Association of a wide range of chronic diseases and apolipoprotein E4 genotype with subsequent risk of dementia in community-dwelling adults: A retrospective cohort study

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Summary

Background Identifying independent and interactive associations of a wide range of diseases and multimorbidity and apolipoprotein E4 (APOE4) with dementia may help promote cognitive health. The main aim of the present study was to investigate associations of such diseases and their multimorbidity with incident dementia.

Methods In this retrospective cohort study, we included 471,485 individuals of European ancestry from the UK Biobank, aged 38–73 years at baseline (2006–10). Dementia was identified using inpatient records and death registers. The follow-up period was between March 16, 2006, and Jan 31, 2021.

Findings During a median follow-up of 11·9 years, 6189 cases of incident all-cause dementia (503 young-onset cases, 5686 late-onset cases) were documented. In multivariable-adjusted analysis, 33 out of 63 major diseases were associated with an increased risk of dementia. The hazard ratio (HR [95% CI]) ranged from 1·12 (1·06–1·19) for obesity to 14·22 (12·33–16·18) for Parkinson's disease. In addition to conventional diseases, respiratory disorders, musculoskeletal disorders, digestive disorders, painful conditions, and chronic kidney disease were associated with increased dementia risk. A larger HR for dementia was observed for a larger number of diseases (3·97 [3·51–4·48] for ≥6 diseases versus no disease). These individual diseases and multimorbidity were more predictive of young-onset dementia than of late-onset dementia. Dementia risk score incorporating multimorbidity, age, and APOE4 status had strong prediction performance (area under the curve [95% CI]: 82·2% [81·7–82·7%]). APOE4 was more predictive of late-onset dementia (HR [95% CI]: 2·90 [2·75–3·06]) than of young-onset dementia (1·26 [1·03–1·54]). Associations of painful conditions, depression, obesity, diabetes, stroke, Parkinson's disease, high cholesterol, and their multimorbidity with incident dementia were stronger among non-APOE4 carriers.

Interpretation Besides conventional diseases, numerous diseases are associated with an increased risk of dementia. These individual diseases and multimorbidity are more predictive of young-onset dementia, whereas APOE4 is more predictive of late-onset dementia. Individual diseases and multimorbidity are stronger predictors of dementia

Abbreviations: AD, Alzheimer's disease; APOE4, apolipoprotein E4; AUC, area under the curve; BMI, body mass index; CAIDE, Cardiovascular Risk Factors, Aging, and Incidence of Dementia; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; FRS, Framingham Heart Study; HbA1c, Glycosylated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; ICD, international classification diseases; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; PAR, Population attributable risk; SD, standard deviation; ROC, receiver operating characteristic curve; VD, vascular dementia; HIV, human immunodeficiency virus

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in non-APOE4 carriers. Although multiple risk factors have been adjusted for in the analysis, potential confounding from unknown factors may have biased the associations.

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Keywords: Dementia; Young-onset dementia; Late-onset dementia; Major chronic diseases; Multimorbidity; Apolipoprotein E4; Interaction

Research in context

Evidence before this study

A literature search was conducted using PubMed, on Sept 14, 2021, using the search terms "multiple diseases", "multiple conditions", "multiple chronic diseases", "multiple chronic conditions", "individual diseases", "individual conditions", "individual chronic diseases", "individual chronic conditions", "major diseases", "major conditions", "major chronic diseases", "major chronic conditions", "multimorbidity", "multimorbidity", "comorbidit*", "co-morbidit*", or "apolipoprotein E" combined with "dementia", or "Alzheimer's disease" with no language restrictions. Although numerous studies have investigated the association between conventional diseases and incident dementia, only a few studies have examined the association between multimorbidity and dementia. Data for the interaction between individual major diseases, multimorbidity, and apolipoprotein E4 (APOE4) for incidence of dementia are limited.

Added value of this study

Using the UK Biobank, we found hearing impairment, hypertension, depression, high cholesterol, diabetes, and obesity were among the leading contributors to dementia, and a wide range of emerging diseases including respiratory disorders, musculoskeletal disorders, painful conditions, digestive disorders, and chronic kidney disease were associated with an increased risk of dementia. These individual diseases and their multimorbidity were more predictive of young-onset dementia than of late-onset dementia. The association between individual diseases and multimorbidity and incident dementia was stronger among non-APOE4 carriers. The multimorbidity (incorporating age and APOE4) risk score for dementia was more accurate than conventional dementia risk scores.

Implications of all the available evidence

We identified numerous emerging diseases in addition to conventional diseases that may help identify individuals at higher risk of dementia, especially young-onset dementia. The multimorbidity risk score may be useful for the prediction and screening of dementia among adults. Individual diseases, multimorbidity, and genetics are independently and interactively associated with dementia, but they may play different potential roles in the development of young-onset and late-onset dementia.

Introduction

Dementia was the seventh leading cause of mortality accounting for 1·6 million deaths globally in 2019.[1] Although age-specific incidence rates of dementia are lower in more recent cohorts compared with cohorts from previous decades in high-income countries including the UK,[2] a modelling study suggests the number of people with dementia in the UK would increase from 0·77 million in 2016 to 1·20 million in 2040 given the increasing ageing population.[3] It is critical to identify important determinants for dementia, as there is no effective way to stop the progression of dementia yet.[2,4]

Chronic conditions including hypertension, obesity, diabetes, hearing loss, depression, and traumatic brain injury have been associated with an increased risk of dementia.[2,5] These diseases together with other well-known risk factors accounted for less than 40% of the development of dementia.[4] A growing number of studies have linked eye diseases to dementia,[6,7] but it is unknown whether the importance of these eye diseases is comparable to that of conventional diseases. There are conflicting results for the association between cancers and Alzheimer's disease (AD) between previous studies.[8] Little is known regarding the association between types of cancers and incident dementia. It is also of great importance to confirm the associations of emerging risk factors for dementia including musculoskeletal disorders, painful conditions,[9] respiratory disorders (such as chronic obstructive pulmonary disease [COPD]),[10,11] chronic kidney disease (CKD),[12] and

digestive disorders[13] with dementia in large prospective cohort studies. A recent prospective study has identified several physical diseases including erysipelas, hypothyroidism, duodenal ulcer, gastritis, and duodenitis (in addition to conventional risk factors), that may increase the long-term risk of dementia.[13] However, this study is limited by investigating a small number of chronic diseases.

Strong evidence has demonstrated the importance of apolipoprotein E4 (APOE4) on the development of dementia especially AD.[14,15] APOE4 has also been considered as a therapeutic target for AD,[16] given that APOE4 may modify the association of multiple biomarkers including vasculature, insulin, and inflammation with AD.[16,17] Investigating the interaction between genetics and individual diseases and multimorbidity for the development of dementia may provide evidence on priority for anti-APOE4 therapy. However, limited data from such studies are available. Although dementia usually develops in older people, young-onset dementia also deserves scrutiny as its more detrimental effect on life.[18] APOE4 has been shown to play a more important role in the development of late-onset AD than in young-onset AD,[14,15] but less is known regarding associations of non-genetic factors such as major diseases with young-onset and late-onset dementia.

Using the data of the UK Biobank study, the main aim of the present study was to investigate associations of a wide range of major diseases and their multimorbidity with incident dementia. Meanwhile, we aimed to create a multimorbidity risk score based on the associations between individual diseases and incident dementia. Thirdly, the analysis for young-onset and late-onset dementia was also conducted. Finally, we examined the interaction between APOE4 and diseases with dementia.

Methods

Study population

This analysis was based on data from the UK Biobank, which is a population-based prospective cohort of more than 500,000 participants aged 38–73 years at baseline between 2006 and 2010.[19] These participants attended one of the 22 assessment centers throughout the UK.[19] The details of design and population have been described elsewhere.[19] Briefly, of approximately 9·2 million eligible invited people aged 38–73 years who were registered with the National Health Service, 502,505 individuals were assessed at baselinewith a participation rate of 5·5%.

The UK Biobank Study's ethical approval has been granted by the National Information Governance Board for Health and Social Care and the NHS North West Multicenter Research Ethics Committee. All participants provided informed consent through electronic signature at recruitment.

Data sources

Datasets of the main UK Biobank (questionnaires, physical examinations, blood tests), genetics, inpatient hospital, and death register were used in the analysis. The main UK Biobank and inpatient hospital data were used to define individual diseases (predictors) of interest. APOE4 was defined using genetic data. Outcome (dementia) cases were identified using inpatient hospital and death register data. Covariates were assessed using the main UK Biobank data. These datasets were combined using unique patient identifiers. Individuals who had both main UK Biobank and inpatient hospital/death register data, those who were of European ancestry, and those without prevalent dementia or cognitive impairmentat baseline were included in the analysis.

Ascertainment of incident dementia

Data on admissions and diagnoses were used to identify dementia (all dementia, AD, and vascular dementia [VD]) cases with a primary/secondary diagnosis using the international classification diseases (ICD) coding system (detailed in Table S1). The Hospital Episode Statistics database, the Scottish Morbidity Record, and the Patient Episode Database were used to document inpatient hospital records in England, Scotland and Wales. Additional cases were defined as underlying/contributory causes of death being dementia through linkage to death register data (ICD codes). Individuals with dementia diagnosed <65 years were classified as young-onset dementia, and those diagnosed ≥65 years were classified as late-onset dementia.[18] The earliest recorded date regardless of sources was used as the onset date of dementia. The follow-up period was between March 16, 2006, and January 31, 2021. Person-years for each participant were calculated from the date of baseline assessment to the date of onset dementia, date of death, or the end of follow-up (December 31, 2020 for England and Wales and January 31, 2021 for Scotland), whichever came first. Incident rates were computed as the number of events per 1000 person-years.

Definition of diseases and multimorbidity

Self-reported outcomes were assessed using a touchscreen questionnaire. Participants were asked, "Has a doctor ever told that you have a disease (for example, diabetes)". Participants who reported that they had ever been told by a doctor that they had a disease were classified as having the specific disease. We included 62 major diseases such as cardiovascular disease, cancer, diabetes, dementia, CKD in the analysis (Field code is listed in Table S2). Additional disease cases at baseline were defined using inpatient data (initial diagnosis date before baseline interview date). Inpatient hospital data for the UK Biobank participants were available since 1997.[19] ICD codes for each of the 62

diseases are listed in Table S3. Body mass index (BMI) was computed based on measured weight and height, and obesity was defined as BMI $\geq$ 30 kg/m^2. Multimorbidity was defined by two or more out of chronic diseases that were statistically significantly associated with dementia risk.

Risk score for dementia

We computed a multimorbidity risk score for dementia based on the estimates for individual diseases that were statistically significantly associated with dementia. The multimorbidity risk score was calculated using the formula: $\sum_i \beta_i$, where β_i is the coefficient (log (hazard ratio [HR]) for incident dementia associated with the i disease. The multimorbidity risk score incorporating age/APOE4 was also computed. We then calculated Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) risk score,[20] and Framingham Heart Study (FRS) score[21] for dementia, which were shown to have good prediction performance.[22] The prediction performance of multimorbidity risk score (plus age/APOE4), CAIDE risk score, and FRS risk score was compared.

Genetic data

Genotyping was conducted by Affymetrix using a bespoke BiLEVE Axiom array or the UK Biobank Axiom array.[23] All genetic data were quality controlled and imputed by UK Biobank. APOE genotype was directly genotyped based on two SNPs (rs7412 and rs429358). APOE4+ dominant model of E3/E4 and E4/E4 was used to define the presence of APOE4. Given the genetic difference between ethnicities, those of non-European ancestry were excluded from the analysis.

Covariates

Information on age, sex, education, ethnicity, and income was self-reported. Sleep duration was assessed with the survey item "About how many hours sleep do you get in every 24 h?" A short form of the International Physical Activity Questionnaire was used to assess physical activity. A healthy diet score was computed based on seven commonly eaten food groups following recommendations on dietary priorities for cardiometabolic health with a higher score representing a healthier diet. A higher healthy diet score has been associated with decreased dementia risk.[24]

Cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride were measured by direct enzymatic methods (Konelab, Thermo Fisher Scientific, Waltham, Massachusetts). Glycosylated haemoglobin (HbA1c) was measured using high-performance liquid chromatography.

Statistical analysis

Data of baseline characteristics were expressed as frequency (percentage), means ± standard deviations (SDs), or median (interquartile range [IQR]) by multimorbidity/APOE4/age/incident dementia.

Cox proportional hazard regression models were used to examine associations of individual diseases of interest with incident dementia and its phenotypes (AD, and VD). The following models were tested: (1) age and gender; (2) model 1 plus education, income, diet score, smoking, alcohol consumption, sleep, physical activity, and BMI (BMI was not included in the analysis for obesity); 3) model 2 plus HDL-C, LDL-C, triglyceride, HbA1c, and blood pressure at baseline. The clustering effect of participants within assessment centers as a random effect was controlled for in all the models. Benjamin-Hochberg's procedure was used to control the false discovery rate at a 5% level for multiple comparisons.[25] The number of diseases was then computed based on those that were statistically significantly associated with incident dementia. The association of individual diseasesand the number of diseases with incident dementia stratified by APOE4 was then tested. Population attributable risk (PAR) of individual diseases, multimorbidity, and APOE4 for dementia was computed based on multivariable-adjusted HR.

The receiver operating characteristic curves (ROCs) were plotted and the area under the curve (AUC) was calculated for risk scores of multimorbidity (plus age/APOE4), CAIDE, and FRS.

The confounding due to socioeconomic factors for the association between multimorbidity and incident dementia could not be adequately corrected by adjustment. We conducted the analysis for the association between multimorbidity and incident dementia stratified by socioeconomic factors. Similarly, multimorbidity and dementia were both highly related to age, and the adjustment for age might not be able to address the confounding. We conducted the analysis for the association between multimorbidity and incident dementia stratified by age.

As the prodromal period of dementia can last many years, dementia developed in the first several years of follow-up might have occurred before the diagnosis of chronic conditions but not be diagnosed. We conducted a sensitivity analysis to examine the association between major diseases and incident dementia by excluding those who developed dementia in the first five years of follow-up.

The diagnosis of dementia in 2020 might be impacted by COVID-19. We conducted a sensitivity analysis to test whether the associations between multimorbidity/APOE4 and incident dementia might be impacted by COVID-19 (set the end of follow-up on December 31, 2019).

The percentage of participants with missing values in physical activity, income, HbA1c, and blood pressure

was 19·5%, 14·5%, 6·7%, and 6·0%, respectively. A much lower missing rate was seen for other covariates. Missing values for categorical variables were assigned as a new single category. Multiple imputations for missing data in continuous variables were conducted for baseline covariates, and we included all covariates in the imputation models to create 10 imputed datasets.

Data analyses were conducted using SAS 9·4 for Windows (SAS Institute Inc.) and all P values were two-sided with statistical significance set at <0·05.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Population selection and baseline characteristics

Baseline data were collected among 502,505 participants. After excluding individuals who were not linked to inpatient hospital/death register data (n = 29), those who were non-European ancestry (n = 30,378), those with prevalent dementia (n = 345) or cognitive impairment (n = 233), or with incident dementia that developed in the first year of follow-up (n = 36), 471,485 adults (54·5% females) aged 38–73 years (mean ± SD: 56·8 ± 8·0) were included in the final analysis (Fig. S1). Participants with dementia occurred in the first year of follow-up were excluded from the analysis because those participants were more likely to have preexisting dementia at baseline which may confound the association between major diseases and incident dementia.

Individuals with multimorbidity were more likely to be older, male, lowly educated, and to have low income and unhealthier lifestyle habits compared to those with zero disease. Multimorbidity was associated with higher BMI, HbA1c, and blood pressure (Table 1). Compared with individuals who did not develop dementia during follow-up, those who developed dementia were more likely to be older, males, APOE4 carriers, and lowly educated and to have higher HbA1c and systolic blood pressure. Adults aged 65 years or over were more likely to be males and lowly educated, and to have higher systolic blood pressure compared with those aged young than 65 years (Table S4). APOE4 carriers were more likely to have higher total cholesterol, LDL-C, and triglycerides compared with non-APOE4-carriers (Table S5).

Incidence of dementia

Over 5624,248 person-years of follow-up (median [interquartile range] length of follow-up: 11·9 [11·2–12·6] years), 6189 cases of incident all-cause dementia, 2597 incident AD cases, and 1381 incident VDcases were documented. Among 377,214 participants who were aged younger than 65 years at baseline, 503 developed young-onset dementia. Whilst 5686 individuals developed late-onset dementia among those who were 65 years or older at the end of follow-up.

Individual diseases and incident dementia

Of 63 diseases of interest, 36 were associated with an increased risk of all-cause dementia after controlling the false discovery rate. The HR (95% CI) ranged from 1·12 (1·06–1·19) for obesity to 14·12 (12·33–16·18) for Parkinson's disease. In addition to Parkinson's disease, there were 9 diseases including depression (2·12 (1·94–2·31)), anxiety (2·06 (1·78–2·39)), diabetes (2·12 (1·97–2·30)), stroke (2·39 (2·14–2·66)), alcohol problems (2·71 (2·18–3·37)), psychoactive substance abuse (3·28 (2·44–4·42)), epilepsy (2·89 (2·47–3·39)), multiple sclerosis (2·20 (1·61–3·02)), and schizophrenia (3·77 (3·05–4·66)) with HR over 2. Associations for 33 diseases remained statistically significant after adjustment for age, gender, education, income, diet score, smoking, alcohol consumption, sleep, physical activity, BMI, HDL-C, LDL-C, triglyceride, HbA1c, and blood pressure at baseline. The association between stomach cancer and incident dementia was attenuated to be non-statistically significant after adjustment for covariates. The HR (95% CI) for all-cause dementia associated with prostate cancer in men was reversed from 1·54 (1·22–1·94) to 0·75 (0·59–0·94) after adjustment for age. Notably, the association of hypertension (HR (95% CI): 1·29 (1·22–1·36)) and high cholesterol (1·30 (1·22–1·38)) with dementia remained statistically significant after even adjustment for blood pressure, HDL-C, LDL-C, and triglyceride at baseline (Table 2).

Well-known risk factors including hearing impairment (PAR(95% CI): 9·6% (7·5–12·0%)), hypertension (6·9% (5·4–8·5%)), depression (5·0% (4·2–5·9%)), high cholesterol (3·7% (2·8–4·7%)), diabetes (2·9% (2·2–3·5%)), and obesity (2·6% (0·2–4·8%)) were among leading contributors to dementia. Painful conditions (3·2% (2·2–4·2%)) and CHD (2·8% (2·2–3·4%)) were also among leading contributors to dementia (Fig. S2).

Similar results were seen for AD (Table S6) and VD (Table S7).

HRs associated with 29 individual diseases were larger for young-onset dementia than for late-onset dementia. For example, the HR (95% CI) associated with hearing impairment was 1·64 (1·38–1·97) for young-onset dementia and 1·22 (1·16–1·28) for late-onset dementia. Obesity was predictive of young-onset dementia (1·43 (1·05–1·95)) but not late-onset dementia (1·09 (0·99–1·19)). Similarly, eczema was predictive of young-onset dementia (1·58 (1·11–2·26)) but not late-onset dementia (1·11 (0·97–1·27)). In contrast, atrial

	Number of major diseases at baseline						
	0	1	2	3	4	5	6
Age (years)	53·60 ± 7·97	55·53 ± 8·00	57·24 ± 7·81	58·79 ± 7·43	59·87 ± 7·06	60·69 ± 6·68	61·19 ± 6·41
Age (years), median (IQR)	53·0 (47·0–60·0)	56·0 (49·0–62·0)	59·0 (51·0–64·0)	60·0 (54·0–65·0)	61·0 (56·0–65·0)	62·0 (57·0–66·0)	63·0 (58·0–66·0)
Gender							
Females	59,754 (63·2)	75,982 (56·8)	54,493 (53·1)	31,800 (49·4)	17,404 (47·3)	9135 (45·6)	8238 (42·3)
Males	34,797 (36·8)	57,691 (43·2)	48,131 (46·9)	32,527 (50·6)	19,365 (52·7)	10,909 (54·4)	11,259 (57·7)
APOE4							
No	69,533 (73·5)	98,809 (73·9)	75,964 (74·0)	47,751 (74·2)	27,181 (73·9)	14,895 (74·3)	14,478 (74·3)
Yes	22,343 (23·6)	31,290 (23·4)	24,051 (23·4)	15,006 (23·3)	8637 (23·5)	4585 (22·9)	4442 (22·8)
Missing	2675 (2·8)	3574 (2·7)	2609 (2·5)	1570 (2·4)	951 (2·6)	564 (2·8)	577 (3·0)
Education							
0–5 years	9177 (9·7)	17,347 (13·0)	17,399 (17·0)	13,766 (21·4)	9495 (25·8)	6276 (31·3)	7341 (37·7)
6–12 years	47,044 (49·8)	66,585 (49·8)	51,431 (50·1)	32,070 (49·9)	17,999 (49·0)	9389 (46·8)	8749 (44·9)
≥13 years	36,734 (38·9)	47,605 (35·6)	32,165 (31·3)	17,463 (27·1)	8658 (23·5)	4024 (20·1)	3049 (15·6)
Missing	1596 (1·7)	2136 (1·6)	1629 (1·6)	1028 (1·6)	617 (1·7)	355 (1·8)	358 (1·8)
Household income (pounds)							
<18,000	11,034 (11·7)	19,523 (14·6)	19,155 (18·7)	14,998 (23·3)	10,375 (28·2)	6665 (33·3)	8068 (41·4)
18,000–30,999	18,093 (19·1)	28,222 (21·1)	23,390 (22·8)	15,122 (23·5)	8722 (23·7)	4794 (23·9)	4200 (21·5)
31,000–51,999	23,821 (25·2)	32,859 (24·6)	23,558 (23·0)	13,409 (20·8)	6720 (18·3)	3159 (15·8)	2298 (11·8)
52,000–100,000	22,642 (23·9)	27,473 (20·6)	17,298 (16·9)	8745 (13·6)	4016 (10·9)	1596 (8·0)	1027 (5·3)
>100,000	6913 (7·3)	7464 (5·6)	4297 (4·2)	1988 (3·1)	817 (2·2)	308 (1·5)	161 (0·8)
Unknown	2567 (2·7)	4401 (3·3)	4054 (4·0)	2979 (4·6)	1922 (5·2)	1195 (6·0)	1422 (7·3)
Not answered	9481 (10·0)	13,731 (10·3)	10,872 (10·6)	7086 (11·0)	4197 (11·4)	2327 (11·6)	2321 (11·9)
Diet score, median (IQR)	4·0 (3·0–5·0)	4·0 (3·0–5·0)	4·0 (3·0–5·0)	4·0 (3·0–5·0)	4·0 (3·0–5·0)	4·0 (3·0–5·0)	4·0 (3·0–5·0)
Physical activity	2505·0	2478·0	2462·0	2445·0	2479·5	2373·0	2160·0
(MET-minutes/week), median (IQR)	(1152·0–3207·5)	(1078·0–3093·0)	(1011·0–2994·0)	(942·0–2862·0)	(904·0–2730·0)	(813·0–2651·9)	(634·0–2651·9)
Smoking							
Never	58,108 (61·5)	76,811 (57·5)	54,511 (53·1)	31,802 (49·4)	16,771 (45·6)	8433 (42·1)	7045 (36·1)
Former	27,056 (28·6)	42,993 (32·2)	37,126 (36·2)	25,324 (39·4)	15,771 (42·9)	9170 (45·7)	9570 (49·1)
Current	9167 (9·7)	13,494 (10·1)	10,613 (10·3)	6950 (10·8)	4042 (11·0)	2330 (11·6)	2733 (14·0)
Missing	220 (0·2)	375 (0·3)	374 (0·4)	251 (0·4)	185 (0·5)	111 (0·6)	149 (0·8)
Sleep duration (hours/day)							
<7	18,662 (19·7)	29,634 (22·2)	25,266 (24·6)	16,951 (26·4)	10,236 (27·8)	5805 (29·0)	6227 (31·9)
7–9	74,929 (79·2)	102,181 (76·4)	75,318 (73·4)	45,469 (70·7)	25,062 (68·2)	13,136 (65·5)	11,595 (59·5)
>9	695 (0·7)	1375 (1·0)	1531 (1·5)	1491 (2·3)	1138 (3·1)	846 (4·2)	1322 (6·8)
Missing	265 (0·3)	483 (0·4)	509 (0·5)	416 (0·6)	333 (0·9)	257 (1·3)	353 (1·8)

Table 1 *(Continued)*

	Number of major diseases at baseline						
	0	1	2	3	4	5	6
Alcohol consumption							
Never	2482 (2·6)	3682 (2·8)	3147 (3·1)	2348 (3·7)	1464 (4·0)	982 (4·9)	1181 (6·1)
Previous	1837 (1·9)	3309 (2·5)	3327 (3·2)	2658 (4·1)	2011 (5·5)	1370 (6·8)	1964 (10·1)
Current	90,189 (95·4)	126,600 (94·7)	96,069 (93·6)	59,256 (92·1)	33,231 (90·4)	17,657 (88·1)	16,300 (83·6)
Missing	43 (0·0)	82 (0·1)	81 (0·1)	65 (0·1)	63 (0·2)	35 (0·2)	52 (0·3)
BMI (kg/m^2)	24·85 ± 2·70	26·23 ± 3·88	27·75 ± 4·58	29·02 ± 4·94	30·15 ± 5·19	30·92 ± 5·27	31·99 ± 5·59
HbA1c (mmol/mol)	34·39 ± 3·99	35·01 ± 4·75	35·78 ± 5·44	36·87 ± 6·61	38·28 ± 8·26	39·66 ± 9·44	41·93 ± 11·32
Cholesterol (mmol/L)	5·83 ± 1·02	5·86 ± 1·04	5·80 ± 1·08	5·63 ± 1·14	5·41 ± 1·18	5·22 ± 1·19	4·97 ± 1·18
HDL-C (mmol/L)	1·54 ± 0·36	1·49 ± 0·35	1·44 ± 0·35	1·40 ± 0·34	1·35 ± 0·33	1·32 ± 0·33	1·28 ± 0·33
LDL-C (mmol/L)	3·63 ± 0·79	3·67 ± 0·80	3·64 ± 0·82	3·53 ± 0·87	3·36 ± 0·89	3·22 ± 0·89	3·03 ± 0·87
Triglycerides (mmol/L)	1·51 ± 0·84	1·65 ± 0·93	1·80 ± 0·99	1·90 ± 1·04	1·99 ± 1·08	2·06 ± 1·12	2·15 ± 1·18
Diastolic blood pressure (mmHg)	79·97 ± 9·32	81·51 ± 9·71	83·11 ± 9·88	83·86 ± 9·85	83·71 ± 9·78	83·09 ± 9·91	81·94 ± 10·18
Systolic blood pressure (mmHg)	133·08 ± 17·20	136·09 ± 17·86	139·34 ± 18·17	141·33 ± 18·12	141·95 ± 17·79	141·75 ± 17·78	140·55 ± 17·96

***Table 1*: Baseline characteristics of participants.**

APOE4, apolipoprotein E4; BMI, body mass index; HbA1c, glycatedhaemoglobin; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol.

*APOE4+ dominant model of E3/E4 and E4/E4 was used to define the presence of APOE4.

†Diet score was computed based on seven commonly eaten food groups following recommendations on dietary priorities for cardiometabolic health with higher score representing healthier diet.

	Participants	Events	Person-years	Incidence rate*	HR (95% CI), Model 1†	HR (95% CI), Model 2	HR (95% CI), Model 3
Hearing impairment‡							
No	270,224	2756	3,232,267	0·85	Reference	Reference	Reference
Yes	201,261	3433	2,388,864	1·44	1·28 (1·22–1·35)	1·25 (1·19–1·32)	1·25 (1·19–1·32)
Obesity‡							
No	357,994	4534	4,267,577	1·06	Reference	Reference	Reference
Yes	113,491	1655	1,353,554	1·22	1·12 (1·06–1·19)	1·12 (1·03–1·23)	1·11 (1·01–1·21)
Hypertension‡							
No	350,404	3485	4,180,853	0·83	Reference	Reference	Reference
Yes	121,081	2704	1,440,278	1·88	1·38 (1·31–1·45)	1·33 (1·26–1·40)	1·29 (1·22–1·36)
High cholesterol‡							
No	410,568	4532	4,901,284	0·92	Reference	Reference	Reference
Yes	60,917	1657	719,847	2·30	1·43 (1·35–1·52)	1·36 (1·28–1·44)	1·30 (1·22–1·38)
Coronary heart disease‡							
No	447,000	5204	5,330,836	0·98	Reference	Reference	Reference
Yes	24,485	985	290,295	3·39	1·84 (1·72–1·97)	1·64 (1·53–1·76)	1·55 (1·44–1·67)
Atrial Fibrillation‡							
No	464,197	5916	5,534,962	1·07	Reference	Reference	Reference
Yes	7288	273	86,169	3·17	1·55 (1·38–1·76)	1·49 (1·32–1·68)	1·45 (1·28–1·64)
Heart failure‡							
No	469,301	6098	5,595,321	1·09	Reference	Reference	Reference
Yes	2184	91	25,810	3·53	1·85 (1·50–2·28)	1·57 (1·27–1·93)	1·45 (1·18–1·79)
Stroke‡							
No	464,276	5841	5,535,558	1·06	Reference	Reference	Reference
Yes	7209	348	85,573	4·07	2·39 (2·14–2·66)	2·05 (1·84–2·29)	1·92 (1·72–2·15)
Peripheral vascular disease							
No	468,564	6097	5,586,101	1·09	Reference	Reference	Reference
Yes	2921	92	35,030	2·63	1·54 (1·25–1·89)	1·29 (1·05–1·59)	1·18 (0·96–1·45)
Other cardiac problem‡							
No	465,758	6013	5,552,476	1·08	Reference	Reference	Reference
Yes	5727	176	68,654	2·56	1·64 (1·41–1·90)	1·46 (1·26–1·70)	1·39 (1·19–1·62)
Diabetes‡							
No	452,227	5448	5,392,832	1·01	Reference	Reference	Reference
Yes	19,258	741	228,298	3·25	2·12 (1·97–2·30)	1·95 (1·80–2·12)	1·72 (1·56–1·89)

Table 2 (Continued)

	Participants	Events	Person-years	Incidence rate*	HR (95% CI), Model 1†	HR (95% CI), Model 2	HR (95% CI), Model 3
COPD‡							
No	468,160	6054	5,581,889	1·08	Reference	Reference	Reference
Yes	3325	135	39,242	3·44	1·87 (1·58–2·22)	1·48 (1·24–1·75)	1·44 (1·21–1·71)
Asthma‡							
No	415,916	5358	4,959,066	1·08	Reference	Reference	Reference
Yes	55,569	831	662,064	1·26	1·25 (1·16–1·35)	1·20 (1·12–1·30)	1·20 (1·11–1·29)
Bronchiectasis							
No	470,096	6155	5,604,625	1·10	Reference	Reference	Reference
Yes	1389	34	16,505	2·06	1·24 (0·88–1·73)	1·20 (0·86–1·68)	1·17 (0·84–1·64)
Depression‡							
No	443,780	5610	5,291,854	1·06	Reference	Reference	Reference
Yes	27,705	579	329,276	1·76	2·12 (1·94–2·31)	1·88 (1·73–2·05)	1·90 (1·74–2·07)
Anxiety‡							
No	463,534	6005	5,526,650	1·09	Reference	Reference	Reference
Yes	7951	184	94,481	1·95	2·06 (1·78–2·39)	1·82 (1·57–2·11)	1·84 (1·59–2·13)
Schizophrenia‡							
No	469,245	6102	5,594,612	1·09	Reference	Reference	Reference
Yes	2240	87	26,519	3·28	3·77 (3·05–4·66)	3·09 (2·50–3·82)	3·13 (2·53–3·87)
Parkinson's disease‡							
No	470,626	5972	5,611,768	1·06	Reference	Reference	Reference
Yes	859	217	9363	23·18	14·12 (12·33–16·18)	13·49 (11·77–15·46)	13·40 (11·68–15·37)
Multiple Sclerosis‡							
No	469,653	6150	5,599,274	1·10	Reference	Reference	Reference
Yes	1832	39	21,856	1·78	2·20 (1·61–3·02)	2·02 (1·47–2·77)	2·05 (1·50–2·82)
Alcohol problems‡							
No	468,855	6107	5,589,767	1·09	Reference	Reference	Reference
Yes	2630	82	31,364	2·61	2·71 (2·18–3·37)	1·82 (1·46–2·27)	1·82 (1·46–2·28)
Psychoactive substance abuse‡							
No	470,250	6145	5,606,554	1·10	Reference	Reference	Reference
Yes	1235	44	14,577	3·02	3·28 (2·44–4·42)	2·33 (1·73–3·15)	2·34 (1·74–3·16)
Migraine							
No	456,894	6042	5,446,086	1·11	Reference	Reference	Reference
Yes	14,591	147	175,045	0·84	0·98 (0·84–1·16)	0·96 (0·82–1·13)	0·99 (0·84–1·16)

Table 2 *(Continued)*

	Participants	Events	Person-years	Incidence rate*	HR (95% CI), Model 1†	HR (95% CI), Model 2	HR (95% CI), Model 3
Epilepsy‡							
No	466,909	6031	5,566,886	1·08	Reference	Reference	Reference
Yes	4576	158	54,245	2·91	2·89 (2·47–3·39)	2·45 (2·09–2·87)	2·47 (2·11–2·90)
Meniere disease							
No	469,814	6156	5,600,936	1·10	Reference	Reference	Reference
Yes	1671	33	20,195	1·63	1·17 (0·83–1·65)	1·11 (0·78–1·56)	1·12 (0·80–1·58)
Chronic sinusitis							
No	467,067	6128	5,568,195	1·10	Reference	Reference	Reference
Yes	4418	61	52,935	1·15	1·03 (0·80–1·32)	1·03 (0·80–1·32)	1·04 (0·81–1·34)
Traumatic brain injury‡							
No	466,073	6084	5,556,434	1·09	Reference	Reference	Reference
Yes	5412	105	64,697	1·62	1·62 (1·34–1·96)	1·44 (1·18–1·74)	1·44 (1·18–1·74)
Other brain problem							
No	470,435	6169	5,608,617	1·10	Reference	Reference	Reference
Yes	1050	20	12,514	1·60	1·48 (0·96–2·30)	1·31 (0·84–2·03)	1·32 (0·85–2·05)
Painful conditions‡							
No	409,559	5074	4,889,420	1·04	Reference	Reference	Reference
Yes	61,926	1115	731,710	1·52	1·33 (1·25–1·42)	1·25 (1·17–1·33)	1·25 (1·17–1·33)
Chronic fatigue syndrome‡							
No	469,332	6157	5,595,323	1·10	Reference	Reference	Reference
Yes	2153	32	25,808	1·24	1·53 (1·08–2·16)	1·43 (1·01–2·02)	1·45 (1·02–2·05)
Connective tissue disorders‡							
No	459,751	5944	5,481,184	1·08	Reference	Reference	Reference
Yes	11,734	245	139,946	1·75	1·30 (1·14–1·47)	1·19 (1·05–1·36)	1·19 (1·04–1·35)
Osteoporosis‡							
No	426,388	5106	5,083,699	1·00	Reference	Reference	Reference
Yes	45,097	1083	537,431	2·02	1·29 (1·21–1·38)	1·20 (1·13–1·29)	1·21 (1·13–1·29)
Fracture‡							
No	469,381	6135	5,596,575	1·10	Reference	Reference	Reference
Yes	2104	54	24,555	2·20	1·63 (1·25–2·13)	1·51 (1·16–1·98)	1·50 (1·15–1·96)
Anorexia							
No	471,100	6187	5,616,511	1·10	Reference	Reference	Reference
Yes	385	2	4619	0·43	1·18 (0·30–4·73)	1·01 (0·25–4·04)	1·01 (0·25–4·05)

Table 2 (Continued)

	Participants	Events	Person-years	Incidence rate*	HR (95% CI), Model 1†	HR (95% CI), Model 2	HR (95% CI), Model 3
Dyspepsia‡							
No	417,998	5103	4,985,899	1·02	Reference	Reference	Reference
Yes	53,487	1086	635,232	1·71	1·25 (1·17–1·34)	1·15 (1·08–1·23)	1·15 (1·08–1·23)
Treated constipation‡							
No	466,486	6049	5,562,139	1·09	Reference	Reference	Reference
Yes	4999	140	58,992	2·37	1·91 (1·61–2·26)	1·66 (1·40–1·96)	1·63 (1·38–1·93)
Pernicious anemia							
No	469,972	6153	5,603,054	1·10	Reference	Reference	Reference
Yes	1513	36	18,077	1·99	1·44 (1·04–2·00)	1·29 (0·93–1·79)	1·25 (0·90–1·73)
Diverticular disease‡							
No	458,797	5851	5,471,108	1·07	Reference	Reference	Reference
Yes	12,688	338	150,023	2·25	1·28 (1·14–1·42)	1·21 (1·09–1·36)	1·22 (1·09–1·36)
Chronic kidney disease‡							
No	468,838	6109	5,589,325	1·09	Reference	Reference	Reference
Yes	2647	80	31,806	2·52	1·69 (1·35–2·10)	1·48 (1·19–1·85)	1·42 (1·14–1·77)
Inflammatory bowel disease							
No	466,585	6103	5,562,747	1·10	Reference	Reference	Reference
Yes	4900	86	58,384	1·47	1·11 (0·95–1·29)	1·06 (0·91–1·23)	1·07 (0·92–1·25)
Irritable bowel syndrome							
No	458,672	6018	5,467,588	1·10	Reference	Reference	Reference
Yes	12,813	171	153,543	1·11	1·26 (1·02–1·56)	1·19 (0·96–1·47)	1·18 (0·96–1·46)
Viral hepatitis							
No	470,078	6166	5,604,122	1·10	Reference	Reference	Reference
Yes	1407	23	17,009	1·35	1·33 (0·88–2·00)	1·32 (0·88–1·99)	1·31 (0·87–1·98)
Chronic liver disease							
No	467,881	6118	5,575,708	1·10	Reference	Reference	Reference
Yes	3604	71	45,423	1·56	1·24 (0·98–1·57)	1·12 (0·88–1·41)	1·11 (0·88–1·40)
Prostate disorders‡,§							
No	203,626	2920	2,427,426	1·20	Reference	Reference	Reference
Yes	11,053	348	130,782	2·66	1·16 (1·04–1·30)	1·14 (1·02–1·27)	1·14 (1·01–1·27)
Endometriosis¶							
No	250,301	2876	2,985,552	0·96	Reference	Reference	Reference
Yes	6505	45	77,371	0·58	0·96 (0·72–1·30)	0·98 (0·73–1·32)	0·99 (0·74–1·33)

Table 2 *(Continued)*

	Participants	Events	Person-years	Incidence rate*	HR (95% CI), Model 1†	HR (95% CI), Model 2	HR (95% CI), Model 3
Polycystic ovary¶							
No	256,123	2916	3,054,857	0·95	Reference	Reference	Reference
Yes	683	5	8066	0·62	0·66 (0·28–1·59)	2·56 (1·07–6·17)	2·54 (1·06–6·12)
Thyroid disorders							
No	442,824	5706	5,280,710	1·08	Reference	Reference	Reference
Yes	28,661	483	340,421	1·42	1·15 (1·05–1·27)	1·10 (1·00–1·21)	1·09 (0·99–1·19)
Eczema‡							
No	453,444	5930	5,404,867	1·10	Reference	Reference	Reference
Yes	18,041	259	216,264	1·20	1·18 (1·04–1·33)	1·16 (1·02–1·31)	1·16 (1·02–1·31)
HIV							
No	471,128	6187	5,616,939	1·10	Reference	Reference	Reference
Yes	357	2	4192	0·48	0·80 (0·20–3·22)	0·69 (0·17–2·78)	0·71 (0·18–2·85)
Glaucoma							
No	466,299	6070	5,560,029	1·09	Reference	Reference	Reference
Yes	5186	119	61,102	1·95	1·05 (0·88–1·26)	1·04 (0·87–1·25)	1·03 (0·86–1·24)
Cataract‡							
No	460,633	5873	5,494,928	1·07	Reference	Reference	Reference
Yes	10,852	316	126,202	2·50	1·26 (1·13–1·42)	1·22 (1·09–1·37)	1·18 (1·06–1·33)
AMD							
No	470,564	6162	5,610,361	1·10	Reference	Reference	Reference
Yes	921	27	10,769	2·51	1·30 (0·89–1·90)	1·28 (0·88–1·87)	1·24 (0·85–1·81)
Lung cancer							
No	471,062	6176	5,616,120	1·10	Reference	Reference	Reference
Yes	423	13	5010	2·59	1·36 (0·79–2·35)	1·10 (0·64–1·89)	1·09 (0·63–1·88)
Skin cancer							
No	466,470	6079	5,561,744	1·09	Reference	Reference	Reference
Yes	5015	110	59,387	1·85	1·05 (0·87–1·27)	1·04 (0·86–1·25)	1·04 (0·86–1·25)
Melanoma							
No	467,477	6113	5,573,346	1·10	Reference	Reference	Reference
Yes	4008	76	47,785	1·59	1·10 (0·88–1·38)	1·13 (0·90–1·41)	1·14 (0·91–1·42)
Stomach cancer							
No	471,165	6176	5,617,252	1·10	Reference	Reference	Reference
Yes	320	13	3878	3·35	1·98 (1·15–3·41)	1·69 (0·98–2·91)	1·63 (0·95–2·82)

Table 2 (Continued)

	Participants	Events	Person-years	Incidence rate*	HR (95% CI), Model 1†	HR (95% CI), Model 2	HR (95% CI), Model 3
Oesophageal cancer							
No	469,800	6146	5,600,911	1·10	Reference	Reference	Reference
Yes	1685	43	20,219	2·13	1·12 (0·83–1·52)	1·00 (0·74–1·35)	1·00 (0·74–1·35)
Colon cancer							
No	469,422	6140	5,596,470	1·10	Reference	Reference	Reference
Yes	2063	49	24,661	1·99	0·81 (0·57–1·15)	0·80 (0·56–1·14)	0·80 (0·56–1·14)
Rectal cancer							
No	470,490	6169	5,609,133	1·10	Reference	Reference	Reference
Yes	995	20	11,997	1·67	0·86 (0·55–1·33)	0·79 (0·51–1·23)	0·79 (0·51–1·22)
Prostate cancer§							
No	211,378	3194	2,519,178	1·27	Reference	Reference	Reference
Yes	3301	74	39,030	1·90	1·54 (1·22–1·94)	0·73 (0·58–0·92)	0·75 (0·59–0·94)
Ovarian cancer¶							
No	255,894	2908	3,052,049	0·95	Reference	Reference	Reference
Yes	912	13	10,874	1·20	0·91 (0·53–1·58)	0·88 (0·51–1·52)	0·88 (0·51–1·53)
Breast cancer¶							
No	245,944	2747	2,933,849	0·94	Reference	Reference	Reference
Yes	10,862	174	129,074	1·35	0·99 (0·85–1·15)	1·00 (0·86–1·17)	1·00 (0·86–1·16)
Uterine cancer							
No	470,098	6156	5,604,394	1·10	Reference	Reference	Reference
Yes	1387	33	16,737	1·97	1·26 (0·89–1·78)	1·22 (0·87–1·72)	1·22 (0·86–1·71)
Other cancers							
No	447,035	5777	5,327,435	1·08	Reference	Reference	Reference
Yes	24,450	412	293,695	1·40	1·03 (0·93–1·14)	1·01 (0·91–1·12)	1·01 (0·92–1·12)

***Table 2*: Risk for all-cause dementia associated with a wide range of diseases.**

APOE4, apolipoprotein E4; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; HR, hazard ratio.

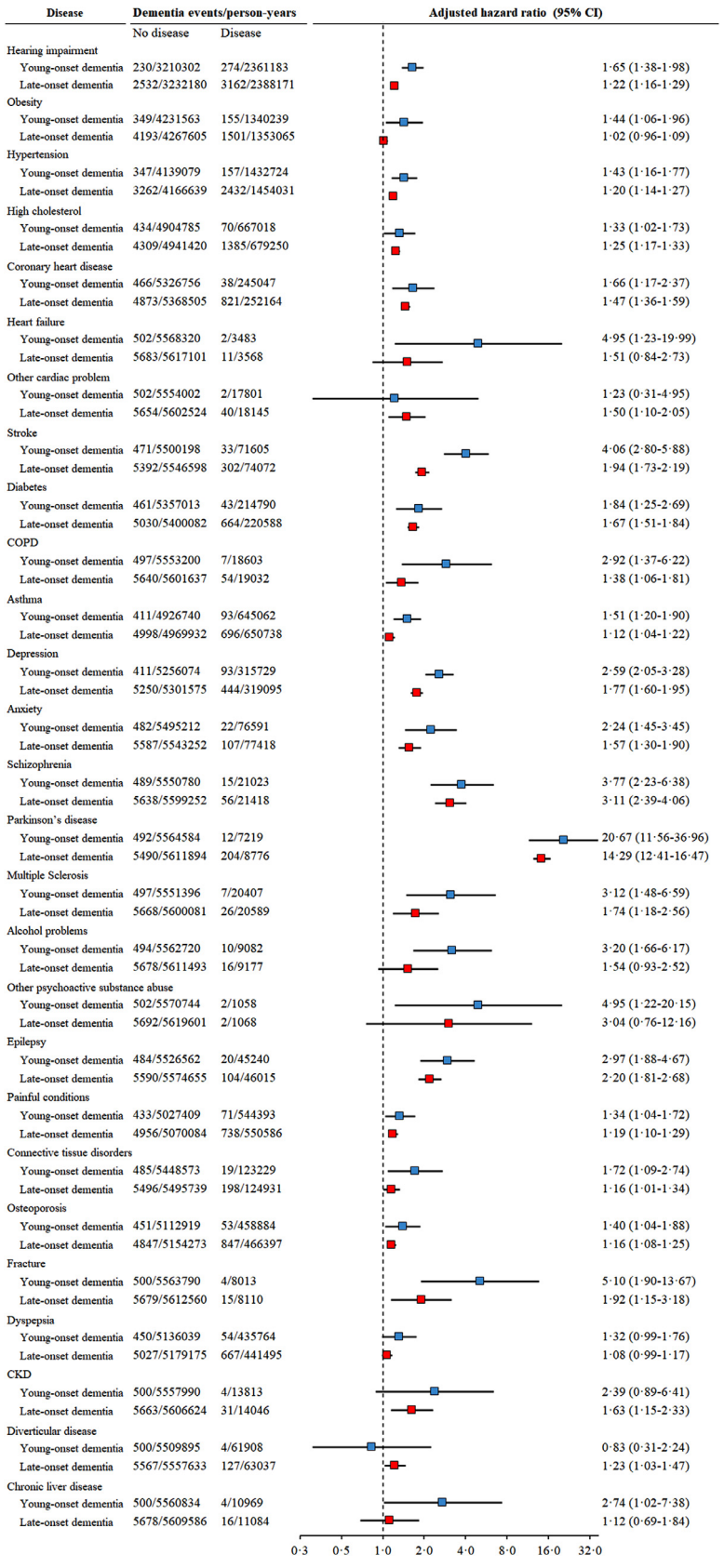
* Refers to number of cases per 1000 person-years.

† Cox proportional hazard regression models were used to examine the association between each of the 61 major diseases at baseline and incident dementia. Model 1 was adjusted for age and gender (Model 1 was unadjusted model for prostate cancer); Model 2 was adjusted for Model 1 plus education, income, BMI, smoking, physical activity, alcohol consumption, sleep duration, and diet; Model 3 was adjusted for blood pressure, HDL-C, LDL-C, triglycerides, and HbA1c.

ǂ Refers to statistically significant association in the multivariable-adjusted model after controlling false discovery rate.There are four steps to run the Benjamini-Hochberg procedure: (1) Rank *p*-values from the smallest to the largest; (2) Assign rank to the *p*-values; (3) Compute Benjamini-Hochberg critical value for each individual *p*-value: critical value = $\frac{i}{m} \times Q$, where i refers to the rank of the *p*-value, m refers to the total number of tests, and Q refers to the false discovery rate (0.05 in the present study); 4) Compare the original *p*-values to corresponding Benjamini-Hochberg critical values and find the largest *p*-value that is smaller than the critical value.

§ Analysis was conducted among males only.

¶ Analysis was conducted among females only.


Disease
Dementia events/person-years
No disease
Disease
Adjusted hazard ratio (95% CI)
Hearing impairment
Young-onset dementia 230/3210302 274/2361183 1·65 (1·38-1·98)
Late-onset dementia 2532/3232180 3162/2388171 1·22 (1·16-1·29)
Obesity
Young-onset dementia 349/4231563 155/1340239 1·44 (1·06-1·96)
Late-onset dementia 4193/4267605 1501/1353065 1·02 (0·96-1·09)
Hypertension
Young-onset dementia 347/4139079 157/1432724 1·43 (1·16-1·77)
Late-onset dementia 3262/4166639 2432/1454031 1·20 (1·14-1·27)
High cholesterol
Young-onset dementia 434/4904785 70/667018 1·33 (1·02-1·73)
Late-onset dementia 4309/4941420 1385/679250 1·25 (1·17-1·33)
Coronary heart disease
Young-onset dementia 466/5326756 38/245047 1·66 (1·17-2·37)
Late-onset dementia 4873/5368505 821/252164 1·47 (1·36-1·59)
Heart failure
Young-onset dementia 502/5568320 2/3483 4·95 (1·23-19·99)
Late-onset dementia 5683/5617101 11/3568 1·51 (0·84-2·73)
Other cardiac problem
Young-onset dementia 502/5554002 2/17801 1·23 (0·31-4·95)
Late-onset dementia 5654/5602524 40/18145 1·50 (1·10-2·05)
Stroke
Young-onset dementia 471/5500198 33/71605 4·06 (2·80-5·88)
Late-onset dementia 5392/5546598 302/74072 1·94 (1·73-2·19)
Diabetes
Young-onset dementia 461/5357013 43/214790 1·84 (1·25-2·69)
Late-onset dementia 5030/5400082 664/220588 1·67 (1·51-1·84)
COPD
Young-onset dementia 497/5553200 7/18603 2·92 (1·37-6·22)
Late-onset dementia 5640/5601637 54/19032 1·38 (1·06-1·81)
Asthma
Young-onset dementia 411/4926740 93/645062 1·51 (1·20-1·90)
Late-onset dementia 4998/4969932 696/650738 1·12 (1·04-1·22)
Depression
Young-onset dementia 411/5256074 93/315729 2·59 (2·05-3·28)
Late-onset dementia 5250/5301575 444/319095 1·77 (1·60-1·95)
Anxiety
Young-onset dementia 482/5495212 22/76591 2·24 (1·45-3·45)
Late-onset dementia 5587/5543252 107/77418 1·57 (1·30-1·90)
Schizophrenia
Young-onset dementia 489/5550780 15/21023 3·77 (2·23-6·38)
Late-onset dementia 5638/5599252 56/21418 3·11 (2·39-4·06)
Parkinson's disease
Young-onset dementia 492/5564584 12/7219 20·67 (11·56-36·96)
Late-onset dementia 5490/5611894 204/8776 14·29 (12·41-16·47)
Multiple Sclerosis
Young-onset dementia 497/5551396 7/20407 3·12 (1·48-6·59)
Late-onset dementia 5668/5600081 26/20589 1·74 (1·18-2·56)
Alcohol problems
Young-onset dementia 494/5562720 10/9082 3·20 (1·66-6·17)
Late-onset dementia 5678/5611493 16/9177 1·54 (0·93-2·52)
Other psychoactive substance abuse
Young-onset dementia 502/5570744 2/1058 4·95 (1·22-20·15)
Late-onset dementia 5692/5619601 2/1068 3·04 (0·76-12·16)
Epilepsy
Young-onset dementia 484/5526562 20/45240 2·97 (1·88-4·67)
Late-onset dementia 5590/5574655 104/46015 2·20 (1·81-2·68)
Painful conditions
Young-onset dementia 433/5027409 71/544393 1·34 (1·04-1·72)
Late-onset dementia 4956/5070084 738/550586 1·19 (1·10-1·29)
Connective tissue disorders
Young-onset dementia 485/5448573 19/123229 1·72 (1·09-2·74)
Late-onset dementia 5496/5495739 198/124931 1·16 (1·01-1·34)
Osteoporosis
Young-onset dementia 451/5112919 53/458884 1·40 (1·04-1·88)
Late-onset dementia 4847/5154273 847/466397 1·16 (1·08-1·25)
Fracture
Young-onset dementia 500/5563790 4/8013 5·10 (1·90-13·67)
Late-onset dementia 5679/5612560 15/8110 1·92 (1·15-3·18)
Dyspepsia
Young-onset dementia 450/5136039 54/435764 1·32 (0·99-1·76)
Late-onset dementia 5027/5179175 667/441495 1·08 (0·99-1·17)
CKD
Young-onset dementia 500/5557990 4/13813 2·39 (0·89-6·41)
Late-onset dementia 5663/5606624 31/14046 1·63 (1·15-2·33)
Diverticular disease
Young-onset dementia 500/5509895 4/61908 0·83 (0·31-2·24)
Late-onset dementia 5567/5557633 127/63037 1·23 (1·03-1·47)
Chronic liver disease
Young-onset dementia 500/5560834 4/10969 2·74 (1·02-7·38)
Late-onset dementia 5678/5609586 16/11084 1·12 (0·69-1·84)
0·3
0·5
1·0
2·0
4·0
8·0
16·0
32·0

fibrillation was a risk factor for late-onset dementia (1·45 (1·28–1·65)) but not young-onset dementia (0·91 (0·41 –2·05)). Diverticular disease was associated with an increased risk of late-onset dementia (1·21 (1·08–1·35)), but not young-onset dementia (1·09 (0·61–1·94), Figure 1). These diseases were greater contributors to young-onset dementia than to late-onset dementia (Fig. S1).

Multimorbidity and incident dementia

Thirty-three diseases with statistically significant association with dementia (listed in Table 2) were used to identify multimorbidity. Individuals with zero disease had a higher survival probability from dementia during follow-up compared to those with one or more diseases (Fig. S3). In the multivariable analysis, a larger number of diseases was associated with larger HR for incident dementia, AD, and VD. The HR associated with multimorbidity was larger for young-onset dementia than for late-onset dementia (Figure 2). PAR (95% CI) of multimorbidity was 51·2% (45·5–56·3%) for all dementia, 64·7% (49·9–75·2%) for young-onset dementia, and 47·4% (40·8–53·2%) for late-onset dementia (data not shown).

APOE4 and dementia

Non-APOE4 carriers had a higher survival probability from dementia during follow-up compared with APOE4 carriers (Fig. S4). As shown in Table 3, HRs (95% CIs) for all-cause dementiaassociated with APOE4 was 2·73 (2·59–2·87). The association was stronger for AD (HR (95% CI): 3·69 (3·41–4·00)) than for VD (2·52 (2·26 –2·81)). APOE4 was a stronger predictor for late-onset dementia (HR (95% CI): 2·90 (2·75–3·06)) but not for young-onset dementia (1·26 (1·03–1·54)).

Multimorbidity risk score

As shown in Fig. S5, multimorbidity, FRS, and CAIDE risk scores showed similar prediction performance. When age/APOE4 was incorporated into the risk score calculation, any multimorbidity score performed better than conventional ones. Multimorbidity+age+APOE4 risk score had the highest prediction performance (AUC (95% CI): 82·2% (81·7–82·7%)) followed by multimorbidity plus age (80·9% (80·5–81·4%)) and multimorbidity plus APOE4 scores (73·0% (72·4 –73·7%), Table S8).

Interaction between APOE4, individual diseases, and multimorbidity for dementia

Statistically significant interaction was observed between APOE4 and painful conditions, depression, psychoactive substance abuse, Parkinson's disease, obesity, diabetes, stroke, or high cholesterol for incident dementia. The association between all these individual diseases and incident dementia was stronger among non-APOE4 carriers (Figure 3).

The association between multimorbidity and incident dementia was stronger among non-APOE4-carriers (*P*-value for interaction<0·0001). In non-APOE4 carriers, individuals with one to ≥six diseases were 1·43 (1·21–1·68), 1·85 (1·58–2·17), 2·30 (1·96–2·71), 2·53 (2·12–3·00), 3·24 (2·70–3·89), 5·01 (4·21–5·96) times more likely to develop dementia compared to those with no observed disease. The corresponding number for APOE4 carriers were 1·12 (0·95–1·30), 1·38 (1·18–1·61), 1·51 (1·28–1·77), 1·69 (1·42–2·01), 2·47 (2·06–2·97), and 2·84 (2·36–3·41), respectively (Figure 4).

APOE4 was a predictor for all-cause dementia across subgroups of disease number, but HR decreased with the accumulation of diseases. PAR of APOE4 for dementia decreased from 39·6% (95% CI: 33·4–45·7%) among individuals with zero disease to 19·6% (15·3 –23·9%) among those with ≥6 diseases (Fig. S6).

Sensitivity analysis

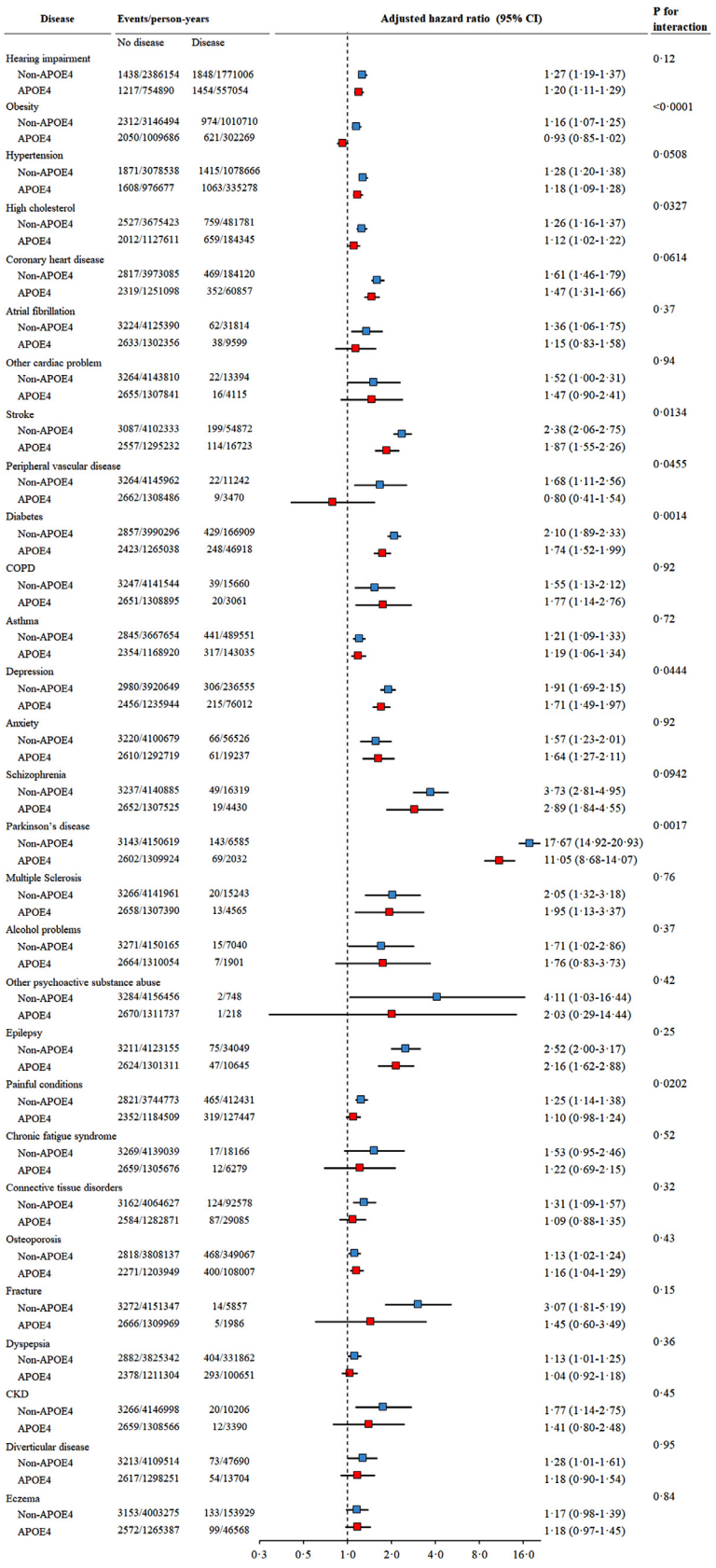
The association between multimorbidity and incident dementia was not moderated by education (*P*-value for interaction = 0·15) or household income (*P*-value for interaction = 0·0568). The association was statistically significant across subgroups of these socioeconomic factors (Table S9). There was a statistically significant interaction between multimorbidity and age for incident dementia (*P*-value < 0·0001). Although multimorbidity was more predictive of dementia in younger than in older individuals, this association was statistically significant among older adults (Table S10).

We repeated the analysis for associations between individual diseases and dementia by excluding those

Figure 1. Risk for young-onset and late-onset dementia associated with individual major diseases

CI, confidence interval; CKD, chronic kidney disease; COPD, Chronic obstructive pulmonary disease.

Young-onset dementia was defined as dementia diagnosed <65 years, and the analysis was conducted among individuals aged younger than 65 years at baseline. Late-onset dementia was defined as dementia diagnosed ≥65 years, and the analysis was conducted among individuals aged older than 65 years at the end of follow-up. Cox proportional hazard regression models were used to examine the association between individual diseases and the incidence of young-onset and late-onset dementia. Analysis was adjusted for age, gender, education, income, BMI, smoking, physical activity, alcohol consumption, sleep duration, diet, blood pressure, HDL-C, LDL-C, triglycerides, and HbA1c. Horizontal lines indicate the ranges of the 95% CIs and the vertical dash lines indicate the hazard ratio of 1·0.


Disease
Events/person-years
No disease
Disease
Adjusted hazard ratio (95% CI)
P for interaction
Hearing impairment 0·12
Non-APOE4 1438/2386154 1848/1771006 1·27 (1·19-1·37)
APOE4 1217/754890 1454/557054 1·20 (1·11-1·29)
Obesity <0·0001
Non-APOE4 2312/3146494 974/1010710 1·16 (1·07-1·25)
APOE4 2050/1009686 621/302269 0·93 (0·85-1·02)
Hypertension 0·0508
Non-APOE4 1871/3078538 1415/1078666 1·28 (1·20-1·38)
APOE4 1608/976677 1063/335278 1·18 (1·09-1·28)
High cholesterol 0·0327
Non-APOE4 2527/3675423 759/481781 1·26 (1·16-1·37)
APOE4 2012/1127611 659/184345 1·12 (1·02-1·22)
Coronary heart disease 0·0614
Non-APOE4 2817/3973085 469/184120 1·61 (1·46-1·79)
APOE4 2319/1251098 352/60857 1·47 (1·31-1·66)
Atrial fibrillation 0·37
Non-APOE4 3224/4125390 62/31814 1·36 (1·06-1·75)
APOE4 2633/1302356 38/9599 1·15 (0·83-1·58)
Other cardiac problem 0·94
Non-APOE4 3264/4143810 22/13394 1·52 (1·00-2·31)
APOE4 2655/1307841 16/4115 1·47 (0·90-2·41)
Stroke 0·0134
Non-APOE4 3087/4102333 199/54872 2·38 (2·06-2·75)
APOE4 2557/1295232 114/16723 1·87 (1·55-2·26)
Peripheral vascular disease 0·0455
Non-APOE4 3264/4145962 22/11242 1·68 (1·11-2·56)
APOE4 2662/1308486 9/3470 0·80 (0·41-1·54)
Diabetes 0·0014
Non-APOE4 2857/3990296 429/166909 2·10 (1·89-2·33)
APOE4 2423/1265038 248/46918 1·74 (1·52-1·99)
COPD 0·92
Non-APOE4 3247/4141544 39/15660 1·55 (1·13-2·12)
APOE4 2651/1308895 20/3061 1·77 (1·14-2·76)
Asthma 0·72
Non-APOE4 2845/3667654 441/489551 1·21 (1·09-1·33)
APOE4 2354/1168920 317/143035 1·19 (1·06-1·34)
Depression 0·0444
Non-APOE4 2980/3920649 306/236555 1·91 (1·69-2·15)
APOE4 2456/1235944 215/76012 1·71 (1·49-1·97)
Anxiety 0·92
Non-APOE4 3220/4100679 66/56526 1·57 (1·23-2·01)
APOE4 2610/1292719 61/19237 1·64 (1·27-2·11)
Schizophrenia 0·0942
Non-APOE4 3237/4140885 49/16319 3·73 (2·81-4·95)
APOE4 2652/1307525 19/4430 2·89 (1·84-4·55)
Parkinson's disease 0·0017
Non-APOE4 3143/4150619 143/6585 17·67 (14·92-20·93)
APOE4 2602/1309924 69/2032 11·05 (8·68-14·07)
Multiple Sclerosis 0·76
Non-APOE4 3266/4141961 20/15243 2·05 (1·32-3·18)
APOE4 2658/1307390 13/4565 1·95 (1·13-3·37)
Alcohol problems 0·37
Non-APOE4 3271/4150165 15/7040 1·71 (1·02-2·86)
APOE4 2664/1310054 7/1901 1·76 (0·83-3·73)
Other psychoactive substance abuse 0·42
Non-APOE4 3284/4156456 2/748 4·11 (1·03-16·44)
APOE4 2670/1311737 1/218 2·03 (0·29-14·44)
Epilepsy 0·25
Non-APOE4 3211/4123155 75/34049 2·52 (2·00-3·17)
APOE4 2624/1301311 47/10645 2·16 (1·62-2·88)
Painful conditions 0·0202
Non-APOE4 2821/3744773 465/412431 1·25 (1·14-1·38)
APOE4 2352/1184509 319/127447 1·10 (0·98-1·24)
Chronic fatigue syndrome 0·52
Non-APOE4 3269/4139039 17/18166 1·53 (0·95-2·46)
APOE4 2659/1305676 12/6279 1·22 (0·69-2·15)
Connective tissue disorders 0·32
Non-APOE4 3162/4064627 124/92578 1·31 (1·09-1·57)
APOE4 2584/1282871 87/29085 1·09 (0·88-1·35)
Osteoporosis 0·43
Non-APOE4 2818/3808137 468/349067 1·13 (1·02-1·24)
APOE4 2271/1203949 400/108007 1·16 (1·04-1·29)
Fracture 0·15
Non-APOE4 3272/4151347 14/5857 3·07 (1·81-5·19)
APOE4 2666/1309969 5/1986 1·45 (0·60-3·49)
Dyspepsia 0·36
Non-APOE4 2882/3825342 404/331862 1·13 (1·01-1·25)
APOE4 2378/1211304 293/100651 1·04 (0·92-1·18)
CKD 0·45
Non-APOE4 3266/4146998 20/10206 1·77 (1·14-2·75)
APOE4 2659/1308566 12/3390 1·41 (0·80-2·48)
Diverticular disease 0·95
Non-APOE4 3213/4109514 73/47690 1·28 (1·01-1·61)
APOE4 2617/1298251 54/13704 1·18 (0·90-1·54)
Eczema 0·84
Non-APOE4 3153/4003275 133/153929 1·17 (0·98-1·39)
APOE4 2572/1265387 99/46568 1·18 (0·97-1·45)
0·3
0·5
1·0
2·0
4·0
8·0
16·0

	Events/person-years		Incidence rate*		HR (95% CI),	HR (95% CI),	HR (95% CI),
	Non-APOE4 Carriers	APOE4 carriers	Non-APOE4 carriers	APOE4 carriers	Model 1†	Model 2	Model 3
All-cause dementia							
All	3281/4,155,062	2667/1,311,270	0·79	2·03	2·65 (2·52–2·79)	2·67 (2·54–2·81)	2·73 (2·59–2·87)
Young-onset‡	349/3,335,485	131/1,053,453	0·10	0·12	1·19 (0·97–1·45)	1·23 (1·00–1·50)	1·26 (1·03–1·54)
Late-onset§	2932/2,798,517	2536/874,175	1·05	2·90	2·83 (2·69–2·99)	2·85 (2·70–3·01)	2·90 (2·75–3·06)
AD							
All	1172/4,161,795	1322/1,315,407	0·28	1·01	3·64 (3·37–3·94)	3·64 (3·36–3·93)	3·69 (3·41–4·00)
Young-onset	97/3,335,485	47/1,053,453	0·03	0·04	1·53 (1·08–2·17)	1·55 (1·09–2·20)	1·58 (1·11–2·24)
Late-onset	1075/2,798,517	1275/874,175	0·38	1·46	3·88 (3·58–4·21)	3·87 (3·57–4·20)	3·93 (3·62–4·27)
VD							
All	758/4,162,776	565/1,317,422	0·18	0·43	2·41 (2·16–2·68)	2·45 (2·19–2·73)	2·52 (2·26–2·81)
Young-onset	56/3,335,485	20/1,053,453	0·02	0·02	1·14 (0·68–1·89)	1·19 (0·71–1·98)	1·27 (0·76–2·13)
Late-onset	702/2,798,517	545/874,175	0·25	0·62	2·55 (2·28–2·85)	2·60 (2·32–2·91)	2·67 (2·39–2·99)

***Table 3*: Risk for dementia associated with APOE4.**

AD, Alzheimer's disease; APOE4, apolipoprotein E4; CI, confidence interval; HR, hazard ratio; VD, vascular dementia.

* Refers to number of cases per 1000 person-years.

† Cox proportional hazard regression models were used to examine the association between APOE4 and incident dementia. Model 1 was adjusted for age and gender; Model 2 was adjusted for Model 1 plus education, income, BMI, smoking, physical activity, alcohol consumption, sleep duration, and diet; Model 3 was adjusted for blood pressure, HDL-C, LDL-C, triglycerides, and HbA1c.

‡ Young-onset dementia was defined as dementia diagnosed <65 years. The analysis was conducted among individuals aged younger than 65 years at baseline.

§ Late-onset dementia was defined as dementia diagnosed ≥65 years. The analysis was conducted among individuals aged older than 65 years at the end of follow-up.

who developed dementia in the first five years of follow-up. In the multivariable-adjusted analysis, 32 diseases were statistically significantly associated with the risk of dementia. Of these diseases, 30 were overlapped with the 33 diseases identified in the main analysis. Obesity (HR (95% CI): 1·08 (0·99–1·19)) was not statistically significantly associated with dementia. Whilst stomach cancer (HR (95% CI): 1·84 (1·07–3·17)) was associated with an increased risk of dementia in the sensitivity analysis where this association was not statistically significant in the main analysis (Table S11).

The number of diagnosed dementia cases dropped off in 2020 (Table S12). The association between multimorbidity and incident all-cause dementia did not substantially change whether the dementia cases diagnosed in 2020 were included in the analysis or not (Table S13). Similarly, the difference in HRs for dementia associated with APOE4 was minimal between different cut-offs for follow-up (Table S14).

Discussion

In this large population of community-dwelling adults, we found 33 out of 63 diseases were associated with an increased risk of incident dementia. Traditional risk factors including obesity, diabetes, hypertension, hearing impairment, and depression were leading contributors to dementia. In addition to these conventional diseases, cardiovascular disease (coronary heart disease, heart failure, and stroke), respiratory disorders (COPD and asthma), musculoskeletal disorders (osteoarthritis, fracture, and connective tissue disorders), digestive disorders (diverticulitis and dyspepsia), painful conditions, and CKD were found to be risk factors of dementia. The larger number of diseases the larger HR for incident dementia was observed. The dementia risk score of multimorbidity incorporating age/APOE4 had better prediction performance than conventional scores. These associations were stronger among non-APOE4 carriers than in APOE4 carriers. Individual diseases and

Figure 2. Risk for dementia associated with the number of diseases at baseline. CI, confidence interval. Young-onset dementia was defined as dementia diagnosed <65 years, and the analysis was conducted among individuals aged younger than 65 years at baseline. Late-onset dementia was defined as dementia diagnosed ≥65 years, and the analysis was conducted among individuals aged older than 65 years at the end of follow-up. Cox proportional hazard regression models were used to examine the association between the number of diseases at baseline (statistically significantly associated with dementia in multivariable-adjusted analysis in Table 2) and incident dementia. The analysis was adjusted for age, gender, education, income, BMI, smoking, physical activity, alcohol consumption, sleep duration, diet, blood pressure, HDL-C, LDL-C, triglycerides, and HbA1c. Reference was the group with no disease of interest at baseline. Horizontal lines indicate the ranges of 95% CIs.

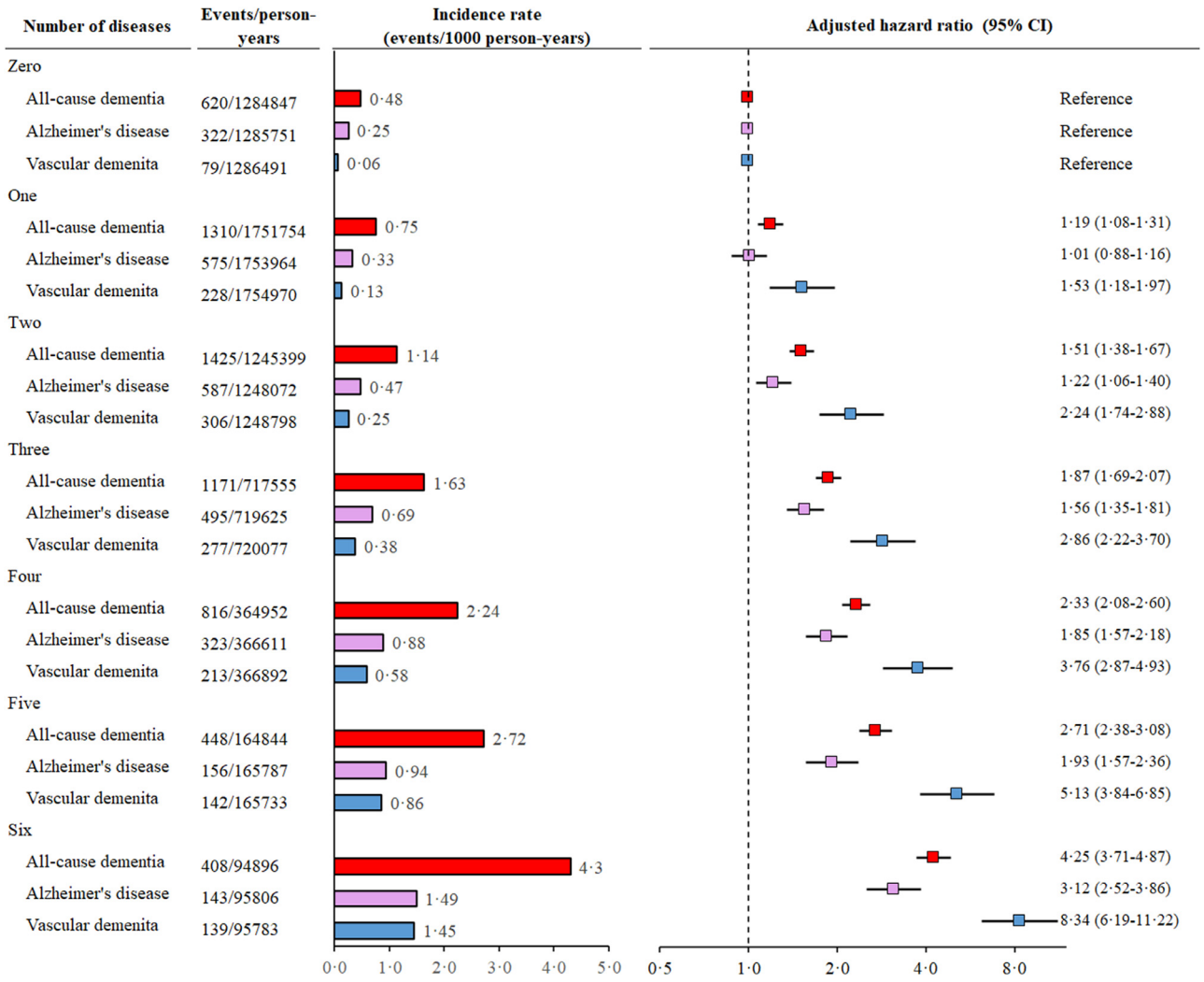


Figure 3. Interaction between individual major diseases and APOE4 for incident dementia. APOE4, apolipoprotein E4; CI, confidence interval; CKD, chronic kidney disease; COPD, Chronic obstructive pulmonary disease. Cox proportional hazard regression models were used to examine the association between individual diseases and incident dementia stratified by APOE4. Analysis was adjusted for age, gender, education, income, BMI, smoking, physical activity, alcohol consumption, sleep duration, diet, blood pressure, HDL-C, LDL-C, triglycerides, and HbA1c. Horizontal lines indicate the ranges of the 95% CIs and the vertical dash lines indicate the hazard ratio of 1·0.

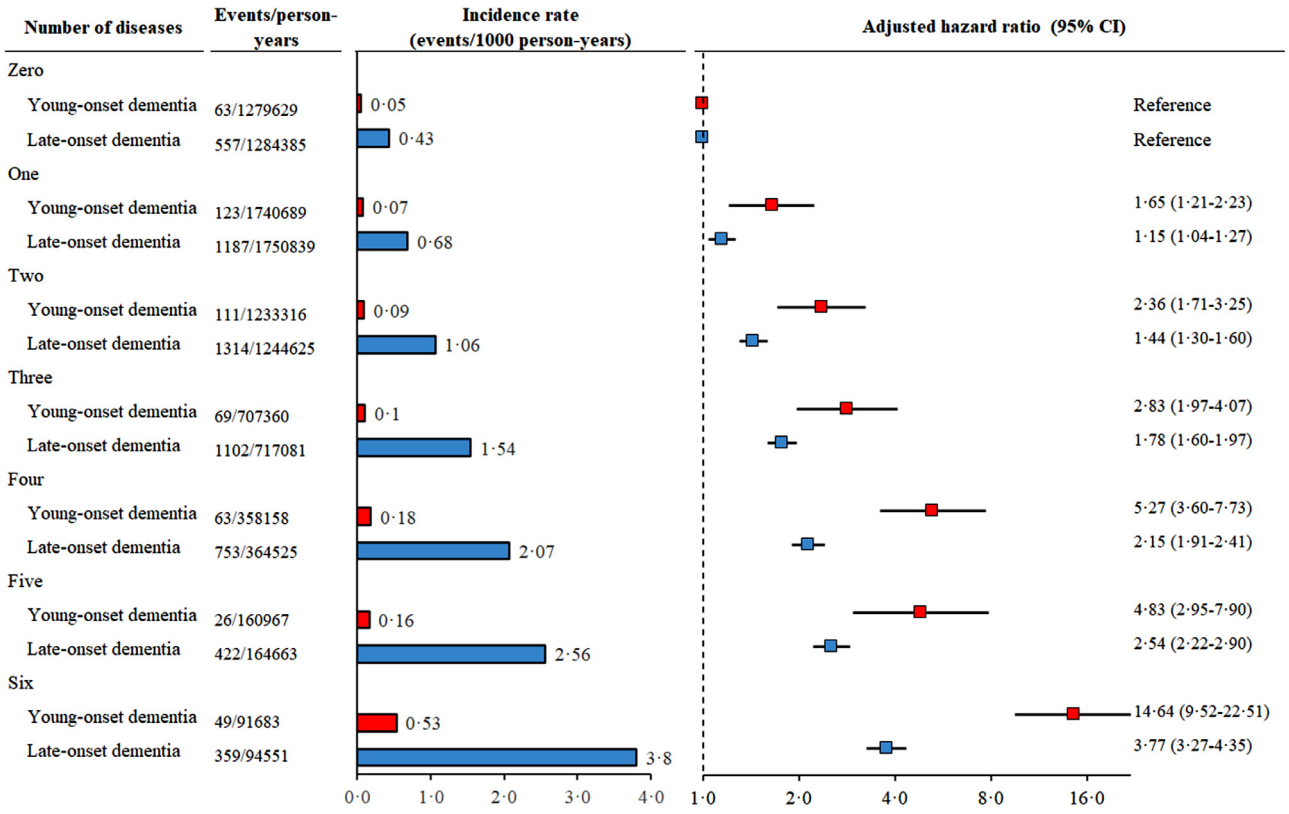


Figure 4. Interaction between APOE4 and multimorbidity with incident dementia. APOE4, apolipoprotein E4; CI, confidence interval; PAR, population attributable risk. *P*-value for interaction between APOE4 and multimorbidity was less than 0·0001 and stratified analysis was conducted. Cox proportional hazard regression models were used to examine the association between the number of diseases at baseline and incident dementia. The analysis was adjusted for age, gender, education, income, BMI, smoking, physical activity, alcohol consumption, sleep duration, diet, blood pressure, HDL-C, LDL-C, triglycerides, and HbA1c. Reference was the group with no disease of interest at baseline. Horizontal lines indicate the ranges of 95% CIs.

multimorbidity were more predictive of young-onset dementia than of late-onset dementia.

The present study has several limitations. Firstly, there may be recall bias for the definition of major diseases using self-reported and inpatient hospital data, which may result in an underestimated prevalence of these diseases. However, this is more likely to bias the association towards the null. Secondly, some cases of all-cause dementia might not be captured in the medical records or death registers. However, previous research has shown that there is a good agreement between dementia case ascertainment with primary care records.[26] Thirdly, because of the observational design of our study, causal relationships cannot be established based on our findings. Fourthly, as the prodromal period of dementia can last many years,[27] dementia might have occurred before the diagnosis of chronic conditions. However, our sensitivity analysis by excluding individuals with dementia developed in the first five years of follow-up showed similar results compared with the main findings. This may have helped rule out reverse causation to some extent. Fifthly, many individuals may have had mild cognitive impairment at baseline. This might have biased the associations, although those with cognitive impairment were excluded from the analysis in a subgroup with corresponding cognitive tests. Sixthly, although multiple risk factors for dementia were adjusted for in the analysis, potential confounding from other sources such as levels of beta-amyloid was unpreventable. Seventhly, our findings might be impacted by COVID-19. However, the sensitivity analysis demonstrated the results by setting the cut-off of follow-up at the end of 2019 were similar to those for the main analysis. Finally, the analysis was restricted to European ancestry participants, thus, our findings especially the multimorbidity risk score for dementia need to be validated in other ethnic groups.

Our research together with previous studies have confirmed the importance of conventional diseases for the development of dementia.[28] In addition to conventional cardiometabolic disorders, stroke, high cholesterol, coronary heart disease, heart failure, and other cardiac problem conferred risk of dementia. This is not surprising as cardiometabolic disorders and dementia may share pathology.[29] Long-term exposure to high blood pressure and cholesterol may increase motor stiffness and reduce compliance,[29,30] and reduce cerebral blood flow and increase cerebrovascular reactivity[28,30] thus resulting in brain damage. Besides depression, numerous psychological and mental disorders including anxiety, schizophrenia, Parkinson's disease, multiple sclerosis, alcohol problems, psychoactive substance abuse, and epilepsy were linked to dementia risk. It could be expected that so many psychological and mental disorders were associated with an increased risk of dementia considering that they shared pathology and numerous risk factors.[18,31,32] In line with previous study,[2] although hearing impairment is not among the diseases with the largest HRs, it is the leading contributor to dementia given its high prevalence in our study. Our study underlines the importance of cardiometabolic disorders, psychological and mental disorders, and hearing impairment on the development of dementia.

Less is known regarding whether other diseases confer risk for the development of dementia. In addition to conventional risk factors, multiple diseases have been linked to dementia in a recent prospective study[13]; however, this study is limited by investigating only 22 hospitalized physical diseases and identifying 8 physical diseases associated with increased dementia risk. We found multiple musculoskeletal disorders (osteoporosis, fracture, and connective tissue disorders), and painful conditions (headache, joint pain) were associated with increased dementia risk, which is consistent with previous studies.[9,13] These associations might be attributed to the fact that individuals with musculoskeletal disorders or painful conditions were less likely to exercise and participate in social activity resulting in an increased risk of dementia. The association between fracture and dementia may be contributed to shared risk factors including APOE4, low levels of physical activity, and vitamin D.[33] Whilst fracture as an independent risk factor of dementia has been reported in several studies.[34,35] Respiratory disorders (COPD and asthma) were also linked to increased dementia in our study. Although the underlying mechanisms are unclear, our study is supported by recent evidence that poor pulmonary function might accelerate cognitive decline.[10,11] Our study is consistent with a previous study demonstrating that digestive disorders (diverticulitis and dyspepsia) were associated with a higher risk of dementia.[13] Inflammation in those with digestive disorders might increase the risk of dementia. In line with previous study,[12] we found CKD was a risk factor for dementia, which might be attributed to shared vascular risk factors and inflammation between CKD and dementia.[36] Our findings suggest respiratory, musculoskeletal, and digestive disorders, painful conditions, and CKD may also play an important role in the development of dementia. In line with our research, several studies have shown that eczema was associated with an increased risk of dementia and decreased cognitive function.[37,38] Eczema is associated with itch, pain, sleep disturbance, depression, and psychological distress,[39] all of which may contribute toward cognitive dysfunction/dementia.

Multimorbidity should not be overlooked given its high prevalence and detrimental effect on health in adults.[40] We found 51·6% of participants had multimorbidity and a larger number of diseases was associated with larger HR for dementia. Individuals with ≥6 diseases were around four times more likely to develop dementia, and around 51·2% of incident dementia was attributed to one or more observed diseases. The score

of multimorbidity incorporating with age was more accurate in dementia prediction than conventional risk scores suggesting a tool based on self-reported information only might be greatly useful for targeting intervention priorities. Only few studies have investigated the association between multimorbidity and incident dementia.[41,42] These studies agree with our research highlighting the importance of multimorbidity on the development of dementia. Further analysis shows, with the accumulation of disease, the development of dementia is becoming less determined by genetics (APOE4). One recent study has examined the role of genetics on the association between multimorbidity and dementia but did not find a statistically significant association.[41] Two previous studies showed that APOE4 might modify the association of diabetes and depression with dementia or cognitive decline.[43,44] A prospective study of 3444 older adults from the USA has reported that stroke was associated with greater cognitive decline among non-APOE4 carriers but not APOE4 carriers.[45] Likely, we found the association of multimorbidity, hypertension, high cholesterol, diabetes, stroke, depression, Parkinson's disease, and painful conditions with dementia was stronger in non-APOE4 carriers than in APOE4 carriers. Our findings suggest the importance of the prevention or delay the development of these diseases and their multimorbidity for minimizing dementia risk, especially in non-APOE4 carriers although APOE4 carriers with multimorbidity had a higher risk of dementia.

Although the prevalence was low,[18] young-onset dementia might be more detrimental as it affects individuals in the midst of their careers. We found young-onset dementia than late-onset dementia was less determined by APOE4. This is consistent with previous studies showing that APOE4 plays a more important role in AD in older than in younger individuals.[14,15] The relative risk for young-onset dementia associated with 29 diseases was larger than that for late-onset dementia. Besides these diseases, chronic liver disease was associated with an increased risk of young-onset dementia but not late-onset dementia. Similarly, a larger relative risk for young-onset dementia associated with multimorbidity was observed for late-onset dementia. Although several diseases have been associated with increased young-onset dementia risk,[46] our study provides evidence on a wide range of diseases as modifiable risk factors for young-onset dementia. This is important as genetics (APOE4) is less predictive of young-onset dementia.

We found a wide range of major chronic diseases (some have not been investigated previously) that might play an important role in the development of dementia. This may help identify individuals at higher risk of dementia. Notably, we created a multimorbidity risk score (plus age and APOE4) with better prediction performance of dementia than conventional risk scores, which would help clinicians to make plans for the prevention of dementia among patients with specific chronic diseases/multimorbidity. To our knowledge, this is the first study to examine the interaction between multiple diseases and multimorbidity and APOE4 for incident dementia. This provides evidence on priority for the emerging anti-APOE4 therapy.[16] This study also uniquely examined associations between diseases/APOE4 and young-onset and late-onset dementia, which is important for a better understanding of the underlying mechanisms of dementia.

In conclusion, 33 well-known and emerging diseases are associated with an increased risk of dementia. A larger number of these diseases is associated with a larger excessive relative risk for dementia. The multimorbidity risk score may be useful for the prediction and screening of dementia. These associations are stronger among non-APOE4 carriers. APOE4 is a strong predictor of dementia, but this association is attenuated with the accumulation of diseases. A larger relative risk associated with individual diseases and their multimorbidity is observed for young-onset dementia than for late-onset dementia, whereas APOE4 is a strong predictor for late-onset but not young-onset dementia. These findings may facilitate the identification of individuals at higher risk of dementia.

Contributors

XS, and MH conceived and designed the study. XS, ZZ, and WW verified the data. XS conducted data analysis, data interpretation and drafted the initial manuscript. XS, ZZ, XLZ, YH, XYZ, JL, HY, WW, ST, ZG, XY, and MH made critical revisions of the manuscript for important intellectual content. All authors read the manuscript and approved the final draft. All authors should confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

Data sharing statement

Data are available in a public, open access repository (https://www.ukbiobank.ac.uk/). The present study was conducted under application number 62,443 of the UK Biobank resource.

Declaration of interests

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101335.

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