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### Insulin resistance

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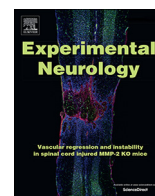
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## Research paper

# Insulin resistance: Genetic associations with depression and cognition in population based cohorts

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## ABSTRACT

Insulin resistance, broadly defined as the reduced ability of insulin to exert its biological action, has been associated with depression and cognitive dysfunction in observational studies. However, it is unclear whether these associations are causal and whether they might be underpinned by other shared factors. To address this knowledge gap, we capitalized on the stability of genetic biomarkers through the lifetime, and on their unidirectional relationship with depression and cognition. Specifically, we determined the association between quantitative measures of cognitive function and depression and genetic instruments of insulin resistance traits in two large-scale population samples, the Generation Scotland: Scottish Family Health Study (GS: SFHS;  $N = 19,994$ ) and in the UK Biobank ( $N = 331,374$ ). In the GS:SFHS, the polygenic risk score (PRS) for fasting insulin was associated with verbal intelligence and depression while the PRS for the homeostasis model assessment of insulin resistance was associated with verbal intelligence. Despite this overlap in genetic architecture, Mendelian randomization analyses in the GS:SFHS and in the UK Biobank samples did not yield evidence for causal associations from insulin resistance traits to either depression or cognition. These findings may be due to weak genetic instruments, limited cognitive measures and insufficient power but they may also indicate the need to identify other biological mechanisms that may mediate the relationship from insulin resistance to depression and cognition.

## 1. Introduction

Insulin resistance (INS-R) is broadly defined as the reduced biological action of insulin at its target tissues. INS-R results in chronic hyperglycemia and dyslipidemia characterised by high levels of total cholesterol and triglycerides, and low levels of high-density lipoprotein (HDL) (Li et al., 2014). INS-R and dyslipidemia are also major components of the metabolic syndrome (Alberti and Zimmet, 1998; Alberti et al., 2009; Balkau and Charles, 1999; Grundy et al., 2005). INS-R and

the associated dyslipidemia are major risk factors for cardiovascular disease and for cardiovascular adversity in type 2 diabetes (T2D) and obesity (Alberti et al., 2009). In addition, insulin has significant functions within the brain (Fateme and Cory, 2013) where it is involved in biological pathways relevant to neuronal survival (Mielke et al., 2006; Valenciano et al., 2006), dendritic outgrowth (Cheng et al., 2003; Govind et al., 2001), synaptic plasticity (Skeberdis et al., 2001; Wang et al., 2003) and cognition, particularly learning and memory (Dou et al., 2005; Wickelgren, 1980).

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Accumulating evidence from observational studies suggests that INS-R, and the associated dyslipidemia, influence cognition and psychopathology. Studies of patients have shown that T2D is associated with significant cognitive dysfunction and increased risk of vascular dementia and Alzheimer's disease (Biessels et al., 2006; Cooper et al., 2015; Cosway et al., 2001; Leibson et al., 1997; Ott et al., 1999; Palta et al., 2014; Peila et al., 2002; Riederer et al., 2017; Sadanand et al., 2016). Studies of general population cohorts have found that lower general cognitive ability at age 11 years is associated with higher risk of developing T2D in middle adulthood while higher polygenic risk scores for T2D are inversely associated with educational attainment (Hagenaars et al., 2016; Mottus et al., 2013). In older adults, the associations between cognitive task underperformance and age-related cognitive decline appear to be weak for the polygenic risk for T2D alone (Luciano et al., 2014) and INS-R traits (Lampert et al., 2009; Young et al., 2006) but become more pronounced when both INS-R and dyslipidemia are present (Yates et al., 2012). Collectively, these studies link abnormalities in glycaemic control to dysfunction in global intellectual function and in specific cognitive domains reflecting verbal fluency, processing speed, memory and cognitive flexibility (Benedict et al., 2012; Ekblad et al., 2015; Palta et al., 2014).

A parallel line of research has examined the relationship between INS-R and psychopathology. Meta-analyses indicate that depression increases the risk for the subsequent development of INS-R (Pan et al., 2012; Penninx, 2017) and T2D (Knol et al., 2006; Mezuk et al., 2008). INS-R alone is a rather modest predictor of depressive symptoms or major depressive disorder (MDD) (Kan et al., 2013) but the association with depression becomes more robust, both cross-sectionally and longitudinally, when significant dyslipidaemia is also present (Marijnissen et al., 2017; van Reedt Dortland et al., 2010; Vogelzangs et al., 2011; Vogelzangs et al., 2014).

The relationships between INS-R, cognition and depression are likely to involve diverse and currently poorly understood biological mechanisms. For example, previous literature implicates low grade inflammation (Liu et al., 2012) as well as activation of the hypothalamic–pituitary–adrenocortical (HPA) axis and of the sympathetic nervous system (Chrousos, 2000; Weber-Hamann et al., 2002). Lifestyle choices and health maintenance decisions are also likely to play a significant role. Both depression and INS-R have been linked to higher caloric intake and obesity (Grossniklaus et al., 2012; Luppino et al., 2010; Preiss et al., 2013) and to low rates of exercise (Golden et al., 2008; Kontinen et al., 2010; Vallance et al., 2011). Antidepressant medications, which are the standard pharmacological treatment for depression, are also known to induce weight gain and metabolic dysregulation (Hiles et al., 2016; Serretti and Mandelli, 2010). Disambiguating the contribution of INS-R to depression and cognition in the context of this complex background remains a major challenge.

We sought to advance our understanding of the causality of INS-R for depression and cognition by capitalizing on the lifetime stability of genetic biomarkers and their unidirectional relationship with clinical and cognitive phenotypes. To maximize statistical power and generalizability, we used measures of depression and cognition from two large genotyped population samples, the Generation Scotland: Scottish Family Health Study (GS:SFHS;  $N = 19,994$ ) and the UK Biobank ( $N = 331,374$ ). This allowed us to employ polygenic profile scoring (Purcell et al., 2009) and inverse-variance weighted (IVW) Mendelian Randomization (MR) (Bowden et al., 2015; Davey Smith and Hemani, 2014; Smith and Ebrahim, 2004) to test genetic associations between INS-R related traits, depression and cognition. We found that the polygenic risk score (PRS) for fasting insulin was associated with verbal intelligence and depression while the PRS for homeostasis model assessment of insulin resistance (HOMA-IR) was associated only with verbal intelligence. However, the MR analyses did not provide evidence for causal associations from INS-R traits to either cognition or depression. It is possible that methodological issues such as weak genetic instruments, limited cognitive measures and insufficient power may have

contributed to these results. Conversely, the associations of INS-R to depression and cognition may not be causal despite some degree of genetic overlap. This study therefore points to the need to extend the scope of research in this field to examine the mediating roles of other biological mechanisms.

## 2. Materials and methods

### 2.1. Cohorts

Genetic, clinical, and cognitive data were extracted from two large-scale population-based cohorts: the Generation Scotland: The Scottish Family Health Study (GS:SFHS) and the UK Biobank.

#### 2.1.1. Generation Scotland: the Scottish Family Health Study (GS:SFHS)

The GS:SFHS ([www.generationscotland.co.uk](http://www.generationscotland.co.uk)) is a family- and population-based study consisting of 23,690 participants recruited through 125 general medical practices across Scotland (Smith et al., 2006; Smith et al., 2013). Genome-wide genotyping data, depression status and measures of logical memory, digit symbol coding, verbal fluency, and verbal intelligence were available for 19,994 individuals (11,773 females) aged 18–99 years (mean age = 47.41 years, SD = 14.98) (Hagenaars et al., 2016; Marioni et al., 2016; Smith et al., 2013; Zeng et al., 2016). A broad definition of depression was based on participants' responses to a single question as to whether they had ever been affected with depression (Zeng et al., 2016). The prevalence of self-reported lifetime depression in this sample was 10%. Cognition was assessed using the logical memory and digit symbol coding subtests of the Wechsler Memory Scale III (Wechsler, 1997), the Controlled Oral Word Association Test (COWAT) (Benton and Hamsher, 1976) and the Mill Hill vocabulary test for senior and junior synonyms combined (Raven, 1958), a test designed to measure verbal intelligence. The quality control processes relating to the genetic, clinical and cognitive data have been described in full elsewhere (Smith et al., 2013; Zeng et al., 2016). Ethical approval for GS:SFHS was granted by the Tayside Research Ethics Committee (reference 05/S1401/89). All participants provided written informed consent.

#### 2.1.2. UK Biobank

The UK Biobank ([www.ukbiobank.ac.uk](http://www.ukbiobank.ac.uk)) is a population-based cohort that has detailed health information and biological measures for 501,726 individuals recruited from across the UK (Bycroft et al., 2018). The genetic and phenotypic data used in the current study were available for 331,374 unrelated individuals (177,775 females) aged 39–73 years (mean age = 57.2 years, SD = 8.1). Individuals with probable Major Depressive Disorder (MDD) were self-identified based on responses to questions about current and lifetime symptoms and diagnosis of depression (Howard et al., 2018). The prevalence of this depression phenotype was 17.4%. Cognitive function was measured using the symbol digit substitution score (UK Biobank Field ID 20159), reaction time (UK Biobank Field ID 20023), numeric memory score (UK Biobank Field ID 20240), and trail making test (mean of UK Biobank Fields 20,156 and 20,157). Detailed information regarding the depression and cognitive variables available within UK Biobank has been published previously (Hagenaars et al., 2016; Howard et al., 2018). The quality control processes relating to the data analysed here have also been described in detail elsewhere (Howard et al., 2018; Luciano et al., 2018). The UK Biobank study was approved by the National Health Service Research Ethics Service (approval letter dated 17th June 2011, reference: 11/NW/0382). The analyses presented here were conducted under UK Biobank application 4844.

### 2.2. Insulin-resistance related traits

The euglycemic insulin clamp (Matsuda and DeFronzo, 1999) and the glucose tolerance tests (Bergman et al., 1987) are considered the

gold standard methods for the measurement of INS-R in research, but their use is cumbersome in clinical practice and infeasible in large, population-based research studies. Here we consider three reliable surrogate measures: fasting insulin (Laakso, 1993), fasting glucose and the homeostasis model assessment of insulin resistance (HOMA-IR) (Matthews et al., 1985), which is based on the dynamic relationship between fasting glucose and corresponding insulin levels. We considered four further traits, HDL cholesterol, Low-density lipoprotein (LDL) cholesterol, triglycerides and total cholesterol, which are components of dyslipidaemia associated with INS-R (Li et al., 2014). In total, we focus on seven, genetically overlapping traits, three representing changes in glycaemic control and four representing dyslipidaemia (Bulik-Sullivan et al., 2015).

### 2.3. Computation of polygenic risk scores in the GS:SFHS

Pleiotropy reflects the overlap between the genetic architecture of two or more traits (Solovieff et al., 2013) and can be assessed using data from single-nucleotide polymorphism (SNP) genotyping. Polygenic profile scoring (Purcell et al., 2009) uses summary data from genome-wide association studies (GWAS) to test whether genetic liability to a particular trait is associated with another phenotype. Here we examined whether genetic liability, expressed as Polygenic Risk Scores (PRS), to the seven INS-R traits described above, is associated with the measures of cognition and depression available in 19,994 individuals from the GS:SFHS. Specifically, polygenic risk scores were based on GWAS results for HOMA-IR (Dupuis et al., 2010), fasting glucose (Dupuis et al., 2010), fasting insulin (Dupuis et al., 2010), HDL cholesterol (Willer et al., 2013), Low-density lipoprotein (LDL) cholesterol (Willer et al., 2013), triglycerides (Willer et al., 2013) and total cholesterol (Willer et al., 2013). Quality controlled autosomal SNPs in GS:SFHS were entered in PRSice v1.25 (Euesden et al., 2015) to compute the PRS of each trait at five SNP set  $P$ -value threshold cutoffs of  $\leq 0.01$ ,  $\leq 0.05$ ,  $\leq 0.1$ ,  $\leq 0.5$  and  $\leq 1$  from the corresponding GWAS summary statistics.

### 2.4. Statistical analyses

#### 2.4.1. Polygenic risk score analyses in the GS:SFHS

We implemented mixed linear model analyses in ASReml-R, to test the association between the PRS of the seven INS-R related traits to cognition and depression in the GS:SFHS; age, sex, the first four multidimensional scaling components to control population stratification, and each of the PRS in turn were fitted as fixed effects. To control for relatedness in the sample, the pedigree structure was fitted as a random effect by creating the inverse of a relationship matrix using pedigree kinship information.  $P$ -values for fixed effects fitted in the model were calculated using Wald's conditional  $F$ -test. After Bonferroni correction for multiple testing, the threshold of significance for the five SNP sets (corresponding to the 5 threshold cut-offs) and the seven INS-R related traits was set at  $P < 1.4 \times 10^{-3}$  [ $0.05/(5 \times 7)$ ].

We note that Richardson et al. (2019) have already published a detailed atlas of the associations between multiple PRS with numerous diverse traits in the UK Biobank, including those of interest to this paper.

#### 2.4.2. Mendelian randomization in the GS:SFHS and UK Biobank

MR exploits the random assignment of genotypes at birth and their stability throughout the lifetime to overcome limitations relating to residual confounding (measured or unmeasured) and reverse causation (Bowden et al., 2015; Davey Smith and Hemani, 2014; Smith and Ebrahim, 2004). MR analyses use genetic variants to assess causal relationships between exposures (here INS-R related traits) and outcomes (here depression and cognition) (Fig. 1). MR analyses were conducted separately in the GS:SFHS and UK Biobank. As instrumental variables for INS-R we used the 53 SNPs (Supplementary Table S1) defined by

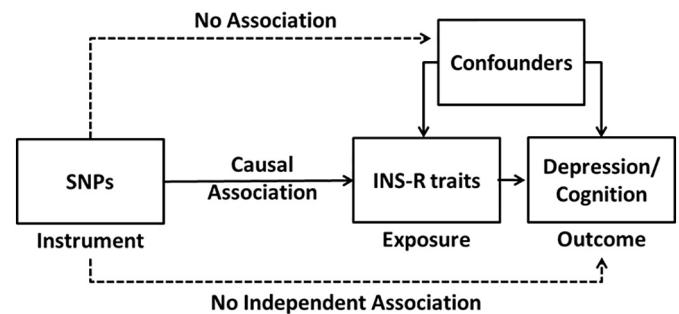


Fig. 1. Model for two-sample Mendelian randomization study. Mendelian randomization can be used to test if the exposure (insulin resistance) causally influences the outcome (depression and cognition) by using instrumental genetic variables (genome-wide significant SNPs) associated with the exposure that are unrelated to potential confounders and only affect the outcome via the exposure.

Lotta and colleagues (Lotta et al., 2017). Lotta and colleagues used all SNPs independently-associated with higher fasting insulin adjusted for body mass index [from up to 108,557 participants of the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC; <https://www.magicinvestigators.org>)] and lower HDL cholesterol and higher triglycerides [from up to 188,577 participants of Global Lipids Genetics Consortium (GLGC; <http://lipidgenetics.org>)]. For fasting glucose, fasting insulin, triglycerides, HDL, LDL, and total cholesterol we used significant GWAS hits available in the MR-Base GWAS catalogue (Hemani et al., 2018) (detailed in Supplementary Table S2). Depression and cognitive measures, as defined in 2.1, were used as outcome variables. All two-sample MR analyses were performed using the MR-Base R package (“TwoSampleMR”) version 0.4.8 (<https://github.com/MRCIEU/TwoSampleMR>) using inverse variance weighted (IVW) method and MR-Egger intercept tests. The IVW method is based on a regression of the exposure and outcome genetic variant vectors with the intercept constrained to zero, as described by Burgess and colleagues (Burgess et al., 2013). In total, 10 two-sample MR tests were performed and the threshold for significance was set at  $P < 5 \times 10^{-3}$  ( $0.05/10$ ) following Bonferroni correction for multiple testing.

## 3. Results

### 3.1. Polygenic risk score analyses in the GS:SFHS

In the GS:SFHS, at  $P < 1.4 \times 10^{-3}$ , the risk of depression was positively associated with higher PRS for fasting insulin while verbal intelligence (assessed with the Mill Hill Vocabulary test) was associated with the PRS for fasting insulin and for HOMA-IR. At the nominal threshold of statistical significance ( $P < .05$ ), additional associations were found between depression and the PRS for HOMA-IR. At the same level, the PRS for HOMA-IR was associated with processing speed (assessed with the digit symbol substitution task), while verbal intelligence was associated with the PRS for triglycerides and fasting glucose. The results of all the PRS analyses in the GS:SFHS are described in Table 1.

According to Richardson et al. (2019; [http://mrcieu.mrsoftware.org/PRS\\_atlas/](http://mrcieu.mrsoftware.org/PRS_atlas/)), in the UK Biobank depression and intelligence were associated with all the INS-R polygenic risk scores; these results can be accessed at [http://mrcieu.mrsoftware.org/PRS\\_atlas](http://mrcieu.mrsoftware.org/PRS_atlas)

### 3.2. Mendelian randomization in the GS:SFHS and UK Biobank

The MR analyses provided no evidence of any significant ( $P < 5 \times 10^{-3}$ ) causal associations from any INS-R related trait to cognition and depression in either GS:SFHS or UK Biobank (Supplementary Tables S3–S9).



**Table 1**Polygenic risk score analysis of the seven INS-R traits on the depression and cognition in GS:SFHS ( $N = 19,994$ ) cohort.

Predicted Trait	Polygenic predictor	Cutoff *	Beta	s.e.	P-value	VarExp	Significant ( $P < .0014$ )	Nominally significant ( $P < .05$ )
Depression	HDL	1	-0.010378	0.007487	0.165714	1.08E-04	No	No
Depression	LDL	0.5	0.011319	0.007625	0.137723	1.28E-04	No	No
Depression	Total cholesterol	0.5	0.005902	0.007522	0.43266	3.48E-05	No	No
Depression	Triglycerides	1	0.01118	0.007793	0.151408	1.25E-04	No	No
Depression	Fasting glucose	0.5	-0.009554	0.007507	0.203142	9.13E-05	No	No
<b>Depression</b>	<b>Fasting insulin</b>	<b>1</b>	<b>0.024652</b>	<b>0.00752</b>	<b>0.001045</b>	<b>6.08E-04</b>	<b>Yes</b>	<b>Yes</b>
Depression	HOMA-IR	1	0.018765	0.007537	0.012783	3.52E-04	No	Yes
Digit symbol coding	HDL	0.01	0.009852	0.00644	0.126037	9.71E-05	No	No
Digit symbol coding	LDL	0.5	-0.007372	0.006594	0.263613	5.43E-05	No	No
Digit symbol coding	Total cholesterol	0.05	-0.002855	0.006469	0.658976	8.15E-06	No	No
Digit symbol coding	Triglycerides	1	-0.016496	0.006729	0.014224	2.72E-04	No	Yes
Digit symbol coding	Fasting glucose	0.05	-0.00782	0.006482	0.227695	6.11E-05	No	No
Digit symbol coding	Fasting insulin	1	-0.018656	0.006491	0.00405	3.48E-04	No	Yes
Digit symbol coding	HOMA-IR	1	-0.018927	0.006501	0.003597	3.58E-04	No	Yes
Logical memory	HDL	1	0.006623	0.007268	0.36217	4.39E-05	No	No
Logical memory	LDL	1	-0.005336	0.007407	0.471247	2.85E-05	No	No
Logical memory	Total cholesterol	0.1	0.002837	0.007295	0.697354	8.05E-06	No	No
Logical memory	Triglycerides	0.05	0.006401	0.007677	0.404398	4.10E-05	No	No
Logical memory	Fasting glucose	1	0.005722	0.007285	0.432181	3.27E-05	No	No
Logical memory	Fasting insulin	0.1	0.007012	0.007305	0.337074	4.92E-05	No	No
Logical memory	HOMA-IR	0.05	-0.004402	0.007312	0.547166	1.94E-05	No	No
Verbal fluency	HDL	0.01	0.012377	0.007494	0.098621	1.53E-04	No	No
Verbal fluency	LDL	0.01	0.011743	0.007544	0.119558	1.38E-04	No	No
Verbal fluency	Total cholesterol	0.01	0.01696	0.007499	0.023714	2.88E-04	No	Yes
Verbal fluency	Triglycerides	0.5	-0.007907	0.007846	0.313574	6.25E-05	No	No
Verbal fluency	Fasting glucose	0.1	0.008079	0.007542	0.28406	6.53E-05	No	No
Verbal fluency	Fasting insulin	0.5	-0.012408	0.007549	0.100234	1.54E-04	No	No
Verbal fluency	HOMA-IR	0.01	-0.009219	0.007542	0.221546	8.50E-05	No	No
Verbal intelligence	HDL	0.05	0.006918	0.007094	0.329451	4.79E-05	No	No
Verbal intelligence	LDL	0.01	0.005926	0.007139	0.406471	3.51E-05	No	No
Verbal intelligence	Total cholesterol	0.1	0.01363	0.007135	0.056078	1.86E-04	No	No
Verbal intelligence	Triglycerides	0.01	0.018914	0.007479	0.011444	3.58E-04	No	Yes
Verbal intelligence	Fasting glucose	0.1	-0.016426	0.007126	0.021154	2.70E-04	No	Yes
<b>Verbal intelligence</b>	<b>Fasting insulin</b>	<b>0.5</b>	<b>-0.027482</b>	<b>0.00713</b>	<b>0.000116</b>	<b>7.55E-04</b>	<b>Yes</b>	<b>Yes</b>
<b>Verbal intelligence</b>	<b>HOMA-IR</b>	<b>1</b>	<b>-0.02521</b>	<b>0.007143</b>	<b>0.000416</b>	<b>6.36E-04</b>	<b>Yes</b>	<b>Yes</b>

s.e.: Standard Error; VarExp: proportion of Predicted Trait variance which explained by Polygenic predictor; Significant level after correction for the multiple test is  $P < .0014$ .

\* Cutoff: the most significant polygenic risk score generated with  $P$ -value cut off threshold.

#### 4. Discussion

We sought to identify causal relationships between INS-R related traits, cognition and depression in two large population-based cohorts using polygenic profiling and Mendelian Randomization. The polygenic profiling indicated a degree of overlap in the genetic architecture of fasting insulin and HOMA-IR with depression and verbal intelligence. The MR analyses however showed no evidence of significant causal relationships from INS-R related traits to depression and cognition.

Our results support observational studies in general population samples reporting phenotypic associations between INS-R traits, cognition (Lampert et al., 2009; Luciano et al., 2014; Yates et al., 2012; Young et al., 2006) and depression (Kan et al., 2013; Pan et al., 2012; Penninx, 2017). The polygenic risk score analyses in the GS:SFHS and results available from similar analyses in the UK Biobank (Richardson et al., 2019) show reproducibility for the association between the PRS for fasting insulin and HOMA-IR with global measures of intelligence and with the risk of depression. These findings suggest a degree of genetic overlap between INS-R traits with depression and cognition. However, the PRS approach is liable to yield substantive false positive rates due to horizontal pleiotropy, the phenomenon whereby a gene (or genes) influences multiple traits (Davey Smith and Hemani, 2014). These pleiotropic effects are very common and PRS scores for one trait seem to be associated with multiple other traits (Richardson et al., 2019).

Mendelian randomization (MR) enables further interrogation of these genetic associations to identify causal pathways between genetic risk factors and complex human traits (Bowden et al., 2015; Davey

Smith and Hemani, 2014; Smith and Ebrahim, 2004). In simple terms, MR examines the effect of INS-R on depression risk (or another trait) by comparing the rates of depression in individuals with and without genotypes that predispose to INS-R. As any particular genotype is randomly assigned at birth and is not subject to reverse causation, the use of genetic variants (such as SNPs) provides a way of “randomising” a sample so that the causality of an observed association can be assessed. Consistent with previous large-scale studies (Bulik-Sullivan et al., 2015; Hagenaars et al., 2016), we found no evidence of directional associations from INS-R traits to cognition and depression. We therefore infer that these associations are likely to be mediated by other mechanisms, that are either consequent on INS-R or interact with INS-R pathways. In the context of diabetes, chronic hyperglycemia may cause cognitive impairment through direct adverse effects on synaptic plasticity (Jacobson et al., 2007) and neurogenesis (Alvarez et al., 2009). Hyperinsulinemia and INS-R can induce neuroglial energy deficits (Zhao and Alkon, 2001) and/or interfere with protein kinase C related synaptic plasticity and neuronal repair (Nelson et al., 2008). Further, hyperinsulinemia has been shown to promote amyloid accumulation within the brain by limiting the degradation and clearance of the amyloid- $\beta$  peptide (Craft and Watson, 2004; Neumann et al., 2008). Alternatively, the link between INS-R and cognitive dysfunction and depression may be mediated by inflammatory pathways (Takeda et al., 2010) and/or oxidative stress linked to mitochondrial dysfunction (Cheng et al., 2010). Mitochondria integrate glucose and lipid metabolism; specifically, insulin regulates mitochondrial metabolism and oxidative capacity through PI3K/Akt signalling (Stiles, 2009). Finally, cardiovascular pathology in the context of INS-R and diabetes may also

play a significant role. For example, in a sample of 2305 individuals aged  $\geq 60$  years Marseglia and colleagues found that cognitive dysfunction was present only among participants who had both uncontrolled diabetes and vascular disorders/risk factors (Marseglia et al., 2016).

There are several methodological considerations pertinent to interpreting the current findings. A particular strength of this study is the availability of data from two large general population samples in which all participants were assessed using harmonised protocols; this contrasts with most large-scale studies that rely on data pooled across diverse cohorts. The instrumental variables used in the analyses were based on the most up-to-date information from the largest GWAS. The polygenic and MR analyses examine the putative causative role of multiple INS-R related traits; however, each of these traits is highly polygenic and instrumental variables tend to explain a small amount of the variance in cognitive ability and depression. The cognitive measures considered in the GS:SFHS and in the UK Biobank covered the domains of cognitive function that have been consistently implicated in INS-R and T2D in observational studies (Benedict et al., 2012; Ekblad et al., 2015; Palta et al., 2014). However, as the hippocampus is enriched in insulin receptors (Dore et al., 1997; Wozniak et al., 1993) and is sensitive to INS-R and depression (Singh et al., 2018) our cognitive battery could have benefited from additional tests targeting hippocampus-linked episodic memory (van Petten, 2004). A further limitation is that case ascertainment was primarily based on self-report which may have led to inaccuracies in the phenotype due to recall bias.

In summary, this study did not find robust evidence for causal associations between INS-R with depression and cognitive ability. Future work should focus on improving instrumental variables, examining a wider range of depression and cognitive phenotypes and focusing on biological mechanisms that may mediate the central effects of INS-R.

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## Declaration of interest

The authors declare that they have no conflict of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.expneurol.2019.04.001>.

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