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Shared whole environmental etiology between Alzheimer's disease and age-related macular degeneration

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The comorbidity of Alzheimer's disease (AD) and age-related macular degeneration (AMD) has been established in clinical and genetic studies. There is growing interest in determining the shared environmental factors associated with both conditions. Recent advancements in record linkage techniques enable us to identify the contributing factors to AD and AMD from a wide range of variables. As such, we first constructed a knowledge graph based on the literature, which included all statistically significant risk factors for AD and AMD. An environment-wide association study (EWAS) was conducted to assess the contribution of various environmental factors to the comorbidity of AD and AMD based on the UK biobank. Based on the conditional Q-Q plots and Bayesian algorithm, several shared environmental factors were identified, which could be categorized into the domains of health condition, biological sample parameters, body index, and attendance availability. Finally, we generated a shared etiology landscape for AD and AMD by combining existing knowledge with our novel findings.

Alzheimer's disease (AD) and age-related macular degeneration (AMD) are common neurodevelopmental disorders with onset typically within the elderly populations, which share numerous clinical and pathological features[1]. Haan et al. discovered that in patients with AD, retinal neurons have been observed to exhibit amyloid deposits and neurofibrillary tangles, mirroring those found in the brain[2]. This finding suggests a potential link between retinal pathology and AD progression and adds evidence for the biological reason for comorbidity between AD and AMD. There are ~50 million people worldwide who live with dementia, and this number is projected to increase to 152 million by 2050[3]. AD, an irreversible neuron degenerative disease with high heritability (~60–80%), has gradually become the major type of dementia and a considerable public health concern[4]. AMD is also an irreversible neuron degenerative disease in the macular area and is the leading common cause of irreversible blindness worldwide, with an estimated number of patients approaching 196 million in 2020 and 288 million in 2040[5].

The global burden of both disorders on healthcare services presents considerable direct costs[6,7]. Studying the common genetic features between Alzheimer's disease (AD) and age-related macular degeneration (AMD) can provide valuable insights into the shared biological pathways and potential underlying mechanisms that contribute to both diseases. By identifying common genetic features, we can uncover shared pathophysiological

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mechanisms that may be involved in the development and progression of both diseases[8]. Understanding these shared pathways can lead to the development of novel therapeutic targets that could potentially benefit individuals affected by either disease. Identifying common genetic features between AD and AMD can help in the development of precision medicine approaches tailored to individuals based on their genetic profiles[9]. By understanding the genetic underpinnings of both diseases, we can potentially identify genetic markers that could be used for early detection, risk assessment, and personalized treatment strategies.

Genome-wide association studies (GWAS) have helped in the understanding of the genetic association between different diseases by revealing thousands of single-nucleotide polymorphisms (SNPs) related to many diseases[10–13]. Recently, we have proven the genetic pleiotropy for AD and AMD and identified APOC1 and APOE as pleiotropic genes, based on GWAS data using a Bayesian algorithm[14]. GWAS have substantially enhanced comprehension of the genetic underpinnings of multifaceted traits and have facilitated the identification of a multitude of loci linked with these traits[15]. GWAS have introduced a high-throughput methodology for exhaustive evaluation of genetic variants across the entire genome. Nonetheless, this methodological approach is insufficient in its failure to account for the intricately heterogeneous and intricate milieu within which human beings operate throughout their lifespan[16].

There is broad consensus that AD and AMD are both complex diseases caused by genetic and environmental factors. Previous GWAS investigations have demonstrated that SNP heritability of AD is ~41%, when taking into account the most considerable heritability estimate, such as APOE4[17,18]. And the emergence of precursor lesions of AMD was found to be ascribable to 49% genetic factors and 51% environmental factors[19]. Despite the abundance of SNPs identified by GWAS in relation to AD and AMD, there is still much that remains unknown about their underlying heritability and mechanisms. It is highly probable that environmental exposure exerts a significant influence on the genetic and cellular systems involved in the two complex traits[20]. Similar to the way that complex traits are influenced by multiple SNPs, the environmental influence on diseases is also driven by numerous factors[21,22].

Many epidemiological reports have been focusing on investigating the environmental variables of AD and AMD individually in which a single or limited number of exposures are analyzed in relation to a phenotype. For example, it is reported that low educational levels and air pollution, despite lifestyle and comorbidities, are well-established risk factors for dementia and are considered to significantly influence the risk of AD[23–25]. On the other hand, the environmental risk factors affecting disease's phenotypes of AMD included smoking, unfavorable diet, reduced physical activity and metabolic and other risk factors[26,27]. In the event that environmental factors demonstrate similar characteristics to genetic factors in terms of being characterized by polyenvironicity and pleiotropy, a comprehensive representation of the entire environome is necessary to capture them. However, the systemic investigation of whole environmental etiology for AD and AMD is still missing, since traditional epidemiology studies cannot integrate all of the environmental factors in a standard bioassay to further detect their relationships with diseases. Therefore, investigating the comorbidity reason for AD and AMD at the whole environmental level is extremely important.

Environment-wide association studies (EWAS) could provide a comprehensive and unbiased approach to examining various environmental exposures in a high-throughput manner, analogous to the method used by GWAS in testing genetic effects, which has been used in type 2 diabetes[28], childhood obesity[29], age-related diseases[30] and so on. However, there is no EWAS study focusing on detecting the overlapped environmental factors for AD or AMD. In this study, the objective was to utilize the EWAS approach to thoroughly and systematically explore potential associations between specific physical environmental factors and AD and AMD on a broad scale in the UK biobank data. Additionally, we aimed to identify common environmental factors that act in a consistent direction for both diseases. We have explored how comorbidity science can draw insights from genomic research to enhance our comprehension and models of environmental influences.

Results

Knowledge graph of environmental factors associated with AMD and AD

In order to comprehensively elucidate the landscape of environmental factors that are associated with the two age-related diseases using the UK Biobank (UKB) dataset, an exhaustive literature review was conducted to identify all relevant studies investigating the role of environmental determinants in both the original National Health Service (NHS) cohort and its subsequent iterations. This rigorous approach enabled a comprehensive evaluation of the existing knowledge base in this domain and facilitated the identification of potential gaps and avenues for further research. Finally, we excavated 64 associated factors for AD/AMD, from 1215 previously published papers. The relationships of these factors were presented as knowledge graph in Fig. 1. Among them, smoking, gout, cataract, cancer, the

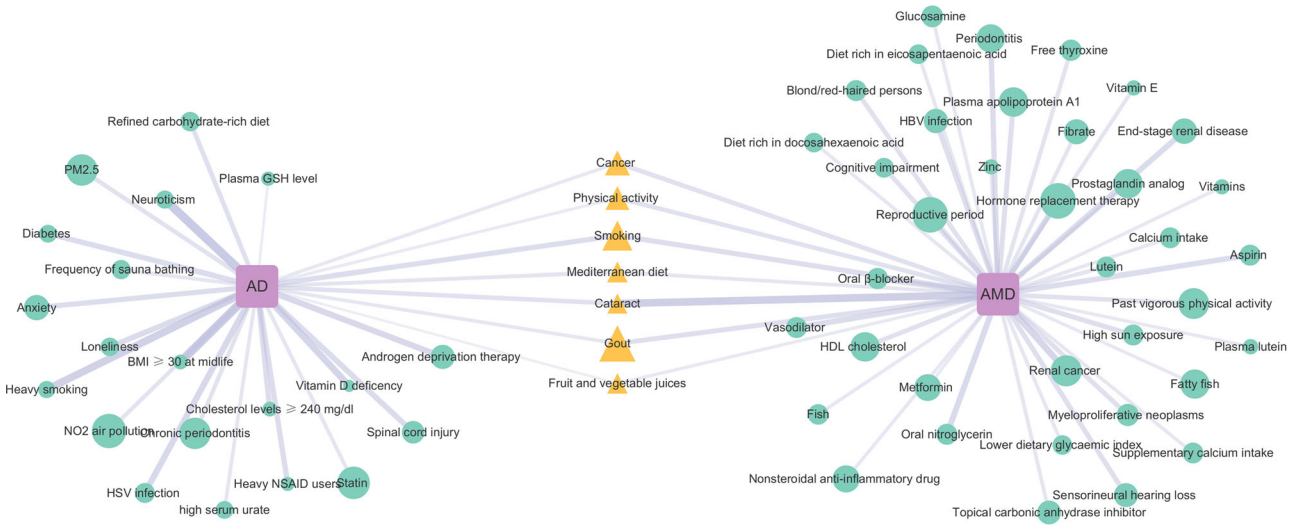

Fig. 1 | The knowledge graph of the environmental factors associated with AMD and AD included in the analysis. The nodes of the graph are environmental factors (green circles), AD (diamonds in purple), AMD (diamonds in purple), and overlap factors for AD and AMD (yellow triangle). Each studied association is shown by an edge whose thickness denotes the degree of the OR between an exposure and a disease. The figure aims to illustrate the body of work derived from published data regarding AD and AMD.

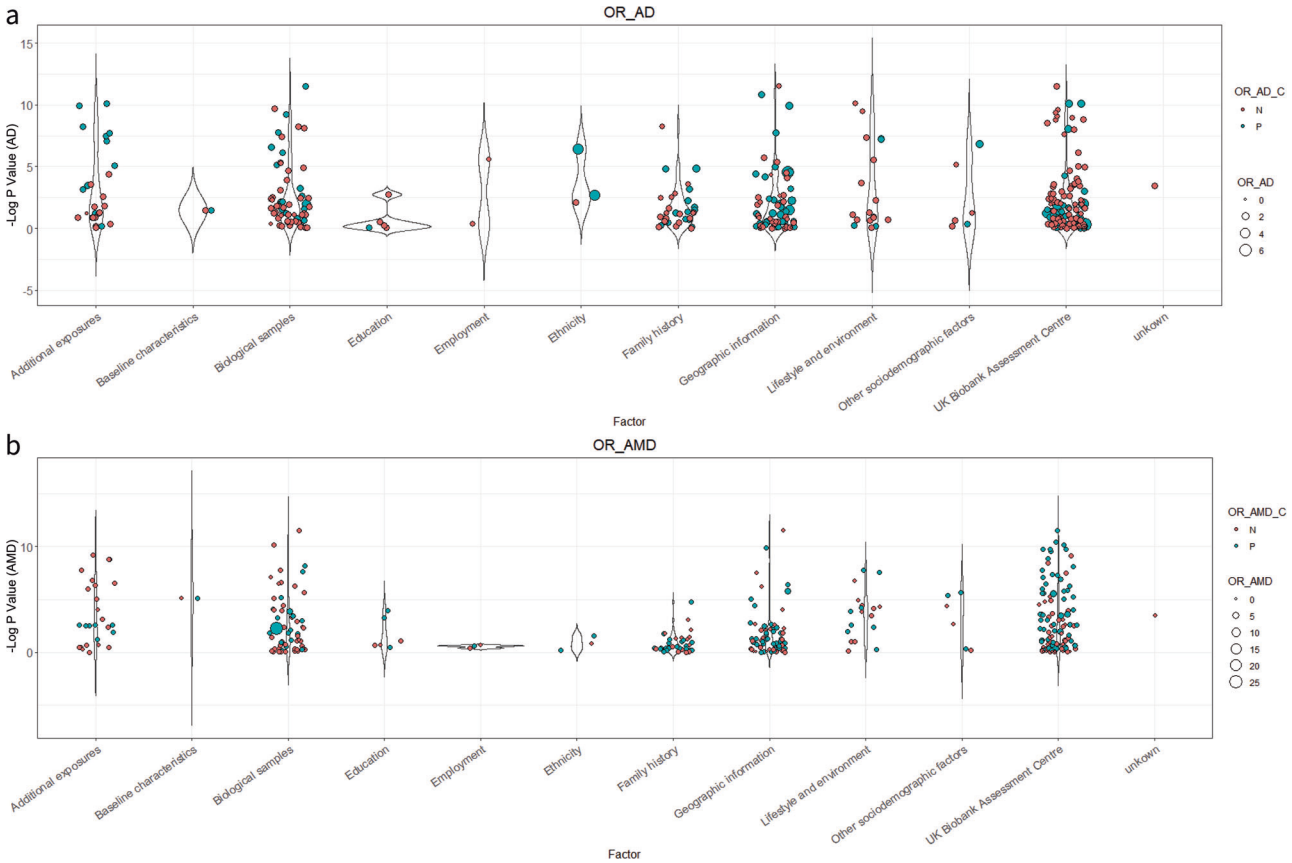

Fig. 2 | Manhattan plot of environmental variables in AD and AMD. Manhattan plot showing *P* values for associations between environmental variables within different categories and AD (**a**) or AMD (**b**). The *Y* axis is the negative log transformation of the estimated *p* value, and the axis is the hazard ratio for AMD or AD. Colors indicate the hazard ratio: negative (red), positive (cyan).

Mediterranean diet and fruit and vegetable juices are found to be associated with AD and AMD.

EWAS for AD and AMD

For the first phase of EWAS, using the UK Biobank dataset we collected whole environmental factors associated with AMD or AD. We included 2943 AD and 7308 AMD patients (86 with both AD and AMD) in the analysis. The AD and AMD "Manhattan plot" analogous to the association results from a GWAS study of discovery and replication EWAS dataset were presented in Fig. 2a, b, respectively. The findings of the EWAS aimed at identifying potential environmental factors associated with AD revealed a total of 112 variables that exhibited statistically significant differences in their levels ($p < 0.05$, OR ≠ 1) between AD cases and controls, with 52 of these factors displaying a positive association with disease risk while 60 demonstrated a protective effect (Table S1). Similarly, the EWAS results for AMD identified a total of 132 environmental determinants that exhibited significant statistical differences in their levels ($p < 0.05$, OR ≠ 1) between cases and controls, with 78 factors being associated with an increased risk of AMD while 54 factors displayed a protective effect (Table S2). These findings offer novel insights into the potential modifiable risk factors that may contribute to the development of these debilitating age-related conditions.

Shared environmental factors between AD and AMD

By utilizing EWAS analytical methods to explore the shared environmental factors of AD and AMD, we identified a total of 29 environmental factors that co-acted in both diseases. Conditional Q-Q plots were plotted to identify the polyenvironicity between AD and AMD (Fig. 3). Several co-environmental factors with OR > 1.0 that were negatively associated with both diseases, including no Started insulin, receive attendance allowance and disability living allowance, no diabetes, logMAR (mean arterial pressure), receive attendance allowance, started insulin within one-year diagnosis of diabetes, cystatin C level, poor health condition, glucose and glycated hemoglobin (HbA1c) (Fig. 4, Table S3). In contrast, biological factors with OR < 1.0 such as hematocrit percentage, cholesterol level, LDL level, hemoglobin concentration, 3 mm asymmetry index for irregular astigmatism level (normal) and 3 mm regularity index for irregular astigmatism level (normal) along with good health condition and diabetes, were positively associated with both AMD and AD (Fig. 4, Table S3). Furthermore, some factors exhibited opposite effects on the two diseases, including NO2 air pollution, weight, whole body fat-free mass, whole body water mass, trunk predicted mass, trunk fat-free mass, arm fat-free mass (left), arm predicted mass (left) and arm fat-free mass (right) (Fig. 3, Table S3).

The landscape of comorbidity reason for AD and AMD

We mapped the shared environmental factors and genes (APOE and APOC1) on the same network to construct the comorbidity landscape for AD and AMD (Fig. 5). Our EWAS results demonstrate a more comprehensive capture of the environmental factors associated with AD and AMD than prior knowledge graphs. Furthermore, they reveal novel associations between many factors and the diseases of interest.

Discussion

The present study applied EWAS analytical method to UK biobank data in order to examine shared environmental factors existing in the AD and AMD. First, multiple environmental factors associated with emerging AD and AMD are listed in the existing literature. Second, using this environment-wide association approach, we identified 112 and 132 environmental factors that were associated with AD and AMD, respectively. These factors cluster in the following domains: health condition, biological samples' parameters, body index and attendance

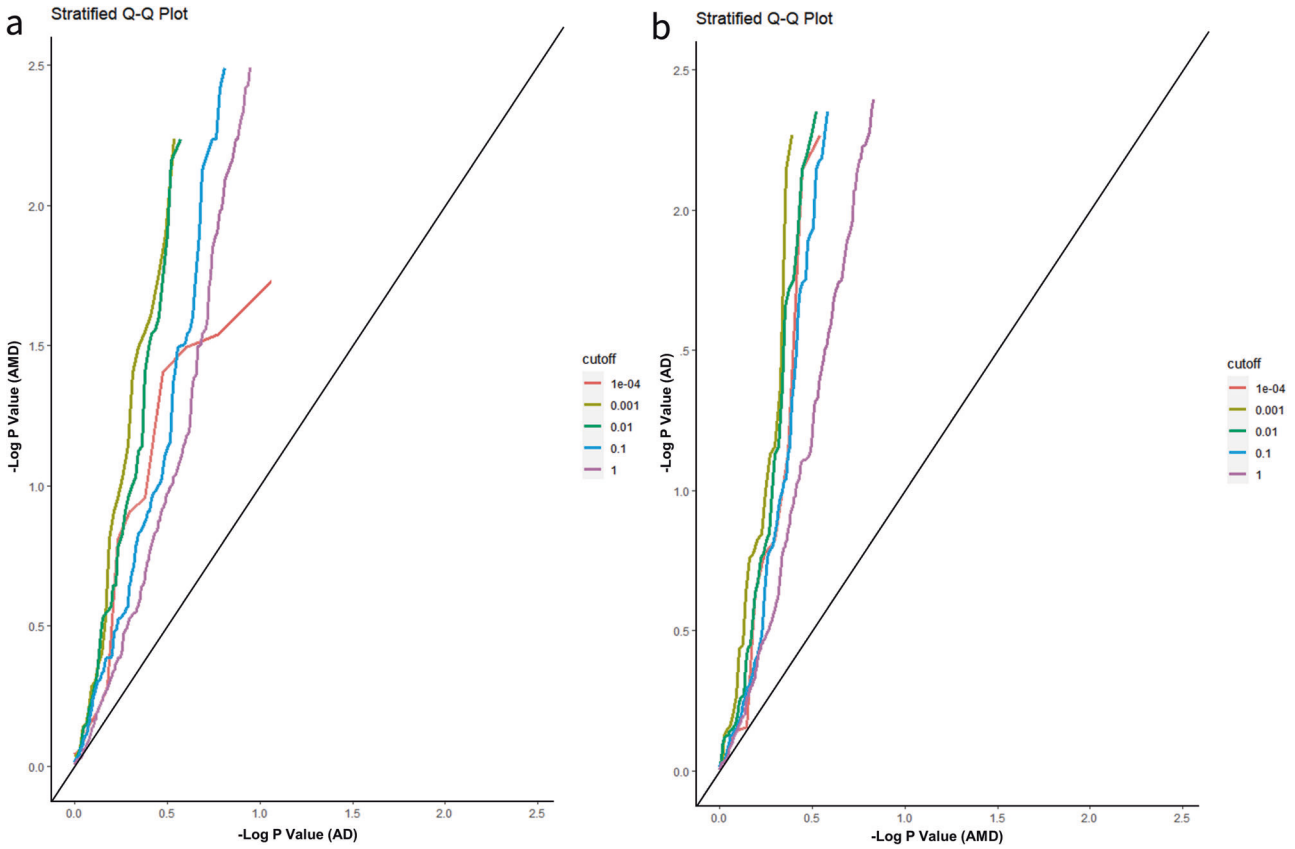

Fig. 3 | Conditional Q-Q plot for AD and AMD. a Conditional Q-Q plot for AD|AMD. **b** Conditional Q-Q plot for AMD|AD. The *x* axis is −log(*P* value of AD environment factors), and the *y* axis is −log (*P* value of AMD environment factors). Different curves represent different cutoffs for the AMD *P* value. A significant left deviation was found among all the curves, indicating obvious polyenvironicity for AD|AMD.

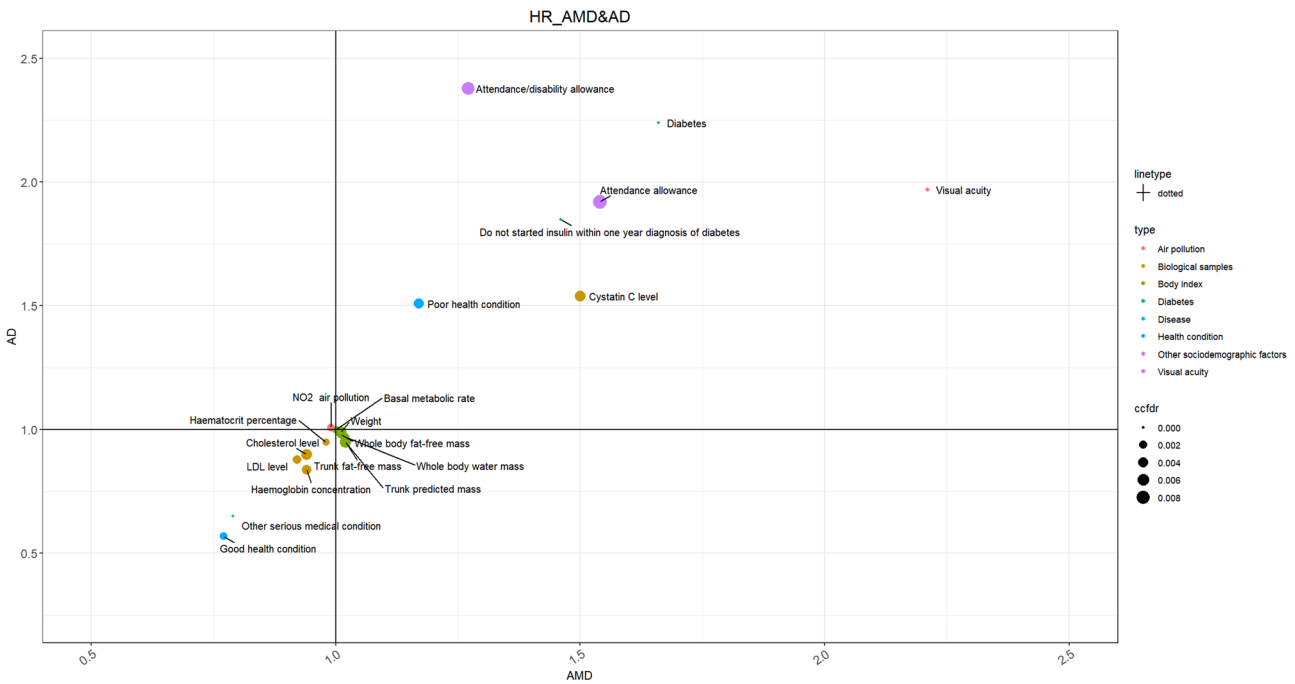

Fig. 4 | Shared environmental factors between AD and AMD. The nodes are the factors, and different colours represent different categories. The size of nodes shows the value of ccFDR.

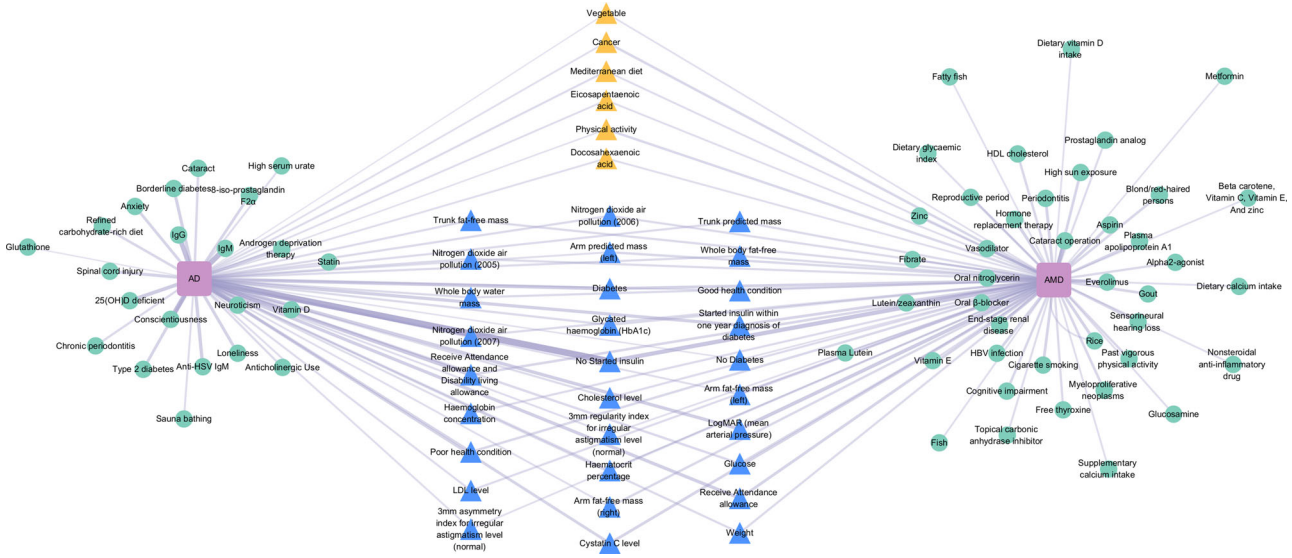

Fig. 5 | Comorbidity landscape for AD and AMD. Purple diamonds represent the diseases (AD and AMD). Green circles represent the independent factors for AD or AMD. The yellow triangle represents the reported shared factors, and the blue ones represent the newly identified shared factors. The line thickness represents the strength of OR.

availability. Moreover, an examination of the co-environmental factors that influence AD and AMD reveals a potential association between AD and AMD.

It remains a matter of debate whether AMD and AD are closely associated. A recent meta-analysis reported no significant association between AMD and incident dementia or AD[31]. On the contrary, another meta-analysis mainly enrolled case-controlled and cross-sectional studies documented the increased risk of AD in patients with AMD[32]. Based on GWAS data from 690,000 participants included in this study from nine multi-omics datasets, our unpublished results showed us that AD and AMD share common genetic factors, such as APOC1 and APOE, which play a substantial role in the etiology. However, environmental exposures may also have a major impact on molecular and cellular systems for many diseases.

Referring to the constructed knowledge graph, most previous research has focused on testing the effect of one or two environmental influences that stemmed from one or two sources. Yet EWAS could provide a practical method to test a variety of exposures in the human environment in an unbiased manner, similar to GWAS tests for genetic effects[33].

After conducting EWAS analyses to explore shared environmental items between AD and AMD, we identified several common risk and protective factors. Factors including "no Started insulin," "Receive Attendance allowance and Disability living allowance," "Diabetes," "logMAR (mean arterial pressure)," "Started insulin within one-year diagnosis of diabetes," "Cystatin C level," "Poor health condition," "Glucose," and "Glycated hemoglobin (HbA1c)" were found to be common risk factors for both diseases. On the other hand, "Hematocrit percentage," "Cholesterol level," "LDL level," "Hemoglobin concentration," "3 mm asymmetry index for irregular astigmatism level (normal)," "3 mm regularity index for irregular astigmatism level (normal)," "Good health condition," and "no Diabetes" were common protective factors for AD.

We found that the risk factors for AD and AMD include "no Started insulin," "Diabetes," "Started insulin within one-year diagnosis of diabetes," "Glucose," and "Glycated hemoglobin (HbA1c)." These findings are consistent with previous research. A few studies have highlighted the substantial similarities between AD and diabetes, including common metabolic alterations and genetic underpinnings. As such, AD has been referred to as "type 3 diabetes" (T3DM)[34–38]. Retinopathy is one of common and feared complications of diabetes, several studies have shown a relationship between glucose disturbance (GD) and AMD[39]. Additionally, a growing body of literature has identified diabetes as a risk factor for AMD[40–42].

Recent investigations have highlighted the correlation between variations in Cystatin C level and various disorders, such as AD and retinal inflammation, the latter being a prominent characteristic of AMD[43–45]. Ten years ago, several studies provided evidence that hypertension is associated with an increased risk of developing AD and AMD[46–48]. Epidemiological studies show a positive association between long-term exposure to nitrogen dioxide (NO_2) air pollution and the risk of cognitive decline in older adults[49,50]. Similar trends were also observed in AMD[51,52].

In addition, some protective factors have also been validated in the literatures. A recent prospective cohort study of 313,448 participants demonstrated a U-shaped association of hematocrit percentage and hemoglobin (HGB) concentration with dementia risk and concluded that HGB was causally associated with AD[53]. Plenty of epidemiological, genetic, and biochemical evidence suggests that cholesterol is a risk factor for AD[54,55] and the receptor-binding domains of apolipoproteins comprise low-density lipoprotein (LDL) receptors that aid in the transport of amyloid peptides across the blood-brain barrier (BBB), thereby clearing them. Enhancing the expression of this receptor could be a promising therapeutic strategy for AD[56,57].

Our study identified 29 shared environmental factors associated with both AD and AMD, exhibiting a consistent trend across the comorbidity landscape. The majority of these factors have been previously validated. This finding may illustrate that there are complex shared environmental risk factors contributing to the pathogenesis of AD and AMD.

Our EWAS study revealed that LDL levels serve as a common environmental factor shared between AD and AMD. Notably, LDL has been established as a pivotal factor in cardiovascular disease (CVD). Through comprehensive literature review, we identified three intersecting biological pathways—the inflammation pathway, oxidative stress pathway, and amyloid pathway—that are shared among AD, AMD, and CVD. Furthermore, our investigation unveiled that the inflammation pathway, oxidative stress pathway, insulin signaling pathway, and lipid metabolism pathway are common pathways linking AD, AMD, and metabolic syndrome. When exploring the biological connections between AD, AMD, and smoking, we observed that four shared pathways —the inflammation pathway, oxidative stress pathway, vascular pathway, and amyloid pathway—offer comprehensive explanations. In our analysis of the biological relationships between AD, AMD, and pollution, we discovered shared pathways encompassing the inflammation pathway, oxidative stress pathway, vascular pathway, neuroinflammation and neurodegeneration pathway, as well as the epigenetic pathway.

Among these shared factors, the inflammation pathway and oxidative stress pathway emerged as pivotal pathways, extending across all conditions. Consequently, these pathways may serve as key contributors to the comorbidity observed in AD and AMD.

In our study, we employed text-mining techniques to elucidate and elaborate on the findings of EWAS. This approach notably elevated the caliber and profundity of insights gleaned from the research. Through the synergistic integration of text mining and data analysis, investigators can furnish a more refined, comprehensive, and insightful elucidation of their results. This concerted effort culminates in a more nuanced comprehension of the research subject, ultimately enriching the scholarly discourse.

EWAS enable capturing the environment across levels, dimensions, and time in unprecedented depth and detail. This EWAS analysis helped us visualize the shared environmental factors between AMD and AD. However, our study has a few limitations that should be considered. Although assessment technologies have rapidly improved in recent years, capturing even one individual's environome in its totality remains impossible to date.

Methods

Knowledge graph

We first retrieved the published papers concerning the environmental factors for AD and AMD on PubMed. We selected the studies that used the Cox regression model to detect the association between environmental factors with AD or AMD. Next, we manually examined the abstracts of the obtained papers and extracted the exposure-phenotype relations and the effect size. More than one exposure might be studied in a paper (Table 1). Finally, 72 studies for AD and AMD were chosen as the data source for the knowledge graph (Fig. 1).

Table 1 | Population characteristics

Disease	Exposure	Effect size	Patient number
AD	Vitamin D deficiency	2.22	171
AD	Androgen deprivation therapy	1.88	16,888
AD	Cancer	0.67	1278
AD	Cataract	1.21	19,954
AD	Chronic periodontitis	1.05	262,349
AD	HSV infection	1.96	3432
AD	Anxiety	1.53	26,193
AD	Plasma GSH level	0.30	391
AD	high serum urate	0.78	1462
AD	HSV infection	3.28	1037
AD	Loneliness	1.69	1905
AD	Mediterranean diet	0.91	2258
AD	Neuroticism	3.10	1671
AD	Refined carbohydrate-rich diet	1.27	2777
AD	Frequency of sauna bathing	0.80	2315
AD	Spinal cord injury	1.71	9257
AD	Statin	0.85	399,979
AD	Physical activity	0.48	716
AD	Diabetes	1.6	1488
AD	Heavy smoking	2.57	1136
AD	PM2.5	1.15	266,725
AD	NO2 air pollution	1.031	804,668
AD	Smoking	1.52	
AD	BMI ≥ 30 at midlife	3.1	477
AD	Cholesterol levels ≥ 240 mg/dl	1.57	469
AD	Gout	0.76	309
AD	Heavy NSAID users	1.57	356
AD	Fruit and vegetable juices	0.24	1836
AMD	Aspirin	1.63	4926
AMD	Vitamins	0.65	560
AMD	Blond/red-haired persons	1.25	4926
AMD	Cataract	2.68	3465
AMD	Smoking	1.48	157,614
AMD	Cognitive impairment	1.24	3157
AMD	Calcium intake	0.73	4751
AMD	Lower dietary glycaemic index	0.76	2924
AMD	Diet rich in docosahexaenoic acid	0.73	2924
AMD	Diet rich in eicosapentaenoic acid	0.74	2924
AMD	End-stage renal disease	1.72	27,232
AMD	Renal cancer	2.14	227,894
AMD	Fatty fish	0.61	114,850
AMD	Fibrate	0.94	22,917
AMD	Fish	0.69	4255
AMD	Free thyroxine	1.04	5573
AMD	Glucosamine	0.756	6720
AMD	Gout	1.39	1,684,314
AMD	HBV infection	1.41	17,796
AMD	HDL cholesterol	1.22	122,735
AMD	High sun exposure	1.41	4926
AMD	Hormone replacement therapy	1.72	1,297,388
AMD	Lutein	0.9	4203
AMD	Mediterranean diet	0.78	4255
AMD	Metformin	0.54	45,524
AMD	Myeloproliferative neoplasms	1.3	7958
AMD	Physical activity	1.19	14,630
AMD	Nonsteroidal anti-inflammatory drug	0.69	51,371
AMD	Oral nitroglycerin	1.81	4926
AMD	Oral β-blocker	1.71	4926
AMD	Past vigorous physical activity	1.23	211,960
AMD	Periodontitis	1.58	83,322
AMD	Plasma apolipoprotein A1	1.4	122,735
AMD	Plasma lutein	0.63	609
AMD	Prostaglandin analog	0.9	118,174
AMD	Cancer	1.25	22,084
AMD	Reproductive period	1.14	1,297,388
AMD	Sensorineural hearing loss	1.399	15,686
AMD	Supplementary calcium intake	0.7	4751
AMD	Topical carbonic anhydrase inhibitor	0.84	14,789
AMD	Vasodilator	1.72	4926
AMD	Fruit and vegetable juices	0.58	4202
AMD	Vitamin E	0.92	560
AMD	Zinc	0.91	560

Characteristics of the exposure-phenotype relations and the effect size in UK Biobank at Baseline.

Data source

The data are publicly accessible via an open-access repository located at https://www.ukbiobank.ac.uk/. The UK biobank is a large-scale cohort of ~500,000 participants aged 40–73 years recruited from March to June 2006 to July 2010 with longitudinal phenotypic data and median 10-year follow-up. Baseline assessments were conducted at 22 assessment centers across the UK[58]. Use of the data was approved by the UK Biobank Ethics Advisory Committee. All study participants provided informed consent in accordance with the principles outlined in the Declaration of Helsinki. Moreover, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline was followed during the course of the study. The present study was conducted under application number 62,443 of the UK Biobank resource.

AD phenotype was collected through hospital in-patient admission records and death registries. The identification of dementia was based on the International Classification of Diseases (ICD) code, including 290.0–290.4, 294.1, 331.0–331.2, and 331.5 in ICD-9 and A81.0, F00, F01, F02, F03, F05.1, F10.6, G30, G31.0, G31.1, and G31.8 in ICD-10, covering Alzheimer's Disease dementia, vascular dementia, and dementias of other causes.

AMD phenotype was defined using a combination of main and secondary ICD-10 (Field IDs 41202, 41204: Code H35.3) and ICD-9 (Field IDs 41203, 41205: Code 3625) diagnoses for macular degeneration, self-reported macular degeneration (Field ID 20002: Code 1528), and macular degeneration from the available general practice data.

EWAS

The EWAS is a theoretical approach akin to GWAS, which takes into account a distinctive panel of environmental assays or "loci", quantified across both cases of diseases and controls, resulting in the identification of several environmental factors exhibiting significant associations with diseases while effectively accounting for multiple hypotheses[28]. EWAS is a well-established methodology that is extensively utilized to investigate environmental factors linked to disease outcomes in large-scale populations and to uncover the underlying epidemiological pathways of disease risk. In this investigation, we undertook an EWAS analysis utilizing UK Biobank data to scrutinize 450 environmental factors. However, not all factors were observed in every cohort. To evaluate the odds ratio (OR) of these factors, we utilized Cox regression models. We established the statistical significance level at a p value of 0.05.

Shared environmental analysis

Stratified quantile-quantile (Q-Q) plots with -log10(P value-exposure) as the x axis and −log10(P value-outcome) as the y axis were used to detect the overall trend between AD|AMD (AD to AMD), and AMD|AD (AMD to AD) in whole environment level[59]. Distinct P value cutoff thresholds were established for exposure in order to demarcate individual curves. The appraisal of the general trend was predicated upon the degree of leftward deviation from the null. This approach was utilized to examine the statistical significance of the association between the predictor variable and the outcome variable.

The false discovery rate (FDR) is a statistical methodology utilized to correct for multiple hypothesis testing. Within the domain of pleiotropy analysis, FDR serves as a metric to capture the probability of an environmental factor exhibiting non-pleiotropic effects. Detection of pleiotropy between two diseases can be enhanced with Bayesian conditional FDR (cFDR), an extension of FDR[60]. This statistical technique offers a refined approach which extends the unconditional FDR from an empirical Bayes perspective. Besides, a novel statistical technique termed conjunction-cFDR (ccFDR) was borrowing to identify environmental factors with polyenvironicity effect underlying the co-occurrence of AD and AMD[59]. In this study, we calculate cFDR from AD to AMD and AMD to AD separately, then select the larger as ccFDR.

The construction of comorbidity landscape for AD and AMD

The identified shared environmental factors, together with previously reported shared factors, were mapped together on the interaction network to construct the comorbidity landscape for AD and AMD. Diseases and factors were represented by different sizes and shapes.

Data availability

All data from the UK Biobank is publicly available.

Code availability

All code is open source.

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