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Alzheimer's disease and type 2 diabetes: shared genetic susceptibility?

John Hardy^{1,2}, Bart de Strooper^{1,3,4}, Valentina Escott-Price⁵

A PubMed search with the terms “diabetes and Alzheimer's disease” yields nearly 9,000 articles, suggesting an established link between the two common conditions. However, although Alzheimer's disease (AD) has been characterised as “type 3 diabetes” (1), no clear link has been demonstrated (2), so we decided to assess whether there was any shared genetic risk between the two conditions. A detailed description of our methodology is provided in the appendix.

The genetic correlation between the two traits shows no evidence for a shared genetic risk between diabetes and AD ($r_g = -0.058$, $SE = 0.04$), $p = 0.155$ between T2D (3) and AD (4) and $r_g = 0.02$ ($SE = 0.06$), $p = 0.728$ between T2D (3) and AD (5), the former despite the large proportion (74.8%) of shared samples from the UK Biobank). We found four regional correlations, after Bonferroni correction for the number of the genomic regions ($N = 2081$) from the input genome partition file. Only one correlation in the region on chromosome 2 was positive (chr2:43309247-44048346, see also *THADA* gene in Table 1), other three (chr14:90075441-92098486, chr22:44317416-44818986, chr8:95810772-96533604) were negative.

When we selected significant SNPs from one GWAS and Bonferroni corrected (study-wise) the corresponding SNPs from the other GWAS, then six AD significant loci were significant in diabetes, but with opposite direction of the association (Table 2). Out of T2D genome-wide significant loci, five loci were significant in AD, but only two in the same direction of association (*THADA* (chr 2) and *PLEKHA1* (chr 10)) (Table 1). *THADA* however has never reached genome-wide significance for AD. This and the positive *local* genetic correlation may indicate that the locus is pleiotropic, however we are hesitant to speculate without further evidence. *PLEKHA1* was reported as AD genome-wide significant gene in (4) for the first time,

when combining the discovery and the replication datasets. Overall, eight loci appear in both tables, but six (*HLA-DQB1*, *JAZF1*, *NDUFAF6*, *CELF1/SPI1*, *DOC2A*, *ACE*) show opposite directions of effect.

None of the SNPs are genome-wide significant in the other disease and those which are nominally significant are approximately evenly split in terms of the direction of their effect (i.e. there is no evidence for co-association). Out of 2147 significant SNPs found in GWAS in AD (4), 25% were also nominally significant in GWAS in type 2 diabetes. Limiting the analysis to AD GWAS index SNPs, which have also shown nominal replication in diabetes (N SNPs= 19), only 7 of them had the same direction of effects (appendix, Supplemental Table 1). All SNPs from the *APOE* region had opposite directions of effects between AD and type 2 diabetes. Out of 5881 GWAS significant T2D SNPs, 23.6% were also nominally significant in AD (4). Of them, looking at independent (index) SNPs only, 23 out 43 (53%) had opposite direction of effects (appendix, Supplemental Table 2). In particular, all SNPs from the *MHC* region were in the opposite direction. A similar pattern of associations' directionality was observed when comparing T2D with AD GWAS without shared samples from the UK Biobank (5), see appendix, Supplemental Table 3.

We also investigated genetic overlap by assessing whether polygenic risk score for type 2 diabetes had any association with pathologically confirmed AD. The polygenic risk score was not significantly associated with AD in the pathology confirmed sample of 1011 cases and 583 controls for all p-value thresholds, with PRS association p-value ranging from $p=0.01$ ($B_{PRS}=-0.137$ ($SE=0.05$)) when combining independent the 161 diabetes GWAS significant SNPs, till $p=0.0048$ ($B=-0.149$ ($SE=0.053$)), combining 65,788 independent T2D SNPs with $p<0.5$ (see appendix, Supplemental Table 4).

In this well-powered approach, we have failed to find convincing evidence for a genetic overlap between AD and type 2 diabetes. Although a shared genetic aetiology has been reported (6), in fact that study found that 57.3% of the shared SNPs have divergent risk alleles in the two diseases, similar to our findings. Alternative explanations for the widely assumed association between the two diseases must exist. The first explanation is that the association is simply wrong or is confounded by the acute effects of diabetes and high glucose

concentrations on cognitive performance, and the second is that both syndromes are independent downstream events of environmental factors, such as a sedentary lifestyle. In either case, the implication of the lack of association is that treatment strategies aimed at alleviating diabetes are unlikely to have a direct effect on the incidence of AD and the second is that it is unlikely to be fruitful to assess insulin resistance pathways as candidate pathways for AD pathogenesis.

Conflict of interest:

VEP and JH declare no conflict of interests. BDS has no direct conflict of interests with the results reported in this manuscript. He has however consulted for several major drug companies and is scientific founder of Augustin TX and Muna TX. He has a small amount of shares in Muna TX.

Data sharing statement:

The results in this paper are based upon publicly available data. The GWAS summary statistics for T2D (3) is available at <https://cnsgenomics.com/content/data>; AD (4) is available <https://www.ebi.ac.uk/gwas/studies/GCST90027158>; AD (5) is available at <https://www.niagads.org/datasets/ng00075>; the individual level genotype data for pathology confirmed sample is available via www.niagads.org.

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Table 1. Comparison of index AD GWAS significant SNPs (4) with T2D SNPs (3) which replicate after study-wise Bonferroni correction. SNPs in bold have the same direction of the effect size. SNPs in italic are in the region with significant SNPs after the study-wise Bonferroni correction.

SNP	CHR	BP (b37)	A1	A2	AD			T2D			Map
					B	SE	P	B	SE	P	
rs660895	6	32577380	G	A	-0.073	0.010	1.8E-12	0.078	0.009	1.0E-18	
rs67250450	7	28174986	C	T	-0.056	0.010	2.0E-08	0.056	0.009	2.6E-09	
rs4734295	8	96000919	G	A	0.049	0.008	2.0E-09	-0.023	0.007	0.002	ND
rs2293579	11	47440758	A	G	0.055	0.008	2.3E-11	-0.016	0.008	0.031	CE
rs12325539	16	30033633	C	T	-0.057	0.008	1.2E-11	0.037	0.008	4.6E-06	D
rs4311	17	61560763	T	C	-0.066	0.008	6.9E-16	0.029	0.008	0.0002	

Table 2. Comparison of index T2D GWAS significant SNPs (3) with AD SNPs (4) which replicate after study-wise Bonferroni correction. SNPs in bold have the same direction of the effect size. SNPs in italic are in the region with significant SNPs after the study-wise Bonferroni correction.

SNP	CHR	BP (b37)	A1	A2	T2D			AD			Map
					B	SE	P	B	SE	P	
rs17334919	2	43707385	T	C	-0.140	0.013	6.7E-28	-0.065	0.014	2.5E-06	
rs1063355	6	32627714	T	G	-0.071	0.008	3.7E-19	0.029	0.008	0.0004	
rs849135	7	28196413	G	A	0.100	0.007	1.0E-43	-0.023	0.008	0.005	
rs7845219	8	95937502	C	T	-0.042	0.007	4.5E-09	0.046	0.008	1.7E-08	ND
rs2421016	10	124167512	T	C	-0.046	0.007	1.5E-10	-0.038	0.008	3.3E-06	

Appendix.

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1. GWAS data sets

We used the latest GWAS summary statistics for type 2 diabetes (T2D) (62,892 T2D cases and 596,424 controls of European ancestry (1) and tested for genetic correlation with two Alzheimer's disease (AD) GWAS: first (2) with sample size 21,982 AD cases, and 41,944 cognitively normal controls, and second, the latest AD GWAS (3) with 39,106 clinically diagnosed AD cases, 46,828 proxy cases and 401,577 controls of European ancestry.

2. GWAS data analysis

MungeSumstats R package was used to harmonise the summary statistics data. As T2D contains the UK Biobank data we ought to use AD GWAS with (3) and without (2) UK Biobank participants. We run genetic correlation analysis with LD Score regression (4) and with SUPERGNOVA approach (5) (the latter reports local genetic correlation). Then we looked at the direct replication of AD GWAS significant SNPs in T2D (and vice versa) at least at the nominal significance level 0.05. When comparing the GWAS significant SNPs we have extracted all SNPs (with $p \leq 5 \times 10^{-8}$) in one study and matched them with all available SNPs in the other. Then we looked at SNPs which were significant at 5% level in the second study and reported the pair with the most GWAS associated SNP (which could be a proxy to the reported index GWAS significant SNP).

3. Polygenic Risk Scores

We assessed polygenic risk scores (PRS) generated with SNPs associated with T2D at a range of p-values thresholds (5×10^{-8} , 10^{-7} , 10^{-5} , 10^{-4} , 0.001, 0.05, 0.1 and 0.5) and tested them in an independent sample of AD pathology confirmed cases (N=1011) and controls (N=583) (9, 10). Prior to PRS calculation, the data was LD pruned, whilst keeping the most associated SNP in ($r^2=0.1$ in 1MB window).

Supplemental Table 1. Comparison of index AD GWAS significant SNPs (3) with T2D SNPs (1) which replicate at nominal significance level ($p=0.05$). SNPs in bold have the same direction of the effect size. SNPs in italic are in the region with significant SNPs after the study-wise Bonferroni correction.

SNP	CHR	BP (b37)	A1	A2	AD			T2D			Mapped gene
					B	SE	P	B	SE	P	
rs74490912	2	127846321	C	A	-0.106	0.010	2.8E-24	0.020	0.010	0.048	<i>BIN1</i>
rs875394	4	11011598	T	G	0.075	0.014	2.9E-08	-0.027	0.014	0.050	<i>CLNK/HS3ST1</i>
rs55695634	5	86299471	T	C	0.074	0.010	2.1E-13	-0.020	0.010	0.042	<i>COX7C</i>
<i>rs660895</i>	<i>6</i>	<i>32577380</i>	<i>G</i>	<i>A</i>	<i>-0.073</i>	<i>0.010</i>	<i>1.8E-12</i>	<i>0.078</i>	<i>0.009</i>	<i>1.0E-18</i>	<i>HLA</i>
<i>rs67250450</i>	<i>7</i>	<i>28174986</i>	<i>C</i>	<i>T</i>	<i>-0.056</i>	<i>0.010</i>	<i>2.0E-08</i>	<i>0.056</i>	<i>0.009</i>	<i>2.6E-09</i>	<i>JAZF1</i>
rs6971558	7	100079857	A	T	-0.071	0.009	1.0E-15	-0.018	0.009	0.033	ZCWPW1/NYAP1
<i>rs4734295</i>	<i>8</i>	<i>96000919</i>	<i>G</i>	<i>A</i>	<i>0.049</i>	<i>0.008</i>	<i>2.0E-09</i>	<i>-0.023</i>	<i>0.007</i>	<i>0.002</i>	<i>NDUFAF6</i>
<i>rs2293579</i>	<i>11</i>	<i>47440758</i>	<i>A</i>	<i>G</i>	<i>0.055</i>	<i>0.008</i>	<i>2.3E-11</i>	<i>-0.016</i>	<i>0.008</i>	<i>0.031</i>	<i>CELF1/SPI1</i>
rs1582763	11	60021948	A	G	-0.086	0.008	1.7E-24	-0.018	0.008	0.026	MS4A
rs527162	11	85715736	C	T	-0.095	0.010	2.6E-20	-0.021	0.010	0.035	PICALM
rs11218343	11	121435587	C	T	-0.165	0.021	1.0E-14	-0.071	0.020	0.0005	SORL1
rs36026988	14	92938382	C	T	-0.071	0.010	6.5E-13	-0.020	0.009	0.037	SLC24A4
rs7179399	15	59165527	T	C	-0.048	0.009	3.4E-08	-0.017	0.008	0.039	ADAM10
<i>rs12325539</i>	<i>16</i>	<i>30033633</i>	<i>C</i>	<i>T</i>	<i>-0.057</i>	<i>0.008</i>	<i>1.2E-11</i>	<i>0.037</i>	<i>0.008</i>	<i>4.6E-06</i>	<i>DOC2A</i>
rs17763086	17	43905481	G	T	-0.053	0.010	4.2E-08	0.018	0.009	0.041	<i>CRHR1</i>
<i>rs4311</i>	<i>17</i>	<i>61560763</i>	<i>T</i>	<i>C</i>	<i>-0.066</i>	<i>0.008</i>	<i>6.9E-16</i>	<i>0.029</i>	<i>0.008</i>	<i>0.0002</i>	<i>ACE</i>
rs440277	19	45361224	A	G	-0.132	0.009	2.5E-44	0.023	0.008	0.0076	<i>APOE</i>
rs718022	20	55003465	A	G	-0.114	0.015	9.2E-15	0.030	0.015	0.045	<i>CASS4</i>
rs2830510	21	28161146	C	T	0.049	0.009	3.6E-08	0.017	0.008	0.033	ADAMTS1

Supplemental Table 2. Comparison of index T2D GWAS significant SNPs (1) with AD SNPs (3) which replicate at nominal significance level ($p=0.05$). SNPs in bold have the same direction of the effect size. SNPs in italic are in the region with significant SNPs after the study-wise Bonferroni correction.

SNP	CHR	BP (b37)	A1	A2	T2D			AD			Mapped gene
					B	SE	P	B	SE	P	
rs12037222	1	40064961	A	G	0.060	0.009	1.5E-12	0.020	0.010	0.036	<i>MACF1</i>
rs12088739	1	51506886	G	A	-0.088	0.013	9.8E-12	-0.040	0.014	0.004	<i>MIR4421</i>
rs340883	1	214145706	T	C	0.051	0.007	1.2E-12	-0.019	0.008	0.020	<i>PROX1-AS1</i>
rs11127491	2	646145	T	C	-0.060	0.010	7.3E-10	0.021	0.011	0.045	<i>TMEM18</i>
rs780094	2	27741237	T	C	-0.069	0.007	5.2E-21	0.018	0.008	0.032	<i>GCKR</i>
rs17334919	2	43707385	T	C	-0.140	0.013	6.7E-28	-0.065	0.014	2.5E-06	<i>THADA</i>
rs243015	2	60588871	G	A	0.050	0.008	2.4E-11	-0.030	0.009	0.0005	<i>MIR4432HG</i>
rs840967	2	65701757	C	A	0.050	0.008	5.4E-10	0.018	0.008	0.031	<i>CEP68</i>
rs10929976	2	161147528	T	C	-0.056	0.009	2.3E-10	0.018	0.009	0.048	<i>RBMS1</i>
rs1899951	3	12394840	T	C	-0.112	0.011	1.6E-24	-0.034	0.013	0.007	<i>PPARG</i>
rs17361324	3	123131254	T	C	-0.082	0.008	3.1E-23	-0.020	0.010	0.036	<i>ADCY5</i>
rs11925227	3	170766618	A	G	-0.053	0.010	2.3E-08	0.029	0.011	0.006	<i>TNIK</i>
rs4689393	4	6287241	T	C	-0.082	0.007	3.4E-28	-0.016	0.008	0.048	<i>WFS1</i>
rs735949	4	185716232	C	T	-0.071	0.011	1.9E-11	0.026	0.012	0.024	<i>ACSL1</i>
rs3900856	5	55833892	A	G	0.114	0.019	7.4E-10	0.048	0.020	0.018	<i>C5orf67</i>
rs7756992	6	20679709	G	A	0.130	0.008	6.0E-62	-0.021	0.009	0.022	<i>CDKAL1</i>
rs1063355	6	32627714	T	G	-0.071	0.008	3.7E-19	0.029	0.008	0.0004	<i>HLA-DQB1</i>
rs853974	6	127068983	T	C	0.060	0.009	7.9E-12	0.021	0.009	0.021	<i>RPS4XP9</i>
rs849135	7	28196413	G	A	0.100	0.007	1.0E-43	-0.023	0.008	0.005	<i>JAZF1</i>
rs11774915	8	9188762	T	C	0.050	0.009	8.7E-09	-0.023	0.009	0.009	<i>LOC157273(TNKS)</i>
rs1073913	8	10611708	A	C	0.045	0.008	6.2E-09	-0.017	0.008	0.046	<i>PINX1</i>

rs17411031	8	19852310	G	C	-0.045	0.008	3.0E-08	0.022	0.009	0.018	LPL
rs2725370	8	30852826	T	C	0.050	0.009	3.7E-09	0.021	0.009	0.017	PURG
rs7845219	8	95937502	C	T	-0.042	0.007	4.5E-09	0.046	0.008	1.7E-08	NDUFAF6/TP53INP1
rs1333051	9	22136489	T	A	-0.149	0.011	1.3E-41	-0.029	0.012	0.013	CDKN2B-AS1
rs2488075	10	94490174	C	T	0.083	0.007	5.1E-30	0.016	0.008	0.050	HHEX
rs10128255	10	114742835	G	A	-0.109	0.008	6.5E-47	0.018	0.009	0.037	TCF7L2
rs2421016	10	124167512	T	C	-0.046	0.007	1.5E-10	-0.038	0.008	3.3E-06	PLEKHA1
rs5215	11	17408630	C	T	0.068	0.007	2.1E-20	0.017	0.008	0.040	KCNJ11
rs7929543	11	49351026	C	A	0.083	0.014	2.2E-09	0.036	0.015	0.014	TYRL
rs1157343	11	72429141	A	G	-0.048	0.008	2.7E-10	-0.018	0.009	0.035	ARAP1
rs1355064	11	92797691	G	A	0.061	0.010	1.6E-10	-0.020	0.010	0.049	MTNR1B
rs2650000	12	121388962	A	C	0.054	0.008	8.4E-13	-0.018	0.009	0.037	OASL
rs825476	12	124568456	C	T	-0.052	0.007	6.8E-13	-0.019	0.008	0.018	ZNF664/FAM101A
rs11635117	15	64112732	A	C	0.044	0.007	5.5E-10	0.018	0.008	0.032	USP3/HERC1
rs12910825	15	91511260	G	A	0.052	0.007	2.2E-12	0.029	0.008	0.0006	PRC1
rs7206790	16	53797908	G	C	0.080	0.007	3.4E-27	-0.017	0.008	0.041	FTO
rs8081417	17	3902650	A	T	0.053	0.008	2.8E-10	-0.019	0.009	0.036	ZZEF1
rs6963	17	40731597	A	T	0.050	0.009	5.4E-09	0.031	0.009	0.0007	STAT3/RETREG3
rs594398	17	46957696	G	C	-0.054	0.008	1.1E-11	0.017	0.008	0.032	UBE2Z
rs12970134	18	57884750	A	G	0.056	0.008	5.3E-12	-0.020	0.009	0.029	MC4R
rs73001065	19	19460541	C	G	0.101	0.015	1.1E-11	0.035	0.017	0.042	SUGP1/MAU2
rs4823182	22	44377442	G	A	0.048	0.008	3.4E-10	-0.019	0.009	0.027	SAMM50

Supplemental Table 3. Comparison of index T2D GWAS significant SNPs (1) with AD SNPs (2) which replicate at nominal significance level ($p=0.05$). SNPs in bold have the same direction of the effect size.

SNP	CHR	BP (b37)	A1	A2	T2D			AD			Mapped gene
					B	SE	P	B_AD	SE_AD	P_AD	
rs636083	1	39821681	C	T	0.049	0.008	2.6E-10	0.032	0.016	0.040	MACF1
rs17106184	1	50909985	A	G	-0.078	0.013	6.8E-10	-0.054	0.024	0.026	FAF1
rs7529073	1	214147889	C	T	-0.050	0.007	4.6E-12	0.035	0.014	0.013	RPS6KC1
rs1367173	2	43449385	T	C	-0.111	0.011	1.7E-22	-0.049	0.022	0.027	HAAO
rs7559813	2	65278023	T	C	-0.052	0.009	9.3E-09	-0.035	0.016	0.034	SLC1A4
rs9860730	3	64701146	G	A	-0.057	0.008	2.8E-13	-0.039	0.015	0.012	ADAMTS9
rs9844972	3	150097635	C	G	0.096	0.015	1.0E-10	-0.066	0.029	0.021	PFN2
rs1374910	3	185531661	T	C	0.111	0.015	7.1E-14	0.059	0.030	0.045	IGF2BP2
rs17086692	4	53134293	T	G	-0.047	0.008	2.5E-08	0.036	0.015	0.020	SPATA18
rs71624138	5	55870395	A	G	0.076	0.012	3.1E-10	0.047	0.023	0.041	C5orf67
rs4712540	6	20763171	G	A	-0.079	0.007	1.4E-27	0.030	0.014	0.037	CDKAL1
rs3095304	6	31092767	T	C	-0.060	0.011	2.1E-08	0.044	0.019	0.020	CDSN
rs1591805	6	126717064	G	A	0.047	0.008	1.6E-09	0.033	0.014	0.023	CENPW
rs2246012	6	131898208	C	T	0.053	0.009	2.4E-08	0.040	0.020	0.043	MED23
rs622217	6	160766770	C	T	-0.049	0.008	3.1E-10	0.030	0.014	0.034	SLC22A2
rs2191348	7	15064255	G	T	-0.065	0.007	3.4E-19	-0.032	0.014	0.025	DGKB
rs849135	7	28196413	G	A	0.100	0.007	1.0E-43	-0.044	0.014	0.002	JAZF1
rs7845219	8	95937502	C	T	-0.042	0.007	4.5E-09	0.046	0.014	0.001	NDUFAF6
rs3802177	8	118185025	A	G	-0.122	0.008	2.3E-52	-0.035	0.016	0.026	SLC30A8
rs7030641	9	22054040	C	T	-0.062	0.007	3.6E-17	-0.034	0.015	0.026	CDKN2B
rs290483	10	114915214	G	T	-0.065	0.008	8.2E-18	-0.030	0.015	0.047	TCF7L2

rs10510109	10	124120457	T	G	-0.046	0.008	3.9E-09	-0.050	0.014	0.0004	<i>BTBD16</i>
rs2074311	11	17421860	A	G	0.055	0.007	6.8E-14	0.032	0.014	0.025	<i>ABCC8</i>
rs11040291	11	49248150	T	C	0.077	0.014	3.6E-08	0.070	0.026	0.007	<i>FOLH1</i>
rs4275659	12	123447928	T	C	-0.044	0.008	2.0E-08	-0.046	0.016	0.003	<i>ABCB9</i>
rs17804744	13	80700707	C	T	-0.058	0.010	5.6E-09	0.039	0.018	0.033	<i>NDFIP2</i>
rs7183842	15	90400030	G	A	0.054	0.009	5.0E-10	-0.034	0.016	0.039	<i>C15orf38-AP3S2</i>
rs4783819	16	53816647	G	C	-0.069	0.008	2.8E-20	-0.032	0.015	0.029	<i>FTO</i>
rs77258096	16	75243772	A	C	-0.117	0.013	1.8E-18	0.057	0.024	0.016	<i>CTRB2</i>
rs2927311	16	81531230	G	C	-0.052	0.010	5.3E-08	0.046	0.017	0.007	<i>CMIP</i>
rs8081417	17	3902650	A	T	0.053	0.008	2.8E-10	-0.041	0.016	0.008	<i>ATP2A3</i>
rs2278524	17	4081975	A	G	0.058	0.008	3.0E-12	-0.037	0.016	0.019	<i>ANKFY1</i>
rs12941356	17	17716531	A	G	0.044	0.008	5.3E-08	-0.030	0.015	0.037	<i>SREBF1</i>
rs302864	17	56757584	A	G	0.071	0.013	2.5E-08	-0.056	0.026	0.033	<i>AC011195.2</i>
rs12970134	18	57884750	A	G	0.056	0.008	5.3E-12	-0.038	0.016	0.019	<i>PMAIP1</i>
rs12973258	19	19488718	C	T	0.053	0.010	4.9E-08	0.037	0.019	0.048	<i>MAU2</i>
rs10404527	19	46160703	A	G	0.057	0.009	4.6E-11	-0.033	0.016	0.042	<i>EML2</i>
rs6066138	20	45594711	A	G	-0.049	0.008	1.9E-09	-0.033	0.016	0.041	<i>EYA2</i>
rs7286205	22	30475154	A	G	-0.073	0.013	1.9E-08	0.056	0.026	0.033	<i>MTMR3</i>

Supplemental Table 4. T2D PRS (Polygenic risk score) prediction of AD case/control status in independent sample of pathology confirmed AD cases and controls.

P_T*	NSNPs	B	SE	p**
5e-8	161	-0.137	0.053	0.010
1e-7	181	-0.113	0.053	0.032
1e-5	426	-0.105	0.053	0.047
1e-4	861	-0.104	0.053	0.048
0.001	2222	-0.141	0.053	0.008
0.05	18153	-0.135	0.053	0.011
0.1	27374	-0.150	0.053	0.005
0.5	65788	-0.149	0.053	0.005

* P-value threshold for SNPs selection from the T2D GWAS.

**The analyses were performed with logistic regression adjusting for age at death, sex and 10 principal components.

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