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Medical risk factors, ApoE haplotype, and Alzheimer's disease: a large-scale analysis

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ABSTRACT

Background: The multifactorial nature of Alzheimer's disease (AD) has become increasingly evident. In addition to well-established features like neurodegeneration, amyloid-beta and tau deposition, or glial changes, other processes—such as metabolic, circulatory, and inflammatory factors—may also play a key role in driving or accelerating AD-related pathology and cognitive decline. These factors represent important targets for slowing disease progression.

Objectives: Although many studies have examined individual risk factors and meta-analyses have been performed, a large-scale, comprehensive comparison using formal medical data from a single, unified cohort is needed.

Design: A retrospective case-control study leveraging comprehensive health database.

Setting: Data were obtained from the UK-Biobank, a large (~500 K people) population-based biomedical database in the United Kingdom.

Participants: The study included participants aged 40-69 at enrollment between 2006 and 2010, comprising 3,843 individuals who were clinically diagnosed with AD by August 2022 and 387,275 individuals without dementia or cognitive-impairment diagnoses.

Measurements: ICD-10-coded diagnoses, recorded at least 10 years prior to AD diagnosis, were analyzed. Logistic regression was used to estimate the impact and significance of various medical conditions and their interactions with genetic risk factors, while accounting for demographic determinants.

Results: The analysis identified 45 medical factors (96 ICD-10 entities) across multiple systems—particularly metabolic, circulatory, gastrointestinal, and sensorimotor—that significantly differentiated individuals with clinical AD from cognitively unimpaired individuals. Interaction analyses revealed that circulatory and metabolic factors had a weaker influence on AD risk in Apolipoprotein E ε4 carriers, suggesting a gene-environment interaction in disease susceptibility.

Conclusions: These findings enhance the understanding of system-level risk factors for clinical AD, highlight the relevance of less frequently reported factors in the AD prevention literature—such as gastrointestinal and sensorimotor disorders—and underscore the complex interplay between genetic susceptibility and vascular risk factors.

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1. Introduction

The view of Alzheimer's disease (AD) as a multifactorial disorder, related to a combination of neuropathological predispositions on the one hand and facilitation of the pathological progression by several factors on the other, has become widely accepted [1–4]. With the modest efficacy of anti-amyloid drugs at the stage of mild cognitive impairment (MCI) or mild dementia, it is clear that while amyloid and tau proteins play a crucial role in AD pathology, multiple other risk factors (RFs) are involved in the development and progression of AD. These include medical, environmental, lifestyle-related, and genetic RFs. Notably, intervention in modifiable RFs during early AD stages may reduce disease risk by up to 40% [1,5,6].

Despite extensive research, the Lancet Commissions on dementia prevention, intervention, and care [7–9] identified only 14 modifiable RFs associated with the development of AD with enough high-quality consistent evidence, collectively accounting for ~40% of worldwide dementias. These include lower education, hypertension, high LDL, visual and hearing impairments, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury (TBI), and air pollution. Importantly, the commission emphasized the need for individualized risk assessment and tailored interventions based on an individual's unique risk profile, preferences, and circumstances. The current work reevaluates all International Classification of Diseases (ICD) codes and their association with AD dementia, providing a comprehensive analysis.

The quest for RFs associated with AD spans over 7,000 studies of varying validity, including interventional studies, meta-analyses, review articles, consensus conferences and working groups [6,10–13], with RFs mostly include vascular risk factors [14]. Few studies have prospectively and comprehensively investigated primary prevention. The FINGER trial [5], a randomized controlled trial (RCT) assessing multidomain interventions (diet, exercise, cognitive training, vascular risk monitoring), showed modest cognitive benefits. While one RCT supported these findings [15], two others [16,17], and a meta-analysis [18] found no evidence that such multidomain interventions prevent dementia. A well-characterized longitudinal population-based study in cognitively unimpaired (CU) older adults identified advancing age as the strongest risk factor, with female sex, lower education level, cardiovascular risk factors, and genetic susceptibility (Apolipoprotein E (ApoE) $\epsilon 4$ allele) as important contributors to AD risk [11]. Sleep disturbances and markers of systemic inflammation (CRP, IL-6), were associated with an increased risk of AD [19]. Additionally, a large-scale analysis of 10 years of clinical records (170 million patients) identified several existing drugs with potential benefits for AD [20], suggesting links between AD and conditions like gastritis [21], epilepsy or pain [22,23], as well as hypercholesterolemia [24], and inflammation [25].

Importantly, not much is known about the association between these risk factors and one another, and specifically the relations between genetic RFs and medical ones. Few studies have investigated the relations between established medical RFs and ApoE $\epsilon 4$ status. While several studies have found that medical RFs such as hyperlipidemia, diabetes, and hypertension have a stronger influence on AD risk in ApoE $\epsilon 4$ carriers [26–28], other studies have not observed this link [29]. Therefore, the relationship between ApoE status and medical RFs has yet to be determined.

Taken together, despite extensive research, the number of validated AD-related RFs remains limited, and their interactions with genetic factors, specifically ApoE haplotypes and demographic determinants, are poorly understood. To address this, we analyzed the UK Biobank, a large-scale longitudinal dataset, to investigate ICD-10-coded diagnoses, and their associations with clinical-AD and ApoE haplotypes.

2. Methods

2.1. Participants

The UKB study enrolled a total of 502,253 participants, aged 40 to 69 years, during the period from 2006 to 2010 [30]. Overall, the collected data include comprehensive health records (ICD-10 codes with dates of diagnosis) from birth to last release (August 2022), as well as clinical screening, cognitive assessments, genetic profiling, neuroimaging, demographic, and wellness self-reported data. Records of participants (Table 1) with ICD-10 clinical diagnosis of AD dementia (Table S1) were selected for the AD group. Participants who died during the recollection period (before August 2022) were excluded, as well as those who were diagnosed with another neurodegenerative disease or dementia during the study period (Table S2). Also excluded were participants who were under the age of 55 at the end of their medical records update (August 2022). Note that results in the group of 55–65-year-old participants were treated separately. This filtering yielded 387,275 participants with no clinical diagnosis of AD dementia or mild cognitive impairment (MCI) by the data release date, labeled as cognitively unimpaired, and 3,843 participants diagnosed with clinical-AD dementia. To minimize reverse causation, ICD-10 diagnoses were counted only if they preceded the AD diagnosis by 10 years or more. Moreover, to address the possibility that some of the participants in the CU group may have developed dementia shortly after the data release, the reference time for the CU group was set to five years before the data release date, while for the clinical-AD group, it was set to the date of clinical-AD diagnosis. Finally, to capture the dependence on age and other covariates as fully as possible, medical conditions were coded dichotomously (present/absent) to create a Boolean participant-ICD-10 code matrix.

2.2. Statistical analysis

Out of all ICD-10 codes, 11,910 were found at least once in the UKB records. Filtering out records with irrelevant dates, further reduced this number to 9,362. Codes that appeared in less than 0.5% of individuals in both groups were excluded, yielding 187 ICD-10 codes for further analysis. For each of these codes, we independently ran logistic regression, predicting clinical-AD from the diagnosis and a number of demographic features. For demographic confounders, age (at reference time), biological sex, and education were considered. For ethnicity, since the vast majority of UKB participants are Caucasian (94.6%), other ethnicities were excluded. Given the substantial influence of age on the

Table 1
Demographics and clinical characteristics of Alzheimer's disease (AD) patients and cognitively unimpaired controls taken from the UK-biobank.

	Values	AD	CU	P
Num Total		3,843	387,275	
Age	55-64	148 (3.9%)	140,356 (36.2%)	<0.0001
	65-74	1,231 (32.0%)	193,135 (49.9%)	
	75-86	2,464 (64.1%)	53,784 (13.9%)	
Sex	Female	2,059 (53.6%)	216,981 (56.0%)	0.0025
	Male	1,784 (46.4%)	170,294 (44.0%)	
Education	Poor	1,519 (39.5%)	74,442 (19.2%)	<0.0001
	High School	1,584 (41.2%)	189,319 (48.9%)	
	Degree	740 (19.3%)	123,514 (31.9%)	
ApoE	$\epsilon 4/\epsilon 4$	503 (13.1%)	8,174 (2.1%)	<0.0001
	$\epsilon 3/\epsilon 4$	1,690 (44.0%)	87,102 (22.5%)	
	$\epsilon 2/\epsilon 4$	94 (2.4%)	9,403 (2.4%)	
	$\epsilon 3/\epsilon 3$	1,195 (31.1%)	222,309 (57.4%)	
	$\epsilon 2/\epsilon 3$	185 (4.8%)	46,519 (12.0%)	
	$\epsilon 2/\epsilon 2$	8 (0.2%)	2,349 (0.6%)	

outcome, which may not be adequately captured by a single linear regressor, we incorporated three age-related regressors in our model: the plain linear age, a SoftPlus (SP) function with a wide transition around 65 years old and another wide SP around 75 years. We used Python's R-based statsmodels package, employing the formula below. In the formula, an asterisk (*) between two predictors indicates that the model includes each predictor separately, along with their interaction (Boolean variable is noted by *is*).

We ran for each code separately a logistic regression of the form:

$$isAD \sim \text{Logit} \left(\sum_{i=0}^I \beta_i \cdot \text{Conf}_i + \beta_{RF} \cdot \text{Bool}_{RF} \right)$$

with confounders (Conf_i) based on age, education and sex. Since the relations between AD prevalence and age are nonlinear [31], the logistic regression model first calculates a score value for each subject as a linear combination of its predictor values. This score is further converted to probability value by application of a logistic function. To account for the nonlinearity dictated by the age-prevalence curve, we included the softplus (SP) function as an additive nonlinear term. We used two softplus functions with different centers (65- and 75-years-old). To these 3 predictors, we added sex (male/female), education (low-/medium/high), as well as all potential interactions among them. The final model therefore contained 23 confounders per single RF related predictor, and is described in R notation as:

$$isAD \sim (Age + Age_SP_65 + Age_SP_75) * Sex * Education + isDiagnosis$$

This model was run using Python's statsmodels package which also calculates the p-value for each predictor. All reported p-values were false discovery rate (FDR)-corrected for multiple comparisons. This procedure yielded a list of ICD-10 codes that significantly differed between clinical-AD and CU participants.

2.3. Categorization

ICD-10 diagnoses were assigned into different categories according to the ICD coding conventions. Similar codes were grouped together into the code with highest OR following a consensus agreement of four certified neurologists (GA, SA, TBH and GAM; Table S3).

2.4. Demographic determinants

To examine differences in demographic determinants, including age, sex, and education, we followed a similar procedure, incorporating an interaction term with the ICD-10 diagnosis. To ensure sufficient statistical power, these analyses were conducted on the ICD-10 categories rather than individual codes. The resulting formula is:

$$isAD \sim (Age + Age_SP_75) * (Sex + Education) + isCategory + isCategory : DemographicVariable$$

Here, the latter variable refers to the variable of interest. This analysis was independently applied to early and late onset clinical-AD (below and above 65 years old, respectively); and sex: (males and females). For education, a single interaction term was used, with ordinal values for the different educational categories (university/college, high school, less than 12 years of formal education).

2.5. Genetics

The RF profile associated with different ApoE haplotypes is hypothesized to interact with AD risk. ApoE profile was extracted from the genomic data, and its prevalence across the groups was calculated (Table S5). Participants with the genotypes $\epsilon 2/\epsilon 2$ and $\epsilon 2/\epsilon 4$ ApoE

haplotypes were excluded due to their very small sample sizes. The remaining haplotypes were ordered based on their AD prevalence ($\epsilon 2/\epsilon 3 < \epsilon 3/\epsilon 3 < \epsilon 3/\epsilon 4 < \epsilon 4/\epsilon 4$) [32] and assigned ordinal values. This vector was then used as a predictor in a logistic regression model, following the same procedure as for the demographic determinants. The resulting formula was:

$$isAD \sim (Age + Age_SM_75) * (Sex + Education + ApoEOneHot) + isCategory + isCategory : ApoEOrdinal$$

with one-hot encoding for control, and the last term as the variable of interest.

2.6. Power estimation for interaction analysis

To estimate the power of the interactions, the clinical-AD probability for each subject was first estimated under the assumption of no interaction. This was then corrected according to the effect size derived from the odds-ratio of the highest rated factors. The corrected probabilities were utilized to simulate Boolean data on which the interaction model was run. Finally, the power was determined as the proportion of iterations, out of 1000, in which the interaction's p-value fell below 0.05.

3. Results

A statistical comparison of ICD-10 codes given to UKB participants at least 10 years prior to diagnosis revealed 96 ICD-10 codes significantly associated ($p < 0.001$, FDR-corrected) with individuals clinically diagnosed with AD dementia, compared to CU UKB participants, while controlling for age, sex, and education. These codes represented 45 medical entities (Fig. 1; Table 2; For examples of codes which were not included see Table S4).

Following studies that showed different relationships between genetic AD-risk and various medical and life-style RFs [33–35], we compared ApoE status to the extracted medical RFs in the category level. Ordinal values were assigned to the ApoE status according to clinical-AD dementia prevalence in the cohort (0,1,2,3 were assigned for $\epsilon 4/\epsilon 4$ (5.8%), $\epsilon 3/\epsilon 4$ (1.9%), $\epsilon 3/\epsilon 3$ (0.55%) and $\epsilon 2/\epsilon 3$ (0.4%), respectively; Table S5). This vector demonstrated a significant interaction with codes categorized under the metabolic ($p = 0.004$, FDR-corrected) and circulatory ($p = 0.001$, FDR-corrected) systems. The OR showed a near-linear increase from 1.6 ($\epsilon 4/\epsilon 4$) to 3.4 ($\epsilon 2/\epsilon 3$) for the metabolic category and from 1.2 ($\epsilon 4/\epsilon 4$) to 2.5 ($\epsilon 2/\epsilon 3$) for the circulatory category (Fig. 2, Table S6). In other words, disorders elucidated in our analysis within the metabolic and circulatory categories were associated with a higher risk of clinical-AD dementia for individuals with ApoE $\epsilon 2/\epsilon 3$ genotype compared to those with ApoE $\epsilon 4/\epsilon 4$ genotype.

Further assessing individual disorders that constitute the metabolic and circulatory categories, showed that the involved codes include hypertension, ischemic heart disease/angina pectoris and hypercholesterolemia, which are considered main vascular risk factors (Fig 3). Type II diabetes, obesity and hyperthyroidism showed a similar trend, although not significant. With respect to early vs. late onset clinical-AD, no category demonstrated a significant effect. However, it is worth noting that the number of participants with early onset clinical-AD was relatively small ($n = 167$) (Table S7). Similarly, no significant differences were observed across risk-factors categories with respect to sex (Table S8) or education level (Table S9).

To further minimize reverse causation, we examined the interaction between each identified risk factor and the number of years since its diagnosis. We found a significant positive interaction for the risk factors with sufficient power, indicating a larger impact with more years elapsed (Table S10).



Fig. 1. Medical risk factors for Alzheimer's Disease. UKB-derived ICD-10 diagnoses identified as risk factors for Alzheimer's disease (AD; represented by circles) are shown, categorized by color according to the ICD-10 classification. The size of each circle corresponds to the prevalence of the specific factor within the AD group. The color intensity of each circle reflects the associated odds ratio. Figure designed by Hagar Segev.

Table 2
Summary statistics for Alzheimer's disease medical risk factors.

#	Code	Name	OR (95% CI)	%CU / %AD	FDR
Endocrine, Nutritional, Metabolic					
1	E10.9	Diabetes Mellitus type I	4.34 [3.06 – 6.17]	0.2% / 1.1%	1.29E-15
2	E11.9	Diabetes Mellitus type II	3.19 [2.74 – 3.71]	1.2% / 6.0%	7.45E-49
3	E66.9	Obesity	2.50 [1.78 – 3.51]	0.4% / 1.1%	2.30E-07
4	E78.0	Hypercholesterolemia	2.05 [1.81 – 2.33]	2.4% / 8.5%	3.86E-27
5	E03.9	Hypothyroidism	2.02 [1.63 – 2.49]	1.0% / 2.8%	2.50E-10
Circulatory System					
6	I50.1	Left ventricular failure	2.42 [1.62 – 3.63]	0.2% / 0.8%	2.40E-05
7	Z92.1	Long-term use of anticoagulants (Z)	2.39 [1.80 – 3.18]	0.4% / 1.7%	5.57E-09
8	I73.9	Peripheral vascular disease	2.38 [1.51 – 3.73]	0.1% / 0.6%	2.37E-04
9	Z86.7	History of disease of the circulatory system (Z)	2.14 [1.74 – 2.63]	0.9% / 3.1%	1.98E-12
10	I10	Essential hypertension	1.90 [1.74 – 2.08]	5.8% / 18.0%	3.53E-42
11	I25.9	Ischemic heart disease	1.77 [1.57 – 2.01]	2.8% / 8.7%	1.15E-18
12	R55	Syncope and collapse (R)	1.73 [1.37 – 2.17]	0.9% / 2.5%	5.18E-06
13	I20.9	Angina pectoris	1.72 [1.54 – 1.91]	4.9% / 11.9%	2.67E-22
14	I48	Atrial fibrillation and flutter	1.72 [1.40 – 2.11]	0.9% / 3.2%	3.82E-07
Eye and Ear					
15	H36.0	Diabetic retinopathy	7.16 [4.57 – 11.22]	0.1% / 0.7%	5.26E-17
16	H91.9	Hearing loss	2.96 [1.80 – 4.87]	0.1% / 0.6%	2.62E-05
17	H26.9	Cataract	1.81 [1.50 – 2.18]	0.9% / 3.7%	1.53E-09
Genitourinary System					
18	N39.0	Chronic UTI	2.15 [1.74 – 2.64]	1.0% / 3.0%	2.48E-12
19	N32.8	Disorders of Bladder	1.42 [1.23 – 1.65]	2.6% / 6.0%	4.52E-06
Mental and Behavioral Disorders					
20	F32.9	Depressive episode	3.10 [2.28 – 4.23]	0.5% / 1.3%	2.48E-12
Nervous System					
21	G40.9	Epilepsy	3.66 [2.58 – 5.20]	0.3% / 1.0%	1.83E-12
22	G47.3	Sleep apnea	2.03 [1.39 – 2.96]	0.4% / 0.8%	2.81E-04
Digestive System					
23	K58.9	Irritable bowel syndrome	2.06 [1.47 – 2.89]	0.5% / 1.1%	3.93E-05
24	K52.9	Noninfective gastroenteritis and colitis	1.66 [1.42 – 1.93]	2.5% / 5.5%	3.34E-10
25	K30	Dyspepsia	1.48 [1.31 – 1.67]	4.3% / 8.4%	1.53E-09
26	K44.9	Diaphragmatic hernia	1.42 [1.25 – 1.62]	3.4% / 7.1%	3.82E-07
Musculoskeletal System					
27	M81.99	Osteoporosis	2.60 [1.70 – 4.00]	0.1% / 0.8%	1.86E-05
28	M13.99	Arthritis	2.34 [1.62 – 3.37]	0.2% / 1.0%	9.74E-06
29	M79.86	Soft tissue disorder	2.27 [1.49 – 3.44]	0.2% / 0.7%	1.63E-04
30	Z96.6	Orthopaedic joint implants	2.20 [1.74 – 2.78]	0.5% / 2.4%	1.00E-10
31	M17.1	Osteoarthritis	2.10 [1.84 – 2.39]	2.3% / 8.1%	1.12E-27
32	M51.1	Radiculopathy	1.77 [1.40 – 2.25]	1.0% / 2.2%	4.52E-06
Neoplasm and Blood					
33	R63.4	Abnormal weight loss (R)	2.73 [1.98 – 3.74]	0.4% / 1.3%	1.53E-09
34	Z51.1	Chemotherapy	2.04 [1.57 – 2.66]	0.8% / 1.8%	2.22E-07
35	D64.9	Anemia	1.83 [1.47 – 2.30]	1.2% / 2.5%	2.40E-07
36	Z85.3	Malignant neoplasm of breast (Z)	1.79 [1.46 – 2.20]	1.1% / 3.0%	4.00E-08
37	D12.6	Benign neoplasm of colon	1.52 [1.32 – 1.75]	2.4% / 6.5%	1.47E-08
Factors Influencing Health					
38	Z86.4	Psychoactive substance use	3.10 [2.52 – 3.81]	0.6% / 3.3%	8.31E-26
39	Z60.2	Living alone	2.58 [1.69 – 3.93]	0.2% / 0.8%	1.55E-05
40	Z72.1	Alcohol use	2.55 [1.67 – 3.87]	0.2% / 0.8%	1.86E-05
41	Z72.0	Tobacco use	2.52 [2.08 – 3.05]	1.3% / 3.4%	1.58E-20
Respiratory System					
42	J44.9	COPD	3.88 [2.83 – 5.31]	0.2% / 1.4%	2.08E-16
43	J22	Lower lobe pneumonia	2.12 [1.58 – 2.85]	0.5% / 1.5%	9.08E-07
44	J45.9	Asthma	1.70 [1.45 – 2.00]	2.4% / 4.7%	3.56E-10
Infectious Diseases					
45	B95.6	Staph aureus cause of diseases	2.45 [1.53 – 3.94]	0.2% / 0.5%	2.74E-04

4. Discussion

Our analyses yielded a list of 45 medical conditions (encompassing 96 ICD-10 codes) whose prevalence was found to be significantly higher in people with a clinical diagnosis of AD dementia. Codes included major vascular RFs (e.g. diabetes, hyperlipidemia, ischemic heart disease, hypertension, atrial fibrillation), sensory (e.g. cataract, hearing loss) and motor deficits (e.g. osteoarthritis, discopathy), mental conditions (depression), gastrointestinal disorders (e.g. gastritis, GERD) or infectious conditions (e.g. chronic UTI, pneumonia). Several unique conditions were noted as well, including epilepsy, sleep apnea, anemia, chemotherapy, tobacco use, and living alone. Notably, vascular RFs (metabolic and circulatory), which have been found to play a major role in AD dementia development in the current and previous studies, were

less significant in individuals carrying the ApoE $\epsilon 4/\epsilon 4$ and $\epsilon 3/\epsilon 4$ haplotypes. Level of education, sex and age did not show any further effect for risk factors in the category level. These are discussed with respect to the different categories and RFs in view of the epidemiologic, clinical and biological determinants and their potential underlying mechanisms.

4.1. ApoE haplotypes interaction with clinical-AD risk factors

While the relationship between ApoE haplotypes and AD are well-documented [36,37], much less is known about the relationship of ApoE haplotypes to AD RFs [38]. RFs that were found more influential in people with ApoE $\epsilon 4$ include diabetes [39], hyperlipidemia [27], and hypertension [26]. However, these results were not consistent [29]. Similarly, physical exercise was found to be more effective in APOE $\epsilon 4$

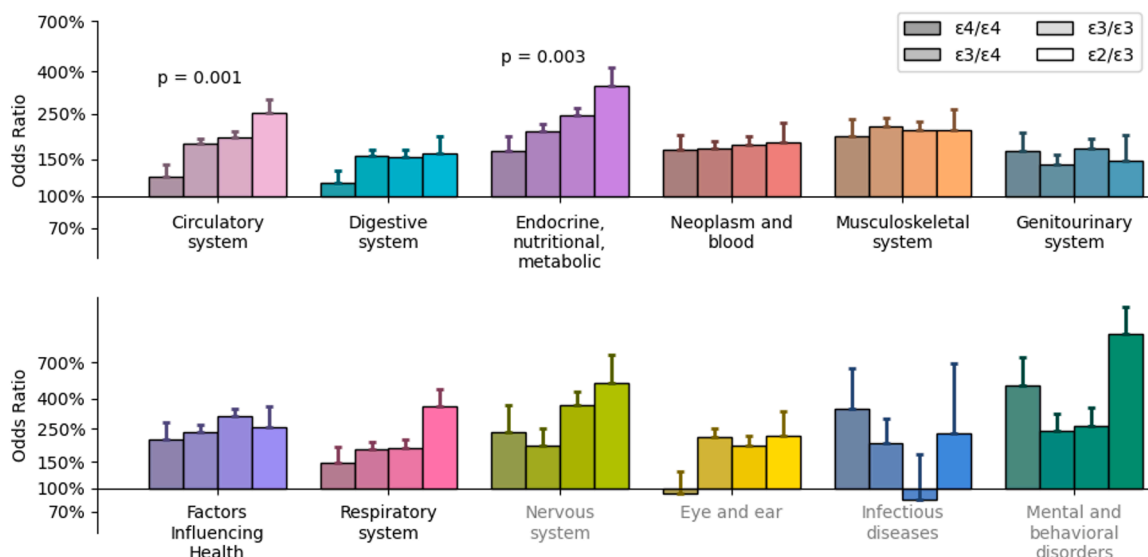


Fig. 2. Interaction between ApoE genotypes and medical risk factors, grouped by category. A significant interaction was observed between ApoE genotypes and the metabolic and circulatory categories, which include vascular risk factors. Genotypes are displayed in the following order: $\epsilon 4/\epsilon 4$ (left, dark), $\epsilon 3/\epsilon 4$, $\epsilon 3/\epsilon 3$, $\epsilon 2/\epsilon 3$ (right, bright). Categories with power lower than 0.8 are labeled in grey. Statistical significance was assessed using a linear trend analysis across genotypes. Odds ratios are shown on a logarithmic scale, with error bars indicating the standard error of the mean (SEM).

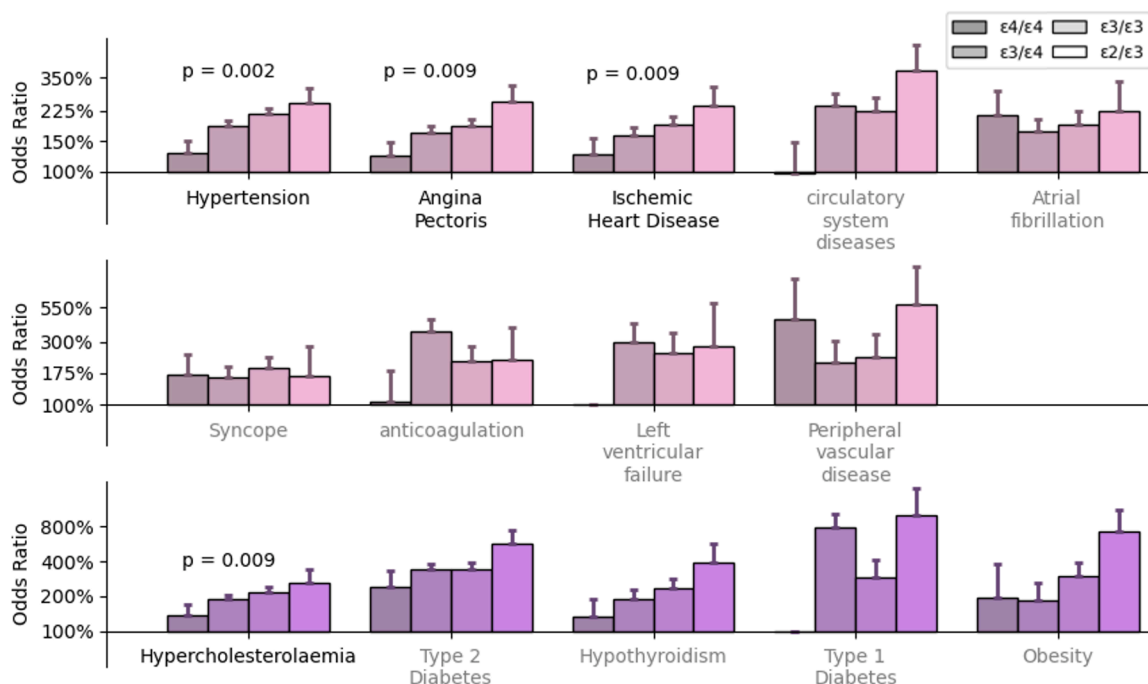


Fig. 3. Interactions between ApoE genotype and metabolic/circulatory ICD-10 codes. Hypertension, ischemic heart disease, angina pectoris, and hypercholesterolemia were found to be more prevalent in individuals with lower ApoE-related genetic risk. Genotypes are displayed in the following order: $\epsilon 4/\epsilon 4$ (left, dark), $\epsilon 3/\epsilon 4$, $\epsilon 3/\epsilon 3$, $\epsilon 2/\epsilon 3$ (right, bright). Codes with power lower than 0.8 are labeled in grey. Statistical significance was assessed using a linear trend analysis across genotypes. Odds ratios are shown on a logarithmic scale, with error bars indicating the standard error of the mean (SEM).

carriers [40]. On the other hand, the association between Mediterranean diet with a reduced risk of AD was not found to differ for APOE $\epsilon 4$ carriers [41]. AD was also found to be associated with increased neuroinflammation in the presence of ApoE $\epsilon 4$, less efficient lipid transport and neuronal repair, and compromised blood-brain barrier integrity [42–44]. Our study shows that circulatory and metabolic RFs are less related to clinical-AD in ApoE $\epsilon 4$ carriers. The fact that the specific RFs mentioned by some previous studies were found to show the opposite effect in our cohort, calls for a closer examination of this important issue

in prospective longitudinal large-scale studies. In view of the diverse mechanisms of ApoE $\epsilon 4$ influence, it is possible that other mechanisms, such as inflammatory or toxic related processes are more relevant for ApoE $\epsilon 4$ carriers than vascular ones. Alternatively, it is possible that once an individual has a strong AD genetic factor, the effect of other RFs diminishes, in particular vascular RFs. Yet another consideration is that for certain groups, such as African American and Hispanic older adults in the US, being an ApoE $\epsilon 4$ carrier is not influential as vascular RFs may be. Additionally, the inverse correlation between ApoE $\epsilon 4$ genotype and

hypercholesterolemia in AD risk, suggests that ApoE ϵ 4 does not mediate its pathogenic effect via its physiological role in lipid transport in the circulation. Moreover, the reduced role of additional systemic cardiovascular and metabolic RFs in AD development supports the notion that the pathogenic role of ApoE ϵ 4 likely operates through its effects on brain cells metabolism rather than on the systemic milieu [45]. Further research is crucially needed in this fundamental aspect of AD.

4.2. Influence of age, sex, and education on Alzheimer's disease risk

Age is a major RF for AD. Our analysis followed the convention of early vs. late onset of clinical-AD with a cutoff of 65 years old. This led to a very low number of younger patients, which might explain the lack of age effect in our analysis. With respect to sex, there is an overall higher prevalence and incidence of clinical-AD in females compared to males, even when figures are adjusted for age and longevity [46]. This is attributed to several potential factors that could be related to RFs [47], including neuroprotective effects of estrogen and its decline during menopause or interactions between ApoE ϵ 4 and estrogen, which could exacerbate AD pathology in women [48]; women's tendency to accumulate more amyloid plaques and neurofibrillary tangles than men, even in the preclinical stages of AD [49]; or a more robust inflammatory response in females than males, which might exacerbate neurodegenerative processes in AD [47]. Finally, epidemiological studies have demonstrated an inverse relationship between education and the risk of developing AD. That is, individuals with higher levels of education exhibited a lower risk of AD [50]. Several mechanisms have been proposed to account for this effect. One line of research suggests intrinsic mechanisms including enhanced neural plasticity, or masking effect [51, 52]. Another line suggests that educated individuals are more likely to engage in health-promoting behaviors (lifestyle, healthcare) [53,54]. No such effect was found in our analysis, supporting the first explanation. More data, enabling comparison of specific RFs (rather than categories) in the individual level may yield more results.

4.3. Pathological classification of the RFs for clinical-AD

Our analysis was based on the classification embedded in the ICD-10 system, as this system is used in the UKB. This is based foremost on classification according to systems. Nonetheless, medical reasoning is based on pathogenic classification, including vascular, inflammatory, infectious, toxic, neoplastic and metabolic factors, that merit further discussion.

4.3.1. Vascular

Vascular RFs were found in our analysis to be the most influential RFs on AD development. The relationship between vascular RFs (mentioned here under both circulatory and metabolic categories) and AD is well-documented [55,56]. Vascular risk factors may contribute to the pathogenesis of AD through various mechanisms. Direct ones include reduced cerebral blood flow and microvascular damage. Specifically, hypoxia can induce the formation of amyloid-beta plaques [57], and hyperglycemia and insulin resistance, common in diabetes, can lead to the development of advanced glycation end products (AGEs) which can exacerbate amyloid-beta accumulation and tau hyperphosphorylation [39]. Cholesterol can influence the processing of amyloid precursor protein (APP), leading to increased production of amyloid-beta (A). Additionally, cholesterol may impact tau phosphorylation and neurofibrillary tangle formation [58]. Vascular RFs can contribute to AD also through systemic inflammation, oxidative stress, and altered metabolism. Another vascular RF, atrial fibrillation (AF), has been related to a greater chance of developing dementia in several recent studies, some based on the UKB [20,59,60]. Suggested mechanisms include cerebral hypoperfusion and micro-embolic strokes, and shared risk factors such as aging, hypertension, diabetes, and obesity. These conditions can contribute to endothelial dysfunction, oxidative

stress, and inflammation, creating a synergistic effect that increases the likelihood of developing both AF and AD dementia [61,62]. In view of the reduced role of vascular RFs in AD pathology in ApoE ϵ 4 carriers, it is important to understand whether this observation is based also on interference with these mechanisms.

4.3.2. Inflammatory

Chronic inflammation is a significant factor in the pathogenesis of AD [63,64]. The role of systemic immune changes in AD has been extensively discussed [64,65]. Peripheral immune responses play a significant role in supporting brain immunity and protecting against neurodegenerative modifications [66]. Inflammatory disorders found in our analysis encompass several systems: gastrointestinal (GI) (esophagitis, gastritis, enteritis, colitis), respiratory (asthma) and musculoskeletal (arthritis). Nonetheless, it remains unclear whether different systemic conditions with an inflammatory component have an additive and/or related effect and can, therefore, be categorized together. The GI system plays a major role among the RF identified. The gut-brain axis represents a bidirectional communication network between the GI tract and the central nervous system. The gut microbiota plays a crucial role in maintaining immune homeostasis and protecting against pathogens. Alterations in gut microbiota composition, which can occur with GI disorders, have been linked to neurodegenerative diseases, including AD [67,68]. Moreover, metabolites produced by gut microbiota, such as short-chain fatty acids, can influence brain function. Dysbiosis in GI disorders can alter production of these metabolites, potentially impacting neurodegeneration. Specifically, certain gut bacteria can produce amyloid proteins [69]. Chronic GI infections might increase the systemic amyloid burden, contributing to AD pathology [70]. Finally, among five drugs which were found to have a significant preventive effect in a large cohort covering over 10 years of clinical records for over 170 million patients, two were related to dyspepsia (pantoprazole and omeprazole [20]).

4.3.3. Infectious

Several infectious diseases have been identified in our analysis including pneumonia, staph aureus related disorders and chronic-UTI. The pathogen hypothesis in AD suggests a multifaceted interaction between infectious agents and the brain's immune response [63,71]. Accumulating evidence supports the notion that chronic infections could play a role in AD pathogenesis [72,73]. Several pathogens have been implicated including *herpes simplex virus type 1* (HSV-1), *Porphyromonas gingivitis*, and *Chlamydia pneumonia* [74–76]. The mechanisms suggested include excessive A β accumulation, immune dysregulation and chronic inflammation, as well as neurotoxicity and blood-brain barrier (BBB) dysfunction [63,71,77,78]. In our study the only chronic-UTI was found to be significantly associated with AD-dementia. It may be the case that such diseases are less well documented in the UKB: HSV-1 is mostly latent in the brain, and HSV-1 encephalitis is a rare disease. Gingivitis is treated by dentists and oral hygienists and may not be documented in the patient's electronic health record (EHR). More research is needed to comprehensively evaluate the role of pathogens in AD development.

4.3.4. Neoplasms

Several RFs related to neoplastic disorders have been identified, including general (neoplasms, chemotherapy, cancer related weight loss) and specific (breast, colon) codes. Suggested mechanisms include genetic factors which can predispose individuals to both AD and cancer [79], cancer-related inflammation which can contribute to neuroinflammation, chemotherapy-related neurotoxicity and mitochondrial dysfunction [80]. Associated weight-loss may cause nutritional deficiency or hormonal imbalance that, in turn, may exacerbate AD-related pathology.

4.3.5. Toxic

Our study identified several toxic agents to be involved in AD. These

include psychoactive substances, tobacco, and alcohol (chemotherapy may also be considered in this category). The most prevalent of these is tobacco use. Increased risk of AD in tobacco users may be related to several mechanisms [81], include oxidative damage in neuronal cells [82], chronic inflammation [83], atherosclerosis [84], and BBB dysfunction [42]. Moreover, evidence suggests that smoking may affect the metabolism of APP, leading to increased production and reduced clearance of A β [85], as well as promotion of hyperphosphorylation and aggregation of tau into neurofibrillary tangles [86]. The interaction of toxic exposure and other RFs is not yet known and may account for these results as well.

4.3.6. Sensorimotor deficits

Our results included several sensory deficits (visual or hearing), including diabetic retinopathy, cataract and hearing loss. Sensory deficits have been increasingly linked to an elevated risk of AD and other forms of dementia [87–90]. Both visual and hearing loss are now included in the 2024 report of the Lancet standing commission [9] as based on several large-scale meta analyses [87,91]. The connections between sensory loss and cognitive decline can be explained through the Cognitive Load Hypothesis. According to this idea, when sensory input is diminished, the brain must work harder to process and interpret limited information. This increased cognitive load can lead to greater cognitive strain over time. This, however, is unlikely, as cognitive activity is protective. It is more likely that in early-stage cognitive decline, the increased cognitive strain unmasks the lack of cognitive reserves. Alternatively, such sensory deficits may lead to decreased social interaction and engagement in cognitive activities. Social isolation is a known risk factor for cognitive decline and dementia [9], as was also demonstrated in our results. Finally, sensory loss and cognitive decline may share common RFs and pathophysiological pathways, such as vascular disease, inflammation, and genetic predispositions [89,92]. Motor deficits - attributed in the current study to osteoarthritis, arthritis, radiculopathy, joint implant, or leg soft tissue disorder - have been increasingly recognized as early indicators and potential RFs for AD [93]. The relationship between motor deficits and AD is complex and multifaceted. Amyloid- β plaques are commonly found in brain regions associated with motor function, and a mediation through inflammation has been proposed [94].

4.3.7. Mental disorders, sleep and epilepsy

Several other single factors have been found to increase AD risk. While not all of them can be discussed here, some of them – depression, social isolation, sleep apnea and epilepsy – merit such a discussion, in view of the underlying mechanisms and clinical implication. Late-life depression is a typical part of the presentation of AD, and may even precede cognitive symptoms [95]. Generally speaking, depression is associated with increased levels of proinflammatory cytokines [96]. More specifically, it has been suggested that stress and depressive symptoms can increase the production and aggregation of amyloid- β and hyperphosphorylated tau proteins [97,98]. Furthermore, depressive symptoms have been linked to *in vivo* amyloid and tau pathology in older adults at risk for AD [99,100]. Another proposal is that depression can lead to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in elevated cortisol, that in turn has been linked to hippocampal atrophy [101]. Depression also involves imbalances in neurotransmitters such as serotonin, norepinephrine, and dopamine, which may play a further role in neurodegeneration [102,103]. In this vein, living alone, and loneliness in general, have been increasingly recognized as a significant RF that can exacerbate AD [104,105]. This relationship can be understood through multiple biological and psychological mechanisms. With respect to biology, chronic stress and its relation to inflammation, as well as the HPA axis, leading to increased cortisol levels have been implicated [63,106,107]. Specifically, socially isolated animals exhibit greater amyloid- β accumulation and more severe cognitive deficits compared to socially housed animals [108]. On

the psychosocial level, social isolation may lead to depression, which is an established RF, and may increase stress, related to inflammation [95, 105].

Sleep apnea may represent a larger group of conditions related to abnormal sleep patterns. While other sleep-related codes did not appear in our analyses, it is possible that these conditions are under-coded in clinical practice. Sleep is essential for cognitive functions such as memory consolidation, learning, and executive function [109]. Sleep deprivation has been identified as a RF for AD in multiple studies and is listed among the Lancet Commission recommendations [8,9] as a modifiable RF. The connection between sleep deprivation and AD can be explained by several mechanisms. Most intriguing, sleep deprivation has been suggested to impair the glymphatic system, leading to reduced clearance of amyloid- β and tau, which may accumulate during wakefulness [110–112]. More generally, chronic sleep deprivation has been linked to systemic inflammation, which is hypothesized to take a central part in AD pathology [19].

Of specific interest is the involvement of epilepsy in AD [113]. Subclinical and clinical epilepsy have been found in individuals with MCI and early AD-dementia [114], suggesting that epilepsy can increase the risk of developing AD. These may be related to neuroinflammation [115] and increased amyloid- β deposition and tau pathology [116], or changes in network properties that accelerate pathological propagation [113]. ApoE ϵ 4 has also been associated with epilepsy [117], though such an interaction was not found here.

4.4. Relations to the Lancet consensus AD risk factors

Of the accepted RFs found by the Lancet 2017, 2020 and 2024 commission [7–9], most modifiable midlife (hearing loss, hypercholesterolemia, depression, diabetes, tobacco use, hypertension, obesity, alcohol use) and late life (social isolation, visual loss) RFs were identified in our analyses, which is a reassuring replication of the Lancet commission. However, physical inactivity and air pollution were not observed; this may be since these factors are typically not coded in clinical settings. TBI was also not found in our analysis. However, the prevalence of TBI in the clinical-AD group was the smallest of all factors (0.49%). Moreover, more than 50% of this latter group suffered TBI less than 1 year before clinical-AD diagnosis, and 66% suffered TBI 2 years before diagnosis, minimizing the potential impact on AD development.

Our study has several limitations. First, participants with AD dementia were diagnosed clinically, without the use of objective biomarkers, as is highlighted throughout the manuscript. Nonetheless, since AD is the most prevalent type of dementia, and since real-world population often presents with mixed forms of dementia, these findings are still important and interesting even if they are not in a biomarker-verified AD cohort, which does not exist nowadays. Moreover, AD diagnosis was based on ICD-10 codes recorded by treating physicians in the participants' medical records. While we did not have access to the full clinical evaluations underlying each diagnosis, these codes reflect real-world clinical decision-making and are part of the UK Biobank's standardized health data. This approach may introduce some diagnostic variability, for example due to differences in how diagnostic criteria are applied across clinicians or settings, or inconsistencies in coding practices. Nonetheless, it enables large-scale analyses that would not be feasible with direct assessments alone. Additionally, we did not include participants with MCI as this diagnosis is less reliable in this setting. Second, the number of patients suffering from AD-dementia in the UKB might not have carried sufficient statistical power to account for the large number of RFs examined and those that were not examined. Certainly, the list of RFs presented here is incomplete and should be expanded. However, it provides a comprehensive view of the role of clinical-AD RFs within different categories, as well as includes many specific ones. Moreover, power analysis at the category level showed significant results for most of the categories. Third, the population reflects Caucasian individuals living in a western country, and more

specifically, the participants who volunteered for UKB were particularly healthy and highly educated limiting generalizability to other populations [118]. Fourth, ICD-10 codes do not capture all the potential RFs of clinical-AD dementia. Moreover, ICD-10 codes may not accurately reflect patients' clinical states. Nonetheless, they may serve as a good basis for the type of analyses conducted here, which can serve as a steppingstone for future studies. The exclusion of ICD-10 codes found in less than 0.5% of participants may have left out several relevant RFs, which are less coded in medical files and are known to play a role in AD, such as gingivitis or obesity. Yet, it helped maintain the high specificity of our results. Finally, data on severity of RFs, treatment presented, compliance and effect over time is crucial for better understanding these RFs and their role in AD prevention. Future participant samples and datasets should be constructed in a fashion that makes such data consistently available for analyses.

Another important aspect that was not discussed in the current study is comorbidities. Generally speaking, the interplay between these RFs can create a vicious circle that exacerbates the pathogenesis of AD. More specifically, if several RFs may lead to AD through inflammation, their combined additive contribution may overcome a certain threshold. Alternatively, a combination of different mechanisms, such as inflammation and reduced clearance of amyloid- β may be more influential. Of special importance are specific combinations of RFs, that have shown a synergistic effect. For instance, in a recent work based on the UKB, researchers have identified higher risk for dementia in people with type-2 diabetes and new onset AF [119]. Further research in a larger sample is needed to reliably elucidate such synergistic effects.

The study also contains several important strengths. First, we had access to a very large real-world sample of older adults with a combination of clinical data from EHR records and genetic testing obtained for both cases (AD-dementia) and controls (CU). Second, our results may be more applicable to a real-world population, that more often presents with mixed forms of dementia. Third, we were powered to look at many RFs within large categories, as well as individually. Fourth, we were able to see the effect of ApoE ϵ 4, a common and strong susceptibility gene for AD that is not typically obtained clinically, in conjunction with these many RFs on the presence or absence of clinical-AD dementia. Fifth, we were able to relate these RFs to demographic characteristics such as age, sex and level of education with regards to the presence or absence of clinical-AD dementia. Finally, we have reordered the ICD-10 categorization into a clinical context using medical-pathological categorization.

4.5. Conclusion

This study has comprehensively analyzed a large-scale dataset to elucidate a large variety of RFs of different categories for clinical-AD development, and their relationship to specific genetic and demographic determinants. The heterogeneity of these factors and sometimes also their underlying mechanism is in line with novel views of clinical-AD as a highly heterogeneous disorder [120]. Our results highlighted entities which are less reported in the AD-prevention literature, such as gastrointestinal and sensorimotor disorders, and underscored the complex interaction between AD major susceptibility gene and vascular RFs. Further research should detect the relationships between specific RFs and certain clinical, genetic, and demographic characteristic, as well as their interactions, with an eye toward personalized prevention of AD.

Data and code availability

Data for this study was obtained from the UKB resource under Application Number 26664. The data is available to bona fide researchers for a fee through the UKB. Source data, along with the source code for all statistical tests, are provided with this paper. The generated

figures used in these analyses are available on GitHub (https://github.com/CompuNeuroPsychiatryLabEinKerem/publications_data/tree/master/UKBB_AD_RiskFactors), with detailed instructions provided in the README.md file.

CRedit authorship contribution statement

Uri Elias: Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Lidor Gazit:** Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Roie Zucker:** Methodology, Data curation. **Amos Stern:** Formal analysis, Data curation. **Michal Linial:** Methodology, Formal analysis, Data curation. **Gilles Allali:** Writing – review & editing. **Tamir Ben-Hur:** Writing – review & editing, Conceptualization. **Gad A. Marshall:** Writing – review & editing, Writing – original draft, Resources, Methodology, Conceptualization. **Shahar Arzy:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Supplementary materials

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