



## Alleles that increase risk for type 2 diabetes mellitus are not associated with increased risk for Alzheimer's disease



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### ABSTRACT

Although epidemiological studies suggest that type 2 diabetes mellitus (T2DM) increases the risk of late-onset Alzheimer's disease (LOAD), the biological basis of this relationship is not well understood. The aim of this study was to examine the genetic comorbidity between the 2 disorders and to investigate whether genetic liability to T2DM, estimated by a genotype risk scores based on T2DM associated loci, is associated with increased risk of LOAD. This study was performed in 2 stages. In stage 1, we combined genotypes for the top 15 T2DM-associated polymorphisms drawn from approximately 3000 individuals (1349 cases and 1351 control subjects) with extracted and/or imputed data from 6 genome-wide studies (>10,000 individuals; 4507 cases, 2183 controls, 4989 population controls) to form a genotype risk score and examined if this was associated with increased LOAD risk in a combined meta-analysis. In stage 2, we investigated the association of LOAD with an expanded T2DM score made of 45 well-established variants drawn from the 6 genome-wide studies. Results were combined in a meta-analysis. Both stage 1 and stage 2 T2DM risk scores were not associated with LOAD risk (odds ratio = 0.988; 95% confidence interval, 0.972–1.004;  $p = 0.144$  and odds ratio = 0.993; 95% confidence interval, 0.983

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<sup>4</sup> Data used in the preparation of this article were obtained from the Genetic and Environmental Risk for Alzheimer's disease (GERAD1) Consortium. As such, the investigators within the GERAD1 consortia contributed to the design and implementation of GERAD1 and/or provided data but did not participate in analysis or writing of this report. A full list of GERAD1 investigators can be found in the acknowledgements section of this manuscript.

–1.003;  $p = 0.149$  per allele, respectively). Contrary to expectation, genotype risk scores based on established T2DM candidates were not associated with increased risk of LOAD. The observed epidemiological associations between T2DM and LOAD could therefore be a consequence of secondary disease processes, pleiotropic mechanisms, and/or common environmental risk factors. Future work should focus on well-characterized longitudinal cohorts with extensive phenotypic and genetic data relevant to both LOAD and T2DM.

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## 1. Introduction

Late-onset Alzheimer's disease (LOAD) and type 2 diabetes mellitus (T2DM) are both common conditions of the elderly individuals with striking commonalities. Epidemiological studies suggest patients with T2DM or borderline T2DM have a greater risk of LOAD (reviewed in Cheng et al., 2012; Kopf and Frolich, 2009; Vagelatos and Eslick, 2013) and increased risk of progression from preclinical dementia to LOAD (Velayudhan et al., 2010). Although contradictory results have also been reported, 2 recent meta-analyses (Cheng et al., 2012; Vagelatos and Eslick, 2013) report an aggregate relative risk of AD for people with diabetes of 1.5 (95% confidence interval [CI]: 1.2–1.8) and a pooled risk ratio adjusted for confounders of 1.57 (95% CI: 1.41–1.75).

There is also increasing evidence for impairment of insulin signaling as a critical and early event in LOAD. There are deficits in cerebrospinal fluid levels of insulin and brain insulin receptors in patients with LOAD (Craft et al., 1998). *Ex vivo* studies of human postmortem brain have demonstrated a markedly reduced response to insulin and basal elevation of insulin receptor substrate-1 phosphorylation, with these biomarkers progressively increasing from elderly normal individuals to LOAD cases independent of diabetes status (Talbot et al., 2012). Insulin has direct effects on human memory; both intravenous (Craft et al., 2003) and intranasal (Reger et al., 2008) administration of insulin improves memory in LOAD patients by acting directly on the brain without affecting peripheral insulin or glucose levels (for intranasal administration). Insulin receptors are widely distributed in the brain, particularly in the hippocampus and cortex, but most of the glucose uptake in the brain is insulin independent, highlighting the importance of central insulin as a trophic factor. There is also evidence that insulin signaling in the brain has effects on the key neuropathologic features of Alzheimer's disease: the accumulation of  $\beta$ -amyloid peptide and neurofibrillary tangles (De Felice et al., 2009). Finally, insulin and  $\beta$ -amyloid are both substrates for the insulin degrading enzyme and compete with each other (Qiu et al., 1998); whereas insulin and A $\beta$ 42 are direct competitors for the insulin receptor (Xie et al., 2002).

As a consequence of these epidemiological and biological associations, we have attempted to dissect the genetic comorbidity between the 2 disorders. We hypothesized that if T2DM has an etiological role in LOAD, for example, as a consequence of mediated pleiotropy, then T2DM genetic risk variants would also influence risk for LOAD. Genetic risk variants can be considered as an unbiased measure of liability not influenced by the potential multiple confounders present in longitudinal or cross-sectional studies. Because individual T2DM genetic risk variants have highly significantly but small effects on disease, we investigated the joint additive effect of risk variants by constructing genotype risk scores (GRS), which have shown to have a better predictive and discriminative value in T2DM compared with risk factors used (Andersson et al., 2013; Cornelis et al., 2009; Hivert et al., 2011; Lango et al., 2008; Meigs et al., 2008) and which give more power to capture associations. We used a 2 stage design. During the first stage, we constructed a GRS made of the top 15 T2DM-associated polymorphisms (Zeggini et al., 2008) and tested for associations with LOAD in >11,000 individuals with data drawn from a genotype study and 6

genome-wide (GWA) studies. We subsequently investigated the association of LOAD with an expanded T2DM score made of 45 well-established T2DM variants (Dupuis et al., 2010; Morris et al., 2012; Voight et al., 2010; Zeggini et al., 2008) drawn from the 6 GWA studies (>10,000 individuals). Results in both stages were combined in a meta-analysis. Contrary to expectation, we found no association between the T2DM-associated genotype risk scores and LOAD.

This is the first study to examine the genetic comorbidity between the 2 disorders using such a systematic approach. Given the increasingly high prevalence of both LOAD and T2DM in elderly populations, and the increasing interest in the insulin pathway as a target for clinical trials in dementia, clarifying the genetic comorbidity of these disorders is a priority.

## 2. Methods

### 2.1. Study design and participants

This study was performed in 2 stages and consisted of 3 study groups.

The first group was the Institute of Psychiatry (IOP) group (1574 LOAD cases and 1349 elderly control subjects) selected from 4 independent cohorts (744 cases and 865 controls from the Medical Research Council [MRC] cohort; 189 cases and 184 controls from the AddNeuroMed cohort (Lovestone et al., 2007); 332 cases and 161 controls from Northern Ireland cohort; and 309 cases and 139 controls from the Greek cohort), all genotyped for 15 well-established T2DM SNPs using the Sequenom platform.

The second group was the MRC-WTCCC2 group (3234 LOAD cases, 1175 controls, and 4989 population controls) consisting of 4 cohorts (3216 LOAD cases and 1165 controls from the Genetic and Environmental Risk for Alzheimer's disease cohort [GERAD1] consortium (Harold et al., 2009) genotyped on the Illumina 610-quad chip; 18 LOAD cases and 10 controls from the MRC Brain cohort, genotyped on the Illumina 666W-Quad chip; and 4989 population controls from the Wellcome Trust Case Control Consortium 2 publically available control cohorts ([www.wtccc.org.uk/cc2/](http://www.wtccc.org.uk/cc2/): the 1958 British Birth Cohort [WTCCC2 1958 BC] and UK Blood Service Collection [WTCCC2 NBS]), genotyped on the Illumina 1.2 M chip.

The third group was the ANM-ADNI group (483 cases and 299 controls) selected from 2 independent cohorts; 153 cases and 112 controls from the AddNeuroMed cohort and 330 cases and 187 controls from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database ([adni.loni.usc.edu](http://adni.loni.usc.edu)) both genotyped on the Illumina 610-Quad chip.

All LOAD cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) AD. All elderly controls were screened for dementia using the Mini Mental State Examination or the Alzheimer's Disease Assessment Scale-Cognition or were determined to be free from dementia at neuropathologic examination or had a Braak score of 2.5 or lower. All individuals used in the analysis excluding the WTCCC2 samples were older than 60 years.

Analysis was performed in 2 stages which contained overlapping samples (approximately 87%).

During stage 1, we used 11,679 individuals to test for the association of a GRS comprising of 15 well-established T2DM SNPs ( $p < 5 \times$

$10^{-8}$ ), which were identified by Zeggini et al. (2008) with LOAD. The 15 SNPs excluded rs9472138 and rs757210 SNPs which showed significant departures from Hardy Weinberg equilibrium. Stage 1 consisted of the IOP group (N = 2923), a subset of n = 8184 from the MRC-WTCCC2 group and a subset n = 572 from the ANM-ADNI group. We used a subset of 8184 individuals from the MRC-WTCCC2 group (reduced from 9398), because there were overlapping samples between GERAD1 cohort and the MRC cohort of the IOP group. We also used a subset of 572 individuals from the ANM-ADNI group (reduced from 782) to remove overlapping individuals from the AddNeuroMed cohort of the IOP group with genotype data.

Imputation took place for the groups with GWA data. Associations between the T2DM GRS and LOAD were sought for each of the 3 groups, and results were pooled using meta-analysis.

For stage 2, we investigated whether an expanded T2DM GRS based on additional T2DM SNPs, which were identified in GWAS and meta-analysis until 2012 (45 SNPs associated at  $p < 5 \times 10^{-8}$ ; Dupuis et al., 2010; Morris et al., 2012; Voight et al., 2010) was associated with LOAD. SNPs which failed to reach genome-wide significance in Morris et al. (2012) ( $p < 5 \times 10^{-8}$ ) were excluded. The SNPs chosen were identified in European populations. We additionally excluded variants in or near the FTO and MC4R genes because of their primary association with obesity. Finally, we excluded the risk variant in DUSP9 gene because it is located on the X-chromosome, and data were not available for all cohorts. To this end, we used the MRC-WTCCC2 group and the ANM-ADNI group and performed meta-analyses for each GRS. The design and stages of this study are presented in Fig. 1. A detailed account of the cohorts and samples used are found in Supplementary Methods 1 and Supplementary Tables 1 and 2, genotyping details are found in Supplementary Methods 2, and GWA quality control and imputation details are found in Supplementary Methods 3.

## 2.2. Genotype risk score construction and statistical analyses

Individuals with  $\geq 5\%$  missing SNPs in each score were excluded from analyses. GRS were constructed assuming that each SNP in the panel acts independently and contributes equally to the risk of LOAD in an additive model. Each SNP was weighted by the odds ratios (OR) or beta coefficient obtained from previous studies (Supplementary Table 3), and for each individual the number of

weighted risk alleles were summed. Because this produced a score of twice the sum of the coefficients (4.181 for stage 1 GRS and 9.026 for stage 2 GRS), all values in each GRS score were divided by the respective (twice) sum of coefficients (4.181 and 9.026) and multiplied with the maximum number of alleles in each score (30 and 90, respectively); to simplify interpretation and to standardize the score of those with missing SNPs to those with full data (Cornelis et al., 2009), Supplementary Table 3 presents the details of the SNPs used for the construction of the GRS.

## 2.3. Statistical analyses

### 2.3.1. Association of the GRS with LOAD

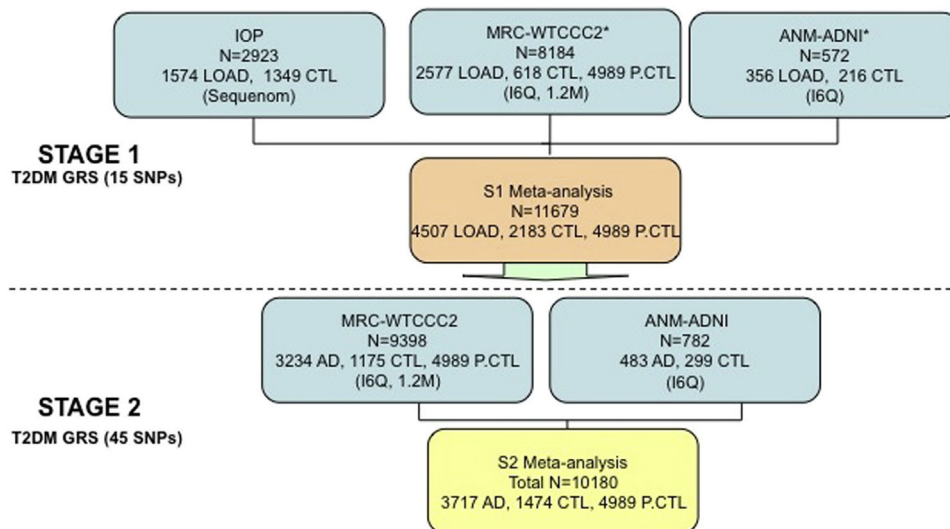
Logistic regression analyses were used to test for the association of GRS with LOAD. After adjusting for principal components and country of origin (Supplementary Methods 3.4). All analyses in the text are presented as a “per risk allele” odds ratio. Results in each stage were combined using inverse-variance fixed effects meta-analysis. All analyses were performed in STATA10 (Stata Statistical Software: Release 10. College Station, TX, USA: StataCorp LP).

### 2.3.2. Additional analyses

**2.3.2.1. Exclusion of population controls.** To avoid any technical confounding introduced by including the WTCCC2 cohorts which had no age information or were younger than 60 years and were genotyped on different platforms and at different times, we repeated logistic regression analyses excluding these population controls.

**2.3.2.2. Covariate adjustment.** Secondary models adjusting additionally for age at baseline visit, gender, and number of APOE  $\epsilon 4$  alleles were tested for association in the MRC group (excluding the population controls) and the ANM-ADNI group. Details on covariate adjustment can be found in Supplementary Methods 3.5.

**2.3.2.3. Information on T2DM.** Information on T2DM status and fructosamine levels measurements were available for a very small subset of the study. Association analyses between T2DM status and/or abnormal fructosamine levels and LOAD, between T2DM status and the T2DM GRS and exclusion of individuals diagnosed with T2DM are described in Supplementary Methods 3.6.



**Fig. 1.** Study design. Number of individuals and SNPs used in each stage of the study and information on the genotyping and/or imputation platform. \* indicates excluding overlapping samples in IOP. Abbreviations: 1.2 M, Illumina 1.2 M chip; CTL, control; GWA, genome-wide association; I6Q, Illumina 610 chip; IOP, Institute of Psychiatry; LOAD, late-onset Alzheimer's disease; P.CTL, population control; S1, stage 1; S2, stage 2; SNP, single-nucleotide polymorphism; T2DM, type 2 diabetes mellitus.

### 3. Results

#### 3.1. Expected effect size for the association between GRS and LOAD

Based on published studies we predicted that T2DM is associated with an increased risk for LOAD (Relative Risk [RR] = 1.5, 95% CI: 1.20–1.77) (Cheng et al., 2012) (Supplementary Fig. 1B) and that each GRS allele is associated with an increased risk of T2DM between RR = 1.06 (95% CI: 1.03–1.08) (Andersson et al., 2013) and RR = 1.12 (95% CI: 1.07–1.17) (Meigs et al., 2008) (Supplementary Fig. 1A). If the GRS is associated with LOAD through its association with T2DM, that is, as a consequence of mediated pleiotropy, then using a triangulation approach, we would expect that the association of the GRS with LOAD (Supplementary Fig. 1C) would be between OR = 1.024 (95% CI: 1.005–1.045) and OR = 1.047 (95% CI:

1.012–1.094) per risk allele. Power calculations showed our study had more than 75% power to capture odds ratios as small as 1.02 per risk allele.

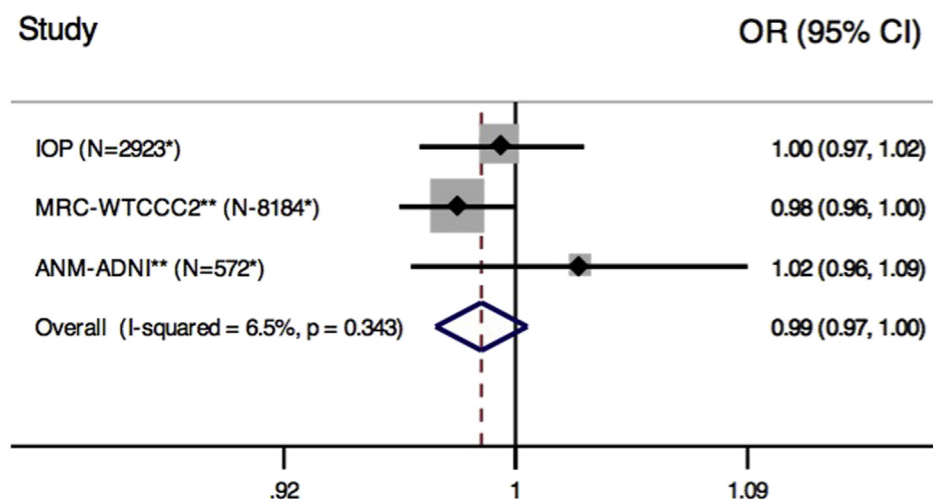
#### 3.2. Stage 1 results

Results of the stage 1 meta-analysis showed no association between the T2DM GRS and increased risk of LOAD (OR = 0.988, 95% CI: 0.972–1.004,  $p = 0.144$  per allele) (Fig. 2).

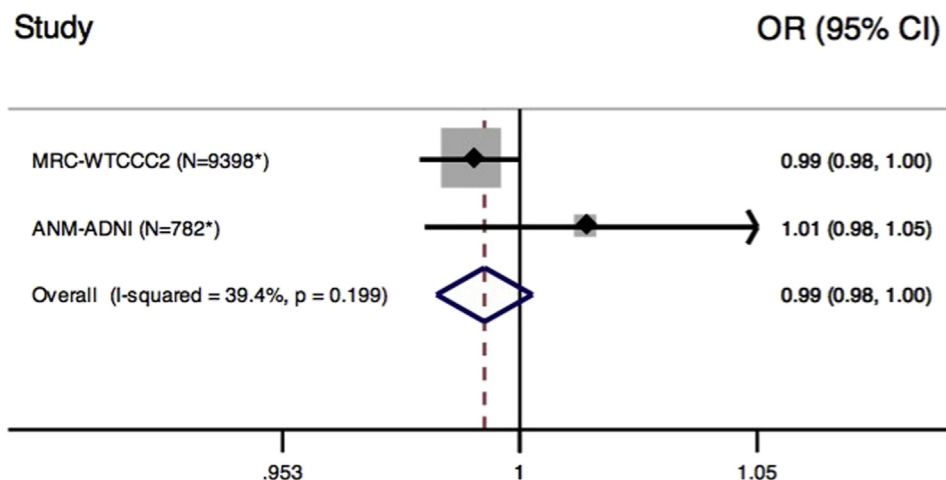
#### 3.3. Stage 2 results

Similarly to stage 1, we observed no association between the extended 45 SNPs T2DM GRS and increased LOAD risk (meta-analysis: OR = 0.993, 95% CI: 0.983–1.003,  $p = 0.149$  per allele) (Fig. 2).

#### Stage 1 (15 SNPs, N=11679\*)



#### Stage 2 (45 SNPs, N=10180\*)



### Odds ratio for LOAD per GRS allele

**Fig. 2.** Association of weighted T2DM GRS with LOAD in stage 1 and stage 2 data sets. OR represent the association of each GRS with LOAD per allele. \* indicates maximum and \*\* indicates excluding overlapping samples in the IOP group. Abbreviations: CI, confidence interval; GRS, genotype risk score; IOP, Institute of Psychiatry; LOAD, late-onset Alzheimer's disease; OR, odds ratio; T2DM, type 2 diabetes mellitus.

### 3.4. Secondary analyses

The results of the analyses with population controls excluded were similar to those including all controls (Supplementary Table 4 and Supplementary Table 5). Logistic regression analyses adjusting for age, gender, and number of APOE  $\epsilon$ 4 alleles (excluding population controls from the MRC-WTCCC2 cohort) produced identical results (Supplementary Tables 6 and 7). Association between T2DM status/abnormal fructosamine levels and LOAD, between T2DM GRS and T2DM status and exclusion of T2DM individuals from analyses are described in Supplementary Results 1 and 2.

## 4. Discussion

T2DM is reported to be a risk factor for LOAD but the biological basis of this relationship is not well understood; in this study, we have examined their shared genetic determinants with the hypothesis that T2DM has an etiological role in LOAD as a consequence of mediated pleiotropy. This relationship between dementia or AD and type 2 diabetes is of considerable interest, both for basic and clinical scientist and is the subject of much disparate research approaches. We have demonstrated that a genotype risk score for T2DM was not associated with an increased risk of LOAD in a large case-control study. Our findings contrast to previously published evidence for an increased risk of LOAD associated with T2DM status and suggest that alternative explanations may be required to elucidate the observational associations between T2DM and LOAD such as shared common environmental risk factors as well as pleiotropic mechanisms.

### 4.1. Strengths and weaknesses

One of the main strengths of our approach is that we used 45 genetic variants combined into a genotype risk score to test for a complex association between these disorders. The loci used for the construction of the GRS were identified in European population GWAs and meta-analyses until 2012 to be associated with T2DM at  $p < 5 \times 10^{-8}$  (Dupuis et al., 2010; Morris et al., 2012; Voight et al., 2010) and excluded variants in or near the FTO and MC4R genes because of their primary association with obesity, as well as the risk variant in DUSP9 gene because data were not available for all cohorts. Taken into consideration, the association from observational studies between T2DM and LOAD and the published association of genotype risk scores with T2DM, our study was well powered (>75% power) to capture odds ratios as small as  $OR = 1.02$  per risk allele if the association with LOAD is mediated through the T2DM GRS. This would correspond to the GRS being associated with an increased risk of T2DM of 1.05 per risk allele. In fact, the stage 2 GRS was associated with a larger increased risk for T2DM (Supplementary Results 2: meta-analysis  $OR = 1.070$ , 95% CI: 1.025–1.117,  $p = 0.002$ ) even in the small subset of subjects with T2DM information, indicating that this GRS had enough power to capture weak associations. As these power calculations are based on the association between the GRS and disease “per risk allele,” the power to capture associations for those individuals at the highest quartiles of the GRS distribution increases dramatically.

Investigating the genetic comorbidity of 2 disorders when trying to delineate their observed epidemiological associations overcomes biases found in nongenetic studies such as confounding and reverse causation, because the effects of the genetic variants are more likely to reflect lifelong exposure to T2DM risk. We acknowledge that we have only used the top 45 candidates associated with T2DM with  $p < 5 \times 10^{-8}$  in GWA and meta-analyses, published until August 2012. To minimize pleiotropic effects we also excluded alleles associated with T2DM through obesity, and we have preferentially

included those which are associated with T2DM through changes in insulin production and/or secretion and glucose homeostasis. It is clear that the alleles used here only represent a proportion of the risk alleles for T2DM and other new candidates have and will be discovered and methods that use the full set of alleles will provide more power although these require access to genotype data for both diseases. However, the variants we have selected explain more than 5.2% of the disease variance assuming a T2DM prevalence of 8% (compared with 5.7% explained by the 63 autosomal SNPs reported by Morris et al., 2012) and include most of those previously used in T2DM genetic risk score analyses (Andersson et al., 2013; Cornelis et al., 2009; Hivert et al., 2011; Lango et al., 2008; Meigs et al., 2008). A limitation of our study was the lack of information on T2DM status. A better approach to establish the causal association between T2DM and LOAD would be to use a large data set with information on both T2DM and LOAD endophenotypes and a full instrumental variable approach. Although T2DM information on a subset of our sample was available, it was too small to capture the small effect size expected (Supplementary Methods 3.6, stage 1  $N = 1431$ ; stage 2  $N = 1053$  for MRC subjects and  $N = 209$  ANM subjects of which 10% or less were diagnosed with T2DM in both stages).

Another limitation of our study was that, although no association was observed between the GRS and age in cases or controls suggesting no mortality effect, LOAD patients were older than controls, and this may have introduced survival bias. Furthermore, individuals in the MRC cohort were overall older compared with those of the ANM and ADNI cohorts. We have also included approximately 6000 population controls, approximately 3000 of which were <60 years and could therefore develop AD in the future and approximately 3000 of which had no age information. However, when we repeated analyses excluding the population controls results were essentially identical (Supplementary Tables 4 and 5).

We must also take into consideration that case-control studies have the potential for selection or ascertainment biases in the inclusion of cases or controls, potentially as a consequence of T2DM diagnosis. There are however currently no large well-characterized prospective LOAD and T2DM cohorts available and analyses would have to be restricted to a few hundred subjects with reduced statistical power to capture any associations. Strength of our large case-control study is that diagnosis of AD is standardized and performed under a research setting. For a proportion of cases and cognitively normal elderly controls diagnosis is confirmed by pathologic examination; notably, neuropathologic studies of cohorts investigating the relationship between T2DM and LOAD risk have not consistently found an association of T2DM with characteristic AD pathology (Alafuzoff et al., 2009 and reviewed in Vagelatou and Eslick, 2013) and a recent study investigating the association of serial serum measures of glucose intolerance and insulin resistance with AD pathology also found no association with AD pathology (Thambisetty et al., 2013).

In conclusion, our study does not provide evidence for substantial shared genetic determinants between the 2 disorders, and therefore, alternative explanations are required to explain the observed epidemiological association. However, when attempting to interpret our findings, it is important to note that we investigated genetic variants that increase risk for T2DM rather than actual clinical status and that the proportion of T2DM variance explained by genes estimated from twin studies is around 40% (Almgren et al., 2011). More variance is explained by well-established environmental risk factors which are also risk factors for LOAD (reviewed in De Felice, 2013). It may therefore be that environmental comorbidity explains, at least partly, the observed epidemiological and biochemical associations and it has been suggested that this could happen through the triggering of inflammatory processes which are related to insulin resistance (De Felice, 2013). Additionally,

environmental risk factors could also interact with T2DM to modify the risk of LOAD such as has been reported, for example, for vascular risk factors (reviewed in [Vagelatos and Eslick, 2013](#)). Finally, because beta amyloid pathology and metabolic changes precede dementia potentially by decades ([Jack et al., 2009](#)), it may be that T2DM could be a metabolic consequence rather than a cause of AD.

#### 4.2. Conclusions

Overall, the lack of the association between T2DM genotype risk scores and LOAD observed here does not support the hypothesis that T2DM genetic liability is associated with elevated LOAD risk and that the observed epidemiological associations require another explanation. Future work should involve the analysis of large well-characterized longitudinal cohorts with extensive phenotypic, genetic, and epidemiological data relevant to both LOAD and T2DM.

#### Disclosure statement

The authors declare that they have no competing interests.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.neurobiolaging.2014.07.023>.

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