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Disease trajectories before dementia: evidence from a large-scale community-based prospective study

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Background

Systemic changes in multiple diseases may influence the onset of dementia. However, the specific temporality between exposure diseases and dementia remains uncertain.

Aims

By characterising the full spectrum of temporal disease trajectories before dementia, this study aims to yield a global picture of precursor diseases to dementia and to provide detailed instructions for risk management and primary prevention of dementia.

Method

Using the multicentre, community-based prospective UK Biobank, we constructed disease trajectories before dementia utilising the phenome-wide association analysis, paired directional test and association quantification. Stratified disease trajectories were constructed by dementia subtypes, gender, age of diagnosis and Apolipoprotein E (*ApoE*) status, respectively.

Results

Our study population comprised 434 266 participants without baseline dementia and 4638 individuals with all-cause dementia. In total, 1253 diseases were extracted as potential components of the disease trajectory before dementia. We identified three clusters of disease trajectories preceding all-cause dementia, initiated by circulatory, metabolic and respiratory diseases occurring approximately 5–15 years before dementia. Cerebral infarction or chronic renal failure following chronic ischaemic heart disease was the specific trajectory before vascular dementia. Apolipoprotein E (*ApoE*) ε4 non-carriers exhibited more complex trajectories compared with carriers. Lipid metabolism disorders remained in the trajectories regardless of dementia subtypes, gender, age of diagnosis and *ApoE* status.

Conclusions

This study provides a comprehensive view of the longitudinal disease trajectories before dementia and highlights the potential targets of midlife cardiometabolic dysfunction for dementia screening and prevention.

Keywords

Dementia; Alzheimer's disease; vascular dementia; disease trajectory; cohort study.

Dementia is a common and irreversible neurodegenerative disorder, affecting 57.4 million people worldwide in 2019.[1] The escalating disease burden is amplified by the combination of the ageing population and increased life expectancy.[1] The heterogeneous etiologies, symptoms and the dynamic continuum spanning the last two decades intensify the challenges and uncertainties for dementia management.[2,3] Because of the absence of effective therapies, identifying risk factors and then early monitoring and prevention are pivotal to alleviate the disease burden of dementia.

Multimorbidity, the coexistence of two or more chronic medical conditions, is highly prevalent in the older population, and people with dementia frequently present with other chronic diseases.[4] Previous meta-analyses of prospective studies have identified several diseases associated with an increased risk of dementia, such as diabetes,[5] hypertension[6] and depression.[7] However, these hypothesis-driven studies had a restricted scope and provided limited evidence in underestimating the complex interactions of health conditions during the development of dementia in a long time span. Recently, several studies based on large-scale population cohorts treated multimorbidity as an exposure mixture, demonstrating that the count and pattern of precursor diseases were associated with the increased risks of subsequent cognitive decline and dementia.[8–13] For instance, participants with a cardiovascular multimorbidity pattern had a 1.7-fold increased risk of progression from cognitive impairment to dementia after an 18-year follow-up, compared with those with an unspecific pattern at baseline.[10]

Previous studies have suggested the significance of exploring the association between precursor diseases and incident dementia for understanding the developmental trajectories to dementia. However, these studies usually preselected the components of multimorbidity, by including only common chronic diseases,[11–13] leading to the loss of instructive information on hub diseases. Furthermore, multimorbidity patterns were often cross-sectional snapshots using baseline health conditions,[10,11,13] limiting the evidence in identifying the longitudinal orders of disease diagnoses. Therefore, the temporal and causal relationships between precursor diseases and dementia remain unclear and warrant further investigation.

The disease trajectory was recently proposed to investigate significant longitudinal relationships between diseases, typically applied to chronic diseases in population-based studies, such as precancerous conditions.[14,15] The trajectories suggested by the data-driven approach have temporal directionality and statistical significance, laying the groundwork for understanding disease progression and building novel hypotheses. The UK Biobank (UKB) is a large national database enrolling half a million UK individuals from 2006 and encompassing multidimensional health-related surveys, in-depth genetic data and periodically updated linked records.[16] This study applied the disease trajectory to the UKB data-set with a long-time span and large sample size, aiming to characterise the complete spectrum of temporal disease trajectories and the timeline of disease diagnoses before dementia. The specific trajectories, stratified by dementia subtypes, gender, age of dementia diagnosis and genetic risk were also mapped to yield a global picture of precursor diseases to dementia and

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provide detailed instructions for risk management and primary prevention of dementia.

Method

Study design and population

The present study utilised data from the UKB, a large-scale prospective cohort study that recruited participants aged 37–73 between 2006 and 2010. Participants completed a baseline assessment including touchscreen questionnaires, verbal interviews, physical examinations and biospecimen collection. Detailed design and data resources are described elsewhere.[16] The UKB received ethical approval from the National Health Service North West Centre for Research Ethics Committee, and all participants provided electronically signed informed consent. This study was conducted under application number 92 718 for UKB resources. Given that the UKB hospitalisation data have covered the majority (96%) of participants since 1997,[16] we set the start date for medical condition records as 1 January 1997 and the end date as 31 December 2019, to avoid the influence of the COVID-19 pandemic. The detailed participant selection procedure and study flowchart are presented in Fig. 1 and Supplementary 1 available at https://doi.org/10.1192/bjp.2024.122. Finally, our study population comprised 434 266 participants without baseline dementia and 4638 individuals with all-cause dementia (ACD).

Transparency declaration

The authors ensure that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ascertainment of dementia

For incident dementia case ascertainment, the earliest records of ACD, Alzheimer's disease and vascular dementia (VaD) were extracted from algorithmically defined dementia outcomes (Field ID 42018-42023), which were developed based on sources from self-reports, hospital admissions and death registers. A validation study reported a positive predictive value of 82.5% for ACD when combining data from primary care, hospital and mortality records.[17] Therefore, dementia records from primary care were supplemented using first occurrence (Category 1712). Specifically, International Classification of Diseases, Tenth Revision (ICD-10) codes F00, F01, F02, F03 and G30 were classified as ACD, F00 and G30 as Alzheimer's disease, and F01 as VaD. The date of death (Field ID40 000), loss to follow-up (Field ID 191) or the end of the study (31 December 2019), whichever occurred first, was considered the end of follow-up. Incident dementia and its subtypes were identified after the date of baseline assessment (Field ID 52).

Records of exposure medical conditions

Except for dementia outcomes, other medical conditions represented by ICD-10 codes were also extracted from first occurrence and the cancer register. In total, 1253 medical records were extracted as potential components of the disease trajectory before dementia, and the full name of the disease codes is presented in Supplementary Table 1. Diseases originating in the perinatal period and congenital diseases (Chapters P and Q in ICD-10) were excluded from the analysis because of their incomplete records before the full coverage of clinical linked data. A detailed study flowchart is shown in Fig. 1(b).

Statistical analysis

Disease trajectory analysis

The disease trajectories before dementia diagnosis were mapped based on disease pairs with statistical significance and temporal directionality among people with dementia. With reference to previous studies on disease trajectory,[14,18,19] three progressive critical steps were incorporated to establish and combine disease pairs to map the sequent trajectories (Fig. 1(a)). (a) Precursor diseases filtration: a phenome-wide association analysis (PheWAS) was conducted in the entire study population, with dementia as the outcome (D2) and other diseases as exposures (D1). The Cox proportional hazards model, adjusted for age, gender and TDI quantiles, was utilised to identify dementia-associated diseases (marked as ICD-10 codes). (b) Pair directional test: among individuals with dementia, binomial tests were performed for all possible disease associations to determine the direction, that is, whether the number of individuals experiencing D1 → D2 was greater than those experiencing D2 → D1. We limited the directional test of disease pairs to those with at least 100 individuals having both D1 and D2.[18] (c) Association quantification: based on the identified disease pairs with temporal directionality (D1 → D2), we employed a 1:2 case-control design matching for gender, TDI quartile groups and age, to better control for those confounding factors. Conditional logistic regression analysis was then applied to ascertain the magnitude of the associations between each disease pair. Finally, significant disease pairs were connected by the same disease to form disease trajectory networks with dementia as the end-point (D1 → D2 and D2 → D3 can be combined as D1 → D2 → D3). To make the final trajectories more concise, the disease trajectory was generated based on all significant disease nodes with more than one edge. Subsequently, the clusters of disease trajectory were then defined according to the class of the initial diseases.

Sensitivity and subgroup analysis

To assure the robustness of the results, we conducted a sensitivity analysis on disease trajectories before ACD where we excluded individuals with a family history of dementia. Participants with both Alzheimer's disease and VaD records were also excluded because of the potential misdiagnosis and the complex nature of mixed dementia. Furthermore, to avoid potential reverse associations, we attempted to limit the record intervals between D1 and D2 among each disease pair to at least 180 days. Since disease trajectory analysis is a data-driven approach, the selection threshold of diseases or disease pairs is critical. With reference to previous research,[19] we limited the PheWAS to diseases experienced by at least 50 people with ACD (approximately 1% of 4638 individuals with ACD), and binomial tests of all possible disease pairs were limited to those experienced by at least 25 people with ACD (approximately 0.5% of individuals with ACD) in the sensitivity analysis.

As two major dementia subtypes, Alzheimer's disease and VaD were separately investigated in subgroup analyses of disease trajectories because of potential differences in risk factors suggested by their distinct pathological mechanisms. Moreover, the *ApoE* ε4 allele is widely identified as the major genetic risk factor for late-onset dementia,[20] with gender and age also reported as common modifiers of health condition. Thus, we performed additional subgroup analyses on disease trajectories among stratified populations by gender (male and female), median age of dementia diagnosis (<74 years and ≥74 years), late-onset dementia (diagnosed at age 65 or above) and *ApoE* ε4 status (carrier and non-carrier).

We performed Mendelian randomisation analysis for the most robust disease pair within the disease trajectories in the primary and subgroup analyses, to address the limitation that the disease trajectories only revealed associations. The detailed methods are

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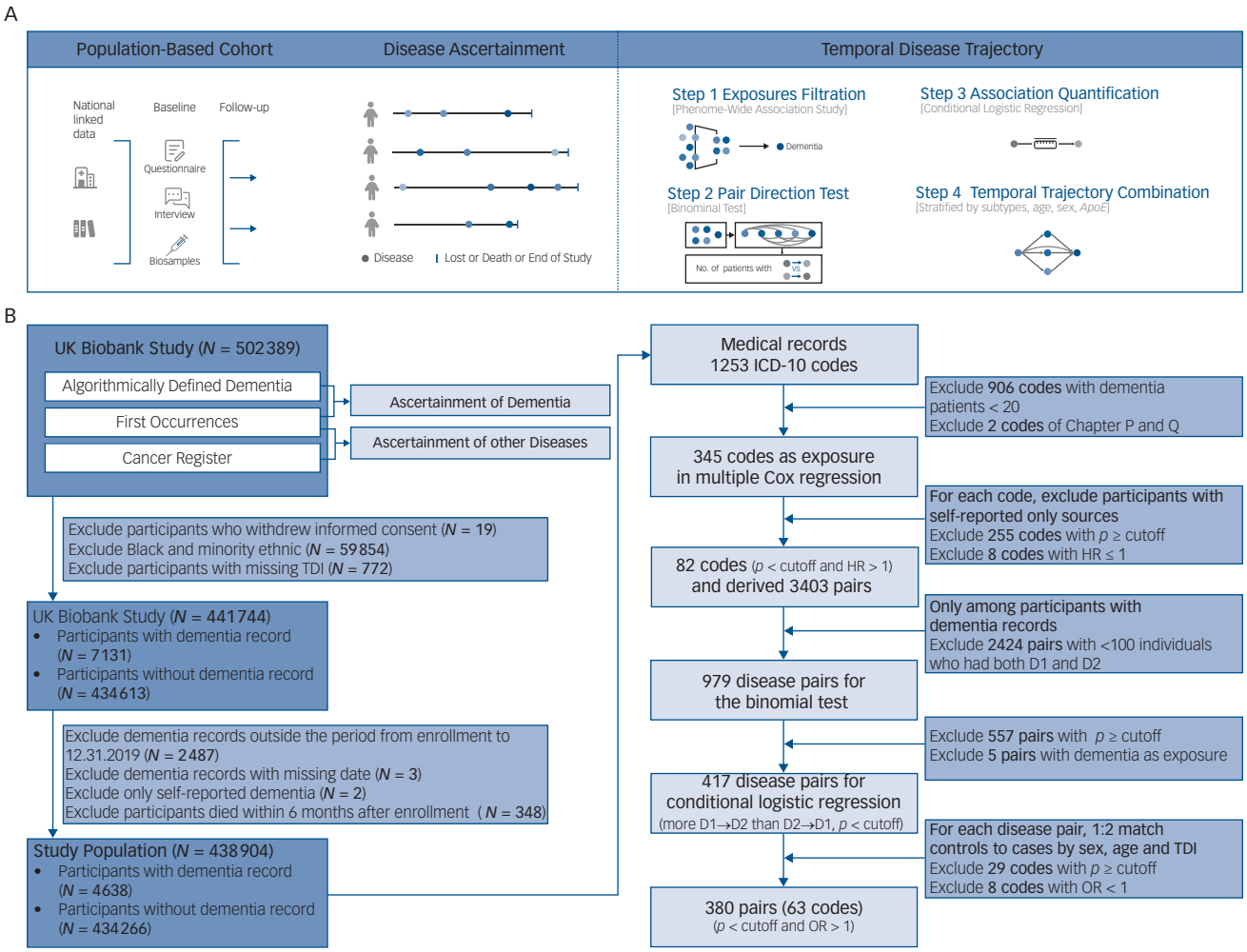

Fig. 1 Participants selection procedure and study flowchart: (a) study design and main process of analysis; (b) participants and diseases selection procedure. *ApoE, apolipoprotein E*; ICD, International Classification of Diseases; HR, hazard ratio; OR, odds ratio; TDI, Townsend deprivation index.

described in Supplementary 1. All statistical tests were two-sided, performing using R (version 4.2.2). To avoid type I error due to multiple testing, the statistical significance level was set at 0·05 after Bonferroni correction. The disease trajectory network was generated using Cytoscape (version 3.9.1).

Results

Disease exposure and risk of incident all-cause dementia

In this population-based cohort study of the UKB, we included a total of 438 904 (Fig. 1(a)), among whom 4638 individuals developed ACD during a median follow-up period of 10.9 years. The median age of the study population at baseline was 58.0 years, with 26.8% participants being apolipoprotein E (*ApoE*) ε4 carriers and 14.5% participants having a family history of dementia (Supplementary Table 2).

Among all 1253 ICD-10 codes, a total of 345 ICD-10 codes were included in the Cox regression for PheWAS, after excluding those diseases with a limited number of cases (Fig. 1(b)). We found that 82 diseases were significantly associated with an increased risk of incident ACD (Bonferroni-adjusted $p < 0.05$) (Fig. 2 and Supplementary Table 3). Specifically, mental and behavioural disorders (Chapter F in ICD-10), as well as nervous system disorders (Chapter G), showed the highest hazard ratios in relation to incident ACD (ICD-10 code F06 had the highest hazard ratio: 12.75). In addition to mental behavioural disorders and nervous system disorders, diseases related to the circulatory (Chapter I) system demonstrated the largest number of associations with incident dementia, with 16 diseases identified as significantly associated with an increased ACD risk.

Temporal patterns of disease trajectories before dementia diagnosis

The total of 82 diseases significantly associated with ACD in PheWAS resulted in 3403 possible combinations of disease pairs. In all, 979 disease pairs had at least 100 people presented, warranting an adequate level of statistical power, and were further tested for the direction of association. A total of 417 (42.6%) disease pairs showed a significant direction (Bonferroni-adjusted $p < 0.05$) and were selected for further analysis, among which 380 disease pairs were found significant in conditional logistic regression (Bonferroni-adjusted $p < 0.05$) (Supplementary Table 4). These disease pairs were structured into disease trajectories based on identical disease nodes, forming multiple disease trajectories before ACD. Disease trajectories before ACD diagnosis were characterised

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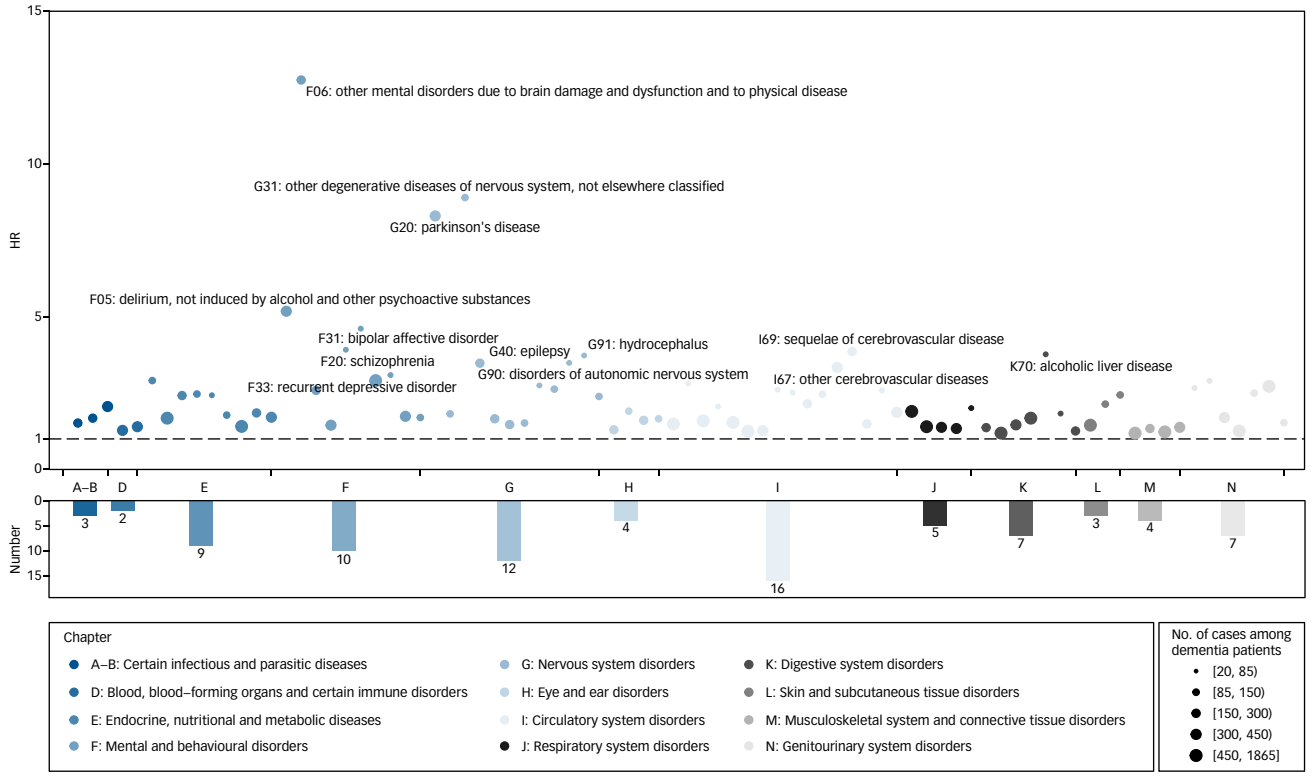

Fig. 2 Hazard ratios of the significant disease exposures for incident all-cause dementia, and the corresponding number of diseases across ICD-10 chapters. ICD, International Classification of Diseases.

into three clusters based on six initial diseases (Fig. 3). Cluster A was initiated by circulatory system disorders, represented by essential primary hypertension and angina pectoris. Cluster B was initiated by endocrine and metabolic disorders, that is non-insulin-dependent diabetes mellitus and lipoprotein metabolism disorders. Cluster C was initiated by respiratory system disorders, including unspecified acute lower respiratory infection and asthma. Figure 4 illustrates the distribution of record times for all the disease nodes in the final disease trajectories before the diagnosis of ACD. The median recording time for the six initial diseases in trajectories (codes in grey in the y axis of Fig. 4(b)) varied from 7.5 to 11.0 years preceding ACD. Other mental disorders due to brain damage and dysfunction and to physical disease had the shortest interval to the subsequent ACD, with a median of 1.7 years.

In the sensitivity analyses, the disease pairs of the primary trajectories were extracted, and the magnitude and significance of their associations were presented in Supplementary Table 5. All disease pairs remained significant after excluding participants with a family history of dementia or mixed dementia, while several pairs showed modest associations when records with less than 180 days interval were excluded (nominal $p < 0.05$ but Bonferroni-adjusted $p > 0.05$). Additionally, 95.3% (362/380) of disease pairs found in primary analysis remained significant using the less strict criteria for exposure disease and disease pair filtration (Supplementary Fig. 1); the three-cluster disease trajectory before ACD was very similar to the primary one, initiated by circulatory, metabolic and respiratory system diseases.

Subgroup analyses by dementia subtype, gender, diagnosis age and *ApoE*

Among 1941 participants with Alzheimer's disease and 434 266 non-dementia participants, 36 disease pairs involving 17 diseases demonstrated significant associations and passed the directional test (Supplementary Fig. 2(a) and Table 6). Hypertension, angina pectoris, non-insulin-dependent diabetes mellitus and lipoprotein metabolism disorders, as the initial diseases in ACD trajectories, were all associated with an increased risk of incident Alzheimer's disease (odds ratio = 1.34, 1.52, 1.42 and 1.32, respectively). Supplementary Figure 2 indicates that disease pairs identified in Alzheimer's disease were almost entirely included in the disease trajectories before ACD. The trajectories before VaD were generated using 1042 people, and 434 266 individuals without dementia (Supplementary Fig. 2 and Table 7). The trajectories preceding VaD remained significant after excluding people with both Alzheimer's disease and VaD diagnoses in the sensitivity analysis, except for the associations between I48 and N18 (Supplementary Table 8). The disease trajectories before VaD initiated by diabetes and lipoprotein metabolism disorders were similar to those before ACD, but chronic ischaemic heart disease exhibited as the characteristic initial disease preceding VaD (OR and 95% CI: 2.23 [1.85, 2.68]), followed by cerebral infarction or chronic renal failure (Supplementary Fig. 2(b)).

Disease trajectories before ACD diagnosis stratified by gender are depicted in Supplementary Fig. 3 and Tables 9 and 10. Chronic obstructive pulmonary disease after lipoprotein metabolism disorders and depression, or chronic ischaemic heart disease after hypertension were significant pairs before ACD in both males and females. Depressive episode and cellulitis were significant nodes in trajectories among relatively young individuals with dementia, while cerebral infraction, as well as atrial fibrillation and flutter were significant nodes among relatively older people with dementia (Supplementary Fig. 4 and Tables 11 and 12). The disease trajectory before ACD among people with late-onset dementia (diagnosed age at 65 or above) had the same initiated

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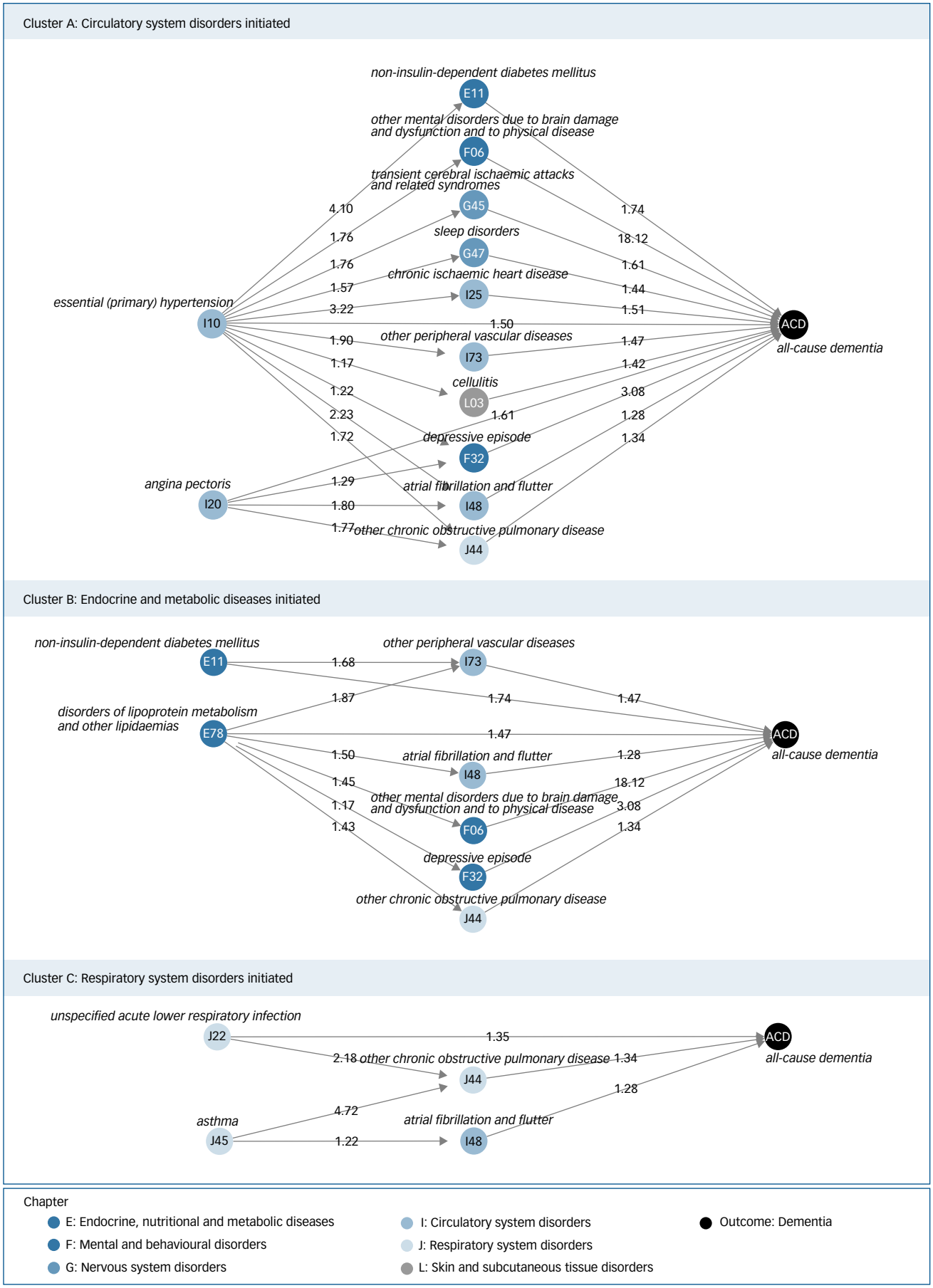

Fig. 3 Disease trajectories clusters before all-cause dementia. The numbers on the arrows indicate the odds ratios of the association between disease exposure and all-cause dementia.

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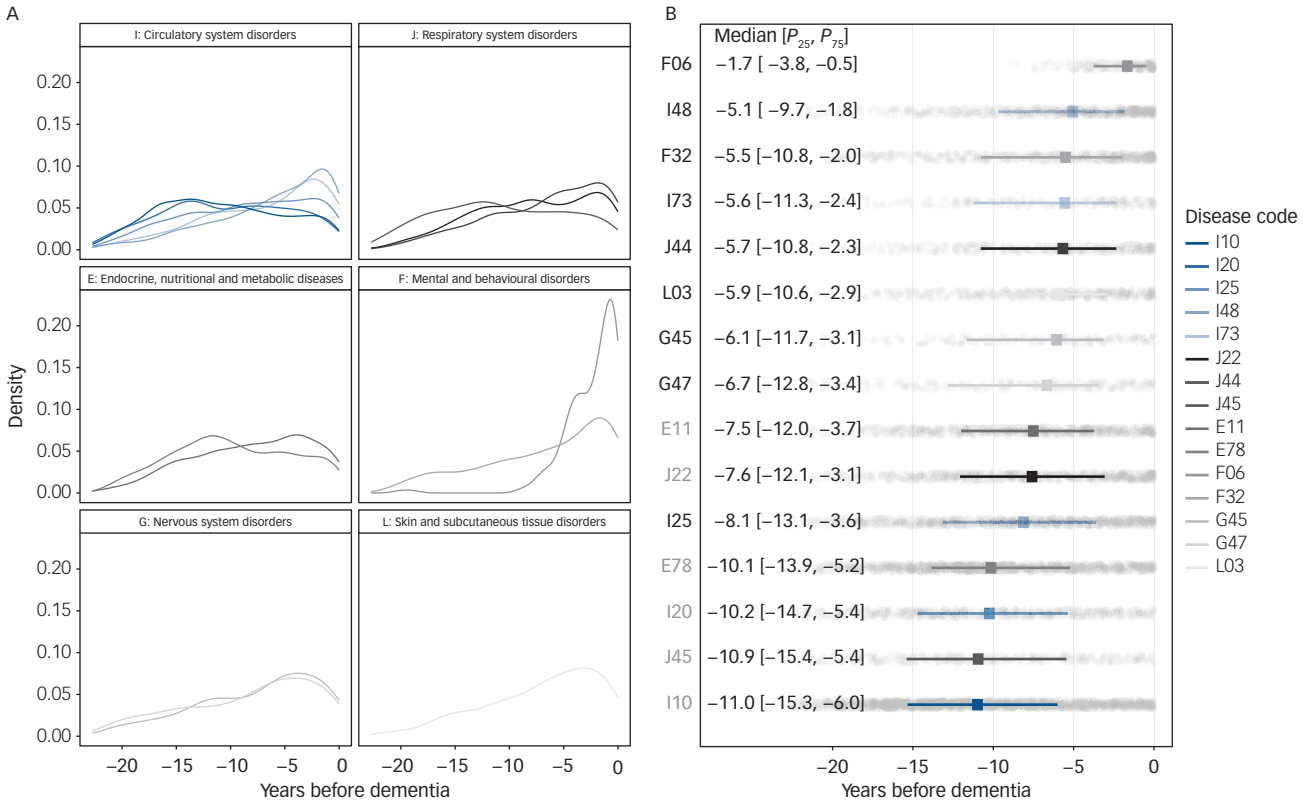

Fig. 4 Record time intervals between disease nodes in trajectories and all-cause dementia: (a) the incidence density histogram of each disease in trajectories before ACD, categorised by ICD-10 chapters; (b) median and [P_{25}, P_{75}] of record time intervals; disease codes in grey are the six initial diseases in trajectories before ACD. The full names of disease codes are in Supplementary Table 1. ACD, all-cause dementia; ICD, International Classification of Diseases.

diseases and similar patterns as the trajectory stratified by median age (Supplementary Fig. 5 and Table 13).

When the study population was grouped by *ApoE* ε4 status, 66 significant temporal disease pairs involving 26 diseases were identified in *ApoE* ε4 carriers, while 263 significant temporal disease pairs involving 54 diseases were identified in non-carriers (Supplementary Tables 14 and 15). The trajectory of hypertension → depression → ACD remained significant in two groups. More significant disease trajectories were observed before ACD diagnosis in *ApoE* ε4 non-carriers, with similar trajectory clusters initiated by circulatory, endocrine and metabolic disorders found in the entire population (Supplementary Fig. 6).

Mendelian randomisation

In the primary and subgroup analyses, the trajectory of lipoprotein metabolism disorders (ICD-10 code: E78) → dementia demonstrated stability and consistency, with further Mendelian randomisation results on the risk of Alzheimer's disease are showed in Supplementary Fig. 7. The instrumental variables for exposures and their basic statistics are described in Supplementary Tables 16 and 17. Most of the Mendelian randomisation methods indicated the odds ratio > 1 for genetically predicted lipoprotein metabolism disorders with Alzheimer's disease; however, the causal association was not statistically significant. As lipoprotein metabolism disorder is a complex disease, we also investigated the causal relationships between relevant biochemical indicators used for diagnosis and Alzheimer's disease outcome. The genetically determined high circulating apolipoprotein A1 (ApoA1) level was associated with decreased risk of Alzheimer's disease, consistent in six Mendelian randomisation methods (odds ratio range: 0.76–0.90, all $p < 0.05$).

Discussion

Based on a large-scale population cohort, this study depicted the temporal disease trajectories preceding dementia, as well as stratifying by dementia subtypes, gender, age of dementia diagnosis and genetic risk of dementia. The findings revealed three primary clusters of disease trajectories before ACD diagnosis, typically initiated by circulatory, metabolic and respiratory system diseases occurring approximately 5–15 years prior to ACD. Cerebral infarction or chronic renal failure following chronic ischaemic heart disease performed as a characteristic trajectory before VaD. *ApoE* ε4 non-carriers exhibited more diverse disease trajectories compared with carriers. Midlife circulatory diseases and lipid metabolism disorders played an important role in the onset of dementia and its subtypes in late life.

Both hypertension and angina pectoris were initial circulatory diseases found in trajectories preceding ACD, and positively associated with other ten diseases and incident ACD. Hypertension triggers hypertrophy or remodelling and disturbs the autoregulation of cerebral vasculature, leading to brain dysfunction and damage.[21] The adaptive alterations in cerebrovascular structure and function form the neuropathological basis of hypertension, supporting its role of a precursor to dementia. The association between angina and dementia was also found in another study based on Danish national patient registries.[22] Our subgroup analysis further suggests that *ApoE* ε4 non-carriers and males should prioritise dementia

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prevention post-angina. The association between cardiovascular diseases and dementia may be attributed to shared risk factors, the systemic nature of vascular diseases and cerebral vascular damage.[23] A trajectory involving hypertension, followed by a depressive episode and subsequent ACD, was observed in this study regardless of *ApoE* ε4 status. Previous meta-analyses of prospective studies reported that midlife hypertension[6] and late-life depression[7] are risk factors for incident dementia, aligning with the observed hypertension → depression→ ACD trajectory. A nested case-control study supported our subgroup results, finding that depression within a 10-year span before dementia onset was strongly associated with dementia, regardless of *ApoE* status.[24] The 'vascular depression hypothesis' suggested that cerebrovascular disease, in particular structural and functional damage to the fronto-subcortical circuit, may predispose, precipitate or perpetuate depressive symptoms in elderly adults.[25] The interaction of numerous biologic (e.g. hypothalamic-pituitary-adrenal axis and autonomic system dysregulation) and behavioural (e.g. smoking and physical inactivity) risk factors for cardiovascular diseases and depression also supported this trajectory.[26]

For metabolic diseases, non-insulin-resistant diabetes (Type 2 diabetes) was associated with an increased risk of ACD, in line with prospective studies.[5] Abnormal lipoprotein metabolism, another initial metabolic disease in predementia disease trajectory clusters, was significantly associated with subsequent atrial fibrillation and flutter in people with VaD, *ApoE* ε4 non-carriers, males or relatively older individuals with ACD. Lipoproteins mainly refer to several lipid-protein complexes with different sizes, composition and functions, including the well-known pro-atherosclerosis low density lipoprotein cholesterol (LDL-C) and anti-atherosclerosis high density lipoprotein cholesterol (HDL-C).[27] Disorders of lipoprotein metabolism constitute a complex group of diseases, with high cholesterol being the most common subtypes of lipid abnormality.[28] Previous analysis of two prospective studies suggested that LDL-C was related with an increased burden of Alzheimer's disease neuropathology, independent of *ApoE* status,[29] supporting the positive association between lipoprotein disorders and Alzheimer's disease in this study. However, higher HDL-C might protect against vascular risk and inflammation accompanying amyloid-β pathology in mild cognitive impairment.[30] Notably, we found a significant causal relationship between genetically predicted ApoA1 and a decreased Alzheimer's disease risk, in line with our previous cohort study on circulating ApoA1 and risk of cognitive decline.[31] ApoA1 is one of the most abundant apolipoproteins in cerebrospinal fluid and is found on nearly all HDL particles.[32] ApoA1 in the central nervous system is believed to originate from the periphery,[32] indicating the biological plausibility of the association between circulating ApoA1 and dementia. The health effects of different lipoprotein disorders vary and may partly explain the insignificant causal relationship between lipoprotein disorders and Alzheimer's disease in our Mendelian randomisation analysis. Generally, lipids and lipoproteins play a critical role in central nervous system homeostasis and dementia development,[33] but the complex relationship and potential mechanisms between lipoprotein disorders and dementia require further research and validation in the future.

Compared to cardiovascular or metabolic diseases, the association between respiratory diseases and dementia is still underestimated. Our research identified asthma as a critical disease triggering the disease trajectories before ACD. A national prospective study reported that baseline asthma increased the risk of incident ACD after 8.1 years of follow-up,[34] which is consistent with our results. The trajectory of asthma → atrial fibrillation → ACD in this study could be attributed to chronic inflammatory activated by asthma.[34]

A previous study based on the Danish National Patient Registry[22] reported the temporal trajectories before Alzheimer's disease and VaD, and indicated nervous, mental or cardiovascular disorders as precursors to dementia. We found similar associations in this study, while additionally finding that cerebral infarction or chronic renal failure following chronic ischaemic heart disease performed as a characteristic trajectory before VaD. Possible mechanisms connecting dysfunction of the heart, kidney and brain include haemodynamic alterations, (neuro) hormonal dysregulation triggered by the renin-angiotensin-aldosterone system, and other related systemic inflammatory or immune mechanisms.[23,35,36] This study extensively discussed the trajectories of population stratification. The subgroup analysis emphasised that *ApoE* ε4 non-carriers exhibited more diverse disease trajectories compared with carriers, which may be attributed to the major genetic risk factor for dementia significantly increasing the risk of dementia while competitively weakening other pathologic pathways.[11] Furthermore, musculoskeletal and connective tissue disorders initiated characteristic trajectories before ACD among *ApoE* ε4 non-carriers. Chronic pain, such as dorsalgia, may accelerate cognitive decline through emotional stress via cortisol pathways.[37] Atrial fibrillation was a significant precursor for dementia in men and people with dementia aged 74 or above. A nationwide study from Norway reported that most comorbidities for atrial fibrillation were more common in men, and the cumulative prevalence of atrial fibrillation increased with age.[38] These results emphasised the critical diseases in trajectories across different subgroups.

Our study has several advantages. The national prospective cohort design of the UKB proactively acquires comprehensive macro-level sociodemographic and micro-level genetic information through a variety of designed epidemiological methods. This database supplements the passively collected electronic medical records and intricately delineates individual health status, enabling subsequent detailed analyses. The combination of disease trajectories with MR analysis methods can provide causal evidence supplemented for observed associations. The precise stratification of the population makes the disease trajectories more instructive for further research and translational applications.

However, several limitations should be acknowledged. First, the selection bias of 'healthy volunteers' existing in the UKB may lead to an underestimation of some diseases with low prevalence; however, the relationships between exposure and diseases found in this study are still instructive,[39] and the reproducibility of our findings needs to be investigated in other populations. Second, the limited number of incident dementia cases may restrict the analysis of other subtypes beyond Alzheimer's disease and VaD, even though these two types are the most common subtypes of dementia and covered over 60% of ACD in this study. Last, this study did not consider the potential impact of medical interventions on disease associations. Since the accessibility and strategy of treatment exhibit significant individual differences, studying the effects of treatments or medications on disease progression under the framework of the entire spectrum of diseases is extremely challenging.

To conclude, this study provides a comprehensive view of the temporal disease trajectories before the diagnosis of dementia, stratified by different population characteristics, and primarily initiated by disorders of the cardiovascular, metabolic and respiratory systems. By tracing the onset of initial diseases approximately 5–15 years before dementia to the subsequent progression of a series of diseases, this study offers a macroscopic perspective for understanding dementia development. Our results highlight the initial role of circulatory and metabolic diseases in the development of dementia. This population-based evidence also supports midlife cardiometabolic dysfunction as a potential target for the prevention and control of late-life dementia. The findings, upon further

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validation, could ultimately be beneficial for risk stratification and primary prevention efforts against dementia.

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Supplementary material

Supplementary material is available online at https://doi.org/10.1192/bjp.2024.122

Data availability

The UKB data used in this study can be accessed on request (www.ukbiobank.ac.uk). The summary statistics in Mendelian randomisation can be extracted from the Medical Research Council Integrative Epidemiology Unit OpenGWAS database (https://gwas.mrcieu.ac.uk/). The analytic code in this study is available from the corresponding author upon reasonable request. The materials supporting the findings are available to other researchers; see under this section heading.

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Author contributions

All authors designed the study, wrote and revised the manuscript. Jialin L., D.X. and M.C. conducted the data curation. Jialin L., D.X. and Jincheng L. performed the statistical analyses. Jialin L. and Y.W. performed the data visualisation. L.J., X.C., C.S. and Y.J. scrutinised the statistics. L.J., C.S. and Y.J. supervised the study. All authors read and approved the final manuscript.

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Declaration of interest

The authors declare that they have no competing interests.

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