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Association of genetic scores related to insulin resistance with neurological outcomes in ancestrally diverse cohorts from the Trans-Omics for Precision Medicine (TOPMed) program



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To better characterize the potential biological mechanisms underlying insulin resistance (IR) and dementia, we derive cross-population and population specific polygenic scores [PSs] for fasting insulin and IR-related partitioned PSs [pPSs]. We conduct a cross-sectional study of the associations of these genetic scores with neurological outcomes in >17k participants (36% men, mean age 55 yrs) from the Trans-Omics for Precision Medicine (TOPMed) program (50% Non-Hispanic White, 23% Black/African American, 21% Hispanic/Latino American, and 4% Asian American). We report significant negative associations ($P < 0.002$) of the cross-population ($P = 1.3 \times 10^{-5}$) and European ($P_{EA} = 3.0 \times 10^{-8}$) fasting insulin PSs with total cranial volume, and of a metabolic syndrome European PS with general cognitive function ($B_{EA} = -0.13$, $P_{EA} = 0.0002$) and lateral ventricular volume ($B_{EA} = 0.09$, $P_{EA} = 0.002$). We identify suggestive negative associations ($P < 0.007$) of metabolic syndrome and obesity pPSs with general cognitive function, and of lipodystrophy pPSs with total cranial volume. A higher genetic predisposition to IR is associated with lower brain size, and a genetic predisposition to specific IR-related type 2 diabetes subtypes, such as metabolic syndrome and mechanisms of IR mediated through obesity and lipodystrophy, is potentially involved in cognitive decline.

Alzheimer's disease (AD) is a slowly progressive neurodegenerative disorder and the most common form of age-related dementia. Genetic factors play a significant role in AD, with heritability estimates from twin studies ranging between 58% and 79%^{1–3}. Type 2 diabetes (T2D) is strongly associated with risk of dementia^{4–8}. Patients with T2D are at higher risk of developing mild cognitive impairment^{5,9}, dementia or AD^{10,11}, and have more rapid progression of AD^{12–15}. Midlife obesity, defined by a BMI higher than 30 kg/m², is also a risk factor for AD^{16,17}.

One pathologic and hallmark feature shared by T2D, obesity, and neuropathological processes underlying cognitive aging and dementia is insulin resistance (IR), an impaired response of the body to insulin action¹⁸. Decreases in the sensitivity of central nervous pathways to insulin, i.e., brain insulin resistance, is an early, common, and major feature in patients with AD, whether they have T2D or not^{19–23}. It is also a major risk factor for

subsequent development of AD^{24–27}. In brains of AD patients, impaired insulin signaling has also been shown to aggravate pathology^{28,29}. Metabolic syndrome, a cluster of cardiometabolic risk factors associated with increased risk of cardiovascular disease (CVD) and T2D and closely related to IR^{30,31}, is a strong risk factor for AD and all-cause dementia, and has been reported associated with cognitive decline and structural brain changes^{32–38}.

Metabolic traits and AD share common clinical or epidemiological risk factors, which could be due to an overlap in causal genes and pathways³⁹. Some genetic variants have been reported associated with both AD and IR disorders in loci like *FTO*, *APOE*, *CLU*, and *TOMM40*⁴⁰. Several studies attempted to better understand the genetic link and etiology between glycemic/metabolic traits, including fasting insulin (FI) and AD/dementia, using genetic correlation analyses, genetic and polygenic scores, and Mendelian Randomization (MR) as described hereafter.

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Some studies evaluated the genetic overlap between insulin-related (including obesity, T2D, metabolic syndrome, fasting glucose, FI, and IR quantified using the Homeostasis Model Assessment for Insulin Resistance [HOMA-IR]) and neuropsychiatric disorders, including AD^{39,41}. One study did not report significant global genetic correlation between AD and FI or HOMA-IR ($R_g = 0.142$, $P = 0.218$)⁴¹. A cross-trait meta-analysis of AD and 10 metabolic traits reported a genetic correlation between FI and AD ($R_g = -0.196$, $P = 0.087$) and identified three loci common to AD and FI (*CLU*, *CR1/CR2*, and *BCL3*)³⁹. One study found that evidence of local correlations between IR-related conditions (T2D, obesity, and metabolic syndrome) and AD can be detected even in the absence of global genetic correlations⁴². A few MR analyses have focused on characterizing the contribution of glycemic traits or IR to AD, but did not find evidence of causality^{43,44}. These studies were conducted in participants of European ancestry and used a small number of genetic loci or variants associated with FI or IR (quantified using HOMA-IR), leading to a modest proportion of variance explained by these genetic instruments.

Using polygenic scores (PSs) as genetic instruments for IR can increase the power of the association analyses. Inconsistent findings have been reported regarding the association of genetic instruments for T2D (genetic scores or PSs) and AD or dementia risk, with some studies reporting significant associations with all-cause dementia and vascular dementia, while other studies did not identify significant association^{45–48}. One of this study, performed predominantly in White European participants, also evaluated association between glycemic traits PSs with dementia and reported negative associations of FI PSs on mixed dementia, and on all-cause dementia, and AD (although not surviving Bonferroni correction)⁴⁵. Leveraging newly developed methods for PS derivation in diverse populations and recently proposed partitioned PSs (pPSs) related to IR based on large clustering analyses of T2D and FI loci^{49–52} that predispose differentially to cardiometabolic disease risk could help disentangle heterogeneity and pinpoint to specific biological mechanisms of IR in AD. It thus represents a complementary strategy to identify relevant pathways on a risk factor that can be intervened on. Furthermore, such PS and pPSs related to IR could be used for risk stratification to help identify subgroup of individuals at higher risk of developing neurological outcomes and who could benefit more from preventive treatments.

Here, we aimed to derive several genetic scores related to IR to demonstrate that leveraging diverse populations improves genetic instruments for IR, to evaluate whether the genetic liability for IR is associated with AD and related traits, and to compare neurological trait associations of IR-

related PS and pPSs to provide insight into specific biological processes underlying IR and AD.

We derived a cross-population PS for FI and compared its performance with population-specific PSs. We also leveraged results from recent large clustering analyses of both T2D and FI loci^{49–52} performed using GWAS from European and multi-ancestry populations, to construct 19 pPSs for T2D subtypes related to IR. We evaluated associations of these IR-related genetic scores with prevalent dementia and AD, and related traits such as general cognitive function and MRI-defined brain volumes in up to 17,000 ancestrally diverse participants from the National Heart, Lung, and Blood Institute (NHLBI) Trans-Omics for Precision Medicine (TOPMed) program⁵³.

We detected significant and negative associations of a cross-population and European population FI PSs with total cranial volume. We also found significant associations of IR-related T2D subtypes pPSs with neurological outcomes, including a liver/lipid pPS with AD, dementia, and general cognitive function, and a metabolic syndrome PS with general cognitive function and lateral ventricular volume.

Results

The analytic strategy to derive the cross-population PS and the pPSs related to IR in TOPMed is presented in Fig. 1.

Associations with HOMA-IR

In the validation set, the proportion of variance explained (PVE) by the cross-population FI PS derived from the population-specific PSs using global shrinkage parameters $\phi = 10^{-6}$, 10^{-4} , 10^{-2} , and 1 was equal to 5.71%, 10.90%, 13.56%, and 13.77%, respectively. We conducted association analyses in the testing set using population-specific PSs derived using $\phi = 1$ to maximize the PVE by the cross-population PS. In the pooled sample included in the testing set, the PVE by the cross-population PS was equal to 11.55% and higher than the population-specific PSs PVEs ($PS_{EA} = 10.76\%$, $PS_{AA} = 1.72\%$, $PS_{HA} = 0.28\%$), Table 1. We confirmed strong positive associations of the cross-population and population-specific FI PSs with HOMA-IR ($P < 10^{-13}$, Table 1). We observed positive associations of all IR-related pPSs with HOMA-IR in the pooled sample ($P \leq 0.001$, Supplementary Tables 6–9) except for the set 3-Suzuki liver/lipid cluster with HOMA-IR, likely due to the low number of genetic variants included in the cluster definition ($n = 3$). We observed the association of most (60 out of 72) of the IR-related pPSs with HOMA-IR in population groups (Supplementary Tables 6–9), even when differing from the ones from which the clusters

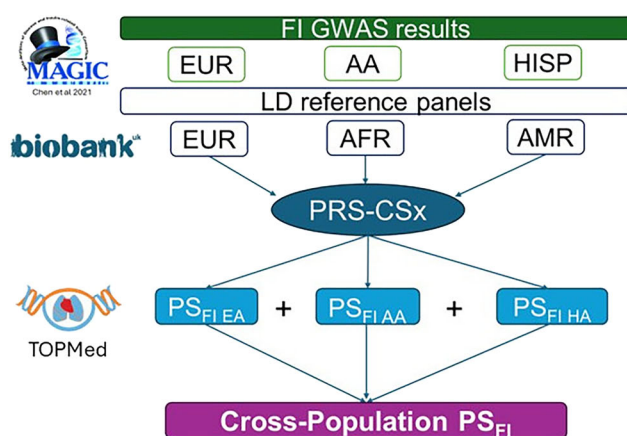
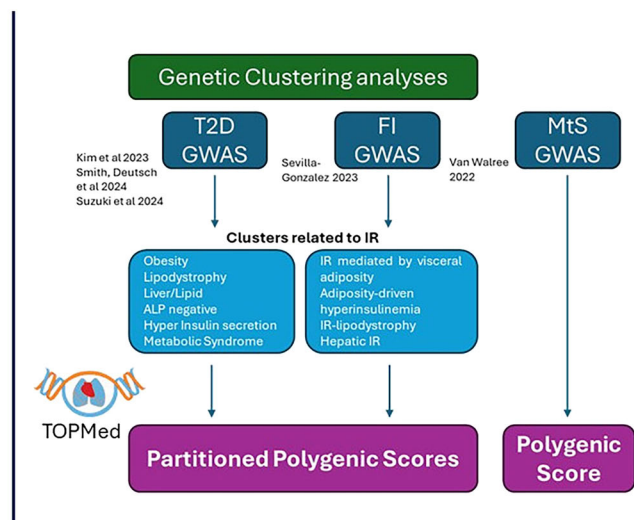


Fig. 1 | Analytic strategy to derive polygenic scores related to insulin resistance in TOPMed. LD Linkage Disequilibrium, T2D Type 2 Diabetes, FI Fasting Insulin, MtS Metabolic Syndrome, ALP alkaline phosphatase. EUR/AFR/AMR denotes LD



reference panels provided by PRS-CSx and constructed using the UK Biobank data (Pan UKBB European ancestry, African ancestry, and Admixed American ancestry); Left-side panel has been adapted from Ruan et al.⁶⁸.

Table 1 | Association results of the fasting insulin (FI) polygenic scores (PSs) with HOMA-IR in the pooled sample of studies included in the testing set

	B	SE	P	Proportion of variance explained ^a
Cross-population PS _{FI}	0.193	0.0037	$<2 \times 10^{-156}$	11.55%
European PS _{FI}	0.237	0.0046	$<2 \times 10^{-156}$	10.76%
African American PS _{FI}	0.129	0.0067	3.1×10^{-82}	1.72%
Hispanic PS _{FI}	0.033	0.0044	5.4×10^{-14}	0.28%

Cross-Population PS_{FI} (weighted linear combination from regression of population-specific scores on HOMA-IR in the validation set): $0.12 \times \text{PS}_{\text{FI_EA}} + 0.10 \times \text{PS}_{\text{FI_AA}} + 0.04 \times \text{PS}_{\text{FI_HA}}$, where EA means Non-Hispanic White, AA Black/African American, and HA Hispanic Latino American.

HOMA-IR The Homeostatic Model Assessment for Insulin Resistance, N = 20,095.

^aProportion of variance explained derived using the function jointScoreTest in the R package Genesis⁸¹ (null model and matrix of scores).

were derived. One example includes the association of the alkaline phosphatase (ALP) negative clusters [set 1-Kim and set 2-Smith, Deutsch] with HOMA-IR in the Asian population group (Supplementary Tables 6 and 7). For both clusters, the genetic variant with the highest weight was in the *ABO* locus, a major determinant for serum ALP levels in the Asian population^{54,55}. Exceptions included the hyper insulin secretion cluster [set 1-Kim] in the African American population, obesity and hyper insulin secretion cluster [set 1-Kim] in the Asian population, hyper insulin secretion and ALP negative [set 2-Smith, Deutsch] in the African American population, ALP negative [set 2-Smith, Deutsch] in the Hispanic/Latino population, obesity [set 2-Smith, Deutsch] in the Asian population, adiposity-driven hyperinsulinemia [set 4-Sevilla-Gonzalez] in the European, Hispanic/Latino and Asian populations, and lipodystrophy [set 4-Sevilla-Gonzalez] and IR mediated by visceral adiposity in the Asian population (Supplementary Tables 6, 7 and 9), that were not found to be associated with HOMA-IR. We detected an association of the metabolic syndrome PS with HOMA-IR in the pooled and European samples, populations in which the GWAS was conducted (Supplementary Table 10).

Associations with neurological diseases and related traits

After multiple-testing correction (i.e., Bonferroni), we detected significant associations of the cross-population and European FI PSs with total cranial volume ($P = 1.3 \times 10^{-5}$; $P_{\text{EA}} = 3.0 \times 10^{-8}$, respectively), Table 2 and Supplementary Table 11. The association remained with greater statistical significance after adjusting for height and BMI ($B_{\text{EA}} = -13.34$, $P_{\text{EA}} = 1.4 \times 10^{-8}$ for the European FI PS tested in the European population group). The effect size was reduced but the association still observed after sensitivity analyses that excluded participants with T2D at the time neurological traits were measured ($B_{\text{EA}} = -12.10$, $P_{\text{EA}} = 1.3 \times 10^{-7}$ for the European FI PS tested in the European population group) or stratifying on *APOE-ε4* allele (non-carriers, $B_{\text{EA}} = -13.11$, $P_{\text{EA}} = 1.2 \times 10^{-7}$ for the European FI PS tested in the European population group), indicating that the association is at least partially distinct from T2D and presence of the *APOE-ε4* allele.

We detected a significant association of the metabolic syndrome PS with general cognitive function ($B = -0.10$, $P = 0.0004$ in the pooled sample; $B_{\text{EA}} = -0.13$, $P_{\text{EA}} = 0.0002$ in the European population group) and lateral ventricular volume ($B = 0.06$, $P = 0.005$ in the pooled sample; $B_{\text{EA}} = 0.09$, $P_{\text{EA}} = 0.002$ in the European population group) after correcting for the number of traits tested, Tables 3 and 4 and Supplementary Table 12. The association was reduced but still observed after excluding participants with prevalent T2D at the time neurological traits were measured from the analysis likely due to a reduced power (in the European population group, association with general cognitive function $B_{\text{EA}} = -0.13$, $P_{\text{EA}} = 0.0004$; association with lateral ventricular volume, $B_{\text{EA}} = 0.07$, $P_{\text{EA}} = 0.01$) indicating that the associations are at least partially distinct from T2D. We did not observe association with cognition in those individuals carrying at least one copy of the *APOE-ε4* allele (likely due to a smaller sample size in that subgroup, $n = 4543$ vs $n = 11117$ non-carriers) and observed consistent and

Table 2 | Association results of the fasting insulin (FI) polygenic scores (PSs) with neurological outcomes in the pooled sample of studies included in the testing set

	Effect estimates in the pooled sample		
	B	SE	P
Dementia (N = 9388; N cases = 1124)			
Cross-population PS _{FI}	0.039	0.039	0.320
European PS _{FI}	0.046	0.048	0.341
African American PS _{FI}	0.021	0.064	0.739
Alzheimer's disease (N = 9388; N cases = 880)			
Cross-population PS _{FI}	0.039	0.044	0.370
European PS _{FI}	0.046	0.054	0.398
African American PS _{FI}	0.025	0.071	0.728
General Cognitive Function (N = 19,191)			
Cross-population PS _{FI}	-0.009	0.007	0.174
European PS _{FI}	-0.008	0.008	0.339
African American PS _{FI}	-0.010	0.01	0.367
Hispanic PS _{FI}	-0.004	0.007	0.591
Hippocampal Volume (N = 7674)			
Cross-population PS _{FI}	0.004	0.009	0.653
European PS _{FI}	-0.004	0.011	0.682
African American PS _{FI}	0.009	0.015	0.559
Hispanic PS _{FI}	0.008	0.009	0.398
Total Brain Volume (N = 7674)			
Cross-population PS _{FI}	-0.395	0.457	0.387
European PS _{FI}	-0.613	0.563	0.276
African American PS _{FI}	-0.950	0.769	0.217
Hispanic PS _{FI}	0.317	0.485	0.512
Lateral Ventricular Volume (N = 7674)			
Cross-population PS _{FI}	0.010	0.005	0.041
European PS _{FI}	0.016	0.006	0.015
African American PS _{FI}	0.004	0.008	0.667
Hispanic PS _{FI}	0.002	0.005	0.674
Total Cranial Volume (N = 7674)			
Cross-population PS _{FI}	-6.135	1.405	1.3×10^{-5}
Cross-population PS _{FI} model adjusted for height	-6.545	1.385	2.3×10^{-6}
European PS _{FI}	-9.847	1.776	3.0×10^{-8}
European PS _{FI} model adjusted for height	-10.088	1.750	8.2×10^{-9}
European PS _{FI} model adjusted for height & BMI	-10.638	1.968	6.5×10^{-8}
European PS _{FI} model adjusted for height, excluding participants with prevalent diabetes at the time of neurological traits measurement	-10.775	1.863	7.3×10^{-9}
European PS _{FI} model adjusted for height in <i>APOE-ε4</i> non-carriers	-10.685	2.154	7.1×10^{-7}
African American PS _{FI}	-2.327	2.338	0.320
Hispanic PS _{FI}	-0.702	1.446	0.627

AD/Dementia: N = 9382 (89% EA, 11% AA); Cross-Population PS_{FI} (weighted linear combination from regression of population-specific scores on HOMA-IR in the validation set):

$0.16 \times \text{PS}_{\text{FI_EA}} + 0.05 \times \text{PS}_{\text{FI_AA}}$, where EA means Non-Hispanic White and AA Black/African American.

General Cognitive Function: N = 17,707 (69% EA, 25% AA, 6% HA); Cross-Population PS_{FI} (weighted linear combination from regression of population-specific scores on HOMA-IR in the validation set): $0.12 \times \text{PS}_{\text{FI_EA}} + 0.11 \times \text{PS}_{\text{FI_AA}} + 0.03 \times \text{PS}_{\text{FI_HA}}$, where EA means Non-Hispanic White, AA Black/African American, and HA Hispanic Latino American.

Brain MRI Volumes and Total Cranial Volume: N = 7567 (61% EA, 21% AA, 16% HA); Cross-Population PS_{FI} (weighted linear combination from regression of population-specific scores on HOMA-IR in the validation set): $0.11 \times \text{PS}_{\text{FI_EA}} + 0.09 \times \text{PS}_{\text{FI_AA}} + 0.08 \times \text{PS}_{\text{FI_HA}}$, where EA means Non-Hispanic White, AA Black/African American, and HA Hispanic Latino American.

Threshold for significance: $P = 0.05/4/7 = 0.0018$.

P-values in bold and italics are significant after multiple-testing correction.

Table 3 | Main associations of partitioned polygenic scores (pPSs) and polygenic score (PS) related to insulin resistance with neurological outcomes in the pooled sample of TOPMed studies

	pPSs				
	Set 1-Kim	Set 2-Smith, Deutsch	Set 3-Suzuki	Set 4-Sevilla-Gonzalez	Van Walree PS
General Cognitive Function					
Metabolic Syndrome pPS or PS	NA	NA	B = −0.062 P = 0.006	NA	B = −0.104 P = 0.0004
Obesity pPS	ns	B = −0.002 P = 0.028	B = −0.065 P = 0.005	NA	NA
Total Cranial Volume					
Lipodystrophy pPS	B = −0.479 P = 0.006	Score 1 B = −0.401 P = 0.035 Score 2 B = −0.613 P = 0.034	ns	B = −0.482 P = 0.031	NA

ns non-significant associations detected (P > 0.05), NA cluster not identified in this study.

Table 4 | Association results of the metabolic syndrome van Walree European GWAS polygenic score (n = 318 genetic variants) [PMID: 35983957] with neurological outcomes in TOPMed

	Effect estimates in the pooled sample		
	B	SE	P
Dementia	0.157	0.168	0.35
Alzheimer's disease	0.087	0.188	0.64
General Cognitive Function	−0.104	0.030	0.0004
General Cognitive Function, excluding participants with prevalent diabetes at the time of neurological traits measurement	−0.109	0.031	0.0005
General Cognitive Function in APOE-ε4 non-carriers	−0.151	0.039	8.7 × 10^{−5}
Hippocampal Volume	−0.047	0.038	0.22
Total Brain Volume	−2.613	1.984	0.19
Lateral Ventricular Volume	0.063	0.023	0.005
Total Cranial Volume	−1.010	6.218	0.87

Threshold for significance: P = 0.05/9 = 0.006.
P-values in bold and italics are significant after multiple-testing correction.
N Dementia and Alzheimer's disease analyses: 9388; N General Cognitive Function analyses: 19,191; N volumes derived from MRI: 7674.

even slightly more significant association in those not carrying the *APOE-ε4* allele (pooled analysis B = −0.15, P = 8.7 × 10^{−5}) indicating that the association is likely distinct from the *APOE-ε4* allele. We did not observe a difference in association with lateral ventricular volume when stratifying on *APOE-ε4* (in the European population group, *APOE-ε4* non-carriers B = 0.06, P = 0.06; *APOE-ε4* carriers B = 0.11, P = 0.06), despite effect size was larger in the *APOE-ε4* carriers group, which could be due to limited power.

We detected significant associations of the liver/lipid set 3-Suzuki pPS with AD (B = −5.78, P = 9.2 × 10^{−11}), dementia (B = −6.15, P = 7.3 × 10^{−10}), and general cognitive function (B = 0.47, P = 0.001, Supplementary Data 1), likely driven by the variant rs429358-T, defining *APOE-ε2*, included in this cluster definition. We found some suggestive associations of the lipodystrophy pPSs (set 1-Kim, set 2-Smith, Deutsch and set 4-Sevilla-Gonzalez) with total cranial volume (B_{set1} = −0.48, P_{set1} = 0.006; B_{set2-lipo1} = −0.40, P_{set2-lipo1} = 0.04, B_{set2-lipo2} = −0.61, P_{set2-lipo2} = 0.03, and B_{set4} = −0.48, P_{set4} = 0.03 respectively), of the obesity pPSs (set 2-Smith, Deutsch and set 3-Suzuki) with general cognitive function (B_{set2} = −0.002, P_{set2} = 0.03 and B_{set3} = −0.07, P_{set3} = 0.005 respectively), and of the metabolic syndrome set 3-Suzuki pPS with total cranial volume (B = −13.98, P = 0.004) and general

cognitive function (B = −0.06, P = 0.006), see Table 3. Results in the pooled sample and by population group are provided in Supplementary Data 1.

As the two metabolic syndrome scores (set 3-Suzuki and van Walree) were negatively associated with cognition, we evaluated their joint association in the same model. Both associations remained (B_{Suzuki} = −0.06, P_{Suzuki} = 0.006, B_{vanWalree} = −0.11, P_{vanWalree} = 0.0004) indicating that these associations are distinct.

Discussion

By deriving FI PSs, we detected statistically significant and negative associations of a cross-population and European population PSs with total cranial volume. Through the construction of IR-related T2D subtypes pPSs, we found significant associations of the liver/lipid (set 3-Suzuki) pPS with AD, dementia, and general cognitive function, and of a metabolic syndrome PS with general cognitive function and lateral ventricular volume.

We did not observe significant association of the FI PSs with AD and dementia in our analysis, which contrasts with the study from Dybjer et al., who evaluated associations between PSs of T2D and glycemic traits with dementia diagnoses and reported negative associations of FI PSs on mixed dementia, and on all-cause dementia and AD (although not surviving Bonferroni correction)⁴⁵. Importantly, the two studies differ in terms of methodologies used to generate PSs (clumping and thresholding for Dybjer et al. versus PRS-CSx in our study), study design (incident analyses in Dybjer et al. versus cross-sectional analyses in our study), population diversity (Dybjer et al. included participants from Sweden, reported as predominantly White Europeans versus multi-ancestry population in our study), and sample size (29,139 participants among which 1914 had all-cause dementia in Dybjer et al. compared to 9388 participants, including 1124 dementia cases in our analyses).

When considering suggestive signals, we detected negative associations of a metabolic syndrome cluster pPS (set 3-Suzuki) and two obesity cluster pPSs (set 2-Smith, Deutsch, and set 3-Suzuki) with general cognitive function, and three lipodystrophy cluster pPSs (set 1-Kim, set 2-Smith, Deutsch, and set 4-Sevilla-Gonzalez) with total cranial volume.

Our analyses identified a negative association of the two metabolic syndrome scores, constructed using different methods and sets of genetic scores, with general cognitive function. The difference in association of the two metabolic syndrome scores with general cognitive function may be due to the number of genetic variants used (318 for van Walree versus 166 for Suzuki) and the higher proportion of European samples in the cognition analysis (~69%). The set 3-Suzuki cluster pPS was much more strongly associated with IR than the van Walree European score (Supplementary Tables 8 and 10) in the pooled sample of TOPMed participants with glycemic traits where the proportion of European samples was ~50%, indicating the power of multi-ancestry scores when analyzing an ancestrally diverse sample. We did not find an overlap between sets of genetic variants

included in the two metabolic syndrome scores (Supplementary Table 13). Joint analysis of the two scores in the same model provided evidence of distinct associations. The metabolic syndrome pPS has been reported by Suzuki et al. to be, in the human brain, significantly enriched for regions of open chromatin in cell types including intratelencephalic (IT) projecting neurons and somatostatin-positive (SST+) GABAergic inhibitory neurons⁵⁰.

We observed a negative association of the two multi-ancestry obesity cluster pPSs (set 2-Smith, Deutsch and set 3-Suzuki) but not of the European obesity cluster pPS (set 1-Kim) with general cognitive function, which could be due again to the number of genetic variants used (35 for set 1-Kim versus 75 for set 2-Smith, Deutsch and 233 for set 3-Suzuki). The sets 2-Smith, Deutsch, and 3-Suzuki cluster pPSs were more strongly associated with IR than the set 1-Kim pPS (Supplementary Tables 6–8), also highlighting the power of multi-ancestry genetic scores when analyzing an ancestrally diverse sample. The overlap between set 2-Smith, Deutsch, and set 3-Suzuki was higher than between set 1-Kim and set 2-Smith, Deutsch/set 3-Suzuki (Supplementary Table 13). The obesity pPS has been reported by Suzuki et al. to be, in the human brain, significantly enriched for regions of open chromatin in cell types including IT projecting neurons, SST+ GABAergic inhibitory neurons, and D1 medium spiny neurons⁵⁰.

Epidemiological associations have been described between metabolic syndrome or obesity and cognition^{56–60}. Genetic studies have identified genetic overlap and shared genetic contributions for BMI, blood pressure or blood lipid levels, and cognition^{61–63}. Genetic variants related to higher cognitive ability are correlated with a lower BMI⁶¹. Genetic risk factors for AD are associated with higher blood lipid levels⁶³. High blood pressure, especially systolic blood pressure, is causally associated with poorer processing speed, verbal memory, and executive function during midlife⁶².

Our analyses highlighted potentially novel associations of PS_{FI}s and of metabolic syndrome and lipodystrophy pPSs with greater lateral ventricular volume and lower total cranial volume, which was only observed among individuals of European descent and independent of body size. These relationships were not observed in total brain volume or other ethnic groups. The PS_{FI}s, metabolic syndrome (1 score among 2 tested, set 3-Suzuki), and lipodystrophy (4 scores among 5 tested) pPSs are associated with lower total cranial volume (significantly for PS_{FI}s, suggestively for lipodystrophy pPSs and metabolic syndrome pPS). In addition, one metabolic syndrome (1 score of 2 tested, van Walree score) pPS is significantly associated with larger lateral ventricular volume. Ventricular enlargement reflecting cerebral atrophy has been reported particularly in elderly patients with T2D. Lateral ventricular enlargement could begin in the early stage of T2D⁶⁴. In late middle-aged adults, IR has been reported associated with progressive atrophy in regions affected by early AD⁶⁵. In a study of depressed and obese children, IR was associated with smaller brain volumes⁶⁶. In cross-sectional studies, T2D is often associated with smaller brain volumes⁶⁷.

Strengths of our study include the derivation of different and complementary genetic scores related to IR, such as cross-population PS and pPSs, to evaluate their strength as predictors of IR in different populations, as well as their associations with neurological outcomes using an ancestrally diverse sample. One of the T2D clustering analysis⁵¹ and the FI clustering analysis⁵² used to derive the pPSs were conducted in populations of European ancestry. The GWAS we used to derive the metabolic syndrome PS was also restricted to participants of European ancestry³¹. We thus complemented our analyses with the inclusion of two recent clustering analyses of T2D loci conducted in diverse populations^{49,50}. We showed that the cross-population PS explained a larger proportion of the variance of HOMA-IR than the population-specific PSs, and the pPSs had stronger association with HOMA-IR compared to PSs derived using top associations from GWAS, particularly when derived from a multi-ancestry population.

Our study includes some limitations. First, a small overlap might exist between the TOPMed studies included in our analyses and the studies included in the clustering analyses of T2D or FI. However, this overlap is not of high concern as our outcomes of interest, the neurological outcomes, were not part of the definition of these clusters. We opted to use FI as a proxy for

IR to select GWAS to derive the PS based on high genetic correlation between FI and HOMA-IR. Derivation of PS using additional diverse GWAS conducted with other traits genetically correlated with HOMA-IR would be worth investigating in future studies. We observed a low variance explained for the Hispanic/Latino PS which could be due to an imperfectly matched LD reference panel⁶⁸ as building such reference panel is challenging for admixed populations⁶⁹, as well as differences in the distribution and representation of Hispanic/Latino population groups in the studies included in the validation (HCHS/SOL) and the testing (MESA and SAFHS) sets (Supplementary Table 15). Additional methods could be considered for building PSs in admixed populations, including penalized-regression-based methods such as inclusive PGS (iPGS) that can capture ancestry-shared genetic effects and does not require LD reference panels or local-ancestry inference⁷⁰, and GAUDI, modeling ancestry-differential effects while borrowing information across segments with shared ancestry in admixed genomes⁷¹. Overlap between studies used in the clustering analyses of T2D loci might exist, particularly as Smith, Deutsch et al. expanded the set of input T2D GWAS used in Kim et al. to include participants of non-European ancestry^{49,51}. As participants with T2D were included in the TOPMed association analyses with neurological outcomes, we conducted sensitivity analyses to evaluate the influence of T2D at the time neurological traits were measured on the associations observed. Some pPSs were not found to be associated with HOMA-IR in some population groups like African American or Asian American, which could be due to the limited sample sizes in these groups, the number of genetic variants included to define these clusters, and a difference in ancestry proportions between the clustering/GWAS study and our pool of participants with glycemic traits. The difference in association with neurological outcomes for clusters representing the same biological mechanism may be explained by the number of genetic variants defining the clusters and their modest to small overlap (Supplementary Table 13), variation in traits selected to define the clusters (Supplementary Table 14), trait and population of the clustering analyses (T2D versus FI, and multi-ancestry versus European), and ancestry proportions in the pool of participants with neurological outcomes.

Conclusion

In conclusion, our findings suggest that a higher genetic predisposition to IR is associated with lower brain size, consistent with literature. Analyzing a diverse sample, our analyses also shed light on a genetic predisposition to specific IR-related T2D subtypes associated with cognitive decline, such as metabolic syndrome and specific mechanisms of IR mediated through obesity and lipodystrophy.

Methods

The Trans-Omics for Precision Medicine (TOPMed) program

The TOPMed program is an NHLBI initiative to improve the understanding of heart, lung, blood, and sleep disorders as well as to advance precision medicine³³. As part of TOPMed, whole-genome sequencing (WGS) and other omics (metabolic profiles, epigenomics, protein and RNA expression patterns) data are being generated and integrated with molecular, behavioral, imaging, environmental, and clinical data. TOPMed includes 196,938 participants from 90 different studies with varying designs, among which 60% were of non-European ancestry.

WGS in TOPMed is performed by several sequencing centers to a median depth of 30X using DNA from blood and Illumina HiSeq X technology. Joint genotype calling is performed across all samples available. Some studies have samples sequenced through both the NHLBI TOPMed program and the NHGRI Centers for Common Disease Genetics (CCDG) program. For these studies, the joint variant identification and genotype calling performed by the TOPMed Informatics Research Center at the University of Michigan includes both TOPMed- and CCDG-funded samples sequenced within the same time frame. For this study, we used TOPMed data freeze 9, for which variant discovery was initially made on ~206,000 samples, including CCDG samples, and then subset to 158,470 TOPMed samples with 2504 1000 Genomes Project samples. A total of

~781 million single-nucleotide variants (SNVs) and 62 million short insertion/deletion variants (indels) were identified and passed variant quality control.

This project included TOPMed studies with information on either glycemic or neurological outcomes and participants representing four major population groups (Non-Hispanic White [EA], Black/African American [AA], Hispanic/Latino American [HA], and Asian American [AS]). A brief description of each study is included in the Supplementary Methods.

Derivation of polygenic scores (PSs) for FI

The Homeostasis Model Assessment for Insulin Resistance [HOMA-IR] is the most extensively validated surrogate of IR⁷². As few multi-ancestry GWASs have been performed on IR, we used FI as a proxy for IR based on high genetic correlation reported between FI and HOMA-IR^{73–75}. We derived three population-specific PSs for FI using PRS-CSx⁶⁸. PRS-CSx, unlike other traditional methods based on clumping and thresholding, does not require a *p*-value threshold and thus uses all genetic variants. We leveraged population-specific summary statistics (European, African American, and Hispanic/Latino) from a recent multi-ancestry meta-analysis of Genome-Wide Association Studies (GWAS) for FI adjusted for BMI conducted by the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC)⁷⁶, and population-specific linkage disequilibrium (LD) reference panels (European ancestry EUR, African ancestry AFR, and Admixed American ancestry AMR) from the UK Biobank⁷⁷ (Fig. 1). To avoid overfitting, we removed the effect of studies that overlap between TOPMed and MAGIC from the FI meta-analyses using the R package MetaSubtract. We derived population-specific scores with PRS-CSx using different global shrinkage parameter ϕ values (e.g., $\phi = 10^{-6}, 10^{-4}, 10^{-2}, 1$). To derive the cross-population PS, we estimated in a validation set weights of a linear combination of the standardized population-specific PSs by regressing IR, quantified using HOMA-IR, on the three population-specific PSs, adjusting for age, sex, study, BMI, and the first 11 genetic principal components using a linear mixed-effects model. The validation set comprised five TOPMed studies (GOLDN, HyperGEN, JHS, WHI, and HCHS/SOL) totaling ~17,000 participants without T2D (33.2% Non-Hispanic White, 28.2% Black/African American, 37.9% Hispanic/Latino, Supplementary Table 1). We then applied the linear combination of the standardized population-specific PSs in a testing set to compute the cross-population PS. This testing set was composed of eight TOPMed studies (ARIC, CARDIA, CHS, FHS, GeneSTAR, GENOA, MESA, and SAFHS) totaling ~21,000 participants without T2D (66.5% Non-Hispanic White, 22.8% Black/African American, 8.2% Hispanic/Latino, Supplementary Table 2). Duplicates within and between studies were excluded. To account for the unbalanced proportion of populations between the validation and the testing sets, we re-weighted each population-specific PS contribution in the linear combination using the ratio of the proportion of populations in the testing and the validation sets (Supplementary Table 3). The exact formula used to derive the cross-population PS for each trait tested is provided in Tables 1 and 2 and Supplementary Table 3.

Construction of partitioned polygenic scores (pPSs) related to IR

We leveraged results from recent and large clustering analyses of both T2D and FI loci to derive 19 pPSs for T2D subtypes related to IR (Fig. 1 and Supplementary Table 4) in TOPMed using weighted sum of risk alleles^{49–52}.

We included three clustering analyses of T2D (one European, set 1-Kim, and two multi-ancestry, set 2-Smith, Deutsch, and set 3-Suzuki)^{49–51} and one clustering analysis of FI (European, set 4-Sevilla-Gonzalez)⁵². We selected 19 clusters positively associated with FI and/or HOMA-IR to derive 19 pPSs: five clusters in set 1-Kim (Obesity, Lipodystrophy, Liver/Lipid, alkaline phosphatase (ALP) negative, and Hyper Insulin secretion), six clusters in set 2-Smith, Deutsch (Obesity, Lipodystrophy 1 and 2, Liver/Lipid, ALP negative, and Hyper Insulin secretion), four clusters in set 3-Suzuki (Obesity, Lipodystrophy, Liver/Lipid, and Metabolic syndrome), and four clusters in set 4-Sevilla-Gonzalez (IR mediated by visceral

adiposity, Adiposity-driven hyperinsulinemia, IR-lipodystrophy, and Hepatic IR). A description of these clusters by study is provided in Supplementary Tables 4 and 14.

One of the T2D clustering analysis (set 1-Kim)⁵¹ and the FI clustering analysis (set 4-Sevilla-Gonzalez)⁵² used to derive the pPSs were conducted in populations of European ancestry. We thus complemented our analyses with the inclusion of two recent clustering analyses of T2D loci conducted in diverse populations (set 2-Smith, Deutsch, and Set 3-Suzuki)^{49,50}. In addition to the pPSs, we derived in TOPMed a PS for metabolic syndrome using 318 lead genetic variants located in 235 genomic risk loci from a recent European GWAS (Fig. 1)³¹. TOPMed studies used in association analyses of pPSs and PS with neurological outcomes were the same as the ones included in the testing set, to which we added back WHI.

Association analyses of the PS and pPSs with HOMA-IR and neurological diseases and related traits

We first evaluated the association of the cross-population and population-specific PSs, and of the pPSs with HOMA-IR to confirm that they are good instruments for IR. We then evaluated if the PSs and pPSs were differentially associated with neurological diseases and related traits. We tested the association of the PSs and pPSs with seven neurological outcomes (prevalent dementia, prevalent AD, general cognitive function⁷⁸, and MRI defined total cranial, total brain, hippocampal, and lateral ventricular volumes) in the pooled sample of all TOPMed studies (Supplementary Table 5) and by population groups (Non-Hispanic White, Black/African American, Hispanic/Latino, and Asian American). A description of the measurement of glycemic (fasting glucose and fasting insulin) and neurological diseases and related traits for each study is included in the Supplementary Methods and Supplementary Data 2 and available elsewhere^{79,80}. We conducted analyses using logistic or linear mixed-effects models adjusted for age, sex, study, and 11 genetic principal components with the GENESIS R package⁸¹. We accounted for relatedness using an empirical kinship matrix and allowed for heterogeneous variance across studies. Association analyses with HOMA-IR were additionally adjusted for BMI and performed in participants without T2D at the time glycemic traits (fasting glucose and fasting insulin) were measured. Analyses with general cognitive function were additionally adjusted for education. Brain volume analyses were additionally adjusted for total cranial volume. As total cranial volume is related to head size, additional adjustments for height (at baseline) and BMI (at time when glycemic traits were measured) were performed as secondary analyses when analyzing this trait. We conducted sensitivity analyses for statistically significant findings with neurological outcomes by excluding individuals with prevalent T2D at the time neurological traits were measured from the analyses to evaluate the influence of T2D on the associations observed, and by stratifying on *APOE-ε4* (carriers vs non-carriers), the major genetic risk factor for late-onset AD, to evaluate the influence of *APOE-ε4* allele on the associations observed. For each analysis, we defined statistical significance using a multiple-testing Bonferroni correction for the number of pPSs, traits, and population groups tested. If several pPSs from different clustering studies reporting IR-related T2D genetic subtypes with the same denomination (e.g., “obesity”) were found to be associated with the same neurological disease/trait, we analyzed them together in the same model to estimate their joint effect.

Analyses evaluating the association of genetic scores with general cognitive function included the Women’s Health Initiative (WHI) study, among other studies. We excluded the WHI study (*n* = 6042) from the testing set and thus from the association analyses conducted with the PSs to maximize the sample size in the validation set.

Statistics and reproducibility

Sample size. 7K participants in the validation set, 21K participants in the testing set for polygenic scores analyses with HOMA-IR; 9.4K, 19.2K, and 7.7K participants for Dementia/AD, general cognitive function, and volumes derived from MRI analyses, respectively.

Sample exclusion. Exclusions have been described above. We excluded duplicates within and between studies, and participants with type 2 diabetes at the time of glycemic traits measurement (for HOMA-IR analyses) and at the time of neurological traits measurement (for Dementia, AD, general cognitive function, and volumes derived from MRI analyses).

Replication. We divided our datasets into a validation and a testing set as described above to assess the robustness of our polygenic scores. We performed association analyses in all TOPMed cohort studies with harmonized neurological outcomes available. The code to derive the polygenic scores is publicly available (http://github.com/chloesar77/FI_PRSCSx_Scores/). The population-specific scoring files derived using PRS-CSx are available on the PGS Catalog (publication ID: PGP000750 and score IDs: PGS005276-5278).

Reporting summary

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

Data availability

Data for each participating study can be accessed through the database of Genotypes and Phenotypes (dbGaP) with the corresponding accession numbers (ARIC, phs001211; CARDIA, phs001612; CHS, phs001368; FHS, phs000974; GeneSTAR, phs001218; GENOA, phs001345; GOLDN, phs001359; HyperGEN, phs001293; HCHS/SOL, phs001395; JHS, phs000964; MESA, phs001416; SAFHS, phs001215; WHI, phs001237). GWAS summary data on glycemic traits have been contributed by MAGIC investigators and downloaded from www.magicinvestigators.org⁷⁶. Study-specific GWAS summary statistics for glycemic traits were provided by the MAGIC consortium. Description of the TOPMed Program, sequence data processing, and TOPMed WGS quality assessment is available in the flagship publication⁵³. The population-specific scoring files derived using PRS-CSx are available on the PGS Catalog (publication ID: PGP000750 and score IDs: PGS005276-5278). URLs: GENESIS: <https://bioconductor.org/packages/release/bioc/html/GENESIS.html>. MAGIC FI GWAS results: <https://magicinvestigators.org/downloads/>. MetaSubtract: <https://cran.r-project.org/web/packages/MetaSubtract/index.html>. PGS Catalog: <https://www.pgscatalog.org/>. PRS-CSx: <https://github.com/getian107/PRSCsx>. T2DGGI: <https://www.diagram-consortium.org/T2DGGI.html>. TOPMed: <https://topmed.nhlbi.nih.gov/>.

Code availability

The code used to generate the polygenic scores and partitioned polygenic scores is publicly available at http://github.com/chloesar77/FI_PRSCSx_Scores/.

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Competing interests

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All study participants provided informed consent, and each study was approved by their respective institutional review boards.

Additional information

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