




RESEARCH LETTER

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Testing for association between exonic glucagon-like peptide 1 receptor mutation with physical and brain health traits in UK Biobank

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1 | INTRODUCTION

Clinical glucagon-like peptide-1 receptor (GLP-1R) agonists have shown efficacy at lowering risk from cardiometabolic conditions, particularly type-2 diabetes (T2D) via several mechanisms, including improved insulin secretion, lower blood pressure (BP) and lowering of body weight and appetite.^{1,2} There is post hoc trial evidence that agonist use in middle-aged to older adults may be associated with cognitive benefits. The REWIND trial reported a 14% lower risk of incident cognitive impairment [i.e. 1.5 standard deviations (SD) from the mean; N = 9901] in participants (with T2D) prescribed dulaglutide versus placebo.³ Limitations include a relatively brief follow-up (5 years) and non-comprehensive cognitive testing based on a screening tool, and Digit Symbol Substitution Test. Ballard et al. reported 53% lower risk

of dementia in participants treated with liraglutide and semaglutide across data from three randomized trials, although the total number of events was low ($n = 47$).⁴ Clinical trial data are critical but given the small number of incident dementia outcomes in previous papers, they are far from definitive. Therefore, an independent approach to enhance information is the exploitation of genetic variants, which mimic pharmacological inhibition of GLP-1R.⁵ Worse cardiometabolic health is a recognized correlate of brain health,⁶ and there is a need for high-quality, relatively large-scale testing of the potential association between GLP-1R and cognitive, structural brain and dementia phenotypes. Scott et al. showed significant association between rs10305492 and lower T2D,⁷ but not Alzheimer's disease (AD); there is need for more data, including multiple relevant diagnostic and continuous phenotypes. Here using the orthogonal approach of naturally

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occurring variation in a low-frequency exonic mutation, rs10305492G>A, which regulates intermediate T2D-related traits including insulin,⁸ we test for associations in the UK Biobank data with cognitive, brain imaging and clinical dementia outcomes (n range = 33 598–322 247 after exclusions).

2 | METHODS

UK Biobank is a large prospective cohort of over 500 000 generally healthy older adults, assessed at baseline in one of 22 assessment centres (2006–2010). Participants completed a range of physical and psychological test batteries including largely on-screen components. Subsamples completed additional cognitive testing over the internet at about 2012, and/or returned for brain magnetic resonance imaging starting 2014.⁹ Details on these assessments are available in open-access protocols.^{6,10} Dementia cases are based on Hospital Episode Statistics (HES) linkage and death registers for mortality.¹¹

To test for associations with T2D/cardiometabolic related traits we examined A allele presence (AA; AG collated) versus absence (GG genotype) with baseline glycated haemoglobin (HbA1c), glucose, body mass index (BMI), waist/hip ratio and systolic BP (SBP; second measurement). We added 15 mmHg to participant SBP if they also self-reported medication for high BP; this is a common approach.¹² We excluded the minority of BMI values <18 or >45 (<1%). Measurement of these phenotypes has been described previously.⁶ We used data from six cognitive tests: log pairs-matching (memory) errors, fluid intelligence (verbal-numeric reasoning), log reaction time (processing speed), matrix completion (executive function; assessed at imaging), digit symbol completion (executive function; assessed over internet) and log trail-making test a + b total (processing speed; assessed over internet).⁶ All-cause dementia, vascular dementia and AD incidence (collated fatal and non-fatal) were extracted from two data sources: hospital admission and death registries. Dates and causes were identified via record linkage to HES (England and Wales) and Scottish Morbidity Records (Scotland), as detailed in open-access reports.¹¹ Hospital admissions data were available until the end of March 2021 for England/Scotland and the end of March 2018 for Wales. Mortality data generally were available until the end of February 2021.

For imaging data, we used imaging derived phenotypes pre-processed centrally by UK Biobank.¹³ We examined phenotypes shown a priori to underlie cognitive impairment: log white matter hyperintensities (WMH), a single unrotated principal component based on 16 subcortical grey matter frontal lobe volumes,⁶ total hippocampal volume, two indices of WM tract microstructure based on 22 tracts—fractional anisotropy and mean diffusivity, total WM and total grey matter normalized for head size.⁶ Participants who self-reported a neurological condition as previously described⁶ were removed (5% at baseline; 2% at imaging). Blood samples were collected at the baseline assessment and DNA extracted, genotyped and quality controlled by the central UK Biobank team.¹⁰

In 2018, UK Biobank released genetic data for 487 409 individuals, genotyped using the Affymetrix UK BiLEVE Axiom or the

Affymetrix UK Biobank Axiom arrays (Santa Clara, CA, USA) containing over 95% common content. Pre-imputation quality control, imputation and post-imputation cleaning were conducted by UK Biobank (described in the UK Biobank release documentation).¹⁰ Locus rs10305492 was directly genotyped [as per all single nucleotide polymorphisms (SNPs) reported herein]. We excluded participants with non-white British ancestry, self-report versus genetic sex mismatch, putative sex chromosomal aneuploidy, excess heterozygosity and missingness rate >0.1. Heterozygosity outliers were as determined by the UK Biobank (data field 22 027). These participants are excluded as their heterozygosity may be a product of a genotyping error and not a true reflection of the participants' genotype. We removed one random participant in cases where two individuals were second cousins or closer.

2.1 | Ethical approval

This secondary-data analysis study was conducted under the generic approval from the NHS National Research Ethics Service (approval letter dated 17 June 2011, ref. 11/NW/0382). Written informed consent was obtained from all participants in the study (consent for research, by UK Biobank). Analyses were completed using UK Biobank project no. 17689.

2.2 | Statistical analysis

We report standardized betas (β) on the per-standard deviation scale, based on linear regressions for continuous outcomes and logistic regression for binary (odds ratio; OR) plus 95% confidence intervals (CI). We controlled for age, sex, eight principal components to account for population stratification and cryptic relatedness (supplied by UK Biobank; <https://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=22009>), genotypic array, apolipoprotein (APOE) e4 allele presence and history of ever-smoking.⁶ We have previously shown that a substantial proportion of the genetic liability to worse brain health is because of APOE e4 rather than non-APOE genetic risk.¹⁴ Stata v14 and PLINK v1.90 were used for analyses. Bonferroni-adjusted statistical significance was ≤ 0.002 .

3 | RESULTS

In the final sample (N = 322 247), n = 10 075 (3.1%) of participants had one A allele and n = 90 (0.03%) had two A alleles. In total, 2820 (0.9%) were recorded as incident dementia (from hospital admission or death records), of which n = 1321 (0.4%) were AD and 610 (0.2%) were vascular dementia. The mean \pm SD ages were 56.8 \pm 8.0 years at baseline and 64.36 \pm 7.7 at imaging. Power analysis using G*Power3 estimated >99% power to find an effect size of Cohen's D = 0.1 in the full sample and 97% in the magnetic resonance imaging subsample. Given the very low number of A homozygous participants, we did not contrast AA versus GG genotypes.

TABLE 1 Associations between rs10305492 A allele presence versus physical and brain health traits

Outcome	β	SE	CI (lower)	CI (upper)	N	r^2	P-value
Imaging							
Log white matter hyperintensity vol.	-0.068	0.031	-0.128	-0.007	25 133	0.269	.028
General factor of Frobal lobe volumes	0.023	0.030	-0.035	0.082	25 996	0.287	.435
General factor of Mean diffusivity	-0.005	0.034	-0.071	0.060	24 534	0.153	.872
General factor of Fractional anisotropy	0.035	0.035	-0.034	0.104	24 534	0.081	.320
Hippocampal vol.	-0.036	0.033	-0.100	0.029	25 993	0.142	.276
White matter vol. (normalized)	-0.030	0.033	-0.096	0.035	25 998	0.113	.364
Grey matter vol. (normalized)	0.046	0.026	-0.005	0.098	25 998	0.445	.078
Cognition							
Matrix completion	0.046	0.038	-0.028	0.120	21 550	0.086	.226
Log trail making a + b	0.031	0.020	-0.007	0.070	66 216	0.168	.114
Digit symbol substitution total	0.001	0.018	-0.035	0.036	76 982	0.204	.975
Log pairs matching (memory) errors	0.001	0.010	-0.020	0.021	290 836	0.028	.955
Fluid intelligence score	0.006	0.017	-0.028	0.040	101 918	0.023	.734
Log reaction time	-0.017	0.010	-0.036	0.002	312 951	0.118	.072
Dementia^a							
All-cause dementia	1.033	0.113	0.833	1.281	312 950	0.153	.766
Alzheimer's disease	1.033	0.164	0.757	1.409	310 690	0.158	.839
Vascular dementia	0.861	0.219	0.523	1.418	312 653	0.132	.556
Physical health							
Body mass index	0.009	0.010	-0.011	0.029	309 794	0.022	.386
Systolic BP	-0.014	0.010	-0.033	0.006	288 221	0.121	.166
Glucose	-0.067	0.011	-0.088	-0.046	272 963	0.017	<.001
HbA1c	-0.042	0.010	-0.062	-0.022	298 223	0.053	<.001
Waist/hip ratio	0.001	0.007	-0.014	0.015	312 509	0.467	.940

Note: betas are on the per-standard deviation scale. Associations corrected for: age, sex, APOE4 allele presence, age, baseline/imaging assessment centre, genotypic array, eight principal components for stratification, and smoking history. Significant associations at $p < .05$ highlighted in bold. Abbreviations: 95% CI, confidence intervals; HbA1c, glycated haemoglobin; SE, standard error. ^aEstimates are odds ratios.

We first tested for associations with cardiometabolic outcomes: A allele presence at rs10305492 was associated with lower HbA1c ($\beta = -0.042$, 95% CIs = -0.062 to -0.022 , $p < .001$), glucose ($\beta = -0.067$, 95% CIs = -0.066 to -0.046 , $p < .001$), and lower risk of prevalent T2D (OR = 0.875, 95% CIs = 0.790-0.969, $p = .011$; case $n = 14\ 901$; 4.63%) but not BMI ($p = .386$), SBP ($p = .166$) or waist/hip ratio ($p = .467$). In terms of cognitive, brain imaging and dementia outcomes, there were largely no associations between A allele presence and average values/risk (all $p > .05$; see Table 1). There was a significant protective association between A allele presence and log WMH volume (-0.07 , 95% CI = -0.128 to -0.007 , $p = .028$), which did not survive correction for multiple testing (i.e. $p > .002$).

3.1 | Additional analyses

There were no significant interactions between rs10305492 and older versus younger age (40-59 vs. ≥ 60 years; all $p > .05$). Results were

generally similar or less significant when we replaced rs10305492 with alternative GLP-1R SNPs rs1042044 (A allele presence 67.6%), rs3765467 (A allele presence 0.53%) or rs6923761 (A allele presence 57.7%) where the highest linkage disequilibrium estimate for rs10305492 was $r = 0.17$ (rs6923761). Estimate values are shown in Supplementary Table S1. Observations of note were between rs1042044 (A presence) versus lower HbA1c (-0.01 SDs, $p = .034$), BMI (-0.01 SDs, $p = .013$) and risk of vascular dementia (OR = 0.791, 95% CIs = 0.662-0.944, $p = .009$), although these were non-significant at the multiple-testing adjusted threshold.

4 | DISCUSSION

GLP-1R agonists are efficacious in lowering glucose, weight, SBP and HbA1c in T2D and are protective for cardiovascular outcomes.¹⁵ We provide orthogonal, genetic-based evidence to support this observation from low-frequency genomic variation in rs10305492, whereby

A allele presence is associated with better glucose, HbA1c and lower risk of T2D in about 300 000 generally healthy middle-aged to older adults. These associations were independent of potential confounds of age, smoking, stratification and/or APOE 'risk' e4 genotype. There was potential evidence of a protective benefit to WMH, a marker of cerebrovascular health although the *p*-value was above the correction for multiple testing and this finding could therefore reflect type-1 error. Better physical/cardiometabolic health is a recognized predictor of better cognitive/brain health;⁶ however, we found modest evidence for this. Any benefit of GLP-1R may be on local rather than global metrics of brain health or alternatively more aggregated markers such as 'overall brain age'.¹⁶

We did not find an association between rs10305492 with SBP, BMI or waist/hip ratio, which suggests it may be a modest instrument for clinical GLP-1R medication.¹ Subsequent studies may investigate additional potential markers such as brain microbleeds, longitudinal change in participants with repeat data, and increased numbers of incident dementias. In this study, we focused on rs103054982, as this has been examined in previous studies. SNPS rs3765467,^{8,17} rs6923761 and rs1042044¹⁷ have been identified as additional potential drivers of reduced insulin secretion; these showed no additional (multiple-testing adjusted) significant associations in subsequent post-hoc analyses. Future studies may investigate other mutations in GLP-1R pathways. There is potential for underestimation of 'true' effect particularly given recognized potential selection bias in UK Biobank generally and particularly the imaging sub-sample⁹; validation in independent cohorts is warranted.

AUTHOR CONTRIBUTIONS

The study concept was performed by NS and DML. DML, JW and NS designed the study. DML and JW performed the analysis. DML wrote the manuscript. Critical revision was performed by all authors.

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PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14879>.

DATA AVAILABILITY STATEMENT

The UK Biobank resource is available to bona fide researchers for health-related research in the public interest. All researchers who wish to access the research resource must register with UK Biobank by completing the registration form in the Access Management System (AMS; <https://www.ukbiobank.ac.uk/enable-your-research/register>).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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