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RESEARCH ARTICLE

Multisystem failure, tipping points, and risk of Alzheimer's disease

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Abstract

INTRODUCTION: Medical conditions including obesity, diabetes, hyperlipidemia, and depression significantly increased risk of Alzheimer's disease (AD). However, effect of their duration, influenced by non-modifiable factors like chromosomal sex and apolipoprotein E (*APOE*) genotype, remains unclear.

METHODS: Data from 5644 UKBiobank participants were analyzed using Cox regression model to identify critical tipping points based on age of onset, risk factor (RF) duration and their interaction with sex and *APOE* genotype.

RESULTS: Hypertension or diabetes before age 62 exerted greater AD risk than *APOEε4* alone. Obesity before age 62 increased AD risk by 54%, with the risk nearly tripling between ages 62–72. Hyperlipidemia and depression were associated with age-independent risk increases of 33% and 69%, respectively. After age 72, *APOEε4* became the dominant RF.

DISCUSSION: Duration of AD-risk-factors can have a greater impact than *APOEε4*. Identification of critical age-related tipping points highlights temporal dynamics of AD progression and role of multisystem failure in AD progression.

KEYWORDS
AD prevention strategies, AD-risk-factors, Alzheimer's disease (AD), APOE genotype, chromosomal sex, Cox proportional hazard model (CPHM), depression, hyperlipidemia (HLP), hypertension (HTN), late onset Alzheimer's disease (LOAD), modifiable risk factors, obesity, type 2 diabetes (T2D), UK Biobank, unmodifiable risk factors

Highlights

- AD risk factors impact AD onset, especially diagnosed between ages 62 and 72.
- Later diagnoses of hypertension, diabetes, and obesity delayed AD onset.
- Hyperlipidemia and depression increased AD risk by 33% and 69%, age-independent.
- APOEε4 carriers regardless of sex exhibited a higher risk increasing with age.
- Trajectories differed between APOEε4 carriers and non-carriers across sex.

1 | BACKGROUND

Alzheimer's disease (AD) is the most prevalent cause of dementia, affecting millions worldwide.[1] Globally, approximately 57.4 million individuals were living with dementia, with projections estimating an increase to 152.8 million by 2050.[1] As the aging population expands, the prevalence of dementia is expected to significantly increase, a number expected to rise to 13.8 million by 2060 in the absence of effective preventive or curative treatments.[2,3] Recent United States Food and Drug Administration (FDA)-approved monoclonal antibodies targeting amyloid exhibited potential in modest slowing cognitive decline during the early stages of AD.[4,5] However, their effectiveness is accompanied by challenges, including high costs and safety concerns.[6]

Beyond these treatment advancements, recent studies have highlighted the critical role of managing modifiable risk factors (RFs) as treatable medical conditions and lifestyle choices for AD prevention and intervention.[2,7,8] Modifiable RFs including type 2 diabetes,[9–11] hyperlipidemia,[12,13] hypertension,[14–16] obesity,[17,18] and depression[19] have emerged as key contributors to AD development and progression. Furthermore, it is estimated that one-third of global AD cases may be attributable to modifiable RFs,[20] with the potential to prevent up to 40% of dementia cases.[3] Therefore, effectively managing these RFs is of critical importance for mitigating the risk of AD and its progression. Early identification and treatment of AD-risk-factors constitute an effective strategy to delay AD onset or progression that aligns with the National Plan to Address AD.[2,8,21–23]

AD-risk-factors can emerge at different ages with the age of onset impacting development of AD.[2] While growing evidence supports the impact of modifiable RFs on AD onset,[13,24] their duration and their relationship with chromosomal sex and apolipoprotein E (*APOE*) genotype remain to be determined.

To explore this relationship, we focused on five AD-risk-factors: diabetes,[9–11] hyperlipidemia,[12,13] hypertension,[14–16] obesity,[17,18] and depression.[19] Using UK Biobank (UKB) health longitudinal data, we conducted a retrospective analysis using an extended Cox proportional hazard model (CPHM) for time-varying covariates. This strategy enabled evaluation of the impact of age-related effect of multiple RFs on AD development, in combination with two non-modifiable RFs: sex and *APOEε4* carrier status.

CPHM approaches have been applied to evaluate the impact of non-modifiable AD-risk-factors alone including age and *APOE* genotype on the progression to mild cognitive impairment (MCI) or AD.[25,26] Bonham et al.[25] analyzed the effect of *APOEε4* genotype and age on the progression from normal to AD from 5381 individuals. Specifically, *APOEε4* genotype and age significantly accelerated the progression to AD and MCI, with risk peak between ages 70–75. Liu et al.[26] identified an age-dependent effect of the *APOEε4* allele on AD risk, that was associated with a more rapid decline at age 80 for men with earlier age of decline at 75 for women. Additionally, studies have associated increased dementia risk with hypertension, and cardiometabolic diseases, particularly among *APOEε4* carriers.[27–30]

A limitation of these studies[25–30] is the absence of the time-dependent nature of AD modifiable RFs, as individuals can exhibit variation in the age of onset of RFs and their duration. Modeling interactions between patient clinical and temporal patterns, integrated with the probability of developing AD remains challenging, particularly when considering multifactorial AD progression.

To address these challenges, we conducted a retrospective analysis using longitudinal medical history data of 5,644 UKB participants (Figure 1). We employed extended Cox regression models with time-varying covariates[31] to evaluate the impact of age of onset and duration of RFs on AD diagnosis. Further analyses were conducted to determine the impact of sex and *APOE* genotype. Overall, our study assessed the following critical tipping points: the differential impact of each RF on the onset of AD, the influence of the age at which each RF emerges, and the effect of the duration of these RFs on AD onset.

RESEARCH IN CONTEXT

1. **Systematic review**: To contextualize research reported herein, the authors reviewed literature on Alzheimer's disease (AD) risk factors and their impact on AD onset using traditional PubMed and Google Scholar. Although literature evidence suggests that modifiable risk factors including obesity, diabetes, hypertension, hyperlipidemia, and depression are significant increased risk of developing AD, their duration and their relationship with chromosomal sex and apolipoprotein E (*APOE*) genotype remain underexplored.
2. **Interpretation**: Results reported herein identified critical age-related tipping points defined by change in AD risk over time of multiple risk factors, controlled by sex and *APOE* genotype.
3. **Future directions**: This report highlights the importance of identifying specific windows of opportunity for AD prevention and proposes a framework for the conduct of additional studies to understand the impact of multisystem failure and secondary prevention strategies targeting AD risk factors.

2 | METHODS

2.1 | UKB study cohort

The UKB is a large-scale biomedical database and research resource, encompassing data from approximately half a million participants aged 40–69 years, with a balanced representation of women and men. Recruitment occurred between 2006 and 2010 across 33 centers throughout the United Kingdom, including different socioeconomic, ethnic, and urban–rural representation.[32] At baseline participants provided information regarding their socio-demographic, lifestyle, environmental, and health-related attributes through touchscreen

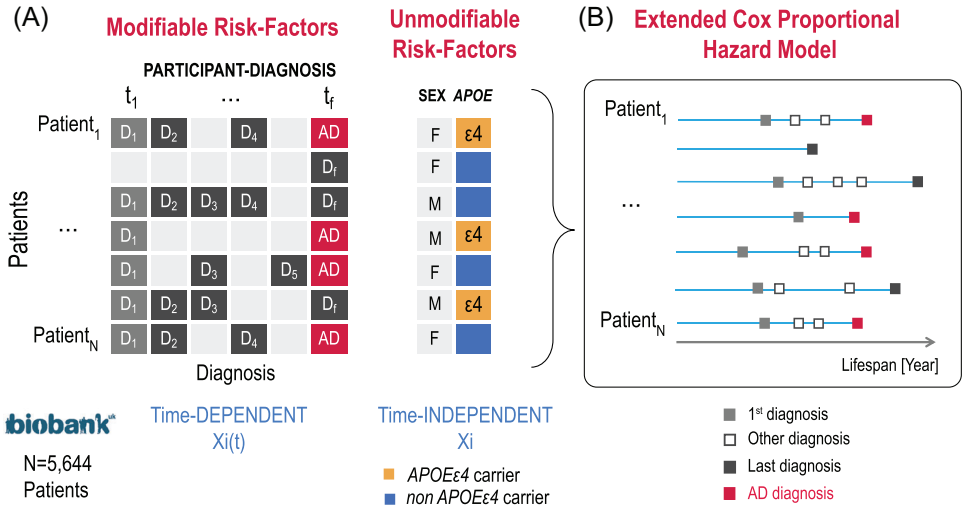

FIGURE 1 Overview of the extended Cox proportional hazard model (CPHM) proposed to evaluate the impact of multiple diagnoses throughout participants' lifespan on Alzheimer's disease (AD) diagnosis. UK Biobank longitudinal diagnosis data of 5644 participants were included as input to the model along with the related sex and apolipoprotein E (*APOE*) genotype. (A) Risk factor diagnoses are modeled as time-dependent covariates $x_i(t)$ while sex and *APOEε4* carrier status are modeled as time-fixed covariates X_i. (B) Time-varying representation of diagnoses included in the Cox model, where each participant can be associated with up to five risk factor diagnoses (i.e., covariates) before the end-point occurrence (i.e., AD or last follow-up diagnosis).

questionnaires and an interview conducted by a nurse. Participants underwent physical assessments and blood samples collected.

For this study, a subpopulation of UKB participants aged over 55 years old without prior history of neurodegenerative diseases, brain cancer, traumatic brain injury, or neurosurgery and with a minimum of 3 years of follow-up were included for analysis.[33] This inclusion criterion was designed to ensure that participants were at risk for developing late-onset AD over the study period while maintaining sufficient follow-up duration to capture disease onset and progression. The 3-year follow-up requirement was selected to balance data availability and statistical power while ensuring a sufficient observation window for AD diagnosis. Notably, participants recruited at age 55 could be followed for up to 13 years, capturing the transition to AD. Follow-up duration was calculated based on date of AD diagnosis and the date of first visit for those without AD diagnosis. Participants with early-onset AD were excluded to ensure a sample of participants at risk for developing late-onset dementia over the study follow-up period.

Diagnoses for the selected participants were extracted from the UKB[34,35] using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes from primary care records (UKB Data Field number: 41202) aggregated into single-level categories.

AD-risk-factors were selected based on findings from our previous analysis that identified medical conditions and drugs associated with increased AD risk.[36] Moreover, these conditions have FDA-approved pharmacological treatments, which allow for potential intervention strategies. In detail, hypertension and hyperlipidemia were included due to their role in cardiovascular risk, and our prior studies highlighted the protective effect of statins, particularly in male *APOEε4* carriers.[35] Diabetes was considered due to its close link with cardiovascular dysfunction, which has been implicated in AD progression.[9–11,37] Obesity was included based on its complex relationship with AD risk, with prior findings suggesting both direct metabolic impacts and sex- and genotype-specific effects.[17,18,35,38–40] Depression was selected as an RF for AD accelerating cognitive decline both before and after dementia onset. Additionally, our recent work has explored the role of antidepressant therapies in modifying AD risk.[41]

The specific ICD-10-CM codes of AD and the five AD-risk-factors (hypertension, type 2 diabetes, hyperlipidemia, obesity, and depression) are listed in Supplementary Material Table S1. Of note, obesity was defined using both ICD-10-CM codes and by selecting participants reporting a body mass index (BMI) > 30 kg/ m^2. For individuals diagnosed with AD, only occurrences of RF diagnoses preceding the AD diagnosis were considered. Although our study focused on individuals aged 55 and older, we accounted for prior exposure to AD-risk-factors by leveraging UKB's comprehensive electronic health records. These records integrate data from hospital inpatient records, enabling a retrospective assessment of RF trajectories before enrollment. While the diagnoses of AD in the UKB cohort were based on clinical assessments using ICD-10-CM codes extracted from UKB primary care records, it is important to acknowledge that this approach does not incorporate biomarker-supported confirmation.

Genetic information of single-nucleotide polymorphisms (SNPs) was available for a subset of participants (N = 299,627) through genotyping arrays and imputation methods.[42] Genotyping arrays included the UK BiLEVE Axiom array and the UKB Axiom array for direct SNP genotyping with imputed genotypes derived from the Haplotype Reference Consortium and UK10K haplotype resource using UKB's computational pipeline. Genetic analysis for this study

employed version 3, published in March 2018, with genotyping quality control centrally carried out by the UKB.[43]

For identification of *APOE* genotype, we focused on the two *APOE*-related key SNPs, rs429358 and rs7412. *APOE*ε4 carriers possess at least one ε4 allele at either of these SNPs. Therefore, participants with genotypes ε2/ε4, ε3/ε4, or ε4/ε4 were classified as *APOE*ε4 carriers. Conversely, individuals with genotypes ε2/ε2, ε2/ε3, or ε3/ε3 do not carry the ε4 allele and were categorized as *APOE*ε4 non-carriers. *APOE* genotype information was available for a total of 248,056 participants.

2.2 | Statistical analysis and pair-matching design

The frequency (percentage) of participants with and without AD diagnosis was computed for categorical variables, whereas mean (standard deviation) were computed for continuous variables. Differences between groups were assessed using Pearson's chi-squared test for categorical variables and analysis of variance (ANOVA) for continuous variables. Statistical significance was set at a two-sided p-value < 0.01.

To minimize the effects of possible confounders in the Cox model between AD and non-AD participants, a probabilistic matching similar to the propensity score (PS) matching design was conducted as in.[34,35] First, features associated with group membership were identified using a logistic regression model, considering the variables: age at first visit, recruitment center, level of education, and Charlson Comorbidity Index (CCI) score. Of note, CCI is a weighted index typically used to quantify the burden of comorbid conditions in patients, and primarily used to predict the risk of mortality and healthcare utilization.[44] CCI is calculated by assigning a weighted scores to 19 chronic conditions based on their severity and impact on survival, where higher total scores (CCI) indicate greater comorbidity burden and increased mortality risk.[44,45] To calculate CCI, we used the R package *comoRbidity*.[46] In this study we calculated the CCI by including only the comorbid conditions not corresponding to the risk factors of interest, these included: myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease (PVD), cerebrovascular disease (CVD), chronic pulmonary disease (CPD), connective tissue disease, peptic ulcer disease (PUD), mild liver disease (MildLiver), moderate to severe liver disease (SevereLiver), and moderate to severe renal disease (RenalMild). We excluded the five AD-risk-factors of interest in the calculation of CCI score.

Pair-matched cohorts were generated using a 3:1 ratio based using the nearest neighbor matching method. The analyses were conducted using the "matchit" and "match.data" functions from the *MatchIt* R package.[47]

2.3 | Nested case–control cox regression model with time-varying covariates

For this analysis, Cox regression model with time-varying covariates,[31] an extension of the CPHM which allows for covariates changing over time, was utilized to examine the impact of multiple AD-risk-factors diagnoses on the development of AD (Figure 1). In the standard Cox models, the hazard rate for an event is modeled as a function of baseline hazard and fixed covariates and assume the covariates remain constant throughout time. However, in real-world context, covariates can change over time during a follow-up period. Cox regression model with time-varying covariates is particularly indicated when covariates dynamically influence the risk of an event, allowing to capture the effect of changes of the covariates over time on an outcome of interest, such as the progression of RFs leading to AD. In this study, AD-risk-factors were considered as time-dependent covariates while controlling for sex and *APOE*ε4 carrier status, which were considered as time-fixed covariates. To incorporate both time-dependent and time-independent covariates, we extended the general hazard model for failure time proposed by Cox to allow time-dependent covariates.[31]

$$\lambda(t|Z(t)) = \lambda_0(t)\, exp\ \left(\beta' x + \gamma' X g(t)\right)$$

where β' and γ' are regression coefficients of time-fixed and time-varying covariate respectively where $\lambda_0(t)$ is the baseline hazard function. In the extended form of the Cox model, Z is a vector of time-fixed and time-varying covariates.

$$Z(t) = \left[x_1, \cdots, x_p, X_1 g(t), \cdots, X_q g(t)\right]$$

where $x_1, \ldots, x_p$ represent the time-fixed covariates (sex and *APOE* genotype), and $X_1 g(t), \ldots, X_q g(t)$ represent the time-varying covariates (AD-risk-factors).

Employing a nested case–control design[48,49] to ensure population matching, the Cox model was implemented to: (1) assess of hazard ratios (HRs) associated with multiple RFs diagnoses and (2) explore the trajectories of multiple RF diagnoses over time.

To model AD RF diagnoses as time-dependent covariates, we considered the time intervals between the age at RF diagnosis and AD onset in the AD diagnosed participants versus the time intervals between age at RF diagnosis and the last ICD-10-CM diagnosis in the non-AD population. Additionally, we considered effect of sex and *APOE*ε4 carrier status by modeling each as time-independent covariates. AD RF diagnoses can be represented as a vector: where m varies from one to six (i.e., maximum number of possible RF diagnoses before the end of follow up) and Age_m is the age at last-follow up or AD diagnosis for AD participants.[50] With this procedure, each participant can be associated with up to five RF diagnoses (i.e., covariates) before the end-point occurrence (i.e., AD or last follow-up diagnosis).

The resulting HR values indicate the risk of progressing to AD associated with the covariates (i.e., AD-risk-factors). An HR greater than 1 indicates an increased risk of AD diagnosis in those with the AD RF compared to those who do not experience an AD RF whereas an HR less than 1 indicates a protective effect or decreased risk. An HR of exactly 1 means there is no difference in risk between the groups. Statistical significance was defined by a p-value < 0.01.

Additional analyses were conducted to test whether the regression coefficients of the covariates are constant over time (time-constant) or time-varying. The Cox model assumes that the regression coefficients are constant across all ages ensuring that the hazard of each covariate

does not change over time.[51] However, if this assumption is violated for a certain covariate (i.e., if the HR associated with a covariate increases or decreases over time), the related effect on the outcome is not constant over time. In this case, the time-varying coefficient can be incorporated into the Cox regression model or, alternatively, the model can be adapted to better describe the data.[31]

Time-varying regression coefficients were identified using Schoenfeld residuals (Rss) statistical test (p-value < 0.01) and Rss graphical diagnostics.[51–53] Graphical diagnostics depicting the residual-time curves were also performed for each coefficient by plotting *logHR* values over time, where the assumption was tested by visually evaluating the curve trends. For the time-varying coefficients, we investigated potential restoration of time-constant coefficients by using a sliding window approach between age 55 and 85 with 1-year intervals. This strategy enabled identification of data-driven critical age tipping points which corresponded to the age groups in which constant coefficients were restored.

Following these analyses, trajectories of the five modifiable RFs were plotted to assess the influence of each RF on the probability of AD onset, accounting for the onset age of each RF. Trajectories were estimated based on the inverse of the hazard function, representing the probability of not developing AD up to a given age. These analyses were conducted using *survminer*,[54] *survival*,[55] and *survcomp*[56] R packages. Code is available at https://github.com/CIBS-lab/AD_Cox.

3 | RESULTS

3.1 | The UKB population

Among 502,412 UKB participants who underwent baseline assessment, 181,770 participants met the inclusion, exclusion, and enrollment criteria (Figure 2A). UKB participants diagnosed with AD were categorized into the AD group (N = 1411), while the remaining participants into the non-AD group (N = 180,359). Detailed clinical and demographic information for AD and non-AD participants for both unadjusted and matched populations is provided in Table 1. Participants were classified as without RF if they did not develop any of the RFs during the observation period.

In the unadjusted population, significant differences between the AD and non-AD group were observed. The population within the AD group had a higher proportion of older individuals (62.4% individuals over 65), whereas the non-AD group had a younger population (28.1% individuals over 65, p-value < 0.001) (Table 1). *APOE*ε4 carrier was more frequent (62.9% in AD group, 26.3% in non-AD group, p-value < 0.001), and mean age at last follow-up was higher in the AD group (mean [SD] age at last follow-up in the non-AD group of 69.3 years [6.4]; mean [SD] age at last follow-up in the AD group of 75 years [4.3]; p-value < 0.001) (Table 1). No significant difference was observed in the sex distribution (56.1% female in non-AD group, 56.4% female in AD group, p-value = 0.821). However, a significant difference (p-value < 0.001) was observed in sex by *APOE* genotype, with a higher prevalence of female ε4 carriers in the AD group (37%) compared to non-AD group (15%), and a higher prevalence of male ε4 carrier in the AD group (26%) compared to non-AD group (12%) (Table 1).

Regarding the AD-risk-factors, significant differences were observed between AD and non-AD groups in the unadjusted populations with respect to hypertension ratio (55.1% in AD group, 34.7% in non-AD group, p-value < 0.001), hyperlipidemia ratio (30.5% in AD group, 18% in non-AD group, p-value < 0.001), diabetes ratio (18.5% in AD group, 8.9% in non-AD group, p-value < 0.001), and depression ratio (13.4% in AD group, 4.9% in non-AD group, p-value < 0.001) (Table 1). No significant difference was observed in obesity ratio (25.8% in non-AD group, 25.4% in AD group, p-value = 0.721) (Table 1).

Following 3:1 pair-matching with covariate balance, a total of 5644 participants were included in the AD and non-AD groups (Figure 2A, B). Among these participants, 1411 (mean [SD] follow-up age of 75 years [4.4], 56.4% female) were diagnosed with AD (AD group) and 4233 (mean [SD] follow-up age of 74 years [5.5], 55% female) (Table 1) were not diagnosed with AD (non-AD group). In the matched population, significantly higher proportions of *APOE*ε4 carrier participants were observed in the AD group compared to the non-AD group (62.9% vs. 26.6%, respectively; p-value < 0.001) (Table 1). Statistics on the UKB participants carrying different numbers of *APOE*ε4 copies are reported in Table S2 and in Table S3 were further stratified by sex, and age at AD diagnosis. More than 95% of 5644 participants were White (Table S4), while a smaller percent represented other ethnic backgrounds, including Asian, Black, and Mixed ancestry.

Furthermore, the occurrence of hypertension (55% in AD group, 50% in non-AD group, p-value < 0.001), diabetes (18.5% in AD group, 14.4% in non-AD group, p-value < 0.001), and depression (13.4% in AD group, 5.5% in non-AD group, p-value < 0.001) was statistically higher in the AD group compared to the non-AD group. Notably the two groups were relatively comparable for occurrence of AD-risk-factors, with 69% of the AD group and 65% of the non-AD group clinically diagnosed with at least one of the five AD-risk-factors (Figure 2E). As far as RF duration, chronic diabetes was significantly higher in the AD group compared to non-AD group (mean diagnosis age 68.84 years (7.52) in AD group, 70.53 years (6.73) years in non-AD group, p-value = 0.002) (Table S5). Comorbidities distribution alone and stratified by sex and *APOE* genotype are reported in Table S6 and S7.

When considering sex and *APOE*ε4 carrier distributions related to each RF, distinct distributions emerged in the AD and non-AD groups. For example, in the non-AD group 67% of participants with a diagnosis of depression were female, with nearly 22% *APOE*ε4 carriers (Table 2). In contrast, 35% of AD participants with a diagnosis of depression were female *APOE*ε4 carriers, followed by 27% of female non-carriers and 38% of males, with an equal distribution of *APOE*ε4 carrier (Table 2). Regarding diabetes in the non-AD group, a higher proportion were males (59%) (Table 2). In contrast, AD participants with diabetes were equally distributed across sex and *APOE* genotype. In terms of obesity, similar distribution of sex was observed in both the AD and non-AD groups. No sex differences were observed for participants with hyperlipidemia in either non-AD or AD groups (Table 2). In the non-AD group, 51% of persons with hypertension were female which increased to 55% in the AD group (Table 2). These data indicate that the major sex

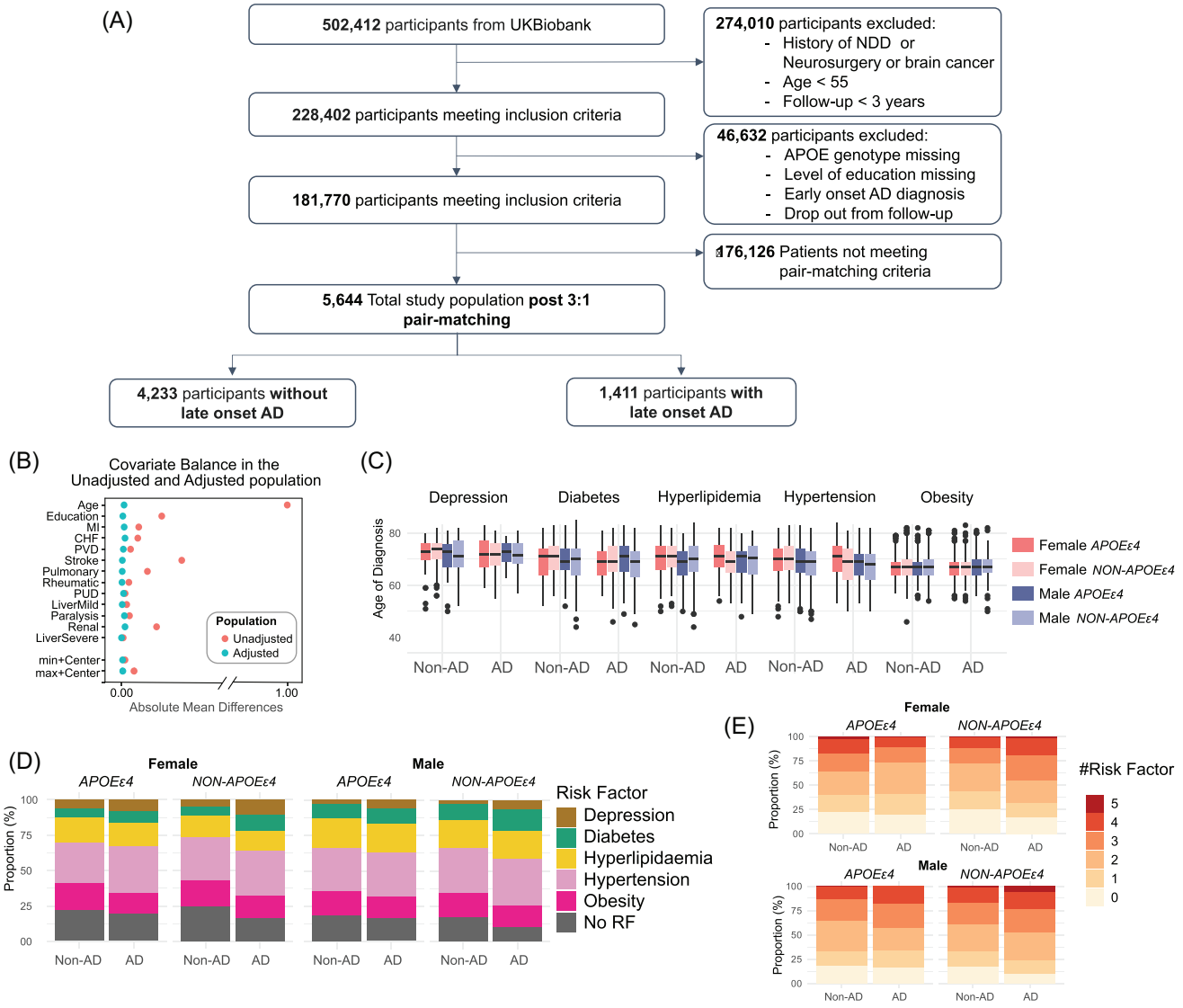

FIGURE 2 Study design and summary of the UK Biobank (UKB) matched cohort main features. (A) Study design and UKB participants selection. (B) Covariate balance before and after pair-matching. The love plot illustrates the standardized mean differences of covariates before (pink) and after (light blue) 3:1 pair-matching. The balance improves post-matching, as indicated by the reduced absolute standardized mean differences across covariates. (C) Age of each risk factor diagnosis by sex and apolipoprotein E (*APOE*) *ε4* carrier status, grouped by Alzheimer's disease (AD) diagnosis. (D) Distribution of risk factor diagnoses by sex and *APOEε4* carrier status, grouped by AD status. Bars are normalized within each AD group to facilitate comparison. (E) Distribution of number of comorbidities by sex and *APOEε4* carrier status, grouped by AD diagnosis. CHF, congestive heart failure; LiverMild, mild liver disease; LiverSevere, moderate to severe liver disease; MI, myocardial infarction; CHF, congestive heart failure; NDD, neurodegenerative disease; Paralysis, hemiplegia or paraplegia; PUD, peptic ulcer disease; Pulmonary, chronic pulmonary disease; PVD, peripheral vascular disease; Renal, moderate to severe renal disease; RF, risk factor; Rheumatic, rheumatologic disease; Stroke, cerebrovascular disease.

differences in AD RF is in depression, whereas the other AD-risk-factors are comparably represented in both sexes. A visual representation of the UKB data utilized in these analyses is reported in Figure 2.

3.2 | Impact of multiple risk factors on AD onset throughout participants' lifespan

To determine the impact of modifiable RFs, sex, and *APOE* genotype on the onset of AD, Cox regression model was applied considering the time-dependent nature of AD-risk-factors. Outcomes of this analysis indicated that both modifiable (depression: HR: 2.56, 95% confidence interval [CI]: 2.02 – 3.25, p-value < 0.001; diabetes: HR: 2.40, 95% CI: 1.96-2.94, p-value < 0.001; hyperlipidemia: HR: 1.63, 95% CI: 1.40 - 1.90, p-value < 0.001; hypertension: HR: 1.69, 95% CI: 1.49-1.92, p-value < 0.001; obesity: HR: 2.32, 95% CI: 1.95-2.76, p-value < 0.001, Table S8) and non-modifiable RFs significantly impacted the development of AD (male vs female: HR: 1.17, 95% CI 1.05-1.31, p-value = 0.004; *APOEε4* carrier: HR: 4.33, 95% CI: 3.86-4.85, p-value < 0.001, Table S8).

TABLE 1 UK Biobank cohorts of non-AD and AD before and after 3:1 pair-matching approach.

	Unadjusted population			Pair-matched population		
	Non-AD	AD		Non-AD	AD	
	n (%)	*n* (%)		*n* (%)	*n* (%)	
No. of participants	**180,359**	**1,411**	***p*-value**	**4,233**	**1,411**	***p*-value**
Age at last follow-up (years)						
Mean (SD)	69.355 (6.424)	75.045 (4.374)	<0.001	74.107 (5.532)	75.045 (4.374)	0.002
Range	55.0- 85.0	54.0 - 84.0		55.0 – 85.0	54.0 - 84.0	
Age at recruitment (years)						
55-60	58,311 (32.3%)	98 (6.9%)	<0.001	287 (6.8%)	98 (6.9%)	>0.99
60-65	71,406 (39.6%)	433 (30.7%)		1289 (30.5%)	433 (30.7%)	
over 65	50,642 (28.1%)	880 (62.4%)		2657 (62.8%)	880 (62.4%)	
Sex						
Female	101,207 (56.1%)	796 (56.4%)	0.821	2327 (55.0%)	796 (56.4%)	0.346
Male	79,152 (43.9%)	615 (43.6%)		1906 (45.0%)	615 (43.6%)	
***APOE* genotype**						
ε4 non-carrier	132,963 (73.7%)	524 (37.1%)	<0.001	3109 (73.4%)	524 (37.1%)	<0.001
ε4 carrier	47,396 (26.3%)	887 (62.9%)		1124 (26.6%)	887 (62.9%)	
Sex by *APOE* genotype						
Female ε4 carrier	26,643 (14.8%)	525 (37.2%)	<0.001	627 (14.8%)	525 (37.2%)	<0.001
Female ε4 noncarrier	74,564 (41.3%)	271 (19.2%)		1700 (40.2%)	271 (19.2%)	
Male ε4 carrier	20,753 (11.5%)	362 (25.7%)		497 (11.7%)	362 (25.7%)	
Male ε4 noncarrier	58,399 (32.4%)	253 (17.9%)		1409 (33.3%)	253 (17.9%)	
AD risk factors						
Depression	8796 (4.9%)	189 (13.4%)	<0.001	232 (5.5%)	189 (13.4%)	<0.001
Diabetes	16,003 (8.9%)	261 (18.5%)	<0.001	609 (14.4%)	261 (18.5%)	<0.001
Hyperlipidemia	32,462 (18.0%)	430 (30.5%)	<0.001	1201 (28.4%)	430 (30.5%)	0.131
Hypertension	62,672 (34.7%)	777 (55.1%)	<0.001	2121 (50.1%)	777 (55.1%)	< 0.001
Obesity	46,514 (25.8%)	357 (25.4%)	0.721	1195 (28.2%)	357 (25.4%)	0.037
Control	87,543 (48.5%)	435 (30.8%)	<0.001	1479 (34.9%)	435 (30.8%)	0.005

Abbreviations: AD, Alzheimer's disease; *APOE*, apolipoprotein E; control, no AD risk factor; SD, standard deviation.

To assess if the impact of these RFs changing over time, we tested if the regression coefficients were time-varying. Outcomes of this analysis indicated that HRs for sex, hyperlipidemia, and depression (*p*-value > 0.2) were constant over time (Figure 3A, Figure S1A, Table S9). In contrast, hypertension (*p*-value < 0.001), diabetes (*p*-value < 0.001), obesity (*p*-value < 0.001), and *APOE*ε4 genotype (*p*-value < 0.001) were associated with non-constant HRs (Figure 3A, Figure S1A, Table S9). To restore constant coefficients for these RFs, three age ranges were identified: younger (< 62 years), middle aged (62-72 years), and older (> 72 years) (*p*-value = 0.098, Table S10, Figure S1B). Outcomes of this analysis identified two critical transition ages. Specifically transition to 62 years of age and the transition from 72 years of age.

The Cox regression model applied considering these three age ranges identified increased risk of AD associated with sex, hyperlipidemia and depression constant in all age groups (sex: HR: 1.10, 95% CI: 1.02–1.19, *p*-value = 0.011; hyperlipidemia, HR: 1.33, 95% CI: 1.20-1.48, *p*-value < 0.001; depression, HR: 1.69, 95% CI: 1.46–1.97, *p*-value < 0.001) (Table 3, Figure 3B). While hypertension and diabetes were associated with an increased AD risk that was: (i) more evident when diagnosed at younger age (hypertension: HR: 2.28, 95% CI: 1.80–2.91, *p*-value < 0.001; diabetes: HR: 2.65, 95% CI: 1.94–3.63, *p*-value < 0.001), (ii) moderately stronger when diagnosed at the middle age, (hypertension: HR: 1.35, 95% CI: 1.19–1.53, *p*-value < 0.001; diabetes: HR: 1.85, 95% CI: 1.55–2.22, *p*-value < 0.001), and (iii) non-significant at older age (hypertension: HR:1.08, 95% CI: 0.94–1.25, *p*-value = 0.277; diabetes: HR: 1.03, 95% CI: 0.82–1.30, *p*-value = 0.777) (Table 3, Figure 3B). Further, obesity was linked with 1.54 increased risk of developing AD when diagnosed at younger age (HR: 1.54, 95% CI: 1.14–2.10, *p*-value = 0.005), with a higher risk when diagnosed at the middle age (HR: 2.91, 95% CI: 2.52-3.36, *p*-value < 0.001), while lower risk at older age which was not significant (HR: 0.88, 95% CI: 0.66–1.19, *p*-value = 0.418) (Table 3, Figure 3B).

TABLE 2 UK Biobank AD risk-factor statistics by sex and *APOE* genotype after 3:1 pair-matching approach.

	Pair-matched population		
	Non-AD	AD	
Parameter	Percentage (%)	Percentage (%)	*p*-value
Depression			
Female ε4 carrier	21.7	35.4	0.08
Female ε4 noncarrier	44.8	27	0.03
Male ε4 carrier	7.9	19.6	0.02
Male ε4 noncarrier	25.6	18	0.2
Diabetes			
Female ε4 carrier	11.3	25.6	0.013
Female ε4 noncarrier	28.7	21	0.25
Male ε4 carrier	14.3	25	0.078
Male ε4 noncarrier	45.7	28.3	0.036
Hyperlipidemia			
Female ε4 carrier	14.9	31.4	0.018
Female ε4 noncarrier	31.8	16	0.02
Male ε4 carrier	14.3	30.2	0.015
Male ε4 noncarrier	39	22.4	0.029
Hypertension			
Female ε4 carrier	13.7	34.6	0.002
Female ε4 noncarrier	37.2	19.3	0.016
Male ε4 carrier	12.5	25.1	0.032
Male ε4 noncarrier	36.6	21	0.035
Obesity			
Female ε4 carrier	15.6	32.1	0.02
Female ε4 noncarrier	38.8	20.7	0.02
Male ε4 carrier	11.6	26.3	0.023
Male ε4 noncarrier	34	20.9	0.079

Note: Statistical significance of the difference between AD and non-AD groups was assessed using a Fisher's exact test.
Abbreviation: AD, Alzheimer's disease; *APOE*, apolipoprotein E.

The estimated HRs of *APOE*ε4 genotype indicated that *APOE*ε4 is a major contributor of increased AD risk particularly in the older group (for ε4 carrier, HR in younger group: 1.57, 95% CI: 1.25–1.98, p-value < 0.001; HR in middle group: 2.92, 95% CI: 2.59–3.29, p-value < 0.001; HR in older group: 3.14, 95% CI: 2.80–3.51, p-value < 0.001) (Table 3, Figure 3B).

3.2.1 | Modifiable RF trajectories by sex and *APOE* genotype

To evaluate the development of AD over time and in relation to the onset age of various RFs, we analyzed RF trajectories, where a drop in the trajectory corresponds to diagnosis of AD (Figure 4). The trajectory of participants without RFs exhibited a better trend compared to the RF trajectories (Figure 4A).

An earlier decline of the trajectory was observed for individuals experiencing obesity while those who experienced depression exhibited a drop more evident at older ages (Figure 4A). Hypertension and diabetes exhibit a less pronounced decline and similar trajectories, whereas hyperlipidemia exhibited a more favorable trajectory (Figure 4A). Upon stratification by sex and *APOE* genotype, the five RF trajectories revealed *APOE*ε4 carrier differences which was evident in both females (Figure 4B vs. 4C) and males (Figure 4D vs 4E). Among *APOE*ε4 carriers, females exhibited a more rapid decline for diabetes and obesity, particularly pronounced in 65–75 age range, while depression, hyperlipidemia, and hypertension exhibited similar trajectories across all ages. In *APOE*ε4 carrier males, obesity was associated with a more rapid decline in AD onset followed by similar curves for hyperlipidemia, depression, diabetes, and hypertension (Figure 4B vs. 4D). In *APOE*ε4 non-carriers, females exhibited a steeper trajectory for diabetes compared to the other RFs (Figure 4C). *APOE*ε4 non-carrier male exhibited similar trajectories for diabetes, depression, and obesity, while hypertension and hyperlipidemia were associated with similar less rapid trend (Figure 4E). Distinct trajectory profiles for each RF, stratified by sex and *APOE* genotype, are reported in Figure S2. The area under the survival curve (AUC)[57] for each trajectory is reported in Table S11.

4 | DISCUSSION

Analyses reported herein of medical data for 5644 participants from the UKB addressed the impact of duration of the five modifiable AD-risk-factors (diabetes, hyperlipidemia, hypertension, depression, and obesity) in the context of non-modifiable RFs, specifically sex and *APOE* genotype.

Previous studies indicate that metabolic, inflammatory, and cardiovascular conditions all increase the risk of developing AD and exacerbate disease progression.[3,58] For example, diabetes disrupts glucose metabolism and insulin signaling, promoting amyloid beta accumulation and accelerating cognitive decline.[10,59] Both obesity and diabetes contribute to mitochondrial dysfunction and oxidative stress, which contribute to neuronal energy deficits.[60,61] Similarly, hyperlipidemia and hypertension contribute to vascular dysfunction and reduce cerebral perfusion, compromising blood flow in the brain. This vascular impairment promotes systemic inflammation and increases the production of pro-inflammatory cytokines, which accelerates AD onset.[62] Chronic inflammation also disrupts the blood–brain barrier and is associated with infiltration into the brain of peripheral immune cells.[63] Furthermore, depression is associated with structural brain changes, neuroinflammation, and dysregulation of neurotransmitter systems, leading to hippocampal atrophy and accelerated cognitive decline.[64]

Outcomes of our analyses replicated the impact of both chromosomal female sex and *APOE*ε4 genotype on increased risk of AD.[34,65] We also replicated the impact of the five medical conditions that have been associated with increased risk of AD.[2,3,7,8,11,13–16,20,22,23,65]

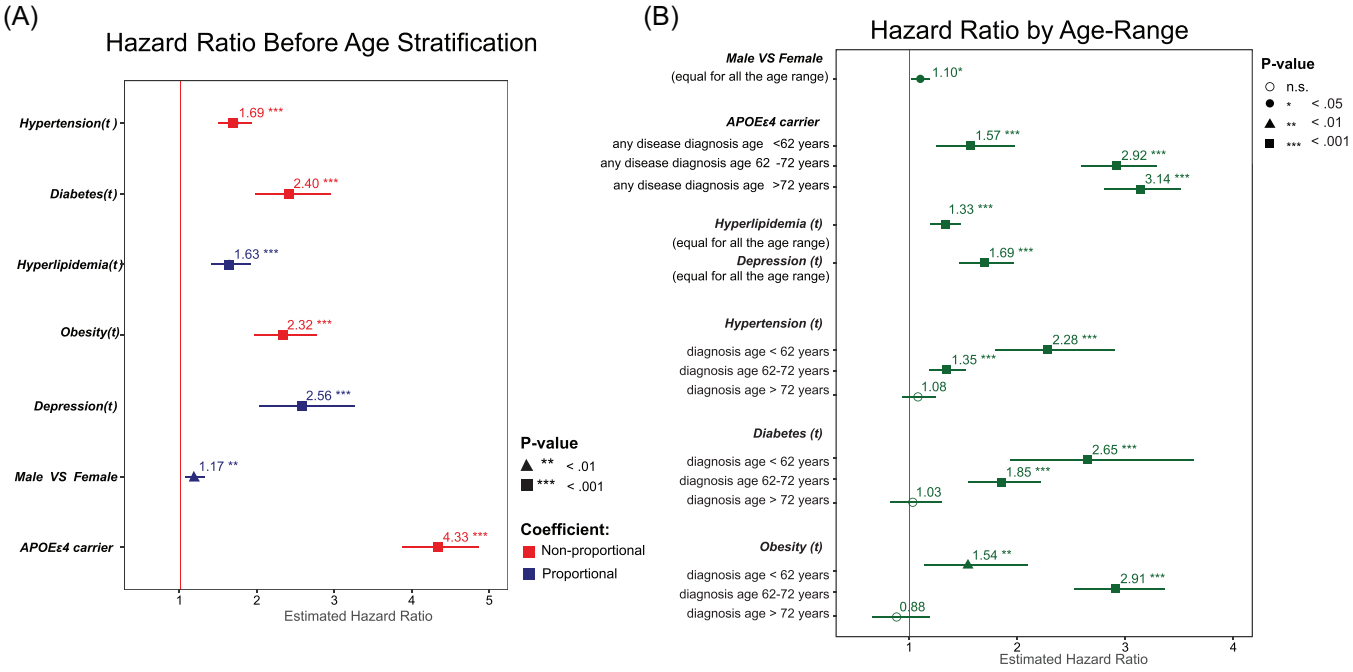

FIGURE 3 Estimated hazard ratios (HRs) and 95% confidence intervals for the associations between Alzheimer's disease (AD) risk factors and non-modifiable risk factors with AD onset in (A) Cox regression model and (B) Cox regression model stratified by time intervals. *APOE*, apolipoprotein E; n.s., not significant.

Furthermore, our data-driven analyses established that the time of the onset of the five RFs significantly impacts AD risk, specifically 62 and 72 years resulted in critical transition ages for RF diagnoses influencing AD development. In detail, prolonged exposure to an AD RF (diagnosis before age 62) was associated with increased risk of AD. Conversely, a delay in RF development (diagnosis after age 72) was associated with delaying in Alzheimer's diagnosis. Trajectories of the five RFs provided insights into the temporal dynamics of multisystem failure, where the cumulative impact of different RFs lead to increased AD risk. Further, the cumulative effect of each RF is consistent with their unique mechanistic pathways which underscore the impact of multisystem failure leading to AD. Thus, delaying the onset of these conditions, especially hypertension and diabetes, could significantly reduce the risk of developing AD.[3,34]

Further, findings reported herein indicated that not all AD-risk-factors exert an equal influence. The HRs derived from our analysis provide a quantifiable measure of these risks, offering clinicians a valuable tool to, for example, stratify patients based on disease susceptibility. The multivariate model revealed that a significantly higher risk of developing AD was associated with an earlier diagnosis (before age 62) of hypertension or diabetes, and obesity diagnosis between the ages 62–72. Interestingly, obesity diagnosed between 62-72 years had an impact comparable to the *APOEε4* genotype, tripling the risk of AD onset. In contrast, the impact of depression and hyperlipidemia onset remained consistent over time, maintaining their influence even in later stages of life. Obesity diagnosed after age 72 was associated with a reduced risk of AD which was not significant, suggesting that post-72 obesity may not exert the same detrimental effects. Higher BMI in older adults could provide metabolic reserves against neurodegeneration and frailty.[66] However, given the heterogeneous literature, further research integrating longitudinal metabolic and neurodegenerative markers is needed.

Regarding non-modifiable RFs, there was no detectable sex effect, indicating a similar impact of AD-risk-factors in both males and females. However, *APOEε4* carriers, regardless of sex, exhibited an amplified effect with increasing age.

The proposed study supports the identification of windows of opportunity for timely and targeted interventions aimed at addressing modifiable RFs during specific stages of life to effectively reduce the risk of AD onset.[3] This approach enables precision medicine prevention by integrating modifiable and non-modifiable factors, allowing clinicians to stratify patients and tailor interventions.[34,35] For example, our findings indicate that hypertension or diabetes diagnosed before age 62 exhibited a significantly higher AD risk, highlighting the importance of early management of these conditions to potentially alter disease trajectories. Targeted prevention strategies—such as lifestyle modifications and early medical management—could exert greatest impact if introduced in midlife.

In this context, addressing depression through early detection and management, including antidepressants, has been associated with significant AD risk reduction.[41] Similarly, managing hypertension and hyperlipidemia through lifestyle modifications and pharmacological interventions can preserve vascular health,[34,35] thereby reducing the risk of cerebral small vessel disease and AD-related pathology. Targeting obesity and diabetes through dietary interventions, regular physical activity, and medication, can mitigate metabolic dysfunction[60,67–69]

TABLE 3 Estimated HRs and 95% CIs for the associations between AD risk factors, non-modifiable risk factors, and AD onset in Cox regression model stratified by time intervals.

Covariate	HR	CI	*p*-value
Male vs. female	1.10	1.02 – 1.19	0.011
APOEε4 carrier			
Any disease diagnosis age < 62 years	1.57	1.25 – 1.98	**<0.001**
Any disease diagnosis age 62–72 years	2.92	2.59 – 3.29	**<0.001**
Any disease diagnosis age > 72 years	3.14	2.80 – 3.51	**<0.001**
Hyperlipidemia(t)	1.33	1.20 – 1.48	**<0.001**
Depression(t)	1.69	1.46 – 1.97	**<0.001**
Hypertension(t)			
Diagnosis age < 62 years	2.28	1.80 – 2.91	**<0.001**
Diagnosis age 62–72 years	1.35	1.19 – 1.53	**<0.001**
Diagnosis age > 72 years	1.08	0.94 – 1.25	0.277
Diabetes(t)			
Diagnosis age < 62 years	2.65	1.94 – 3.63	**<0.001**
Diagnosis age 62-72 years	1.85	1.55 – 2.22	**<0.001**
Diagnosis age > 72 years	1.03	0.82 – 1.30	0.777
Obesity(t)			
Diagnosis age < 62 years	1.54	1.14 – 2.10	**0.005**
Diagnosis age 62-72 years	2.91	2.52 – 3.36	**<0.001**
Diagnosis age > 72 years	0.88	0.66 – 1.19	0.418

Note: A grid search of critical change points of HRs found that 62 years and 72 years were the transition ages to restore constant coefficients. Based on these transition ages, we identified three age groups: Younger (< 62 years), middle-aged (62–72 years), and an older group (> 72 years).
Abbreviations: AD, Alzheimer's disease; *APOE*, apolipoprotein E; CI, confidence interval; HR, hazard ratio.

and AD pathogenesis.[70] Cholesterol-lowering statins have been associated with reduced AD and dementia risk,[35] with beneficial effects mitigated by sex and *APOE* genotype.[34]

One of the advantages of Cox analyses conducted herein is the inclusion of the time-dependent nature of AD-risk-factors since time-varying patterns can confound analysis.[25] Traditional approaches often impose arbitrary time windows, potentially overlooking key pattern in disease progression.[71] By adopting a data-driven strategy, we overcame these limitations, enabling the model to delineate temporal thresholds and tipping points that reveal the dynamic interplay between RFs and disease progression. This iterative approach facilitates a more comprehensive understanding of temporal dynamics governing associations between the onset of RFs and the progression to AD. To address this, proportionality of coefficients was assessed in the Cox model, using Schoenfeld residuals, providing statistical and visual analyses of non-proportionality. Alternative approaches, such as cumulative sum of residuals, Kaplan-Meier, and log-log plots could be evaluated in future studies.[72]

The UKB dataset is a large, contemporary, community-based cohort including thousands of participants and their medical history which enabled a comprehensive analysis of AD occurrence and its associated RFs. Further the UKB is linked to the UK National Health System providing access to clinical diagnoses which eliminates the reliance on self-report. A limitation of the UKB is the potential for non-generalizability to more diverse populations due to volunteer participation and limited ethnic and racial diversity,[73] which could limit comprehensive conclusions about the relationship between AD onset and various RFs across diverse populations.

In the UKB cohort used in this study, the co-occurrence of multiple RFs reflects the well-established phenomenon of multimorbidity in aging populations.[74] Specifically, 22.2% of individuals in the non-AD group and 23.4% in the AD-group had two modifiable RFs, while 14.9% of the non-AD group and 16% of the AD group had three or more. However, due to the limited number of participants in each subgroup, we were unable to assess the joint contribution of multiple RFs accounting for their age of onset in these analyses. This could limit statistical power and result in inaccurate estimates for both HRs and longitudinal trajectory analyses, making it challenging to draw reliable conclusions, especially when further stratifying by sex and *APOE*. Future studies with larger sample sizes or alternative methodological approaches may be necessary to better capture the probable interaction between multiple RFs, genetic predisposition, and AD progression. Additionally, the effect of *APOEε4* dose on AD risk and age of onset is well-documented, with homozygous carriers exhibiting a significantly higher risk and earlier disease onset compared to heterozygous carriers.[75] However, in this study, *APOE* allele-specific ages of AD onset differences were not significant. The small number of homozygous *APOEε4* carriers in the non-AD group ($n = 81$, 1.9%) limited statistical power to enable *APOEε4* dose stratification. For this reason, we pooled *APOEε4* carriers; however, future analyses can be conducted to explore dose-dependent effects in larger cohorts.

Furthermore, we acknowledge that lifestyle-related factors, such as physical activity and diet,[2] play a significant role in AD risk. However, the focus of this study was on modifiable medical conditions with established pharmacological interventions, not including lifestyle variables. While this is a limitation, it is an avenue for future research on their interaction with AD risk. Additionally, this study relied on clinical diagnoses for AD which might be less reliable than biomarker-supported diagnoses of AD. Future studies based on large datasets incorporating biomarker data (e.g., blood-based biomarkers, cerebrospinal fluid [CSF], positron emission tomography [PET] imaging) are needed to validate these results in pathologically confirmed AD cases.

Going forward, future studies will investigate how therapeutics approved to treat the five AD-risk-factors and treatment duration impacts AD development. Understanding the impact of long-term therapy on AD progression could provide valuable insights into optimizing treatment strategies to mitigate cognitive decline. Integrating these findings into public health policies could advance early detection programs, improve risk stratification models, and promote evidence-based lifestyle and clinical interventions to mitigate AD risk at the population level.

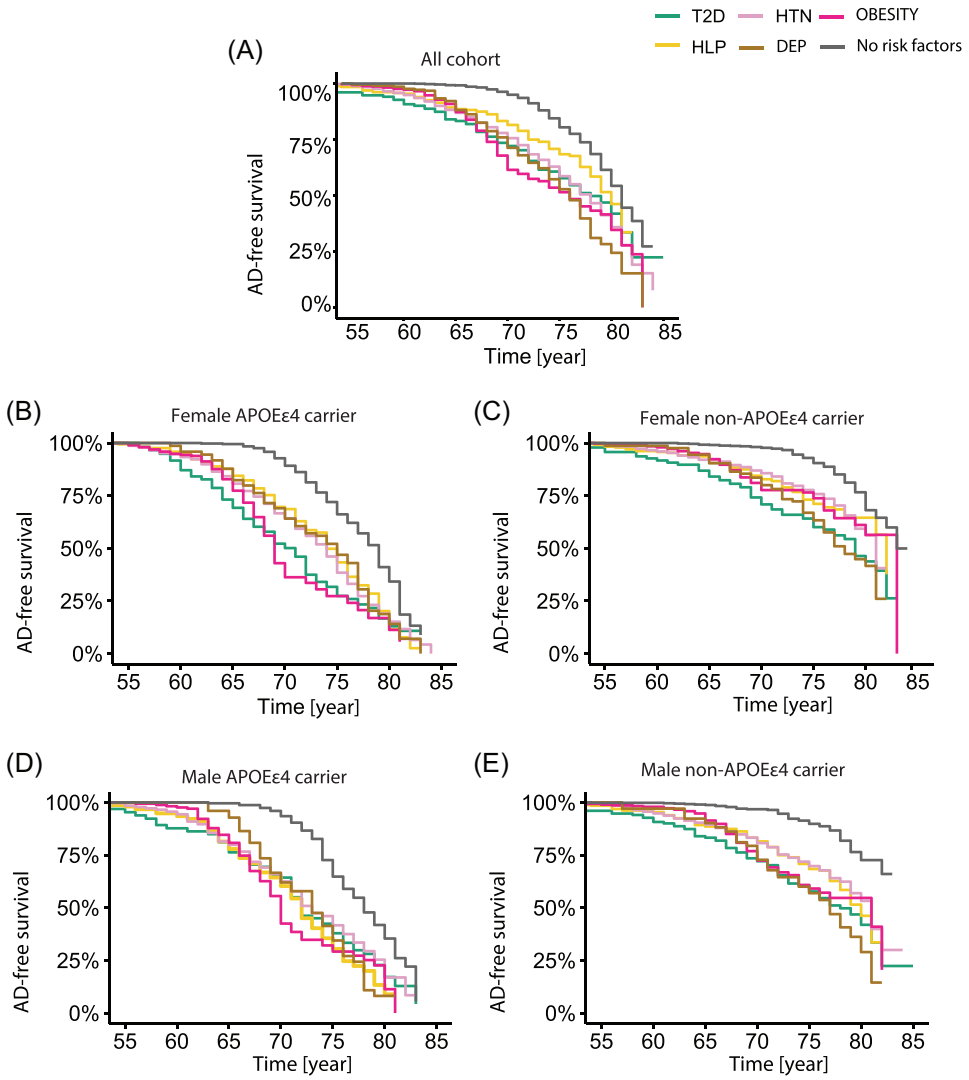

FIGURE 4 Trajectories stratified by sex and apolipoprotein E (*APOE*) genotype for type 2 diabetes (T2D), hyperlipidemia (HLP), hypertension (HTN), obesity (OBESITY), depression (DEP), and absence of AD-risk-factors (No risk factors). (A) All cohort trajectories. (B) Female *APOEε4* carrier. (C) Female *APOEε4* noncarrier. (D) Male *APOEε4* carrier. (E) Male *APOEε4* noncarrier.

The escalating prevalence of individuals diagnosed with multiple AD-risk-factors is projected to rise significantly in the coming decades, underscoring the urgency of understanding their collective impact for patients, caregivers, healthcare systems, and society at large. Leveraging data-driven strategies to quantify the synergistic effect of RF co-occurrence offers a promising avenue for clinical decision making.

This study, focusing on the analysis of the impact of RFs and their duration on the AD onset in the context of sex and *APOE* genotype, provided crucial insights into the impact of multisystem failure, the potential for secondary prevention strategies targeting the AD RFs, and highlighted the importance of identifying specific windows of opportunity for AD prevention interventions.

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CONFLICT OF INTEREST STETEMENT

Authors declare no competing interests. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All participants provided electronically signed consent for their data to be used in health-related research. UK Biobank received ethical approval from North West Multi-centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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