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Diabetic Phenotypes and Late Life Dementia Risk: A Mechanism-Specific Mendelian Randomization Study

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Abstract

Background—Mendelian Randomization (MR) studies have reported that type 2 diabetes (T2D) was not associated with Alzheimer's Disease (AD). We adopted a modified, mechanism-specific MR design to explore this surprising result.

Methods—Using inverse-variance weighted MR analysis, we evaluated the association between T2D and AD using data from 39 single nucleotide polymorphisms (SNPs) significantly associated to T2D in DIABetes Genetics Replication And Meta-analysis (DIAGRAM) and the corresponding associations of each SNP with AD risk obtained from the International Genomics of Alzheimer's Project (IGAP, n=17,008 AD cases and n=37,154 controls). We evaluated mechanism-specific genetic subscores, including beta-cell function, insulin sensitivity, and adiposity, and repeated analyses in 8,501 Health and Retirement Study (HRS) participants for replication and model validation.

Results—In IGAP, the overall T2D polygenic score did not predict AD (odds ratio (OR) for the T2D polygenic score = 1.01, 95% confidence interval (CI): 0.96, 1.06) but the insulin sensitivity polygenic score predicted higher AD risk (OR=1.17, CI: 1.02, 1.34). In HRS, polygenic scores

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All authors declare that no conflict of interest exists.

were associated with T2D risk; the associations between insulin sensitivity genetic polygenic score and cognitive phenotypes were not statistically significant.

Conclusion—Evidence from polygenic scores suggests insulin sensitivity specifically may affect AD risk, more than T2D overall.

Keywords

Dementia; Alzheimer's Disease; Type 2 Diabetes Mellitus; Mendelian Randomization Study; Insulin Sensitivity

Many epidemiological studies have shown that individuals with type 2 diabetes mellitus (T2D) are at higher risk of dementia, Alzheimer's Disease (AD), and related memory impairments in old age. There are several biological mechanisms that could link T2D with the pathophysiologic changes underlying dementia, including micro- and macro-cerebrovascular damage and exacerbation of amyloid processes via chronic inflammation, oxidative stress, and/or advanced glycation end products.^{1,2} However, there are many plausible confounders of T2D and dementia, casting doubt on causal inferences from observational studies.³⁻⁵

As it is neither possible nor ethical to randomize people to T2D, this important question cannot be studied in a randomized controlled trial. Evaluating possible causal links between these conditions using conventional observational epidemiologic studies is challenging because the pathophysiology of T2D and dementia both originate years and perhaps decades before clinical diagnosis. This lag between exposure to risk factors and diagnosed disease exacerbates the potential for bias from confounding or the reverse causation intrinsic to observational research designs. Many risk factors, such as adiposity and childhood economic disadvantage, have been linked to both T2D⁶ and the risk of developing dementia.⁷⁻⁹ Similarly, very early neurologic changes associated with incipient dementia might change dietary patterns¹⁰ and the frequency or intensity of physical activity¹¹, all of which influence the risk of T2D.

Although it is impossible to address all the potential biases in conventional observational research designs, these challenges can be circumvented in Mendelian Randomization (MR) studies by using genetic factors that predispose individuals to develop T2D.^{12,13} Combined into a Genetic Risk Index (T2D-GRI), these SNPs predict T2D but could not plausibly be influenced by either incipient dementia or any lifestyle or socioeconomic risk factors for dementia. A recent study adopted this approach and reported the surprising finding that the polygenic risk score for T2D had no association with AD, which is the most common etiology of dementia.¹⁴ We hypothesize that this finding is due to the heterogeneous nature of T2D: the causal effect of T2D on AD may arise from only a specific aspect of T2D. The complex physiology of metabolic dysregulation in T2D – characterized by progressive insulin resistance and hyperglycemia – makes it difficult to identify the specific etiologic mechanisms linking T2D and AD. It is unclear, for instance, whether hyperglycemia, insulin resistance, or both have adverse long-term consequences for AD risk.^{1,15}

In this study, we evaluate associations between AD and AD-related phenotypes and global and mechanism-specific T2D-GRIs. Figure 1 illustrates the hypothesized causal model. If T2D or its subcomponents causally affect AD or related phenotypes, the T2D-GRI or respective polygenic scores should also be associated with those phenotypes. Unlike earlier MR studies investigating the association between T2D and dementia, we hypothesized effect heterogeneity of specific aspects of T2D. We therefore subdivided SNPs on the basis of their presumed biological mechanism linking them to T2D, and used these subscores to investigate the effects of specific biological processes associated with T2D on AD-related phenotypes.

Methods

Study Population and Outcome Definition

The primary study sample used publicly available data from the International Genomics of Alzheimer's Project (IGAP) on 7,055,881 single nucleotide polymorphisms (SNPs) and their association with late onset Alzheimer's disease (LOAD). IGAP includes 17,008 LOAD cases and 37,154 cognitively normal elderly controls from four previously-published GWAS datasets: the European Alzheimer's Disease Initiative (EADI); the Alzheimer Disease Genetics Consortium (ADGC); Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE); and Genetic and Environmental Risk in AD (GERAD) from http://www.pasteur-lille.fr/en/recherche/u744/igap/igap_download.php, accessed Sept. 2nd 2014.¹⁶ To test MR assumptions, we then used individual level data from 8,501 self-reported European ancestry participants in the Health and Retirement Study (HRS), a nationally representative cohort study initiated in 1992.¹⁷⁻¹⁹ HRS assessed memory function and dementia probability using direct cognitive assessments and proxy informants. A substudy of HRS showed the dementia probability score to have a c-statistic of 0.64 for DSM-IV dementia.²⁰

Genetic Instruments—The primary predictor in our analyses is the “instrumental variable (IV)”, a polygenic risk index for T2D (T2D-GRI). We considered data for 39 SNPs confirmed as genome-wide significant predictors of T2D, with the meta-analyzed odds ratios (ORs) reported in Morris et al.¹² Assuming an additive genetic model, we calculated the T2D-GRI by multiplying each individual's number of risk alleles by the reported β coefficient (log odds ratio) for that polymorphism, and summing the products across all 39 loci. In sensitivity analyses, we examined two alternative T2D-GRIs based on the paper by Mahajan et al; these consisted of 61 SNPs (identified from analyses limited to participants of European ancestry) and 72 SNPs (identified from the trans-ancestry GWAS).¹³

We subdivided the 39 SNP T2D-GRI into 4 subscores (adiposity-related, beta-cell function related, insulin sensitivity related, and other biological factors) corresponding to biological mechanisms thought to link each genetic locus to T2D. To create the subscores, each SNP was assigned to the closest gene and each gene to a specific group based on a literature review; the relevant references and justifications are provided in Supplementary Table 1. These subscores were defined a priori on the basis of the literature review, and we have published previously on the link between these subscores and other outcomes.²¹ We used

these subscores for mechanism-specific analyses testing for example whether dysregulation related to insulin sensitivity specifically predicted dementia.

From the IGAP Stage 1 analyses, we extracted summary data on SNP-LOAD associations from T2D-related SNPs. Two SNPs – rs6878122 in the zinc finger, BED-type containing 3 gene (ZBED3) and rs3130501 in the POU class 5 homeobox 1 gene (POU5F1) – were not available in IGAP (but they were available in HRS), and were excluded from the corresponding T2D-GRI (supplementary table S3).

Mendelian Randomization Analysis: We used the associated log odds ratios for T2D and LOAD to construct an inverse-variance weighted MR effect estimate using summary data as proposed by Burgess et al.²²

MR estimates in the primary analyses are odds ratios for late onset Alzheimer's dementia per genetically predicted unit increase in log-odds of having T2D. For the confirmatory analysis using HRS, the MR estimates are odds ratios that correspond to the effect of T2D (binary) on logit of dementia probability and risk differences for the effect of T2D (binary) on the memory score (see supplementary information for a detailed description of the HRS study sample, the outcome measures, and the creation of the genetic instruments).

Model Validation and Mechanism-specific Analysis: To confirm the strength and specificity of T2D-GRI in HRS, we predicted self-reported diabetes and evaluated the relationship of T2D-GRI to a number of biomarkers assessed via lab assays, chosen because they are closely related to T2D (glycosylated hemoglobin (HbA1c, %)), or because we expected them to be unrelated to genetic determinants of T2D (high density lipoprotein (mg/dL), total cholesterol (mg/dL)).²³ When MR analyses show significant effects, it is important to evaluate whether this might be due to pleiotropic pathways of some polymorphisms, or whether the exposure (T2D) has subcomponent phenotypes with distinct effects on the outcome.²⁴ Evaluating pleiotropy is less important when results are null, because such pleiotropism could account for null results only in the unlikely event of perfectly counterbalancing pleiotropic pathways.

To test for pleiotropic effects and evaluate whether subcomponent phenotypes have different effects, we used Egger regression, a method recently recognized as a powerful tool for evaluating and accounting for potential biases in MR analyses. Egger regression, traditionally used to evaluate publication bias, is based on regressing the magnitude of the association between each SNP and AD on the magnitude of the association between each SNP and T2D (in a data set with one observation per SNP).²⁵ Under the assumption that the effect of each SNP on T2D is independent of that SNP's direct effect on AD, Egger regression can provide a valid MR effect estimate. The intercept in the Egger regression estimates the average bias in the SNPs, if such a bias exists.

We used overidentification tests on the mechanism-specific subscores to assess the null hypothesis that the MR estimates from each of the subscores are identical. We expect the test to be statistically significant if either some genes have pleiotropic pathways or effects of various aspects of the T2D phenotype on dementia differ.

Because the outcomes from IGAP and HRS are not precisely identical, we refrained from meta-analyzing results. We used two-sided tests and considered $p < 0.05$ to be statistically significant. All analyses were done using R 3.0.1.²⁶

Results

In IGAP, we observed no association between the overall T2D-GRI and LOAD with the 39 SNP score (OR= 1.01, 95%-CI: 0.96, 1.06), or the two augmented scores using additional SNPs (Table 1). Egger regression showed no evidence of genetic pleiotropy under the assumptions of independent biasing pathways (OR_{intercept}=1.00, 95%-CI: 0.99, 1.02, $p = 0.7$). Subdivision of the T2D-GRI into four biologically relevant pathway scores showed a nominally significant association for the insulin-sensitivity pathway (OR= 1.17, 95%-CI: 1.02 - 1.34) (Table 1, supplementary Figure S1 for SNP specific associations with AD). This association was marginally significant when a conservative Bonferroni correction was applied to preserve the family-wide error rate ($p_{\text{Bonferroni}} = 0.08$). The over-identification test for the equality of effects showed a marginally statistically significant heterogeneity in effects of the four component T2D phenotypes ($p=0.05$).

For replication and model validation, we applied these risk scores to the HRS sample. Confounded observational analysis showed that self-reported diabetes was associated with a lower memory score ($\beta = -0.02$ SD, 95% confidence interval, [CI]: -0.03, -0.01) and with higher log-odds of dementia ($\beta = 0.50$, 95% CI: 0.34, 0.65). In HRS, the genetic instrument (F-statistic = 20.32) and its biologically relevant subscores were strongly associated with self-reported diabetes (Table 2). T2D-GRI explained about 2% of the variation (partial R^2) in the probability of self-reported diabetes (3% using Nagelkerke's R^2 from a logistic regression). For comparison, age explained 0.5% and gender 0.7% (Nagelkerke's R^2) of the variation in self-reported diabetes in HRS. As expected, the T2D-GRI predicted HbA1c – a biomarker of T2D – but not age, sex, high-density lipoprotein or total cholesterol (Supplementary Table S2). As in IGAP, HRS provided no evidence of an association between T2D-GRI and memory function or the log-odds of dementia, although, as expected, CIs were much wider in the smaller HRS sample (Table 3).

Augmenting the original T2D-GRI by including additional SNPs as noted above increased the explained variation for T2D by 0.2%. The insulin-sensitivity subscore was not significantly associated with reduced memory function or increased log-odds of dementia, although the point estimates were in a direction consistent with IGAP results (Table 3).

Discussion

Using a novel mechanism-specific MR study design, we found no evidence of a causal effect of overall T2D on LOAD, memory, or probability of dementia in two large studies. However, polygenic scores formed from a subset of T2D risk loci related to insulin sensitivity were nominally significantly associated with LOAD in IGAP. The evidence suggests that T2D is a complex phenotype and that the underlying causes leading to the expression of T2D may define its effect on dementia risk.

There is substantial prior observational evidence implicating diabetes in the development of dementia, and we replicate those findings with individual-level data from the HRS. Plausible biological pathways have been proposed. T2D is strongly associated with stroke and (silent) brain infarcts, both of which are associated with dementia.^{27,28} T2D may influence AD via chronic inflammation, which may accelerate neurodegeneration.^{1,29-31} A deleterious effect of T2D on AD could also occur through hyperglycemia, leading to the development of advanced glycation end products (AGEs).^{2,32} However, all prior findings showing that increased AD risk is associated with T2D in humans have relied on observational studies assuming no unmeasured common causes of T2D and AD. This non-confounding assumption is controversial and unlikely to be strictly true.

Two trials that examined the effects of glycemic control on cognitive decline among older adults with diabetes report mixed results. The first evaluated whether a diabetes control program prevented cognitive decline among older adults with diabetes and whether the effect was mediated by improved biomarkers strongly associated with T2D, such as blood pressure, low-density lipoprotein and HbA1c.³³ The authors found that the program reduced cognitive decline (measured by the Comprehensive Assessment and

Referral Evaluation (CARE)-Diagnostic Scale), and that better glycemic control, as measured by HbA1c, mediated the effect. However, the CARE Diagnostic Scale includes components of self-reported cognition, so intervention benefits may reflect that participants in the intervention group rate their cognition better than people in the control group.

The second trial, which focused on cognitive and memory outcomes associated with intensive (median HbA1c = 6.6%) vs standard (median HbA1c = 7.5%) glycemic control, did not report statistically significant differences by HbA1c level.³⁴

Like randomized trials, MR analyses reduce confounding by identifying exposure status using the random allocation at conception of genetic loci associated with higher T2D risk. And, like randomized trials, MR analyses rely on crucial assumptions (depicted in Figure 1) to provide valid inferences. First, the instrument (T2D-GRI) must be associated with the phenotype of interest (T2D). Second, the instrument must be independent of unmeasured confounding factors of the phenotype of interest and the outcome under study. Third, the instrument must be associated with the outcome only through the exposure of interest. The first assumption was met, as shown in prior GWAS and confirmed in HRS. With regard to the second assumption, our expectation that the T2D-GRI would be independent of confounders because the genetic variants are inherited independently of environmental factors was supported by evidence that the T2D-GRI was not associated with major confounders or related biomarkers. The third assumption would be violated if there were a direct effect of any of the genetic markers on dementia risk, not mediated by T2D. To our knowledge, there is no evidence in the literature suggesting the SNPs used to create T2D-GRI are associated with AD either directly or through another pathway (see Supplementary Table S2 for a detailed SNP by SNP evaluation of the literature). Nor do the results of our Egger regression model provide evidence for bias in the MR effect estimates.

Oestergard et al. recently published an MR study investigating the effect of many cardiovascular risk factors on AD, including T2D. Like our publication, it also used data from IGAP and an overlapping SNP set to identify T2D, and found no effect of overall T2D on AD.¹⁴ They constructed a separate polygenic risk score to instrument insulin resistance, and reported a non-significant increase in the odds of AD (OR=1.32, 95%-CI: 0.88 -1.98) per SD increase in genetically instrumented log-fasting insulin. Unlike that study, we did not create separate polygenic risk scores from a GWAS of another phenotype, but grouped genome-wide significant predictors of T2D and associated genes into biologically functional groups that contribute to the expression of the T2D phenotype, following our prior approach with other heterogeneous phenotypes, such as body mass index.³⁵ The “insulin sensitivity” group in our study consists of nine SNPs presumed on the basis of physical proximity to represent genes whose functions influence insulin sensitivity. Although some of the SNPs are related to genes that were also included in Oestergard's insulin resistance polygenic score (Insulin Receptor Substrate 1 (IRS1), Peroxisome Proliferator-Activated Receptor Gamma (PPARG)), they were rescaled in the current paper according to their association with T2D. Unlike Oestergard et al., we observed a significant increase in AD associated with a polygenic score composed of putative insulin sensitivity genes. Insulin resistance and decreased production of insulin by pancreatic beta-cells are key factors in the dynamic etiology of T2D that evolves over years.³⁶ While both of these factors are interdependent, the degree to which one or the other is responsible for the expression of the T2D phenotype varies in affected individuals,³⁷ and it is therefore plausible that only one of the two factors may influence risk for AD.

The primary limitation of our findings is that the IGAP results are based on published, secondary data, meaning that we cannot directly assess the validity of the MR assumptions in the primary study sample. To overcome this limitation, we replicated the findings in a somewhat smaller, longitudinal cohort representative of the US population. In this sample, we confirmed that the total and subcomponent genetic scores for T2D were strongly associated with diabetes. However, we lacked the statistical power to successfully replicate the MR results; this is evidenced by the large confidence intervals, which can be interpreted as the set of non-refuted values. As our analytic approach is intended to exclude variation in T2D risk that could be due to confounders of the relationship between T2D and LOAD, it is effectively based solely on the study participants' genetic predisposition to develop T2D. Although our MR point estimate of the effect of T2D on LOAD is very close to null, the confidence interval includes both moderately protective and moderately harmful effects. It is noteworthy, though, that the confidence interval from the primary analysis (OR= 1.01, 95%-CI: 0.96, 1.06) does not include the confidence limits of a recent observational finding from a meta-analysis that estimated a relative risk for T2D-related dementia of 1.51 (95%-CI: 1.31, 1.71).^{38,39} This effect estimate is substantially closer to our IV estimate for the insulin-sensitivity subscore in IGAP.

An additional important limitation relates to the uncertainty of identifying causal genetic loci associated with each SNP and establishing the function of each locus.⁴⁰ It is certainly plausible that SNPs that we classified as related to insulin sensitivity may in the future be reclassified to another mechanism. Our results should thus be viewed as exploratory and interpreted cautiously until confirmed through replications and further confirmation on the

functions of specific alleles. Particular caution is merited because the insulin-sensitivity pathway is only marginally significantly associated with AD ($p_{\text{Bonferroni}} = 0.08$) when the stringent Bonferroni correction method is applied to preserve the family-wide error rate.

In conclusion, our results do not support a causal effect of *overall* T2D on AD in older adults, but potentially implicate the more specific mechanism of insulin sensitivity in increased AD risk. These findings are in line with the previously reported MR result that showed no estimated effect of T2D on AD, but also open the path towards a more detailed investigation of etiologic processes linking T2D and AD. These results are not conclusive, but highlight important insights that may be gained from mechanism-specific MR analyses, helping not only to avoid the confounding that besets traditional observational studies, but also to refine the causal phenotype definition. MR analysis identifies the causal effect of T2D on AD among participants whose T2D status has changed because of their genetic predisposition. At present, there is no evidence to believe that T2D caused by genetic risk factors would have different effects on brain health than T2D caused exclusively by environmental risk factors such as an unhealthy diet or lack of physical exercise. Nonetheless, our approach, which investigates differences between subscore effects, indicates that there may be some T2D phenotypes with worse effects on AD. The heterogeneous nature of T2D as a phenotype is therefore an important question for future empirical research.

That being said, although no single study can or should invalidate the large body of prior evidence on T2D and AD-related phenotypes, it is important to recognize the limitations that are common to nearly all epidemiological studies of this relationship. With the exception of a small number of randomized trials that focus on managing prevalent diabetes, all prior studies rest on the implausible assumption of no unmeasured confounders. Given the clinical and public-health importance of understanding the relationship between T2D and AD, more research that can clearly mitigate the biases so often present in observational research is needed. Evidence of the importance of specific aspects of T2D for dementia risk will help guide more effective interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Causal Genetic Model for Instrumental Variable Analysis

Table 1

Analysis using Single SNP Association Results from the International Genomics of Alzheimer's Project (IGAP) weighted by the SNP specific association with T2D and summarized in a polygenic risk index.

	β	95% Confidence Interval	P
T2D-GRI	1.01	0.96 1.06	0.79
<i>Mechanism-specific T2D-GRI scores</i>			
T2D-GRI Adiposity	0.93	0.74 1.15	0.49
T2D-GRI Beta-Cell Function	1.00	0.94 1.07	0.89
T2D-GRI Insulin Sensitivity	1.17	1.02 1.34	0.02
T2D-GRI Other	0.90	0.79 1.04	0.14
<i>Extended SNP base from Trans-Ethnic GWAS</i>			
T2D-GRI (70 SNPs)	1.01	0.97 1.06	0.63
T2D-GRI (59 SNPs)	1.01	0.97 1.06	0.66

Table 2
First Stage Estimates: Risk Difference Estimates from a Linear Probability Model with the T2D-GRI Predicting Type 2 Diabetes in HRS replication sample

	β	95% Confidence Interval	p	Partial R^2
T2D-GRI	0.89	0.76, 1.02	1.96×10^{-37}	1.98%
<i>Mechanism-specific T2D-GRI scores</i>				
T2D-GRI Adiposity	0.88	0.28, 1.49	4.40×10^{-3}	0.09%
T2D-GRI Beta-Cell Function	0.90	0.74 1.07	1.05×10^{-24}	1.28%
T2D-GRI Insulin Sensitivity	0.92	0.56 1.28	8.08×10^{-7}	0.29%
T2D-GRI Other	0.90	0.56 1.25	4.84×10^{-7}	0.30%

β – increase in the probability of having diabetes associated with a unit increase in the genetic probability of having diabetes. A coefficient close to 1 indicates that the score derived from the external GWAS is appropriate and valid in the HRS sample. Partial – R^2 – partial variation explained by T2D-GRI from model adjusting for age at DNA collection, sex, and 6 genetic eigenvectors.

Table 3
Mendelian Randomization Estimates for the Effect of Type 2 Diabetes on Memory and Dementia Instrumented with T2D-GRI in HRS

	IV Estimated Effect of T2D on Memory [*]		IV Estimated Effect of T2D on logit dementia probability	
	β	95% Confidence Interval	β	95% Confidence Interval
<i>Overall T2D-GRI scores</i>				
T2D-GRI (39 SNPs)	0.02	-0.04 0.09	0.04	-0.92 1.01
61 SNPs	0.02	-0.04 0.07	0.03	-0.85 0.79
72 SNPs:	0.01	-0.04 0.07	-0.00	0.82 0.81
<i>Mechanism-specific T2D-GRI scores</i>				
T2D-GRI Adiposity	-0.07	-0.36 0.22	2.23	-2.12 6.59
T2D-GRI Beta-Cell Function	0.05	-0.03 0.13	-0.49	-1.70 0.73
T2D-GRI Insulin Sensitivity	-0.04	-0.21 0.14	1.59	-0.99 4.18
T2D-GRI Other	0.00	-0.16 0.17	0.21	-2.28 2.71

* 8,501 participants with valid measures of memory function were included.

** 8,403 participants with estimates for dementia probability were included.

The estimates reported in the table are the mean differences (β) of the linear regression analysis of memory score and logit dementia probability on the predicted risk of T2D (T2D-GRI) adjusted for age, sex, and six population eigenvectors.