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Cross-trait analysis of Alzheimer's disease and gastrointestinal tract disorders identifies shared loci highlighting immune-related and statin pathways

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Abstract

Several observational studies suggest a relationship between Alzheimer's disease (AD) and gastrointestinal tract (GIT) disorders; however, their underlying mechanisms remain unclear. Here, we analysed several genome-wide association studies (GWAS) summary statistics (N = 34,652 – 456,327) to assess AD and GIT disorders relationships. We found a significant genetic overlap and correlation between AD and each of gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), medications for GERD or PUD (PGM), gastritis-duodenitis, irritable bowel syndrome and diverticulosis, but not inflammatory bowel disease. Our analysis suggests a partial causal association between AD and gastritis-duodenitis, diverticulosis and medication for PUD. GWAS meta-analysis identified seven loci ($P < 5 \times 10^{-8}$, *PDE4B*, *CD46*, *SEMA3F*, *HLA-DRA*, *MTSS2*, *PHB*, and *APOE*) shared by AD and PGM, six of which are novel. These loci were replicated using GERD and PUD GWAS and reinforced in gene-based analyses. Lipid metabolism, autoimmune system, lipase inhibitors, PD-1 signalling, and statin pathways were significantly enriched for AD and GIT disorders. These findings support shared genetic susceptibility in AD and GIT disorders. Lipase inhibitors and statins may provide novel therapeutic avenues for AD, GIT disorders, or their comorbidity.

Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia, characterised by neurodegeneration and a progressive decline in cognitive ability beyond what would be expected from the normal ageing process ^{1,2}. The disorder ranks as a subject of significant global public health importance with consequences for wide-ranging social and economic adverse impacts on sufferers, their families, and the society at large ¹. By the year 2030, over 82 million people—and about 152 million by 2050—are projected to suffer from AD ^{1,2}. The annual global economic costs of the disorder are currently estimated at nearly one trillion US dollars and predicted to reach two trillion US dollars in 2030 ¹⁻⁴. While AD has no known curative treatments, and its pathogenesis is yet to be clearly understood, a comprehensive assessment of its shared genetics with diseases (comorbidities) can provide a deeper understanding of its underlying biological mechanisms and those of its comorbidities.

Several studies have reported a pattern of co-occurrence of dementia (and AD in particular) with certain gastrointestinal tract (GIT) disorders, microbiota or medications commonly used in the treatment of peptic ulcer disease (PUD) ⁵⁻¹¹. For example, an observational study reported more than twice the odds of dementia in individuals with gastritis (adjusted odds ratio (OR): 2.42, $P < 0.001$, 95% confidence interval (CI): 1.68 – 3.49) ⁵. Another observational study found a significant association between regular use of proton-pump inhibitors (PPI, medications for the treatment of gastritis-duodenitis, gastroesophageal reflux disease (GERD) or PUD) and increased risk of incident dementia (hazard ratio [HR]: 1.44 [95% CI, 1.36 – 1.52]; $P < 0.001$) ⁶. Similarly, lansoprazole (a PPI) is reported to promote amyloid-beta (Ab) production ⁷, the accumulation of which is central to one of the core hypotheses for the development of AD ¹². More recently, a large population-based longitudinal study reported a

more than a six-fold increased risk of AD in individuals with inflammatory bowel disease (IBD) [HR: 6.19, 95%CI: 3.31 – 11.57], predicting over five-fold increased incidence across all forms of dementia ⁹.

Taken together, evidence suggests comorbidity between AD and GIT disorders, although it is not clear whether GIT traits are risks for AD or vice versa. Regardless, these findings agree with the concept of the ‘gut-brain’ axis or the ‘gastric mucosa-brain’ relationship, which has been implicated in the association between GIT-related traits and central nervous system (CNS) disorders including depression and Parkinson’s disease ¹³⁻¹⁶. In support of a possible link between AD and GIT traits, a recent animal model-based study indicates that intra-gastrointestinal accumulation of Ab may induce gastric function alteration, CNS amyloidosis, and subsequent AD-like dementia ¹⁷. Comorbidity of AD and GIT disorders may worsen the quality of life of sufferers while contributing significantly to increased healthcare costs.

Despite the increasing number of studies reporting an association between AD and GIT traits, the biological mechanism(s) underlying this association remains unclear. Moreover, contrasting evidence exists ^{9,18,19}, and many questions are unanswered. First, is there a risk-increasing association between AD and GIT disorders (including medicines commonly used for PUD, GERD, or gastritis-duodenitis)—PGM? This question assumes great importance in the face of contrasting evidence and longstanding debates on this subject ¹⁸⁻²⁰. Second, is there a causal relationship between AD and GIT disorders (vertical pleiotropy)? Third, are there genetic components—e.g., single nucleotide polymorphism (SNPs), genes, and genomic loci—shared by AD and GIT disorders (biological pleiotropy)? Last, what biological pathways, processes, or mechanisms underlie any association between AD and GIT disorders?

Large-scale genome-wide association studies (GWAS), identifying an increasing number of SNPs, genes, and susceptibility loci, have been conducted separately for AD and a range of GIT traits²¹⁻²⁴. Findings from these GWAS provide compelling evidence for the roles of genetics in the aetiologies of AD and GIT disorders including PUD, PGM, gastritis-duodenitis, GERD, irritable bowel syndrome (IBS), diverticular disease, and IBD²¹⁻²⁴. However, to the best of our knowledge, no study has leveraged the possible pleiotropy between AD and GIT disorders as a basis for discovering new shared SNPs, genes and/or susceptibility loci. Hence, it is unclear whether AD shares genetic susceptibility with any of these GIT disorders.

Moreover, studies assessing the mechanism(s) of association between AD and GIT disorders, based on the analysis of molecular genetic data, are lacking. We use a set of statistical genetics approaches in the analysis of well-powered GWAS data to comprehensively assess the genetic relationship between AD and GIT disorders—PUD, GERD, PGM, IBS, gastritis-duodenitis, diverticular disease, and IBD. The outcomes of this study have the potential to improve our understanding of the genetic architecture of AD and each of the GIT disorders, provide insights into their possible underlying biology, and characterise potential targets for further investigation.

Results

A schematic of the workflow for this study is presented in Figure 1. Also, the GWAS summary statistics analysed are summarised in Table 1 with further cohort-specific details provided in Supplementary Table 1.

Genetic overlap between AD and GIT disorders

We first tested for SNP-level genetic overlap between AD and GIT disorders using the SNP effect concordance analysis (SECA) method²⁵. Briefly, SECA performs a bi-directional analysis, assessing the effects of AD-associated SNPs (dataset 1) on each of GIT disorders (dataset 2) and vice versa. We found a significant concordance of SNP risk effects between the AD GWAS and each of the GERD, PUD, PGM, gastritis-duodenitis, IBS and diverticular disease GWAS, indicating that there is a strong genetic overlap between AD and each of these disorders. Table 2 summarises the results of the primary test for the concordance of effects in which 144 SNP subsets were tested, with AD as P1 (dataset 1) and GERD as P2 (dataset 2). All these SNP subsets showed significant concordance of effects ($OR > 1$ and $P < 0.05$) with a permuted P-value ($P_{\text{permuted}} = 9.99 \times 10^{-4}$). A total of 26,963 linkage disequilibrium (LD)-independent SNPs ($r^2 < 0.1$) were common to both the AD and GERD GWAS (at $P1_{\text{GWAS-data}} = P2_{\text{GWAS-data}} \leq 1$), 13,955 (52%) of which exhibit significant effect concordance across the two GWAS ($OR = 1.18$, $P_{\text{Fisher's-exact}} = 4.65 \times 10^{-11}$) [Table 2].

As expected, a pattern of increasing strength of association between AD and GERD (measured using the OR values) was observed as the P-values for SNP subsets (P1 and P2) decreases. For example, at AD ($P1_{\text{GWAS-data}} < 0.05$) and GERD ($P2_{\text{GWAS-data}} < 0.05$), the proportion of SNP effect concordance increases to 58% ($OR = 1.84$, $P_{\text{Fisher's-exact}} = 1.74 \times 10^{-6}$). In a reverse analysis (GERD as dataset 1 (P1) and AD as dataset 2 (P2)) using SECA, we also found all the 144 subsets of SNPs ($OR > 1$ and $P < 0.05$, $P_{\text{permuted}} = 9.99 \times 10^{-4}$) showing significant concordance of SNP risk effects across the two disorders [Supplementary Note I]. These results indicate that AD-associated SNPs are also associated with GERD, and vice versa—supporting evidence of highly significant genetic overlap between the two disorders.

Analogous to the highly significant results observed between AD and GERD, SECA analyses found significant genetic overlap between AD and each of PGM, gastritis-duodenitis, diverticulosis and PUD. SECA similarly found a significant genetic overlap between AD and IBS, although the strength of association was comparatively less than for the other GIT disorders (Supplementary Note I). For AD and IBD, SECA revealed significant concordance of SNP risk effects when AD was assessed (as dataset 1) against IBD (as dataset 2) [$OR > 1$ and $P_{\text{GWAS-data}} < 0.05$, $P_{\text{permuted}} = 0.025$] but not the other way around (Supplementary Note I).

Genetic correlation between AD and GIT disorders

We used the linkage disequilibrium score regression (LDSC) method to further assess and quantify the SNP-level genetic correlation between AD and GIT disorders (Table 3). The apolipoprotein E (*APOE*) region has a large effect on the risk of AD; hence, we excluded *APOE* and the 500 kilobase (kb) flanking region (hg19, 19:44,909,039 – 45,912,650) from our AD GWAS. Given the complex LD structure in the human major histocompatibility complex (MHC), we also excluded SNPs in the 26 to 36 megabase region of chromosome six from data. In analyses both with and without the *APOE* and MHC regions, LDSC reveals a significant genetic correlation between AD and several of the GIT traits (Table 3).

LDSC reveals a positive and significant genetic correlation of AD with GERD ($r_g = 0.19$, $P = 8.78 \times 10^{-7}$), PUD ($r_g = 0.26$, $P = 2.92 \times 10^{-4}$), PGM ($r_g = 0.15$, $P = 1.43 \times 10^{-4}$), gastritis-duodenitis ($r_g = 0.19$, $P = 5.40 \times 10^{-3}$), IBS ($r_g = 0.16$, $P = 2.36 \times 10^{-2}$), and diverticular disease ($r_g = 0.18$, $P = 1.59 \times 10^{-3}$). These results are all consistent with our findings using SECA. Moreover, our results were based on the unconstrained genetic covariance intercept, hence the significance

of our estimates may be conservative given the negligible, or complete absence of, sample overlap between the pairs of traits assessed.

Using LDSC, we did not find a significant genetic correlation between AD and IBD ($r_g = -0.05$, $P = 3.80 \times 10^{-1}$) [Table 3], a result that is partially consistent with our SECA findings—highlighting how SECA differs (a bidirectional assessment of the relationships) as well as complements LDSC. Table 3 summarises the findings of all these analyses. We also performed cross-trait LDSC analysis assessing the relationship between each of the GWAS included in this study (Supplementary Table 2). Notably, there was a non-significant relationship of IBD with each of the other GIT-disorders, except IBS ($r_g = 14$, $P = 4.41 \times 10^{-3}$) [Supplementary Table 2]. Conversely, we found a significant genetic correlation between all the other pairs of GIT disorders (Supplementary Table 2).

SNPs and loci shared by AD and GIT disorders

Leveraging the significant genetic overlap and correlation as well as the substantial sample sizes of PGM, GERD and PUD, we performed cross-disorder meta-analyses of AD with each of these disorders. Our analyses identified shared SNPs and susceptibility loci, some of which are novel for both AD and GIT disorders. The primary objective of this analysis was to identify SNPs and loci which were not genome-wide significant in the individual AD or GIT disorder GWAS (i.e., $5 \times 10^{-8} < P_{\text{GWAS-data}} < 0.05$) but reached genome-wide significance ($P_{\text{meta-analysis}} < 5 \times 10^{-8}$) following a meta-analysis (Table 4). We additionally identified SNPs and loci which were already established (genome-wide significant, $P_{\text{GWAS-data}} < 5 \times 10^{-8}$) in AD (Sentinel AD SNPs/loci), which were also significantly associated with a GIT disorder, and vice versa, following the GWAS meta-analysis.

AD and PGM GWAS meta-analysis

A total of 42 SNPs reached genome-wide significance ($P_{\text{meta-analysis}} < 5 \times 10^{-8}$) in the cross-disorder meta-analysis of AD and PGM GWAS (Supplementary Table 3). None of these 42 SNPs was genome-wide significant in the individual AD or PGM GWAS (before meta-analysis) [$P_{\text{GWAS-data}} > 5 \times 10^{-8}$] but they were at least nominally significant ($P_{\text{GWAS-data}} < 0.05$) in each of the traits ($5 \times 10^{-8} < P_{\text{GWAS-data}} < 0.05$). Of the 42 genome-wide significant SNPs, 11 were moderately independent ($r^2 < 0.6$), from which we characterised seven lead SNPs at seven genomic loci ($r^2 < 0.1$) [Table 4]. A search in the PhenoScanner ²⁶ (accessed on 04/05/2021), revealed that one of the 11 independent SNPs, rs11083749 (on chromosome 19q13.32, *NECTIN2*), has been reported for association with AD at a genome-wide significant level. Our study provides evidence that this SNP and locus are equally associated with PGM given the substantial reduction in the GWAS meta-analysis P-value.

Of the remaining nine independent SNPs, at six genomic loci, none was previously found to be associated with AD, GERD, or PUD at a genome-wide level of significance, suggesting them to be novel SNPs and loci for the analysed traits (Table 4). Moreover, the results for m-value posterior probability and the binary effect P-value (BE) indicate that all the identified SNPs and loci, except the 3p21.31 locus (SNPs rs709210 [*HYAL2*] and rs7642934 [*SEMA3F*]), are associated with both AD and PGM. The m-value for each of the remaining SNPs was > 0.90 , predicting that they have effects in both GWAS (Table 4). Notably, the 3p21.31 locus (*HYAL2* and *SEMA3F*), was subsequently identified to have effects both in AD and GIT-trait (based on the binary effect P-value results) in the meta-analysis of AD and PUD GWAS (Table 4).

We identified an additional 23 SNPs, at three independent loci ($r^2 < 0.1$), that reached genome-wide suggestive association ($P_{\text{meta-analysis}} < 1 \times 10^{-5}$) in the meta-analysis of AD and

PGM (supplementary Table 4). Of these, the rs33998678 SNP (at 16q22.1, *IL34*) is in high LD ($r^2 = 0.91$) with one of the genome-wide significant SNP loci (rs34644948, at 16q22.1, *MTSS2*, Table 4) identified in the meta-analysis of AD and PGM. The finding, thus, supports the involvement of the locus (16q22.1, *MTSS2*) in both AD and GERD or PUD (traits represented by PGM GWAS). Similarly, the rs663576 (at 17q21.32, *PHOSPHO1*) is moderately correlated ($r^2 = 0.41$) with another genome-wide significant SNP (rs2584662 at 17q21.33, *PHB*, Table 4), identified in the meta-analysis. This locus (17q21.33) was reproduced in the meta-analysis of AD and GERD (SNP rs2584662 near *PHB*), lending support for its involvement in AD and PUD or GERD. Notably, all the three loci reaching suggestive associations were predicted, using m-value and the BE P-value methods, to have effects in both AD and PGM.

AD and GERD GWAS meta-analysis

A meta-analysis of AD and GERD identified a total of 119 SNPs reaching genome-wide significant association ($P_{\text{meta-analysis}} < 5 \times 10^{-8}$, Supplementary Table 5), none of which was previously genome-wide significant in the individual AD or GERD GWAS ($5 \times 10^{-8} < P_{\text{GWAS-data}} < 0.05$). From these, we characterised 11 independent SNPs ($r^2 < 0.6$) and seven lead SNPs ($r^2 < 0.1$) at seven genomic loci (Table 4). The identified loci included those implicated in the meta-analysis of AD and PGM at a genome-wide level of significance ($P_{\text{meta-analysis}} < 5 \times 10^{-8}$)—1p31.3, 3p21.31, 6p21.32, 17q21.33 and 19q13.32—and at a genome-wide suggestive association level ($P_{\text{meta-analysis}} < 1 \times 10^{-5}$)—16q22.1 and 1q32.2.

Also, we found one (nearby) locus, 17q21.32 (SNP rs8067459, *ZNF652*, Table 4) reaching genome-wide significance in the AD and GERD meta-analysis. This locus was genome-wide suggestive in the AD vs PGM GWAS meta-analysis (SNP rs663576, 17q21.32, LD between rs663576 and rs8067459 = 0.86), providing additional evidence for the locus being shared by

AD and the GIT disorders (GERD and PUD). An additional 175 independent SNPs at 121 loci reached a genome-wide suggestive association ($P_{\text{meta-analysis}} < 1 \times 10^{-5}$) reproducing some of the genome-wide significant loci in the AD and PGM or the AD and GERD meta-analysis. The loci include 1p31.3 (rs2840677, *PDE4B*), 1q31.1 (rs10753964, *BRINP3*) and 1q32.2 (rs4147104, *CD46*) [Supplementary Table 6]. Thus, the results support the loci being shared by AD and GERD. Other SNPs and loci reproduced at the suggestive association (or in high LD with identified loci) are highlighted in Supplementary Table 6.

AD and PUD GWAS meta-analysis

We identified 22 SNPs reaching genome-wide significance in the meta-analysis of AD and PUD GWAS ($P_{\text{meta-analysis}} < 5 \times 10^{-8}$, Supplementary Table 7). From these, we characterised seven independent SNPs at six genomic loci (Table 4) associated with both AD and PUD. Both the m -value (> 0.90) and the BE methods predict that the identified SNPs and loci have effects in AD and PUD (Table 4). Of the loci identified in the AD and PGM meta-analysis, four were replicated in the AD and PUD meta-analysis. Two of the four loci, the 19q13.32 (rs28363848 near *BCL3*), and the 6p21.32 (rs9270599, *HLA-DRA*), were replicated at a genome-wide level of significance, while the remaining two—rs709210, 3p21.31, $P_{(\text{FE})} = 5.24 \times 10^{-3}$, *HYAL2*; and rs6695557, 1p31.3, $P_{(\text{FE})} = 2.94 \times 10^{-4}$, *PDE4B*—were replicated at a nominal level (significant reduction in P-value after AD and PUD meta-analysis, Supplementary Table 8). The SNP rs530324, at 8p21.1 (*SCARA3*, Table 4), identified in the AD and PUD meta-analysis, is in strong LD ($r^2 = 0.91$) with another SNP (rs4732732, *CLU*) which reached a suggestive association for AD and PUD (Supplementary Table 9). The finding, thus, provides additional evidence for the involvement of the locus (8p21.1) in both AD and PUD. Supplementary Table 9 presents 24

independent SNPs, at 21 genomic loci, reaching genome-wide suggestive association ($P_{\text{meta-analysis}} < 1 \times 10^{-5}$) for AD and PUD.

Shared genomic regions

Using a colocalization analysis in GWAS-PW²⁷, we assessed shared genomic regions between AD and each of PGM and GERD (Supplementary Table 10). The results of this analysis confirm that all the loci identified in the meta-analyses (except in chromosome 3) are shared by AD and the respective GIT traits (model 4 posterior probability [PPA 4] > 0.9, Supplementary Table 10). While the findings also suggest that the causal variants might be different (in some of the loci—PPA 3 < 0.5), we note that when variants in a locus are in strong LD, which is likely the case here, GWAS-PW is limited in its ability to correctly distinguish model 3 (PPA 3) from model 4 (PPA 4)²⁷. Additional shared genomic regions, in chromosomes 1, 6, 16, 17 and 19 having PPA 4 > 0.90 were identified for AD and the GIT traits (Supplementary Table 10). Also, we identified another locus on chromosome 17, having PPA 3 > 0.80, and implicating the SNP rs2526380 (17q22, *TSPOAP1*) in both AD and GERD. The posterior probability that this SNP is a causal variant under model 3²⁷ is high at 0.99 (Supplementary Table 10).

Partial causal associations between AD and GIT disorders

We assessed the causal relationship between AD (as the outcome variable) and GERD (as the exposure variable) using the two-sample Mendelian randomisation (MR) method. We found no evidence of a causal relationship between AD and GERD, irrespective of the direction of the analysis (AD or GERD as the outcome or exposure variable) [Table 5]. For sensitivity testing, we implemented five additional models of MR analysis—MR-Egger, weighted median, simple mode, weighted mode and the MR-PRESSO (Mendelian Randomization Pleiotropy

RESidual Sum and Outlier)—since a true finding will be consistent across the multiple methods. Results of all these methods agree with those of the Inverse Variance Weighted (IVW) model supporting a lack of evidence for a causal association between AD and GERD (Table 5 and Supplementary Table 11). We carried out further MR analysis assessing AD against each of PUD, PGM, IBS, diverticular disease, and IBD. Findings similarly reveal no evidence for a causal relationship between AD and each of the GIT-disorders assessed (Supplementary Note II, and Supplementary Table 11).

We also used the Latent Causal Variable (LCV) approach²⁸ to test for a causal relationship between AD and each of the GIT disorders. The results of LCV suggest a partial causal influence of gastritis-duodenitis (genetic causal proportion [GCP] = -0.69, P = 0.0026, Table 6), IBD (GCP = -0.52, P = 0.002319, Table 6) and lansoprazole (GCP = -0.38, P = 0.001129) on AD. The result was in the reverse direction for diverticular disease (GCP = 0.23, P = 0.000272), suggesting a partial causal influence of AD on this disorder.

Gene-based association analysis

Using a gene-based analysis of the SNPs that overlapped between the AD and PGM GWAS, we identified a total of 18,763 protein-coding genes for each of the traits. Applying a threshold P-value of 2.66×10^{-6} ($0.05/18763$ —Bonferroni correction for testing 18,763 genes), we identified 64 genome-wide significant ($P_{\text{gene}} < 2.66 \times 10^{-6}$) genes for AD (Supplementary Table 12), 75 for PGM (Supplementary Table 13), and 44 for GERD (Supplementary Table 14). Using the Fisher's Combined P-value (FCP) method, a total of 44 genome-wide significant ($P_{\text{FCP}} < 2.66 \times 10^{-6}$) genes shared by AD and PGM were identified, 11 of which were not previously significant in the individual AD or PGM GWAS (Supplementary Table 15). It is noteworthy that

some of the identified AD and PGM shared genes are in chromosomal locations found in our meta-analysis, including 1p31.3 (*PDE4B*), 3p21.31, (*SEMA3F*, *HYAL2*), 6p21.32 (*HLA-DRA*) and 19q13.32 (several apolipoprotein genes). We replicated a similar pattern of findings using the AD and the GERD GWAS (Supplementary Table 16).

Biological pathways and mechanisms shared by AD and GIT disorders

To identify significantly enriched biological pathways, mechanisms, and processes shared by AD and GIT disorders, we performed pathway-based functional enrichment analyses in the g:Profiler platform²⁹. These analyses enable us to functionally interpret genes overlapping between AD and GIT disorders and can provide biological insight from their commonalities. First, we investigated genes overlapping AD and GERD (at $P_{\text{gene}} < 0.05$, FCP < 0.02) and identified several biological pathways that were overrepresented (Supplementary Table 17, and Figure 2), implying they have a role in the mechanisms underlying both AD and GERD.

Pathways related to the metabolism, alteration, lowering or inhibition of lipids were significantly enriched for both traits (Supplementary Table 17). These included plasma lipoprotein assembly, remodelling, and clearance ($P_{\text{adjusted}} = 2.01 \times 10^{-3}$), cholesterol metabolism ($P_{\text{adjusted}} = 4.99 \times 10^{-2}$), plasma lipoprotein assembly ($P_{\text{adjusted}} = 3.45 \times 10^{-5}$), and triglyceride-rich plasma lipoprotein particle ($P_{\text{adjusted}} = 5.23 \times 10^{-9}$), among others. Also, lipase inhibitors ($P_{\text{adjusted}} = 6.08 \times 10^{-3}$) and the statin (3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) pathway ($P_{\text{adjusted}} = 3.99 \times 10^{-2}$) were significantly enriched for AD and GERD (Supplementary Table 17).

Pathways related to the immune system were also overrepresented for both AD and GERD as evidenced by the identification of immune or autoimmune-related disorders such as asthma

($P_{\text{adjusted}} = 3.53 \times 10^{-3}$), systemic lupus erythematosus ($P_{\text{adjusted}} = 7.88 \times 10^{-3}$), and type I diabetes mellitus ($P_{\text{adjusted}} = 2.47 \times 10^{-2}$). Other immune-related pathways identified include intestinal immune network for IgA production ($P_{\text{adjusted}} = 4.07 \times 10^{-2}$), programmed cell death protein 1 (PD-1) signalling ($P_{\text{adjusted}} = 5.24 \times 10^{-3}$), translocation of ZAP-70 to immunological synapse ($P_{\text{adjusted}} = 2.44 \times 10^{-3}$), and interferon-gamma signalling pathways ($P_{\text{adjusted}} = 2.45 \times 10^{-2}$) [Supplementary Table 17].

Following enrichment mapping and auto-annotation, the identified biological pathways were clustered into six themes of biological mechanisms, namely: 'lipoprotein particle clearance,' 'receptor signalling pathway,' 'side membrane vesicle and cell adhesion,' 'peptide antigen binding,' 'intestinal immune network,' and 'interferon-gamma signalling' (Figure 2). Moreover, a pathway-based analysis using genes that were overlapping between the AD and PGM GWAS (at $P_{\text{gene}} < 0.05$) replicated some of the pathways identified for AD and GERD, including 'plasma lipoprotein assembly, remodelling, and clearance' ($P_{\text{adjusted}} = 3.01 \times 10^{-4}$), 'peptide antigen binding' ($P_{\text{adjusted}} = 2.28 \times 10^{-3}$), and 'triglyceride-rich plasma lipoprotein particle' ($P_{\text{adjusted}} = 6.60 \times 10^{-8}$) [Supplementary Table 18, and Supplementary Note III]. Figure 3 summarises the relationships of these mechanisms and how they may apply in AD and GIT disorders.

Discussion

We present the first comprehensive assessment of the genetic relationship between AD and GIT disorders by analysing large scale GWAS summary data using multiple statistical genetics approaches. We found a significant genetic overlap and correlation between AD and each of GERD, PUD, PGM (medications for PUD or GERD), gastritis-duodenitis, IBS, and diverticular

disease. These results support evidence of shared genetic susceptibility between AD and these GIT traits. Also, we identified several independent SNPs, susceptibility loci, genes and biological pathways shared by AD and each of GERD and PUD. These findings not only confirm the results of previous observational studies⁵⁻¹¹ which have suggested a co-occurring association of AD with GIT disorders but also provide novel insights into the mechanisms underlying the observed associations.

The use of multiple, complementary statistical genetic approaches enables a comprehensive analysis of the genetic associations between AD and GIT disorders and is a major strength of this study. Also, we analysed well-powered GWAS data, meaning our findings are not affected by the small sample sizes, possible reverse causality, or confounders that conventional observational studies often suffer from. One potential limitation of our data is that the GWAS for AD combined clinically diagnosed cases of AD with proxies (AD-by-proxy—individuals whose parents were diagnosed with AD). Given the high correlation between the GWAS with and without the ‘AD-by-proxy’ cases²¹, we argue that combining them is valid, especially for sample size improvement. However, likely, some of the proxy samples will not develop AD. This observation may influence the significance of our causality estimates. Hence, causal associations between AD and GIT disorders may not be ruled out.

In contrast to the strong positive genetic correlation between AD and the GIT traits examined, we did not find a significant genetic correlation between AD and IBD using LDSC, which may be due to the relatively small number of cases in the IBD GWAS. Supporting this premise, SECA revealed a significant genetic overlap between the disorders when AD was assessed as dataset 1 against IBD as dataset 2, but not the other way around. The AD GWAS has a much larger case and total sample size and therefore provides a more robust association on which

to condition (select independent) SNPs for concordance analysis. Alternatively, IBD may have a different mechanism from the rest of the GIT disorders and is not associated with AD. This position is suggested by the non-significant genetic correlation of IBD with the other GIT disorders, except IBS. Given these findings, other results in our study (e.g., LCV finding) potentially supporting IBD mechanisms, and the highly significant association between AD and IBD reported in a previous study ⁹, future studies need to further investigate the relationship between AD and IBD using more powerful IBD GWAS.

Evidence of significant genetic overlap and correlation reflects not only shared genetic aetiologies (biological pleiotropy) but also suggests a possible causal association between AD and the GIT traits (vertical pleiotropy). Using LCV, we detected a partial causal association between AD and each of gastritis-duodenitis, lansoprazole, IBD and diverticular disease. However, when we attempted to reproduce findings for gastritis-duodenitis using another GWAS (also for lansoprazole using PGM), this causal association was not evident; hence, a reassessment of the inconclusive LCV results, in future studies, may be warranted. Conversely, MR analyses did not provide evidence for a significant causal relationship between AD and GIT disorders, indicating that shared genetics and biological pathways best explain the association between AD and these GIT disorders.

We performed GWAS meta-analysis to identify shared SNPs and susceptibility loci, leveraging the larger sample sizes of the PGM, GERD and PUD GWAS, and the significant pleiotropy identified between AD and each of these GIT traits. Our meta-analysis of the AD and PGM GWAS identified seven shared independent loci reaching genome-wide significance for association with both traits. Several of these loci were also identified in meta-analyses of AD with GERD and PUD, providing strong support for their involvement in both AD and GIT

disorders. Results from ‘m-value,’ binary effect ³⁰, and GWAS-PW ²⁷ methods, overall, robustly support these results. Moreover, many of the loci, including 1p31.3 (*PDE4B*), 3p21.31 (*SEMA3F*, *HYAL2*), 6p21.32 (*HLA-DRA*), and 19q13.32 (*APOE*, *APOC2*, *ERCC2*, *BCL3*, and *KLC3* genes) were replicated in our gene-based association analyses. Following a search in PhenoScanner, six of these loci—1p31.3 (*PDE4B*), 1q32.2 (*CD46*), 3p21.31 (*SEMA3F*, *HYAL2*), 6p21.32 (*HLA-DQA2*, *HLA-DRA*), 16q22.1 (*MTSS2*), 17q21.33 (*PHB*)—have not previously been reported, at a genome-wide level of significance, for AD, GERD, or PUD, indicating they are putative novel loci associated with these traits. The remaining locus (19q13.32), harbouring the *APOE* gene, has a well-established association with AD, and our results suggest it is also involved in these GIT disorders. Consistent with this position, the *APOE* genotype is associated with the gut microbiome ³¹, and IBD ^{32,33}.

Notably, the independent SNP rs12058296 (1p31.3), which reached genome-wide significance for both AD and PGM, mapped to the phosphodiesterase 4B (*PDE4B*) gene. Inhibition of *PDE4B* (or its subtypes) has shown promise as a treatment for inflammatory diseases ³⁴⁻³⁷. Indeed, consistent recent evidence supports the potent anti-inflammatory, pro-cognitive, neuro-regenerative, and memory-enhancing properties of PDE4 inhibitors (*PDE4B*, in particular ³⁸), making them plausible therapeutic targets for AD ^{36,37} and GIT disorders ³⁵. Other identified independent genome-wide significant SNPs and loci mapped to genes including *CD46*, *SEMA3F*, *HLA-DRA*, *MTSS2*, *PHB*, and *APOE*. The *CD46* gene is a complement regulator which is bactericidal to *Helicobacter (H) pylori* ³⁹ and was also recently identified to be associated with AD in a transcriptome analysis ⁴⁰, making it a plausible candidate in both AD and GIT disorders.

404 Using pathway-based analyses, we identified biological pathways, mechanisms and processes
405 significantly enriched for AD and GIT disorders. Notably, lipid-related, and autoimmune
406 pathways were overrepresented. There is a close link between autoimmunity and lipid
407 abnormalities ⁴¹, and our findings highlight abnormal lipid profiles as risks for AD and GIT
408 disorders, consistent with findings in previous studies ⁴²⁻⁴⁶. In AD, for example,
409 hypercholesterolemia is believed to increase the permeability of the blood-brain barrier
410 system, facilitating the entry of peripheral cholesterol into the CNS, and resulting in abnormal
411 cholesterol metabolism in the brain ^{42,43}. Amyloidogenesis, alteration of the amyloid
412 precursor protein degradation, accumulation of Ab, and subsequent cognitive impairment
413 have all been linked with elevated cholesterol in the brain ^{43,47-49}. While the exact roles of
414 lipids in GIT disorders are unclear, *H. pylori* is believed to cause or worsen abnormal serum
415 lipid profiles through chronic inflammatory processes, and eradication of the infection
416 enhances lipid homeostasis ^{45,46}.

417 The mechanisms of association between AD and lipid dysregulation relate to the 'gut-brain
418 axis', alterations in GIT microbiota and the immune system ⁴³. This observation is consistent
419 with our findings, revealing the potential of lipid-lowering therapies such as lipase inhibitors
420 and statins (identified in our study) for the treatment of AD and GIT disorders or their
421 comorbidity. Lipase inhibitors such as orlistat prevent intestinal dietary lipid absorption,
422 thereby decreasing total plasma triglycerides and cholesterol levels ^{50,51}, making them a
423 preferred pharmacological treatment for obesity ⁵⁰. The acknowledged connection between
424 AD, lipid dysregulation and the 'gut-brain axis' ⁴³, supports the potential utility of lipase
425 inhibitors in AD. Other lipases, including monoacylglycerol, diacylglycerol, and lipoprotein

426 lipases are involved in AD pathology, and can also effectively be inhibited by orlistat ⁵¹. Thus,
427 we hypothesise that lipase inhibitors may be promising in comorbid AD and GIT disorders.

428 Statins (cholesterol-lowering medications) are also therapeutically beneficial in AD and GIT
429 disorders ⁵²⁻⁵⁶. Evidence indicates that statins possess anti-inflammatory, immune-
430 modulating and gastroprotective properties ^{52,53}, and their active use is associated with a
431 significant PUD risk reduction ⁵², and *H. pylori* eradication ⁵⁴. Further, statins improve
432 cognitive ability and reduce neurodegeneration risks, making them potentially beneficial in
433 AD ^{55,56}. However, there is (controversial) evidence suggesting a paradoxical predisposition to
434 reversible dementia for statins ^{55,56}. While this finding has been challenged ⁵⁵, it highlights a
435 clear need to identify AD patients for whom statins will be beneficial, consistent with the
436 model of personalised health. Hence, we hypothesise that statins may be beneficial in
437 individuals with comorbid AD and GIT disorders.

438 Our findings have implications for practice and further studies. First, results highlighting lipid-
439 related mechanisms support the roles of abnormal lipid profiles in the aetiologies of the
440 disorders, which may be potential biomarkers for AD and GIT disorders (or their comorbidity).
441 Second, our findings underscore the importance of lipid homeostasis. The dietary approach
442 is one effective non-pharmacologic approach for the management of hyperlipidaemia, and
443 overall, this is consistent with findings in this study. Indeed, adherence to a 'Mediterranean'
444 diet (low in lipids) is recognised as beneficial both in AD ⁵⁷ and GIT disorders ⁵⁸. Thus, a
445 recommendation for healthy diets, early in life, may form part of the lifestyle modifications
446 for preventing AD and GIT disorders. Third, our study identifies lipase inhibitors and statin
447 pathways in the mechanisms of AD and GIT disorders which may be a potential therapeutic
448 avenue to explore in the disorders. Hence, we hypothesise that individuals with comorbid AD

and GIT traits may gain benefits from these therapies. Fourth, our study implicates the *PDE4B*, and given the evidence in the literature ³⁵⁻³⁸, we propose that treatment targeted at its inhibition may be promising in comorbid AD and GIT traits. Future studies, including randomised control trials, are needed to test these hypotheses. Lastly, the finding of significant genetic overlap between AD and GIT disorders suggests that it would be beneficial for healthcare providers to test for GIT disorders in individuals presenting with signs or symptoms of impaired cognition and vice versa, to improve early detection.

In summary, this study provides a novel insight into the relationship between AD and GIT disorders, implicating shared genetic susceptibility in the mechanisms of their association. To our knowledge, this is the first study to comprehensively assess these relationships using statistical genetics approaches. Overall, these findings advance our understanding of the genetic architecture of AD and GIT disorders. The shared genetic components and biological pathways identified are important targets for further investigation in AD and each of the GIT disorders.

Methods

Datasets

The GWAS data utilised in the present study were sourced from publicly available GWAS databases and repositories and are summarised in Supplementary Table 1. The recently published ‘clinically diagnosed AD and AD-by-proxy’ ²¹, with a large sample size, was used as our AD GWAS data. GIT traits including gastritis-duodenitis, GERD, PUD, IBS, diverticular disease, and IBD were assessed against AD, and the GWAS for these traits were obtained through the GWAS Atlas ²⁴ or the recently published GIT GWAS ²². Additionally, we utilised a

well-characterised GWAS for GERD, which combined datasets from the UK Biobank and the QSKIN study²³ (https://figshare.com/articles/GERD_GWAS_summary/8986589), and gastritis-duodenitis (ftp://share.sph.umich.edu:21/UKBB_SAIGE_HRC/PheCode_535_SAIGE_MACge20.txt.vcf.gz). GWAS with a large sample size for medication use in PUD and GERD (PGM) are available and we utilised these as proxies to examine the relationship between AD and GIT disorders (PUD and GERD, in particular). A comprehensive description of the quality control procedures for each of the GWAS data and their analysis has previously been reported in the corresponding publications (Supplementary Table 1).

SNP effect concordance analysis (SECA)

We used the standalone version of the SECA software pipeline (<https://sites.google.com/site/qutsgel/software/seca-local-version>) to perform SNP-level genetic overlap assessment and statistical tests between AD and GIT disorders. A detailed description of the SECA software and methods has been published²⁵. Briefly, SECA accepts a pair of GWAS data (dataset 1 and dataset 2) as input and performs a range of analyses to determine whether there is a genetic overlap between a pair of traits. First, we carried out quality control to exclude all non-rsID(s) and duplicate variants in dataset 1, align SNP effects to the same effect allele across dataset 1 and dataset 2 and perform a P-value informed test for linkage disequilibrium (LD) clumping in the dataset 1 using PLINK⁵⁹. Second, SECA partitions independent SNPs resulting from LD clumping (at $r^2 < 0.1$) into 12 subsets of SNPs according to the P-value for dataset 1 as follows: $P1 \leq (0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0)$. SECA subsequently performs Fisher's exact tests (FT) to assess the presence of excess SNPs in which the direction of effects is concordant across dataset 1 and dataset 2

(that is, for the corresponding P-value derived 12 subsets of SNPs associated in dataset 2, P2). Hence, a total of 144 SNP subsets (a 12 by 12 matrix from dataset 1 and dataset 2) was assessed for SNP effect concordance. In the present study, we first assessed AD GWAS as dataset 1 and each of the GIT disorders as dataset 2. For comparison, we also assessed each of the GIT disorders as dataset 1 against AD as dataset 2. Thus, using SECA, we assessed the effects of AD-associated SNPs on each of GIT disorders and vice versa. This is an important analysis step to account for instances where SNPs that are strongly associated with AD do not affect GIT disorder traits and vice versa.

Linkage disequilibrium score regression analysis (LDSC)

LDSC assesses and distinguishes the contributions of polygenicity, sample overlaps, and population stratification to the heritability and genetic correlation between traits⁶⁰. In the present study, we performed LDSC analysis using the standalone version of the software and by following the procedures provided by the program developer (<https://github.com/bulik/ldsc>). We conducted cross-trait bivariate LDSC to estimate the genetic correlation between AD and each of the GIT disorders assessed in this study. To avoid a potential bias from residual confounding, we did not constrain the genetic covariance intercepts in any of our genetic correlation analyses; this practice may be conservative and reduce the significance of correlation estimates in instances where there is no sample overlap between the pair of traits being assessed.

GWAS Cross-disorder meta-analysis

GWAS meta-analysis pools the results of GWAS data, thereby increasing the sample sizes and augmenting the detection of genetic variants with small to modest effect sizes. In the present

study, we used the GWAS meta-analysis method of pooling AD GWAS with each of the GIT traits (cross-disorder or cross-trait meta-analysis). We used two models of meta-analysis: the Fixed Effect (FE), and the modified Random Effect (RE2) ⁶¹ models, implemented in the METASOFT software (<http://genetics.cs.ucla.edu/meta/>). The FE model estimates the FE P-value using the inverse-variance weighted method, which assumes that the AD and each of the GIT disorders' GWAS are assessing the same (fixed) effect. The presence of effect heterogeneity is a limitation of the model. On the other hand, by estimating P-values using the modified random-effects, the RE2 model ⁶¹ allows for differences in SNP effects and the method is powerful in the presence of SNP effect heterogeneity. Furthermore, given the possibility of slight sample overlap between the AD GWAS and the GWAS for some of the GIT traits, we utilised an additional meta-analysis model, the RE2C model (modified Random Effect Correlation model) ⁶². This method is suitable for GWAS meta-analysis of correlated statistics ⁶². In the present study, we meta-analysed SNPs overlapping AD and each of the GIT disorders using the FE, and the RE2 models complementarily. In the meta-analyses for AD and GERD (genetic covariance intercept = 0.0133, se = 0.005) and AD and PGM (genetic covariance intercept = 0.0135, se = 0.006), we utilised the RE2C as an additional model to account for the slight sample overlap between the respective pairs of traits.

Genomic loci characterisation

Using the outputs of our cross-trait meta-analyses for AD and each of the GIT disorders, we carried out some downstream analyses including functional annotation of SNPs, and genomic loci characterisation in line with practice in previous studies ^{14,63,64}. Briefly, SNPs that were not genome-wide significant in the individual AD and GIT disorder GWAS, but which reached genome-wide significance following the meta-analysis were identified. From these, we

characterised independent SNPs at $r^2 < 0.6$, and lead SNPs at $r^2 < 0.1$. We defined the genomic locus as the region within 250 kb of each lead SNP. We assigned lead SNPs within this region to the same locus, meaning two or more lead SNPs may be present in one locus. Several of these downstream analyses were performed in the FUMA software (an online platform) ⁶³.

Assessment using the posterior probability (m-value) method

To identify loci shared by AD and GIT disorders, we performed a further analysis using the posterior probability (m-value) method and the complementary binary effects (BE) P-value estimates ³⁰. Briefly, cross-study information was utilised in estimating the m-value to predict whether a SNP or locus has effects in each of the studies meta-analysed, particularly in the presence of effect heterogeneity ³⁰. M-value ranges from 0 to 1, where a value > 0.9 predicts that effect exists for the SNP or locus in the study (e.g., AD GWAS or PUD GWAS). On the other hand, an m-value < 0.1 predicts that an effect does not exist in the study. M-values from 0.1 to 0.9 predict an ambiguous effect. We used these methods to verify whether the SNPs or loci identified in our GWAS meta-analysis have effects (shared) by the two traits under investigation, especially where the test for heterogeneity was significant. We interpreted the results of the m-value alongside the BE P-value. It is expected that, where effects exist in both traits being assessed, the BE P-value estimates will be less than the P-value for the respective GWAS. We implemented the BE and m-value methods alongside the FE, and the RE2 meta-analysis models using the METASOFT software.

Pairwise GWAS analysis

We performed co-localisation analysis utilising the pairwise GWAS (GWAS-PW) method ²⁷ to further assess the regions in the genome shared by AD and GIT-disorders. Briefly, GWAS-PW

software implements the Bayesian pleiotropy association test and identifies genomic regions that influence a pair of correlated traits²⁷. We used this method to assess whether the loci reaching genome-wide significance in our GWAS meta-analyses were truly shared by AD and the GIT disorders. Also, we investigated other shared genomic regions which may not have been found in the GWAS meta-analysis. We combined the summary data for AD with the data for each of the GIT disorders and estimated the posterior probability of association (PPA) of a genomic region using the GWAS-PW software. We modelled four PPAs: i) that a genomic region is associated with AD only (PPA-1), ii) that a genomic region is associated with the GIT trait only (PPA-2), iii) that a genomic region is associated with both AD and the GIT trait (PPA-3), and iv) that a specific genomic region is associated with both AD and the GIT trait but through separate causal variants (PPA-4)²⁷.

Causal relationships assessment

Using Mendelian randomisation (MR)⁶⁵ analysis methods, we examine the potential causal association between AD and each of the GIT disorders assessed in this study. Mimicking randomised control trials (RCTs), MR analysis incorporates genetics into epidemiological study designs to assess causality⁶⁵. In the present study, we used the two-sample MR method (<https://mrcieu.github.io/TwoSampleMR/articles/introduction.html>) for a bidirectional association assessment between AD and each of the GIT disorders. Independent ($r^2 < 0.001$) genome-wide significant SNPs ($P < 5 \times 10^{-8}$) associated with AD (as the exposure variable) were utilised as instrumental variables (IVs) and assessed against each of the GIT disorders' GWAS (outcome variables) analysed in this study.

Reversing the direction of analysis, independent SNPs robustly associated with each of the GIT disorders' GWAS (exposure variable) were similarly utilised as IVs and assessed against AD (as the outcome variable). We used the inverse variance weighted (IVW) model of MR as the primary method for causal association assessment, and for validity testing, we performed a heterogeneity test (Cochran's Q-test), a 'leave-one-out' analysis, a horizontal pleiotropy check (MR-Egger intercept) and individual SNP MR analyses. Also, we used other MR analysis models including the weighted mode, simple mode, MR-Egger, weighted median^{66,67}, and the 'Mendelian randomisation pleiotropy residual sum and outlier' (MR-PRESSO)⁶⁸ methods for sensitivity testing. All MR analyses were performed in R (4.0.2).

We performed an additional assessment of the causal or partial causal association between AD and each of the GIT disorders using the Latent Causal Variable (LCV) method²⁸. LCV estimates causality proportion (GCP) ranging from -1 to 1 where a value close to 1 indicates a potential causal association between two traits in the forward direction and -1 in the backward direction²⁸. This analysis was performed in the online platform of the CTG virtual laboratory (<https://vl.genoma.io/analyses/lcv>)^{28,69}.

Gene-based association analysis

We performed gene-based association analyses to identify genome-wide significant genes shared by both AD and each of the GIT disorders assessed in this study. This analysis complements the SNP-based studies. However, beyond the SNP-level analysis, gene-based association analysis provides greater power for identifying genetic risk variants since it aggregates the effects of multiple SNPs, and it is generally not limited by small effect sizes or correlations among SNPs. Moreover, genes are more closely related to biology than SNPs,

meaning gene-level analysis can offer better insights into the underlying biological mechanisms of complex traits.

In the present study, we carried out gene-based association analysis separately for AD and each of the GIT disorders using the MAGMA software, implemented in FUMA⁶³. Based on the results of the gene-based analysis, we identified genome-wide significant genes for each of the traits. Also, using the Fisher Combined P-value (FCP) method, we identified genes shared by AD and each of the GIT traits.

Pathway-based functional enrichment analysis

For a better understanding of the potential biological mechanisms underlying the relationship of AD with GIT disorders, we carried out pathway-based functional enrichment analyses using the online platform of the g:GOST tool in the g-profiler software²⁹. The analysis enables us to functionally interpret genes overlapping AD and GIT disorders. We included genes that were overlapping between AD and each of GERD and PGM at $P_{gene} < 0.05$ (FCP < 0.02) in this analysis, and followed established protocols⁷⁰. Functional category term sizes were restricted to values from 5 to 350⁷⁰. For multiple testing corrections, we applied the default 'g: SCS algorithm' recommended in the protocol⁷⁰ and reported the significantly enriched biological pathways at the multiple testing adjusted P-value [$P_{adjusted}$] < 0.05.

Data availability

The GWAS summary data for AD and GIT disorders utilised in the present study are available in the public domain and can be accessed using the links provided herewith:

AD GWAS: https://ctg.cncr.nl/documents/p1651/AD_sumstats_Jansenetal_2019sept.txt.gz,

PUD: https://cnsgenomics.com/data/wu_et_al_2021_nc/1_PUD_summary

GERD: https://figshare.com/articles/GERD_GWAS_summary/8986589, Gastritis-duodenitis:
ftp://share.sph.umich.edu:21/UKBB_SAIGE_HRC/PheCode_535_SAIGE_MACge20.txt.vcf.gz,
IBS: https://cnsgenomics.com/data/wu_et_al_2021_nc/4_IBS_summary,
PGM: https://cnsgenomics.com/data/wu_et_al_2021_nc/3_PGM_summary,
IBD: https://cnsgenomics.com/data/wu_et_al_2021_nc/5_IBD_summary,
IBD: ftp://ftp.sanger.ac.uk/pub/consortia/ibdgenetics/iibdgc-trans-ancestry-filtered-
summary-stats.tgz, Diverticular disease:
ftp://share.sph.umich.edu:21/UKBB_SAIGE_HRC/PheCode_562_SAIGE_MACge20.txt.vcf.gz

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Author contributions

Conceived the Study: EOA., TP., SML; designed the study: EOA., EKO., TP., SML.; conducted the analysis: EOA.; interpreted the results: EOA., EKO., DRN., TP., SML.; drafted the manuscript: EOA.; made critical revisions to the manuscript: EOA., EKO., DRN., TP., SML; Funding: SML

Competing interests

All authors declare no competing interests

Genetic overlap between AD and GIT disorders Tables and Figures

Table 1: Summary of GWAS datasets analysed

S/N	GWAS	Cases	Control	Sample size	Ancestry
1	Clinically diagnosed AD and AD-by-proxy	71,880	383,378	455,258	European
2	Gastroesophageal Reflux Disease (GERD)	71,522	261,079	332,601	
3	Gastritis-Duodenitis-UKBB_SAIGE_PheCode_535	28,941	378,124	407,065	
4	Gastritis-Duodenitis	14,477	286,314	300,791	
5	Peptic ulcer disease (PUD)	16,666	439,661	456,327	
6	Gastroesophageal Reflux Disease (GORD)	54,854	401,473	456,327	
7	Irritable Bowel Syndrome (IBS)	28,518	426,803	455,321	
8	Inflammatory Bowel Disease (IBD)	7045	426803	456,327	
9	PUD and GERD medication	90,175	366,152	456,327	
10	Diverticulosis and diverticulitis-UKBB_PheCode_562	27,311	334,783	362,094	
11	Diverticular Disease	14,028	286,763	300,791	
12	Lansoprazole	13,559	266,884	280,443	
13	IBD (from GWAS Atlas)	12,882	21,770	34,652	

AD: Alzheimer's disease, GERD: gastroesophageal reflux disease, PUD: peptic ulcer disease, GORD: gastroesophageal reflux disease from another source, IBS: irritable bowel disease, IBD: inflammatory bowel disease. Note: the GWAS were obtained from multiple sources as more comprehensively described in Supplementary Table 1.

Table 2: Results of genetic overlap assessment between AD (P1) and GERD (P2)

P1	P2	Ind-SNPs- overlapping	Concordant	Prop- Overlap	OR	P Fishers-exact
≤1	≤1	26963	13955	0.52	1.18	4.65×10^{-11}
0.9	0.9	24237	12653	0.52	1.19	7.46×10^{-12}
0.8	0.8	21551	11289	0.52	1.21	3.02×10^{-12}
0.7	0.7	18759	9860	0.53	1.23	2.64×10^{-12}
0.6	0.6	16001	8483	0.53	1.27	2.48×10^{-14}
0.5	0.5	13297	7081	0.53	1.30	7.54×10^{-14}
0.4	0.4	10432	5603	0.54	1.35	3.42×10^{-14}
0.3	0.3	7638	4173	0.55	1.45	6.22×10^{-16}
0.2	0.2	4936	2755	0.56	1.6	2.86×10^{-16}
0.1	0.1	2283	1315	0.58	1.85	4.06×10^{-13}
0.05	0.05	1015	585	0.58	1.84	1.74×10^{-6}
0.05	0.01	322	199	0.62	2.59	3.66×10^{-5}
0.01	0.05	439	266	0.61	2.39	1.03×10^{-5}
0.01	0.01	152	93	0.61	2.34	1.47×10^{-2}

AD: Alzheimer's disease, GERD: gastroesophageal reflux disease, P1: P-value for the dataset, P2: P-value for dataset 2, P1P2snp: Independent SNPs overlapping AD (P1) and GERD (P2) at each of the SNP subsets, Concord: number of concordant SNPs, SNP: Single Nucleotide Polymorphism, Ftest: Fisher's Exact test, OR: Odds ratio for the effect direction concordance association test for P1 and P2. Pval: Fisher's exact P-value for the effect direction concordance association test between AD (P1) and GERD (P2).

Table 3: Genetic correlation between AD and GIT disorders

Phenotype 1	Phenotype 2	r_g	se	P	Gencov_int	gencov se
(A) AD without APOE and MHC regions	AD	1.00	1.97×10^{-6}	0.00000	0.995	0.008
	GERD	0.19	3.82×10^{-2}	8.78×10^{-7}	0.015	0.005
	Gastritis-and-duodenitis	0.19	6.68×10^{-2}	5.40×10^{-3}	0.008	0.005
	PGM	0.15	3.99×10^{-2}	1.43×10^{-4}	0.016	0.006
	PUD	0.26	7.10×10^{-2}	2.92×10^{-4}	0.004	0.005
	IBS	0.16	6.91×10^{-2}	2.36×10^{-2}	0.004	0.005
	Diverticular disease	0.18	5.78×10^{-2}	1.59×10^{-3}	-0.004	0.006
	IBD	-0.05	5.90×10^{-2}	3.80×10^{-1}	0.010	0.006
Phenotype 1	Phenotype 2	r_g	se	P	Gencov_int	gencov se
(B) AD with APOE region	AD	1.00	3.06×10^{-6}	0.00000	1.049	0.051
	GERD	0.24	6.59×10^{-2}	3.00×10^{-3}	0.013	0.005
	Gastritis-and-duodenitis	0.26	9.90×10^{-1}	8.60×10^{-3}	0.005	0.005
	PGM	0.21	7.58×10^{-2}	6.30×10^{-3}	0.014	0.006
	PUD	0.33	1.24×10^{-1}	7.50×10^{-3}	0.004	0.005
	IBS	0.19	9.45×10^{-2}	4.44×10^{-2}	0.005	0.005
	Diverticular disease	0.23	8.27×10^{-2}	4.66×10^{-3}	-0.005	0.005
	Lansoprazole medication	0.25	1.22×10^{-1}	3.72×10^{-2}	0.006	0.005
	IBD	-0.07	7.21×10^{-2}	3.27×10^{-1}	0.012	0.007

AD: Alzheimer's disease, GIT: gastro-intestinal tract, GERD: gastroesophageal reflux disease, PUD: peptic ulcer disease, PGM: medications for GERD and PUD, IBS: irritable bowel syndrome, IBD: Inflammatory bowel disease, r_g : genetic correlation, se: standard error, P: P-value, MHC: major histocompatibility complex, gencov_int: genetic covariance intercept.

900 **Table 4: Genome-wide significant independent SNPs and loci for AD and GIT disorders**

Independent SNPs	Locus	Lead SNPs	Chr	BP	EA	NEA	I ²	Nearest coding genes/cytoband	Meta-analysis		AD		GIT Disorders	
									P-value	BE	P-value	M-value	P-value	M-value
SNPs and loci reaching genome-wide significance after a meta-analysis of AD GWAS and PGM GWAS														
rs2840677	1	rs12058296	1	66333877	A	T	66.10	PDE4B/ 1p31.3	2.43 × 10 ⁻⁸	4.56 × 10 ⁻⁸	5.73 × 10 ⁻³	0.94	2.20 × 10 ⁻⁷	1.00
rs6695557			1	66349013	A	G	57.16	PDE4B/ 1p31.3	8.46 × 10 ⁻⁹	2.08 × 10 ⁻⁸	3.02 × 10 ⁻³	0.97	1.89 × 10 ⁻⁷	1.00
rs12058296			1	66402424	A	C	84.60	PDE4B/ 1p31.3	5.02 × 10 ⁻⁹	9.37 × 10 ⁻⁸	3.22 × 10 ⁻⁵	0.99	8.68 × 10 ⁻⁶	1.00
rs4147104	2	rs4147104	1	207882194	A	G	13.54	CD46 / 1q32.2	5.47 × 10 ⁻⁹	1.48 × 10 ⁻⁸	1.02 × 10 ⁻⁶	1.00	6.12 × 10 ⁻⁴	1.00
rs709210	3	rs7642934	3	50357869	A	C	93.99	HYAL2 / 3p21.31	4.39 × 10 ⁻⁸	1.59 × 10 ⁻⁷	1.55 × 10 ⁻²	NA	6.28 × 10 ⁻⁸	NA
rs7642934			3	50174848	A	G	93.64	SEMA3F / 3p21.31	2.78 × 10 ⁻⁸	1.51 × 10 ⁻⁷	7.47 × 10 ⁻³	0.01	8.19 × 10 ⁻⁸	1.00
rs2858331	4	rs2858331	6	32681277	G	A	61.35	HLA-DQA2/ 6p21.32	3.08 × 10 ⁻¹⁰	7.14 × 10 ⁻¹⁰	1.24 × 10 ⁻⁷	1.00	1.18 × 10 ⁻⁴	1.00
rs28895026			6	32391695	C	T	0.00	HLA-DRA/6p21.32	5.43 × 10 ⁻⁹	1.38 × 10 ⁻⁸	1.48 × 10 ⁻⁷	1.00	8.38 × 10 ⁻³	0.98
rs34644948	5	rs34644948	16	70681658	T	C	0.00	MTSS2 / 16q22.1	2.11 × 10 ⁻⁸	5.63 × 10 ⁻⁸	1.98 × 10 ⁻⁷	1.00	3.13 × 10 ⁻²	0.95
rs2584662	6	rs2584662	17	47470487	C	A	0.00	PHB / 17q21.33	3.94 × 10 ⁻⁹	1.00 × 10 ⁻⁸	1.98 × 10 ⁻⁷	1.00	4.91 × 10 ⁻³	0.99
rs11083749	7	rs11083749	19	45384105	T	C	0.00	APOE / 19q13.32	2.84 × 10 ⁻⁸	7.35 × 10 ⁻⁸	1.98 × 10 ⁻⁷	1.00	3.45 × 10 ⁻²	0.95
SNPs and loci reaching genome-wide significance after a meta-analysis of AD GWAS and GERD GWAS														
rs12058296	1	rs12058296	1	66402424	A	C	85.75	PDE4B/ 1p31.3	1.05 × 10 ⁻⁸	2.10 × 10 ⁻⁷	3.22 × 10 ⁻⁵	0.99	1.74 × 10 ⁻⁵	1.00
rs2503185			1	66461401	G	A	91.93	PDE4B/ 1p31.3	3.44 × 10 ⁻⁸	1.21 × 10 ⁻⁸	9.53 × 10 ⁻⁴	0.25	9.60 × 10 ⁻⁷	1.00
rs12561863	2	rs12561863	1	190897608	A	T	96.02	BRINP3/ 1q31.1	1.68 × 10 ⁻⁸	2.89 × 10 ⁻⁷	5.76 × 10 ⁻³	0.00	1.05 × 10 ⁻⁷	1.00
rs3774745*	3	rs3774745	3	50204745	T	C	92.74	SEMA3F/ 3p21.31*	2.01 × 10 ⁻⁹	2.57 × 10 ⁻⁹	2.55 × 10 ⁻⁴	0.36	1.64 × 10 ⁻⁷	1.00
rs28895026	4	rs28895026	6	32391695	C	T	0.00	HLA-DRA/6p21.32	2.06 × 10 ⁻⁸	5.37 × 10 ⁻⁸	1.48 × 10 ⁻⁷	1.00	4.26 × 10 ⁻²	0.94
rs8067459	5	rs2584662	17	47444113	C	T	0.00	ZNF652/ 17q21.32	3.07 × 10 ⁻⁸	8.09 × 10 ⁻⁸	2.15 × 10 ⁻⁷	1.00	4.48 × 10 ⁻²	0.93
rs2584662			17	47470487	C	A	0.00	PHB/17q21.33	7.72 × 10 ⁻⁹	1.96 × 10 ⁻⁸	1.54 × 10 ⁻⁷	1.00	1.02 × 10 ⁻²	0.98
rs11083749	6	rs1132899	19	45384105	T	C	0.00	APOE/ 19q13.32	2.63 × 10 ⁻⁸	6.88 × 10 ⁻⁸	2.46 × 10 ⁻⁷	1.00	3.14 × 10 ⁻²	0.95
rs1132899			19	45448036	T	C	94.99	APOC2/ 19q13.32	1.19 × 10 ⁻⁸	1.57 × 10 ⁻⁷	5.41 × 10 ⁻⁸	1.00	5.53 × 10 ⁻³	0.00
rs117501883	7	rs117501883	19	45841296	A	G	0.00	KLC3/ 19q13.32	8.96 × 10 ⁻⁹	2.32 × 10 ⁻⁸	7.13 × 10 ⁻⁸	1.00	3.78 × 10 ⁻²	0.94
rs76692930			19	45875851	T	C	50.22	ERCC2/ 19q13.32	3.51 × 10 ⁻⁸	8.60 × 10 ⁻⁸	3.18 × 10 ⁻⁶	1.00	8.32 × 10 ⁻⁴	0.99

SNPs and loci reaching genome-wide significance after a meta-analysis of AD GWAS and PUD GWAS														
rs36133610	1	rs36133610	2	234067884	A	G	0.00	INPP5D/ 2q37.1	1.24×10^{-8}	3.41×10^{-8}	5.85×10^{-8}	1.00	4.90×10^{-2}	0.92
rs9270599	2	rs9270599	6	32561656	G	A	26.29	HLA-DRA/6p21.32	9.12×10^{-9}	2.59×10^{-8}	5.60×10^{-8}	1.00	2.72×10^{-2}	0.92
rs530324	3	rs530324	8	27491186	C	G	76.92	SCARA3/ 8p21.1	2.27×10^{-8}	6.17×10^{-8}	3.32×10^{-7}	1.00	2.00×10^{-3}	0.96
rs73976310	4	rs73976310	17	5014212	A	G	31.11	USP6/ 17p13.2	1.20×10^{-8}	3.67×10^{-8}	7.04×10^{-8}	1.00	2.70×10^{-2}	0.90
rs28363848	5	rs28363848	19	45257201	T	G	41.06	BCL3/ 19q13.32	1.04×10^{-8}	2.96×10^{-8}	5.63×10^{-8}	1.00	2.60×10^{-2}	0.91
rs3852865	6	rs3852865	19	51714065	A	G	58.20	CD33/ 19q13.41	1.81×10^{-8}	5.19×10^{-8}	1.63×10^{-7}	1.00	9.90×10^{-3}	0.94
rs7245846			19	51731176	A	G	5.22	CD33/ 19q13.41	2.32×10^{-8}	6.71×10^{-8}	1.19×10^{-7}	1.00	4.00×10^{-2}	0.91

SNP: Single nucleotide polymorphism; Chr: Chromosome; EA: Effect allele; NEA: Non-effect allele; I2: I-square for heterogeneity assessment; Se: Standard error; P: P-value; Meta-analysis model use was RE2C and RE2. RE2C: GWAS meta-analysis methods that account for sample overlap and heterogeneity. RE2: adjusts for heterogeneity. *The m-value suggests that the SNP rs3774745 has an effect on GERD but is ambiguous for AD. Comparing the results with results of BE, and P-value, the locus is more likely to influence both traits.

Table 5: Summary of MR analysis results for AD and GIT disorders

Exposure (nSNPs)	Outcome	IVW	Weighted median		MR-Egger		MR-PRESSO						MR-Egger Intercept	
		Beta	P	Beta	P	Beta	P	Global test P	Raw Beta	P	Corrected Beta	P	Intercept	P
AD (28)	GERD	-0.053	0.266	0.011	0.860	-0.059	0.362	0.113	-0.052	0.276	-	-	0.00034	0.879
GERD (24)	AD	0.014	0.351	-0.002	0.920	-0.053	0.597	0.435	0.0136	0.361	-	-	0.0025	0.502
AD (28)	PGM	-0.061	0.112	-0.016	0.769	-0.045	0.391	0.231	-0.061	0.123	-	-	-0.001	0.631
PGM (17)	AD	0.023	0.322	-0.005	0.837	-0.148	0.199	0.017	0.023	0.337	0.009	0.661	0.007	0.133
AD (28)	PUD	0.036	0.651	0.144	0.211	0.071	0.504	0.113	0.036	0.60	-	-	-0.002	0.612
PUD (8)	AD	0.021	0.238	0.025	0.122	0.055	0.658	0.0104	0.021	0.277	0.0331	0.053	-0.00291	0.770
AD (28)	Diverticular	-0.055	0.597	-0.214	0.105	-0.12	0.397	0.094	-0.055	0.601	-	-	0.0034	0.483
Diverticular (16)	AD	-0.001	0.883	-0.001	0.905	0.007	0.811	0.316	-0.001	0.884	-	-	-0.00076	0.773
AD (28)	IBS*	0.043	0.623	0.142	0.123	-0.016	0.888	0.0012	0.043	0.626	0.010	0.892	0.0032	0.438
AD (28)	Gastritis-D*	-0.085	0.267	-0.101	0.273	-0.173	0.098	0.034	-0.085	0.277	-	-	0.0046	0.196
AD (28)	IBD	0.254	0.104	0.365	0.094	0.277	0.231	0.327	0.254	0.115	-	-	-0.00097	0.885
IBD (24)	AD	-0.0005	0.895	-0.003	0.526	0.004	0.607	0.316	-0.0005	0.895	-	-	0.00073	0.497

nSNP: number of SNPs utilised as instrumental variables, SNP: single nucleotide polymorphism, AD: Alzheimer's disease, GERD: gastroesophageal reflux disease, PUD: peptic ulcer disease, PGM: medications for GERD or PUD, Diverticular: diverticular disease, IBS: irritable bowel syndrome, IBD: inflammatory bowel disease, IVW: inverse variance weighted, P: P-value, MR-PRESSO: Mendelian Randomization Pleiotropy RESidual Sum and Outlier, Gastritis-D: Gastritis-duodenitis, * Only one genome-wide significant SNPs available for IBS, and 3 for Gastritis-D, so we are unable to carry out MR using the traits as the exposure variable. Note spaces marked with a dash indicate that there were no outlier SNPs and hence there was no outlier corrected results in the MR-PRESSO analysis.

Table 6: Partial causality assessment using the Latent Causal Variable approach

Trait 1	Trait 2	GCP	SE	P	r_g	r_g -P
AD	Gastritis-duodenitis (Main ICD10: K29)	-0.69	0.27	0.0026	0.39	0.033
	Gastritis-duodenitis (PheCode_535_SAIGE)	-0.36	0.39	0.43	0.25	0.018
	PGM	-0.45	0.37	0.22	0.21	0.0064
	PUD	0.49	0.32	0.24	0.33	0.0077
	IBS	0.35	0.29	0.38	0.19	0.043
	GERD	-0.01	0.58	0.64	0.25	0.060
	Diverticular disease (Main ICD10: K57)	0.23	0.10	0.000272	0.26	0.0396
	IBD	-0.52	0.44	0.002319	-0.0397	0.6832
	Lansoprazole	-0.38	0.17	0.001129	0.43	0.0176

AD: Alzheimer's disease, GCP: Genetic causal proportion, SE: Standard error, P: P-value, r_g : genetic correlation, r_g -P: genetic correlation P-value, GERD: gastroesophageal reflux disease, PUD: peptic ulcer disease, PGM: GWAS for medication use in GERD and PUD, IBD: inflammatory bowel disease.

Fig 1: Simplified workflow for AD and GIT disorders relationship analysis

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1. Gene Ontology: Biological Pathway

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2. Gene Ontology: Cellular Components

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3. Gene Ontology: Molecular Function

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4. KEGG: Kyoto Encyclopedia of Genes and Genomes

intestinal immune network

5. Reactome, Wiki pathway and Transcription Factor Binding sight
assembly clearance plasma

Figure 2: Clusters of significantly enriched biological pathways for AD and GERD

Figure 3: Summary of findings suggesting potential mechanisms of AD and GIT disorders

GIT: gastrointestinal tract, H. pylori: *Helicobacter pylori*, CNS: central nervous system, BBB: the blood-brain barrier. Findings in this study indicate shared genetic susceptibility in AD and GIT disorders, consistent with the concept of the gut-brain axis and the suggestions of some observational studies. Potential mechanisms implicated include those related to autoimmunity, lipids metabolism, lipase inhibitors and statins pathways. There is a connection between autoimmunity and dyslipidaemia, and consistent with our findings, previous studies suggest lipids play a role in both AD and GIT disorders. For example, hypercholesterolemia is believed to increase the permeability of BBB, facilitating the entry of peripheral cholesterol into the CNS, resulting in abnormal cholesterol metabolism in the brain, and subsequently in AD pathology. Similarly, *H. pylori* is believed to cause or worsen abnormal serum lipid profiles through chronic inflammatory processes. Lipid inhibitors and statins may thus find therapeutic applications in these disorders or their comorbidity.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryNotesandfiguresADGITdisordermanuscript.pdf](#)
- [SupplementaryTableADGITdisordermanuscript.xlsx](#)