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Transferability of genetic loci and polygenic scores for cardiometabolic traits in British Pakistanis and Bangladeshis

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Abstract

Background: Individuals with South Asian ancestry have higher risk of heart disease than other groups in Western countries; however, most genetic research has focused on European-ancestry (EUR) individuals. It is unknown whether reported genetic loci and polygenic scores (PGSs) for cardiometabolic traits are transferable to South Asians, and whether PGSs have utility in clinical settings.

Methods: Using data from 22,000 British Pakistani and Bangladeshi individuals with linked electronic health records from the Genes & Health cohort (G&H), we conducted genome-wide association studies (GWAS) and characterised the genetic architecture of coronary artery disease (CAD), body mass index (BMI), lipid biomarkers and blood pressure. We applied a new technique to assess the extent to which loci from GWAS in EUR samples were transferable. We tested how well existing findings from EUR studies performed in genetic risk prediction and Mendelian randomisation in G&H.

Results: Trans-ancestry genetic correlations between G&H and EUR samples for the tested traits were not significantly lower than 1, except for BMI (r_g=0.85, p=0.02). We found evidence for transferability for the vast majority of loci from EUR discovery studies that were sufficiently powered to replicate in G&H. PGSs showed variable transferability in G&H, with the relative accuracy compared to EUR (ratio of incremental r^2/AUC) ≥0.95 for HDL-C, triglycerides, and blood pressure, but lower for BMI (0.78) and CAD (0.42). We observed significant improvement in categorical net reclassification in G&H (NRI=3.9%; 95% CI 0.9–7.0) when adding a previously developed CAD PGS to clinical risk factors (QRISK3). We used transferable loci as genetic instruments in trans-ancestry Mendelian randomisation and found evidence of an increased CAD risk for higher LDL-C and BMI, and for lower HDL-C in G&H, consistent with our findings for EUR samples.

Conclusions: The genetic loci for CAD and its risk factors are largely transferable from EUR studies to British Pakistanis and Bangladeshis, whereas the transferability of PGSs varies

1   greatly between traits. Our analyses suggest clinical utility for addition of PGS to existing

2   clinical risk prediction tools for this population.

3

4   ## Clinical Perspective

5   **What is new?**

6   ● This is the first study to explore the transferability of GWAS findings and PGSs for CAD

7   and related cardiometabolic traits in British Pakistani and Bangladeshi individuals from

8   a cohort with real-world electronic clinical data.

9   ● We propose a new approach to assessing transferability of GWAS loci between

10   populations, which can serve as a new methodological standard in this developing

11   field.

12   ● We find evidence of overall high transferability of GWAS loci in British Pakistanis and

13   Bangladeshis. BMI, lipids and blood pressure show the highest transferability of loci,

14   and CAD the lowest.

15   ● The transferability of PGSs varied between traits, being high for HDL-C, triglycerides

16   and blood pressure but more modest for CAD, BMI and LDL-C.

17   ● Our results suggest that, for some traits, the use of transferable GWAS loci improves

18   the robustness of Mendelian randomisation estimates in non-Europeans.

19

20   **What are the clinical implications?**

21   ● The polygenic score for CAD derived from genetic studies of European individuals

22   improves reclassification on top of clinical risk factors in British Pakistanis and

23   Bangladeshis. The improvement was driven by identification of more cases in younger

24   individuals (25–54 years old), and of controls in older individuals (55–84 years old).

25   ● Incorporation of the polygenic score for CAD into risk prediction models is likely to

26   prevent cardiovascular events and deaths in this population.

27

1   Introduction

2   Individuals with South Asian ancestry (SAS) account for more than a fifth of the global

3   population and experience a higher risk of coronary artery disease (CAD) than other

4   ancestries. For example, British South Asians have three- to four-fold higher CAD risk than

5   White British people [1]. Understanding the determinants of excess CAD burden in SAS

6   populations and improving prediction to enable preventive interventions represent important

7   public health priorities.

8

9   Common genetic variation is an important determinant of CAD and of upstream risk factors

10   such as blood pressure, lipids, and body mass index (BMI). The genetic component of disease

11   risk can be harnessed to identify underlying disease genes and pathways, to estimate the

12   unconfounded effects of risk factors by Mendelian randomisation (MR), and to improve risk

13   prediction through the application of polygenic scores (PGS). However, the genetic basis of

14   CAD risk is not well characterised in SAS populations because genome-wide association

15   studies (GWAS) have been mostly limited to European-ancestry (EUR) populations [2].

16

17   Fundamental questions remain about the extent to which the genetic determinants of

18   cardiometabolic traits are shared by EUR and SAS populations. These have important

19   implications to translational applications of genetic data such as causal inference with MR

20   which could prioritise different prevention strategies or drug targets between ancestries, and

21   clinical risk prediction. Whilst the predictive performance of PGSs derived from EUR

22   populations in non-EUR individuals decreases with genetic distance [3–6], the extent to which

23   this attenuation is due to genetic drift (differences in linkage disequilibrium and allele frequency

24   [7]) *versus* heterogeneity of causal genetic effects remains unclear. Furthermore, the potential

25   clinical utility of a CAD PGS in a real-world healthcare system is largely unknown, since

26   previous studies have mostly examined research cohorts composed of volunteers who are

27   healthier and wealthier than average (e.g. UK Biobank [8–12]).

1

2   Here, we perform a comparative analysis of the genetics of CAD and upstream

3   cardiometabolic traits in EUR and SAS populations, using data from the Genes & Health

4   (G&H) cohort [13]. G&H is a community-based cohort of British Pakistani and Bangladeshi (BPB)

5   individuals with linked electronic health record (EHR) data (N=22,490 individuals). This unique

6   cohort represents an understudied and clinically vulnerable population with high levels of

7   socioeconomic deprivation, and this is the first major genetic study focused on it. We apply

8   new approaches to the replication of genomic risk loci across populations, perform ancestry-

9   specific and trans-ancestry MR analysis, investigate the transportability of PGSs for CAD and

10   its risk factors, and estimate the incremental improvement in CAD prediction when

11   incorporating the CAD PGS into clinical risk tools.

Methods

12

Genes & Health cohort

13

14   Genes & Health (G&H) is a community-based cohort of BPB individuals recruited primarily in

15   East London [13]. All participants have consented for lifelong EHR access and genetic analysis.

16   The study was approved by the London South East NRES Committee of the Health Research

17   Authority (14/LO/1240). 97.4% of participants in G&H are in the lowest two quintiles of the

18   Index of Multiple Deprivation in the UK. About two thirds are British Bangladeshi and the

19   remainder British Pakistani. The median age at recruitment was 37 and 43 years for female

20   and male participants, respectively (**Figure S1**). The cohort is broadly representative of the

21   background population with regard to age, but slightly over-sampled females and those with

22   medical problems since two-thirds of people were recruited in healthcare settings such as GP

23   surgeries [13]. We used the 2020 February data release which contained 28,022 individuals

24   genotyped on the Illumina Infinium Global Screening Array v3 chip (with the additional multi-

25   disease variants). Of these, 22,490 (80%) individuals had linkage to primary or secondary care

4

1 data, of which 56.5% were female. Having identified related individuals (second degree or

2 closer; kinship coefficient >0.0884) using KING v2.2.4[14], we performed principal component

3 analysis (PCA) in unrelated samples, and projected the remainder onto the same PC space

4 using smartpca from EIGENSOFT v7.2.1[15].

Quality control and imputation of genotype data from Genes & Health

7 Quality control of genotype data was performed using Illumina's GenomeStudio and plink v1.9.

8 We first removed variants with cluster separation scores <0.57, Gentrain score <0.7, excess

9 of heterozygotes >0.03, or ChiTest 100 (Hardy-Weinberg test) <0.6 in GenomeStudio, as well

10 as variants that were included on the array in order to tag specific structural variants. We

11 removed samples with low call rate (<0.995 for male samples and <0.992 for female samples

12 across all 637,829 variants including those on Y chromosome for males) and those that failed

13 gender checks. When there were duplicate samples, we retained the sample with the highest

14 call rate. Using plink, we further removed variants with low call rate (<0.99), and the variant

15 with the lowest call rate amongst duplicate variant pairs. We excluded rare variants with minor

16 allele frequency (MAF) <1%. The high levels of autozygosity in this cohort can cause variants

17 to fail Hardy-Weinberg equilibrium test. We thus removed variants that failed the Hardy-

18 Weinberg test ($p<1\times10^{-6}$) in a subset of samples with low level of autozygosity. To define these

19 'low-autozygosity' individuals, we pruned SNPs (LD r^2 >0.8) and called runs of homozygosity

20 (RoHs) using plink1.9 with default parameters, then took the 64% of the individuals who had

21 a fraction of the genome in RoHs <0.5%. We excluded individuals who did not have

22 Bangladeshi or Pakistani ancestry (further than +/- 3 standard deviations [SD] from the mean

23 of PC1 for the individuals who self-reported as coming from that group), and those who self-

24 reported as coming from other ethnic groups or who did not report this information (**Figure**

25 **S2**).

26

1   We used the Michigan Imputation Server[16] to perform imputation with the GenomeAsia pilot

2   reference panel[17], imputing from 336,133 autosomal, biallelic SNPs with matched alleles.

3   Eagle v2.4 and Minimac v4 were used for phasing and imputation, respectively. We excluded

4   SNPs with imputation INFO score <0.3 or MAF <0.1%, which left 9,527,863 autosomal SNPs.

5   Quality control and imputation of genotype data from eMERGE

6   We used EUR samples from the eMERGE cohort (henceforth eMERGE), a consortium of US

7   medical research institutions, to compare with BPB individuals from G&H. Network Phase III

8   data (N=61,377) were downloaded from dbGaP (Accession number: phs001584.v1.p1).

9   Quality control of genotype data and imputation to the Human Reference Consortium (HRC)

10   reference panel have been described previously [18]. To identify EUR samples, we performed

11   PCA in samples from the 1000 Genomes project phase 3 dataset, and projected eMERGE

12   participants onto the same PC space using smartpca from EIGENSOFT v7.2.1[15]. For PCA,

13   we restricted to LD-pruned common SNPs (MAF ≥1%) with imputation INFO score ≥0.98 in

14   eMERGE. We identified samples that were clustered together with the EUR samples from the

15   1000 Genomes project using a dimension reduction method, Uniform Manifold Approximation

16   and Projection (UMAP), applied to the first 20 PCs, performed using the R package "umap"

17   v0.2.6.0[19]. Self-reported Hispanic or Latino, African, Asian, American Indian or Alaska Native

18   individuals were excluded. This resulted in 43,877 EUR individuals available for the

19   comparison with G&H. Well-imputed (INFO ≥0.3) bi-allelic SNPs with MAF ≥0.1%

20   (N=11,625,805) were retained for downstream analysis.

21   Phenotype and covariate definitions from electronic health-

22   record data in Genes & Health

23   Of the 22,490 genotyped G&H individuals with EHR data, 20,830 had primary care data

24   available through the Discovery Data Service[20] which includes clinical observations as well as

1   current and historic diagnoses (coded using READ version 2 codes, and recently converted

2   to SNOMED CT codes using standard mapping protocols[21]). 17,226 had diagnosis and

3   procedure codes (ICD10 and OPCS4 codes, respectively) extracted from the UK's largest

4   secondary care health provider, Barts Health NHS Trust.

5

6   Coronary artery disease (CAD) cases and controls were defined using the same ICD10 and

7   OPCS4 codes as Khera *et al.* [22] (**Table S1**). We defined CAD cases as those with myocardial

8   infarction or coronary revascularization in either primary and secondary care data. We

9   excluded individuals with angina, chronic ischemic heart disease, aneurysm or atherosclerotic

10   cardiovascular disease from the control sample [23]. Since procedure codes were not available

11   in eMERGE, we performed a sensitivity analysis in G&H to investigate the effects of excluding

12   OPCS4 codes in CAD ascertainment. For this, we defined CAD solely using ICD10 codes in

13   individuals with secondary care data, ignoring OPCS codes and primary care data; we

14   excluded individuals without secondary care data for this analysis.

15

16   We used median adult height and weight measurements within the past 5 years to calculate

17   BMI. For lipids, we took the latest adult measurements and corrected for statin usage if lipid

18   levels were measured between the start and end date of any statin prescriptions. No

19   adjustment was made on HDL cholesterol (HDL-C) or triglycerides. Adjustment of lipids

20   followed the procedure in Liu *et al.* [24], as follows. To correct for statin usage, total cholesterol

21   (TC) was replaced by TC/0.8. LDL cholesterol (LDL-C) levels were calculated using the

22   Friedewald equation, and statin-adjusted LDL-C was recalculated using adjusted TC levels as

23   follows: corrected LDL-C = uncorrected LDL-C + 0.2*adjusted TC. LDL-C/0.7 was used for 32

24   individuals for whom we couldn't find a TC measurement on the same date. Rank-based

25   inverse normal transformation was applied to the lipid levels.

26

27   We extracted the latest systolic blood pressure (SBP) and diastolic blood pressure (DBP)

28   measurements and adjusted for blood pressure medication use by adding 15 and 10 mmHg

1   to SBP and DBP, respectively, if the measurement coincided with any prescription date [25].

2   Sample sizes are shown in **Table 1** (all individuals) and **Table S2** (unrelated)**.**

3

4   To calculate a standard clinical risk score to compare with the PGS, we calculated the QRISK3

5   10-year predicted risk for CAD [26] in G&H using the R package "QRISK3" v0.3.0 [27]. QRISK3

6   was calculated based on the data available up until 1 January, 2010, which is about 10 years

7   prior to the latest data extraction. We excluded about one third of CAD cases whose diagnosis

8   was made earlier than this assessment date (prevalent cases) and used incident cases who

9   developed CAD later. Follow-up varied for cases and was fixed at 10 years for controls. We

10   used clinical data that were extracted earlier than the assessment date (1 January 2010) to

11   calculate QRISK3. The QRISK3 algorithm has variables that indicate whether a patient has a

12   variety of other diseases, and these were defined using the codes shown in **Table S3**,

13   following [10]. Medication use (hypertension treatment, corticosteroid, and atypical antipsychotic

14   medication) was defined as two or more prescriptions, with the most recent one having been

15   issued within 28 days prior to the assessment. We used the most recent measurements taken

16   prior to the assessment date, and kept individuals with at least three non-missing

17   measurements out of four (height, weight, SBP, and TC). Pattern of missingness is shown in

18   **Figure S3**. Townsend index was not available in G&H, so we used the mean value (3.307) of

19   the lowest two quintiles from the 2011 census data in the UK [28]. HDL-C levels were all

20   measured later than 2010 in G&H, so for TC/HDL-C ratio, we used 3.905 and 4.882 (averages

21   calculated using later data) for females and males, respectively. To deal with missing data, we

22   applied multiple imputation which accounts for sex, age, and genetically-defined ancestry

23   (Bangladeshi *versus* Pakistani; identified using PCA-UMAP), using the R package "mice"

24   v3.13.0 to impute height, weight, SBP, SD of SBP measurements within 2 years, and smoking

25   status.

Phenotype definitions from electronic health-record data in eMERGE

Phenotype data in eMERGE were downloaded from dbGaP (phs001584.v1.p1, phs000888.v1.p1, phs001584.v2.p2). Individuals younger than 16 years old were excluded. BMI was provided and we took the median value from adult measurements. Lipid and blood pressure measurements were taken from dataset phs000888.v1.p1. Data on medications affecting lipid and BP measurements were not available, so the highest measurements for LDL, TC, SBP, and DBP were used when comparing PGSs with G&H in order to minimise the effects of medications. CAD was ascertained using ICD9/10 codes which were available in the updated eMERGE Phase III dataset (phs001584.v2.p2). Coronary artery disease (CAD) cases and controls were defined based on secondary care ICD10 codes as described above for G&H (**Table S1**).

Genome-wide association analyses in Genes & Health

GWAS was performed with SAIGE [29] and adjusted for age, age^2, sex and the first twenty principal components. For total cholesterol and LDL-C, adjustments were made for use of statins as described above. We followed the QC procedure in [30] (*EasyQC* package) with the following exclusion criteria for variants: monomorphic variants, missing / invalid estimates, allele mismatch and allele frequency difference of >0.2 with reference panel, imputation INFO score <0.7 (<0.9 for downstream analysis i.e. correlation and colocalisation), MAF <0.005 (<0.01 for downstream analysis i.e. correlation and colocalisation).

Heritability and trans-ancestry correlations

Datasets that were used in analyses are provided in **Table S4**. We used GCTA to estimate SNP heritability in G&H and eMERGE[31]. We excluded one sample in each pair of 3rd-degree relatives (kinship coefficient >0.0442 calculated using KING v2.2.4[14]). We used SNPs with

1   INFO >0.9 and MAF >0.01 in each cohort separately. We also calculated SNP heritability using

2   the intersection of these SNP sets in both cohorts. For CAD, we estimated SNP heritability on

3   the liability scale using 6.7% as the prevalence estimate in the US [32], and 3.33% for the UK

4   background population from which G&H is sampled, defined as all people from South Asian

5   ethnicities (N=255,066 aged ≥20 years) registered with a primary health physician/GP in four

6   east London boroughs.

7

8   For the genetic correlation analyses, we used GWAS summary statistics generated in EUR

9   individuals from UK Biobank (UKBB), since we needed a larger sample size of ancestrally

10   homogeneous individuals than is available through eMERGE to obtain accurate estimates.

11   We used Popcorn (https://github.com/brielin/Popcorn) to estimate the trans-ancestry genetic

12   correlations between G&H and UKBB EUR individuals while accounting for differences in LD

13   structure [33] (i.e. the correlation of causal-variant effect sizes across the genome at SNPs

14   common to both populations). Variant LD scores were estimated for ancestry-matched 1000

15   Genomes v3 data for each study combination (i.e. SAS-EUR). The estimation of LD scores

16   failed for chromosome 6 for some groups, so we left out the major histocompatibility complex

17   (MHC) region (positions 28,477,797 to 33,448,354) from chromosome 6 from all comparisons.

18   Variants with INFO score <0.9 or MAF <0.01 were excluded. A p-value <0.05 indicated that

19   the genetic correlation was significantly less than 1 i.e. r_g <1.0.

Assessment of transferability of established loci

21   Previous studies that evaluated reproducibility of GWAS loci in SAS individuals did not formally

22   account for differences in power or LD patterns [34–36]. We assessed whether established trait-

23   associated loci were reproducible in G&H by performing a lookup of loci identified in non-SAS

24   ancestry GWAS (**Table S4**). Credible sets for established loci were generated and consisted

25   of lead (independent) variant plus proxy SNPs (r^2 >=0.8) within a 50kb window (based on the

26   EUR 1000 Genomes data) of the sentinel variant and with p-value <100 $\times$ $p_{sentinel}$. The locus

1 was defined as being 'transferable' if at least one variant from the credible set was associated

2 at p <0.05 with the relevant trait in G&H, and the direction of effect matched in both datasets.

3 For loci harbouring multiple signals, we only kept the most strongly associated variant (i.e.

4 smallest p-value). Expected power for replication was calculated using alpha=0.05, the effect

5 size estimated in the EUR GWAS, and the allele frequency of the variant and sample size in

6 G&H. The power of lead variants per locus was summed up and divided by the number of loci

7 to give an estimate of the number of expected significant loci per trait, which was compared

8 with the observed number of such loci; to our knowledge, this is a novel approach for

9 assessing reproducibility of GWAS findings. Loci were only deemed to be 'non-transferable' if

10 they contained at least one variant in the credible set with >80% power and yet none of the

11 variants in the credible set had p <0.05 and no variant within 50kb of locus had p <1×10^{-3} in

12 G&H. LocusZoom (http://locuszoom.org/) was to create regional association plots.

13

Trans-ancestry colocalisation

15 We used the Trans-ethnic colocalisation method (TEColoc)

16 (https://github.com/KarolineKuchenbaecker/TEColoc)[37] which tests whether a specific locus

17 has the same causal variant in two groups with different ancestry, and applied it to G&H and

18 UKBB EUR individuals. This method adopts the joint likelihood mapping (JLIM) statistic

19 developed by Chun and colleagues[38] that estimates the posterior probabilities for

20 colocalisation between GWAS signals and compares them to probabilities of distinct causal

21 variants while explicitly accounting for LD structure. For this, LD scores were estimated using

22 a subset of samples from the 1000 Genomes Project v3 that had matching ancestry to all

23 Europeans for UK Biobank. For G&H we used raw genotype data and LD was estimated

24 directly for these samples. JLIM assumes only one causal variant within a region in each study.

25 We therefore used small windows of 50Kb for each known locus to minimise the risk of

26 interference from additional association signals. Distinct causal variants were defined by

27 separation in LD space by r^2 ≥0.8 from each other. We excluded loci where the overlap

1   between UKBB and G&H was <10 SNPs and the proportion of well-imputed SNPs overlapping

2   between cohorts (SNP coverage) was <10%; this left no loci to consider for CAD, SBP and

3   DBP. We used a significance threshold of p <0.05 to determine evidence of sharing.

4   LocusZoom (http://locuszoom.org/) was to create regional association plots.

Construction of polygenic risk scores

6   We evaluated the performance of PGSs in G&H and eMERGE. We first assessed PGSs that

7   were previously constructed (mostly optimised in EUR samples) from the PGS Catalog [39]. We

8   restricted to 7,353,388 bi-allelic SNPs that had INFO ≥0.3 and MAF ≥0.1% in both eMERGE

9   and G&H. Variant information in existing PGS was harmonised to GRCh37 using dbSNP

10   mappings from Ensembl Variation and liftover. We calculated PGSs as weighted sums of

11   imputed allele dosages using plink2.0 --score function. There were often multiple PGSs that

12   were previously developed from different studies available for each trait, and below we report

13   the one that had the highest accuracy in each cohort. The best PGS (defined as described in

14   the next section of the Methods) for BMI was derived from GWAS conducted in primarily EUR

15   samples and optimised in EUR individuals, and those for lipids and BP contained genome-

16   wide significant variants identified in EUR GWASs. We selected different PGSs for CAD in

17   eMERGE and G&H, with the former optimised in EUR individuals and the latter in SAS

18   individuals; in both cases these were based on GWAS conducted in primarily EUR samples.

19   The details of each PGS are in **Table S5**.

20

21   Next we calculated PGSs using the clumping and p-value thresholding method (C+T) and

22   optimised PGSs in G&H and eMERGE separately. We used GWAS summary data from

23   primarily EUR samples (**Table S4**). We used LD estimated using EUR samples (N=503) from

24   the 1000 Genomes project for clumping using PRSice2 v2.2.11[40]. We calculated multiple

25   scores using combinations of various LD r^2 thresholds (0.1, 0.2, 0.5, 0.8) and p-value

26   thresholds (5×10^{-8}, 1×10^{-7}, 5×10^{-7}, 1×10^{-6}, 5×10^{-6}, 1×10^{-5}, 5×10^{-5}, 1×10^{-4}, 5×10^{-4}, 0.001,

1   0.005, 0.01, 0.02, 0.05, 0.08, 0.1, 0.2, 0.3, 0.4, 0.5, 0.8, 1) for each trait, and reported the PGS

2   with the best predictive performance within each target cohort.

3

4   Lastly, we calculated meta-PGSs proposed by Marquez-Luna et al.[41] that incorporate GWAS

5   summary data from the target populations. We downloaded GWAS summary data that were

6   generated in SAS samples of the UKBB from the Pan-UK Biobank website

7   (https://pan.ukbb.broadinstitute.org), and constructed scores (PGS_{SAS}) using the C+T method

8   described above and using SAS samples from the 1000 Genomes project for the LD

9   reference. We combined the scores derived from EUR GWASs (PGS_{EUR}) and PGS_{SAS} in linear

10   regression to construct meta-PGSs.

Assessment of PGS accuracy and clinical performance

12   We excluded one sample in each pair of 2nd-degree relatives (kinship coefficient >0.0884

13   calculated using KING v2.2.4[14]). Individuals with the highest number of relatives (and controls,

14   if the trait is binary) were removed first. Sample sizes for each trait are in **Table S2**.

15   Quantitative traits were inverse normal transformed. Age at recruitment was used as a

16   covariate for analysis of disease status, and age at measurement for analysis of quantitative

17   traits. PGSs were standardised to a mean of 0 and SD of 1. We fitted the following two models:

18   (1) the full model which had PGS and covariates namely sex, age, age^2, and the first 10 genetic

19   PCs, and (2) the reference model which accounted for the covariates only. For continuous risk

20   factors, linear regression was fitted, and the gain in R^2 when adding PGS as an additional

21   predictor, or incremental R^2, was calculated as the difference between the R^2 of the full model

22   and the reference model. Logistic regression was used to assess the associations between

23   PGSs and CAD. The area under the receiver operating characteristic curve (AUC) was

24   estimated for both models with the R package "pROC" v1.16.2 and incremental AUC was

25   calculated similarly. We performed bootstrap resampling of individuals 1,000 times to estimate

26   the 95% confidence intervals for incremental R^2 and incremental AUC. The best PGS per trait

1 was the one with the highest incremental R^2 for continuous risk factors and the one with the

2 highest incremental AUC for CAD. We estimated the effect size (or odds ratio for binary traits)

3 per SD of PGS from the full model. Effect size or odds ratio for quintiles, and for top 10%

4 versus middle 40-60% were reported as well. Relative accuracy was calculated as the ratio of

5 incremental AUC (or incremental R^2 for continuous traits) in G&H to that in eMERGE.

6

7 QRISK3 scores were calculated for 8,112 unrelated individuals as described above (420 CAD

8 cases and 7,702 controls). To integrate QRISK3 scores with PGS for CAD, we followed

9 Riveros-Mckay et al.[10] and calculated an integrated score by multiplying the odds converted

10 from the QRISK3 score with the odds ratio given an individual's PGS, where the odds ratio

11 per SD of PGS was estimated using a logistic regression in which QRISK3 and their interaction

12 were accounted for. The logistic regression was performed in males and females separately.

13 We used the most accurate PGS for CAD in SAS from the PGS Catalog, which was developed

14 by Wang et al.[42]; this score was derived from EUR GWAS using LDpred and tuned in SAS

15 individuals in UKBB. We regressed out 10 PCs from the PGS, and used the scaled residuals

16 in the Cox regression analysis. Cox regression was performed using the R package "survival"

17 v3.2-7. The concordance indices (C-indices) of the following models were compared: (1) age

18 at assessment + gender, (2) PGS + age at assessment + gender, (3) QRISK3, and (4) the

19 integrated score. We calculated the continuous net reclassification index (NRI) and categorical

20 NRI (using 10% as the threshold to classify high-risk individuals) for the integrated score

21 compared to QRISK3 alone. NRI was calculated as the sum of NRI for cases and NRI for

22 controls (noncases):

23   NRI = P(up|case) - P(down|case) + P(down|noncase) - P(up|noncase)

24 For continuous NRI, P(up|case) and P(down|case) indicate the proportions of cases that had

25 higher or lower risk estimates using the integrated score, respectively. For categorical NRI,

26 P(up|case) indicates the proportions of cases that were reclassified as high-risk individuals

27 (i.e. with <10% risk by QRISK3 but >10% by the integrated scores). We calculated NRI in two

28 age groups (25–54 versus 55–84 years old at baseline, chosen since the average age of onset

14

1   in this cohort was 55.3 years old), as well as in sex-by-gender subgroups. Bootstrap

2   resampling (1,000 times) was used to estimate confidence intervals for NRI.

Mendelian randomisation analysis

4   We modelled liability to CAD as our outcome within a two-sample Mendelian randomisation[43]

5   (MR) framework using the risk factors (BMI, SBP, DBP, LDL-C, HDL-C, TG) as exposures. To

6   identify genetic instruments for the exposure, we explored three alternative approaches: (a)

7   established loci significant at $p<5\times10^{-8}$ in the original EUR GWAS; (b) transferable loci defined

8   as described above, taking the effect size from the original EUR GWAS; and (c) loci significant

9   at $p<5\times10^{-8}$ in the SAS ancestry group of the Pan-UKBB GWAS, LD-clumped to an $r^2<0.2$ with

10   a LD window of 50kb, based on SAS 1000 Genomes project LD reference. Where insufficient

11   genome-wide significant instruments were identified, we used a more permissive p-value

12   threshold of $p<5\times10^{-5}$ for instrument selection in UKBB SAS. The primary MR analysis was

13   performed using, as outcome, summary association data from the G&H CAD GWAS

14   performed as described above, using the inverse-variance weighted method under a random

15   effect model, implemented with the TwoSampleMR R package[44]. For comparison, a two-

16   sample MR approach was also performed using summary data for CAD from eMERGE and

17   established loci significant at $p<5\times10^{-8}$ in the original EUR GWAS. We also undertook several

18   sensitivity analyses. In brief, we evaluated the MR-Egger intercept to assess directional

19   pleiotropy and Cochran's Q statistic[45] as an indicator of heterogeneity. MR analysis using

20   weighted median[46] and weighted methods[47] models were additionally performed in the

21   presence of heterogeneity.

Results

23   In G&H, 4.9% (N=1,110) of the individuals had coronary artery disease (CAD), with the age of

24   onset ranging from 17 to 97 years old (median 55). A quarter of the G&H participants were on

1   active statin prescriptions, 23% on BP medications, 29% had high TC levels (>5 mmol/L), and

2   30% had high LDL-C levels (>3 mmol/L; **Table S6**)[48]. Datasets that were used in each analysis

3   are provided in **Table S4**.

Shared genetic architecture of cardiometabolic traits

5   We compared the genetic architecture of coronary artery disease (CAD) and upstream risk

6   factors, namely HDL-C, LDL-C, triglycerides (TG), total cholesterol (TC), systolic and diastolic

7   blood pressure (SBP & DBP), between British Pakistanis and Bangladeshis (BPB) from G&H,

8   and European-ancestry populations (EUR) (**Figure 1**). We used EUR individuals from the

9   EHR-based eMERGE cohort to estimate heritability, since phenotypes had been ascertained

10   in a similar way to G&H (i.e. EHRs). All traits were found to have significant SNP heritability

11   (h^2= 0.03–0.23) in G&H, with estimates similar to those in eMERGE (**Table S7**, **Figure 2A**),

12   except for LDL-C, SBP and DBP which had significantly lower values in G&H than eMERGE

13   (e.g. for LDL-C, h^2 was 0.21 [95% CI: 0.17–0.25] in eMERGE and 0.06 [95% CI: 0.02–0.10] in

14   G&H). Conclusions were unchanged when restricting the heritability estimates to the same set

15   of well-imputed SNPs in both cohorts (**Table S7**). We observed high genetic correlations

16   between G&H and EUR from UKBB for all traits, with the lowest value seen for SBP (r_g=0.71

17   [95% CI: 0.36–1.06], p=0.09; **Figure 2B**). The only trait for which the genetic correlation

18   differed significantly from one was BMI (r_g=0.85 [95% CI: 0.71–0.99], p=0.02).

19
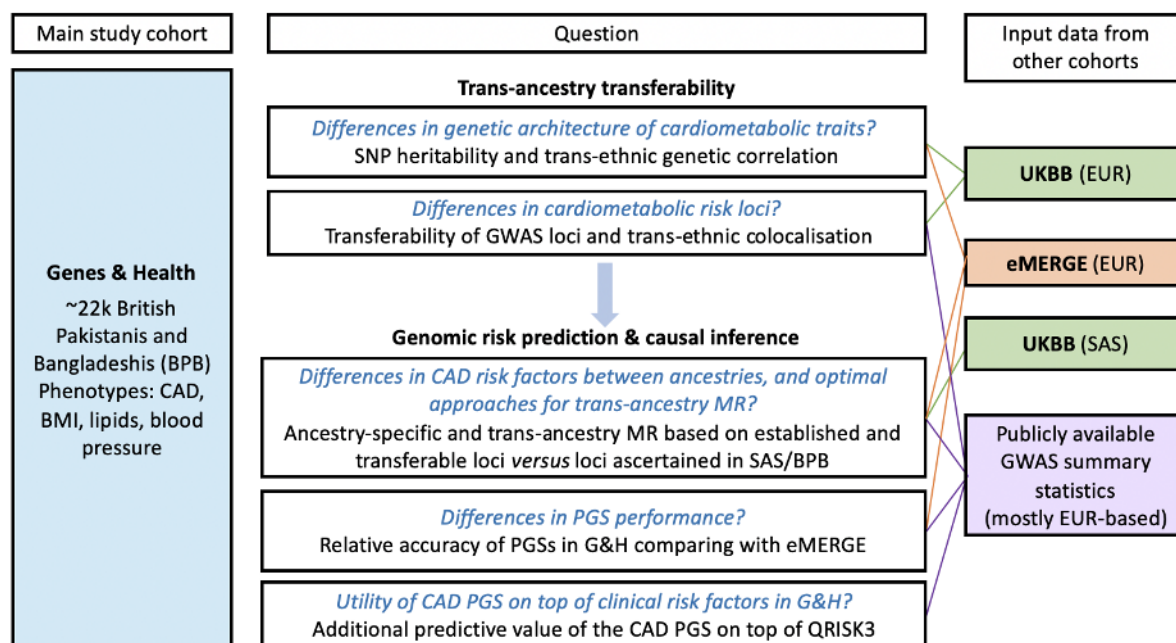
1

2 **Figure 1. Summary of study design, research questions and analyses conducted.** The coloured

3 boxes indicate input data. Within the white boxes, black text indicates the analyses we used to address

4 the questions in blue. BPB: British Pakistanis and Bangladeshi ancestry; EUR: European ancestry;

5 SAS: South Asian ancestry; CAD: coronary artery disease; BMI: body mass index; SNP: single

6 nucleotide polymorphism; GWAS: genome-wide association study; MR: Mendelian randomisation;

7 PGS: polygenic score; UKBB: UK Biobank. Datasets and discovery GWAS that were used in each

8 analysis are provided in **Table S4**.

9

10

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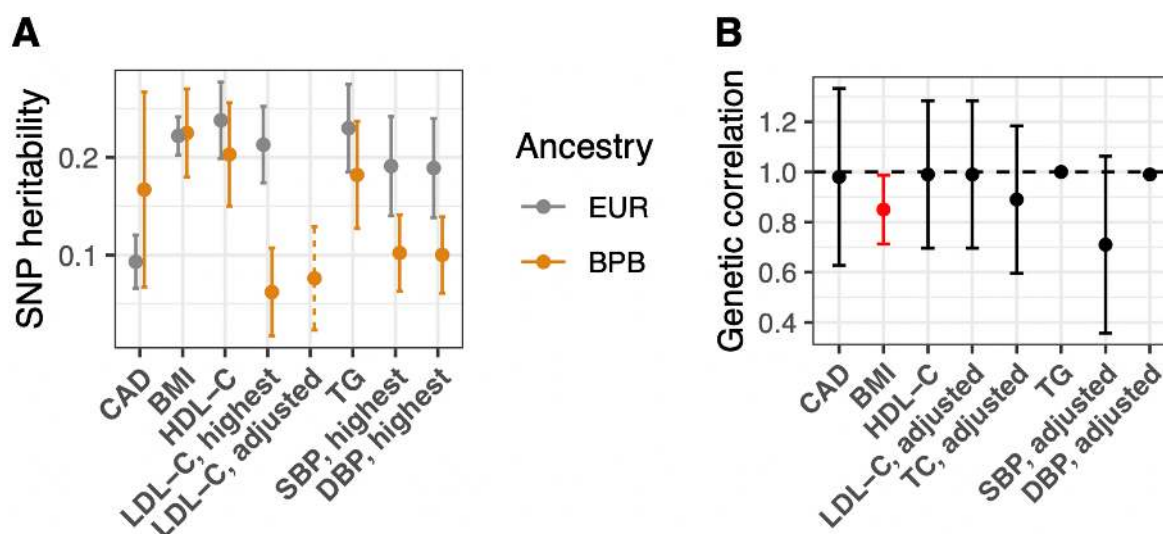
1 **Figure 2. SNP heritability and trans-ancestry genetic correlations for cardiometabolic traits. A.**

2 SNP heritability was estimated using GCTA in G&H (orange) and eMERGE (grey) for cardiometabolic

3 traits. Dashed line indicates statin-adjusted LDL cholesterol levels in G&H which are not available in

4 eMERGE. Error bars represent 95% confidence intervals in both plots. **B.** Genetic correlations were

5 estimated using GWAS summary statistics generated from G&H and European-ancestry individuals

6 from UK Biobank. Red indicates that the genetic correlation is significantly lower than 1 (p-value = 0.02

7 for BMI). BMI: body-mass index; BPB: British Pakistani ancestry; CAD: coronary artery disease; EUR:

8 European ancestry; LDL-C: low-density lipoprotein cholesterol; G&H: Genes & Health; HDL-C: high-

9 density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure.

10

High transferability of cardiometabolic loci

12 We assessed whether published trait-associated genomic loci identified in predominantly EUR

13 populations were shared by the BPB population represented by G&H. To account for

14 differences in LD patterns, our assessment of transferability was based on the credible sets

15 of variants per locus, likely to contain the causal variant, rather than the sentinel variants alone.

16 Low numbers of transferable loci may be due to limited statistical power rather than lack of

17 causal variant sharing. Therefore, we compared the number of observed transferable loci with

18 the number expected given the sample size and allele frequency in G&H if all causal variants

19 were shared. The number of expected transferable loci varied widely between traits (e.g. we

20 expected to be able to detect significant associations for 56% of HDL-C loci but only for 18%

21 of SBP loci), highlighting the importance of accounting for power when assessing

22 transferability. Across most traits examined, the observed number of transferable loci closely

23 matched the loci we expected (**Table 1** and **Table S8**). For example, for BMI we expected to

24 be able to find evidence for transferability for 20% of loci and we did indeed observe

25 transferability for 21% of loci. However, the exception was CAD for which the number of

26 observed transferable loci (13%) was below the expected number (21%), although this

27 difference was only marginally significant (binomial p-value = 0.05).

1

2 **Table 1**. Reproducibility of loci for cardiometabolic phenotypes in British Pakistani and Bangladeshis.

3 Note that when assessing sharing of causal variants, we excluded loci where the overlap between

4 UKBB and G&H was <10 SNPs and SNP coverage of the region was low (<10%). *For SBP and DBP,

5 power was calculated with observed effect size in normalised BP values.

Trait	N. samples (cases:controls)	N. established loci	N. observed transferable loci (%)	Percentage of expected transferable loci	Observed/ Expected	N. transferable loci with shared causal variant/N. transferable loci assessed (%)
BMI	16890	662	140 (21%)	20%	1.05	15/58 (26%)
LDL-C	12746	82	51 (62%)	50%	1.24	15/32 (47%)
HDL-C	14944	103	66 (64%)	56%	1.14	14/29 (48%)
TC	15641	107	61 (57%)	49%	1.16	23/38 (61%)
TG	13037	95	47 (49%)	47%	1.04	14/25 (56%)
DBP	18536	175	36 (21%)	21%*	1.00	NaN
SBP	18536	171	30 (18%)	18%*	1.00	NaN
CAD	22008 (1110:20898)	71	9 (13%)	21%	0.62	NaN

6

7

8 We also assessed whether there were any specific loci that were not transferable despite

9 being well powered to observe an association (power >80%). Out of a total of 184 well-

10 powered loci tested across all traits, only nine were non-transferable; that is, no variant in the

11 credible set was significant at p<0.05 and no variant within 50kb of locus was significant at

12 p<1x10^{-3} (**Figure S4**). These nine loci were all associated with lipid traits: *EVI5, NBEAL1,*

13 *GPAM, CETP, STAB1, TTC39B, SH2B3, ACP2* and *NECAP2* (**Table 2**). Of these loci, *CETP,*

1   which was previously associated with LDL-C levels in Europeans (established variant in

2   Europeans - rs7499892), was strongly associated with HDL-C in G&H (p=7.08x10^{-56}), but not

3   with LDL-C levels (p=0.23) (**Figure S5**) despite having >80% power for replication.

4

5   **Table 2**. Established loci from European-ancestry GWAS inferred to be non-transferable to British

6   Pakistani and Bangladeshis. * Tag SNP: rs7499892, r^2=1.

Trait	SNP	Chromo some	Position	Locus	Other allele/effect allele	Effect allele frequency	p-value	Effect size
LDL	rs7515577	1	93009438	*EVI5*	C/A	0.96	0.88	0.005
LDL	rs2255141	10	113933886	*GPAM*	A/G	0.8	0.15	-0.023
LDL	rs11076175*	16	57006378	*CETP*	A/G	0.16	0.23	-0.021
HDL	rs13326165	3	52532118	*STAB1*	A/G	0.89	0.19	-0.022
HDL	rs643531	9	15296034	*TTC39B*	C/A	0.95	0.09	0.043
HDL	rs2167079	11	47270255	*ACP2*	C/T	0.48	0.09	0.019
HDL	rs3184504	12	111884608	*SH2B3*	T/C	0.92	0.99	0
TC	rs7515577	1	93009438	*EVI5*	C/A	0.96	0.7	-0.011
TC	rs2351524	2	203880992	*NBEAL1*	T/C	0.98	0.39	-0.032
TC	rs2255141	10	113933886	*GPAM*	A/G	0.8	0.05	-0.028
TG	rs4841132	8	9183596	*NECAP2*	A/G	0.9	0.44	-0.016

7

8

9   Even when there are associations in the same region in two ancestry groups, it is possible

10   that they are driven by different causal variants, as previously seen [49]. To assess the extent

11   of sharing of causal variants between ancestries at previously reported loci with evidence of

12   transferability, we applied trans-ancestry colocalisation for G&H with UKBB EUR samples as

13   the reference. We found evidence for the most extensive sharing of causal variants for

1 transferable lipid loci: total cholesterol (61% of loci had significant colocalisation), followed by

2 TG (56%), HDL-C (48%) and LDL-C (47%) (**Table 1**). For BMI we found evidence for sharing

3 of causal variants for only 26% of transferable loci assessed (**Table 1** and **Table S9**). Causal

4 variants in major lipid loci such as *PCSK9* were among variants that were consistently not

5 shared (p_{JLIM}>0.05) between the two populations (**Figure S6** and **Table S9**).

6

Variable transferability of polygenic scores

8 Polygenic scores (PGSs) for CAD have been shown to have predictive value over risk scores

9 based on clinical factors alone [10,11,42,50–54]. To assess the transferability of PGSs for

10 cardiometabolic traits derived from EUR populations into BPB individuals, we compared

11 predictive performance in G&H to that in EUR individuals from eMERGE. We quantified

12 predictive accuracy using the "incremental AUC" statistic for CAD and the "incremental R^2"

13 statistic for continuous risk factor traits; these are the gain in AUC or R^2 when adding the PGS

14 to the regression of phenotype on the baseline covariates (sex, age and genetic PCs).

15

16 We first evaluated the previously published PGSs from the PGS Catalog (**Table S5**). The

17 PGSs for risk factors were developed using data from primarily EUR individuals, and the CAD

18 PGSs that proved to have the best performance in G&H and eMERGE were two different

19 scores optimised in SAS [42] and EUR samples [53], respectively. PGSs for all traits assessed

20 were significant predictors in G&H (**Table S5**, **Figure 3A**). For prediction in G&H, the

21 incremental R^2 for BP was low (~1.8%), but it was higher for lipids and BMI, ranging from 3.9%

22 to 6.7%. Relative accuracy of PGS in eMERGE and G&H, determined by the ratio of

23 incremental AUC or R^2, was close to 1 for HDL-C, TG, SBP and DBP, and lower for CAD

24 (42%, 95% CI: 30%–59%) and BMI (78%, 95% CI: 68%–88%; **Figure 3B**). Amongst the risk

25 factors, prediction of LDL-C had the lowest relative accuracy (66%, 95% CI: 53%–79%),

26 probably due to the fact that we did not adjust for statin usage since medication data were not

21

1   available in eMERGE, and BPB individuals were more likely to be treated with statins [55].

2   Incremental R^2 for the PGS for LDL-C increased from 3.9% (3.3%–4.5%) to 6.2% (5.3%–

3   7.1%) when using statin-adjusted LDL-C in G&H (**Table S5**, **Figure 3A**), although the

4   heritability was not significantly different (**Figure 2A**). In a sensitivity analysis, the relative

5   accuracy of the CAD PRS in eMERGE *versus* G&H was consistent when defining CAD based

6   on diagnostic codes only, rather than with the inclusion of procedure codes in the G&H

7   definition (**Table S5**).

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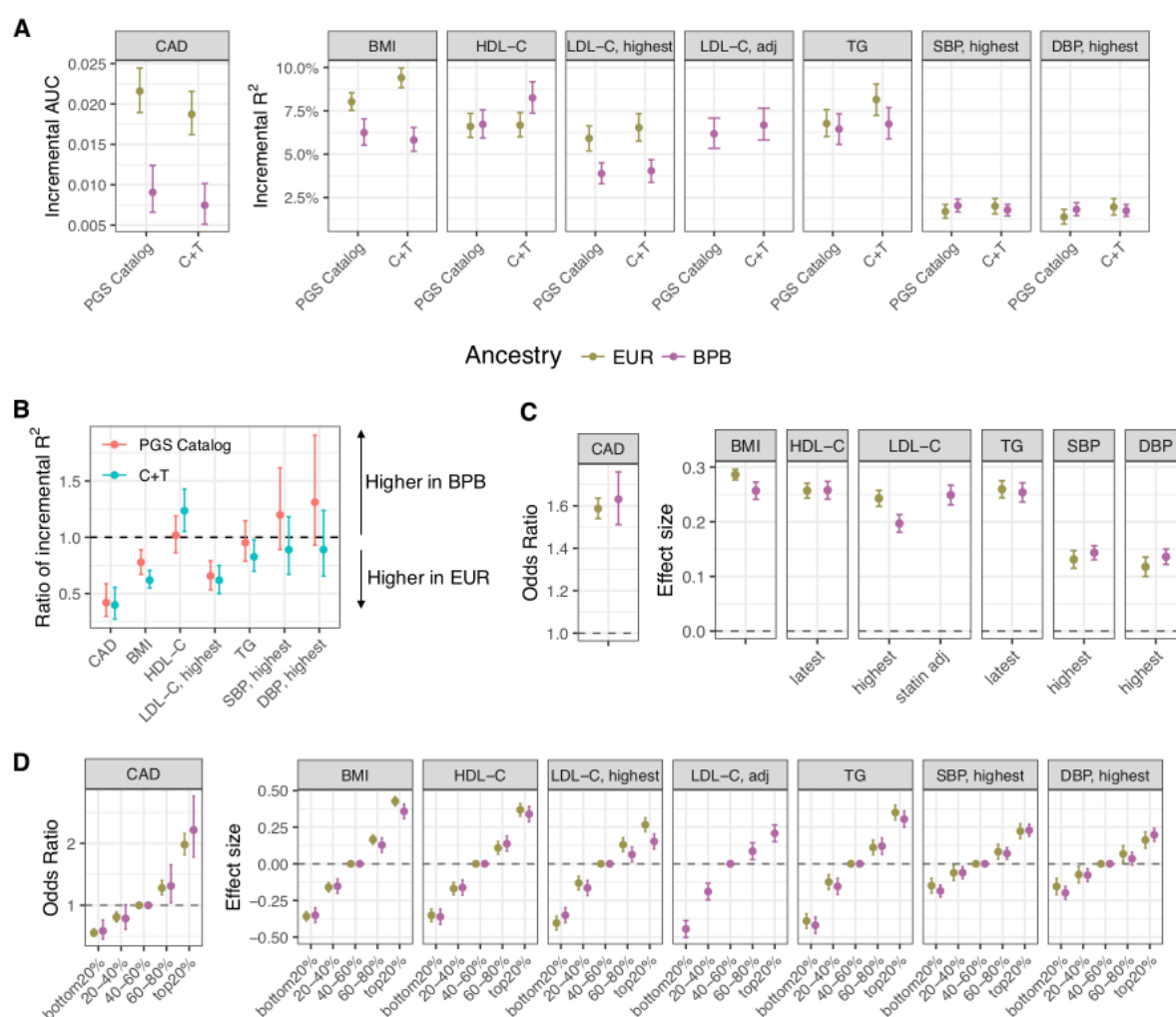
10   **Figure 3. Comparison of the predictive accuracy of polygenic scores in people of British**

11   **Pakistani and Bangladeshi versus European ancestry. A.** Predictive accuracy of polygenic scores

12   (PGSs) for cardiometabolic traits in British Pakistani and Bangladeshi (BPB) individuals from G&H

13   (purple) and European-ancestry (EUR) individuals from eMERGE (green). Incremental AUC was

1   calculated for coronary artery disease (CAD), and incremental R^2 was calculated for its continuous risk

2   factors. Error bars indicate 95% confidence intervals (CIs) estimated by bootstrap resampling of

3   samples. The highest measurements for low-density lipoprotein cholesterol (LDL-C), systolic blood

4   pressure (SBP), and diastolic blood pressure (DBP) are compared between eMERGE and G&H, and

5   statin-adjusted LDL-C data are also shown for G&H. **B.** Relative accuracy of PGSs (i.e. the ratio of

6   incremental AUC for CAD or incremental R^2 for risk factors estimated in G&H to that in eMERGE) for

7   PGS Catalog scores (red) and C+T scores (blue). Error bars represent 95% bootstrap CIs. Panel **C** and

8   **D** show the effect sizes of PGSs from the PGS Catalog. **C**. The odds ratio per standard deviation (SD)

9   of PGS is shown for CAD on the left panel, and the differences in phenotypic SD per SD of PGS are

10   shown for quantitative traits on the right panel. **D**. The odds ratio for CAD comparing the four quintiles

11   to the middle quintile (40–60%) is shown on the left panel. Quintiles are determined in controls. The

12   differences in phenotypic SD compared to the reference quintile are shown on the right panel. Error

13   bars show 95% CIs estimated using the standard error in **C** and **D**.

14

15

16   To assess whether the performance of PGS based on EUR GWAS could be improved in BPB,

17   we next constructed PGS using the clumping and P-value thresholding (C+T) method and

18   optimised them separately within G&H and eMERGE. The numbers of SNPs in the best C+T

19   PGSs are similar between eMERGE and G&H, and PGSs for lipids contained fewer SNPs

20   (194 to 454) than other traits (>20,000; **Table S10**, **Figure S7**). C+T PGSs and PGSs from

21   the PGS Catalog showed similar performance in G&H across traits, although they were

22   optimised in different ancestry populations (BPB and primarily EUR, respectively; **Figure 3A)**.

23   For BMI, triglycerides and HDL-C, we observed slightly larger differences in predictive

24   accuracies between G&H and eMERGE for C+T PGSs than observed with the PGS Catalog

25   scores (**Figure 3B**).

26

27   We then assessed whether PGS methods that account for ancestry differences improved

28   predictive accuracy in G&H. PGSs were constructed using a meta-score strategy [41], combining

29   the EUR-derived PGS (described above) and that from UKBB SAS samples. The improvement

1 in accuracy was modest (5–11%) (**Figure S8**). This may be due to the low sample sizes in the

2 UKBB SAS GWASs.

3

Modest improvement in CAD risk prediction by adding PGS to clinical risk score

6 A CAD PGS derived from EUR GWAS summary statistics and tuned in SAS individuals from

7 UKBB[42] (PGS000296 in the PGS Catalog), showed the highest predictive accuracy in BPB

8 individuals in G&H. This score had an OR per SD of 1.63 (95% CI: 1.51–1.76) and incremental

9 AUC of 0.009 (95% CI: 0.006–0.012; **Table S5**). Individuals in the top quintile of PGS were

10 predicted to have a 2.2-fold increase (95% CI: 1.78–2.76) in disease risk relative to the middle

11 quintile (quintiles were determined in controls; **Figure 3D**). We investigated the additional

12 predictive power of PGS on top of established clinical risk factors for CAD, and the net

13 reclassification improvement (NRI) achieved by adding the PGS to a clinical risk score.

14

15 To calculate the clinical risk score, we used the QRISK3 algorithm to estimate 10-year risk of

16 cardiovascular disease at a baseline time point, selected so that the participants in G&H had

17 about 10 years of follow-up. QRISK3 was a strong predictor of CAD events and had a

18 concordance index (C-index) of 0.843 (95% CI: 0.828–0.858; **Figure 4A, Table S11**).

19 Consistent with previous findings in EUR individuals[10], the CAD PGS was uncorrelated with

20 QRISK3 (Pearson's correlation coefficient r=-0.0056 and p-value=0.62). We followed Riveros-

21 Mckay *et al.*[10] to construct an integrated score combining QRISK3 and the CAD PGS. The

22 integrated score had a non-significant improvement in the C-index (0.853, 95% CI: 0.838–

23 0.867). However, compared with QRISK3 alone, the integrated score showed significant

24 improvement in reclassification (categorical NRI: 3.9%; 95% CI: 0.9%–7.0%) using a 10-year

25 risk threshold of 10% based on the threshold for preventive intervention with statin treatment

26 recommended by National Institute for Health and Care Excellence [56]. The integrated score

1 reclassified 3.2% of the population as high risk and 2.5% as low risk (**Table S11**). This

2 improvement was mostly driven by the enhanced identification of CAD cases in people at 25–

3 54 years old (NRI in cases being 7.0% *versus* NRI in controls being -1.2%), and of controls in

4 people at 55–84 years old (NRI in cases being 0.0% versus NRI in controls being 6.8%)

5 (**Figure 4B**, **Table S11**). The QRISK3 classified most (91.4%) of the individuals at 55–84 years

6 old as high risk. Using the integrated score, 7.6% of the individuals older than 55 years were

7 down-classified from high to low risk (**Table S11**). Using continuous NRI, the integrated score

8 showed significant improvement (27.0%; 95% CI: 17.7%–36.2%) and similar trends in age

9 groups (**Figure S9**, **Table S11**).

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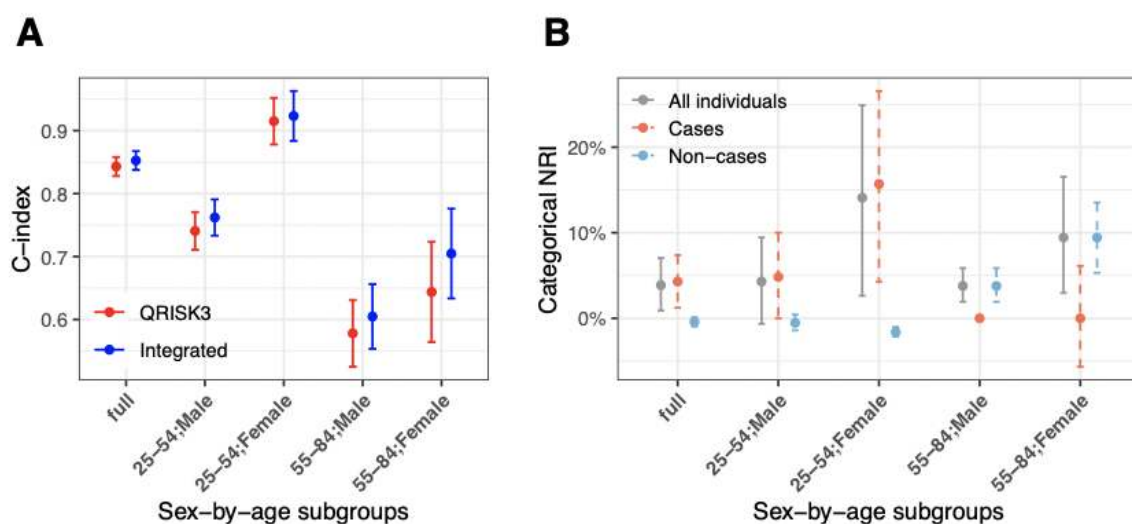
11

12 **Figure 4. Model discrimination and net reclassification index for coronary artery disease with**

13 **addition of a polygenic score to QRISK3. A.** The concordance index (C-index) of QRISK3 (red) and

14 an integrated score that combines QRISK3 and a polygenic score (PGS) for CAD (blue) in all British

15 Pakistani and Bangladeshi individuals from G&H as well as in age-by-gender subgroups. The error bars

16 represent 95% confidence intervals (CIs) estimated using the standard error. **B.** Categorical net

17 reclassification index (NRI) for the integrated score compared to QRISK3 in all samples as well as in

18 age-by-gender subgroups. NRI in cases (red) and controls (blue) are also shown. The error bars

19 indicate 95% CIs estimated using the bootstrap method.

20

25

1 Causal effects of CAD risk factors largely consistent across

2 ancestries

3 We carried out two-sample Mendelian randomisation (MR) analyses to assess the causal

4 effects of the risk factors on CAD in G&H and compared findings with EUR samples from

5 eMERGE. For G&H, we used transferable loci as genetic instruments to benefit from the

6 precision of large EUR discovery GWAS whilst ensuring only valid instruments are used. In

7 eMERGE, causal effects for BMI, BP and lipids, except TG, were statistically significant

8 (**Figure 5**). Consistent with this, we found that higher BMI (OR=1.73, p-value=0.01), higher

9 LDL-C (OR=1.55 p-value=4×10^{-4}) and lower HDL-C levels (OR=0.75, p-value=8×10^{-3}) were

10 causally associated with increased risk of CAD in G&H. The OR for LDL-C was larger than

11 the one in eMERGE (OR=1.15) although with overlapping confidence intervals (CI: 1.03-1.29

12 in eMERGE, CI: 1.22-2.00 in G&H). The effects for SBP and DBP were not statistically

13 significant in G&H. However, both had relatively small numbers of loci as instruments and

14 confidence intervals of the effect estimates were wide.
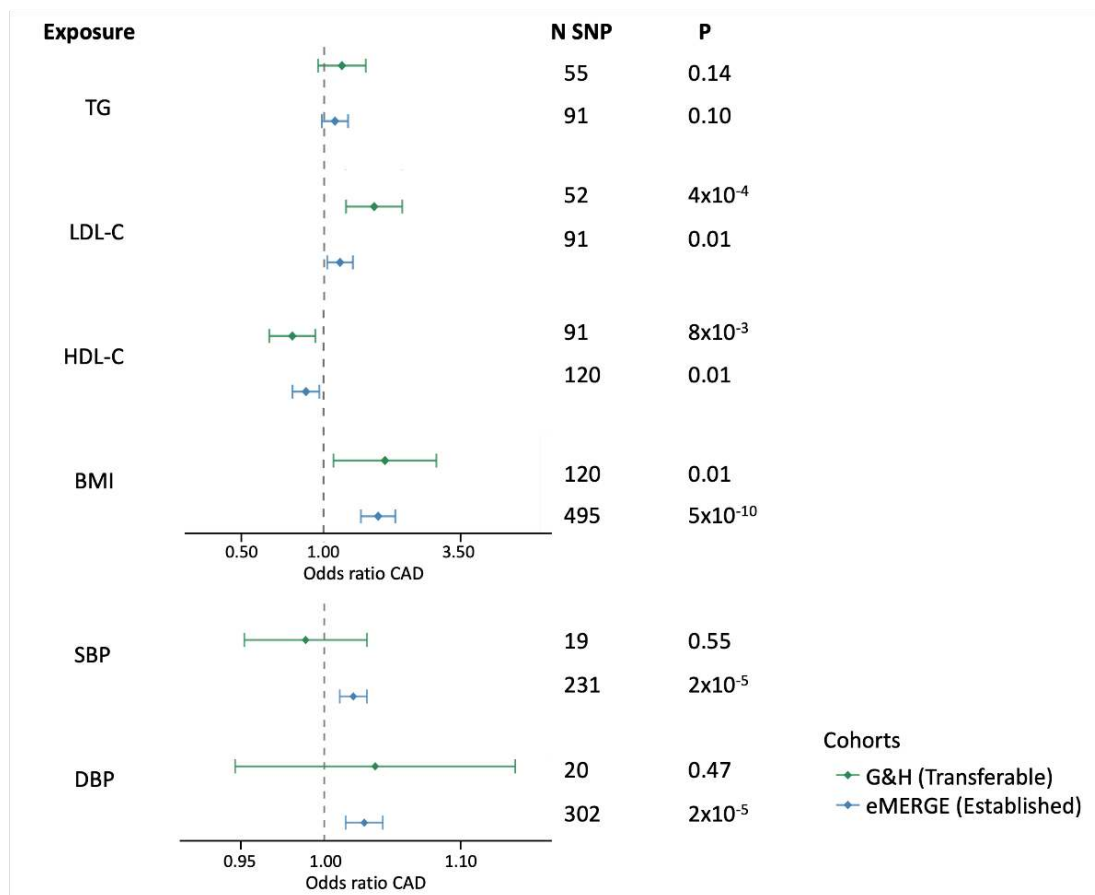
Figure 5. Estimates of causal effects of risk factors on coronary artery disease in European (eMERGE) and British South Asian (G&H) ancestry individuals. Two-sample Mendelian randomisation (MR) estimates for the causal effects are presented based on genetic instrument variables identified from EUR discovery GWAS for each risk factor. All independent genome-wide significant loci were used as instruments for eMERGE and only the transferable loci for G&H. Effect estimates are presented as odds ratios with 95% confidence intervals per standard deviation increase in the reported unit of the trait: triglycerides (TG), systolic blood pressure (SBP), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), diastolic blood pressure (DBP), body mass index (BMI). The p-value (P) and number of single nucleotide polymorphism instruments (N SNPs) included in the MR analysis are shown for each exposure.

We also assessed different strategies for instrument selection in G&H, such as using all loci associated at genome-wide significance in EUR GWAS for the risk factors (**Figure S11**). When following the standard approach of using an independent ancestry-matched sample (UKBB

27

1   SAS) to derive the instruments, an insufficient number of genome-wide significant instruments

2   ($p<5\times10^{-8}$) were identified (**Figure S10**). To address this, we also tested a less stringent p-

3   value threshold ($p<5\times10^{-5}$) for selecting instruments. For the lipid biomarkers, the results were

4   consistent regardless of which loci were chosen as instruments (**Figure S11**). However, the

5   association of BMI with CAD was significant only for transferable loci (**Figure S11**).

6

7   We found evidence of heterogeneity between causal estimates based on Cochran's Q statistic

8   for DBP when using the established loci as instruments (p-value=0.04), LDL-C when using the

9   UKBB SAS-ascertained loci (p-value=0.02) and HDL-C for transferable loci ($p\text{-value}=1\times10^{-3}$).

10   However, the results of the weighted median and weighted mode models were consistent with

11   those obtained by the inverse-variance weighted MR model (**Table S12**).

12

Discussion

14

15   We conducted the first study to systematically assess the transferability of genetic loci and

16   PGSs for cardiometabolic traits in SAS individuals with real-world clinical data, using ~22,000

17   individuals from the G&H cohort. For lipids and blood pressure, we found evidence that causal

18   genetic variants at known loci and beyond are widely shared with EUR. The prediction

19   accuracy of PGSs derived from EUR GWASs for these traits was similar between G&H and

20   EUR samples. However, the predictive performance of BMI and CAD PGS was reduced by

21   22 and 58%, respectively (for the PGS Catalog scores), in G&H, and CAD also had fewer

22   transferable loci. A CAD PGS optimised for South Asians nonetheless yielded an appreciable

23   improvement in risk reclassification when combined with the QRISK3 clinical risk score.

24

25   Other genetic studies of CAD and related traits that have evaluated reproducibility of

26   established loci in SAS populations have either been limited by small sample sizes or have

28

1   restricted their comparisons to the index SNP identified in the GWAS, which does not take LD

2   into account [34–36]. A recent study compared genetic determinants of >200 lipid metabolites in

3   5,000 South Asians from Pakistan and 13,000 Europeans and found high overlap in the

4   detected associations [57]. Using a new method, our paper goes further by empirically

5   demonstrating that, in most cases where loci do not replicate, it is due to lack of power. These

6   findings suggest that, in large part, the genes and pathways that influence risk of CAD are

7   shared between these ancestrally divergent populations. One surprising finding was that the

8   major LDL-C locus at *CETP* was not associated with this biomarker in G&H but exhibited

9   pleiotropic effects particularly on HDL-C. Abnormalities in *CETP* are linked to accelerated

10   atherosclerosis and might play an important role in increasing risk in SAS [58].

11

12   Of those previously reported cardiometabolic loci that contained variants significantly

13   associated in G&H, 30–74% did not show evidence of shared causal variants. This suggests

14   that, although the genes and pathways are likely to be shared between ancestral groups, there

15   is heterogeneity with respect to the causal alleles. BMI had the lowest proportion of

16   transferable loci with shared causal variants as well as lower transferability of the PGS in G&H

17   and a genetic correlation significantly lower than one. SAS individuals are known to have

18   higher visceral fat at the same BMI compared to EUR individuals in Western countries [59,60].

19   Consistent with this, the causal effect of BMI was significant only when using the transferable

20   loci as instruments in the Mendelian randomisation analysis. Visceral adiposity is a strong risk

21   factor for cardiometabolic diseases, independent of total fat mass; these findings warrant

22   further study and may suggest that BMI may not be an optimal biomarker of adiposity in SAS[61].

23

24   Mendelian randomisation has emerged as a powerful tool to explore the causal effects of risk

25   factors on disease outcomes. Statistical power can be the limiting factor when extending these

26   analyses to non-EUR populations because independent ancestry-matched GWAS for risk

27   factors of interest may not be sufficiently large. To increase power to estimate the causal

28   effects of risk factor traits on CAD in BPB, we used genetic instruments derived from large

29

1 EUR GWAS. Some of the loci may be invalid instruments for other populations. However,

2 restricting the established loci to the ones that were transferable in this population successfully

3 addressed this issue for BMI and shows promise as a new approach for trans-ancestry

4 Mendelian randomisation. An assumption that requires further study is whether the effect sizes

5 of transferable loci are the same for each ancestry group.

6

7 We observed variable levels of PGS transferability from EUR into BPB individuals for the

8 cardiometabolic traits that were investigated in this work, with relative accuracy in G&H versus

9 eMERGE ranging from 131% for DBP to 42% for CAD. Consistent with previous studies [37,62],

10 PGSs for HDL-C and triglycerides had similar predictive accuracy between the two ancestry

11 groups. We explored the factors that may impact relative accuracy of PGSs. Based on a

12 recently proposed theory, relative accuracy is proportional to the product of the trans-ethnic

13 genetic correlation and the ratio of heritability estimates [7]. We considered the effect on the

14 relative accuracy of the trans-ethnic genetic correlation, ratio of heritability estimates in G&H

15 versus eMERGE, as well as the product of the previous two terms. However, none of them

16 showed a significant association with the relative PGS performance (**Figure S12**). This may

17 be because the theory was derived for PGSs based on genome-wide significant SNPs

18 (whereas our PGSs include many SNPs with less significant p-values), and because the

19 relative accuracy also depends on differences in allele frequencies and LD patterns at these

20 SNPs between populations, which we have not factored in and may differ between traits.

21

22 Based on findings in lipid traits, the Global Lipids Genetics Consortium recently claimed that

23 GWASs with high enough sample sizes could lead to PGSs with equally high accuracy across

24 ancestry populations, even if the GWASs were conducted in predominantly EUR samples [62].

25 However, we do not fully agree that this claim can be generalised beyond lipid traits, since it

26 depends on the extent to which the causal variants are shared across ancestry groups. For

27 example, the accuracy of C+T PGS for BMI decreased by 38% in G&H, whereas that for TG

28 decreased by only 17% and that for HDL-C did not decrease, although the sample size of the

30

1   input GWAS for BMI was much larger than that for lipids (about 700,000 versus 300,000;

2   **Table S4**). This is likely due to the relatively lower fraction of shared causal variants (26%) at

3   transferable loci for BMI and the relatively lower genetic correlation (significantly lower than 1

4   for BMI while close to 1 for lipids), which will not be ameliorated with larger sample sizes of

5   Europeans.

6

7   Several groups have shown improvements in PGS performance in non-Europeans when

8   incorporating summary statistics from ancestry-matched samples [41,63]. Incorporating UKBB

9   SAS GWAS data in meta-PGSs proposed by Marquez-Luna et al. [41,63] did not show large

10   improvement in G&H. A likely reason is the limited sample size of the SAS samples in UKBB

11   for some of the traits. Larger samples of SAS individuals are needed to examine if ancestry-

12   matched GWAS data can improve prediction accuracy over and above what would be

13   expected from the increased sample size. For traits for which the causal variants are shared,

14   there is more to be gained from more powerful EUR GWASs, even without adding samples of

15   the target ancestry. However, increasing diversity in GWASs will greatly improve the resolution

16   of fine-mapping and the power to identify the causal variants by leveraging the LD differences

17   across ancestries [64].

18

19   We assessed the clinical value of the PGS for CAD on top of the traditional clinical risk factors

20   captured in the QRISK3 algorithm. Similar work has been done previously in research cohorts

21   [9–12]; our study represents an important addition since it captures the noise with which QRISK3

22   is actually measured within a real-world clinical setting (as opposed to using comprehensive

23   measures taken for research purposes), which may affect performance of integrated risk

24   models combining these factors with PGSs. We note that only about 4% of the ~8 million

25   individuals used for developing QRISK3 were of South Asian ancestry [26], and the weights for

26   each conventional risk factor might not be optimal for SAS individuals. QRISK3 was developed

27   to predict cardiovascular disease (CVD), which is a composite outcome of CAD and stroke.

28   However, our analysis focused on CAD, which is an important component of CVD and the

31

1   main focus in GWASs and genetic prediction studies. The PGS for CAD developed by Wang

2   *et al.* showed robust association with CAD in G&H, with a similar OR per SD in PGS (1.63,

3   95% CI: 1.51–1.76) as in their study (1.60, 95% CI: 1.32–1.94) [42]. The integrated score

4   combining PGS and QRISK3 showed significant reclassification improvement against QRISK3

5   alone (NRI 3.9% (95% CI: 0.9–7.0%)). Previous studies in UKBB EUR samples reported

6   similar improvement, with NRI estimates of 3.5% (95% CI: 2.4–4.5%) [10] and 3.7% (95% CI:

7   3.0–4.4%) [9] in two different analyses using CAD as the outcome. However, these NRI

8   estimates are probably inflated by using UKBB samples that are healthier than the general UK

9   population without recalibrating risk to a primary care setting[11]. In G&H, the PGS improved

10 identification of high-risk individuals in people younger than 55 years, and correctly down-

11 classified low-risk individuals in people older than 55 years, both of which are important in a

12 clinical setting. We anticipate that, like EUR individuals [9–11], the British Pakistani and

13 Bangladeshi community (and potentially other SAS populations) would also benefit from the

14 use of integrating PGS in primary prevention settings.

15

16 Our study has several limitations. Firstly, due to the limited sample size in each age-by-sex

17 subgroup, we could not recalibrate risk prediction models in G&H to what would be expected

18 in an unbiased primary care setting [11]. Secondly, while the G&H cohort has enabled us to

19 assess the potential utility of genetics in an under-represented population using data from

20 electronic records, each of the cohorts examined here is unique. Differences in ascertainment

21 (including the age distribution) and clinical measurements within different cohorts and

22 healthcare systems may have impacted the genetic associations. Ideally future studies would

23 compare populations with different ancestries collected in the same real-world healthcare

24 setting, but with sufficient sample sizes in each ancestry group to enable well-powered

25 comparisons. The BioMe biobank in New York contains individuals from multiple ancestries

26 with linked EHR data, but the number of self-reported SAS individuals is very limited (N=622)

27 [65].

28

1 In conclusion, our work provides the first comprehensive assessment of the transferability of

2 cardiometabolic loci to a non-EUR population and its impact on two key applications of

3 genetics, causal inference and risk prediction. Our protocol and our new approach for

4 transferability can serve as methodological standards in this developing field. We have shown

5 high transferability of GWAS loci across several cardiometabolic traits between EUR and BPB

6 populations. The transferability of PGSs is trait-specific. Our results suggested there would be

7 clinical value in adding PGS to conventional risk factors in the prediction of CAD in primary

8 care settings to improve the more efficient use of preventive interventions, such as lipid-

9 lowering medications. Our investigation contributes to the increasing representation of

10 individuals of non-European ancestry and lower socio-economic status in research studies,

11 which we hope will help to decrease health disparities.

12

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Supplementary Materials

Supplementary Figures 1–12

Supplementary Tables 1–12

1 References

2 1. Barnett AH, Dixon AN, Bellary S, Hanif MW, O'hare JP, Raymond NT, Kumar S. Type 2

3   diabetes and cardiovascular risk in the UK south Asian community. *Diabetologia*.

4   2006;49:2234–2246.

5 2. Gurdasani D, Barroso I, Zeggini E, Sandhu MS. Genomics of disease risk in globally

6   diverse populations. *Nat Rev Genet*. 2019;20:520–535.

7 3. Morales J, Welter D, Bowler EH, Cerezo M, Harris LW, McMahon AC, Hall P, Junkins

8   HA, Milano A, Hastings E, Malangone C, Buniello A, Burdett T, Flicek P, Parkinson H,

9   Cunningham F, Hindorff LA, MacArthur JAL. A standardized framework for

10   representation of ancestry data in genomics studies, with application to the NHGRI-EBI

11   GWAS Catalog. *Genome Biol*. 2018;19:21.

12 4. Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. Clinical use of current

13   polygenic risk scores may exacerbate health disparities. *Nat Genet*. 2019;51:584–591.

14 5. Duncan L, Shen H, Gelaye B, Meijsen J, Ressler K, Feldman M, Peterson R, Domingue

15   B. Analysis of polygenic risk score usage and performance in diverse human

16   populations. *Nat Commun*. 2019;10:3328.

17 6. Majara L, Kalungi A, Koen N, Zar H, Stein DJ, Kinyanda E, Atkinson EG, Martin AR.

18   Low generalizability of polygenic scores in African populations due to genetic and

19   environmental diversity [Internet]. Cold Spring Harbor Laboratory. 2021 [cited 2021 Feb

20   23];2021.01.12.426453. Available from:

21   https://www.biorxiv.org/content/10.1101/2021.01.12.426453v1

22 7. Wang Y, Guo J, Ni G, Yang J, Visscher PM, Yengo L. Theoretical and empirical

23   quantification of the accuracy of polygenic scores in ancestry divergent populations. *Nat*

24   *Commun*. 2020;11:3865.

1 8. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, Collins R, Allen NE.

2   Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank

3   Participants With Those of the General Population. *Am J Epidemiol*. 2017;186:1026–

4   1034.

5 9. Elliott J, Bodinier B, Bond TA, Chadeau-Hyam M, Evangelou E, Moons KGM, Dehghan

6   A, Muller DC, Elliott P, Tzoulaki I. Predictive Accuracy of a Polygenic Risk Score–

7   Enhanced Prediction Model vs a Clinical Risk Score for Coronary Artery Disease.

8   *JAMA*. 2020;323:636–645.

9 10. Riveros-Mckay F, Weale ME, Moore R, Selzam S, Krapohl E, Sivley RM, Tarran WA,

10   Sørensen P, Lachapelle AS, Griffiths JA, Saffari A, Deanfield J, Spencer CCA,

11   Hippisley-Cox J, Hunter DJ, O'Sullivan JW, Ashley EA, Plagnol V, Donnelly P. An

12   Integrated Polygenic Tool Substantially Enhances Coronary Artery Disease Prediction.

13   *Circ Genom Precis Med* [Internet]. 2021;Available from:

14   http://dx.doi.org/10.1161/CIRCGEN.120.003304

15 11. Sun L, Pennells L, Kaptoge S, Nelson CP, Ritchie SC, Abraham G, Arnold M, Bell S,

16   Bolton T, Burgess S, Dudbridge F, Guo Q, Sofianopoulou E, Stevens D, Thompson JR,

17   Butterworth AS, Wood A, Danesh J, Samani NJ, Inouye M, Di Angelantonio E.

18   Polygenic risk scores in cardiovascular risk prediction: A cohort study and modelling

19   analyses. *PLoS Med*. 2021;18:e1003498.

20 12. Weale ME, Riveros-Mckay F, Selzam S, Seth P, Moore R, Tarran WA, Gradovich E,

21   Giner-Delgado C, Palmer D, Wells D, Saffari A, Sivley RM, Lachapelle AS, Wand H,

22   Clarke SL, Knowles JW, O'Sullivan JW, Ashley EA, McVean G, Plagnol V, Donnelly P.

23   Validation of an Integrated Risk Tool, Including Polygenic Risk Score, for Atherosclerotic

24   Cardiovascular Disease in Multiple Ethnicities and Ancestries. *Am J Cardiol* [Internet].

25   2021;Available from: http://dx.doi.org/10.1016/j.amjcard.2021.02.032

13. Finer S, Martin HC, Khan A, Hunt KA, MacLaughlin B, Ahmed Z, Ashcroft R, Durham C, MacArthur DG, McCarthy MI, Robson J, Trivedi B, Griffiths C, Wright J, Trembath RC, van Heel DA. Cohort Profile: East London Genes & Health (ELGH), a community-based population genomics and health study in British Bangladeshi and British Pakistani people. *Int J Epidemiol*. 2020;49:20–21i.

14. Manichaikul A, Mychaleckyj JC, Rich SS, Daly K, Sale M, Chen W-M. Robust relationship inference in genome-wide association studies. *Bioinformatics*. 2010;26:2867–2873.

15. Patterson N, Price AL, Reich D. Population structure and eigenanalysis. *PLoS Genet*. 2006;2:e190.

16. Das S, Forer L, Schönherr S, Sidore C, Locke AE, Kwong A, Vrieze SI, Chew EY, Levy S, McGue M, Schlessinger D, Stambolian D, Loh P-R, Iacono WG, Swaroop A, Scott LJ, Cucca F, Kronenberg F, Boehnke M, Abecasis GR, Fuchsberger C. Next-generation genotype imputation service and methods. *Nat Genet*. 2016;48:1284–1287.

17. GenomeAsia100K Consortium. The GenomeAsia 100K Project enables genetic discoveries across Asia. *Nature*. 2019;576:106–111.

18. Stanaway IB, Hall TO, Rosenthal EA, Palmer M, Naranbhai V, Knevel R, Namjou-Khales B, Carroll RJ, Kiryluk K, Gordon AS, Linder J, Howell KM, Mapes BM, Lin FTJ, Joo YY, Hayes MG, Gharavi AG, Pendergrass SA, Ritchie MD, de Andrade M, Croteau-Chonka DC, Raychaudhuri S, Weiss ST, Lebo M, Amr SS, Carrell D, Larson EB, Chute CG, Rasmussen-Torvik LJ, Roy-Puckelwartz MJ, Sleiman P, Hakonarson H, Li R, Karlson EW, Peterson JF, Kullo IJ, Chisholm R, Denny JC, Jarvik GP, eMERGE Network, Crosslin DR. The eMERGE genotype set of 83,717 subjects imputed to ~40 million variants genome wide and association with the herpes zoster medical record phenotype. *Genet Epidemiol*. 2019;43:63–81.

19. McInnes L, Healy J, Melville J. UMAP: Uniform Manifold Approximation and Projection for Dimension Reduction [Internet]. arXiv [stat.ML]. 2018;Available from: http://arxiv.org/abs/1802.03426

20. Discovery Data Service [Internet]. [cited 2021 Apr 7];Available from: https://wiki.discoverydataservice.org/index.php?title=Welcome_to_the_Discovery_Data_Service_knowledge_base

21. NHS UK Read Codes · TRUD [Internet]. [cited 2021 Apr 7];Available from: https://isd.digital.nhs.uk/trud3/user/guest/group/0/pack/9

22. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, Natarajan P, Lander ES, Lubitz SA, Ellinor PT, Kathiresan S. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet*. 2018;50:1219–1224.

23. Nelson CP, Goel A, Butterworth AS, Kanoni S, Webb TR, Marouli E, Zeng L, Ntalla I, Lai FY, Hopewell JC, Giannakopoulou O, Jiang T, Hamby SE, Di Angelantonio E, Assimes TL, Bottinger EP, Chambers JC, Clarke R, Palmer CNA, Cubbon RM, Ellinor P, Ermel R, Evangelou E, Franks PW, Grace C, Gu D, Hingorani AD, Howson JMM, Ingelsson E, Kastrati A, Kessler T, Kyriakou T, Lehtimäki T, Lu X, Lu Y, März W, McPherson R, Metspalu A, Pujades-Rodriguez M, Ruusalepp A, Schadt EE, Schmidt AF, Sweeting MJ, Zalloua PA, AlGhalayini K, Keavney BD, Kooner JS, Loos RJF, Patel RS, Rutter MK, Tomaszewski M, Tzoulaki I, Zeggini E, Erdmann J, Dedoussis G, Björkegren JLM, EPIC-CVD Consortium, CARDIoGRAMplusC4D, UK Biobank CardioMetabolic Consortium CHD working group, Schunkert H, Farrall M, Danesh J, Samani NJ, Watkins H, Deloukas P. Association analyses based on false discovery rate implicate new loci for coronary artery disease. *Nat Genet*. 2017;49:1385–1391.

24. Liu DJ, Peloso GM, Yu H, Butterworth AS, Wang X, Mahajan A, Saleheen D, Emdin C,

1 Alam D, Alves AC, Amouyel P, Di Angelantonio E, Arveiler D, Assimes TL, Auer PL,

2 Baber U, Ballantyne CM, Bang LE, Benn M, Bis JC, Boehnke M, Boerwinkle E, Bork-

3 Jensen J, Bottinger EP, Brandslund I, Brown M, Busonero F, Caulfield MJ, Chambers

4 JC, Chasman DI, Chen YE, Chen Y-DI, Chowdhury R, Christensen C, Chu AY, Connell

5 JM, Cucca F, Cupples LA, Damrauer SM, Davies G, Deary IJ, Dedoussis G, Denny JC,

6 Dominiczak A, Dubé M-P, Ebeling T, Eiriksdottir G, Esko T, Farmaki A-E, Feitosa MF,

7 Ferrario M, Ferrieres J, Ford I, Fornage M, Franks PW, Frayling TM, Frikke-Schmidt R,

8 Fritsche LG, Frossard P, Fuster V, Ganesh SK, Gao W, Garcia ME, Gieger C, Giulianini

9 F, Goodarzi MO, Grallert H, Grarup N, Groop L, Grove ML, Gudnason V, Hansen T,

10 Harris TB, Hayward C, Hirschhorn JN, Holmen OL, Huffman J, Huo Y, Hveem K,

11 Jabeen S, Jackson AU, Jakobsdottir J, Jarvelin M-R, Jensen GB, Jørgensen ME,

12 Jukema JW, Justesen JM, Kamstrup PR, Kanoni S, Karpe F, Kee F, Khera AV, Klarin

13 D, Koistinen HA, Kooner JS, Kooperberg C, Kuulasmaa K, Kuusisto J, et al. Exome-

14 wide association study of plasma lipids in >300,000 individuals. *Nat Genet.*

15 2017;49:1758–1766.

16 25. Evangelou E, Warren HR, Mosen-Ansorena D, Mifsud B, Pazoki R, Gao H, Ntritsos G,

17 Dimou N, Cabrera CP, Karaman I, Ng FL, Evangelou M, Witkowska K, Tzanis E,

18 Hellwege JN, Giri A, Velez Edwards DR, Sun YV, Cho K, Gaziano JM, Wilson PWF,

19 Tsao PS, Kovesdy CP, Esko T, Mägi R, Milani L, Almgren P, Boutin T, Debette S, Ding

20 J, Giulianini F, Holliday EG, Jackson AU, Li-Gao R, Lin W-Y, Luan J 'an, Mangino M,

21 Oldmeadow C, Prins BP, Qian Y, Sargurupremraj M, Shah N, Surendran P, Thériault S,

22 Verweij N, Willems SM, Zhao J-H, Amouyel P, Connell J, de Mutsert R, Doney ASF,

23 Farrall M, Menni C, Morris AD, Noordam R, Paré G, Poulter NR, Shields DC, Stanton A,

24 Thom S, Abecasis G, Amin N, Arking DE, Ayers KL, Barbieri CM, Batini C, Bis JC,

25 Blake T, Bochud M, Boehnke M, Boerwinkle E, Boomsma DI, Bottinger EP, Braund PS,

26 Brumat M, Campbell A, Campbell H, Chakravarti A, Chambers JC, Chauhan G, Ciullo

27 M, Cocca M, Collins F, Cordell HJ, Davies G, de Borst MH, de Geus EJ, Deary IJ,

1   Deelen J, Del Greco M F, Demirkale CY, Dörr M, Ehret GB, Elosua R, Enroth S,

2   Erzurumluoglu AM, Ferreira T, Frånberg M, et al. Genetic analysis of over 1 million

3   people identifies 535 new loci associated with blood pressure traits. *Nat Genet*.

4   2018;50:1412–1425.

5   26. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk

6   prediction algorithms to estimate future risk of cardiovascular disease: prospective

7   cohort study. *BMJ*. 2017;357:j2099.

8   27. Li Y, Sperrin M, van Staa T. R package "QRISK3": an unofficial research purposed

9   implementation of ClinRisk's QRISK3 algorithm into R [Internet]. F1000Research.

10   2019;8:2139. Available from: http://dx.doi.org/10.12688/f1000research.21679.1

11 28. Yousaf S, Bonsall A. UK Townsend Deprivation Scores from 2011 census data.

12   *Colchester, UK: UK Data Service* [Internet]. 2017;Available from:

13   http://statistics.digitalresources.jisc.ac.uk.s3.amazonaws.com/dkan/files/Townsend_Dep

14   rivation_Scores/UK%20Townsend%20Deprivation%20Scores%20from%202011%20ce

15   nsus%20data.pdf

16 29. Zhou W, Nielsen JB, Fritsche LG, Dey R, Gabrielsen ME, Wolford BN, LeFaive J,

17   VandeHaar P, Gagliano SA, Gifford A, Bastarache LA, Wei W-Q, Denny JC, Lin M,

18   Hveem K, Kang HM, Abecasis GR, Willer CJ, Lee S. Efficiently controlling for case-

19   control imbalance and sample relatedness in large-scale genetic association studies.

20   *Nat Genet*. 2018;50:1335–1341.

21 30. Winkler TW, Day FR, Croteau-Chonka DC, Wood AR, Locke AE, Mägi R, Ferreira T,

22   Fall T, Graff M, Justice AE, Luan J 'an, Gustafsson S, Randall JC, Vedantam S,

23   Workalemahu T, Kilpeläinen TO, Scherag A, Esko T, Kutalik Z, Heid IM, Loos RJF,

24   Genetic Investigation of Anthropometric Traits (GIANT) Consortium. Quality control and

25   conduct of genome-wide association meta-analyses. *Nat Protoc*. 2014;9:1192–1212.

31. Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. *Am J Hum Genet*. 2011;88:76–82.

32. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Shay CM, Spartano NL, Stokes A, Tirschwell DL, VanWagner LB, Tsao CW, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation*. 2020;141:e139–e596.

33. Brown BC, Asian Genetic Epidemiology Network Type 2 Diabetes Consortium, Ye CJ, Price AL, Zaitlen N. Transethnic Genetic-Correlation Estimates from Summary Statistics. *Am J Hum Genet*. 2016;99:76–88.

34. Braun TR, Been LF, Singhal A, Worsham J, Ralhan S, Wander GS, Chambers JC, Kooner JS, Aston CE, Sanghera DK. A replication study of GWAS-derived lipid genes in Asian Indians: the chromosomal region 11q23.3 harbors loci contributing to triglycerides. *PLoS One*. 2012;7:e37056.

35. Shahid SU, Shabana NA, Rehman A, Humphries S. GWAS implicated risk variants in different genes contribute additively to increase the risk of coronary artery disease (CAD) in the Pakistani subjects. *Lipids Health Dis*. 2018;17:89.

36. Chambers JC, Elliott P, Zabaneh D, Zhang W, Li Y, Froguel P, Balding D, Scott J, Kooner JS. Common genetic variation near MC4R is associated with waist circumference and insulin resistance. *Nat Genet*. 2008;40:716–718.

41

37. Kuchenbaecker K, Telkar N, Reiker T, Walters RG, Lin K, Eriksson A, Gurdasani D, Gilly A, Southam L, Tsafantakis E, Karaleftheri M, Seeley J, Kamali A, Asiki G, Millwood IY, Holmes M, Du H, Guo Y, Kumari M, Dedoussis G, Li L, Chen Z, Sandhu MS, Zeggini E, Understanding Society Scientific Group. The transferability of lipid loci across African, Asian and European cohorts. *Nat Commun*. 2019;10:4330.

38. Chun S, Casparino A, Patsopoulos NA, Croteau-Chonka DC, Raby BA, De Jager PL, Sunyaev SR, Cotsapas C. Limited statistical evidence for shared genetic effects of eQTLs and autoimmune-disease-associated loci in three major immune-cell types. *Nat Genet*. 2017;49:600–605.

39. Lambert SA, Gil L, Jupp S, Ritchie SC, Xu Y, Buniello A, McMahon A, Abraham G, Chapman M, Parkinson H, Danesh J, MacArthur JAL, Inouye M. The Polygenic Score Catalog as an open database for reproducibility and systematic evaluation. *Nat Genet* [Internet]. 2021;Available from: https://doi.org/10.1038/s41588-021-00783-5

40. Choi SW, O'Reilly PF. PRSice-2: Polygenic Risk Score software for biobank-scale data. *Gigascience* [Internet]. 2019;8. Available from: http://dx.doi.org/10.1093/gigascience/giz082

41. Márquez-Luna C, Loh P-R, South Asian Type 2 Diabetes (SAT2D) Consortium, SIGMA Type 2 Diabetes Consortium, Price AL. Multiethnic polygenic risk scores improve risk prediction in diverse populations. *Genet Epidemiol*. 2017;41:811–823.

42. Wang M, Menon R, Mishra S, Patel AP, Chaffin M, Tanneeru D, Deshmukh M, Mathew O, Apte S, Devanboo CS, Sundaram S, Lakshmipathy P, Murugan S, Sharma KK, Rajendran K, Santhosh S, Thachathodiyl R, Ahamed H, Balegadde AV, Alexander T, Swaminathan K, Gupta R, Mullasari AS, Sigamani A, Kanchi M, Peterson AS, Butterworth AS, Danesh J, Di Angelantonio E, Naheed A, Inouye M, Chowdhury R, Vedam RL, Kathiresan S, Gupta R, Khera AV. Validation of a Genome-Wide Polygenic

1   Score for Coronary Artery Disease in South Asians. *J Am Coll Cardiol*. 2020;76:703–

2   714.

3   43. Burgess S, Davey Smith G, Davies NM, Dudbridge F, Gill D, Glymour MM, Hartwig FP,

4   Holmes MV, Minelli C, Relton CL, Theodoratou E. Guidelines for performing Mendelian

5   randomization investigations. *Wellcome Open Res*. 2019;4:186.

6   44. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, Laurin C, Burgess S,

7   Bowden J, Langdon R, Tan VY, Yarmolinsky J, Shihab HA, Timpson NJ, Evans DM,

8   Relton C, Martin RM, Smith GD, Gaunt TR, Haycock PC. The MR-Base platform

9   supports systematic causal inference across the human phenome [Internet]. eLife.

10   2018;7. Available from: http://dx.doi.org/10.7554/elife.34408

11   45. Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity Analyses for

12   Robust Causal Inference from Mendelian Randomization Analyses with Multiple Genetic

13   Variants. *Epidemiology*. 2017;28:30–42.

14   46. Bowden J, Smith GD, Haycock PC, Burgess S. Consistent Estimation in Mendelian

15   Randomization with Some Invalid Instruments Using a Weighted Median Estimator

16   [Internet]. Genetic Epidemiology. 2016;40:304–314. Available from:

17   http://dx.doi.org/10.1002/gepi.21965

18   47. Hartwig FP, Smith GD, Bowden J. Robust inference in summary data Mendelian

19   randomization via the zero modal pleiotropy assumption [Internet]. International Journal

20   of Epidemiology. 2017;46:1985–1998. Available from:

21   http://dx.doi.org/10.1093/ije/dyx102

22   48. High cholesterol - Cholesterol levels [Internet]. [cited 2021 May 10];Available from:

23   https://www.nhs.uk/conditions/high-cholesterol/cholesterol-levels/

24   49. Gelernter J, Sun N, Polimanti R, Pietrzak RH, Levey DF, Lu Q, Hu Y, Li B,

25   Radhakrishnan K, Aslan M, Cheung K-H, Li Y, Rajeevan N, Sayward F, Harrington K,

Chen Q, Cho K, Honerlaw J, Pyarajan S, Lencz T, Quaden R, Shi Y, Hunter-Zinck H, Gaziano JM, Kranzler HR, Concato J, Zhao H, Stein MB, Department of Veterans Affairs Cooperative Studies Program (No. 575B), Million Veteran Program. Genome-wide Association Study of Maximum Habitual Alcohol Intake in >140,000 U.S. European and African American Veterans Yields Novel Risk Loci. *Biol Psychiatry*. 2019;86:365–376.

50. Ganna A, Magnusson PKE, Pedersen NL, de Faire U, Reilly M, Arnlöv J, Sundström J, Hamsten A, Ingelsson E. Multilocus genetic risk scores for coronary heart disease prediction. *Arterioscler Thromb Vasc Biol*. 2013;33:2267–2272.

51. Abraham G, Havulinna AS, Bhalala OG, Byars SG, De Livera AM, Yetukuri L, Tikkanen E, Perola M, Schunkert H, Sijbrands EJ, Palotie A, Samani NJ, Salomaa V, Ripatti S, Inouye M. Genomic prediction of coronary heart disease. *Eur Heart J*. 2016;37:3267–3278.

52. Tada H, Melander O, Louie JZ, Catanese JJ, Rowland CM, Devlin JJ, Kathiresan S, Shiffman D. Risk prediction by genetic risk scores for coronary heart disease is independent of self-reported family history. *Eur Heart J*. 2016;37:561–567.

53. Inouye M, Abraham G, Nelson CP, Wood AM, Sweeting MJ, Dudbridge F, Lai FY, Kaptoge S, Brozynska M, Wang T, Ye S, Webb TR, Rutter MK, Tzoulaki I, Patel RS, Loos RJF, Keavney B, Hemingway H, Thompson J, Watkins H, Deloukas P, Di Angelantonio E, Butterworth AS, Danesh J, Samani NJ, UK Biobank CardioMetabolic Consortium CHD Working Group. Genomic Risk Prediction of Coronary Artery Disease in 480,000 Adults: Implications for Primary Prevention. *J Am Coll Cardiol*. 2018;72:1883–1893.

54. Mars N, Koskela JT, Ripatti P, Kiiskinen TTJ, Havulinna AS, Lindbohm JV, Ahola-Olli A, Kurki M, Karjalainen J, Palta P, FinnGen, Neale BM, Daly M, Salomaa V, Palotie A,

44

1   Widén E, Ripatti S. Polygenic and clinical risk scores and their impact on age at onset

2   and prediction of cardiometabolic diseases and common cancers. *Nat Med*.

3   2020;26:549–557.

4   55. Homer K, Boomla K, Hull S, Dostal I, Mathur R, Robson J. Statin prescribing for primary

5   prevention of cardiovascular disease: a cross-sectional, observational study. *Br J Gen*

6   *Pract*. 2015;65:e538–44.

7   56. Overview | Cardiovascular disease: risk assessment and reduction, including lipid

8   modification | Guidance | NICE. [cited 2021 May 10];Available from:

9   https://www.nice.org.uk/guidance/cg181

10   57. Harshfield EL, Fauman EB, Stacey D, Paul DS, Ziemek D, Ong RMY, Danesh J,

11   Butterworth AS, Rasheed A, Sattar T, Zameer-ul-Asar, Saleem I, Hina Z, Ishtiaq U,

12   Qamar N, Mallick NH, Yaqub Z, Saghir T, Hasan Rizvi SN, Memon A, Ishaq M,

13   Rasheed SZ, Memon F-U-R, Jalal A, Abbas S, Frossard P, Saleheen D, Wood AM,

14   Griffin JL, Koulman A. Genome-wide analysis of blood lipid metabolites in over 5,000

15   South Asians reveals biological insights at cardiometabolic disease loci [Internet].

16   bioRxiv. 2020;Available from:

17   http://medrxiv.org/lookup/doi/10.1101/2020.10.16.20213520

18   58. Rashid S, Sniderman A, Melone M, Brown PE, Otvos JD, Mente A, Schulze K,

19   McQueen MJ, Anand SS, Yusuf S. Elevated cholesteryl ester transfer protein (CETP)

20   activity, a major determinant of the atherogenic dyslipidemia, and atherosclerotic

21   cardiovascular disease in South Asians. *Eur J Prev Cardiol*. 2015;22:468–477.

22   59. Sniderman AD, Bhopal R, Prabhakaran D, Sarrafzadegan N, Tchernof A. Why might

23   South Asians be so susceptible to central obesity and its atherogenic consequences?

24   The adipose tissue overflow hypothesis. *Int J Epidemiol*. 2007;36:220–225.

25   60. Shah AD, Kandula NR, Lin F, Allison MA, Carr J, Herrington D, Liu K, Kanaya AM. Less

1 favorable body composition and adipokines in South Asians compared with other US

2 ethnic groups: results from the MASALA and MESA studies. *Int J Obes* . 2016;40:639–

3 645.

4 61. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu C-Y, Vasan RS,

5 Murabito JM, Meigs JB, Cupples LA, D'Agostino RB Sr, O'Donnell CJ. Abdominal

6 visceral and subcutaneous adipose tissue compartments: association with metabolic

7 risk factors in the Framingham Heart Study. *Circulation*. 2007;116:39–48.

8 62. Graham SE, Clarke SL, Wu K-HH. The power of genetically diverse individuals in

9 genome-wide association studies of blood lipid levels. *under review*.

10 63. Weissbrod O, Kanai M, Shi H, Gazal S, Peyrot W, Khera A, Okada Y, Martin A,

11 Finucane H, Price AL. Leveraging fine-mapping and non-European training data to

12 improve trans-ethnic polygenic risk scores. *medRxiv* [Internet]. 2021;Available from:

13 https://www.medrxiv.org/content/10.1101/2021.01.19.21249483v1.abstract

14 64. Zaitlen N, Paşaniuc B, Gur T, Ziv E, Halperin E. Leveraging genetic variability across

15 populations for the identification of causal variants. *Am J Hum Genet*. 2010;86:23–33.

16 65. Belbin GM, Cullina S, Wenric S, Glicksberg BS, Soper ER, Glicksberg BS, Torre D,

17 Moscati A, Wojcik GL, Shemirani R, Beckmann ND, Cohain A, Sorokin EP, Park DS,

18 Ambite J-L, Ellis S, Auton A, CBIPM Genomics Team, Regeneron Genetics Center,

19 Bottinger EP, Cho JH, Loos RJF, Abul-Husn NS, Zaitlen NA, Gignoux CR, Kenny EE.

20 Towards a fine-scale population health monitoring system. *Cell*. 2021;184:2068–

21 2083.e11.

22