

Helicobacter pylori, herpes simplex virus-1, varicella zoster virus, and dementia incidence in the UK-based EPIC-Norfolk cohort

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Introduction

- *Helicobacter pylori* (*H. pylori*), herpes simplex virus-1 (HSV-1) and varicella zoster virus (VZV) occur throughout the life-course and have a high seroprevalence in western populations (~60%).
- These infectious pathogens have been implicated in dementia risk but previous studies have been limited by:
 - a small number of dementia cases
 - short follow-up periods
 - a lack of investigation into the role of individual antibody levels

Aim: To investigate the association between *H. pylori*, HSV-1, and VZV seropositivity and antibody levels with dementia risk in a large cohort with more than a thousand dementia cases occurring over 24 years of follow-up.

Methods

Population: Participants were selected from EPIC-Norfolk, a cohort of women and men aged 40-79 years recruited between 1993-97 in the county of Norfolk, UK. Between 1998-2000, participants attended a repeat assessment where they completed questionnaires on lifestyle and health, underwent physical examinations and provided blood samples.



Participants recruited to EPIC-Norfolk health check 1
25,639

Health check 1 participants seen at health check 2
15,028

Participants with infectious disease serology data available
9,205

Study population
8,550

Exposures: Antibody responses to antigens of *H. pylori*, HSV-1 and VZV were measured using a quantitative multiplex serology panel from serum samples collected at health check 2. These antibody responses were further used to determine seropositivity status for each infectious pathogen.

No serological measures
5,823

Exclusion criteria
<50 years old: **600**
Prevalent dementia: **1**
Missing data: **54**

Flow chart demonstrating selection of final sample

Outcome: All-cause dementia was identified from longitudinally collected electronic hospital inpatient and death records available up to 2022.

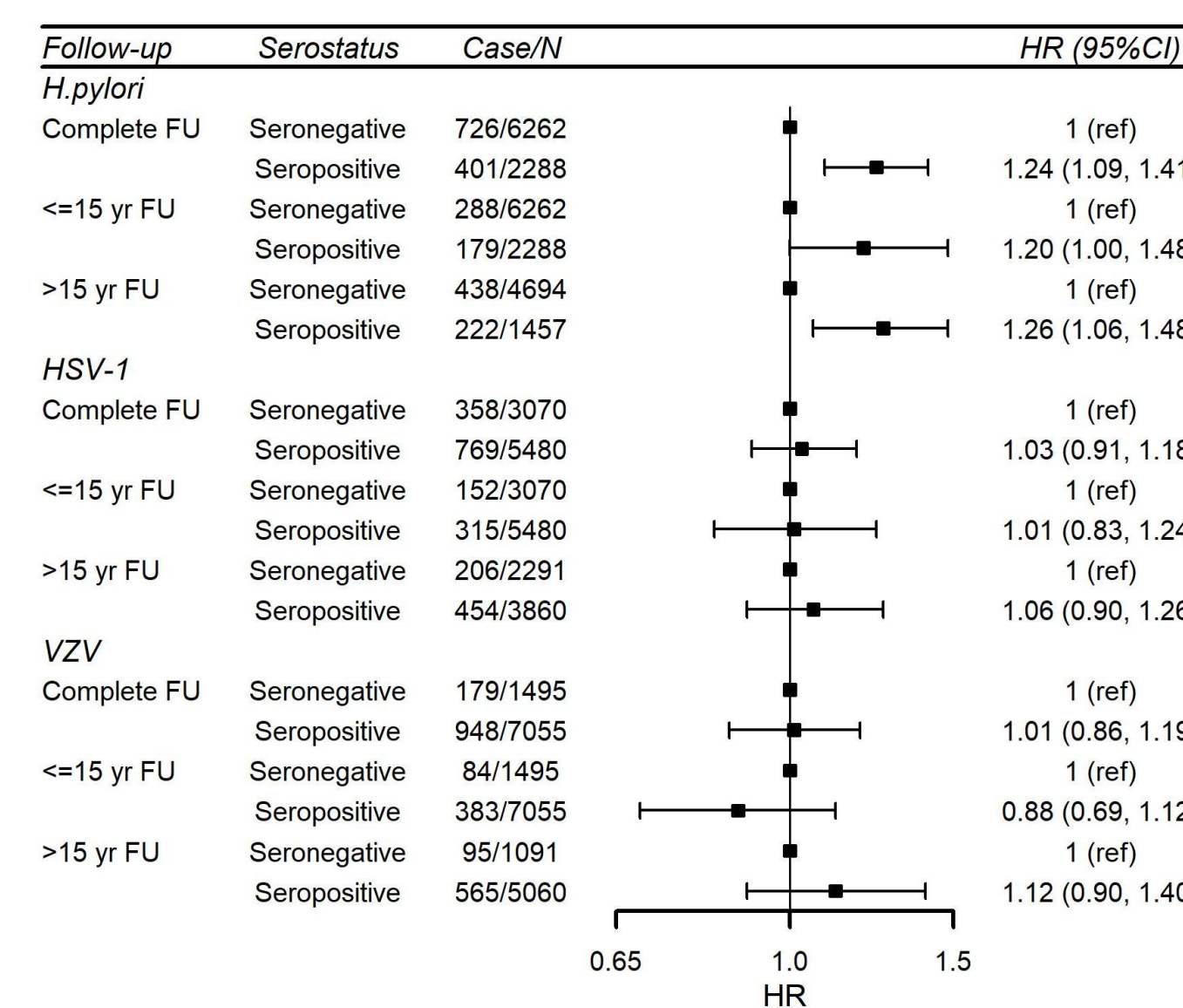
Analysis: Cox proportional-hazards models were used to investigate the association between *H. pylori*, HSV-1, and VZV and dementia risk. Models were adjusted for age, sex, education, occupational social class, area-level SES, BMI, smoking, alcohol, physical activity, hypertension and diabetes

Results

Over 24 years of follow-up (median=22 years), 1,127 participants developed incident dementia.

Main findings

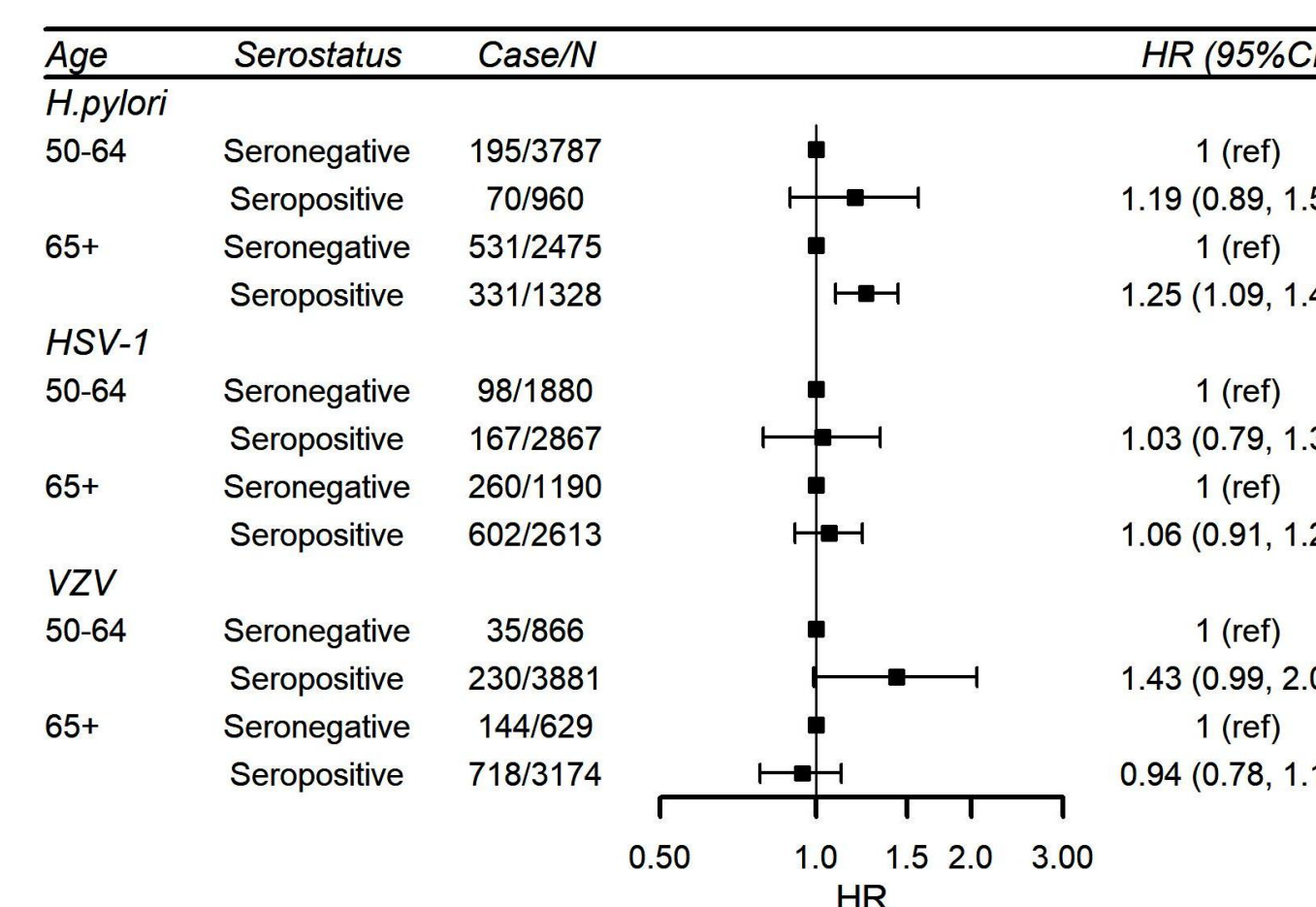
Seropositivity for *H. pylori*, but not HSV-1 or VZV, was associated with an increased risk of dementia. The findings for *H. pylori* remained similar when restricting to dementia cases that occurred more than 15 years later.



Modification by age

VZV was associated with dementia risk in 50-64 year olds but not 65+, year olds ($p=0.04$ for interaction between VZV and age).

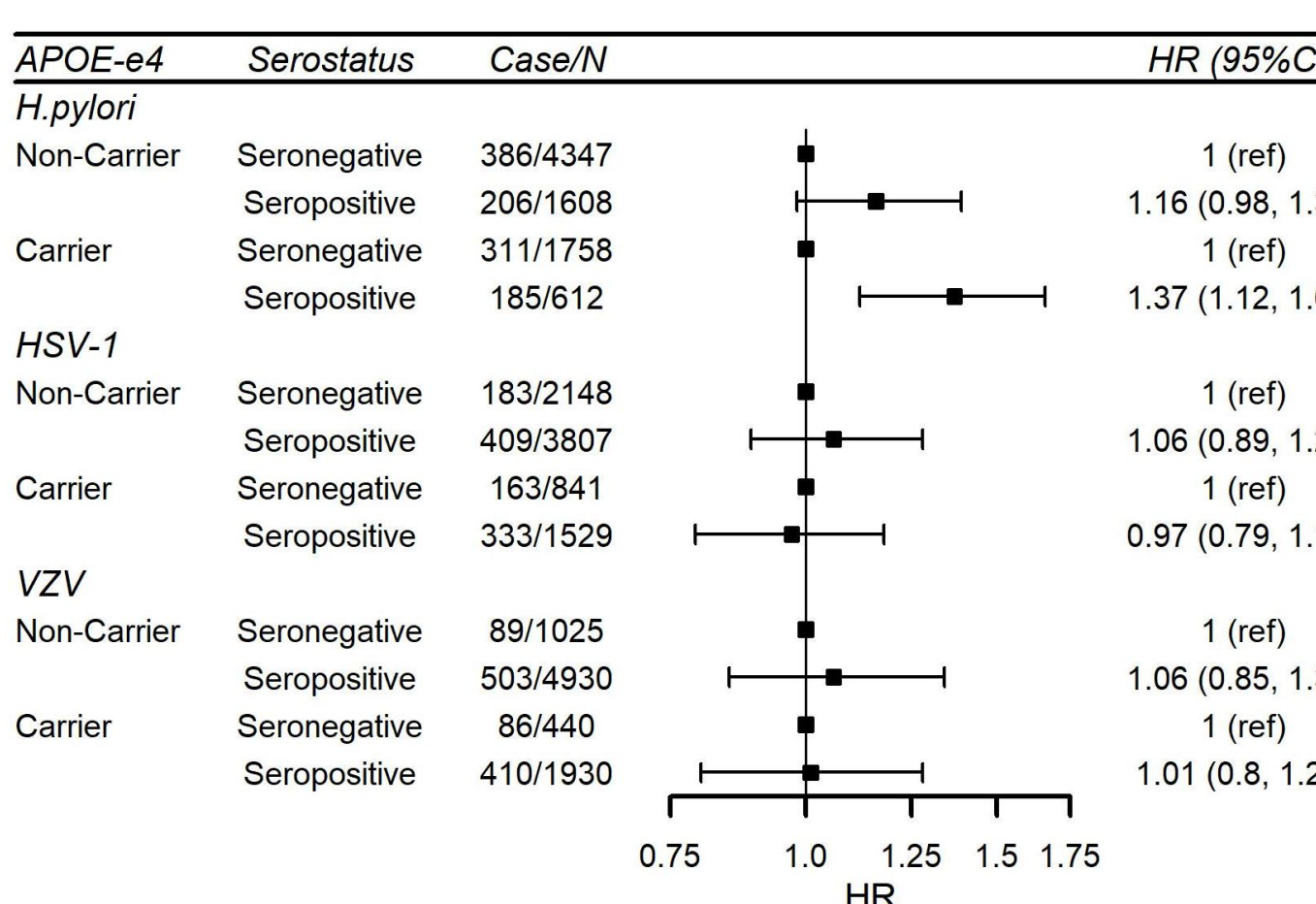
The interactions between age and 1) *H. pylori* ($p=0.61$) and 2) HSV-1 ($p=0.93$) were non-significant.



Modification by APOE-e4

The associations remained similar to the main findings when stratifying by APOE-e4 carrier status.

The interactions between APOE-e4 and 1) *H. pylori* ($p=0.29$), 2) HSV-1 ($p=0.23$) and 3) VZV ($p=0.57$) were non-significant.



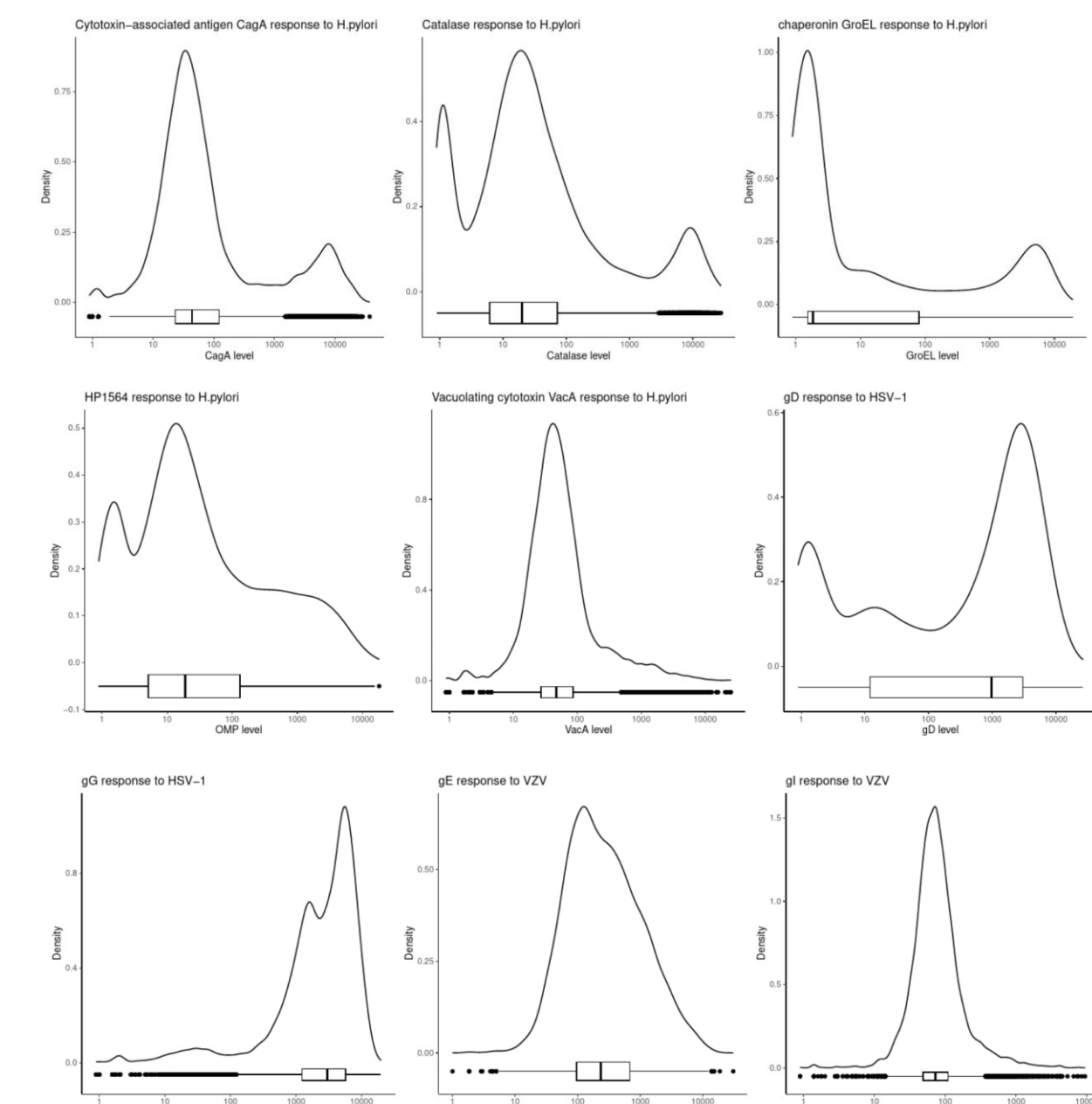
Conclusions

- *H. pylori* seropositivity was associated with an increased risk of dementia after adjusting multiple confounding factors and restricting to cases >15 years later.
- HSV-1 and VZV seropositivity were not associated with dementia risk, except for VZV amongst 50-64 year olds.
- The *H. pylori* antibodies, CagA and GroEL, were associated with dementia risk. CagA is highly pathogenic and is linked to gastric cancer risk.
- *H. pylori* could represent a novel modifiable target for dementia risk reduction, however, accounting for potential confounders occurring in childhood remains an important gap to address.

Antibody distributions

Antibody responses to 5 *H. pylori* antigens, 2 HSV-1 antigens and 2 VZV antigens were measured on the multiplex serology panel.

Individual antibodies could provide mechanistic insights into the relationship between infectious exposures and dementia risk.

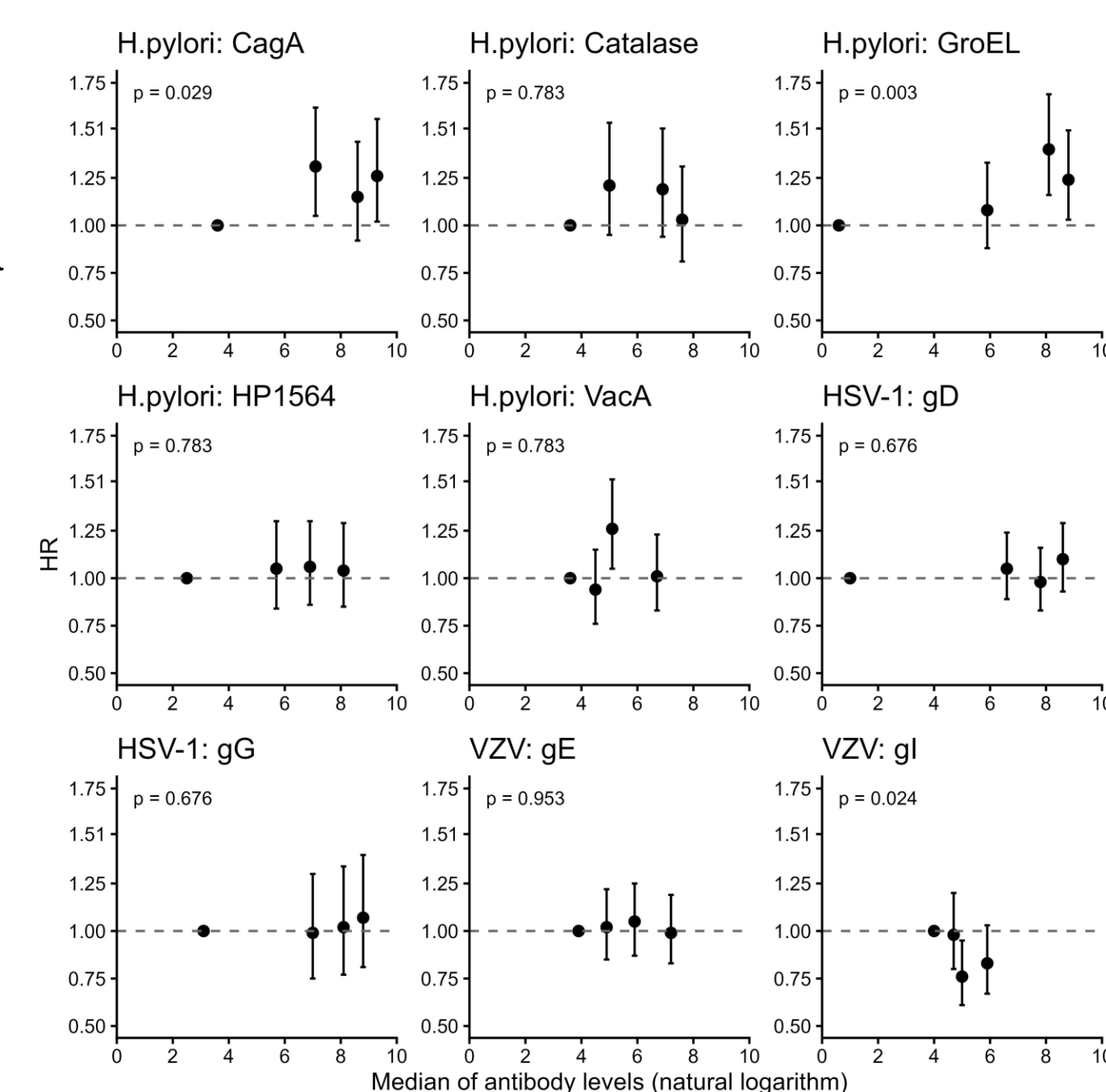


Antibody associations

H. pylori-CagA ($p=0.007$) and *H. pylori*-GroEL ($p=0.001$) were associated with an increased dementia risk.

VZV-gI ($p=0.01$) was inversely associated with dementia risk.

No associations were observed for HSV1-gD ($p=0.42$), HSV1-gG ($p=0.34$), VZV-gE ($p=0.95$), *H. pylori*-catalase ($p=0.26$), *H. pylori*-HP1564 ($p=0.54$), or *H. pylori*-VacA ($p=0.27$) and dementia.



Acknowledgments

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