BRAIN COMMUNICATIONS

Helicobacter pylori, persistent infection burden and structural brain imaging markers

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Persistent infections, whether viral, bacterial or parasitic, including *Helicobacter pylori* infection, have been implicated in non-communicable diseases, including dementia and other neurodegenerative diseases. In this cross-sectional study, data on 635 cognitively normal participants from the UK Biobank study (2006–21, age range: 40–70 years) were used to examine whether *H. pylori* seropositivity (e.g. presence of antibodies), serointensities of five *H. pylori* antigens and a measure of total persistent infection burden were associated with selected brain volumetric structural MRI (total, white, grey matter, frontal grey matter (left/right), white matter hyperintensity as percent intracranial volume and bi-lateral sub-cortical volumes) and diffusion-weighted MRI measures (global and tract-specific bi-lateral fractional anisotropy and mean diffusivity), after an average 9–10 years of lag time. Persistent infection burden was calculated as a cumulative score of seropositivity for over 20 different pathogens. Multivariable-adjusted linear regression analyses were conducted, whereby selected potential confounders (all measures) and intracranial volume (sub-cortical volumes) were adjusted, with stratification by Alzheimer's disease polygenic risk score tertile when exposures were *H. pylori* antigen serointensities. Type I error was adjusted to 0.007. We report little evidence of an association between *H. pylori* seropositivity and persistent infection burden with various volumetric outcomes ($P > 0.007$, from multivariable regression models), unlike previously reported in past research. However, *H. pylori* antigen serointensities, particularly immunoglobulin G against the vacuolating cytotoxin A, GroEL and outer membrane protein antigens, were associated with poorer tract-specific white matter integrity ($P < 0.007$), with outer membrane protein serointensity linked to worse outcomes in cognition-related tracts such as the external capsule, the anterior limb of the internal capsule and the cingulum, specifically at low Alzheimer's disease polygenic risk. Vacuolating cytotoxin A serointensity was associated with greater white matter hyperintensity volume among individuals with mid-level Alzheimer's disease polygenic risk, while among individuals with the highest Alzheimer's disease polygenic risk, the urease serointensity was consistently associated with reduced bi-lateral caudate volumes and the vacuolating cytotoxin A serointensity was linked to reduced right putamen volume ($P < 0.007$). Outer membrane protein and urease were associated with larger sub-cortical volumes (e.g. left putamen and right nucleus accumbens) at middle Alzheimer's disease polygenic risk levels ($P < 0.007$). Our results shed light on the relationship between *H. pylori* seropositivity, *H. pylori* antigen levels and persistent infection burden with brain volumetric structural measures. These data are important given the links between infectious agents and neurodegenerative diseases, including Alzheimer's disease, and can be used for the development of drugs and preventive interventions that would reduce the burden of those diseases.

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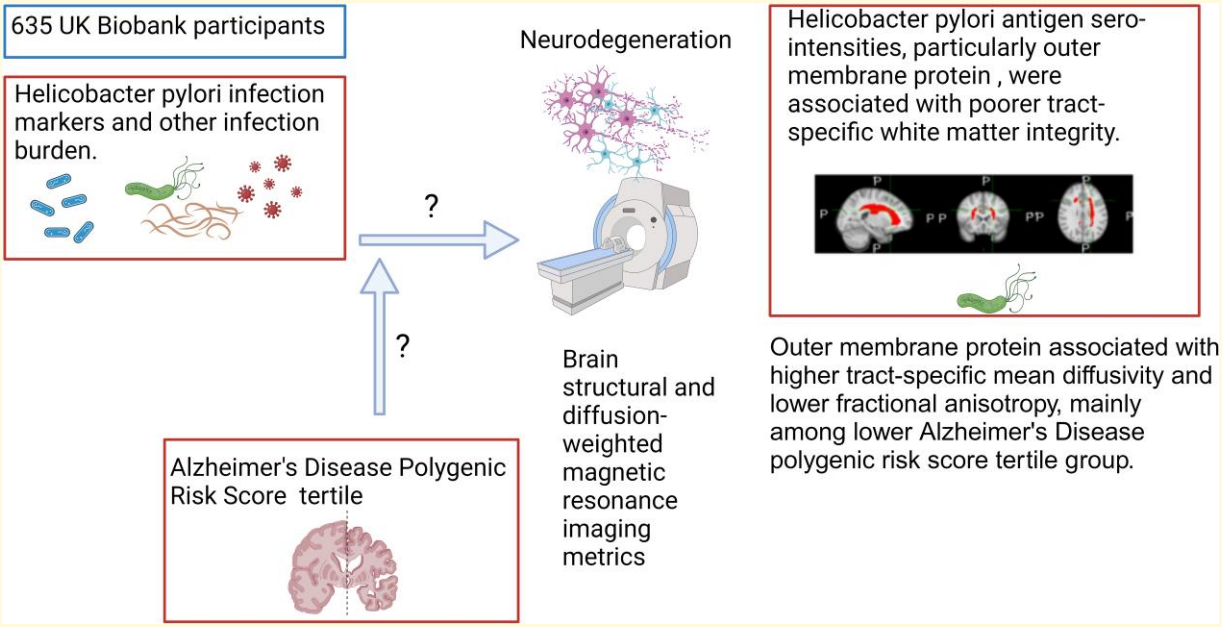
Graphical Abstract



Introduction

Dementia is a major cause of global disability that affects function in multiple cognitive domains. The estimated prevalence rate of dementia among adults over 60 years is 4.7%,[1] with 4.6–7.7 million cases accrued each year worldwide [3.5–10.5 per 1000].[2-4] Approximately, 60–80% of dementia cases are of the Alzheimer's disease sub-type.[4] Alzheimer's disease is a progressive neurodegenerative disorder known for its multifactorial aetiology, often manifesting initially as episodic memory deterioration followed by impairment in other cognitive domains.[5] Generally believed as the outcome of age-dependent and progressive Aβ-amyloid brain deposition through the 'amyloid cascade hypothesis',[6] Alzheimer's disease is also characterized by neurofibrillary tangles, a pathological hallmark arising from hyper-phosphorylated tau protein.[7] Alzheimer's disease is a leading cause of geriatric disability, carrying the greater healthcare burden in developed countries with costs of $236 billion in long-term care and hospice care ascribed to dementia in the USA in 2016.[8-10] With no effective treatment for dementia, prevention becomes crucial, reinforcing the need to uncover modifiable risk factors. Although late-onset Alzheimer's disease has been associated with specific genetic factors (e.g. apolipoprotein, *APOE* ε4), the *Lancet Commissions* reported in 2020 that nearly 40% of the population attributable risk for dementia can be explained by adverse effects of multiple potentially modifiable factors such as early-life lower education, mid-life hearing loss, traumatic brain injury, hypertension, alcohol use and obesity, as well as later-life smoking, depression, social isolation, physical inactivity, air pollution and diabetes.[11] It is also important to note that antecedent socio-economic factors such as low education are often thought to induce poorer lifestyles or exposure to air pollution, which in turn can lead to poorer health profiles, the latter being

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directly associated with poor cognition and dementia risk.[12-15] Identification of novel mid-life risk factors is key to preventive efforts and to planning cost-effective interventions. More recently, infectious agents have gained the attention of researchers, with some implicated in the aetiology of Alzheimer's disease and related dementias[8,16] including *Helicobacter pylori* (*Hp*).[1,17-27]

A curved gram-negative bacterium, *Hp*, is found in ~50% of the human gastric mucosa.[28] It was first described in 1984 as a bacterium in the stomachs of patients affected by gastritis and peptic ulceration.[28] Worldwide, it is among the most common infectious agents,[28] with a prevalence rate estimated to be as high as 80–90% in developing countries and ranging between 35 and 40% in the USA and Europe.[27,29] With an estimated incidence of 0.5–1.0%/year in the US population,[29] *Hp* infection is often acquired during childhood, becoming chronic during adulthood with failed treatment.[29] The *Hp* seroprevalence increases markedly with age, with low iron stores potentially protecting individuals against chronic infection and iron-deficiency anaemia observed during acute infection.[30] Despite the availability of numerous published studies, *Hp* transmission routes and reservoirs are still not entirely understood,[31] but direct person-to-person transmission is thought to be the most common route.[32] *Hp* seroprevalence is also higher under poor socio-economic conditions, poor hygiene, high crowding and among minority groups.[24,33,34] Over the last decade, studies have associated chronic *Hp* infection with various extra-digestive manifestations, including atherosclerosis,[35,36] hypertension[37,38] and stroke,[39] and a growing body of evidence has suggested that this infection may play a causal role in neurocognitive and neuropsychiatric disorders, including all-cause and Alzheimer's disease dementia.[20,22,40-55] *Hp* infections can cause these disorders by affecting the brain and the vascular system.[20,22,40-55] In fact, these disorders may be triggered by *Hp* infection–associated disruptions in nutrient bioavailability, gut microbiome changes, oxidative stress and metabolic factors.[20,22,40-55] *Hp* infections can also initiate Alzheimer's disease–like pathology.[20,22,40-55] Therefore, prevention of chronic *Hp* infection can potentially have an important effect on these disorders and their prognosis.

Many other persistent infections, whether viral, bacterial or parasitic, have been implicated in non-communicable diseases, including dementia and other neurodegenerative diseases.[8] In order to dissect the potential impact of *Hp* on neurodegenerative disease from that of overall infection burden, it is important to examine both infection measures and assess their relative effects on markers of brain degeneration and examine them both overall and across Alzheimer's disease genetic risk groups. The present study used data from the UK Biobank cohort to test the association between *Hp* seropositivity (*Hps*) and overall persistent infection burden (PIB) on volumetric and white matter (WM) integrity brain MRI markers that are relevant to the Alzheimer's disease phenome.[56] The associations are tested overall and where possible across levels of genetic Alzheimer's disease risk as determined by a previously computed Alzheimer's disease genetic risk score.

Materials and methods

Database

The UK Biobank is a prospective study of ~500 000 adults with baseline ages of 37–73 years residing in the UK and recruited between 2006 and 2010 from 22 assessment centres located within 24 miles from place of residence in either England, Scotland or Wales.[57,58] The study's design and rationale are detailed elsewhere.[58,59] Participants completed a self-administered, touch-screen questionnaire in addition to a face-to-face interview,[58,60] and trained staff examined them by taking phenotypic measurement and biological samples including physical measures, blood and urine sample collections, as well as whole body imaging for a sample of respondents.[58,60] The study was approved by the North West Multi-Centre Research Ethics Committee, and participants provided written informed consent for data collection, data analysis and record linkage, provided that the data were de-identified.[57,58,61] In 2014, MRI scanning of a sub-group of 100 000 participants began, and this is ongoing. Furthermore, of the initial ~500 000 UK Biobank participants, a random sample of around 10 000 UK Biobank participants was chosen at random to obtain serum samples, in order to analyse seropositivity for 20 selected infectious agents.

The studies involving human participants were reviewed and approved by the UK Biobank with approval from the Institutional Review Boards, namely, the North West Multi-Centre Research Ethics Committee for the UK, from the National Information Governance Board for Health and Social Care for England and Wales and from the Community Health Index Advisory Group for Scotland. All participants gave informed consent for the study via a touch-screen interface that required agreement for all individual statements on the consent form as well as the participant's signature on an electronic pad. Written informed consent for participation was not required for this study in accordance with the National Legislation and the Institutional Requirements. The present study is part of the UK Biobank application number 77963 and was approved by the National Institutes of Health Institutional Review Board.

Study sample

Of the initial 502 389 UK Biobank participants, 39 989 had available data on the selected structural MRI (sMRI) and diffusion-weighted MRI (dMRI) phenotypic data. Of these sub-sets, 635 had brain imaging, serology and Alzheimer's disease polygenic risk score (PGS) data. No further exclusions were made, as all 635 selected participants were dementia free even after 1 year of follow-up from baseline assessment (see Supplementary Method 1). All other covariates were imputed using chain equations, with 5 imputations and 10 iterations, given that their missingness rate was

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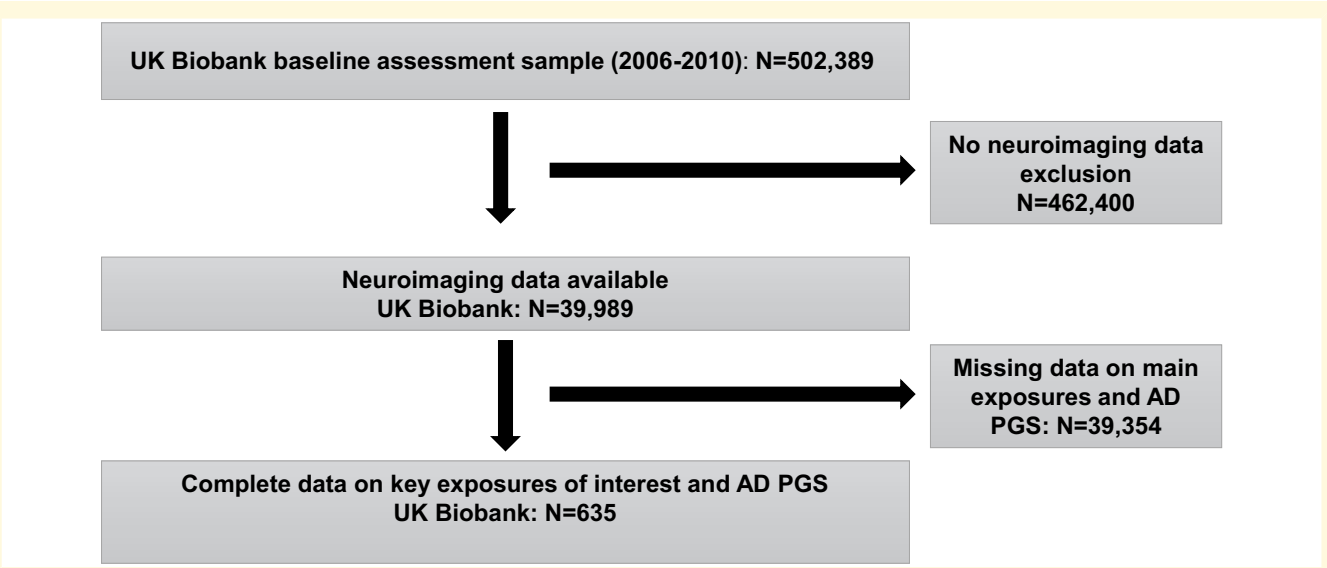

Figure 1 Participant flowchart. The flowchart shows sample selection starting from the total UK Biobank study sample of over 500 000, selection of participants with neuroimaging sMRI and dMRI and finally inclusion of those who had complete data on serology, including *Hp* seropositivity, serointensities and PIB components, and on Alzheimer's disease PGS. AD, Alzheimer's disease; PGS, polygenic score; PIB, Persistent infection burden; UK, United Kingdom.

<10% each. Thus, the final analytic sample consisted of 635 participants aged 40–70 years at the baseline assessment visit (55.4% female; Fig. 1).

Brain MRI acquisition and processing

The UK Biobank imaging visit carried out MRI brain scans across sites in the areas of Reading, Newcastle and Cheadle Manchester.[62,63] Acquired on the same 3T Siemens Skyra scanner, all brain images followed a freely available protocol (http://www.fmrib.ox.ac.uk/ukbiobank/protocol/V4_23092014.pdf), documentation (http://biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf) and publication.[64,65] Scans from the top of the head to the neck were conducted using a 256-cm superior–inferior field of view.[62,63] Volumetric outcomes and WM tract–averaged water molecular diffusion indices were processed and made available to approved researchers by the UK Biobank as imaging-derived phenotypes (IDPs), with full detail on image processing and QC pipeline found elsewhere.[64,65] Details are provided in Supplementary Method 1.

In the present study, the release of brain MRI data as of November of 2022 was used (i.e. ~45 000 participants). Volumetric outcomes were labelled 'sMRI' outcomes (T_1-weighted and T_2 fluid-attenuated inversion recovery), whereas fractional anisotropy (FA) and mean diffusivity (MD) phenotypes were labelled 'dMRI' outcomes. In general, UK Biobank IDPs were not normalized for brain or head size. Therefore, we included total intracranial volume (ICV) among potential confounders to adjust for head size, where applicable, specifically for sub-cortical volumes. The selected imaging phenotypes were *a priori* shown to be associated with worse cognitive ability and decline. For 'sMRI', those were total WM and grey matter (GM) volumes, bi-lateral frontal GM volume (e.g. Tank *et al.*[66]), sub-cortical volumes including hippocampal volume (see Supplementary Table 1 for details) and $\log_e$-transformed white matter hyperintensity (WMH) volume, expressed as per cent of ICV. For 'dMRI', average FA and MD across the WM tracts listed in Supplementary Table 1 were considered as key outcomes of interest.

PIB, *Hps* and *Hp* serointensities

The UK Biobank Infectious Disease Working Group selected 20 infectious agents that were relevant to UK public health given their known associations with cancer and other chronic non-communicable diseases.[67] A random selection of UK Biobank participants (n of ~10 000) were included in this pilot study, and serological antibody responses, or total antibody levels, were measured against these 20 pathogens using Multiplex Serology methodology. Specifically, serum antibody levels against the following infectious agents were measured: herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), varicella zoster virus (VZV), Epstein–Barr virus (EBV), human cytomegalovirus (CMV), human herpesvirus-6, human herpesvirus-7, Kaposi's sarcoma-associated herpesvirus, hepatitis B virus, hepatitis C virus (HCV), *Toxoplasma gondii* (*T. gondii*), human T-lymphotropic virus-1, human immunodeficiency virus 1, human papillomavirus 16, human papillomavirus 19, human polyomavirus 2 or JC virus, BK virus, Merkel cell polyomavirus, *Chlamydia trachomatis* and *Hp*. Details about assay protocols and validation have been described previously.[67] Seropositivity of each antigen was determined using mean fluorescence intensity (MFI) cut-offs and definitions as described by the working group[67] and detailed in Supplementary Table 2 and Method 2. MFI for

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each antigen was used for serointensity calculations. *Hps* was computed using the cut-offs detailed in Supplementary Table 2 for the different serointensities excluding CagA, which was only measured for half of the sample. The following antigens were measured for *Hp*: CagA (cut-off: 400 MFI), VacA (cut-off: 100 MFI), OMP (cut-off: 170 MFI), GroEL (cut-off: 80 MFI), catalase (cut-off: 180 MFI) and urease (cut-off: 130 MFI). PIB is the sum of the seropositivities of all the viral, bacterial and parasitic pathogens listed above, which was also computed using pre-set cut-offs for each serointensity. The overall seroprevalence for all the pathogens in the UK Biobank cohort is listed in Supplementary Table 2.

Alzheimer's disease PGS

Using a Bayesian approach, polygenic risk scores (PGS) scores were generated and were applied to meta-analysed (and, when possible, ancestry specific) summary statistic genome-wide association studies (GWAS) data, which were extracted either entirely from external GWAS data (the standard PGS set) or from a combination of external and internal UK Biobank data (the enhanced PGS set). The standard PGS set (also known as the 'UKB-Free' set) of 28 diseases and 8 quantitative traits was obtained using external GWAS data, a process described in the main published paper's supplementary information by Thompson *et al.*[68] (https://www.medrxiv.org/content/10.1101/2022.06.16.22276246v1.supplementary-material?versioned=true), and was made available for the entire UK Biobank sample. From the standard PGS set, we selected Alzheimer's disease PGS, initially obtained from the PGS Catalog (https://www.pgscatalog.org/). We selected a version of the Alzheimer's disease PGS that included APOE genotypic variants among the constituent single nucleotide polymorphisms.

Covariates

Covariates included age at baseline assessment, sex and race/ethnicity. Participants' self-reported race/ethnicity was initially categorized as White, Black, South Asian and others, but re-grouped into non-White and White. Socio-economic status (SES) was operationalized with three different measures: education, income and the Townsend deprivation index (TDI). Based on at least one previous study,[69] lower to higher level of education is 0 = low, combining none, 'CSEs/equivalent', 'NVQ/HND/HNC/equivalent' and 'other professional qual'; 1 = intermediate, combining 'O levels/GCSEs/equivalent' and 'A/AS level equivalent; or 2 = higher level or 'college/university'. Total household income before tax was measured on a 5-point scale, kept as continuous in the present analysis, where 1 denoted <£18,000, 2 denoted £18 000–£29 999, 3 denoted £30 000–£51,999, 4 denoted £52 000–£100 000 and 5 denoted >£100 000. TDI scores were computed based on national census data measuring residential postcode-level car ownership, household overcrowding, owner occupation and unemployment. The total score reflects higher socio-economic deprivation with higher TDI.[70] Lifestyle factors included smoking and alcohol use measures, physical activity, diet quality, nutritional biomarkers and measures of social support. Health-related factors included a co-morbidity index, body mass index, the allostatic load (AL; Supplementary Table 5) and self-rated health. Those are detailed in Supplementary Methods 3 and 4, along with Supplementary Tables 3 and 4.

Statistical analysis

Most analyses were conducted using Stata software, version 17[71] (StataCorp, College Station, TX). We used multivariate imputation by chained equations[72] for all covariates with missing data (see the 'Covariates' section) aside from main exposures and outcomes of interest. Main analyses were conducted overall and were then stratified by sex for most analyses and by Alzheimer's disease PGS tertiles for parts of the analysis. Comparison across categorical groups were made using ordinary least square (OLS) linear and multinomial logit models with the grouping variable entered as a predictor, comparing means and proportions of key characteristics of interest. We first examined various characteristics, including exposures, outcomes and covariates, across *Hps* and tertiles of PIB in the overall sample. Second, we examined *Hps* and PIB total count in relation to 'sMRI' and 'dMRI' outcomes of interest, overall and by sex. Four models were constructed, with Model 1 adjusting only for age, sex, race, Alzheimer's disease PGS and time between baseline assessment and neuroimaging visit (in days), as well as ICV for small sub-cortical volumes. Model 2 further adjusted Model 1 for other socio-demographic and socio-economic factors. Model 3 adjusted Model 2 for all other variables including lifestyle and health-related factors. For full models with *Hps* as the primary exposure (Model 3), an additional covariate was added, namely, PIB count excluding *Hps* from the count.

Another set of analyses consisted of examining each *Hp* antigen serointensity ($\log_e$ transformed) as a predictor for all sMRI and dMRI outcomes overall and across Alzheimer's disease PGS tertiles. This set of analyses was carried out using a reduced Model 1 and the full model, which further adjusted Model 1 for all covariates including PIB without *Hps* (i.e. Model 3). To test effect modification by Alzheimer's disease PGS, the score was interacted in the form of tertiles, with each serologic exposures for *Hp* ($\log_e$ transformed) as well as with the raw count value of the PIB. Type I error was set to 0.05 in all analyses prior to correction for multiple testing. In the main analyses, excluding descriptive findings, correction for multiple testing in reduced models (i.e. Model 1) in the overall and Alzheimer's disease PGS tertile stratified samples took into account multiplicity in exposures while considering outcomes as separate hypotheses of interest, using the familywise Bonferroni correction approach.[73] Thus, type I error was adjusted to $0.05/7 = 0.007$. Findings with $P < 0.014$ but ≥ 0.007 were considered marginally significant.

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Table 1 Selected study sample characteristics by *Hp* seropositivity: UK Biobank 2006–21[a]

	Hp seropositivity			
	Overall	Hps^-	Hps^+	P_{Hps}
	N = 635	*N* = 479	*N* = 156	
Socio-demographic				
Baseline age, years	55.8 ± 0.30	55.6 ± 0.34	56.4 ± 0.6	0.31
Sex, % female	55.4	58.2	46.8	0.013
Race/ethnicity				0.011
White	96.8	97.9	93.6	
Non-White	3.1	2.1	6.4	
Socio-economic status				
Education				
Low	12.8	12.6	13.5	0.47
Intermediate	33.8	31.3	41.4	0.014
High	53.4	56.1	45.1	Ref
Income[a]	2.96 ± 0.05	2.97 ± 0.06	2.93 ± 0.10	0.71
Townsend deprivation index	−1.96 ± 0.11	−2.13 ± 0.12	−1.46 ± 0.24	0.007
sMRI outcomes, mm^3				
ICV	1 545 728 ± 6098	1 536 935 ± 6876	1 572 728 ± 12 851	0.011
Total brain volume	1 154 860 ± 4571	1 149 546 ± 5171	1 171 177 ± 9623	0.042
Total GM	612 520 ± 2306	610 164 ± 2612	619 755 ± 4846	0.073
Total WM	542 340 ± 2485	539 382 ± 2809	551 422 ± 5229	0.037
Genetic risk, follow-up time and *Hp* antigen IgG serointensities				
Alzheimer's disease PGS	+0.0244 ± 0.0405	+0.068 ± 0.048	−0.108 ± 0.075	0.062
Follow-up time, days	3313 ± 23.7	3294.5 ± 48.8	3294.0 ± 48.4	0.65
Hp antigen IgG serointensities, log_e transformed				
Catalase	3.77 ± 0.07	3.26 ± 0.05	5.36 ± 0.17	<0.001
GroEL	3.23 ± 0.11	2.13 ± 0.07	6.62 ± 0.20	<0.001
OMP	3.79 ± 0.08	3.07 ± 0.07	6.02 ± 0.14	<0.001
Urease	3.56 ± 0.08	3.02 ± 0.08	5.21 ± 0.17	<0.001
VacA	3.22 ± 0.06	2.76 ± 0.06	4.64 ± 0.13	<0.001
PIB				
PIB_{total}	7.70 ± 0.07	7.28 ± 0.08	8.97 ± 0.13	<0.001
$PIB_{minusHps}$	7.45 ± 0.07	7.28 ± 0.08	7.97 ± 0.13	<0.001

GM, grey matter; *Hp*, *H. pylori*; Hps, *H. pylori* seropositivity; ICV, intracranial volume; IgG, immunoglobulin G; PGS, polygenic score; PIB, persistent infection burden; sMRI, structural MRI; WM, white matter.
[a]See the 'Covariates' section for details on these covariates. Values are percentages or means ± standard errors (SE).

All other results, such as incrementally adjusted models and tests for heterogeneity across Alzheimer's disease PGS tertiles, were considered sensitivity analyses. Thus, a type I error of 0.05 was applied in those instances. To further adjust for potential selection bias, an inverse mills ratio (IMR) was added to all models, using a two-stage Heckman selection process,[74] as a sensitivity analysis and results were compared. IMR is a function of the probability of being selected into the final sample versus those excluded from the original sample, conditional on baseline age, sex and race/ethnicity. Tract-specific dMRI findings (JHU, 48 tracts), particularly standardized effect sizes (*b*), were visualized using FSLeyes software (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLeyes), focusing on the *Hp* antigen serointensity findings in the overall sample from the reduced Model 1, whereby both the exposures and outcomes were transformed into *Z*-scores. Only findings with a $P < 0.007$ are presented. Standardized effect sizes between 0.10 and 0.20 were considered weak to moderate, while effect sizes above 0.20 were considered moderate to strong.

Results

Table 1 along with Supplementary Table 6 (with full details) presents descriptive findings of key study characteristics across *Hps* and PIB tertiles. PIB was calculated as a cumulative score of seropositivity of over 20 different pathogens (Supplementary Table 2). In general, *Hps* and PIB were associated with lower SES, particularly higher TDI, a computed deprivation index and a higher likelihood of being a current smoker. In addition, *Hps* was associated with greater ICV and total WM volumes, but reduced nucleus accumbens volume with higher PIB tertile ($P < 0.05$). Social support characteristics had inconsistent association with *Hps* and PIB.

Supplementary Table 7 shows results of a set of multiple linear regression models examining associations of *Hps* and PIB count with sMRI volumetric outcomes. The findings indicated that neither *Hps* nor PIB was associated with the volumetric outcomes considered, including sub-cortical volumes of interest after adjustment for ICV. A similar set of models were applied to global dMRI outcomes (mean FA

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Table 2 *Hp* seropositivity, persistent infection burden (PIB_{total}) and global dMRI white matter integrity outcomes: UK Biobank 2006–21[a,b]

	Hp seropositivity			Persistent infection burden total count		
	β	SE	P_{Hps}	β	SE	$P_{PIBtotal}$
Mean FA						
Model 1	−0.0009	0.0017	0.59	0.00004	0.00041	0.91
Model 2	−0.001	0.0017	0.56	0.00003	0.00041	0.93
Model 3	−0.0005	0.0017	0.79	−0.000469	0.00178	0.79
Mean MD						
Model 1	1.61E−06	2.66E−06	0.55	−2.77E−07	6.40E−07	0.67
Model 2	2.36E−06	2.70E−06	0.38	−1.34E−07	6.47E−07	0.84
Model 3	1.37E−06	2.79E−06	0.62	1.37E−06	2.79E−06	0.62

dMRI, diffusion MRI; FA, fractional anisotropy; *Hp*, *H. pylori*; Hps, *H. pylori* seropositivity; MD, mean diffusivity; PGS, polygenic score; PIB_{total}, persistent infection burden, total count.
[a]Values are β-coefficients with associated standard errors and *P*-values from a series of OLS multiple linear regression models with dMRI WM integrity outcomes and main exposure being *Hp* seropositivity and PIB total count.
[b]Model 1 adjusted for age, sex, race (non-White versus White), Alzheimer's disease PGS, time elapsed between baseline and neuroimaging visit (days) and the IMR; Model 2 further adjusted Model 1 for education, income and TDI; Model 3 further adjusted Model 2 for three measures of smoking, alcohol consumption, Healthy Diet Index total score, three measures of social support, one physical activity measure, vitamin D status, red cell distribution width, self-rated health, the AL and body mass index. Model 3 with *Hps* was additionally adjusted for infection burden excluding *Hps*.

Table 3 *Hp* antigen serointensity measures and their association with selected key sMRI volumetric outcomes, overall and across Alzheimer's disease PGS tertiles: UK Biobank 2006–21[a,b,c]

	Full model				
	Overall	Alzheimer's disease PGS T_1	Alzheimer's disease PGS T_2	Alzheimer's disease PGS T_3	$P_{ADPGStert \times Hp}$
WMH					
Catalase	0.007 ± 0.021	0.057 ± 0.040	0.027 ± 0.038	−0.065 ± 0.039	**0.049**
GroEL	−0.009 ± 0.014	0.042 ± 0.024	−0.025 ± 0.025	**−0.054 ± 0.025***	**0.031**
OMP	**0.039 ± 0.017***	0.042 ± 0.031	0.057 ± 0.030	−0.002 ± 0.030	0.58
Urease	0.006 ± 0.017	−0.001 ± 0.029	0.048 ± 0.028	−0.037 ± 0.033	0.57
VacA	0.040 ± 0.023	0.044 ± 0.041	**0.121 ± 0.040*****	−0.048 ± 0.050	0.13
Hippocampus, left					
Catalase	−12.749 ± 10.768	−15.679 ± 20.480	−8.386 ± 19.139	−19.930 ± 20.521	0.75
GroEL	−11.906 ± 6.846	−1.478 ± 12.183	**−25.010 ± 12.108***	−17.475 ± 13.425	0.22
OMP	−1.723 ± 8.624	6.716 ± 15.688	−13.361 ± 15.154	1.136 ± 16.145	0.57
Urease	4.683 ± 8.504	2.864 ± 14.876	4.924 ± 14.212	0.156 ± 17.745	0.66
VacA	4.857 ± 11.552	31.210 ± 20.881	2.016 ± 20.588	−11.067 ± 22.316	0.18
Hippocampus, right					
Catalase	1.988 ± 11.349	10.843 ± 21.899	1.962 ± 19.881	8.015 ± 21.724	0.59
GroEL	−8.613 ± 7.211	−4.561 ± 12.876	−15.120 ± 12.646	−6.097 ± 14.148	0.38
OMP	2.646 ± 9.082	18.840 ± 16.638	−23.313 ± 15.621	16.770 ± 16.881	0.66
Urease	−0.641 ± 8.951	−4.925 ± 15.802	−0.160 ± 14.755	9.563 ± 18.567	0.76
VacA	−0.031 ± 12.151	33.734 ± 22.141	−7.071 ± 21.377	−14.596 ± 23.430	0.076

AD, Alzheimer's disease; *Hp*, *H. pylori*; ICV, intracranial volume; PGS, polygenic score; sMRI, structural MRI; WMH, white matter hyperintensity. *$P < 0.05$; ***$P < 0.007$. Bolded values with *** indicate statistical significance after adjustment for multiple testing. All other bolded and non-bolded values did not pass correction for multiple testing.
[a]Values are β-coefficients with associated standard errors and *P*-values from a series of OLS multiple linear regression models with sMRI volumetric outcomes and main exposures being either of five *Hp* antigen serointensities.
[b]All models adjusted for age, sex, race (non-White versus White), Alzheimer's disease PGS, time elapsed between baseline and neuroimaging visit (days) and the IMR as well as other variables including socio-economic factors (education, income and TDI), lifestyle and health-related factors (three measures of smoking, alcohol consumption, Healthy Diet Index total score, three measures of social support, one physical activity measure, vitamin D status, red cell distribution width, self-rated health, the AL, body mass index and infection burden minus *Hps*). Models with sub-cortical volumes as outcomes, adjusted all models for ICV.
[c]Models were conducted in the overall sample and stratified by Alzheimer's disease PGS tertiles. Heterogeneity across Alzheimer's disease PGS tertiles was formally tested using two-way interactions.

and mean MD) in Table 2. The findings indicated that neither *Hps* nor PIB was associated with global FA or MD both in reduced and in fully adjusted models.

Table 3 along with Supplementary Table 8 presents five different *Hp* antigen serointensity measures and their association with sMRI volumetric outcomes, overall and across Alzheimer's disease PGS tertiles. Upon correction for multiple testing (type I error of 0.007), notable findings included the association of VacA serointensity with greater WMH volume among individuals with mid-level Alzheimer's

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Table 4 *Hp* antigen serointensity measures and their association with global dMRI white matter integrity outcomes, overall and across Alzheimer's disease PGS tertiles: UK Biobank 2006–21[a,b,c]

	Overall	Alzheimer's disease PGS T_1	Alzheimer's disease PGS T_2	Alzheimer's disease PGS T_3	$P_{ADPGStert \times Hp}$
Reduced model					
Mean FA					…
Catalase	−0.00021 ± 0.00043	−0.00066 ± 0.00082	+0.00014 ± 0.00072	−0.00010 ± 0.00072	…
GroEL	−0.00010 ± 0.00027	−0.00026 ± 0.00048	+0.00004 ± 0.00045	+0.00002 ± 0.00050	…
OMP	−0.00077 ± 0.00035*	−0.00132 ± 0.00064*	−0.00095 ± 0.00058	−2.60E−06 ± 0.0006	…
Urease	−0.00012 ± 0.00035	−0.00045 ± 0.0006	−0.00008 ± 0.00055	+0.00030 ± 0.00067	…
VacA	−0.00052 ± 0.00046	−0.00064 ± 0.00060	−0.00082 ± 0.00076	+0.00003 ± 0.00082	…
Mean MD					
Catalase	+6.93E−08 ± 6.69E−07	1.31E−06 ± 1.25E−06	−1.05E−06 ± 1.14E−06	+6.82E−08 ± 1.11E−06	
GroEL	+1.43E−07 ± 4.24E−07	8.78E−08 ± 7.36E−07	1.68E−07 ± 7.23e097	+1.36E−07 ± 7.66E−07	…
OMP	+1.17E−06 ± 5.44E−07*	1.70E−06 ± 9.87E−07	+1.64E−06 ± 9.23E−07	+1.33E−08 ± 9.38E−07	…
Urease	+4.28E−07 ± 5.44E−07	4.46E−07 ± 9.63E−07	5.65E−07 ± 8.73E−07	5.16E−08 ± 1.04E−06	…
VacA	+1.09E−06 ± 7.23E−07	9.75E−07 ± 1.32E−06	1.17E−06 ± 1.21E−06	7.46E−07 ± 1.26E−06	…
Full model					
Mean FA					
Catalase	−0.00013 ± 0.00045	−0.0010 ± 0.00086	+0.00035 ± 0.00080	+0.00012 ± 0.00084	0.43
GroEL	−0.00011 ± 0.00028	−0.00059 ± 0.00052	−7.74E−06 ± 0.00051	+0.00031 ± 0.00054	0.47
OMP	−0.00072 ± 0.00036*	−0.00138 ± 0.00067*	−0.00101 ± 0.00064	+0.0003 ± 0.0007	0.13
Urease	+0.00003 ± 0.00035	−0.00009 ± 0.00064	+0.00008 ± 0.00059	+0.00033 ± 0.00071	0.49
VacA	−0.00056 ± 0.00048	−0.00097 ± 0.00090	−0.00074 ± 0.00085	−0.00020 ± 0.00090	0.54
Mean MD					
Catalase	+4.90E−08 ± 6.99E−07	1.57E−06 ± 1.38E−06	−6.98E−07 ± 1.25E−06	−2.74E−07 ± 1.27E−06	0.47
GroEL	+2.56E−07 ± 4.45E−07	2.75E−07 ± 8.17E−07	4.69E−07 ± 8.05E−07	−2.03E−07 ± 8.34E−07	0.80
OMP	+1.23E−06 ± 5.57E−07*	1.64E−06 ± 1.05E−06	1.97E−06 ± 9.993–07	−1.84E−07 ± 9.98E−07	0.38
Urease	2.79E−07 ± 5.50E−07	−1.42E−07 ± 1.00E−06	4.62E−07 ± 9.29E−07	−1.84E−07 ± 1.10E−06	0.97
VacA	+1.25E−06 ± 7.47E−07	1.17E−06 ± 1.41E−06	1.42E−06 ± 1.34E−06	+6.89E−07 ± 1.38E−06	0.97

AD, Alzheimer's disease; dMRI, diffusion MRI; FA, fractional anisotropy; *Hp*, *H. pylori*; MD, mean diffusivity; PGS, polygenic score; sMRI, structural MRI; UK, United Kingdom. *$P < 0.05$.
[a]Values are β-coefficients with associated standard errors and *P*-values from a series of OLS multiple linear regression models with dMRI WM integrity outcomes and main exposures being either of five *Hp* antigen serointensities.
[b]All models adjusted for age, sex, race (non-White versus White), Alzheimer's disease PGS, time elapsed between baseline and neuroimaging visit (days) and the IMR as well as other variables including socio-economic factors (education, income and TDI), lifestyle and health-related factors (three measures of smoking, alcohol consumption, Healthy Diet Index total score, three measures of social support, one physical activity measure, vitamin D status, red cell distribution width, self-rated health, the AL, body mass index and infection burden minus *Hps*).
[c]Models were conducted in the overall sample and stratified by Alzheimer's disease PGS tertiles. Heterogeneity across Alzheimer's disease PGS tertiles was formally tested using two-way interactions.

disease risk. Among individuals with highest Alzheimer's disease risk, urease serointensity was linked to reduced caudate volumes (L/R) and VacA serointensity was associated with reduced right putamen volume. OMP and urease were associated with larger sub-cortical volumes—that is, left putamen and right nucleus accumbens, respectively—at middle Alzheimer's disease PGS risk levels ($P < 0.007$).

Table 4 examines five different *Hp* antigen serointensity measures and their association with global dMRI WM integrity outcomes, overall and across Alzheimer's disease PGS tertiles. Findings from both reduced and fully adjusted models indicated that the OMP serointensity was associated with poorer white matter integrity (WMI), overall and in the lowest Alzheimer's disease PGS tertile, both in terms of higher MD and lower FA ($P < 0.05$). We examined the relationship between *Hp* serointensity with tract-specific FA and MD (Figs 2–4; Supplementary Table 9). A worse outcome in several tracts appeared to be consistently linked with greater OMP levels, at a corrected type I error of 0.007. In the overall sample, those included greater MD in the corona radiata tracts (anterior and inferior), in tracts involved in cognition, including the left brain external capsule, the anterior limb of the internal capsule and the cingulum. In addition, OMP, VacA and GroEL levels were consistently associated with higher MD and/or lower FA in the superior and inferior cerebellar peduncle tracts (Fig. 2). Figures 3 and 4 indicate that most of the findings across Alzheimer's disease PGS tertiles pertained to the OMP serointensity in the lower Alzheimer's disease PGS tertile, particularly at a type I error of 0.007. In general, effects in absolute terms ranged between −0.10 and +0.20, indicating weak to moderate associations between *Hp* serointensity and WMI. Within the lowest Alzheimer's disease PGS tertile, catalase, OMP and VacA were consistently associated with greater MD in the left fronto-occipital fasciculus, a tract directly involved in cognitive function, and both left and right tapetum FA were inversely related to OMP ($P < 0.010$).

Discussion

Summary of findings

The present study is one of the few to examine associations of *Hps*, *Hp* serointensities and PIB with various brain imaging

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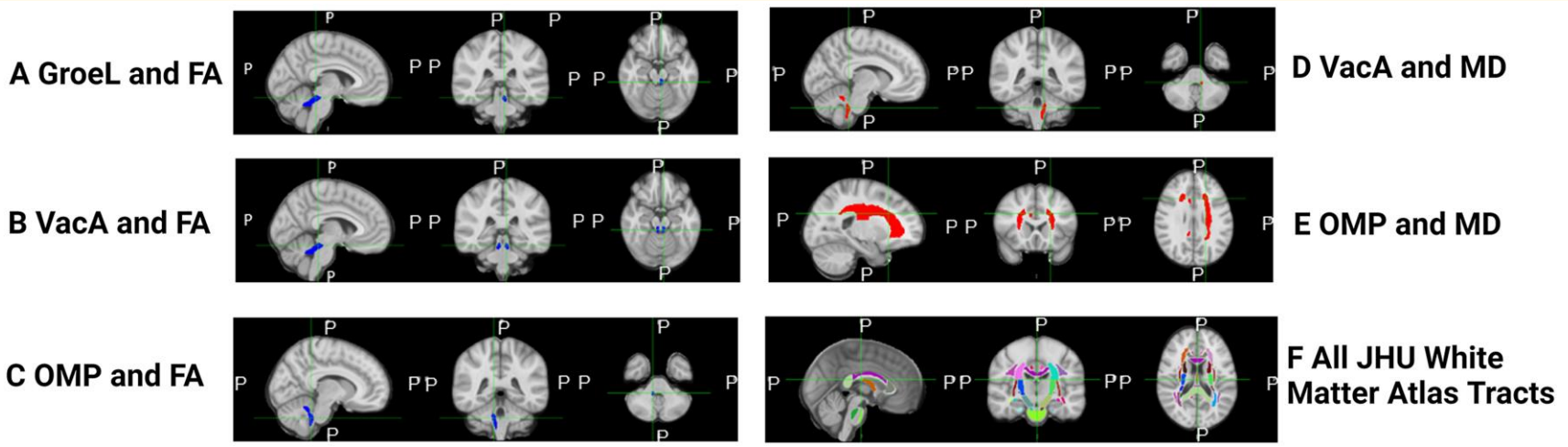

Figure 2 *Hp* antigen serointensities and measures of WM integrity: UK Biobank 2006–21. Colour schemes are directions (**A–E**) of regression coefficients (exposures versus outcomes) from OLS multiple linear regression models, with alternative outcomes being tract-specific FA and MD and main alternative exposures being Hp serointensities (Cat, GroeL, OMP, UreA and VacA). Models were adjusted for age, sex, race (non-White versus White), Alzheimer's disease PGS, time elapsed between baseline and neuroimaging visit (days) and the IMR. Sample size for all analyses is $N = 635$. Outcomes and exposures are standardized Z-scores. Cold colour represents inverse relationships ($\beta < 0$, $P < 0.007$), while warm colour represents positive relationships ($\beta > 0$, $P < 0.007$) for parts **A–E**. Image in part **F** includes all WM JHU tracts. Full results are presented in Supplementary Table 9. Cat, catalase; FA, fractional anisotropy; JHU, Johns Hopkins University; MD, mean diffusivity; OLS, ordinary least square; OMP, outer membrane protein; PGS, polygenic score; ROI, region of interest; VacA, vacuolating cytotoxin A (see Supplementary Table 1 for full list of ROIs/tracts linked to FA and MD dMRI analysis and Supplementary Table 9 for quantitative findings).

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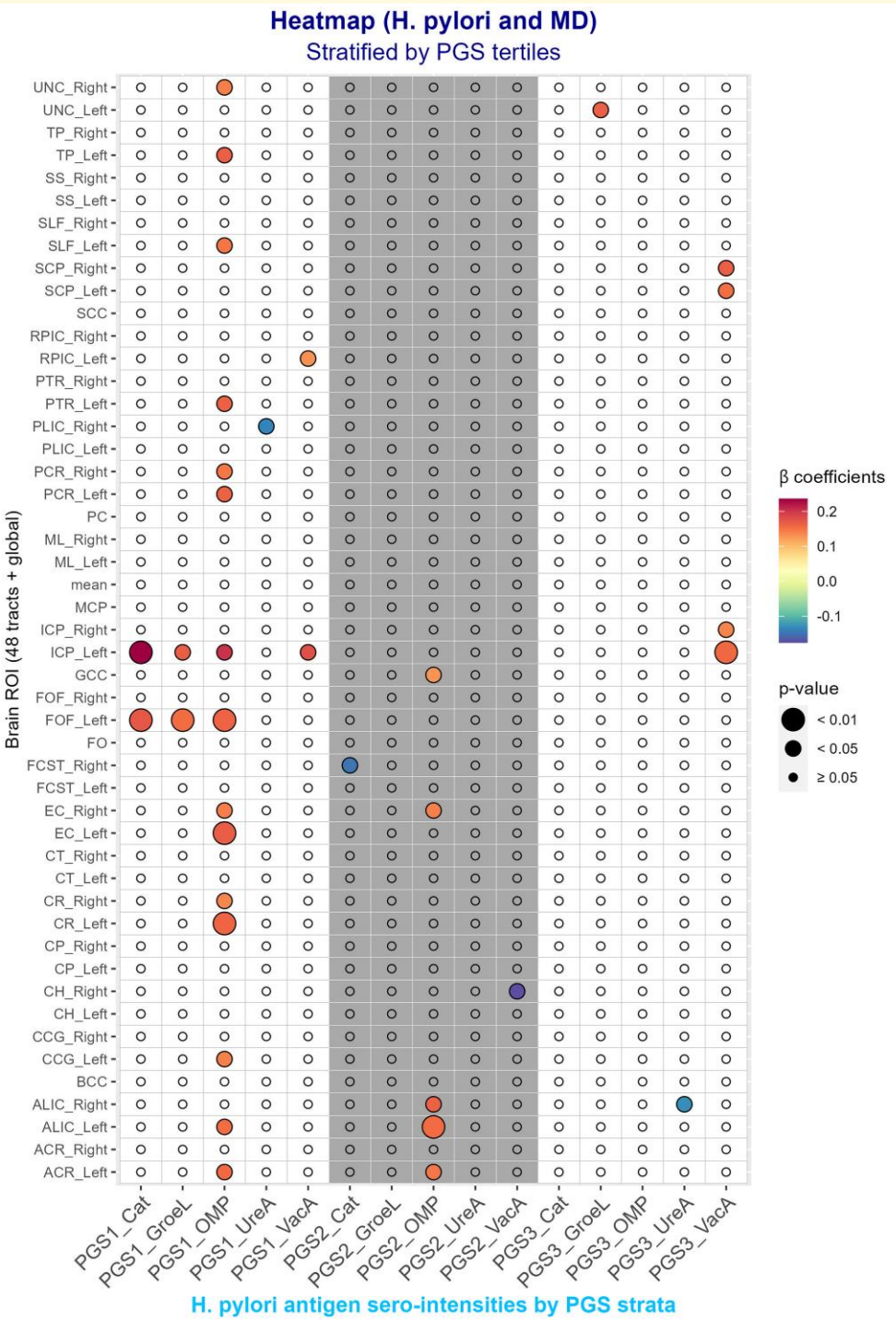

Figure 3 Heat map for *Hp* antigen serointensities and measures of WM integrity (MD) across Alzheimer's disease polygenic risk level: UK Biobank 2006–21. Values and directions of regression coefficients (exposures versus outcomes) from OLS multiple linear regression models, with alternative outcomes being tract-specific MD and main alternative exposures being Hp serointensities (Cat, GroeL, OMP, UreA and VacA). Models were adjusted for age, sex, race (non-White versus White), Alzheimer's disease PGS, time elapsed between baseline and neuroimaging visit (days) and the IMR. Models were stratified by Alzheimer's disease PGS tertile. Outcomes and exposures are standardized *Z*-scores. Means of MD were also entered as two alternative outcomes. Sample sizes for Alzheimer's disease PGS T_1, T_2 and T_3 were 212, 212 and 211, respectively. Cold colours represent inverse statistically significant standardized effect sizes ($\beta < 0$, $P < 0.05$), while warmer colours represent positive statistically significant standardized effect sizes ($\beta > 0$, $P < 0.05$). Size of the circle is inversely proportional to the *P*-value. Depth of the colour is proportional to the absolute standardized effect size. ACR, anterior corona radiata; ALIC, anterior limb of the internal capsule; BCC, body of the corpus callosum; Cat, catalase; CCG, cingulum cingulate gyrus; CH, cingulum hippocampus; CP, cerebral peduncle; CR, superior corona radiata; CT, corticospinal tract; EC, external capsule; FA, fractional anisotropy; FCST, fornix cres–stria terminalis; FO, fornix; FOF,

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markers of age-related neurodegeneration. Data from the UK Biobank were used including serology markers of persistent infection at baseline assessment, and various volumetric and WM integrity measures assessed on average 9–10 years later. Our study shows little evidence of an association between *Hps* seropositivity and the total burden of persistent infections with various volumetric outcomes. Nevertheless, *Hp* antigen serointensities, particularly IgG against the VacA, GroEL and OMP antigens, were associated with poorer WM integrity in specific tracts, with OMP serointensity linked to poorer WM integrity in areas related to cognition such as the external capsule, the anterior limb of the internal capsule and the cingulum, particularly among individuals with low Alzheimer's disease risk. Moreover, among notable findings, VacA serointensity was associated with greater WMH volume among individuals with mid-level Alzheimer's disease risk. Among individuals with highest Alzheimer's disease risk, urease serointensity was consistently associated with reduced caudate volumes (L/R), and the VacA serointensity was linked to reduced right putamen volume. A few other findings indicated that some antigens, including OMP and urease, may be associated with larger sub-cortical volumes (e.g. left putamen and right nucleus accumbens) at middle Alzheimer's disease PGS risk levels ($P < 0.007$).

Previous studies

Infectious diseases have been associated with neurocognitive function and abnormal brain structure. In a small study of 40 participants with asymptomatic HCV infection and 31 healthy controls, hepatitis C infection was associated with decreased cognitive function and decreased WM integrity.[75] Prior studies have evaluated whether *Hp* infection or eradication was associated with neurocognitive disorders. Several case–control studies have suggested a positive association between *Hps* or infection and Alzheimer's disease or mild cognitive impairment occurrence,[17,20,21,41] whereas an intervention study concluded that among *Hp*-positive Alzheimer's disease cases, successful *Hp* eradication can reduce the rate of cognitive decline, further reinforcing possible causal associations between Hp and Alzheimer's disease.[18] Furthermore, lower mortality risk was found with successful versus unsuccessful Hp eradication in another intervention study (hazard ratio = 0.29, 95% CI: 0.11–0.73) adjusted for age and Mini-Mental State Examination (MMSE).[19] In addition, *Hp* infection among 53 Alzheimer's disease patients was related to reduced MMSE score ($P = 0.024$) and greater CSF phosphorylated tau 181 ($P = 0.014$) and tau ($P = 0.021$) levels.[27] Malaguarnera *et al.*[41] demonstrated that the presence of Alzheimer's disease and vascular dementia was related to high Hp IgG and IgA concentrations and homocysteine levels, although dementia severity did not correlate with these levels. In contrast, two Japanese case–control studies failed to observe an association between *Hp* infection and Alzheimer's disease or cognitive impairment,[22,23] although these studies did not match by either age or sex and the first study[23] used urinary IgG, which is an unreliable diagnostic method, and had a high Hp infection prevalence (~70%), likely rendering the analysis underpowered.

Previous research has investigated associations between *Hp* and cognitive function. While not all findings have shown main effect associations between cognitive function and *Hps*,[46] cross-sectional studies have generally implicated *Hps* as a risk factor for cognitive impairment. Based on a nationally representative study using data from the third National Health and Nutrition Examination Survey (NHANES III) phase 1 data (1988–91), worse performance was detected among Hp IgG seropositive versus IgG seronegative older adults (aged 60–90 years) on a verbal memory test, while other sex-specific and race-specific associations were found between *Hps* and poor performance on tests of psychomotor speed, verbal memory and orientation.[24] A recently conducted retrospective cohort study of adults aged 45 years or more linked NHANES III ($n = 3684$) and NHANES 1999–2000 ($n = 2243$), with up to 22 years of follow-up, and found a positive association between *Hps* and Alzheimer's disease mortality among men ($HR_{adj,pooled} = 4.33$, 95% CI: 1.51–12.41, $P = 0.006$) and with incident Alzheimer's disease ($HR_{adj,pooled} = 1.45$, 95% CI: 1.03–2.04, $P = 0.035$) and $HR_{adj,III} = 1.99$ (95% CI: 1.24–3.17, $P = 0.004$) for NHANES III, associations found also positive for higher SES groups.[76] Similarly, Roubaud Baudron *et al.*[26] found that among 603 noninstitutionalized individuals aged 65 years and older living in the southwest of France and followed between 1989 and 2008, serology-determined Hp infection was associated with a 46% increased risk of incident dementia (HR = 1.46, $P = 0.040$) after adjustment for key potential confounders, which included socio-economic level, cardiovascular health and baseline cognitive performance based on the MMSE total score.

By contrast, later cohort studies conducted in the USA and among European older adults failed to detect an association between *Hps* and dementia outcomes[77,78] or main associations with cognitive function,[79] while other studies that combined Hp with seropositivity of additional infections to create an infectious burden index found potential synergism between various infections and *Hp* in predicting dementia risk.[78,80,81] The

Figure 3 Continued

superior fronto-occipital fasciculus; GCC, genu of the corpus callosum; ICP, inferior cerebellar peduncle; MD, mean diffusivity; ML, medial lemniscus; MCP, middle cerebellar peduncle; OLS, ordinary least square; OMP, outer membrane protein; PC, pontine crossing; PCR, posterior corona radiata; PGS, polygenic score; PLIC, posterior limb of the internal capsule; PTR, posterior thalamic radiation; ROI, region of interest; RPIC, retrolenticular part of the internal capsule; SS, sagittal striatum; SCC, splenium of the corpus callosum; SCP, superior cerebellar peduncle; SLF, superior longitudinal fasciculus; TP, tapetum; UNC, uncinate; UreA, urease; VacA, vacuolating cytotoxin A (see Supplementary Table 1 for full list of ROIs/tracts linked to FA and MD dMRI analysis).

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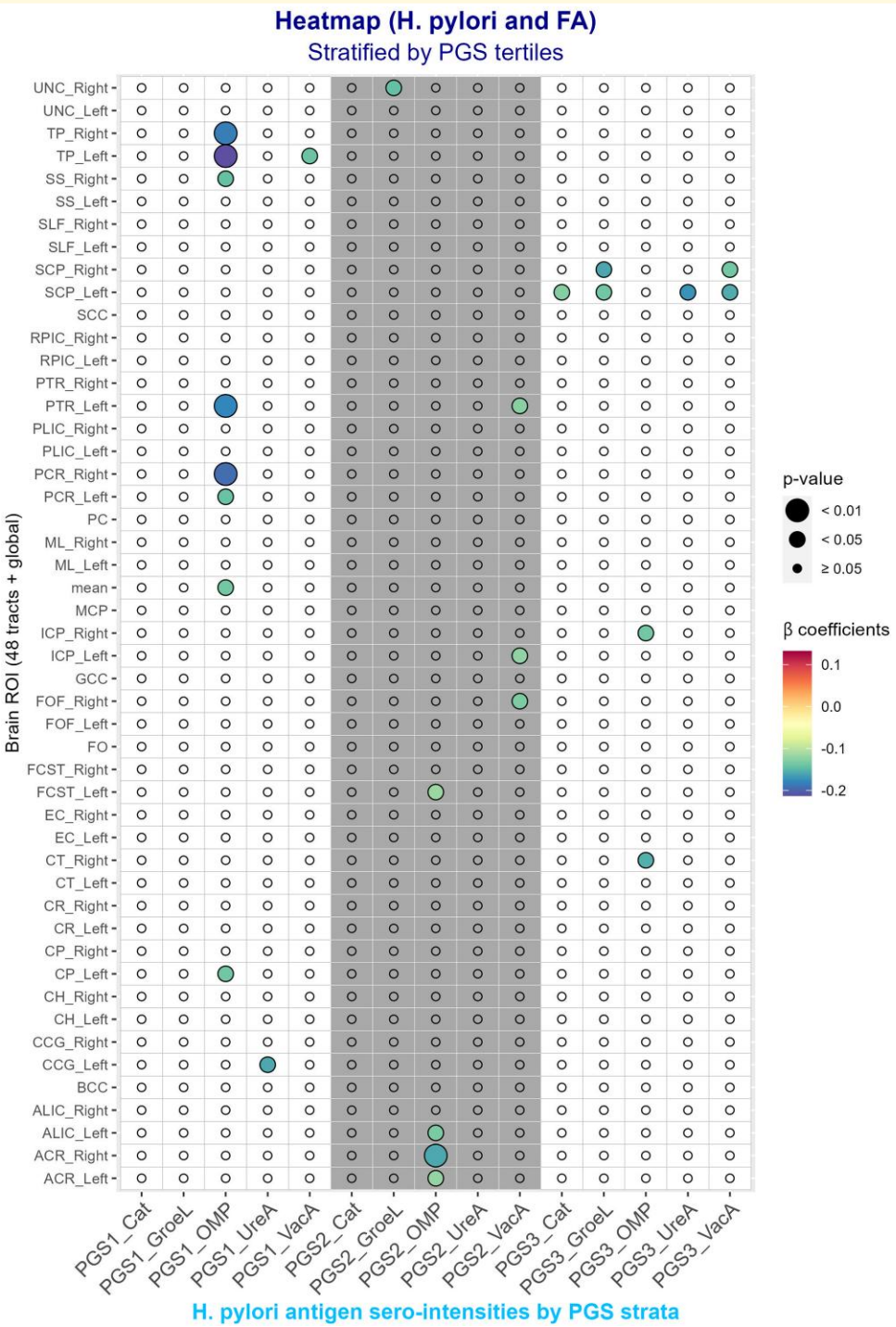

Figure 4 Heat map for *Hp* antigen serointensities and measures of WM integrity (FA) across Alzheimer's disease polygenic risk level: UK Biobank 2006–21. Values and directions of regression coefficients (exposures versus outcomes) from OLS multiple linear regression models, with alternative outcomes being tract-specific FA and main alternative exposures being Hp serointensities (Cat, GroeL, OMP, UreA and VacA). Models were adjusted for age, sex, race (non-White versus White), Alzheimer's disease PGS, time elapsed between baseline and neuroimaging visit (days) and the IMR. Models were stratified by Alzheimer's disease PGS tertile. Outcomes and exposures are standardized *Z*-scores. Means of FA were also entered as two alternative outcomes. Sample sizes for Alzheimer's disease PGS T_1, T_2 and T_3 were 212, 212 and 211, respectively. Cold colours represent inverse statistically significant standardized effect sizes ($\beta < 0$, $P < 0.05$), while warmer colours represent positive statistically significant standardized effect sizes ($\beta > 0$, $P < 0.05$). Size of the circle is inversely proportional to the *P*-value. Depth of the colour is proportional to the absolute standardized effect size. ACR, anterior corona radiata; ALIC, anterior limb of the internal capsule; BCC, body of the corpus callosum; Cat, catalase; CCG, cingulum cingulate gyrus; CH, cingulum hippocampus; CP, cerebral peduncle; CT, corticospinal tract; EC, external capsule; FA, fractional anisotropy; FCST, fornix cres–stria terminalis; FO, fornix; FOF, superior fronto-occipital fasciculus;

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most recent meta-analysis found that on average, *Hp* infection and/or seropositivity was associated with an increased risk of all-cause dementia in pooled findings from five case–control and five cohort studies: odds ratio (OR) = 1.36 (95% CI: 1.11–1.67), but the results were less conclusive for Alzheimer's disease dementia, from cohort studies (1.33, 95% CI: 0.86–2.05) or from case–control studies (1.72, 95% CI: 0.97–3.04).[40] Later evidence suggested that in a sample of 822 men who underwent 3-T brain MRI and had cross-sectional data on *Hp* infection using histological assessment, *Hp* infection was associated with overall ($P = 0.022$), parietal ($P = 0.008$) and occipital ($P = 0.050$) brain cortical thinning, even after adjustment for age, education, alcohol, smoking and ICV.[82] Using 3D topographical analysis, the study showed that *Hp*-infected men exhibited cortical thinning in several other smaller areas (false discovery rate corrected, $Q < 0.050$),[82] even after further adjustment for an inflammatory marker (C-reactive protein) and several metabolic characteristics (obesity, dyslipidaemia, fasting glucose and blood pressure).[82] Other types of brain lesions have been associated with *Hp*. In patients with migraine, WM lesions were more common (adjusted OR: 2.48, 95% CI: 1.65–3.72) in the patients also seropositive for *Hp*,[83] suggesting further that *Hp* might affect brain structure. Although current evidence suggesting an association between *Hp* infection and structural brain lesions is compelling, additional research including multiple waves of brain MRI data to examine the longitudinal association between *Hp* infection and neurodegeneration would help better characterize possible associations between *Hp* and structural brain lesions. Biological mechanisms behind sex differences, if any, in the association between *Hp* and dementia risk are lacking. In fact, the association among men between *Hp* infection and neurodegeneration based on brain MRI data is supportive of previous findings regarding *Hps*' association with incident dementia among men only, from a retrospective cohort study that used NHANES III-Medicare data.[76,82]

To our knowledge, few studies have examined associations between indices of infection burden and brain structure. In one of the few related available studies,[84] cerebral microbleeds were associated (adjusted OR: 3.00, 95% CI, 1.11–8.15) with an infection burden based on seropositivity to several different types of bacteria (*Chlamydia pneumoniae*, *Hp*, *Mycoplasma pneumoniae* and *Borrelia burgdorferi*) and viruses (CMV, EBV, HSV-1 and HSV-2). A study investigating associations between *C. pneumoniae*, *Hp*, CMV, HSV-1, HSV-2 and stroke found that while each individual was not significantly associated with stroke, a weighted infection burden index comprising all five pathogens was associated with stroke risk.[51] In our study, we did not find associations between an index of infection burden and structural brain lesions, which could be because our index of infection burden was based on summed seropositivity from different pathogens and not on summed serointensities of the different pathogens included in the index. Inasmuch as serointensity might provide a better measure of host immune and inflammatory responses than seropositivity alone, additional research basing indices of infection burden on serointensity might better characterize associations between overall infection burden and structural brain lesions.

Biological mechanisms

Several mechanisms have implicated *Hp* in various neurocognitive and neuropsychiatric disorders, ultimately affecting the brain and its vascular system. Such mechanisms generally fall under two categories: (i) disruption in nutrient bioavailability (specifically vitamins and homocysteine) caused by endothelial damage and (ii) apoptosis triggered by factors such as T cell–mediated immune response.

Atrophic gastritis (or chronic inflammation of the stomach mucosa) is a common consequence of *Hp* infections and damages the endothelial layer responsible for absorbing nutrients. Two vitamins in particular, folate and B12, play an important role in the metabolism and recycling of homocysteine. Their malabsorption due to gastritis leads to homocysteine accumulation,[41,42] which is linked to cardiovascular problems and dementia.[43] Many cellular processes in the nervous system also use these vitamins as cofactors, especially in the synthesis of the myelin sheath surrounding nerve cells and neurotransmitters involved in signalling.[44] Deficiencies in vitamin B12 specifically have been linked to memory loss and reversible dementia and may be involved in other impairments in cognition.[22] In addition, interactions between *Hps* and folate cycle factors could be involved in cognitive function. In one study, *Hps* interacted with decreased 5-methyltetrahydrofolate concentration to worsen function on the digit symbol coding task, although there were no main effects of either *Hps* or 5-methyltetrahydrofolate concentration alone on performance on the digit symbol coding task.[46]

Further, microbiome, immunological and biochemical changes associated with *Hp* infection could lead to brain changes. As some variations in the gut microbiome are associated with cognitive function,[45] it is plausible that *Hp*-induced changes in the gut microbiome could affect brain regions associated with cognitive function. *Hp* also affects

Figure 4 Continued
GCC, genu of the corpus callosum; ICP, inferior cerebellar peduncle; MD, mean diffusivity; ML, medial lemniscus; MCP, middle cerebellar peduncle; OLS, ordinary least square; OMP, outer membrane protein; PC, pontine crossing; PCR, posterior corona radiata; PGS, polygenic score; PLIC, posterior limb of the internal capsule; PTR, posterior thalamic radiation; ROI, region of interest; RPIC, retrolenticular part of the internal capsule; SS, sagittal striatum; SCC, splenium of the corpus callosum; SCP, superior cerebellar peduncle; SLF, superior longitudinal fasciculus; TP, tapetum; UNC, uncinate; UreA, urease; VacA, vacuolating cytotoxin A (see Supplementary Table 1 for full list of ROIs/tracts linked to FA and MD dMRI analysis).

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dendritic cell interleukin-12 secretion,[47] and *Hp* is associated with oxidative stress, inflammatory and metabolic factors that could alter brain integrity.[20]

CNS small vessel disease has been associated with cognitive function, dementia and cerebral integrity, including WMH. Furthermore, small vessel disease has been associated with various infections including CMV, hepatitis B, hepatitis C and VZV, among others.[48] Similarly, more severe COVID-19 has been associated with MRI findings including WMH and microhaemorrhages.[49] Thus, one potential mechanism underlying cognitive decline associated with infectious pathogens includes cerebrovascular changes. In fact, some[50] but not all[51] evidence implicates *Hp* infection as a risk factor for stroke, further suggesting that cerebrovascular changes from *Hp* could be involved with structural brain changes associated with *Hp*. Accordingly, research exploring associations between *Hp* and small vessel disease as a potential mechanism by which *Hp* is associated with brain structure is needed.

Another potential mechanism by which *Hp* could affect WM integrity is apoptosis, which can be triggered by T cell–mediated immunity but which is also often a result of molecular mimicry, as evidenced by increased levels of autoantibodies in the serum when the *Hp* titre increases.[85] Some *Hp* epitopes mimic the molecular structures of gastric H^+/K^+-ATPase, an enzyme involved in acidification of the stomach, so that T lymphocytes targeting the foreign antigen also end up lysing the native ATPase, which induces inflammation of the mucosa.[53] Another case of molecular mimicry involves the *Hp* exotoxin VacA: IgG antibodies against VacA also target the Na^+/K^+ ATPase pump that maintains membrane potential,[52] and its disruption causes demyelination and may explain the poor WM integrity observed. *Hp* infection can also lead to apoptosis and vascular lesions through other inflammatory responses by activating platelets, fibrinogen, eicosanoids and especially interleukins.[54]

Hp strains can vary in virulence. In this regard, VacA has two domains, each with its own allelic variability. This mosaic organization contributes to variability in *Hp* strains and correlates with varying degrees of virulence in different strains.[86] Several population studies have linked specific variants of VacA with specific allelic variations of *Hp* OMPs belonging to either the Hop or Hom families, which suggests a genetic association between them.[87] Although the role of some of these OMPs is unclear, HopS, HopP, HopQ and HomB all seem involved in *Hp* adhesion and colonization of the gastric epithelium. Whether they directly induce neuroinflammation is unclear, but they may do so through an interaction with VacA.

Hp also might initiate Alzheimer's disease–like pathology directly. *Hp* produce *Hp* histidine-rich protein, which appears to induce an amyloid-like protein and in *in vitro* models can cross gastric epithelium and the blood–brain barrier.[55]

Strengths and limitations

Our present study has many notable strengths. First, it is one of very few and the largest study to date examining the association between *Hps*, *Hp* serointensity and PIB and various brain MRI markers of the Alzheimer's disease phenome, reflecting both volumetric and WM integrity outcomes. Second, it was adequately powered to conduct stratified analyses by sex and Alzheimer's disease PGS tertiles. Third, the UK Biobank has a vast number of variables that could be controlled for in our analyses, allowing for unbiased estimates of exposure–outcome associations, through adjustment for key potential confounders. Nevertheless, our study findings should be interpreted with caution in light of several limitations. First, the cross-sectional design of this study precludes us from inferring causality or temporality of associations. Second, while *Hps* is used as the main exposure of interest in most previous studies and in the current one, this serologic test has limitations compared with the gold standard, which is the histologic analysis of gastric mucosa biopsy samples. In fact, IgG seropositivity does not identify the time of initial infection, precluding evaluating how length of *Hps* could affect associations between *Hp* and brain structure. While IgM antibodies tend to indicate acute infection, seropositivity is unable to discriminate between current and old infections. Such distinction is required since current *Hp* infection induces humoral and cellular immune responses that, owing to the sharing of homologous epitopes (molecular mimicry), cross-react with nerve components, thus affecting or perpetuating neural tissue damage.[88] Third, the PIB was based on a sum of the number of identified infections identified via antibodies and did not consider the antibody levels (i.e. serointensity) of each infection. As our results suggest, serointensity may be a useful predictor of outcome. Fourth, residual confounding is still possible, even though we have included a large number of independent potential confounders in our models. Finally, despite partial adjustment using a two-stage Heckman selection model, selection bias cannot be ruled out.

Conclusion

In conclusion, while this cross-sectional study with a lag time between exposure and outcome of an average of 9–10 years shows little evidence of an association between *Hps* or PIB with various volumetric outcomes, it found that *Hp* antigen serointensities, particularly IgG against the VacA, GroEL and OMP antigens, were associated with poorer WM integrity in specific tracts, with OMP serointensity linked to poorer WM integrity in areas related to cognition, particularly among individuals with low polygenic Alzheimer's disease risk. Other notable findings also pertained to VacA serointensity association with greater WMH volume among individuals with mid-level Alzheimer's disease risk and with reduced putamen volume at higher Alzheimer's disease risk. In that group, urease serointensity was also linked to reduced left and right caudate volumes. Future longitudinal studies should examine those associations using repeated measurements on brain volumetric and WM integrity outcomes in comparable populations, further uncovering the potential role played by various *Hp* antigens in neurodegeneration.

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Supplementary material

Supplementary material is available at *Brain Communications* online.

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Competing interests

The authors report no competing interests. The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of Fort Belvoir Community Hospital, the Defense Health Agency, the Department of Defense or the U.S. Government. Reference to any commercial products within this publication does not create or imply any endorsement by Fort Belvoir Community Hospital, the Defense Health Agency, the Department of Defense or the U.S. Government.

Data availability

The data analysed in this study are subject to the following licences/restrictions: UK Biobank is a large-scale biomedical database and research resource, containing in-depth genetic and health information from half a million UK participants. The database is regularly augmented with additional data and is globally accessible to approved researchers undertaking vital research into the most common and life-threatening diseases. Requests to access these data sets should be directed to https://www.ukbiobank.ac.uk/.

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