Gastrointestinal Diseases, Genetic Risk, and Incident Dementia: A Prospective Cohort Study in 352,463 Middle-Aged Adults

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Digestive System Diseases, Genetic Risk, and Incident Dementia: A Prospective Cohort Study

Running head: Digestive diseases and dementia

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Abstract

Introduction: Although digestive system disease affects gut microbiota and their metabolites associated with dementia risk, the association between digestive system diseases and incident dementia has not yet been established.

Methods: This cohort analysis included 458,181 participants free of baseline dementia in the UK Biobank (2006-2021). The associations of fourteen digestive system diseases with dementia incidence were examined in 2022 using Cox proportional hazards regression models. Analyses were performed to differentiate the associations for early- (< 65 years) and late-onset (≥ 65 years) dementia. Interaction and stratification analyses were performed for polygenic risk score (RPS), and apolipoprotein E (APOE).

Results: During a median follow-up of 12.4 years, 6415 incident dementia cases were diagnosed. Eleven digestive system diseases showed significant associations with an increased risk of dementia after controlling for covariates and multiple testing. Compared to individuals without digestive system diseases, the hazard ratios of

dementia increased from 1.15 (95% confidence interval 1.09-1.23) for patients with intestinal diverticular disease to 2.31 (95% confidence interval 1.98-2.70) for patients with cirrhosis. The associations were different between certain digestive system diseases and dementia by onset age. The associations appeared to be stronger for cirrhosis (Q = 0.001), irritable bowel syndrome (Q < 0.001), gastritis and duodenitis (Q =0.002), gastroesophageal reflux disease (Q < 0.001), ulcerative colitis (Q=0.047), gallbladder disease (Q=0.012) and peptic ulcer (Q = 0.030) with early-onset dementia. There were no interactions for PRS or APOE (P >0.05).

Conclusions: These findings suggest an increased need for dementia prevention among patients with digestive system diseases.

Keywords: digestive system; dementia; Gut-brain axis; cohort study

Introduction

Due to the population aging, the number of patients with dementia keeps raising and is projected to increase to 152 million by 2050 worldwide.[1] Few potentially modifiable risk factors have been identified for dementia, such as low education level, traumatic brain injury, smoking, and possibly physical inactivity and air pollution[1], and the mechanisms of the disease remains largely uncovered. Thus, it is urgent to explore other risk factors for dementia with the aims of deepening the understanding of the disease as well as identifying preventive measures.

With increasing data on the microbiome, the gut-brain axis hypothesis of

communication between the central nervous system and the gastrointestinal tract has been widely explored.[2] The development of dementia caused by damage to central nervous cells has been associated with gut inflammation and an alteration of gut microbiota and their related metabolites[3, 4]. Population-based observational studies have found inconsistent evidence of an elevated risk of cognitive decline and dementia among patients with inflammatory bowel disease[5] and liver diseases[6, 7, 8]. Another study observed that treatment with proton pump inhibitors (PPIs), which are widely used for some digestive system diseases, was associated with higher dementia risk.[9] Given conflicting and limited data as well as unknown associations for other digestive system diseases, this study were conducted to comprehensively investigate the associations of 14 digestive system diseases with the risk of dementia.

Methods

Study Population

This study leveraged data from the UK Biobank, which is an ongoing national prospective cohort project that enrolled over 500,000 individuals from the UK during 2006-2010. In this study, individuals with baseline dementia or those diagnosed with dementia in the first year of follow-up (n=1087) and individuals without genetic information (n=43,222) were included. In total, 451,818 participants were included in the final analysis (Appendix Figure 1). Longitudinal data were collected in 2006-2021 and the statistical analyses were performed in 2022. Ethical approval was granted for the UK Biobank by the North West-Haydock Research Ethics Committee (REC

reference: 21/NW/0157).

Measures

This study focused on fourteen digestive system diseases, including gastroesophageal reflux disease (GERD), gastritis and duodenitis, celiac disease, Crohn's disease, ulcerative colitis, intestinal diverticular disease, irritable bowel syndrome (IBS), peptic ulcer, pancreatitis, gallbladder and biliary diseases, non-alcoholic fatty liver disease (NAFLD), chronic liver cirrhosis, appendicitis, and overall gastrointestinal cancer (esophageal, gastric, small intestinal, colorectal, pancreatic, gallbladder, and hepatic cancers). These diseases were ascertained by diagnostic codes from nationwide inpatient datasets, primary care datasets, cancer registries, and self-report diagnosis. Except for individual disease, a compound outcome (i.e., overall digestive diseases) were defined as individuals who have diagnosis of any studied diseases at baseline. The associations of the number of digestive diseases with the risk of dementia were assessed given that some digestive diseases may co-occur. Detailed diagnostic codes are displayed in Appendix Tables 1-2. The accuracy of these diagnostic codes has been found to be high (>89%) in the annual report by the Audit Commission.[10]

The diagnostic codes for all-cause dementia and its subtypes had been used in previous studies and shown to be valid (Appendix Table 3).[11] To differentiate the etiology of dementia subtypes, two common subtypes, Alzheimer's disease (AD) and

vascular dementia (VaD), were defined using diagnostic codes shown in Appendix Table 3**.** AD is caused by changes in the brain, including abnormal buildups of proteins known as amyloid plaques and tau tangles while VaD is caused by conditions that damage blood vessels in the brain or interrupt the flow of blood and oxygen to the brain.[12] Dementia were classified into early-onset (i.e., with the age at diagnosis <65 years) and late-onset (≥65 years) dementia by diagnosis age. Early-onset dementia comprises a heterogeneous range of dementias. Its presentation varies and may include cognitive, psychiatric and neurological symptoms.[13]

A polygenic risk score (PRS) were constructed for dementia based on 39 well-established genetic variants from large-scaled genome-wide association analyses on AD [14] . The PRS was generated by multiplying the genotype dosage of each risk allele for each variant by its respective weight and then summing across all variants. The weights given for the score were derived from International Genomics of Alzheimer's Project (IGAP) studies [14]. Details of used genetic variants are presented in the Appendix Table 4**.** Of note, *APOE* gene was not included in the PRS. The *APOE* haplotypes (ε2/ε3/ε4) were genotyped and determined by 2 genetic variants (i.e., rs429358 and rs7412). Participants with 1 or 2 ε4 alleles were defined as *APOE* ε4 carriers and otherwise as *APOE* ε4 noncarriers.

Information on age at recruitment, sex, ethnicity (white and nonwhite), educational attainment (college and below college), smoking status (never and ever), alcohol

consumption (none-to-moderate and excessive), physical activity (adequate and inadequate), BMI, and family history of dementia were included. Diet quality was assessed by a dementia-associated healthy diet score with data from food frequency questionnaires. The Townsend deprivation index (TDI) was a complex indicator of socioeconomic status. History of hypertension, stroke, and depression were defined by data from the self-reported questionnaires, electronic health-related records, drug prescription, and baseline blood pressure measurement. Regular use of PPIs and nonsteroidal anti-inflammatory drugs (NSAIDs) were recorded in a verbal interview. Multiple imputation for missing data was performed using the multivariate imputation by chained equations method. Detailed information and definition of covariates are presented in Appendix Table 5**.** Based on the prior knowledge about the underlying biologic mechanisms as well as qualitative direction between variables[15]**,** a directed acyclic graph was generated[16] (Appendix Figure 2).

Statistical Analysis

Baseline characteristics by incident disease status were summarized for continuous and categorical variables. Baseline characteristics between the individuals with and without genetic data were described. The incidence rate and cumulative risk of dementia were calculated based on the Kaplan–Meier curve. Treating age as timescale, the Cox proportional hazard regression was used to estimate the associations of digestive diseases with the risk of incident dementia and its subtypes. Three models were performed: 1) model 1 adjusted for age and sex; 2) model 2

additionally adjusted for TDI, educational attainment, BMI, physical activity, diet, smoking status, alcohol consumption, hypertension, stroke, family history of dementia, and depression; and 3) model 3 further adjusted for PRS. Person-years were calculated from the baseline date to the date of diagnosis, death, loss, or the end of follow-up, whichever came first. To rule out the influence of competing risk of death, cumulative risk curves of dementia and death and a multivariable competing risk model based on model 3 were performed.[17]

The associations of digestive diseases with the risk of dementia subtypes were performed. Heterogeneity between disease subtypes was calculated using the contrast test method.[18] For early-onset dementia, the analysis was limited to the population with age less than 65 years (n=368,498). The associations of overall digestive diseases and the number of digestive diseases with the risk of incident all-cause dementia were also explored. Multiplicative interaction and further performed stratification analysis were assessed for PRS categories, *APOE* ε4 carrying status, sex, educational attainment, smoking status, alcohol consumption, baseline depression, baseline hypertension, and family history. Relative excess risk due to interaction was calculated to assess interaction at additive scale using "InteractionR" package.[19] To examine the robustness of the results, several sensitivity analyses were performed: 1) the analysis excluding incident cases diagnosed in the first 3 years of follow-up; 2) the analysis including individuals who developed incident digestive diseases, and 3) the analysis excluding participants with incident Parkinson's disease, a major

neurodegenerative disease; 4) analysis excluding dementia cases identified only in mortality data (n=183); 5) the analysis only including participants with age at recruitment more than 55 years (n=271,639). This analysis can control age of participants at study entry to further address immortal time bias;[20] 6) analysis additionally adjusted for NSAID use. Given PPIs are routinely used among patients with digestive diseases and have been associated with dementia,[9] a sensitivity analysis with further adjustment for PPI use were performed. Multiple comparisons were corrected with the false discovery rate (FDR) method. All statistical analyses were conducted using R 4.1.2. Two-sided FDR-adjusted *P* value (Q value) < 0.05 were deemed significant.

Results

During a median follow-up of 12.4 years (interquartile range 11.4-13.0), 6415 incident dementia cases were identified. The baseline characteristics of participants by incident dementia are displayed in Table 1. Individuals with genetic data were more likely to be older, more educated and have lower TDI scores than those without data (Appendix Table 6).

The incident dementia cases and person-years stratified by digestive system diseases were presented in Appendix Table 7. As shown in Appendix Table 8, individuals with baseline digestive diseases more often had a numerically higher 10-year risk of developing dementia. In multivariable cox models (Figure 1), the hazard ratio (HR) of

dementia from largest to smallest was 2.31 (95% confidence interval [CI] 1.98, 2.70; *Q*<0.001) for cirrhosis, 1.83 (95% CI 1.60, 2.09; *Q*<0.001) for NAFLD, 1.53 (95% CI 1.29, 1.83; *Q*<0.001) for pancreatitis, 1.42 (95% CI 1.12, 1.80; *Q*=0.005) for Crohn's disease, 1.40 (95% CI 1.28 1.52; *Q*<0.001) for peptic ulcer, 1.38 (95% CI 1.30, 1.47; *Q*<0.001) for gastritis and duodenitis, 1.34 (95% CI 1.12, 1.59; *Q*=0.002) for ulcerative colitis, 1.33 (95% CI 1.23, 1.43; *Q*<0.001) for gallbladder disease, 1.23 (95% CI 1.16, 1.31; *Q*< 0.001) for GERD, 1.16 (95% CI 1.06, 1.27; *Q*=0.003) for IBS, and 1.15 (95% CI 1.09, 1.23; *Q*<0.001) for intestinal diverticular disease. Consistent results were generated by the competing risk model with certain associations attenuating slightly but remaining significant (Appendix Table 9 and Appendix Figure 3-4).

When considering multiple conditions of digestive diseases (Appendix Table 10), results showed that having any digestive disease was associated with a higher risk of all-cause dementia compared with digestive disease-free participants (HR 1.37, 95% CI 1.30, 1.44, Q<0.001). The number of comorbid digestive diseases at baseline was positively associated with dementia risk ($HR_{\text{each additional disease}}$ 1.18, 95% CI 1.15, 1.20; Q<0.001).

Figure 2 shows the associations of 14 digestive system diseases with risk of incident AD and VaD. For AD, six associations (gastritis and duodenitis, peptic ulcer, pancreatitis, gallbladder disease, NAFLD, and cirrhosis) were significant in model 3

after FDR correction. For VaD, nine associations (gastritis and duodenitis, peptic ulcer, IBS, GERD, and intestinal diverticular disease, pancreatitis, gallbladder disease, NAFLD, and cirrhosis) remained in model 3 after FDR correction. No heterogeneity was detected in the associations of digestive system diseases with risk of incident AD and VaD (Q value for heterogeneity>0.05).

The associations of digestive diseases differed with between early- and late-onset dementia (Figure 3). Compared to that for late-onset dementia, the associations for early-onset dementia appeared to be stronger with cirrhosis, NAFLD, ulcerative colitis, peptic ulcer, gastritis and duodenitis, GERD, gallbladder disease, and appendicitis. Heterogeneity was detected for these associations between early- and late-onset dementia (*Q* value for heterogeneity < 0.05).

There was no evidence from both multiplicative or additive scale that supported the interactions of digestive system diseases with sex, educational attainment, depression, hypertension, family history, smoking status, and alcohol consumption on the risk of dementia after FDR correction (Q value for interaction > 0.05, Appendix Table 11-15). PRS categories were significantly associated with the risk of dementia (Appendix Table 16)**.** No interactions were detected between digestive system diseases and PRS or *APOE ε4* carrying status (*P-interaction* > 0.05, Appendix Figure 3-4).

The associations remained after a series of sensitivity analyses (Appendix Table 17).

In the analysis excluding individuals who developed subsequent digestive system diseases after baseline, only seven digestive diseases in association with dementia remained significant (Appendix Table 18). Certain associations attenuated slightly albeit remained significant in the sensitivity analysis with further adjustment for regular PPI use (Appendix Table 17).

Discussion

This large-scale prospective cohort study found that eleven digestive system diseases were associated with a 15%-131% increased risk of dementia. As for dementia subtypes, the associations were similar for AD and VaD. However, the associations of cirrhosis, NAFLD, ulcerative colitis, peptic ulcer, gastritis and duodenitis, GERD, gallbladder disease, and appendicitis appeared to be more strongly associated with early-onset dementia compared to late-onset dementia. There were no interactions of digestive system diseases with genetic risk or *APOE ε4*.

The associations between different digestive system diseases and dementia have been investigated in some previous studies mainly focusing on liver disease,[6-8] IBS,[21] gastritis,[22] GERD,[23] and diverticular disease[24]. Most of these studies found positive links between digestive system diseases and the risk of dementia, which is in line with this study based on a large-scaled cohort including more than 5000 incident cases. However, most of the above studies were based on the East Asian population[5, 21, 24] that has a different pattern of digestive diseases compared to other populations due to

dietary habits and a high prevalence of *Helicobacter pylori* infection[25]. This study thus adds novel information in support of the positive associations between a broad range of digestive diseases and dementia risk in the western world. The associations of NAFLD and cirrhosis with dementia were inconsistent among previous studies.[6-8] A meta-analysis pointed to NAFLD as a risk factor for dementia, which is consistent with current findings.[26] With respect to differences in the literature, this is likely to be a result of inconsistent definitions for NAFLD. A study based on diagnostic codes reported a higher risk (reported HR=1.32),[6] whereas studies based on fatty liver index tended to report a smaller or nonsignificant increased risk of dementia (reported HRs 0.92 to 1.08).[26] This may imply that the risk of dementia is significantly different depending on the degree of NAFLD disease or surveillance bias (only 1 in 1000 NAFLD cases are diagnosed at hospitals). The association between cirrhosis and dementia may be influenced by residual confounding from alcohol consumption[27] even though the primary analysis was adjusted for self-reported alcohol consumption.

No significant differences were observed between the associations of AD and VaD with digestive system diseases. An interesting finding of the current study is the strong association of certain digestive system diseases with early-onset dementia compared to late-onset dementia. The possible reason for the differences may be that early-onset dementia is mainly caused by vascular comorbidities that have a high prevalence rate among patients with gastrointestinal dysfunction[28]. These findings not only deepen understanding of the etiological differences between early- and late-onset

dementia but also may guide the secondary prevention for patients with different gastrointestinal conditions. There were no consistent multiplicative and additive interaction effects of digestive system diseases with a wide range of phenotypic and genetic factors on dementia risk. In other words, the dementia prevention should target the overall population.

The underlying pathways linking digestive system diseases to dementia remain to be established; however, there are several plausible mechanisms that may explain the observed positive associations. The most important bridge is the gut microbiome. The onset of digestive system diseases that alters the normal function and microenvironment of the gastrointestinal tract impacts the diversity, components, and intensity of gut microbiota and the levels of their metabolites[29]. Animal studies have found that fecal microbiota transplantation between AD mice and healthy controls changed the levels of amyloid and tau, memory function and neurogenesis in the hippocampus.[30, 31] In addition, the metabolites of gut microbiota, like bile acid and indole-3 propionate, have been identified as potential mediators contributing to cognitive impairment and nerve repair.[3, 32, 33] Treatments of digestive system diseases, such as PPIs, are positively associated with dementia.[9] These findings showed that most associations slightly attenuated with further adjustment for regular PPI use, which may be partly, explained by the previouly reported PPI-dementia associations. *Helicobacter pylori* infection that is a frequent pathogen of gastric disease may also play a role.[22] Recent literature has proven that *Helicobacter pylori* accelerates AD

development via outer membrane vesicles in an animal model.[34] However, the magnitude of the effect of this pathway on AD pathogenesis in humans is uncertain since the association between *Helicobacter pylori* infection and dementia risk is mixed in different cohorts[35, 36] and the prevalence of *Helicobacter pylori* infection is quite low in the U.K. For vascular morbidity related digestive system diseases, the increased burden of stroke may mediate the associations with in particular early-onset and VaD. For gastritis, duodenitis, and IBS that have inflammation as a key pathogenic symptom, cumulative chronic inflammation may increase the risk of dementia by facilitating neurocognitive changes and subsequent functional decline.[37] Further study is needed to explore whether the extent and severity of gut inflammation of these diseases are also contributing to the pathogenesis of dementia.

Limitations

Several limitations should be noted when interpreting this study. First, this is an observational cohort study, which cannot infer causality. However, possible biases were minimized from reverse causation and residual confounding by excluding incident cases diagnosed during the first year of follow-up in the primary analysis and adjusted for vital risk factors for dementia. Second, there might be misclassifications of digestive system diseases even though the used diagnostic codes have been found to be valid [10]. Due to the prospective design of the study, these misclassifications should be nondifferential. Third, except for PPIs and NSAIDs, other treatments for gastrointestinal disorders were not taken into consideration; neither did this study

consider acute and chronic gastrointestinal condition nor the duration of digestive diseases separately in the associations with risk of dementia. Fourth, the study might have had insufficient power to detect weak associations owing to few cases for infrequent digestive system diseases. Fifth, a genome-wide cross-trait analysis revealed shared genetic architecture between AD and digestive system diseases.[38] Thus, the study could not completely rule out the possibility that the observed associations were caused by shared genetic risk factors even though study results were robust in the analysis with the additional adjustment for the family history of dementia and PRS.

Conclusions

In summary, this cohort study found associations of eleven digestive system diseases with an increased risk of incident dementia. The associations appeared to be stronger for early-onset dementia compared to late-onset dementia. The study provides novel understandings about the etiology of early- and late-onset dementia and emphasizes the great importance of dementia prevention among patients with digestive system diseases.

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The datasets analysed during the current study are available in a public, open access repository (https://www.ukbiobank.ac.uk/).

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The authors declare that they have no competing interests

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References

1. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. Aug 8 2020;396(10248):413-446. doi:10.1016/s0140-6736(20)30367-6

2. Mayer EA, Tillisch K, Gupta A. Gut/brain axis and the microbiota. *J Clin Invest*. Mar 2 2015;125(3):926-38. doi:10.1172/jci76304

3. MahmoudianDehkordi S, Arnold M, Nho K, et al. Altered bile acid profile associates with cognitive impairment in Alzheimer's disease-An emerging role for gut microbiome. *Alzheimers Dement*. Jan 2019;15(1):76-92. doi:10.1016/j.jalz.2018.07.217

4. Qian XH, Song XX, Liu XL, Chen SD, Tang HD. Inflammatory pathways in Alzheimer's disease mediated by gut microbiota. *Ageing Res Rev*. Jul 2021;68:101317. doi:10.1016/j.arr.2021.101317

5. Zhang B, Wang HE, Bai YM, et al. Inflammatory bowel disease is associated with higher dementia risk: a nationwide longitudinal study. *Gut*. Jan 2021;70(1):85-91. doi:10.1136/gutjnl-2020-320789

6. Shang Y, Widman L, Hagström H. Nonalcoholic Fatty Liver Disease and Risk of Dementia: A Population-Based Cohort Study. *Neurology*. Aug 9 2022;99(6):e574-e582. doi:10.1212/wnl.0000000000200853

7. Newton JL, Hollingsworth KG, Taylor R, et al. Cognitive impairment in primary biliary cirrhosis: symptom impact and potential etiology. *Hepatology*. Aug 2008;48(2):541-9. doi:10.1002/hep.22371

8. Xiao T, van Kleef L, Ikram MK, De Knegt R, Ikram MA. Association of Nonalcoholic Fatty Liver Disease and Fibrosis With Incident Dementia and Cognition: The Rotterdam Study. *Neurology*. Aug 9

2022;99(6):e565-e573. doi:10.1212/wnl.0000000000200770

9. Gomm W, von Holt K, Thomé F, et al. Association of Proton Pump Inhibitors With Risk of Dementia: A Pharmacoepidemiological Claims Data Analysis. *JAMA Neurol*. Apr 2016;73(4):410-6. doi:10.1001/jamaneurol.2015.4791

10. Commission A. Improving data quality in the NHS: annual report on the PbR assurance programme. Accessed August 1, 2022. https://www.bl.uk/collection-items/improving-data-quality-in-the-nhs-annual-report-on-the-pbr-assurance-programme

11. Calvin CM, Wilkinson T, Starr JM, et al. Predicting incident dementia 3-8 years after brief cognitive tests in the UK Biobank prospective study of 500,000 people. *Alzheimers Dement*. Dec 2019;15(12):1546-1557. doi:10.1016/j.jalz.2019.07.014

12. Kalaria R. Similarities between Alzheimer's disease and vascular dementia. *Journal of the Neurological Sciences*. 2002;203:29-34. doi:10.1016/S0022-510X(02)00256-3

13. Loi SM, Cations M, Velakoulis D. Young-onset dementia diagnosis, management and care: a narrative review. *Medical Journal of Australia*. 2023;218(4):182-189. doi:https://doi.org/10.5694/mja2.51849

14. Ebenau JL, van der Lee SJ, Hulsman M, et al. Risk of dementia in APOE ε4 carriers is mitigated by a polygenic risk score. *Alzheimers Dement (Amst)*. 2021;13(1):e12229. doi:10.1002/dad2.12229

15. Bellou V, Belbasis L, Tzoulaki I, Middleton LT, Ioannidis JPA, Evangelou E. Systematic evaluation of the associations between environmental risk factors and dementia: An umbrella review of systematic reviews and meta-analyses. *Alzheimers Dement*. Apr 2017;13(4):406-418. doi:10.1016/j.jalz.2016.07.152

16. Hernán MA, Hernández-Díaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *Am J Epidemiol*. Jan 15 2002;155(2):176-84. doi:10.1093/aje/155.2.176

17. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association*. 1999/06/01 1999;94(446):496-509. doi:10.1080/01621459.1999.10474144

18. Wang M, Spiegelman D, Kuchiba A, et al. Statistical methods for studying disease subtype heterogeneity. *Stat Med*. Feb 28 2016;35(5):782-800. doi:10.1002/sim.6793

19. Alli BY. InteractionR: An R package for full reporting of effect modification and interaction. *Software Impacts*. 2021/11/01/ 2021;10:100147. doi:https://doi.org/10.1016/j.simpa.2021.100147

20. Yadav K, Lewis RJ. Immortal Time Bias in Observational Studies. *JAMA*. 2021;325(7):686-687. doi:10.1001/jama.2020.9151

21. Chen CH, Lin CL, Kao CH. Irritable Bowel Syndrome Is Associated with an Increased Risk of Dementia: A Nationwide Population-Based Study. *PLoS One*. 2016;11(1):e0144589. doi:10.1371/journal.pone.0144589

22. Kountouras J, Gavalas E, Boziki M, Zavos C. Helicobacter pylori may be involved in cognitive impairment and dementia development through induction of atrophic gastritis, vitamin B-12 folate deficiency, and hyperhomocysteinemia sequence. *Am J Clin Nutr*. Sep 2007;86(3):805-6; author reply 806-7. doi:10.1093/ajcn/86.3.805

23. Gau SY, Lai JN, Yip HT, Wu MC, Wei JC. Higher Dementia Risk in People With Gastroesophageal Reflux Disease: A Real-World Evidence. *Front Aging Neurosci*. 2022;14:830729. doi:10.3389/fnagi.2022.830729

24. Peng YC, Lin CL, Yeh HZ, Tung CF, Chang CS, Kao CH. Diverticular disease and additional

comorbidities associated with increased risk of dementia. *J Gastroenterol Hepatol*. Nov 2016;31(11):1816-1822. doi:10.1111/jgh.13389

25. Huang J, Lucero-Prisno DE, 3rd, Zhang L, et al. Updated epidemiology of gastrointestinal cancers in East Asia. *Nat Rev Gastroenterol Hepatol*. May 2023;20(5):271-287. doi:10.1038/s41575-022-00726-3

26. Lu LY, Wu MY, Kao YS, Hung CH. Non-alcoholic fatty liver disease and the risk of dementia: A meta-analysis of cohort studies. *Clin Mol Hepatol*. Oct 2022;28(4):931-932. doi:10.3350/cmh.2022.0259

27. Yuan S, Chen J, Ruan X, et al. Smoking, Alcohol consumption, and 24 Gastrointestinal Diseases: Mendelian Randomization Analysis. *Elife*. Feb 2 2023;12doi:10.7554/eLife.84051

28. Argollo M, Gilardi D, Peyrin-Biroulet C, Chabot JF, Peyrin-Biroulet L, Danese S. Comorbidities in inflammatory bowel disease: a call for action. *Lancet Gastroenterol Hepatol*. Aug 2019;4(8):643-654. doi:10.1016/s2468-1253(19)30173-6

29. de Vos WM, Tilg H, Van Hul M, Cani PD. Gut microbiome and health: mechanistic insights. *Gut*. May 2022;71(5):1020-1032. doi:10.1136/gutjnl-2021-326789

30. Kim N, Jeon SH, Ju IG, et al. Transplantation of gut microbiota derived from Alzheimer's disease mouse model impairs memory function and neurogenesis in C57BL/6 mice. *Brain Behav Immun*. Nov 2021;98:357-365. doi:10.1016/j.bbi.2021.09.002

31. Kim MS, Kim Y, Choi H, et al. Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer's disease animal model. *Gut*. Feb 2020;69(2):283-294. doi:10.1136/gutjnl-2018-317431

32. Huang YL, Lin CH, Tsai TH, et al. Discovery of a Metabolic Signature Predisposing High Risk Patients with Mild Cognitive Impairment to Converting to Alzheimer's Disease. *Int J Mol Sci*. Oct 9 2021;22(20)doi:10.3390/ijms222010903

33. Sun J, Zhang Y, Kong Y, et al. Microbiota-derived metabolite Indoles induced aryl hydrocarbon receptor activation and inhibited neuroinflammation in APP/PS1 mice. *Brain Behav Immun*. Nov 2022;106:76-88. doi:10.1016/j.bbi.2022.08.003

34. Xie J, Cools L, Van Imschoot G, et al. Helicobacter pylori-derived outer membrane vesicles contribute to Alzheimer's disease pathogenesis via C3-C3aR signalling. *J Extracell Vesicles*. Feb 2023;12(2):e12306. doi:10.1002/jev2.12306

35. Beydoun MA, Beydoun HA, Elbejjani M, Dore GA, Zonderman AB. Helicobacter pylori seropositivity and its association with incident all-cause and Alzheimer's disease dementia in large national surveys. *Alzheimers Dement*. Sep 2018;14(9):1148-1158. doi:10.1016/j.jalz.2018.04.009

36. Fani L, Wolters FJ, Ikram MK, et al. Helicobacter pylori and the risk of dementia: A population-based study. *Alzheimers Dement*. Oct 2018;14(10):1377-1382. doi:10.1016/j.jalz.2018.05.005

37. Walker KA, Gottesman RF, Wu A, et al. Systemic inflammation during midlife and cognitive change over 20 years: The ARIC Study. *Neurology*. Mar 12 2019;92(11):e1256-e1267. doi:10.1212/wnl.0000000000007094

38. Adewuyi EO, O'Brien EK, Nyholt DR, Porter T, Laws SM. A large-scale genome-wide cross-trait analysis reveals shared genetic architecture between Alzheimer's disease and gastrointestinal tract disorders. *Commun Biol*. Jul 18 2022;5(1):691. doi:10.1038/s42003-022-03607-2

Table 1. Baseline characteristics by incident dementia

Characteristic	Without incident dementia (n = 451,766)	Incident dementia (n = 6415)
Age at baseline in years	56.65 (8.01)	64.15 (4.92)
Sex (%)		
Female	245752 (54.4)	3056 (47.6)
Male	206014 (45.6)	3359 (52.4)
Townsend deprivation index	-1.46 (2.99)	-1.01 (3.28)
Educational attainment (%)		
Below college degree	302137 (67.5)	5006 (79.6)
College degree	145264 (32.5)	1280 (20.4)
Physical activity (%)		
Inadequate	136800 (30.3)	2364 (36.9)
Adequate	314966 (69.7)	4051 (63.1)
Smoking status (%)		
Never smoked	243499 (54.1)	2893 (45.4)
Previous or current smokers	206677 (45.9)	3479 (54.6)
Alcohol consumption (%)		
None to moderate	356366 (78.9)	5257 (82.1)
Heavy	95092 (21.1)	1145 (17.9)
BMI in kg/m^2	27.39 (4.77)	27.79 (4.96)
Healthy diet (%)		
Unhealthy	123718 (28.6)	1634 (28.1)
Healthy	308556 (71.4)	4190 (71.9)
APOE ε4 carrier (%)	185898 (41.1)	3869 (60.3)
Polygenic risk score category (%)		
Low	89108 (19.7)	935 (14.6)
Intermediate	270587 (59.9)	3704 (57.7)
High	92071 (20.4)	1776 (27.7)
Baseline depression (%)	99876 (22.1)	1510 (23.5)
Baseline hypertension (%)	315273 (69.9)	5287 (82.6)
Baseline stroke (%)	6600 (1.5)	350 (5.5)
Family history of dementia (%)	50197 (11.1)	1215 (18.9)

BMI, body mass index. Continuous variables were expressed in mean (standard deviation, SD) and categorical variables in number (%).

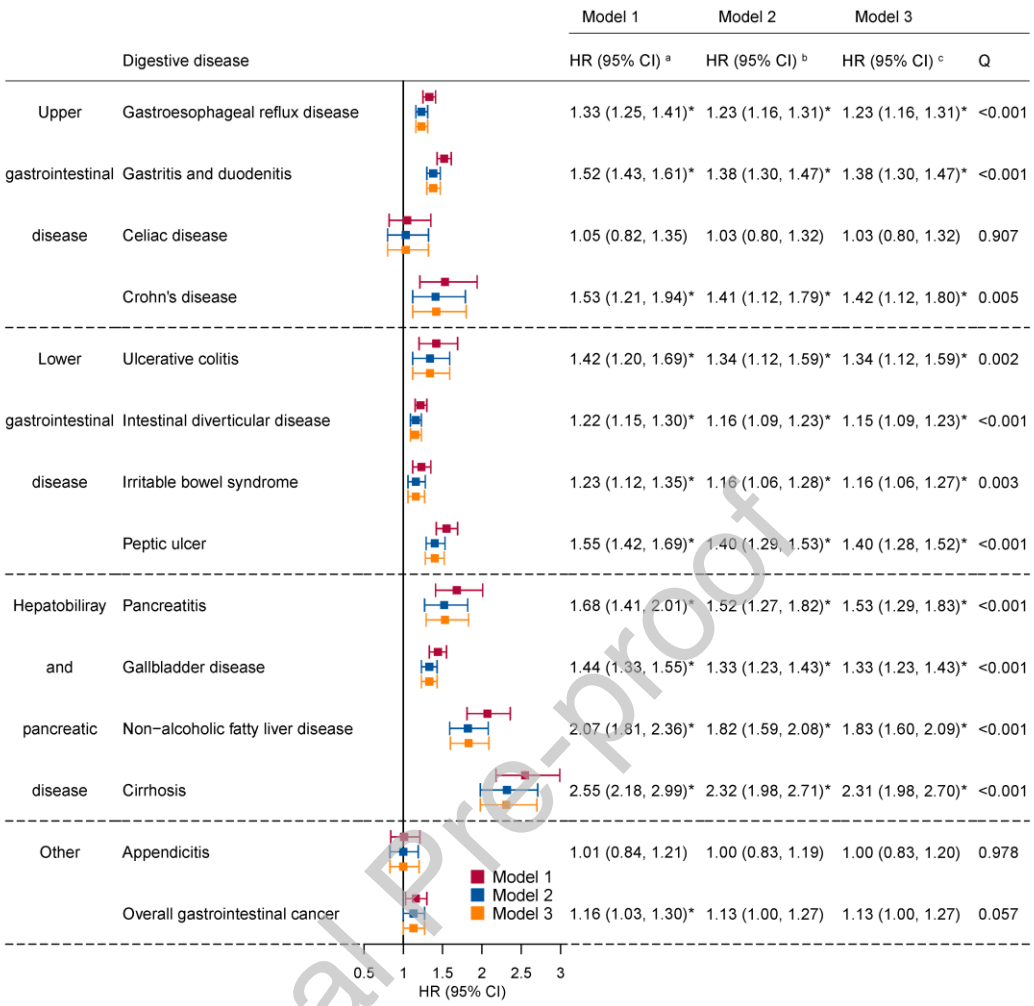

Figure 1. Associations between baseline digestive system diseases and risk of incident dementia. CI, confidence interval; HR, hazard ratio. [a] adjusted for age and sex; [b] further adjusted for age, sex, Townsend deprivation index, educational attainment, BMI, physical activity, diet, smoking status, alcohol consumption, baseline hypertension, baseline stroke, history of dementia, depression; [c] further adjusted for polygenic risk scores. * Representing a significant association after FDR correction for multiple comparison. *P* for heterogeneity was two-sided FDR-adjusted.

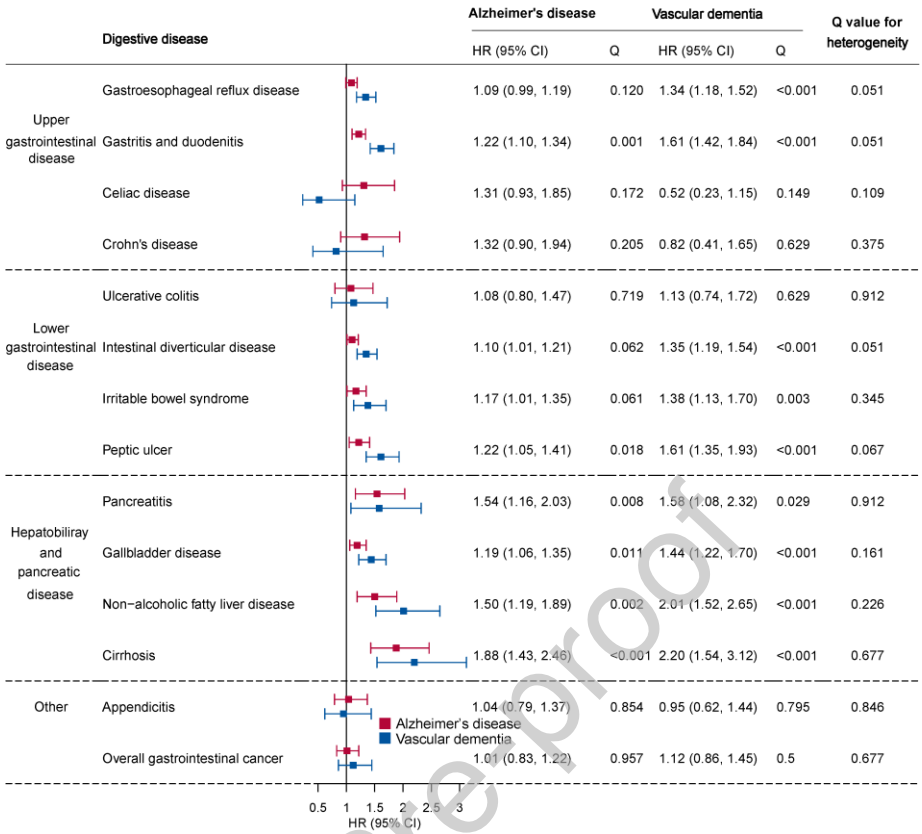

Figure 2. Associations between digestive system diseases and risk of incident Alzheimer's disease and vascular dementia. CI, confidence interval; HR, hazard ratio. * Representing a significant association after FDR correction for multiple comparison. *P* for heterogeneity was two-sided FDR-adjusted.

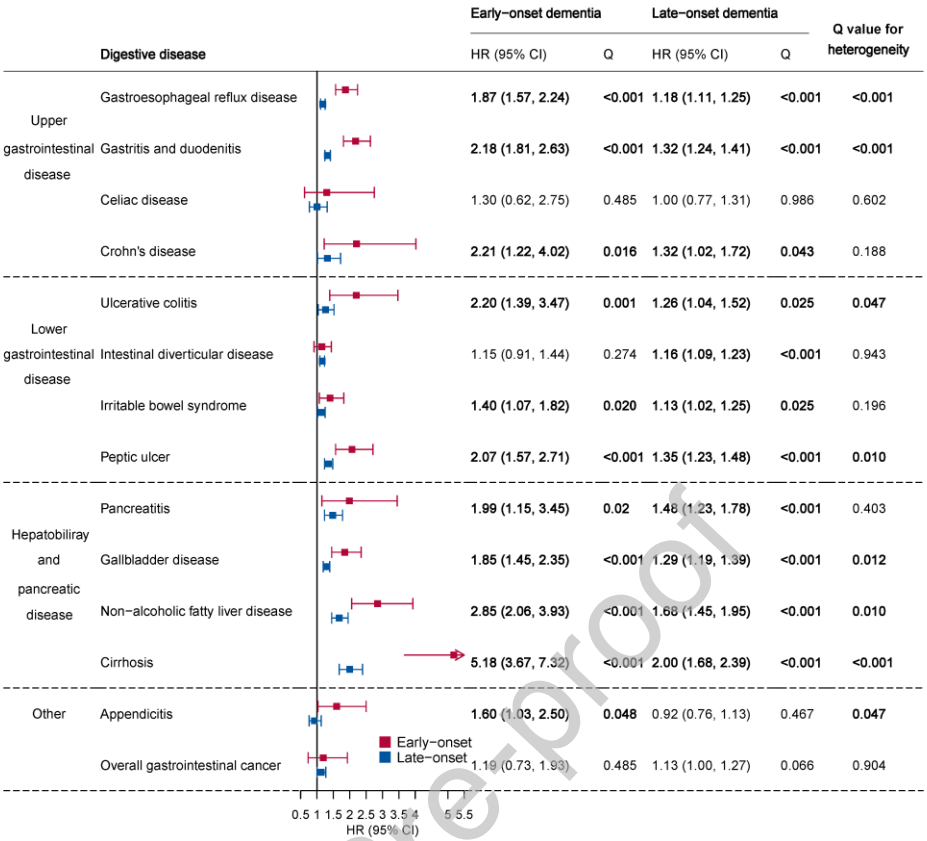

Figure 3. Associations between baseline digestive system diseases and risk of incident dementia by onset age. CI, confidence interval; HR, hazard ratio. * Representing a significant association after FDR correction for multiple comparison. *P* for heterogeneity was two-sided FDR-adjusted.

CRediT authorship contribution statement

All authors read and approved the final manuscript.

Shuai Yuan (Conceptualization: Supporting; Methodology: Leading; Writing - original draft: Leading; Writing - review & editing: Leading)

Lintao Dan (Conceptualization: Supporting; Formal analysis: Leading; Writing - original draft: Supporting)

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