

Supplemental Material

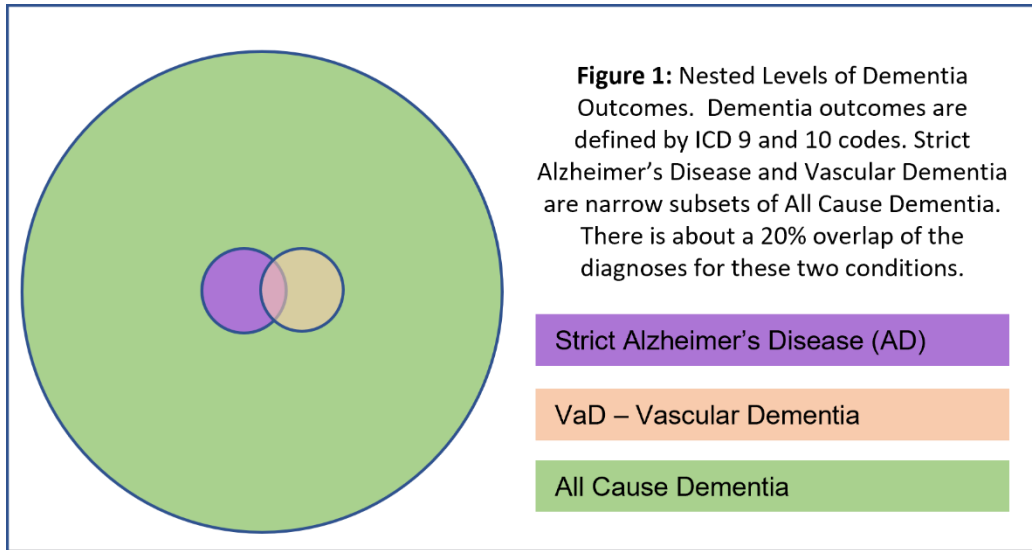


Figure S1: Nested Levels of Dementia Outcomes. NOTE: Dementia outcomes are defined by ICD 9 and 10 codes. Alzheimer's disease and vascular dementia are narrow subsets of all-cause dementia. There is about a 20% overlap of the diagnoses for these two conditions.

Table S1: Dementia Subtypes and Corresponding ICD 9 and 10 Codes. The full set of dementia codes are provided to show the context of possible diagnoses. Our analysis focused on AD, VaD, and all-cause dementia which encompasses the entire table.

| Cognitive Disorder | ICD-9-CM Diagnostic Code | ICD-10-CM Diagnostic Code |
|---|--|--|
| <i>Alzheimer's Disease AD</i> | | |
| | 331.0 Alzheimer's Disease, Excludes early onset AD ICD 10: G30.0 – AD+, Excludes subjects with an ICD code for AD prior to age 65 | G30.1 Alzheimer's Disease, with late onset, G30.8 Other Alzheimer's Disease, G30.9 , Alzheimer's Disease, unspecified |
| <i>AD+ = AD + Non-specific Dementia Listed Below</i> | | |
| | 290.0 Senile Dementia, Uncomplicated, 290.2 Senile Dementia, with delusional or depressive features, 290.20 Senile Dementia, with Delusional Features, 290.21 Senile Dementia, with Depressive Features, 290.3 Senile Dementia, with Delirium | |
| | 294.2 Dementia, Unspecified, 294.20 Dementia, Unspecified Dementia, without Behavioral Disturbance, 294.21 Unspecified Dementia, with Behavioral Disturbance, 294.8 Other Persistent Mental Disorders | F03.90 Unspecified dementia without behavioral disturbance, F03.91 Unspecified Dementia, with behavioral disturbance |
| <i>AD+ = AD+ and Related Dementias (through Vascular Dementia below)</i> | | |
| | 331.1 Frontotemporal Dementia, 331.19 Other frontotemporal dementia, 331.2 Senile Degeneration of Brain, 331.82 Lewy Body Dementia | G31.0 Frontotemporal Dementia, G31.09 Other frontotemporal dementia, G31.1 Senile Degeneration of Brain, Not Elsewhere Classified, G31.83 Lewy Body Dementia |
| | 290.1 Presenile Dementia, 290.10 Presenile Dementia, uncomplicated, 290.11 Presenile Dementia, with delirium, 290.12 Presenile Dementia, with delusional features, 290.13 Presenile Dementia, with depressive features | F03.90 Unspecified Dementia, without behavioral disturbance, F05 Delirium due to known physiological condition |
| | 331.5 Idiopathic Normal Pressure Hydrocephalus (INPH) | G91.2 Idiopathic Normal Pressure Hydrocephalus (INPH) |
| <i>Vascular Dementia (VaD)</i> | | |
| | 290.40 Vascular Dementia, Uncomplicated, 290.41 Vascular Dementia, with Delirium, 290.42 Vascular Dementia, with Delusions, 290.43 Vascular Dementia, with Depressed Mood | F01.50 Vascular Dementia, without Behavioral Disturbance, F01.51 Vascular Dementia, with Behavioral Disturbance |
| <i>Non-specific Dementia not Mentioned Above</i> | | |
| | 294.1 Dementia in conditions classified elsewhere, 294.10 Dementia in conditions classified elsewhere without behavioral disturbance, 294.11 Dementia in conditions classified elsewhere with behavioral disturbance | F02.80 Dementia in other diseases classified elsewhere without behavioral disturbance, F02.81 Dementia in other diseases classified elsewhere with behavioral disturbance |
| <i>Specific Dementia Not Mentioned Above</i> | | |
| | 333.4 Huntington's Disease, 331.11 Pick's Disease | G10 Huntington's Disease, A81.00 Creutzfeldt-Jakob Disease, G31.01 Pick's disease, F10.96 Korsakoff Syndrome |

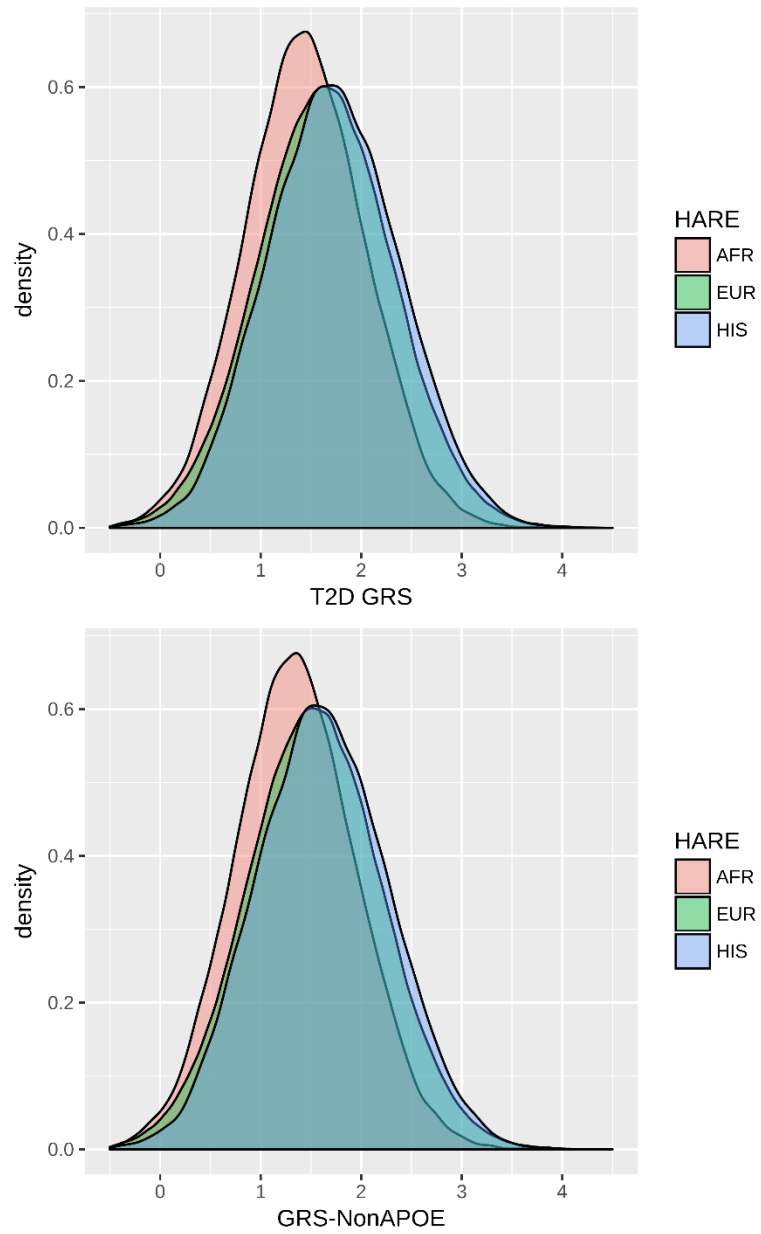


Figure S2: Distribution of GRS and GRS-NonAPOE by HARE group. In both the GRS and the GRS-NonAPOE, AFR (African American) is distinct from the EUR (European) and HIS (Hispanic) race/ethnicities.

Table S2: Sensitivity Test Results for Mutually Exclusive VaD and AD Outcomes

| Beta estimate | Std_Error | Z.score | p-value | Control | Case | Outcome | Race/Ethnicity | GRS |
|---------------|-----------|---------|---------|---------|------|-----------|----------------|-------------|
| 0.0204 | 0.0257 | 0.7940 | 0.4272 | 253800 | 3592 | AD | EUR | T2D GRS |
| 0.0611 | 0.0257 | 2.3732 | 0.0176 | 253800 | 3592 | AD | EUR | GRS-NonAPOE |
| 0.0111 | 0.0284 | 0.3912 | 0.6956 | 253800 | 2927 | AD_No_VaD | EUR | T2D GRS |
| 0.0517 | 0.0284 | 1.8183 | 0.0690 | 253800 | 2927 | AD_No_VaD | EUR | GRS-NonAPOE |
| 0.1102 | 0.0272 | 4.0474 | 0.0001 | 253800 | 3145 | VaD | EUR | T2D GRS |
| 0.1351 | 0.0273 | 4.9560 | 0.0000 | 253800 | 3145 | VaD | EUR | GRS-NonAPOE |
| 0.1233 | 0.0306 | 4.0338 | 0.0001 | 253800 | 2480 | VaD_No_AD | EUR | T2D GRS |
| 0.1440 | 0.0306 | 4.7069 | 0.0000 | 253800 | 2480 | VaD_No_AD | EUR | GRS-NonAPOE |
| 0.0668 | 0.0763 | 0.8753 | 0.3814 | 40035 | 500 | AD | AFR | T2D GRS |
| 0.1272 | 0.0764 | 1.6655 | 0.0958 | 40035 | 500 | AD | AFR | GRS-NonAPOE |
| 0.0670 | 0.0879 | 0.7627 | 0.4457 | 40035 | 372 | AD_No_VaD | AFR | T2D GRS |
| 0.1167 | 0.0880 | 1.3265 | 0.1847 | 40035 | 372 | AD_No_VaD | AFR | GRS-NonAPOE |
| 0.1132 | 0.0594 | 1.9048 | 0.0568 | 40035 | 821 | VaD | AFR | T2D GRS |
| 0.1435 | 0.0595 | 2.4110 | 0.0159 | 40035 | 821 | VaD | AFR | GRS-NonAPOE |
| 0.1235 | 0.0643 | 1.9197 | 0.0549 | 40035 | 693 | VaD_No_AD | AFR | T2D GRS |
| 0.1427 | 0.0644 | 2.2159 | 0.0267 | 40035 | 693 | VaD_No_AD | AFR | GRS-NonAPOE |
| -0.0147 | 0.0972 | -0.1515 | 0.8796 | 16794 | 270 | AD | HIS | T2D GRS |
| 0.0154 | 0.0973 | 0.1582 | 0.8743 | 16794 | 270 | AD | HIS | GRS-NonAPOE |
| -0.0036 | 0.1091 | -0.0332 | 0.9735 | 16794 | 211 | AD_No_VaD | HIS | T2D GRS |
| 0.0238 | 0.1093 | 0.2176 | 0.8278 | 16794 | 211 | AD_No_VaD | HIS | GRS-NonAPOE |
| 0.0419 | 0.0946 | 0.4426 | 0.6581 | 16794 | 276 | VaD | HIS | T2D GRS |
| 0.0594 | 0.0947 | 0.6270 | 0.5307 | 16794 | 276 | VaD | HIS | GRS-NonAPOE |
| 0.0608 | 0.1061 | 0.5730 | 0.5666 | 16794 | 217 | VaD_No_AD | HIS | T2D GRS |
| 0.0727 | 0.1062 | 0.6846 | 0.4936 | 16794 | 217 | VaD_No_AD | HIS | GRS-NonAPOE |

Table S3: Interaction tests of the APOE $\epsilon 4$ dosage and GRS-NonAPOE score

| Beta estimate | Std Error | p-value | Term | Outcome | Control | Case | Race/Ethnicity |
|---------------|-----------|----------|--------------|-----------|---------|-------|----------------|
| 0.034 | 0.022 | 1.14E-01 | Interaction | All-Cause | 249029 | 19176 | EUR |
| 0.144 | 0.044 | 1.02E-03 | Interaction* | AD | 249029 | 3492 | EUR |
| 0.027 | 0.050 | 5.84E-01 | Interaction | VaD | 249029 | 3072 | EUR |
| -0.051 | 0.057 | 3.71E-01 | Interaction | All-Cause | 36153 | 2745 | AFR |
| 0.030 | 0.123 | 8.08E-01 | Interaction | AD | 36153 | 445 | AFR |
| -0.102 | 0.101 | 3.13E-01 | Interaction | VaD | 36153 | 739 | AFR |
| -0.032 | 0.093 | 7.30E-01 | Interaction | All-Cause | 16481 | 1337 | HIS |
| -0.061 | 0.180 | 7.34E-01 | Interaction | AD | 16481 | 268 | HIS |
| 0.035 | 0.183 | 8.48E-01 | Interaction | VaD | 16481 | 271 | HIS |

NOTE: Results of tests of the interaction of the APOE $\epsilon 4$ dosage and GRS-NonAPOE score with dementia sub-types. The tests that met our significance threshold (0.017) are marked with *.

Table S5: Calculation of cumulative probabilities $P(X \geq x)$ given a binomial distribution of counts for 330 variants using a nominal significance threshold of 0.05.

| Count | p.value | Ancestry | Test |
|-------|---------|----------|--------------------|
| 30 | 0.0013 | EUR | All_Cause_Dementia |
| 18 | 0.3867 | EUR | StrictAD |
| 22 | 0.1065 | EUR | Vascular_Dementia |
| 14 | 0.7709 | AFR | All_Cause_Dementia |
| 17 | 0.4848 | AFR | StrictAD |
| 18 | 0.3867 | AFR | Vascular_Dementia |
| 17 | 0.4848 | HIS | All_Cause_Dementia |
| 25 | 0.0270 | HIS | StrictAD |
| 17 | 0.4848 | HIS | Vascular_Dementia |

Table S6: Tests of concordance of direction of effect between diabetes and dementia across race/ethnicities. Calculation of cumulative probabilities $P(X \geq x)$ given binomial distribution of counts of variants with the same direction of effect using an expectation under the null of 50%. The column marked 330 Variants:Same designates the number of variants with the same direction of effect between diabetes and dementia. For the nominally significant variants, the Count column shows the number that met nominal statistical significance in an association with dementia. The Same column shows the number of variants with the same direction of effect as diabetes within the nominally significant variants for that race/ethnicity/diagnosis combination.

| Ancestry | Clinical Diagnosis | 330 Variants | | Nominally Significant Variants | | |
|----------|--------------------|--------------|----------|--------------------------------|------|---------|
| | | Same | p-value | Count | Same | p-value |
| EUR | All_Cause_Dementia | 214 | 3.77E-08 | 30 | 19 | 0.1002 |
| EUR | StrictAD | 184 | 0.0208 | 18 | 10 | 0.4073 |
| EUR | Vascular_Dementia | 196 | 0.0004 | 22 | 15 | 0.0669 |
| AFR | All_Cause_Dementia | 189 | 0.0048 | 14 | 9 | 0.2120 |
| AFR | StrictAD | 182 | 0.0346 | 17 | 9 | 0.5000 |
| AFR | Vascular_Dementia | 175 | 0.1478 | 18 | 12 | 0.1189 |
| HIS | All_Cause_Dementia | 177 | 0.1027 | 17 | 9 | 0.5000 |
| HIS | StrictAD | 162 | 0.6500 | 25 | 13 | 0.5000 |
| HIS | Vascular_Dementia | 181 | 0.0439 | 17 | 9 | 0.5000 |

HbA1c Genetic Risk Score Analysis

Methods

To explore the mechanisms that might inform the relationship between diabetes and dementia, we tested measures of genetically-raised glycated hemoglobin (HbA1c) with our clinical dementia diagnoses. In a similar manner to the diabetes genetic risk scores, we constructed an HbA1c genetic risk score consisting of 91 variants from the trans-ancestry results identified in Chen et al., 2021 (1). Additionally, we constructed a genetic risk score of 23 variants from the glycemic class (Cluster G) when identified in the 'hard' clustering structure from the same analysis (1). Both of these GRS values were standardized to a mean of zero and standard deviation of one.

The Chen research utilized MANTRA (2) to identify the variants that did not demonstrate strong evidence of between-ancestry heterogeneity. We utilized variants that had a MANTRA log10 Bayes Factor ≥ 6 in our analysis. Since there were no trans-ancestry weights reported in the Chen paper, we used METAL (3) to build trans-ancestry fixed effect estimates using the European, African, and Hispanic ancestries as input with a standard error weighting factor between ancestries. We standardized the GRS values to a mean of zero and a standard deviation of one.

We used multivariable regression to test the GRSs with all-cause-dementia and clinically diagnosed AD and VaD, adjusting for age, sex, and 10 genetic PCs, with a significance threshold of 0.017 (0.05/3 clinical diagnoses). We tested the same samples as those identified in the primary diabetes GRS/dementia analysis.

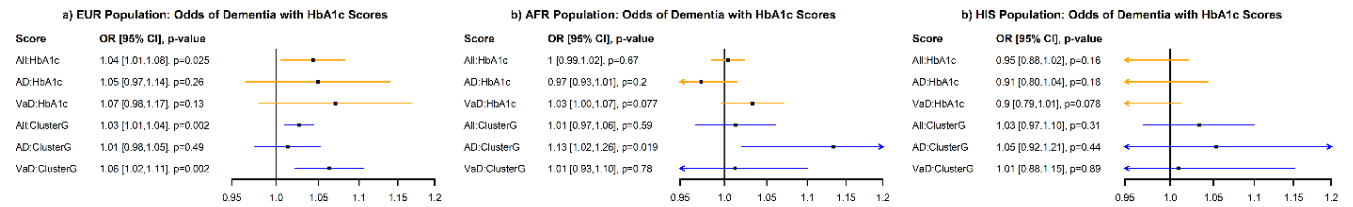
Results

Two associations met our significance threshold in EUR testing (Supplementary Figure S3a) of the HbA1c GRSs with dementia: Cluster G with all cause dementia (OR = 1.03 per 1-SD increase in the GRS, $P = .002$) and Cluster G with clinically diagnosed VaD (OR = 1.06, $P = .002$). In general, genetically-upregulated HbA1c and Cluster G were associated with an increased risk of dementia in EUR, even when the significance threshold was not met. In AFR (Supplementary Figure S3b), no associations met our significance threshold, but Cluster G had a large effect estimate with clinically diagnosed AD and nominal significance (OR = 1.13, $P = 0.019$). In HIS (Supplementary Figure S3c), no associations met the significance threshold but, in general, genetically-upregulated Cluster G was associated with an increased risk of dementia.

HbA1c Genetic Risk Score Conclusion

The results of the HbA1c and Cluster G GRS association testing with 3 clinical diagnoses of dementia are suggestive of potential biological pathways in the relationship between diabetes and dementia. As HbA1c is known to be elevated by multiple mechanisms, we felt that it was important to isolate the glycemic class cluster as it is the most likely to be related to diabetes. Additionally, as the genetics of HbA1c are known to differ between African-Americans and those of European descent, the distinct relationship of the Cluster G GRS with clinically diagnosed AD in AFR is of interest for future studies.

Figure S3: Odds ratios and confidence intervals for the association tests of the HbA1c genetic risk scores and Cluster G risk score with clinically diagnosed dementia. All: all cause dementia, AD: clinically diagnosed Alzheimer’s disease, VaD: clinically diagnosed vascular dementia. ClusterG: glycemic class.



1. Chen J, Spracklen CN, Marenne G, Varshney A, Corbin LJ, Luan J, et al. The trans-ancestral genomic architecture of glycemic traits. *Nat Genet.* 2021 Jun;53(6):840–60.
2. Morris AP. Transethnic Meta-Analysis of Genomewide Association Studies. *Genet Epidemiol.* 2011 Dec;35(8):809–22.
3. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics.* 2010 Sep 1;26(17):2190–1.