral genomic architecture of glycemetic traits

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The Trans-Ancestral Genomic Architecture of Glycemic Traits

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459

460

461 **Abstract**

462 Glycemic traits are used to diagnose and monitor type 2 diabetes, and cardiometabolic health. To
463 date, most genetic studies of glycemic traits have focused on individuals of European ancestry. Here,
464 we aggregated genome-wide association studies in up to 281,416 individuals without diabetes (30%
465 non-European ancestry) with fasting glucose, 2h-glucose post-challenge, glycated hemoglobin, and
466 fasting insulin data. Trans-ancestry and single-ancestry meta-analyses identified 242 loci (99 novel;
467 $P < 5 \times 10^{-8}$), 80% with no significant evidence of between-ancestry heterogeneity. Analyses restricted
468 to European ancestry individuals with equivalent sample size would have led to 24 fewer new loci.
469 Compared to single-ancestry, equivalent sized trans-ancestry fine-mapping reduced the number of
470 estimated variants in 99% credible sets by a median of 37.5%. Genomic feature, gene-expression
471 and gene-set analyses revealed distinct biological signatures for each trait, highlighting different
472 underlying biological pathways. Our results increase understanding of diabetes pathophysiology by
473 use of trans-ancestry studies for improved power and resolution.

474 Fasting glucose (FG), 2h-glucose post-challenge (2hGlu), and glycated hemoglobin (HbA1c) are
475 glycemic traits used to diagnose diabetes¹. In addition, HbA1c is the most commonly used biomarker
476 to monitor glucose control in patients with diabetes. Fasting insulin (FI) reflects a combination of
477 insulin secretion and insulin resistance, both components of type 2 diabetes (T2D), and insulin
478 clearance². Collectively, all four glycemic traits can be useful to better understand T2D
479 pathophysiology³⁻⁵ and cardiometabolic outcomes⁶.

480

481 To date, genome-wide association studies (GWAS) and analysis of MetaboChip and exome arrays
482 have identified >120 loci associated with glycemic traits in individuals without diabetes⁷⁻¹⁵. However,
483 despite considerable differences in the prevalence of T2D risk factors across ancestries¹⁶⁻¹⁸, most
484 glycemic trait GWAS have insufficient representation of individuals of non-European ancestry and
485 limited resolution for fine-mapping of causal variants and effector transcript identification. Here, we
486 present large-scale trans-ancestry meta-analyses of GWAS for four glycemic traits in individuals
487 without diabetes. We aimed to identify additional glycemic trait-associated loci; investigate the
488 portability of loci and genetic scores across ancestries; leverage differences in effect allele frequency
489 (EAF), effect size, and linkage disequilibrium (LD) across diverse populations to conduct fine-mapping
490 and aid causal variant/effector transcript identification; and compare the genetic architecture of
491 glycemic traits to further elucidate underlying biology and T2D pathophysiology.

492

493 Results

494 Study design and definitions

495 To identify loci associated with glycemic traits FG, 2hGlu, FI, and HbA1c, we aggregated GWAS in up
496 to 281,416 individuals without diabetes, ~30% of whom were of non-European ancestry [13% East
497 Asian, 7% Hispanic, 6% African-American, 3% South Asian, and 2% sub-Saharan African (Ugandan
498 data only available for HbA1c)]. Each cohort imputed data to the 1000 Genomes Project reference
499 panel¹⁹ (phase 1 v3, March 2012, or later; **Methods, Supplementary Table 1, Extended Data Figure
500 1, Supplementary Note**). Up to ~49.3 million variants were directly genotyped or imputed, with
501 between 38.6 million (2hGlu) and 43.5 million variants (HbA1c) available for analysis after exclusions
502 based on minor allele count (MAC < 3) and imputation quality (imputation r^2 or INFO score < 0.40) in
503 each cohort. FG, 2hGlu and FI analyses were adjusted for BMI¹⁵ but for simplicity they are
504 abbreviated as FG, 2hGlu and FI (**Methods**).

505

506 We first performed trait-specific fixed-effect meta-analyses *within* each ancestry using METAL²⁰. We
507 defined “single-ancestry lead” variants as the strongest trait-associated variants ($P < 5 \times 10^{-8}$) within a
508 1Mb region in an ancestry (**Table 1**). Within each ancestry and each autosome, we used approximate
509 conditional analyses in GCTA^{21,22}, to identify “single-ancestry index variants” ($P < 5 \times 10^{-8}$) that exert
510 conditionally distinct effects on the trait (**Table 1, Methods, Supplementary Note**). This approach
511 identified 124 FG, 15 2hGlu, 48 FI and 139 HbA1c variants that were significant in at least one
512 ancestry (**Supplementary Table 2**).

513

514 Next, we conducted trait-specific *trans-ancestry* meta-analyses using MANTRA (**Methods,
515 Supplementary Table 1, Supplementary Note**) to identify genome-wide significant “trans-ancestry
516 lead variants”, defined as the most significant trait-associated variant across all ancestries (\log_{10}
517 Bayes Factor [BF] > 6, equivalent to $P < 5 \times 10^{-8}$)²³ (**Table 1, Methods**). Here, we present trans-ancestry
518 results as our primary results (**Supplementary Table 2**).

519

520 Causal variants are expected to affect related glycemic traits and may be shared across ancestries.
521 Therefore, we combined all single-ancestry lead variants, single-ancestry index variants, and/or
522 trans-ancestry lead variants (for any trait) mapping within 500Kb of each other, into a single “trans-
523 ancestry locus” bounded by 500Kb flanking sequences (**Table 1, Extended Data Figure 2**). As defined,

524 a trans-ancestry locus may contain multiple causal variants affecting one or more glycemic traits,
525 exerting their effect in one or more ancestry.

526

527 **Glycemic trait locus discovery**

528 Trans-ancestry meta-analyses identified 235 trans-ancestry loci, of which 59 contained lead variants
529 for more than one trait. In addition, we identified seven “single-ancestry loci” that did not contain
530 any trans-ancestry lead variants (**Table 1, Supplementary Table 2**). Of the 242 combined loci, 99
531 (including 6 of the 7 single-ancestry) had not been previously associated with any of the four
532 glycemic traits or with T2D, at the time of analysis (**Figure 1, Supplementary Table 3, Supplementary**
533 **note**). However, based on recent East Asian and trans-ancestry T2D GWAS meta-analyses²³⁻²⁷, the
534 lead variants at 27/99 novel glycemic trait loci have strong evidence of association with T2D ($P < 10^{-4}$;
535 13 loci with $P < 5 \times 10^{-8}$), suggesting they are also important in T2D pathophysiology (**Supplementary**
536 **Tables 2 and 4**).

537

538 Of the six single-ancestry novel loci, three were unique to non-European ancestry individuals
539 (**Supplementary Table 3**). An African American association for FI (lead variant rs12056334) near
540 *LOC100128993* (an uncharacterized RNA gene; **Supplementary Note**). An African American
541 association for FG (lead variant rs61909476) near *ETS1* and a Hispanic association for FG (lead
542 variant rs12315677) within *PIK3C2G* (**Supplementary Table 3**). Despite broadly similar EAF across
543 ancestries, rs61909476 was only significantly associated with FG in African American individuals (EAF
544 ~7%, $b = 0.0812$ mmol/l, $SE = 0.01$ mmol/l, $P = 3.9 \times 10^{-8}$ vs EAF 10-17%, $b = 0.002$ mmol/l, $se = 0.003$ -
545 0.017 mmol/l, $P = 0.44$ - 0.95 in all other ancestries, **Supplementary table 2, Supplementary note**). The
546 nearest gene, *ETS1*, encodes a transcription factor that localizes to insulin-positive cells, and its
547 overexpression decreases glucose-stimulated insulin secretion in mouse islets²⁸. Located within the
548 *PIK3C2G* gene, rs12315677 has an 84% EAF in Hispanic (70-94% in other ancestries) and is only
549 significantly associated with FG in this ancestry ($b = 0.0387$ mmol/l, $SE = 0.0075$ mmol/l, $P = 4.0 \times 10^{-8}$ vs
550 $b = -0.0128$ - 0.010 mmol/l, $SE = 0.003$ - 0.018 mmol/l, $P = 0.14$ - 0.76 in all other ancestries,
551 **Supplementary note**). In mice, deletion of *Pik3c2g* leads to a phenotype characterized by reduced
552 glycogen storage in the liver, hyperlipidemia, adiposity, and insulin resistance with increasing age, or
553 after a high fat diet²⁹. Instances of similar EAFs but differing effect sizes between populations, could
554 be due to genotype-by-environment or other epistatic effects. Alternatively, lower imputation
555 accuracy in smaller sample sizes could deflate effect sizes, although imputation quality for these
556 variants was good (average $r^2 = 0.81$). Finally, the variants detected here may be in LD with ancestry-
557 specific causal variants not interrogated here that differ in frequency across ancestries. However, we
558 could not find evidence of rarer alleles in the cognate populations from the 1000G project
559 (**Supplementary Table 5**). The final three single-ancestry loci were identified in individuals of
560 European ancestry (**Supplementary note**).

561

562 Next, by rescaling the standard errors of allelic effect sizes to artificially boost the sample size of the
563 European meta-analysis to match that of trans-ancestry meta-analysis, we determined that 21 of the
564 novel trans-ancestry loci would not have been discovered with an equivalent sample size comprised
565 exclusively of European ancestry individuals (**Supplementary note**). Their discovery was due to the
566 higher EAF and/or larger effect size in non-European ancestry populations. In particular, two loci
567 (near *LINC00885* and *MIR4278*) contain East Asian and African American single-ancestry lead
568 variants, respectively, suggesting that these specific ancestries may be driving the trans-ancestry
569 discovery (**Supplementary Tables 2-3**). Combined with the three single-ancestry non-European loci
570 described above, our results show that 24% (24/99) of novel loci were discovered due to the
571 contribution of non-European ancestry participants, strengthening the argument for expanding
572 genetic studies in diverse populations.

573

574 **Allelic architecture of glycemic traits**

575 Single-ancestry and trans-ancestry results combined increased the number of established loci for FG
576 to 102 (182 signals, 53 novel loci), FI to 66 (95 signals, 49 novel loci), 2hGlu to 21 (28 signals, 11
577 novel loci), and HbA1c to 127 (218 signals, 62 novel loci) (**Supplementary Table 2**), with significant
578 overlap across traits (**Extended Data Figure 3**). We also detected ($P < 0.05$ or $\log_{10}BF > 0$) the vast
579 majority (~90%) of previously established glycemc signals, 70-88% of which attained genome-wide
580 significance (**Supplementary Note, Supplementary Table 6**). Given that analyses for FG, FI, and
581 2hGlu were performed adjusted for BMI, we confirmed that collider bias did not influence >98% of
582 signals discovered (**Supplementary note**)³¹. As expected, given the greater power due to increased
583 sample sizes, new association signals tended to have smaller effect sizes and/or EAFs in European
584 ancestry individuals compared to established signals (**Extended Data Figure 4**).

585

586 **Characterization of lead variants across ancestries**

587 To better understand the transferability of trans-ancestry lead variants across ancestries, we
588 investigated the pairwise EAF correlation and the pairwise summarized heterogeneity of effect sizes
589 between ancestries³² (**Methods, Supplementary Note**). Consistent with population history and
590 evolution, these results demonstrated considerable EAF correlation ($\rho^2 > 0.70$) between European
591 and Hispanic, European and South Asian, and Hispanic and South Asian populations, consistent
592 across all four traits, and between African Americans and Ugandans for HbA1c (**Extended Data**
593 **Figure 5**). Despite significant EAF correlations, some pairwise comparisons exhibited strong evidence
594 for effect size heterogeneity between ancestries that was less consistent between traits (**Extended**
595 **Data Figure 5**). However, sensitivity analyses demonstrated that, across all comparisons, the
596 evidence for heterogeneity is driven by a small number of variants, with between 81.5% (for HbA1c)
597 and 85.7% of trans-ancestry lead variants (for FG) showing no evidence for trans-ancestry
598 heterogeneity ($P > 0.05$) (**Supplementary Note**).

599

600 **Trait variance explained by associated loci**

601 The trait variance explained by genome-wide significant loci was assessed using the single-ancestry
602 variants only or a combination of single-ancestry and trans-ancestry variants (**Supplementary Table**
603 **7**) with betas extracted from the relevant single-ancestry meta-analysis results (**Methods**). The
604 variance explained was assessed by linear regression in a subset of the contributing cohorts
605 (**Methods, Supplementary Tables 8-11**). In general, the approach that explained the most variance
606 was to begin with the trans-ancestry lead variants that had $P < 0.1$ in the relevant single-ancestry
607 meta-analysis, then add in all single-ancestry variants that were not in LD with the trans-ancestry
608 variants ($LD\ r^2 < 0.1$) (List C, **Supplementary Tables 8-11, Figure 2**). Using this approach, the mean
609 variance in the trait distribution explained was between 0.7% (2hGlu in EUR) and 6% (HbA1c in AA).
610 The European-based estimates explained more variance relative to previous estimates of 2.8% for
611 FG and 1.7% for HbA1c³³ (**Supplementary Note**).

612

613 **Transferability of EUR ancestry-derived polygenic scores**

614 To investigate the transferability of polygenic scores across ancestries we used the PRS-CSauto
615 software³⁴ to first build polygenic scores for each glycemc trait based on European ancestry data.
616 However, the training set for 2hGlu was too small so this trait was excluded. To build the polygenic
617 scores (PGS), for each trait we first removed five of the largest European cohorts from the European
618 ancestry meta-analysis. These five cohorts were meta-analyzed and used as our European ancestry
619 test dataset, for each trait. The remaining European ancestry cohorts were also meta-analyzed and
620 used as the training dataset, from which we derived a PGS for each trait (**Methods**). We used PRS-
621 CSauto to revise the effect size estimates for the variants in the score (obtained from the training
622 European datasets) based on the LD of the test population. PRS-CSauto does not have LD reference
623 panels for South Asian or Hispanic ancestry and as such we were unable to test the transferability of
624 the PGS into those populations. The “gtx” package³⁵ (**Methods**) was used to obtain the R^2 for each
625 test population (**Figure 3, Supplementary Table 12**). Consistent with other complex traits³⁶, the

626 European ancestry-derived PGS had greater predictive power into test data of European ancestry
627 than other ancestry groups.

628

629 **Fine-mapping**

630 We fine-mapped, 231 trans-ancestry and six single-ancestry autosomal loci (**Supplementary Table 2,**
631 **Supplementary note**). Using FINEMAP with ancestry-specific LD and an average LD matrix across
632 ancestries, we conducted fine-mapping both within (161 loci with single-ancestry lead variants) and
633 across ancestries (231 loci) for each trait (**Methods**). Because 59 of the 231 trans-ancestry loci were
634 associated with more than one trait, we conducted trans-ancestry fine-mapping for a total of 305
635 locus-trait associations. Of these 305 locus-trait combinations, FINEMAP estimated the presence of a
636 single causal variant at 186 loci (61%), while multiple distinct causal variants were implicated at 126
637 loci (39%), for a total of 464 causal variants (**Figure 4A**).

638

639 *Credible sets for causal variants*

640 At each locus, we next constructed credible sets (CS) for each causal variant that account for $\geq 99\%$
641 of the posterior probability of association (PPA). We identified 21 locus-trait associations (at 19 loci)
642 for which the 99% CS included a single variant, and we highlight four examples (**Methods,**
643 **Supplementary Note, Figure 4B, Supplementary Table 13**).

644

645 At *MTNR1B* and *SIX3* we identified, respectively, rs10830963 (PPA>0.999, for both HbA1c and FG)
646 and rs12712928 (PPA=0.997, for FG) as the likely causal variants. At both loci previous studies
647 confirm these variants affect transcriptional activity^{37,38,39} (**Supplementary note**). At a locus near
648 *PFKM* associated with HbA1c, trans-ancestry fine-mapping identified rs12819124 (PPA>0.999) as the
649 likely causal variant. This variant has been previously associated with mean corpuscular
650 hemoglobin⁴⁰, suggesting an effect on HbA1c via the red blood cell (RBC, **Supplementary note**). At
651 *HBB*, we identified rs334 (PPA>0.999; Glu7Val) as the likely causal variant associated with HbA1c.
652 rs334 is a causal variant of sickle cell anemia⁴¹, previously associated with urinary albumin-to-
653 creatinine ratio in Caribbean Hispanic individuals⁴², severe malaria in a Tanzanian study population⁴³,
654 hematocrit and mean corpuscular volume in Hispanic/Latino populations⁴⁴, and RBC distribution in
655 Ugandan individuals⁴⁵, all pointing to a variant effect on HbA1c via non-glycemic pathways.

656

657 The remaining locus-trait associations with a single variant in the 99% CS (**Supplementary Table 13**)
658 point to variants that could be prioritized for functional follow-up to elucidate impact on glycemic
659 trait physiology.

660

661 At an additional 156 locus-trait associations trans-ancestry fine-mapping identified 99% CS with 50
662 or fewer variants (**Figure 4B, Supplementary Table 13**). Consistent with the potential for >1 causal
663 variant in a locus, 74 locus-trait associations contained 88 variants with PPA>0.90 that are strong
664 candidate causal variants (**Supplementary Table 14**). For example, 10 are coding variants including
665 several missense such as the *HBB* Glu7Val mentioned above, *GCKR* Leu446Pro, *RREB1* Asp1771Asn,
666 *G6PC2* Pro324Ser, *GLP1R* Ala316Thr, and *TMPRSS6* Val736Ala, each of which have been proposed or
667 shown to affect gene function^{12,46-50}. We additionally identified *AMPD3* Val311Leu (PPA=0.989) and
668 *TMC6* Trp125Arg (PPA>0.999) variants associated with HbA1c which were previously detected in an
669 exome array analysis but had not been fine-mapped with certainty due to the absence of backbone
670 GWAS data³⁰. Our fine-mapping now suggest these variants are likely causal and identify their
671 cognate genes as effector transcripts.

672

673 Finally, we evaluated the resolution obtained in the trans-ancestry versus single-ancestry fine-
674 mapping (**Methods, Supplementary Note**). We compared the number of variants in 99% CS across
675 98 locus-trait associations which, as suggested by FINEMAP, had a single causal variant in both trans-
676 ancestry and single-ancestry analyses. Fine-mapping within and across ancestries was conducted

677 using the same set of variants. At 8 of 98 locus-trait associations single-ancestry fine-mapping
678 identified a single variant in the CS. In addition, at 72 of the 98 locus-trait associations, the number
679 of variants in the 99% CS was smaller in the trans-ancestry fine-mapping (**Figure 4C**), which likely
680 reflects the larger sample size and differences in LD structure, EAFs, and effect sizes across diverse
681 populations. To quantify the estimated improvement in fine-mapping resolution attributable to the
682 multi-ancestry GWAS, we then compared 99% CS sizes from the trans-ancestry fine-mapping to
683 single-ancestry-specific data emulating the same total sample size by rescaling the standard errors
684 (**Methods**). Of the 72 locus-trait associations with estimated improved fine-mapping in trans-
685 ancestry analysis, resolution at 38 (53%) was improved because of the larger sample size in the
686 trans-ancestry fine-mapping analysis (**Figure 4C**), and this estimated improved resolution would
687 likely have been obtained in a European-only fine-mapping effort with equivalent sample size.
688 However, at 34 (47%) loci, the inclusion of samples from multiple diverse populations yielded the
689 estimated improved resolution. On average, ancestry differences led to a reduction in the median
690 number of variants in the 99% CS from 24 to 15 variants (37.5% median reduction; **Figure 4C**),
691 demonstrating the value of conducting fine-mapping across ancestries.

692

693 **HbA1c Signal Classification**

694 HbA1c-associated variants can exert their effects on HbA1c levels through both glyceic and non-
695 glyceic pathways^{7,51} and their correct classification can affect T2D diagnostic accuracy^{7,52}. Using
696 prior association results for other glyceic, RBC, and iron traits, and a fuzzy clustering approach we
697 classified variants into their most likely mode of action (**Methods, Supplementary note**). Of the 218
698 HbA1c-associated variants, 27 (12%) could not be characterized due to missing data and 23 (11%)
699 could not be classified into a “known” class (**Supplementary note**). The remaining signals were
700 classified as principally: a) glyceic (n=53; 24%), b) affecting iron levels/metabolism (n=12; 6%), or c)
701 RBC traits (n=103; 47%). A genetic risk score (GRS) composed of all HbA1c-associated signals was
702 strongly associated with T2D risk (OR=2.4, 95% CI 2.3-2.5, $P=2.7 \times 10^{-298}$). However, when using
703 partitioned GRSs composed of these different classes of variants (**Methods**), we found the T2D
704 association was mainly driven by variants influencing HbA1c through glyceic pathways (OR=2.6,
705 95% CI 2.5-2.8, $P=2.3 \times 10^{-250}$), with weaker evidence of association (despite the larger number of
706 variants in the GRS) and a more modest risk (OR=1.4, 95% CI 1.2-1.7, $P=4.7 \times 10^{-4}$) imparted by signals
707 in the mature RBC cluster that were not glyceic (i.e. where those specific variants had $P>0.05$ for
708 FI, 2hGlu and FG) (**Extended Data Figure 6, Supplementary note**). This contrasts our previous finding
709 where we found no significant association between a risk score of non-glyceic variants and T2D⁷.
710 Our current results could be partly driven by T2D cases being diagnosed based on HbA1c levels that
711 may be influenced by the non-glyceic signals, or by glyceic effects not captured by FI, 2hGlu or
712 FG measures.

713

714 **Biological signatures of glyceic trait associated loci**

715 To better understand distinct and shared biological signatures underlying variant-trait associations,
716 we conducted genomic feature enrichment, eQTL co-localization, and tissue and gene-set
717 enrichment analyses across all four traits.

718

719 **Epigenomic landscape of trait-associated variants**

720 We explored the genomic context underlying glyceic trait loci by computing overlap enrichment
721 for annotations such as coding, conserved regions, and super enhancers merged across multiple cell
722 types⁵³⁻⁵⁵ using the GREGOR tool⁵⁶. We observed that FG, FI and HbA1c signals (**Supplementary**
723 **Table 7**) were significantly ($P<8.4 \times 10^{-4}$, Bonferroni threshold for 59 annotations) enriched in
724 evolutionarily conserved regions (**Fig 5A, Extended Data Figure 7, Supplementary Table 15**).

725
726 We then considered epigenomic landscapes defined in individual cell/tissue types. Previously,
727 stretch enhancers (StrE, enhancer chromatin states $\geq 3\text{kb}$ in length) in pancreatic islets were shown
728 to be highly cell-specific and strongly enriched with T2D risk signals⁵⁷. Considering StrEs across 31
729 cell-types³⁹, FG and 2hGlu signals showed the highest enrichment in islets (FG: fold-
730 enrichment=4.70, $P=2.7 \times 10^{-24}$; 2hGlu: fold-enrichment=5.51, $P=3.6 \times 10^{-4}$ **Figure 5A, Supplementary**
731 **Table 16**), highlighting the importance of islets for these traits. FI signals were enriched in skeletal
732 muscle (fold-enrichment=3.17, $P=7.8 \times 10^{-6}$) and adipose StrEs (fold-enrichment=3.27, $P=1.8 \times 10^{-7}$)
733 consistent with these tissues as targets of insulin action (**Figure 5A**). StrEs in individual cell types
734 showed higher enrichment than super enhancers merged across cell types, highlighting the
735 importance of cell-specific analyses (**Figure 5A**). HbA1c signals were enriched in StrEs of multiple cell
736 types and tissues, but have the strongest enrichment in K562 blood-derived leukemia cells (fold-
737 enrichment=3.24, $P=1.2 \times 10^{-7}$, **Figure 5A**). Among the “hard” glycemic and red blood cell (mature +
738 reticulocyte) HbA1c signals, glycemic signals were enriched in islet StrEs (fold-enrichment=3.96,
739 $P=3.7 \times 10^{-16}$) while red blood cell signals were enriched in K562 StrEs (fold-enrichment=7.5,
740 $P=2.08 \times 10^{-14}$, **Figure 5B, Supplementary Table 17**). These analyses suggest that these glycemic trait-
741 associated variants influence the function of tissue-specific enhancers.

742
743 Independent analyses with fGWAS⁵⁸ and GARFIELD⁵⁹ yielded consistent results (**Extended Data**
744 **Figures 8 and 9, Supplementary Tables 16 and 18**). Notably, FI signals at a lenient threshold of $P < 10^{-5}$
745 were enriched in liver StrEs using GARFIELD (odds ratio=1.92, $P=1.7 \times 10^{-4}$) (**Extended Data Figure**
746 **9A**). This suggests that liver regulatory annotations are relevant for FI GWAS signals, but that we lack
747 power to detect significant enrichment using the genome-wide significant loci and the current set of
748 reference annotations.

749
750 We next explored the 27 loci driving the FI enrichment in adipose and skeletal muscle, 11 of which
751 overlapped StrEs in both tissues (**Figure 5C**). At the *COL4A2* locus, variants within an intronic region
752 overlap StrEs in adipose tissue, skeletal muscle, and a human skeletal muscle myoblast (HSMM) cell
753 line that are not shared across other cell/tissue types. Among these, rs9555695 (in the 99% CS) also
754 overlaps accessible chromatin regions in adipose (**Figure 5D**). At a narrow signal with no proxy
755 variants (LD $r^2 > 0.7$ in Europeans), the lead trans-ancestry variant rs62271373 (PPA = 0.94) located in
756 an intergenic region $\sim 25\text{kb}$ from the *LINC01214* gene overlaps StrEs specific to adipose and HSMM
757 and an active enhancer chromatin state in skeletal muscle (**Figure 5E**). Collectively, the tissue-
758 specific epigenomic signatures at GWAS signals provide an opportunity to nominate tissues where
759 these variants are likely to be active. This map may help future efforts to deconvolute GWAS signals
760 into tissue-specific disease pathology.

761 762 **Co-localization of GWAS and eQTLs**

763 Among the 99 novel glycemic trait loci, we identified co-localized eQTLs at 34 loci in blood,
764 pancreatic islets, subcutaneous or visceral adipose, skeletal muscle, or liver, providing suggestive
765 evidence of causal genes (**Supplementary Table 19**). The co-localized eQTLs include several genes
766 previously reported at glycemic trait loci: *ADCY5*, *CAMK1D*, *IRS1*, *JAZF1*, and *KLF14*⁶⁰⁻⁶². For some
767 additional loci, the co-localized genes have prior evidence for a role in glycemic regulation. For
768 example, the lead trans-ancestry variant and likely causal variant, rs1799815 (PPA=0.993),
769 associated with FI is the strongest variant associated with expression of *INSR*, encoding the insulin
770 receptor, in subcutaneous adipose from METSIM ($P=2 \times 10^{-9}$) and GTEx ($P=5 \times 10^{-6}$). The A allele at
771 rs1799815 is associated with higher FI and lower expression of *INSR*, consistent with the relationship
772 between insulin resistance and reduced *INSR* function⁶³. In a second example, rs841572, the trans-
773 ancestry lead variant associated with FG, has the highest PPA (PPA=0.535) among the 20 variants in
774 the 99% CS and is in strong LD ($r^2=0.87$) with the lead eQTL variant (rs841576, also in the 99% CS)
775 associated with *SLC2A1* expression in blood (eQTLGen $P=1 \times 10^{-8}$). *SLC2A1*, also known as *GLUT1*,

776 encodes the major glucose transporter in brain, placenta, and erythrocytes, and is responsible for
777 glucose entry into the brain⁶⁴. rs841572-A is associated with lower FG and lower *SLC2A1* expression.
778 While rare missense variants in *SLC2A1* are an established cause of seizures and epilepsy⁶⁵, our data
779 suggest that *SLC2A1* variants also affect plasma glucose levels within a population. These co-
780 localized signals provide possible regulatory mechanisms for variant effects on genes to influence
781 glycemic traits.

782
783 The co-localized eQTLs also provide new insights into the mechanisms at glycemic trait loci. For
784 example, rs9884482 (in the 99% CS) is associated with FI and *TET2* expression in subcutaneous
785 adipose ($P=2\times 10^{-20}$); rs9884482 is in high LD ($r^2=0.96$ in Europeans) with the lead *TET2* eQTL variant
786 (rs974801). *TET2* encodes a DNA-demethylase that can affect transcriptional repression⁶⁶. Adipose
787 *Tet2* expression is reduced in diet-induced insulin resistance in mice⁶⁷, and knockdown of *Tet2*
788 blocked adipogenesis^{67,68}. Consistently, in human adipose tissue, rs9884482-C was associated with
789 lower *TET2* expression and higher FI. In a second example, rs617948 is associated with HbA1c (in the
790 99% CS) and is the lead variant associated with *C2CD2L* expression in blood (eQTLGen $P=3\times 10^{-96}$).
791 *C2CD2L*, also known as *TMEM24*, regulates pulsatile insulin secretion and facilitates release of
792 insulin pool reserves^{69,70}. rs617948-G was associated with higher HbA1c and lower *C2CD2L*, providing
793 evidence for a role of this insulin secretion protein in glucose homeostasis. Our HbA1c “soft”
794 clustering assigned this signal to both the “unknown” (0.51 probability) and “reticulocyte” (0.42
795 probability) clusters. rs617948 is strongly associated with HbA1c ($P<6.8\times 10^{-8}$), but not with FG, FI or
796 2hGlu ($P>0.05$, **Supplementary Table 20, Supplementary Note**). This suggests an effect of this
797 variant on reticulocyte biology, and on insulin secretion, potentially influencing HbA1c levels through
798 different tissues, and providing a plausible explanation for the classification as “unknown”.

799 **Tissue Expression**

801 Consistent with effector transcript expression analysis using GTEx data³⁰, we found significant
802 differences in tissue expression across the glycemic trait signals. FG signals were enriched for genes
803 expressed in the pancreas (FDR<0.05), while there were an insufficient number of significant
804 associations in 2hGlu to identify enrichment for any tissue or cell type at FDR<0.2 threshold. FI
805 signals were enriched for connective tissue and cells (which includes adipose tissue), endocrine
806 glands, blood cells, and muscles (FDR<0.2) and HbA1c signals were significantly enriched for genes
807 expressed in the pancreas, hemic, and immune system (FDR<0.05) (**Figure 6, Supplementary Table**
808 **21**). Consistent with previous analysis³⁰, FI-enrichment for connective tissue was driven by adipose
809 tissue (subcutaneous and visceral), while the newly described enrichment with endocrine glands was
810 driven by the adrenal glands and cortex (**Supplementary Table 21**). Beyond enrichment for genes
811 expressed in glycemic-related tissues, HbA1c signals were enriched with genes expressed in blood,
812 consistent with the role of RBC in this trait and our previous results³⁰.

813
814 The association between FI signals and genes expressed in adrenal glands is notable, suggesting a
815 possible direct role for these genes in insulin resistance. These genes might influence cortisol levels,
816 which could contribute to insulin resistance and FI levels through impaired insulin receptor signaling
817 in peripheral tissues, as well as influencing body fat distribution, stimulate lipolysis, and other
818 indirect mechanisms^{71,72}.

819 820 821 **Gene-set Analyses**

822 Next, we performed gene-set analysis using DEPICT (**Methods**). In keeping with previous results³⁰,
823 we found distinct gene-sets enriched (FDR<0.05) for each glycemic trait except 2hGlu, which had
824 insufficient associations to have power in this analysis. FG-associated variants highlighted gene-sets
825 involved in metabolism and gene-sets involved in general cellular function such as “cytoplasmic
826 vesicle membrane” and “circadian clock” (**Figure 7A**). In contrast, in addition to metabolism-related

827 gene-sets, FI-associated variants highlighted pathways related to growth, cancer and reproduction
828 (**Figure 7B**). This is consistent with the role of insulin as a mitogenic hormone, and with
829 epidemiological links between insulin and certain types of cancer⁷³ and reproductive disorders such
830 as polycystic ovary syndrome⁷⁴. HbA1c-associated variants highlighted many gene-sets (**Figure 7C**),
831 including those linked to metabolism and hematopoiesis, again recapitulating our postulated effects
832 of variants on glucose and RBC biology. Additional pathways from HbA1c-associated variants also
833 highlighted previous “CREBP PPI” and lipid biology related to T2D⁷⁵ and HbA1c⁷⁶, respectively, and
834 potential new biology through which variants may influence HbA1c.

835

836 Discussion

837 Here we describe a large glycemic trait meta-analysis of GWAS for which 30% of the population was
838 composed of East Asian, Hispanic, African-American, South Asian and sub-Saharan African
839 participants. This effort identified 242 loci (235 trans-ancestry and seven single-ancestry), which
840 jointly explain between 0.7% (2hGlu in European ancestry individuals) and 6% (HbA1c in African
841 American ancestry individuals) of the variance in glycemic traits in any given ancestry. While
842 114/242 loci are associated with T2D ($P < 10^{-4}$; 83 loci with $P < 5 \times 10^{-8}$, **Supplementary Table 4**),
843 absence of strong evidence of association at the remaining loci ($P \geq 10^{-4}$) suggests that for alleles
844 more frequent than 5% we can exclude T2D ORs ≥ 1.07 with 80% power ($\alpha = 5 \times 10^{-8}$; and ORs ≥ 1.05
845 for $\alpha = 10^{-4}$) given a current study of 228,499 T2D cases and 1,178,783 controls²⁷. We identified
846 486 signals associated with glycemic traits, of which eight have MAF $< 1\%$, and 45 have $1\% \leq \text{MAF} < 5\%$
847 in all ancestries, highlighting that 89% of signals identified are common in at least one ancestry
848 studied.

849

850 A key aim of our study was to evaluate the added advantage of including population diversity in
851 genetic discovery and fine-mapping efforts. Beyond the larger sample size included in the trans-
852 ancestry meta-analysis, we were able to estimate the contribution of non-European ancestry data in
853 locus discovery and fine-mapping resolution. We found that 24 of the 99 newly discovered loci owe
854 their discovery to the inclusion of East Asian, Hispanic, African-American, South Asian and sub-
855 Saharan African participant data, due to differences in EAF and effect sizes across ancestries.

856

857 Comparison of 295 trans-ancestry lead variants (315 locus-trait associations) across ancestries
858 demonstrated that between 81.5% (HbA1c) and 85.7% (FG) of the trans-ancestry lead variants had
859 no evidence of trans-ancestry heterogeneity in allelic effects ($P > 0.05$).

860

861 Given sample size and power limitations, genome-wide significant trait-associated variants in a
862 single-ancestry explain only a modest proportion of trait variance in that ancestry (**Figure 2**). We
863 demonstrate that trans-ancestry lead variants explain more trait variance than the ancestry-specific
864 variants (**Figure 2**). This shows that even though some trans-ancestry lead variants are not genome-
865 wide significant in all ancestries, they contribute to the genetic architecture of the trait in most
866 ancestries.

867

868 We evaluated for the first time the transferability of European ancestry-derived glycemic trait PGS
869 into other ancestries. Consistent with other traits^{36,77,78}, we confirm that European ancestry-derived
870 PGS perform much worse when the test dataset is from a different ancestry. Each trait-specific PGS
871 improves trait variance explained by between 3.5-fold (HbA1c) and 6-fold (FG) in the European
872 dataset (**Figure 3, Supplementary Table 12**) compared to a score built only from trans-ancestry lead
873 variants and European index variants (**Figure 2, Supplementary tables 9-12**).

874

875 Despite development of approaches to derive polygenic risk scores⁷⁹, we note the difficulty in using
876 summary level data to build a PGS in one ancestry and then apply it in test datasets of different
877 ancestry. While PRS-CSauto³⁴ is able to use summary level data, revision of the effect size estimates

878 to account for LD required reference panels that matched the ancestry of the test dataset. However,
879 the current software lacks appropriate reference panels for many ancestries, precluding its broad
880 application. **Future developments of trans-ancestry PGS are required for improved cross-ancestry**
881 **performance.**

882

883 We show that fine-mapping resolution is improved in trans-ancestry, compared to single-ancestry
884 fine-mapping efforts. In ~50% of our loci, we showed that the improvement was due to differences
885 in EAF, effect size, or LD structure between ancestries, and not just due to the overall increased
886 sample size available for trans-ancestry fine-mapping. By performing trans-ancestry fine-mapping,
887 and co-localizing GWAS signals with eQTL signals and coding variants, we identified new candidate
888 causal genes. Altogether, these results motivate continued expansion of genetic and genomic efforts
889 in diverse populations to improve understanding of these traits in groups disproportionately affected
890 by T2D.

891

892 Given data on four different glyceic traits and their utility to diagnose and monitor T2D and
893 metabolic health, we also sought to characterize biological features underlying these traits. We
894 show that despite significant sharing of loci across the four traits, each trait is also characterized by
895 unique features based on StrE, gene expression and gene-set signatures. Combining genetic data
896 from these traits with T2D data will further elucidate pathways driving normal physiology and
897 pathophysiology, and help further develop useful predictive scores for disease classification and
898 management^{4,5}.

899

900

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1246 Competing interests statement

1248 A. Astrup is the recipient of honoraria as speaker for a wide range of Danish and international
1249 concerns and receives royalties from textbooks, and from popular diet and cookery books. A. Astrup
1250 is also co-inventor of a number of patents, including Methods of inducing weight loss, treating
1251 obesity and preventing weight gain (licensee Gelesis, USA) and Biomarkers for predicting degree of
1252 weight loss (licensee Nestec SA, CH), owned by the University of Copenhagen, in accordance with
1253 Danish law. I. Barroso and spouse own stock in GlaxoSmithKline and Incyte Corporation. B.H. Chen is
1254 now an employee of Life Epigenetics, Inc.; all work was completed prior to employment at Life
1255 Epigenetics. A.Y. Chu is now an employee of Merck & Co.; all work was completed prior to
1256 employment by Merck & Co. J.C. Florez has received consulting honoraria from Janssen. J. Gayan is
1257 now an employee of F. Hoffmann-La Roche Ltd, and owns stock of Roche and GlaxoSmithKline. A.L.
1258 Gloyn has received honoraria from Merck and Novo Nordisk. As of June 2019, ALG discloses that her
1259 spouse is an employee of Genentech and hold stock options in Roche. E. Ingelsson is now an
1260 employee of GSK; all work was completed prior to his employment by GSK. W. März has received
1261 grants and/or personal fees from the following companies/corporations: Siemens Healthineers,
1262 Aegerion Pharmaceuticals, AMGEN, Astrazeneca, Sanofi, Alexion Pharmaceuticals, BASF, Abbott
1263 Diagnostics Numares AG, Berlin-Chemie, Akzea Therapeutics, Bayer Vital GmbH , bestbion dx GmbH,
1264 Boehringer Ingelheim Pharma GmbH Co KG, Immundiagnostik GmbH, Merck Chemicals GmbH, MSD
1265 Sharp and Dohme GmbH, Novartis Pharma GmbH, Olink Proteomics, and Synlab Holding
1266 Deutschland GmbH. M.I. McCarthy has served on advisory panels for Pfizer, NovoNordisk, Zoe Global
1267 and received honoraria from Merck, Pfizer, NovoNordisk and Eli Lilly. He holds stock options in Zoe
1268 Global and has received research funding from Abbvie, Astra Zeneca, Boehringer Ingelheim, Eli Lilly,
1269 Janssen, Merck, NovoNordisk, Pfizer, Roche, Sanofi Aventis, Servier, Takeda. He is now an employee
1270 of Genentech and a holder of Roche stock. J.B. Meigs has consulted for Quest Diagnostics, Inc., who
1271 manufacturers of an HbA1c assay. M.E. Montasser has received grant funding from Regeneron
1272 Pharmaceutials. M.E. Montasser is also an inventor on a patent that was published by the United
1273 States Patent and Trademark Office on December 6, 2018 under Publication Number US 2018-
1274 0346888, and international patent application that was published on December 13, 2018 under
1275 Publication Number WO-2018/226560; all work was completed before these COI arose, and are
1276 unrelated to this work. D. Mook-Kanamori is a part-time clinical research consultant for Metabolon.
1277 J.L. Nadler is a member of the Scientific Advisory Board for Veralox Therapeutics Inc. C.N.A. Palmer
1278 has received research support from GlaxoSmithKline and AstraZeneca unrelated to this project. B.M.
1279 Psaty serves on the Steering Committee of the Yale Open Data Access Project funded by Johnson &
1280 Johnson. N. Sattar has consulted for Astrazeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Napp
1281 and Sanofi and received grant support from Boehringer Ingelheim. R.A. Scott is an employee and
1282 shareholder of GlaxoSmithKline. T. Spector is the founder of Zoe Global Ltd. J. Tuomilehto receives
1283 research support from Bayer, is a consultant for Eli Lily, and holds stock in Orion Pharma and
1284 Aktivolabs Ltd.

1285

1286 **Figure Legends**

1287

1288 **Figure 1 - Summary of all 242 loci identified in this study.** 235 trans-ancestry loci are shown in
1289 orange (novel) or black (established) along with seven single-ancestry loci (blue) represented by
1290 nearest gene. Each locus is mapped to corresponding chromosome (outer segment). Each set of
1291 rows shows the results from the trans-ancestry analysis (orange) and each of the ancestries:
1292 European (purple), African American (tan), East Asian (grey), South Asian (green), Hispanic (yellow),
1293 sub-Saharan African (Ugandan-pink). Loci with a corresponding type 2 diabetes signal are
1294 represented by red circles in the middle of the plot.

1295 **Figure 2 – Trait variance explained by associated loci.** The boxplots show the maximum, first
1296 quartile, median, third quartile and minimum of trait variance explained when using a genetic score
1297 with single-ancestry lead and index variants (EUR, AA, EAS, HISP and SAS) or a combination of
1298 individual trait trans-ancestry lead variants and single-ancestry lead and index variants (TA+EUR,

1299 TA+AA, TA+EAS, TA+HISP and TA+SAS). Variance explained for each trait (FG, FI and HbA1c) in each
1300 ancestry is shown on different panels and in different colors. R^2 was estimated in 1 to 11 cohorts
1301 with sample sizes ranging from 489 to 9,758 (**Supplementary Tables 8-11**).

1302 **Figure 3 – Transferability of PGS across ancestries.** For each trait, the barplots represent trait
1303 variance explained when using a European ancestry-derived PGS in European, East Asian and African
1304 American test datasets. Variance explained (the height of each bar) for each trait (FG, FI and HbA1c)
1305 in each ancestry is shown on different panels and in different colors.

1306
1307 **Figure 4 - Trans-ancestry fine-mapping.** A) Number of plausible causal variants at each locus-trait
1308 association derived from FINEMAP. B) Number of variants within each 99% credible set. Twenty-one
1309 locus-trait associations at 19 loci were mapped to a single variant in the 99% credible set. C) Fine-
1310 mapping resolution. For each of the 98 locus-trait associations with a predicted single causal variant
1311 in both trans-ancestry and single-ancestry analyses, the number of variants included in the 99%
1312 credible set in the single-ancestry fine-mapping (x axis; logarithmic scale) is plotted against those in
1313 the trans-ancestry fine-mapping (y axis; logarithmic scale). Trans-ancestry and single-ancestry fine-
1314 mapping were based on the same set of variants. After removing eight locus-trait associations with
1315 one variant in the 99% credible sets in both trans-ancestry and single-ancestry analyses, there were
1316 18 locus-trait associations (in grey) where trans-ancestry fine-mapping did not improve the
1317 resolution of fine-mapping results (i.e. number of variants in the 99% credible set did not decrease).
1318 Of the 72 locus-trait associations with improved trans-ancestry fine-mapping resolution (blue and
1319 red) further analyses in European fine-mapping emulating the total sample size in trans-ancestry
1320 fine-mapping demonstrated that 34 locus-trait associations (in red) were improved because of both
1321 total sample size and differences across ancestries, while 38 locus-trait associations (in blue) were
1322 only improved due to increased sample size in the original trans-ancestry fine-mapping analysis.

1323 **Figure 5 - Epigenomic landscape of trait-associated variants.** A: Enrichment of GWAS variants to
1324 overlap genomic regions including ‘Static Annotations’ which are common or ‘static’ across cell types
1325 and ‘Stretch Enhancers’ which are identified in each tissue/cell type. The numbers of signals for each
1326 trait are indicated in parentheses. Enrichment was calculated using GREGOR⁵⁶. One-sided test for
1327 significance (red) is determined after Bonferroni correction to account for 59 total annotations
1328 tested for each trait; nominal significance ($P < 0.05$) is indicated in yellow. B: Enrichment for HbA1c
1329 GWAS signals partitioned into “hard” Glycemic and Red Blood Cell cluster (signals from “hard”
1330 mature Red Blood Cell and reticulocyte clusters together) to overlap annotations including StrEs in
1331 Islets and the blood-derived leukemia cell line K562, respectively (additional partitioned results in
1332 **Supplementary Table 17**). C: Individual FI GWAS signals that drive enrichment in Adipose and
1333 Skeletal Muscle StrEs. D, E: Genome browser shots of FI GWAS signals – intronic region of the
1334 *COL4A2* gene (D) and an inter-genic region ~25kb from *LINC01214* gene (E) showing GWAS SNPs
1335 (lead and LD $r^2 > 0.8$ proxies), ATAC-seq signal tracks and chromatin state annotations in different
1336 tissues/cell types.

1337 **Figure 6 - Tissues and cell types significantly enriched for genes within glycemic-associated loci.**
1338 Top panel FG-associated loci, middle panel FI-associated loci, bottom panel HbA1c-associated loci.
1339 FDR thresholds are shown in red ($q < 0.05$), orange ($q < 0.2$), grey ($q \geq 0.2$).

1340 **Figure 7 - Gene-set enrichment analyses.** Results from affinity-propagation clustering of significantly
1341 enriched gene-sets ($FDR < 0.05$) identified by DEPICT for A) FG, B) FI, and C) HbA1c. Each node is a
1342 cluster of gene-sets represented by an exemplar gene-set with similarities between the clusters
1343 represented by the Pearson correlation coefficients ($r > 0.3$). The nodes are colored according to the
1344 minimum gene-set enrichment p-value for gene-sets in that cluster. Example clusters are expanded
1345 to show the contributing gene-sets.

1346

1347 **Tables**

1348

1349 **Table 1 – Glossary of terms** - This study combined analyses of trait-associations across multiple correlated
1350 glycemic traits and across multiple ancestries, which has presented challenges in our ability to apply commonly
1351 used terms with clarity. For this reason, we define below terms often used in the field with variable meaning,
1352 as well as definitions of new terms used in this study.
1353

| Term | Definition |
|--------------------------------|--|
| EA (Effect allele) | The effect allele was that defined by METAL based on trans-ancestry FG results and aligned such that the same allele was kept as the effect allele across all ancestries and traits, irrespective of its allele frequency or effect size for that particular ancestry and trait, in this way the effect allele is not necessarily the trait-increasing allele. |
| Single-ancestry lead variant | Variant with the smallest p-value amongst all with $P < 5 \times 10^{-8}$, within a 1Mb region, based on analysis of a single trait in a single ancestry. |
| Single-ancestry index variants | Variants identified by GCTA analysis of each autosome, and that appear to exert conditionally distinct effects on a given trait in a given ancestry ($P < 5 \times 10^{-8}$). As defined, these include the single-ancestry lead variants. |
| Trans-ancestry lead variant | Variant identified by trans-ethnic meta-analysis of a given trait that has the strongest association for that trait ($\log_{10}BF > 6$, which is broadly equivalent to $P < 5 \times 10^{-8}$) within a 1Mb region. |
| Single-ancestry locus | 1Mb region centred on a single-ancestry lead variant which does not contain a lead variant identified in the trans-ancestry meta-analysis (i.e., does not contain a trans-ancestry lead variant). |
| Signal | Conditionally independent association between a trait and a set of variants in LD with each other and which is noted by the corresponding index variant. |
| Trans-ancestry locus | A genomic interval that contains trans-ancestry trait-specific lead variants, with/out additional single-ancestry index variants, for one or more traits. This region is defined by starting at the telomere of each chromosome and selecting the first single-ancestry index variant or trans-ancestry lead variant for any trait. If other trans-ancestry lead variants or single-ancestry index variants mapped within 500kb of the first signal, then they were merged into the same locus. This process was repeated until there were no more signals within 500kb of the previous variant. A 500kb interval was added to the beginning of the first signal, and the end of the last signal to establish the final boundary of the trans-ancestry locus (Extended Data Figure 2). As defined, a trans-ancestry locus may not have a single lead trans-ancestry variant, but may instead contain multiple trans-ancestry lead variants, one for each trait. |

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1363 **Online Methods**

1364 **Study design and participants**

1365 This study included trait data from four glycemic traits: fasting glucose (FG), fasting insulin (FI), 2hr
1366 post-challenge glucose (2hGlu), and glycated hemoglobin (HbA1c). The total number of contributing
1367 cohorts ranged from 41 (2hGlu) to 131 (FG), and the maximum sample size for each trait ranged
1368 from 85,916 (2hGlu) to 281,416 (FG) (**Supplementary Table 1**). Overall, European ancestry (EUR)
1369 participants dominated the sample size for all traits, representing between 68.0% (HbA1c) to 73.8%
1370 (2hGlu) of the overall sample size. African Americans (AA) represented between 1.7% (2hGlu) to
1371 5.9% (FG) of participants; individuals of Hispanic ancestry (HISP) represented between 6.8% (FG) to
1372 14.6% (2hGlu) of participants; individuals of East-Asian ancestry (EAS) represented between 9.9%
1373 (2hGlu) to 15.4% (HbA1c) of participants; and South-Asian ancestry (SAS) individuals represented
1374 between 0% (no contribution to 2hGlu) to 4.4% (HbA1c) of participants. Data from Ugandan
1375 participants were only available for the HbA1c analysis and represented 2% of participants.

1376

1377 **Phenotypes**

1378 Analyses included data for FG and 2hGlu measured in mmol/l, FI measured in pmol/l, and HbA1c in
1379 % [where possible, studies reported HbA1c as a National Glycohemoglobin Standardization Program
1380 (NGSP) percent]. Similar to previous MAGIC efforts⁷, individuals were excluded if they had type 1 or
1381 type 2 diabetes (defined by physician diagnosis); reported use of diabetes-relevant medication(s); or
1382 had a FG ≥ 7 mmol/L, 2hGlu ≥ 11.1 mmol/L, or HbA1c $\geq 6.5\%$, as detailed in **Supplementary Table 1**.
1383 2hGlu measures were obtained 120 minutes after a glucose challenge in an oral glucose tolerance
1384 test (OGTT). Measures for FG and FI taken from whole blood were corrected to plasma level using
1385 the correction factor 1.13⁸⁰.

1386

1387 **Genotyping, quality control, and imputation**

1388 Each participating cohort performed study-level quality control, imputation, and association
1389 analyses following a shared analysis plan. Cohorts were genotyped using commercially available
1390 genome-wide arrays or the Illumina CardioMetaboChip (MetaboChip) array (**Supplementary Table**
1391 **1**)⁸¹. Prior to imputation, each cohort performed stringent sample and variant quality control (QC) to
1392 ensure only high-quality variants were kept in the genotype scaffold for imputation. Sample quality
1393 control checks included removing samples with low call rate $< 95\%$, extreme heterozygosity, sex
1394 mismatch with X chromosome variants, duplicates, first- or second-degree relatives (unless by
1395 design), or ancestry outliers. Following sample QC, cohorts applied variant QC thresholds for call rate
1396 ($< 95\%$), Hardy-Weinberg Equilibrium (HWE) $P < 1 \times 10^{-6}$, and minor allele frequency (MAF). Full
1397 details of QC thresholds and exclusions by participating cohort are available in **Supplementary Table**
1398 **1**.

1399

1400 Imputation was performed up to the 1000 Genomes Project phase 1 (v3) cosmopolitan reference
1401 panel⁸², with a small number of cohorts imputing up to the 1000 Genomes phase 3 panel¹⁹ or
1402 population-specific reference panels (**Supplementary Table 1**).

1403

1404 **Study level association analyses**

1405 Each of the glycemic traits (FG, natural log FI, and 2hGlu) were regressed on BMI (except HbA1c),
1406 study-specific covariates, and principal components (unless implementing a linear mixed model).
1407 Analyses for FG, FI, and 2hGlu were adjusted for BMI as we had previously shown this did not
1408 materially affect results for FG and 2hGlu but improved our ability to detect FI-associated loci¹⁵. For
1409 simplicity, we refer to the traits as FG, FI and 2hGlu. For a discussion on collider bias see
1410 **Supplementary Note section 2c**. Both the raw and rank-based inverse normal transformed residuals
1411 from the regression were tested for association with genetic variants using SNPTTEST²³ or
1412 Mach2Qtl^{83,84}. Poorly imputed variants, defined as imputation $r^2 < 0.4$ or INFO score < 0.4 , were
1413 excluded from downstream analyses (**Supplementary Table 1**). Following study level QC,

1414 approximately 12,229,036 variants (GWAS cohorts) and 1,999,204 variants (MetaboChip cohorts)
1415 were available for analysis (**Supplementary Table 1**).

1416

1417 **Centralized quality control**

1418 Each contributing cohort shared their summary statistic results with the central analysis group who
1419 performed additional QC using EasyQC⁸⁵. Allele frequency estimates were compared to estimates
1420 from 1000Gp1 reference panel⁸², and variants were excluded from downstream analyses if there
1421 was a minor allele frequency difference > 0.2 for AA, EUR, HISP, and EAS populations against AFR,
1422 EUR, MXL, and ASN populations from 1000 Genomes Phase 1, respectively, or a minor allele
1423 frequency difference > 0.4 for SAS against EUR populations. At this stage, additional variants were
1424 excluded from each cohort file if they met one of the following criteria: were tri-allelic; had a minor
1425 allele count (MAC) < 3; demonstrated a standard error of the effect size ≥ 10 ; or were missing an
1426 effect estimate, standard error, or imputation quality. All data that survived QC (approximately
1427 12,186,053 variants from GWAS cohorts and 1,998,657 variants from MetaboChip cohorts) were
1428 available for downstream meta-analyses.

1429

1430 **Single-ancestry meta-analyses**

1431 Single-ancestry meta-analyses were performed within each ancestry group using the fixed-effects
1432 inverse variance meta-analysis implemented in METAL²⁰. We applied a double-genomic control (GC)
1433 correction^{15,86} to both the study-specific GWAS results and the single-ancestry meta-analysis results.
1434 Study-specific MetaboChip results were GC-corrected using 4,973 SNPs included on the MetaboChip
1435 array for replication of associations with QT-interval, a phenotype not correlated with our glycemic
1436 traits¹⁵.

1437

1438 **Identification of single-ancestry index variants**

1439 To identify distinct association index variants across each chromosome within each ancestry (**Table**
1440 **1**), we performed approximate conditional analyses implemented in GCTA²¹ using the --cojo-slc
1441 option (autosomes) and distance-based clumping (X chromosome). Linkage disequilibrium (LD)
1442 correlations for GCTA were estimated from a representative cohort from each ancestry: WGHS
1443 (EUR); CHNS (EAS); SINDI (SAS); BioMe (AA); SOL (HISP) and Uganda (for itself). The results from
1444 GCTA were comparable when using alternative cohorts for the LD reference. For any index variant
1445 with a QC flag which caused reason for concern, we performed manual inspection of forest plots to
1446 decide whether the signal was likely to be real (**Supplementary note**). Among 335 single-ancestry
1447 index variants across all traits, this manual inspection was done for 40 signals of which 32 passed
1448 and 8 failed after inspection. Thus, a total of 327 single-ancestry index variants passed and 8 failed.

1449

1450 **Trans-ancestry meta-analyses**

1451 To leverage power across all ancestries, we also conducted trait-specific trans-ancestry meta-
1452 analysis by combining the single-ancestry meta-analysis results using MANTRA (**Supplementary**
1453 **note**)⁸⁷. We defined \log_{10} Bayes' Factor (BF) > 6 as genome-wide significant, approximately
1454 comparable to $P < 5 \times 10^{-8}$.

1455

1456 **Manual curation of trans-ancestry lead variants**

1457 To ensure trans-ancestry lead variants were robust, we performed manual inspection of forest plots
1458 by at least two authors, for any variants with flags indicating possible QC issues (**Supplementary**
1459 **note**). Of 463 trans-ancestry lead variants across all traits, 184 passed without inspection, 131
1460 passed after inspection, and 148 failed after inspection.

1461

1462 **Correlation in EAF and heterogeneity in effect sizes of TA lead variants across ancestries**

1463 For each pair of ancestries, we calculated Pearson's correlation in EAFs for each trans-ancestry lead
1464 variant. The pairwise summarized heterogeneity of effect sizes between ancestries was then tested

1465 using the joint F-test of heterogeneity³². The test statistic is the sum of Cochran Q-statistics for
1466 heterogeneity across all trans-ancestry signals. Under the null hypothesis, the statistics follows the χ^2
1467 distribution with n degrees of freedom, where n is the number of the trans-ancestry lead variants.
1468

1469 **LD-pruned variant lists**

1470 Several downstream analyses (for example, genomic feature enrichment, genetic scores, and
1471 estimation of variance explained by associated variants) require independent LD-pruned variants
1472 ($r^2 < 0.1$) to avoid double-counting variants which might otherwise be in LD with each other and that
1473 do not provide additional “independent” evidence. Therefore, for these analyses we generated
1474 different lists of either TA or single-ancestry LD pruned ($r^2 < 0.1$) variants, keeping in each case the
1475 variant with the strongest evidence of association (**Supplementary Table 7**). Subsequently, we
1476 combined TA and single-ancestry variant lists and conducted further LD pruning. For some analyses,
1477 we took the TA pruned variant list and added single-ancestry signals if the LD $r^2 < 0.1$, while for others
1478 we started with the single-ancestry pruned lists and supplemented with TA lead variants if the LD
1479 $r^2 < 0.1$. One exception was the list used for eQTL co-localizations, which included all single-ancestry
1480 European signals (without LD pruning) and supplemented with any additional TA lead variants
1481 (starting from the variants with the most significant P-values) in EUR LD $r^2 < 0.1$ with any of the
1482 variants already in list, and that reached at least $P < 1 \times 10^{-5}$ in the European ancestry meta-analysis.
1483

1484 **Trait variance explained by associated loci**

1485 To determine how much of the phenotypic variance of each trait could be explained by the
1486 corresponding trait-associated loci, variants were combined in a series of weighted genetic scores
1487 (GS). The analysis was performed in a subset of the cohorts included in the discovery GWAS (with
1488 representation from each ancestry) and in a smaller number of independent cohorts (European
1489 ancestry only). Up to three different GS were derived per trait (and for each ancestry) in order to
1490 evaluate the potential for the trans-ancestry meta-GWAS identified loci to provide additional
1491 information above and beyond that contributed by the ancestry-specific meta-analysis results. These
1492 GS comprised: List A - single-ancestry signals; List B - single-ancestry signals plus trans-ancestry
1493 signals; and List C - trans-ancestry signals plus single-ancestry signals (**Supplementary Table 7**). In
1494 the case of the European ancestry cohorts that contributed to the GWAS, we employed the method
1495 of Nolte *et al.*³³ to adjust the effect sizes (betas) from the GWAS for the contribution of that cohort,
1496 providing sets of cohort-specific effect sizes that were then used to generate the GS. The association
1497 between each GS and its corresponding trait was tested by linear regression and the adjusted R^2
1498 from the model extracted as an estimate of the variance explained.
1499

1500

1501 **Transferability of European ancestry-derived polygenic scores (PGS) across ancestries**

1502 We used the PRS-CSauto³⁴ software to first build European ancestry-derived PGS for each glycemic
1503 trait (FG, FI, 2hGlu, HbA1c) on the basis of summary statistics. However, PRS-CSauto does not
1504 perform well when the training dataset is relatively small and the genetic architecture is sparse³⁴.
1505 Consequently, 2hGlu was excluded from this analysis. For each trait, to obtain European ancestry
1506 training and test datasets, we first removed all cohorts only genotyped on the MetaboChip which
1507 were not included in this analysis. From the remaining cohorts we then removed five of the largest
1508 European cohorts contributing to the respective European ancestry meta-analysis. For each trait,
1509 these five cohorts were meta-analyzed and used as the European ancestry test dataset.
1510 Subsequently, the remaining European ancestry cohorts were also meta-analyzed and used as the
1511 European ancestry training dataset. For each of the other ancestries, cohorts only genotyped on the
1512 MetaboChip were also removed, and the remaining cohorts were meta-analyzed, and used as the
1513 non-European ancestry test datasets. Variants with MAF < 0.05 or missing in over half of the
1514 individuals in the training dataset were removed^{34,88}. The PGS for each trait was built using PRS-
1515 CSauto with default settings³⁴ with the effect size estimates based on the European training dataset

1516 being revised based on an LD reference panel matching the test dataset. The proportion of the trait
1517 variance explained by the European ancestry-derived PGS (R^2) was estimated using the R package
1518 “gtx”⁸⁹ based on the revised effect sizes and summary statistics from the test dataset for each
1519 ancestry.

1520

1521

1522 **Fine-mapping**

1523 Of the 242 loci identified in this study, 237 were autosomal loci which we took forward for fine-
1524 mapping (**Supplementary Table 2**). We used the Bayesian fine-mapping method FINEMAP⁹⁰ (version
1525 1.1) to refine association signals and attempt to identify likely causal variants at each locus.

1526 FINEMAP estimates the maximum number of causal variants at each locus, calculates the posterior
1527 probability of each variant being causal, and proposes the most likely configuration of causal
1528 variants. The posterior probabilities of the configurations in each locus were used to construct 99%
1529 credible sets.

1530

1531 We performed both single-ancestry and trans-ancestry fine-mapping. In both analyses, only data
1532 from cohorts genotyped on GWAS arrays were used, and analyses were limited to trans-ancestry
1533 lead variants and other single-ancestry lead variants present in at least 90% of the samples for each
1534 trait. For the single-ancestry fine-mapping, FINEMAP estimates the number of causal variants in a
1535 region up to a maximum number, which we set to be two plus the number of distinct signals
1536 identified from the GCTA signal selection. FINEMAP uses single-ancestry and trait-specific z-scores
1537 from the fixed-effect meta-analysis in METAL²⁰ and an ancestry-specific LD reference, which we
1538 created from a subset of cohorts (combined sample size > 30% of the sample size for that ancestry),
1539 weighting each cohort by sample size. In the trans-ancestry fine-mapping, FINEMAP was similarly
1540 used to estimate the number of causal variants starting with two, and trait-specific z-scores and LD
1541 maps were generated from the sample size weighted average of those used in the single-ancestry
1542 fine-mapping. The maximum number of causal variants was iteratively increased by one until it was
1543 larger than the number of causal variants supported by data (Bayes factor), which was the estimated
1544 maximum number of causal variants used in the final run of fine-mapping analysis.

1545

1546 To compare fine-mapping results obtained from the single-ancestry and trans-ancestry efforts,
1547 analyses were limited to fine-mapping regions with evidence for a single likely causal variant in both,
1548 enabling a straightforward comparison of credible sets (**Supplementary note**). To ensure any
1549 difference in the fine-mapping results was not driven by different sets of variants being present in
1550 the different analyses, we repeated the single-ancestry fine-mapping limited to the same set of
1551 variants used in the trans-ancestry fine-mapping. The fine-mapping resolution was assessed based
1552 on comparisons of the 99% credible sets in terms of number of variants included in the set, and
1553 length of the region. To assess whether the improvement in the trans-ancestry fine-mapping was
1554 due to differences in LD, increased sample size, or both, we repeated the trans-ancestry fine-
1555 mapping mimicking the sample size present in the single-ancestry fine-mapping by dividing the
1556 standard errors by the square root of the sample size ratio and compared the results with those
1557 from the single-ancestry fine-mapping.

1558

1559 **Functional Annotation of trait-associated variants**

1560

1561 ***HbA1c signal classification***

1562 There were 218 HbA1c-associated signals from either the single-ancestry (i.e. all GCTA-signals from
1563 any ancestry) or trans-ancestry meta-analyses. To classify these signals in terms of their likely mode
1564 of action (i.e., glycemic, erythrocytic, or other⁷), we examined association summary statistics for the
1565 lead variants at the 218 signals in other large European datasets for 19 additional traits: three
1566 glycemic traits from this study (FG, 2hGlu and FI); seven mature red blood cell (RBC) traits^{91,92} (red

1567 blood cell count, mean corpuscular volume, hematocrit, mean corpuscular hemoglobin, mean
1568 corpuscular hemoglobin concentration, hemoglobin concentration and red cell distribution width);
1569 five reticulocyte traits (reticulocyte count, reticulocyte fraction of red cells, immature fraction of
1570 reticulocytes, high light scatter reticulocyte count and high light scatter percentage of red cells)^{91,92},
1571 and four iron traits (serum iron, transferrin, transferrin saturation and ferritin)⁹³. Of the 218 HbA1c
1572 signals, data were available for the lead (n=183) or proxy (European LD $r^2 > 0.8$, n = 8) variants at 191
1573 signals.

1574

1575 The additional traits were clustered using hierarchical clustering to ensure biologically related traits
1576 would cluster together (**Supplementary note**). We then used a non-negative matrix factorization
1577 (NMF)⁹⁴ process to cluster the HbA1c signals. Each cluster was labelled as glycemic, reticulocyte,
1578 mature RBC, or iron related based on the strength of association of signals in the cluster to the
1579 glycemic, reticulocyte, mature RBC and iron traits (**Supplementary note**). To verify that our cluster
1580 naming was correct, we used HbA1c association results conditioned on either FG or iron traits, or
1581 type 2 diabetes association results (**Supplementary note**).

1582

1583 ***HbA1c genetic risk scores (GRSs) and type 2 diabetes (T2D) risk***

1584 We constructed GRS for each cluster of HbA1c-associated signals (based on hard clustering) and
1585 tested the association of each cluster with T2D risk using samples from the UK Biobank. Pairs of
1586 HbA1c signals in LD (EUR $r^2 > 0.10$) were LD pruned by removing the signal with the less significant *P*-
1587 value of association with HbA1c. The GRS for each cluster was calculated based on the logarithm of
1588 odds ratios from the latest T2D study summary statistics⁹⁵ and UK Biobank genotypes imputed to the
1589 Haplotype Reference Consortium¹⁹. From 487,409 UK Biobank samples (age between 46 and 82
1590 years, and 55% female), we excluded participants for the following reasons: 373 with mismatched
1591 sex; 9 not used in the kinship calculation; 78,365 non-European ancestry individuals; and 138,504
1592 with missing T2D status, age, or sex information. We further removed 26,896 related participants
1593 (kinship > 0.088, preferentially removing individuals with the largest number of relatives and
1594 controls where a T2D case was related to a control). T2D cases were defined by: (i) a history of
1595 diabetes without metformin or insulin treatment, (ii) self-reported diagnosis of T2D, or (iii) diagnosis
1596 of T2D in a national registry (N = 17,022, age between 47 and 79 years, and 36% female). Controls
1597 were participants without a history of T2D (N = 226,240, age between 46 and 82 years, and 56%
1598 female). We tested for association between each GRS and T2D using logistic regression including
1599 covariates for age, sex, and the first five principal components. Significance of association was
1600 evaluated by a bootstrap approach to incorporate the variance of each HbA1c associated signal in
1601 the T2D summary data. To do this, we generated the GRS of each cluster 200 times by resampling
1602 the logarithm of odds ratio of each signal with T2D. For each non-glycemic class that had a GRS
1603 significantly associated with T2D, we performed sensitivity analyses to evaluate whether the
1604 association was driven from variants that also belonged to a glycemic cluster when using a soft
1605 clustering approach (the signals were classified as also glycemic in the soft clustering or had an
1606 association $P \leq 0.05$ with any of the three glycemic traits).

1607

1608 ***Chromatin states***

1609 To identify genetic variants within association signals that overlapped predicted chromatin states,
1610 we used a previously published, 13 chromatin state model that included 31 diverse tissues, including
1611 pancreatic islets, skeletal muscle, adipose, and liver³⁹. Briefly, this model was generated from
1612 cell/tissue ChIP-seq data for H3K27ac, H3K27me3, H3K36me3, H3K4me1, and H3K4me3, and input
1613 control from a diverse set of publicly available data^{53,57,96,97} using the ChromHMM program⁹⁸. As
1614 reported previously³⁹, StrEs were defined as contiguous enhancer chromatin state (Active Enhancer
1615 1 and 2, Genic Enhancer and Weak Enhancer) segments longer than 3kb⁵⁷.

1616 ***Enrichment of genetic variants in genomic features***

1617 We used GREGOR (version 1.2.1) to calculate the enrichment of GWAS variants overlapping static
1618 and StrEs⁵⁶. For calculating the enrichment of glycemetic trait-associated variants in these annotations,
1619 we used the filtered list of trait-associated variants as described above (**Supplementary Table 7**) as
1620 input. For calculating the enrichment of sub-classified HbA1c variants, we included the list of loci
1621 characterized as Glycemic, another list of loci characterized as Reticulocyte or mature Red Blood
1622 Cell, collectively representing the red blood cell fraction, along with lists of iron related or
1623 unclassified loci (**Supplementary Table 17**). We used the following parameters in GREGOR
1624 enrichment analyses: European r^2 threshold (for inclusion of variants in LD with the lead variant) =
1625 0.8, LD window size = 1 Mb, and minimum neighbour number = 500.

1626
1627 We used fGWAS (version 0.3.6)⁵⁸ to calculate enrichment of glycemetic trait-associated variants in
1628 static and StrE annotations using summary level GWAS results. We used the default fGWAS
1629 parameters for enrichment analyses for individual annotations for each trait. For each annotation,
1630 the model provided the natural log of maximum likelihood estimate of the enrichment parameter.
1631 Annotations were considered as significantly enriched if the log₂ (parameter estimate) and
1632 respective 95% confidence intervals were above zero or significantly depleted if the log₂ (parameter
1633 estimate) and respective 95% confidence intervals were below zero.

1634
1635 We tested enrichment of trait-associated variants in static and StrE annotations with GARFIELD
1636 (v2)⁵⁹. We formatted annotation overlap files as required by the tool; prepared input data at two
1637 GWAS thresholds - of 1×10^{-5} and a more stringent 1×10^{-8} by pruning and clumping with default
1638 parameters (garfield-prep-chr script). We calculated enrichment in each individual annotation using
1639 garfield-test.R with $-c$ option set to 0. We also calculated the effective number of annotations using
1640 the garfield-Meff-Padj.R script. We used the effective number of annotations for each trait to obtain
1641 Bonferroni corrected significance thresholds for enrichment for each trait.

1642 1643 **eQTL analyses**

1644 To aid in the identification of candidate casual genes at the European-only and trans-ancestry
1645 association signals, we examined whether any of the lead variants associated with glycemetic traits
1646 (**Supplementary Table 7**) were also associated with expression level (FDR < 5%) of nearby transcripts
1647 located within 1 Mb in existing eQTL data sets of blood, subcutaneous adipose, visceral adipose,
1648 skeletal muscle, and pancreatic islet samples^{60,61,99-102}. LD was estimated from the collected cohort
1649 pairwise LD information, where available, else from the European samples in 1000G phase 3. GWAS
1650 and eQTL signals likely co-localize when the GWAS variant and the variant most strongly associated
1651 with the expression level of the corresponding transcript (eSNP) exhibit high pairwise LD ($r^2 > 0.8$;
1652 1000 Genomes Phase 3, EUR). At these signals, we conducted reciprocal conditional analyses to test
1653 association between the GWAS variant and transcript level when the eSNP was also included in the
1654 model, and vice versa. We report GWAS and eQTL signals as co-localized if the association for the
1655 eSNP was not significant (FDR $\geq 5\%$) when conditioned on the GWAS variant; we also report signals
1656 from the eQTLGen whole blood meta-analysis data that meet only the LD threshold because
1657 conditional analysis was not possible.

1658 1659 **Tissue and gene-set analysis**

1660 We performed enrichment analysis using DEPICT (Data-driven Expression-Prioritized Integration for
1661 Complex Traits) version 3, specifically developed for 1000 Genomes Project imputed meta-analysis
1662 data¹⁰³ to identify cell types and tissues in which genes at trait-associated variants were strongly
1663 expressed, and to detect enrichment of gene-sets or pathways. DEPICT data included human gene
1664 expression data for 19,987 genes in 10,968 reconstituted gene sets, and 209 tissues/cell types.
1665 Because gene expression data in DEPICT is based on European samples and LD, we selected trait-
1666 associated variants with $P < 10^{-5}$ in the European meta-analysis and tested for enrichment of signals in
1667 each reconstituted gene-set, and each tissue or cell type. Enrichment results with a false discovery

1668 rate (FDR)<0.05 were considered significant. We ran DEPICT based on association results for all traits
1669 among: (i) cohorts with genome-wide data, or (ii) all cohorts (genome-wide and Metabochip
1670 cohorts). Because results were broadly consistent between the two approaches, we present results
1671 from the analysis that contained all cohorts as it had greater statistical power.

1672

1673 **Statistics and reproducibility**

1674

1675 *Sample size*

1676 No statistical method was used to predetermine sample size. We aimed to bring together the largest
1677 possible sample size with GWAS data from individuals of diverse ancestries (European, Hispanic,
1678 African American, East Asian, South Asian and sub-Saharan African) without diabetes and with data
1679 for one or more of the following traits: fasting glucose, fasting insulin, 2hr post-challenge glucose,
1680 and glycated hemoglobin. The sample sizes were 281,416 (FG), 213,650 (FI), 215,977 (HbA1c) and
1681 85,916 (2hGlu) (**Supplementary Table 1**). Our sample size was sufficiently powered to detect
1682 common variant associations with each of the glycemc traits and was able to detect associations at
1683 242 loci.

1684

1685 *Randomization/ Blinding*

1686 This is a study of continuous traits therefore there were no experiments to randomize and there was
1687 no “outcome” to which investigators needed to be blinded to.

1688

1689 *Data exclusions*

1690 Prior to conducting this study, we identified reasons for which data should be excluded from the
1691 analysis at either the cohort or summary level; these exclusions are as follows. Sample quality
1692 control checks included removing samples with low call rate < 95%, extreme heterozygosity, sex
1693 mismatch with X chromosome variants, duplicates, first- or second-degree relatives (unless by
1694 design), or ancestry outliers. Following sample QC, cohorts applied variant QC thresholds for call rate
1695 (< 95%), Hardy-Weinberg Equilibrium (HWE) $P < 1 \times 10^{-6}$, and minor allele frequency (MAF). Full
1696 details of QC thresholds and exclusions by participating cohort are available in **Supplementary Table**
1697 **1**. Each contributing cohort shared their summary statistic results with the central analysis group
1698 who performed additional QC using EasyQC. Allele frequency estimates were compared to estimates
1699 from 1000Gp1 reference panel, and variants were excluded from downstream analyses if there was
1700 a minor allele frequency difference > 0.2 for AA, EUR, HISP, and EAS populations against AFR, EUR,
1701 MXL, and ASN populations from 1000 Genomes Phase 1, respectively, or a minor allele frequency
1702 difference > 0.4 for SAS against EUR populations. At this stage, additional variants were excluded
1703 from each cohort file if they met one of the following criteria: were tri-allelic; had a minor allele
1704 count (MAC) < 3; demonstrated a standard error of the effect size ≥ 10 ; imputation $r^2 < 0.4$ or INFO
1705 score < 0.4; or were missing an effect estimate, standard error, or imputation quality.

1706

1707

1708 **Data Availability**

1709 Ancestry-specific and overall meta-analysis summary level results are available through the MAGIC
1710 website (<https://www.magicinvestigators.org/>). Summary statistics are also available through the
1711 GWAS catalogue (<https://www.ebi.ac.uk/gwas/>) with the following accession codes: GCST90002225,
1712 GCST90002226, GCST90002227, GCST90002228, GCST90002229, GCST90002230, GCST90002231,
1713 GCST90002232, GCST90002233, GCST90002234, GCST90002235, GCST90002236, GCST90002237,
1714 GCST90002238, GCST90002239, GCST90002240, GCST90002241, GCST90002242, GCST90002243,
1715 GCST90002244, GCST90002245, GCST90002246, GCST90002247, and GCST90002248.

1716

1717 **References for Methods**

1718

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