

FEATURED ARTICLE

Hypertension, a dementia polygenic risk score, APOE genotype, and incident dementia

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Abstract

Introduction: There is inconsistent evidence on whether genetic risk for dementia modifies the association between hypertension and dementia.**Methods:** In 198,965 dementia-free participants aged ≥ 60 years, Cox proportional-hazards models were used to investigate the association between hypertension and incident dementia. A polygenic risk score (PRS) based on 38 non-apolipoprotein E (APOE) single nucleotide polymorphisms and APOE $\epsilon 4$ status were used to determine genetic risk for dementia.**Results:** Over 15 years follow-up, 6270 participants developed dementia. Hypertension was associated with a 19% increased risk of dementia (hazard ratio = 1.19, 95% confidence interval 1.11–1.27). The associations remained similar when stratifying by genetic risk, with no evidence for multiplicative interaction by dementia PRS ($P = 0.20$) or APOE $\epsilon 4$ status ($P = 0.16$). However, the risk difference between those with and without hypertension was larger among those at higher genetic risk.**Discussion:** Hypertension was associated with an increased risk of dementia regardless of genetic risk for dementia.

KEYWORDS

apolipoprotein E, dementia, genetics, hypertension, longitudinal, polygenic risk, UK Biobank

1 | BACKGROUND

The global prevalence of dementia is projected to increase from 57 million cases in 2019 to approximately 153 million cases by 2050, largely due to population growth and population aging.¹ Consequently, there is an urgent need to identify risk factors that can be effectively targeted to reduce the risk of dementia. The 2020 Lancet Commission on dementia prevention identified mid-life hypertension as a key modifiable risk factor for dementia.² Studies have found that hypertension is not only associated with an increased risk of vascular dementia, but also other forms of dementia such as Alzheimer's disease (AD).^{3,4} For instance, a recent meta-analysis of seven longitudinal studies found

that mid-life hypertension was associated with an 18% increased risk of AD.⁵

Genetics also plays an important role in dementia risk, with the apolipoprotein E (APOE) $\epsilon 4$ allele associated with three and fourteen times the risk of AD in $\epsilon 4$ heterozygotes and homozygotes, respectively, compared to $\epsilon 3/\epsilon 3$ carriers.⁶ The APOE gene is involved in lipid metabolism and APOE $\epsilon 4$ has been implicated in an increased risk of various adverse vascular events, such as coronary heart disease and subarachnoid hemorrhage.^{7–9} There is evidence that the presence of both APOE $\epsilon 4$ and vascular disease synergistically interact to confer a greater risk of developing AD.¹⁰ Several longitudinal studies have investigated whether APOE $\epsilon 4$ interacts with hypertension to increase

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the risk of dementia but these have produced mixed findings.^{11–13} However, these studies only included a small number of dementia cases ($n = 48$,¹² $n = 204$,¹³ $n = 519$ ¹¹) so there is a need to investigate the interaction among hypertension, APOE $\epsilon 4$, and dementia risk in larger populations.

As well as APOE, recent genome-wide association studies have identified additional single nucleotide polymorphisms (SNPs) potentially implicated in AD development.¹⁴ These SNPs can be combined to produce a “polygenic risk score” (PRS), which provides an indicator of overall genetic risk for dementia.^{15,16} PRS are increasingly being considered powerful tools for risk stratification and disease prediction.^{17,18} In addition to APOE $\epsilon 4$, it is important to consider whether non-APOE genetic predisposition to dementia modifies associations between risk factors and dementia. Studies have investigated whether dementia PRS interacts with lifestyle and health-related factors to modify dementia risk; however, to our knowledge, the interaction with hypertension has not been previously explored.^{19,20}

In the current study, we aimed to address these gaps in the literature by investigating whether hypertension is associated with an increased risk of dementia, and whether any observed association is modified by (1) non-APOE polygenic risk for dementia (hereafter referred to as “dementia PRS”) or (2) APOE $\epsilon 4$ carrier status (either APOE $\epsilon 3/\epsilon 4$ or APOE $\epsilon 4/\epsilon 4$) carrier status.

2 | METHODS

2.1 | UK Biobank

UK Biobank is a population-based prospective cohort study of approximately half a million women and men aged 40 to 69 years at recruitment between 2006 and 2010.²¹ All participants attended one of 22 baseline assessment centers located throughout England, Scotland, and Wales. At baseline participants provided information on sociodemographic, lifestyle, environmental, and health-related factors collected via a touchscreen questionnaire and a nurse-led verbal interview; underwent a range of physical measures; and provided blood samples. These samples were processed and stored for future enhancements including genome-wide genotyping.²² All participants provided electronic signed consent for their data to be used in health-related research. UK Biobank received ethical approval from the National Health Service (NHS) North West Centre for Research Ethics Committee (Ref: 11/NW/ 0382). Of the 502,490 participants who attended baseline assessment, we excluded 285,010 participants aged <60 years old. This was to restrict the sample to participants at baseline who were at risk of developing late-onset dementia over the study follow-up period.

2.2 | Hypertension

Hypertension was defined as meeting at least one of three criteria: (1) self-reported doctor diagnosis of hypertension, (2) self-reported use of

RESEARCH IN CONTEXT

1. **Systematic review:** A PubMed search identified several studies that investigated whether genetic risk of dementia modified the association between hypertension and dementia. Previous research has produced inconsistent findings but only focused on apolipoprotein E (APOE) $\epsilon 4$ status within small populations.
2. **Interpretation:** In a large population-based study of approximately 200,000 participants aged ≥ 60 at study baseline, we found that hypertension was associated with a 19% increased risk of incident all-cause dementia. Genetic risk of dementia based on either APOE $\epsilon 4$ status or non-APOE polygenic risk did not modify these associations. However, the risk difference between hypertension and no hypertension was greater in those with a higher genetic risk of dementia.
3. **Future directions:** Replication of these findings in other large cohorts is warranted, with particular focus on the role of non-APOE genetic risk for dementia as well as whether differential associations are observed for dementia subtypes such as vascular dementia and Alzheimer's disease.

antihypertensive medication, or (3) measured systolic blood pressure ≥ 140 mm of mercury (mmHg) or diastolic blood pressure ≥ 90 mmHg. The cut-off points for the third criteria were in line with the internationally recommended definition of hypertension at time of blood pressure measurement in UK Biobank in 2006 through 2010.²³

Participants who responded “High blood pressure” to the touchscreen question “Has a doctor ever told you that you have had any of the following conditions?” or reported having hypertension during the verbal interview were defined as having doctor-diagnosed hypertension. Participants who responded “Blood pressure medications” to the touchscreen question “Do you regularly take any of the following medications?” or reported an antihypertensive medication (beta blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers, calcium channel blockers, alpha blockers, or diuretics) during the verbal interview were defined as using antihypertensive medication. Two measures of blood pressure were collected, at least 1 minute apart, using an Omron HEM 7015-T automated sphygmomanometer. In the current study, a mean of both measures was used to determine systolic and diastolic blood pressure in mmHg.

2.3 | Genetics

Genome-wide genotyping and imputation was performed by UK Biobank, with further detail on the collection and processing of the genetic data published elsewhere.²⁴

The dementia PRS was based on a 39-SNP score (available on the Polygenic Score Catalog online as PGS001775) developed by Ebenau et al.²⁵ Ebenau et al. selected variants of genome-wide significance from publicly available genome-wide association study summary statistics for late-onset AD.^{17,26,27} The weights given for the score were derived in the International Genomics of Alzheimer's Project.^{26,27} PLINK 2²⁸ with hard call threshold 0.1 was used to ensure that none of the SNPs were in linkage disequilibrium with the APOE SNPs ($R^2 < 0.3$). One SNP had minor allele frequency < 0.005 and was excluded. The final score consisted of 38 SNPs, where all SNPs had imputation information > 0.9 and no SNPs were ambiguous.

The dementia PRS was split into quintiles, and further categorized into "low" (quintile 1), "intermediate" (quintiles 2–4), and "high" (quintile 5) groups, with a higher PRS indicating a greater dementia risk. APOE $\epsilon 4$ status was derived using the APOE SNPs rs429358 and rs7412, which were directly genotyped.

For both genetic exposures, participants who were related (third degree or higher), sex discordant, or who were outliers for genotype missingness or heterozygosity based on UK Biobank-derived sample quality control data were excluded. For APOE, $\epsilon 1/\epsilon 3$ and $\epsilon 2/\epsilon 4$ genotypes could not be accurately distinguished from the unphased genotype data and were excluded.

2.4 | Dementia

Dementia was ascertained using hospital inpatient and death registry records. Hospital inpatient records were obtained from Hospital Episode Statistics for England, Scottish Morbidity Record for Scotland and Patient Episode Database for Wales. Death registry records were obtained from NHS Digital for England and Wales and Information and Statistics Division for Scotland. Primary and secondary hospital diagnoses and causes of deaths were recorded using the International Classification of Diseases (ICD) coding system. The codes were selected and validated by the UK Biobank outcome adjudication group and are provided in Table S1 in supporting information.²⁹

2.5 | Covariates

Sociodemographic, lifestyle, and health-related characteristics associated with both hypertension³⁰ and dementia risk² were identified as potential confounders and incorporated as covariates in the analyses. Townsend deprivation score was used as an indicator of material deprivation and was assigned to each participant corresponding to their residential postcode at recruitment.³¹ Educational qualifications, ethnicity, household income, and smoking status were captured on the touchscreen questionnaire. Standard alcohol units (alcohol by volume equivalents) were derived from touchscreen questions on the number of typical volume drinks for each type of alcohol consumed per week. Physical activity was assessed using questions adapted for the touchscreen questionnaire from the validated short International Physical Activity Questionnaire.³² The time spent in vigorous, mod-

erate, and walking activity was weighted by the energy expended for these categories of activity to produce total metabolic equivalent task minutes per week. Comorbidities included the following conditions reported during the verbal interview: cardiovascular disease, diabetes, arrhythmia, asthma, chronic obstructive pulmonary disease, asthma, migraine, epilepsy, anxiety or stress, depression, and osteoporosis or other joint disorders. The comorbidities selected were based on prevalence in middle-aged UK population, clinical significance, and inclusion in previous multimorbidity studies.³³ Body mass index (BMI; kg/m²) was derived from weight (kg) using scales and standing height (meters) measured during the physical examination. Country of residence was defined as location of assessment center attended at baseline.

2.6 | Statistical analysis

Baseline characteristics by hypertension status were age standardized. Cox proportional-hazards models using time on study as the underlying time scale were used to estimate the association between hypertension and incident dementia. Time on study in years was calculated from date of attending baseline assessment until date of first incident dementia diagnosis, date of death, date of loss-to follow-up, or end of follow-up, whichever occurred first. End of follow-up was based on the availability of the medical record data in UK Biobank, which was censored at September 30, 2021 for England; July 31, 2021 for Scotland; and February 28, 2018 for Wales. The proportional hazards assumption was visually assessed using scaled Schoenfeld residuals. There was no evidence that any of the variables included in the analyses violated the proportional hazards assumption. All analyses were first minimally adjusted for age in years and sex, and then additionally adjusted in the main model for ethnicity (White, non-White), Townsend deprivation index (quintiles), education (primary, secondary, post-secondary non-tertiary, tertiary), household income in British pound sterling ($< 18,000$, $18,000$ – $30,999$, $31,000$ – $51,999$, $52,000$ – $100,000$, $> 100,000$), country (England, Scotland, Wales), smoking status (never, former, current), weekly alcohol intake in units, physical activity in metabolic equivalent (MET) minutes per week (≤ 1200 , > 1200), BMI (< 25 , ≥ 25 – < 30 , ≥ 30), and number of comorbidities (0, 1, 2, ≥ 3). Models that included the dementia PRS were also adjusted for the first 10 principal components of ancestry. Participants with missing data or who responded "prefer not to answer/do not know" for any of the covariates were assigned to a separate category for that covariate.

To investigate whether associations differ by length of follow-up, the main analysis was repeated with restriction to participants who were followed-up for < 5 years, 5 to < 10 years, and ≥ 10 years of follow-up. The interaction between hypertension and (1) age (60–64 vs. ≥ 65 years old) and (2) sex was investigated by entering hypertension \times age and hypertension \times sex interaction terms into the main model.

The interaction between hypertension and genetic risk was investigated by entering hypertension \times dementia PRS (low, intermediate, high) and hypertension \times APOE $\epsilon 4$ carrier status (absence of $\epsilon 4$, presence of $\epsilon 4$) interaction terms separately into the main model. Effect estimates within each strata of genetic risk were obtained for

TABLE 1 Age-standardized baseline characteristics of 198,965 participants by hypertension

Characteristic	Hypertension (%)	
	No N = 45,170	Yes N = 153,795
Age in years, mean (SD)	63.8 (2.8)	64.3 (2.9)
Women	63.8	49.2
Non-White ethnicity	2.3	3.2
Townsend deprivation index, quintiles		
1 (least deprived)	20.7	19.8
2	20.4	19.8
3	19.8	20.1
4	20.1	19.9
5 (most deprived)	18.9	20.3
Education		
Primary	24.4	29.2
Secondary	47.0	43.2
Post-secondary non-tertiary	11.4	10.6
Tertiary	17.2	17.0
Household income in GBP		
<18,000	33.7	35.4
18,000–30,999	32.8	32.6
31,000–51,999	20.9	20.3
52,000–100,000	10.1	9.5
>100,000	2.6	2.2
Country		
England	90.1	88.9
Scotland	6.3	7.0
Wales	3.7	4.1
Smoking status		
Never	51.1	49.0
Former	39.8	43.1
Current	9.1	7.9
Weekly alcohol intake in units, mean (SD)	9.6 (10.6)	11.8 (12.6)
High physical activity, >1200 MET minutes per week	66.2	64.9
BMI		
Normal	41.3	24.4
Overweight	43.3	46.1
Obese	15.4	29.6
Number of comorbidities		
0	56.1	55.8
1	34.3	32.1
2	8.1	9.7
≥3	1.5	2.4

(Continues)

TABLE 1 (Continued)

Characteristic	Hypertension (%)	
	No N = 45,170	Yes N = 153,795
Dementia PRS		
Low	19.8	20.1
Intermediate	59.6	60.1
High	20.6	19.8
APOE ε4 carrier	26.3	26.5

Abbreviations: APOE, apolipoprotein E; BMI, body mass index; GBP, British pound sterling; MET, metabolic equivalent of task; N, number of participants; PRS, polygenic risk score; SD, standard deviation.

hypertension versus no hypertension. These analyses were repeated with exclusion of participants of non-White genetic ancestry.

To investigate possible joint effects by genetic risk and hypertension, a 12-level categorical variable was derived containing each combination of dementia PRS categories, APOE ε4 carrier status, and hypertension. The main analysis was repeated with this variable entered with “low dementia PRS, absence of ε4, and no hypertension” as the reference group.

The cumulative incidence of dementia by hypertension and genetic risk was obtained using the cumulative incidence function of competing risk regression.³⁴

All P-values were two sided, with statistical significance set at <0.05. Analyses were performed using STATA/MP version 17 (StataCorp). The cumulative incidence analyses were performed using the “cmprsk” package in R software version 4.0.3.

3 | RESULTS

Of 217,408 participants aged ≥60 years, 166 with prevalent dementia and 18,349 with missing hypertension status were excluded, resulting in a final sample of 198,965 participants. Of these, 153,795 (77.3%) participants had hypertension, with 53% of hypertensive participants self-reporting a diagnosis, 47% self-reporting medication use, and 81% having high blood pressure measured at baseline assessment (Table S2 in supporting information). Table 1 shows age-standardized baseline characteristics by hypertension and Table S3 in supporting information shows these characteristics without age standardization.

A total of 6270 (3.2%) participants developed incident dementia over 2,353,031 person-years of follow-up (mean = 11.8, standard deviation = 2.2). A Kaplan-Meier plot demonstrates clear differences in the probability of remaining dementia-free by hypertension status after 5 years of follow-up (Figure 1). In age- and sex-adjusted analyses, hypertension was associated with an increased risk of dementia (hazard ratio [HR] = 1.19, 95% confidence interval [CI] 1.12–1.27; Table 2). The direction and strength of this association remained the same when fully adjusting for additional covariates (HR = 1.19, 95% CI 1.11–1.27). When restricting to participants who were censored ≤5 years, >5 to

FIGURE 1 Nelson–Aalen plot for cumulative hazard of dementia by hypertension. * Number at risk at 2-year intervals from baseline

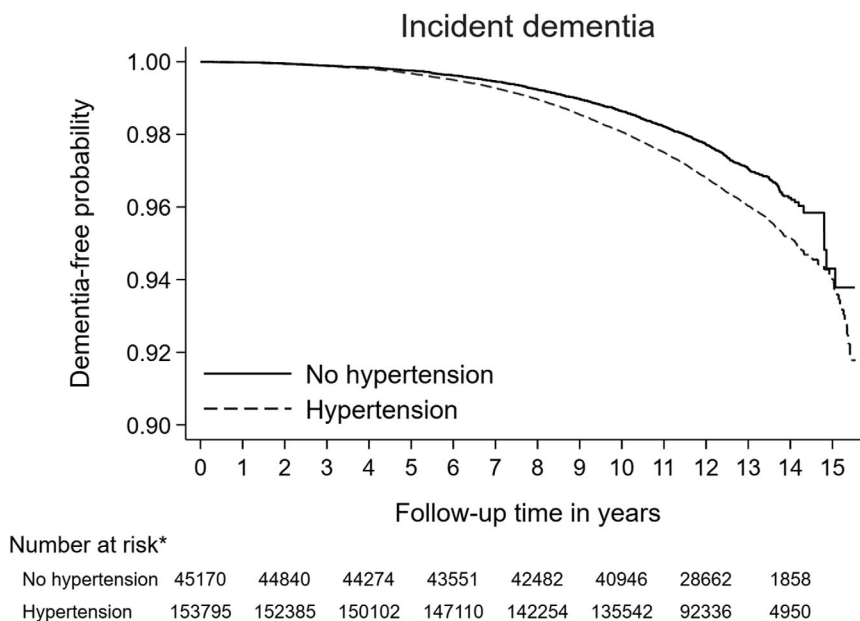


TABLE 2 Cox proportional-hazards models investigating the association between hypertension and incident dementia by different follow-up periods

	Cases/population	Minimally adjusted ^a HR (95% CI)	P-value	Fully adjusted ^b HR (95% CI)	P-value
Complete follow-up					
No hypertension	1,133/45,170	1 (Reference)		1 (Reference)	
Hypertension	5,137/153,795	1.19 (1.12–1.27)	<0.001	1.19 (1.11–1.27)	<0.001
≤5 years					
No hypertension	107/45,170	1 (Reference)		1 (Reference)	
Hypertension	487/153,795	1.14 (0.92–1.41)	0.22	1.15 (0.93–1.42)	0.21
>5 to 10 years					
No hypertension	480/43,926	1 (Reference)		1 (Reference)	
Hypertension	2,315/148,722	1.24 (1.12–1.37)	<0.001	1.25 (1.13–1.38)	<0.001
>10 years					
No hypertension	546/40,946	1 (Reference)		1 (Reference)	
Hypertension	2,335/135,542	1.16 (1.05–1.27)	0.002	1.14 (1.03–1.25)	0.008

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aModels adjusted for age and sex.

^bModels adjusted for age, sex, ethnicity, Townsend deprivation index, education, household income, country, smoking status, alcohol intake, physical activity, body mass index, number of comorbidities.

10 years, and >10 years, the fully adjusted HRs were 1.15 (95% CI 0.93–1.42), 1.25 (95% CI 1.13–1.38), and 1.14 (1.03–1.27), respectively. There was no significant interaction between hypertension and age (60–64 vs. ≥65 years old) or sex, with the overall associations remaining similar to the main findings when stratifying by these characteristics (Table S4 in supporting information). Compared to no hypertension, each component used to define hypertension was individually associated with an increased risk of dementia (Table S5 in supporting information).

Compared to those with a low dementia PRS, the fully adjusted HRs for risk of incident dementia were 1.31 (95% CI 1.21–1.42) and 1.83 (95% CI 1.67–2.00) for intermediate and high dementia PRS, respectively. These associations remained highly similar when additionally adjusting for APOE: intermediate dementia PRS (HR = 1.31, 95% CI 1.21–1.43) and high dementia PRS (HR = 1.83, 95% CI 1.67–2.01). Carriers of APOE ε4 had an increased risk of dementia compared to non-carriers (fully adjusted HR = 3.17, 95% CI 3.01–3.34, additional adjustment for dementia PRS HR = 3.15, 95% CI 2.97–3.33).

TABLE 3 Cox proportional-hazards models investigating the association between hypertension and incident dementia by dementia polygenic risk score

Dementia PRS	Cases/population	Minimally adjusted ^a HR (95% CI)	P-value	Fully adjusted ^b HR (95% CI)	P-value
Low					
No hypertension	122/7,252	1 (Reference)		1 (Reference)	
Hypertension	621/24,823	1.27 (1.05–1.55)	0.02	1.27 (1.05–1.54)	0.02
Intermediate					
No hypertension	537/21,790	1 (Reference)		1 (Reference)	
Hypertension	2,366/74,431	1.14 (1.04–1.25)	0.007	1.14 (1.03–1.25)	0.008
High					
No hypertension	231/7,533	1 (Reference)		1 (Reference)	
Hypertension	1,084/24,541	1.30 (1.13–1.50)	<0.001	1.31 (1.14–1.52)	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; PRS, polygenic risk score.

^aModels adjusted for age, sex, and first 10 principal components of ancestry.

^bModels adjusted for age, sex, ethnicity, Townsend deprivation index, education, household income, country, smoking status, alcohol intake, physical activity, body mass index, number of comorbidities, and first 10 principal components of ancestry.

P-value for interaction between hypertension and polygenic risk for dementia and incident dementia in minimally adjusted model = 0.31, and fully adjusted model = 0.20.

TABLE 4 Cox proportional-hazards models investigating the association between hypertension and incident dementia by APOE ε4 carrier status

APOE ε4 carrier status	Cases/population	Minimally adjusted ^a HR (95% CI)	P-value	Fully adjusted ^b HR (95% CI)	P-value
Non-APOE ε4 carrier					
No hypertension	484/31,578	1 (Reference)		1 (Reference)	
Hypertension	2,291/107,263	1.25 (1.13–1.37)	<0.001	1.23 (1.11–1.36)	<0.001
APOE ε4 carrier					
No hypertension	580/11,322	1 (Reference)		1 (Reference)	
Hypertension	2,488/38,568	1.13 (1.03–1.24)	0.008	1.12 (1.02–1.22)	0.02

Abbreviations: APOE, apolipoprotein E; CI, confidence interval; HR, hazard ratio.

^aModels adjusted for age and sex.

^bModels adjusted for age, sex, ethnicity, Townsend deprivation index, education, household income, country, smoking status, alcohol intake, physical activity, body mass index, number of comorbidities.

P-value for interaction between hypertension and APOE ε4 carrier status and incident dementia in minimally adjusted model = 0.15, and fully adjusted model = 0.16.

In the fully adjusted models, there was no statistically significant interaction between hypertension and dementia PRS (*P*-value for interaction = 0.20), or hypertension and APOE ε4 (*P*-value for interaction = 0.16) and risk of incident dementia. The association between hypertension and dementia remained similar to the main analysis when stratifying by low, intermediate, and high dementia PRS (Table 3) as well as stratifying by APOE ε4 carrier status (Table 4). The findings also remained similar after excluding participants of non-White genetic ancestry (Table S6 in supporting information). In models investigating the joint effect of genetic risk of dementia and hypertension, the highest risk of dementia was observed in those with a high dementia PRS, and presence of APOE ε4 and hypertension (HR = 8.10, 95%

CI 6.14–10.69), compared to those with a low dementia PRS, and absence of APOE ε4 and without hypertension (Table S7 in supporting information).

Among participants with a high dementia PRS the 12-year cumulative incidence of dementia was 4.3% among those with hypertension compared to 2.8% among those without hypertension (Figure 2A). Among APOE ε4 carriers the incidence was 6.2% among those with hypertension compared to 4.7% among those without hypertension (Figure 2B). The 12-year cumulative incidence of dementia was lower within each combination of dementia PRS and APOE ε4 stratum for those without hypertension compared to those with hypertension (Figure 2C).

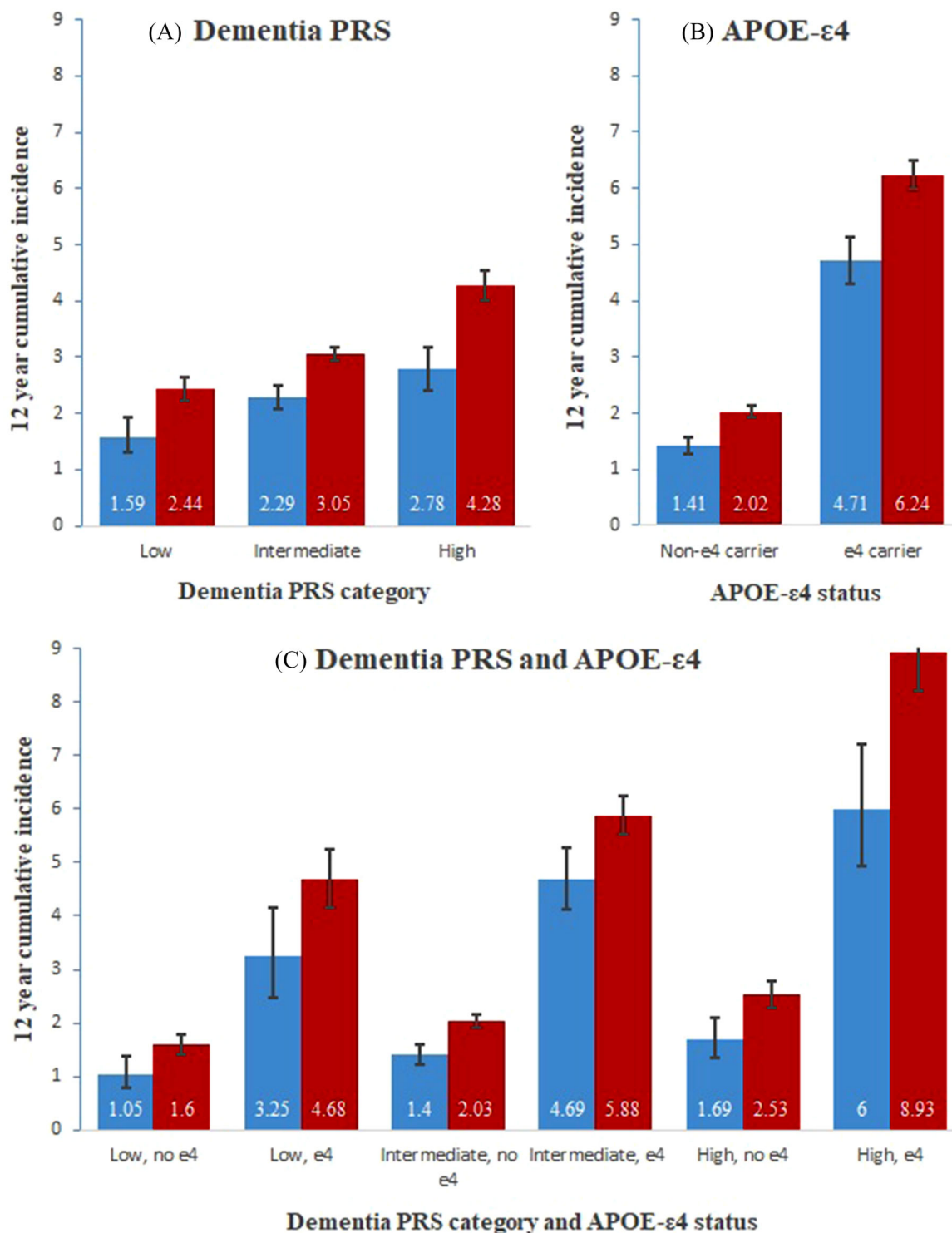


FIGURE 2 Twelve-year risk of incidence dementia by hypertension and genetic risk for dementia. Abbreviations: APOE, apolipoprotein E; PRS, polygenic risk score. Error bars indicate 95% confidence intervals

The risk differences attributable to hypertension were higher within participants with an increased genetic predisposition for dementia. For instance, the cumulative incidence of dementia in those with hypertension compared to no hypertension was 0.85, 0.76, and 1.50 percentage points higher in the low, intermedi-

ate, and high dementia PRS groups, respectively (Figure 2A). The cumulative incidences for dementia were 0.61 and 1.53 percentage points higher for APOE ε4 non-carriers and carriers, respectively, among those with hypertension compared to no hypertension (Figure 2B).

4 | DISCUSSION

In this large population-based cohort of almost 200,000 women and men aged ≥ 60 , hypertension was associated with a 19% increased risk of dementia. The direction and strength of this association was consistent within 5, >5 to 10, >10 years of follow-up. Both a higher dementia PRS and APOE $\epsilon 4$ were independently associated with dementia risk. Hypertension was consistently associated with an increased risk of dementia regardless of dementia PRS category or APOE $\epsilon 4$ carrier status. However, the risk difference between no hypertension and hypertension was substantially larger in those with the highest genetic risk of dementia. The cumulative incidence of dementia over 12 years was eight times higher in those with highest genetic risk of dementia and hypertension compared to those with the lowest genetic risk of dementia and no hypertension.

Our findings are in line with current evidence from observational studies suggesting that hypertension is a strong modifiable risk factor for dementia, including both vascular and non-vascular dementias such as AD.^{2,4,5,35} Previous studies have investigated blood pressure and dementia risk in UK Biobank. One found a U-shaped association between systolic blood pressure and dementia, while another found a similar shaped association in men but a dose-response association in women.^{36,37} We also found that clinically defined cut-points for hypertension based on systolic (≥ 140 mmHg) and diastolic (≥ 90 mmHg) blood pressure was associated with dementia risk. However, we did not find a significant interaction between sex and hypertension for risk of dementia.

Furthermore, we found no interaction between hypertension and age and risk of dementia. The role of age in the association between hypertension and dementia is complex, with hypertension generally considered a strong risk factor for dementia in mid-life (aged 45–65 years) but not late-life (>65 years).^{2,5,38} The lack of association in later-life might be due to reverse causation, for example, ill health and weight loss resulting in lower blood pressure, or it might be due to more aggressive treatment in at-risk individuals. This is consistent with findings that declining blood pressure from mid- to late-life is associated with an increased risk of dementia.³⁵ The lack of interaction with age in the current study is likely due to the narrow age range at baseline (ages 60–69) and a follow-up period limited to up to 15 years.

Several studies have investigated the relationship among hypertension, genetic risk for dementia based on APOE $\epsilon 4$, and incident dementia. In 1287 Finnish participants, Kivipelto et al. found no evidence of an interaction between high systolic blood pressure and APOE and dementia risk over a mean of 21 years, but did find an additive effect on risk of AD when combining high blood pressure, APOE $\epsilon 4$, and high cholesterol levels.¹² In 966 Swedish participants, Qiu et al. found that APOE $\epsilon 4$ carrier status interacted with low diastolic blood pressure to increase AD risk over 6 years, but found no interaction between APOE $\epsilon 4$ with systolic blood pressure or antihypertensive medication use and risk of AD.¹³ In 9349 American participants, Pillai et al. found that hypertension was associated with an increased dementia risk in non-APOE $\epsilon 4$ carriers aged >65 years over an average of 6 years, but found no association in those aged ≤ 65 years or in younger or older

APOE $\epsilon 4$ carriers.¹¹ Longitudinal studies on cognitive decline or cognitive impairment have either found evidence for an interaction,^{39,40} evidence for an interaction on certain outcomes but not others or for certain exposure subtypes (i.e., untreated vs. treated hypertension),^{41–44} or no interaction.^{45–50}

The interpretation of the findings from previous studies is complicated by the different approaches used to define hypertension. Our definition included current blood pressure as well as history using self-reported doctor diagnosis and antihypertensive use. We incorporated historical information as a one-off blood pressure measure does not account for treatment history or the various factors that influence the likelihood of hypertension treatment and control. In UK Biobank, an increased prevalence of comorbidities, smoking, low physical activity, and higher material deprivation was associated with a greater likelihood of controlled compared to uncontrolled hypertension.³³ These associations are consistent with the hypothesis that individuals with a greater risk of cardiovascular disease are more likely to be aggressively treated with antihypertensives.³³ We found that antihypertensive use was associated with an increased risk of dementia and this likely reflects confounding by indication, that is, antihypertensive use is associated with a history of high blood pressure which in turn is associated with dementia. Studies with repeat measures of blood pressure as well as more detailed information on length and intensity of blood pressure treatment could help elucidate these complex relationships.

Although there is a lack of evidence that genetic predisposition for dementia interacts with hypertension to modify dementia risk, it is important to acknowledge that an individual with hypertension typically presents with other conditions.³⁰ Multimorbidity, which is the co-occurrence of two or more long-term conditions, is estimated to affect a third of individuals globally, and rises substantially with age.⁵¹ A recent study found that multimorbidity, in particular cardiovascular morbidity, was associated with dementia risk and this association was significantly stronger in APOE $\epsilon 4$ carriers.⁵² Future studies investigating hypertension in the context of other diseases, and whether genetic risk modifies any associations with dementia, are warranted.

This study has several strengths. To our knowledge, it is the largest study to investigate the interaction between APOE $\epsilon 4$ and hypertension and future risk of dementia, and the first to additionally explore the interaction between hypertension and non-APOE genetic risk for dementia. Loss to follow-up was minimal as cases were captured through cohort-wide linkage to electronic medical records. These records have been demonstrated to have high validity for ascertaining dementia in UK Biobank.²⁹ This study also has several limitations. We were unable to investigate the associations with specific dementia subtypes, such as vascular dementia or AD, as the hospital inpatient and death registry data does not accurately discriminate between different causes of dementia.²⁹ Furthermore, the lack of other sources, for example, primary care records, means that dementia will be underascertained in the current study. Only 3% of the UK Biobank sample identified as non-White, and the PRS was derived and validated using populations of European genetic ancestry. A large proportion of the sample met our definition of hypertension (77%). This is slightly higher compared to the general population based the Health

Survey for England (HSE) 2008, which found 62% of 65- to 74-year-olds had hypertension.⁵³ This is likely due to a difference in our definition of hypertension, for instance the inclusion of self-reported diagnosis in our study, which was absent from the HSE definition. However, there is also evidence of a “healthy volunteer” selection bias in UK Biobank, so the prevalence and incidence rates cannot be generalized to other populations.⁵⁴ Due to the observational nature of the study residual confounding cannot be ruled out and causality cannot be determined.

5 | CONCLUSION

In the current study, hypertension was associated with an increased risk of dementia regardless of genetic risk for dementia based on either non-APOE polygenic risk or presence of APOE ε4. However, the differences in risk of dementia based on hypertensive status were larger in those with an inherited predisposition of dementia, consistent with a similar relative risk for hypertension acting on a higher baseline inherited risk. Control of blood pressure in middle life may reduce dementia risk across all categories of inherited predisposition.

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CONFLICTS OF INTEREST

The authors have no competing interests to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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