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RESEARCH ARTICLE

Apathy and *APOE* in mild behavioral impairment, and risk for incident dementia

Daniella Vellone[1] | **Maryam Ghahremani**[1,2] | **Zahra Goodarzi**[1,3,4,5,6] | **Nils D. Forkert**[1,7,8,9] | **Eric E. Smith**[1,8] | **Zahinoor Ismail**[1,2,3,4,5,6,8,10]

[1]Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

[2]Department of Psychiatry, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

[3]Mathison Centre for Mental Health Research and Education, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

[4]Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

[5]Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

[6]O'Brien Institute for Public Health, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

[7]Department of Radiology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

[8]Department of Clinical Neurosciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

[9]Alberta Children's Hospital Research Institute, University of Calgary, Calgary, Alberta, Canada

[10]College of Medicine and Health, University of Exeter, Exeter, UK

Correspondence
Zahinoor Ismail, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, 3280 Hospital Dr. NW, Calgary, Alberta T2N 4Z6, Canada.
E-mail: ismailz@ucalgary.ca

Statistical analysis performed by: Maryam Ghahremani, PhD.

Daniella Vellone and Maryam Ghahremani are co-first authors and equal contributors.

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Abstract

Introduction: Mild behavioral impairment (MBI) is a high-risk state for incident dementia and comprises five core domains including affective dysregulation, impulse dyscontrol, social inappropriateness, psychotic symptoms, and apathy. Apathy is among the most common neuropsychiatric symptoms (NPS) in dementia but can also develop in persons with normal cognition (NC) or mild cognitive impairment (MCI). The later-life emergence and persistence of apathy as part of the MBI syndrome may be a driving factor for dementia risk. Therefore, we investigated MBI-apathy–associated progression to dementia, and effect modification by sex, race, cognitive diagnosis, and apolipoprotein E (*APOE*) genotype.

Methods: Dementia-free National Alzheimer's Coordinating Center participants were stratified by persistent apathy status, based on Neuropsychiatric Inventory (NPI)–Questionnaire scores at two consecutive visits. Hazard ratios (HRs) for incident dementia for MBI-apathy and NPI-apathy relative to no NPS, and MBI-apathy relative to no apathy, were determined using Cox proportional hazards regressions, adjusted for baseline age, sex, years of education, race, cognitive diagnosis, and *APOE* genotype. Interactions with relevant model covariates were explored.

Results: Of the 3932 participants (3247 with NC), 354 had MBI-apathy. Of all analytic groups, MBI-apathy had the greatest dementia incidence (HR = 2.69, 95% confidence

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interval [CI]: 2.15–3.36, $P < 0.001$). Interaction effects were observed between cognitive diagnosis and *APOE* genotype with the NPS group. The contribution of apathy to dementia risk was greater in NC (HR = 5.91, 95% CI: 3.91–8.93) than in MCI (HR = 2.16, 95% CI: 1.69–2.77, interaction $P < 0.001$) and in all *APOE* genotypes, was greatest in *APOE* ε3 (HR = 4.25, 95% CI: 3.1–5.82, interaction $P < 0.001$).

Discussion: Individuals with MBI-apathy have a markedly elevated risk for future dementia, especially when symptoms emerge in those with NC. Both cognitive status and *APOE* genotype are important moderators in the relationship between MBI-apathy and incident dementia. MBI-apathy may represent a group in whom apathy is a preclinical or prodromal manifestation of dementia and identify a precision medicine target for preventative interventions.

KEYWORDS
Alzheimer's disease, apathy, apolipoprotein E, dementia, mild behavioral impairment, mild cognitive impairment, neuropsychiatric symptoms

1 | BACKGROUND

The neurodegenerative process in Alzheimer's disease (AD) starts long before clinical diagnosis[1] and historically, early cognitive decline as seen in mild cognitive impairment (MCI) has provided an opportunity for earlier detection. Longitudinal studies have demonstrated that behavior or personality change can occur prior to cognitive decline in 30% of AD cases.[2,3] Incorporation of this behavioral prodrome may assist with earlier detection, especially in normal cognition (NC). Mild behavioral impairment (MBI) is characterized by the *de novo* emergence of persistent neuropsychiatric symptoms (NPS) in later life.[4] This construct was developed to leverage behavioral changes for detection of the high-risk group, and has proven successful for prognosticating dementia compared to conventional measures of psychiatric symptoms.[5,6] Two MBI criteria confer this improvement in specificity: symptoms (1) emerge *de novo* after the age of 50 and reflect a change from longstanding patterns of behavior (to distinguish from psychiatric disorders); and (2) persist for ≥6 months (to increase the likelihood that they are secondary to neurodegenerative disease rather than life stressors).[2,4,7]

MBI comprises five core domains of NPS including affective dysregulation, impulse dyscontrol, social inappropriateness, psychotic symptoms, and apathy.[4] Apathy, characterized by decreased interest, initiative, and emotional reactivity, is one of the most common, stable, and persistent NPS.[8] Apathy in AD is associated with lower quality of life, poorer health, greater caregiver distress and burden, and higher mortality.[9] Apathy can also present in prodromal disease and is associated with incident dementia,[10] amyloid beta (Aβ), and tau.[11,12] Therefore, apathy may be an important marker of disease. Longitudinal investigation is required to better visualize patterns of change across time. As apathy has been suggested as a driving factor in dementia risk conferred by MBI,[13] MBI-apathy may be a robust marker for prognosticating incident dementia.[4] However, research in this context is limited.

Here, we investigated MBI-apathy–associated progression to dementia compared to no NPS and no apathy. We also investigated progression to dementia among those with apathy at their first visit without consideration of past psychiatric history compared to no NPS. Additionally, we incorporated the apolipoprotein E (*APOE*) genotype (*APOE* ε2/ε3/ε4), which plays a prominent role in AD, to explore effect modification. We hypothesized that MBI-apathy would have greater rates of incident dementia than no NPS and no apathy, and that the *APOE* ε2 allele would have protective effects, mitigating dementia risk across groups, compared to *APOE* ε3 and *APOE* ε4.

- Rate of progression to dementia was explored in mild behavioral impairment (MBI)-apathy, Neuropsychiatric Inventory-apathy, no apathy, and no neuropsychiatric symptoms (NPS).
- Interactions between MBI-apathy and cognitive status and apolipoprotein E (*APOE*) genotype were tested.
- Progression rate to dementia in MBI-apathy was twice that of no-NPS and no-apathy.
- The contribution of MBI-apathy to dementia risk was greater in normal cognition than mild cognitive impairment.
- The contribution of MBI-apathy to dementia risk was greater among non-*APOE* ε4 groups.

2 | METHODS

2.1 | Study population: National Alzheimer's Coordinating Center

Data were drawn from the National Alzheimer's Coordinating Center (NACC; https://naccdata.org/). NACC was established by the National Institute on Aging (NIA) and comprises several NIA-funded Alzheimer's Disease Research Centers (ADRCs) recruiting and collecting data

RESEARCH IN CONTEXT

1. **Systematic Review**: A PubMed search identified studies investigating apathy- and apolipoprotein E (*APOE*)-associated dementia risk. Apathy and *APOE* ε4 are associated with greater dementia risk and *APOE* ε2 with lower risk. However, interactions between apathy and the *APOE* genotype remain unexplored.
2. **Interpretation**: In a longitudinal study of 3932 National Alzheimer's Coordinating Center participants with normal cognition (NC) and mild cognitive impairment (MCI), mild behavioral impairment (MBI)-apathy was associated with a 2.69- and 2.61-fold greater dementia progression rate than no neuropsychiatric symptoms (NPS) and no apathy, respectively. Interactions were evident between NPS status (MBI-apathy vs. no-NPS and no apathy) and cognitive status and *APOE* genotype. The contribution of MBI-apathy to dementia risk was greater in NC than MCI and ε3 than ε4, but not ε3 versus ε2 or ε2 versus ε4. MBI-apathy may be a predictor of dementia, with effect modification by cognitive status and *APOE* genotype.
3. **Future Directions**: Findings should be replicated in more diverse cohorts and extended by including Alzheimer's disease biomarkers, neuroimaging, and additional apathy measures.

from individuals along the cognitive spectrum ranging from normal to dementia.[14] The NACC Uniform Data Set (UDS) is a large prospective and longitudinal clinical evaluation comprising demographics, neurological examination results, and diagnoses collected approximately annually.[14]

Cognitive diagnosis, as per the clinician UDS D1 form, was used to operationalize both baseline cognitive status (NC, MCI), and outcome, which included all dementia subtypes. A comprehensive description of the cohort and neuropsychological test batteries included in the UDS is provided elsewhere.[14–17]

NACC *APOE* genotype, as informed by the Center's Neuropathology Data Form and the Alzheimer's Disease Genetics Consortium, is reported as ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4. *APOE* genotype was stratified by carrier status as follows: *APOE* ε2 (ε2/ε2, ε2/ε3), *APOE* ε3 (ε3/ε3), and *APOE* ε4 (ε4/ε3, ε4/ε4). To maintain group mutual exclusivity, participants with the *APOE* ε2/ε4 genotype were excluded. A December 2021 NACC-UDS data freeze was used for this study.

2.2 | Standard protocol approvals, registrations, and patient consents

As determined by the University of Washington Human Subjects Division, use of the NACC database itself is exempt from institutional review board (IRB) review. However, all contributing ADRCs were required to obtain informed consent from their participants and to obtain IRB approval from their institution prior to submitting data to NACC.

2.3 | Participant selection

Study flow for primary analysis is shown in Figure 1 and secondary analyses in Figures S1 and S2 in supporting information, respectively. NACC participants enrolled between 2005 and 2021 were considered. Participants were eligible for this study if they had complete Neuropsychiatric Inventory Questionnaire (NPI-Q)[18] domain scores, had two consecutive annual study visits, and were either NC or MCI at baseline. Consistent with the MBI criterion of later life symptom emergence, participants were not included if they had past psychiatric, developmental, or neurological conditions, including post-traumatic stress disorder, bipolar disorder, schizophrenia, obsessive-compulsive disorder, anxiety, depression, Down syndrome, Huntington's disease, or Parkinson's disease. Finally, participants with no follow-up visits and those with missing values for the covariates of interest (age, sex, years of education, race, cognitive diagnosis, and *APOE* genotype) were excluded.

For MBI status, NPI-Q scores were transformed into MBI domain scores using a published algorithm.[19] The MBI-apathy domain score was obtained from the NPI-Q apathy domain score. To meet the MBI-apathy persistence criterion, apathy (apathy > 0) was captured at two consecutive visits any time prior to a dementia diagnosis, the second of which defined the baseline for onset of MBI-apathy. Individuals were included in the MBI-apathy group irrespective of whether they had other NPS and/or tested positive on other MBI domains in addition to apathy. The MBI negative (no-NPS) group included participants without any symptoms of MBI for each of their NACC visits (i.e., MBI total score = 0) prior to dementia onset, where the second visit was defined as the baseline. Participants were excluded from analyses if NPS were present at either the first or second visit but not both, due to symptom impersistence, not consistent with the MBI symptom persistence criterion. A no-apathy group was derived as an additional comparator group to MBI-apathy for secondary analyses. This group included participants without MBI-apathy for each of their NACC visits (i.e., MBI-apathy total score = 0) irrespective of the presence or absence of other MBI domains. To explore the utility of a more conventional approach of incorporating apathy into dementia prognostication, a third group was also derived (NPI-apathy). This group included participants with apathy (NPI-Q apathy > 0) at their first visit without consideration of past psychiatric history.

2.4 | Statistical analysis

Primary and secondary analyses involved time-to-event comparisons between MBI-apathy and no-NPS, MBI-apathy and no-apathy, and NPI-apathy and no-NPS. Baseline demographic characteristics included age, sex, years of education, race, cognitive diagnosis, and

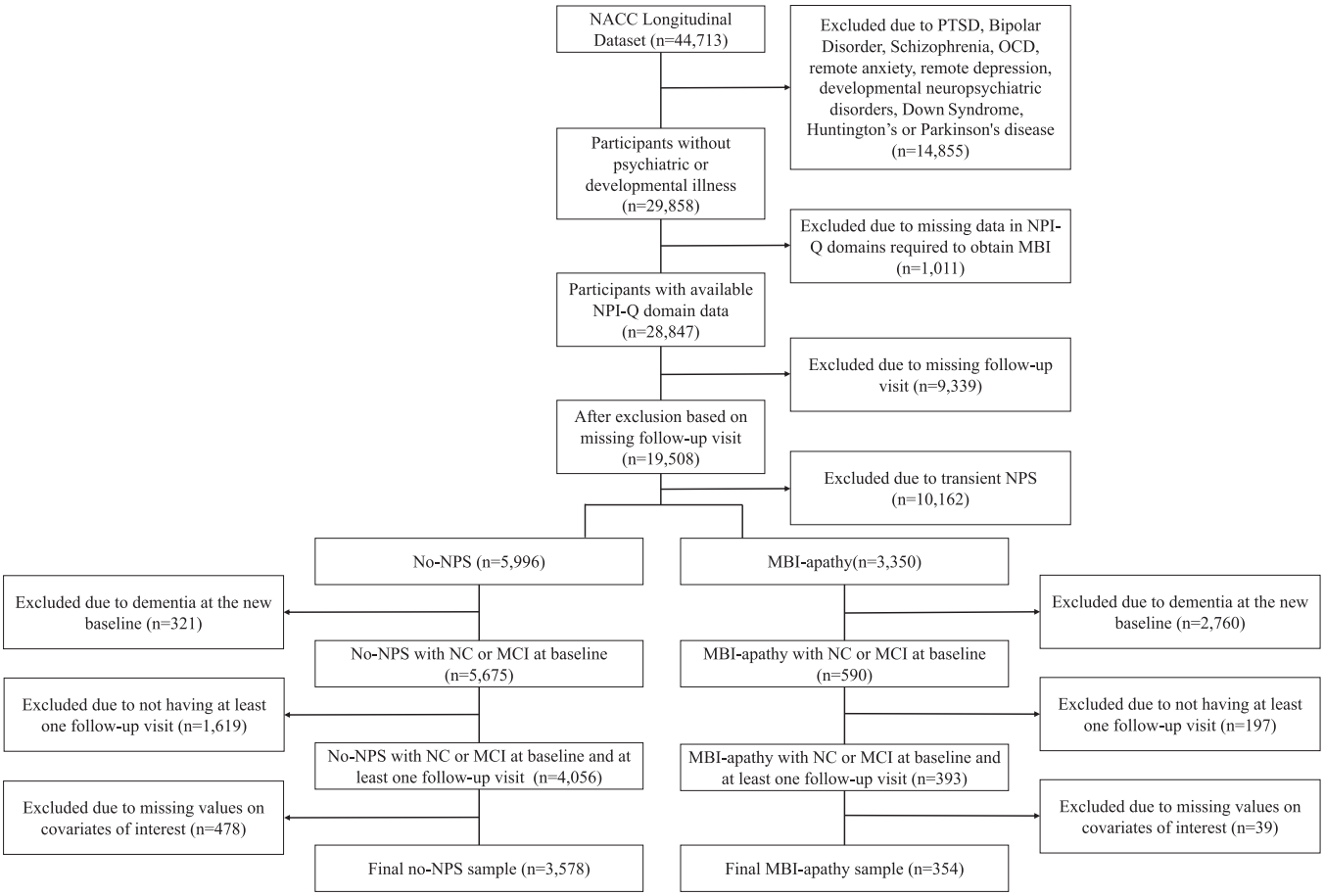

FIGURE 1 Flowchart of participants from NACC included for primary analysis. MBI, mild behavioral impairment; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Center; NPI-Q, Neuropsychiatric Inventory Questionnaire; NPS, neuropsychiatric symptoms; NC, normal cognition; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder

APOE genotype. Racial categories included White, Black, or Other (Asian, American Indian, or Alaska Native, Native Hawaiian or other Pacific Islanders, or other races merged into one category due to small sample sizes). Between-group differences were examined for MBI-apathy and no-NPS, MBI-apathy and no-apathy, and NPI-apathy and no-NPS, using χ^2 tests for categorical variables and two-sample *t* tests for continuous variables.

Kaplan–Meier (KM) survival curves were generated to compare 10-year dementia-free survival across NPS groups and *APOE* genotypes, with a log-rank test applied to assess between-group differences. Cox proportional hazards regression models adjusted for baseline age, sex, years of education, race, cognitive diagnosis, and *APOE* genotype were implemented to determine hazard ratios (HRs) for progression to dementia over 10 years. Participants without a dementia diagnosis at their last visit were censored. Interactions between NPS groups and sex, race, cognitive diagnosis, and *APOE* genotype were evaluated to determine whether exposure-outcome measures of the effect differed between levels of covariates.[20] The HR for MBI-apathy was calculated within each stratum of sex, race, cognitive diagnosis, and *APOE* genotype compared to the no-NPS group for the primary analysis, and to the no-apathy group for secondary analysis. Multiplicative tests of interaction assessed between-strata significance of the observed interactions. The HR for NPI-apathy was also calculated and compared to no NPS for secondary analysis.

All analyses were conducted in RStudio v1.3.1093, using the survival package v3.2.7 for Cox models, and ggplot2 v3.3.2 and survminer v0.4.8 packages for KM curves and forest plots. Assumptions for proportional hazards were assessed using the scaled Schoenfeld residuals via the cox.zph function from the survival package. Alpha was set at $P \leq 0.05$.

3 | RESULTS

3.1 | Primary analysis of differences in dementia incidence between MBI-apathy and no-NPS

Sample characteristics are described in Table 1. The sample comprised 3578 no-NPS participants and 354 MBI-apathy participants prior to dementia diagnosis. Compared to no-NPS, the MBI-apathy group was older (mean age = 76.2 ± 8.84 vs. 72.9 ± 9.82, $P < 0.001$) and had a higher proportion of males (65% vs. 37.4%, $P < 0.001$), White

TABLE 1 Characteristics of participants

	No-NPS (N=3578)	MBI-apathy (N=354)	*P*-value
Age			
Mean (SD)	72.9 (9.82)	76.2 (8.84)	<0.001[b]
Median [min, max]	73.0 [23.0, 101.0]	76.0 [36.0, 102.0]	
Years of education			
Mean (SD)	15.9 (2.93)	15.5 (3.33)	0.0549[b]
Median [min, max]	16.0 [1.00, 29.0]	16.0 [2.00, 26.0]	
Sex			
Male	1337 (37.4%)	230 (65.0%)	<0.001[a]
Female	2241 (62.6%)	124 (35.0%)	
Race			
White	2745 (76.7%)	302 (85.3%)	<0.001[a]
Black	676 (18.9%)	36 (10.2%)	
Other	157 (4.4%)	16 (4.5%)	
Clinical cognitive diagnosis			
NC	3100 (86.6%)	147 (41.5%)	<0.001[a]
MCI	478 (13.4%)	207 (58.5%)	
APOE genotype			
ε3	2016 (56.3%)	187 (52.8%)	0.182[a]
ε2	468 (13.1%)	42 (11.9%)	
ε4	1094 (30.6%)	125 (35.3%)	

Abbreviations: *APOE*, apolipoprotein E; MBI, mild behavioral impairment; MCI, mild cognitive impairment; NC, normal cognition; NPS, neuropsychiatric symptoms; SD, standard deviation.
[a]χ^2 tests.
[b]Two-sample *t* tests.

participants (85.3% vs. 76.7%, $P < 0.001$), and MCI (58.5% vs. 13.4%, $P < 0.001$). There were no statistically significant differences in years of education or *APOE* genotype.

The results of the KM analysis showed that, compared to the no-NPS group, dementia-free survival was lower in the MBI-apathy group ($P < 0.0001$). The unadjusted 5-year dementia-free survival probability for the no-NPS group was 90.4% (95% confidence interval [CI]: 89.1–91.7), while for the MBI-apathy group it was only 46.7% (95% CI: 40.2–54.2) (Figure S3A in supporting information).

The proportional hazards assumption was tested using scaled Schoenfeld residuals; assumptions were not violated ($\chi^2 = 0.848$, $P = 0.357$). Cox regressions demonstrated significant main effects with a greater progression rate in MBI-apathy compared to no-NPS reference (adjusted HR = 2.69, 95% CI: 2.15–3.36, $P < 0.001$; Table 2). Of the 39.8% (n = 141) MBI-apathy participants who progressed to dementia, 80.9% (n = 114) developed AD, 4.3% (n = 6) behavioral variant frontotemporal dementia (bv-FTD), 5.0% (n = 7) Lewy body dementia (LBD), and 2.8% (n = 4) vascular dementia (VaD). Comparatively, of the 7.4% (n = 266) with no NPS who progressed, 89.1% (n = 237) developed AD, 1.1% (n = 3) bv-FTD, 1.1% (n = 3) LBD, and 1.9% (n = 5) VaD. Patients with MCI were more likely to develop dementia than NC (HR = 10.97, 95% CI: 8.71–13.82, $P < 0.001$; Table 2). Compared to the *APOE* ε3 carrier reference group, *APOE* ε2 carriers were less likely to develop dementia (HR = 0.66, 95% CI: 0.45–0.97, $P = 0.036$), while *APOE* ε4 carriers were more likely to develop dementia (HR = 2.1, 95% CI: 1.7–2.6, $P < 0.001$; Table 2).

Interaction effects between subgroups and MBI-apathy are shown in Figure 2. Interaction effects between sex and race with MBI-apathy were not significant but were significant between cognitive diagnosis and MBI-apathy (Figures 2 and 3). While MBI-apathy was associated with a greater progression rate to dementia compared to no-NPS in both NC and MCI, the contribution of apathy to dementia was greater in NC (HR = 5.91, 95% CI: 3.91–8.93) than in MCI (HR = 2.16, 95% CI: 1.69–2.77, interaction $P < 0.001$). Significant interaction effects were also observed for the *APOE* genotype (Figures 2 and 4). While MBI-apathy was associated with a greater progression rate to dementia compared to no-NPS for all *APOE* genotypes, the contribution of apathy to dementia risk was greater for ε3 (HR = 4.25, 95% CI: 3.1–5.82) versus ε4 (HR = 1.81, 95% CI: 1.32–2.47, $P < 0.001$); but not for ε3 (HR = 4.25, 95% CI: 3.1–5.82) versus ε2 (HR = 2.6, 95% CI: 1.2–5.6, $P = 0.24$); or ε2 (HR = 2.6, 95% CI: 1.2–5.6) versus ε4 (HR = 1.81, 95% CI: 1.32–2.47, $P = 0.39$).

3.2 | Secondary analysis of differences in dementia incidence between MBI-apathy and no-apathy

Sample characteristics are described in Table S1 in supporting information. The no-apathy group consisted of 7193 individuals with no apathy prior to dementia diagnosis and differed from the MBI-apathy group with respect to age ($P < 0.001$), sex ($P < 0.001$), race ($P < 0.001$), and cognitive diagnosis ($P < 0.001$).

The KM survival curves demonstrated that compared to no-apathy, dementia-free survival was lower in MBI-apathy ($P < 0.0001$). Unadjusted 5-year dementia-free survival probability for no-apathy was 87.6% (95% CI: 86.7–88.6), while for MBI-apathy it was only 46.7% (95% CI: 40.2–54.2; Figure S3B).

We tested the proportional hazards assumption using the scaled Schoenfeld residuals and found no evidence that the assumption was violated ($\chi^2 = 0.65$, $P = 0.42$). Adjusted Cox regressions demonstrated significant main effects. Compared to no-apathy, MBI-apathy had a greater risk for dementia (HR = 2.61, 95% CI: 2.16–3.14, $P < 0.001$; Table S2 in supporting information). Of the 10.5% (n = 757) with no apathy who progressed to dementia, 88.4% (n = 668) progressed to AD, 1.3% (n = 10) to bv-FTD, 1.3% (n = 10) to LBD, and 1.5% (n = 12) to VaD. Patients with MCI were more likely to develop dementia than those with NC (reference; HR = 10.83, 95% CI: 9.31–12.60, $P < 0.001$; Table S2). Compared to the *APOE* ε3 carrier reference group, *APOE* ε4 carriers were significantly more likely to develop dementia (HR = 2.12, 95% CI: 1.84–2.44, $P < 0.001$) while *APOE* ε2 carriers did not significantly differ (HR = 0.92, 95% CI: 0.72–1.18, $P = 0.533$; Table S2).

There were no significant interaction effects between sex and race and NPS group. Significant interaction effects were observed for cognitive diagnosis (Table S3 in supporting information). While MBI-apathy

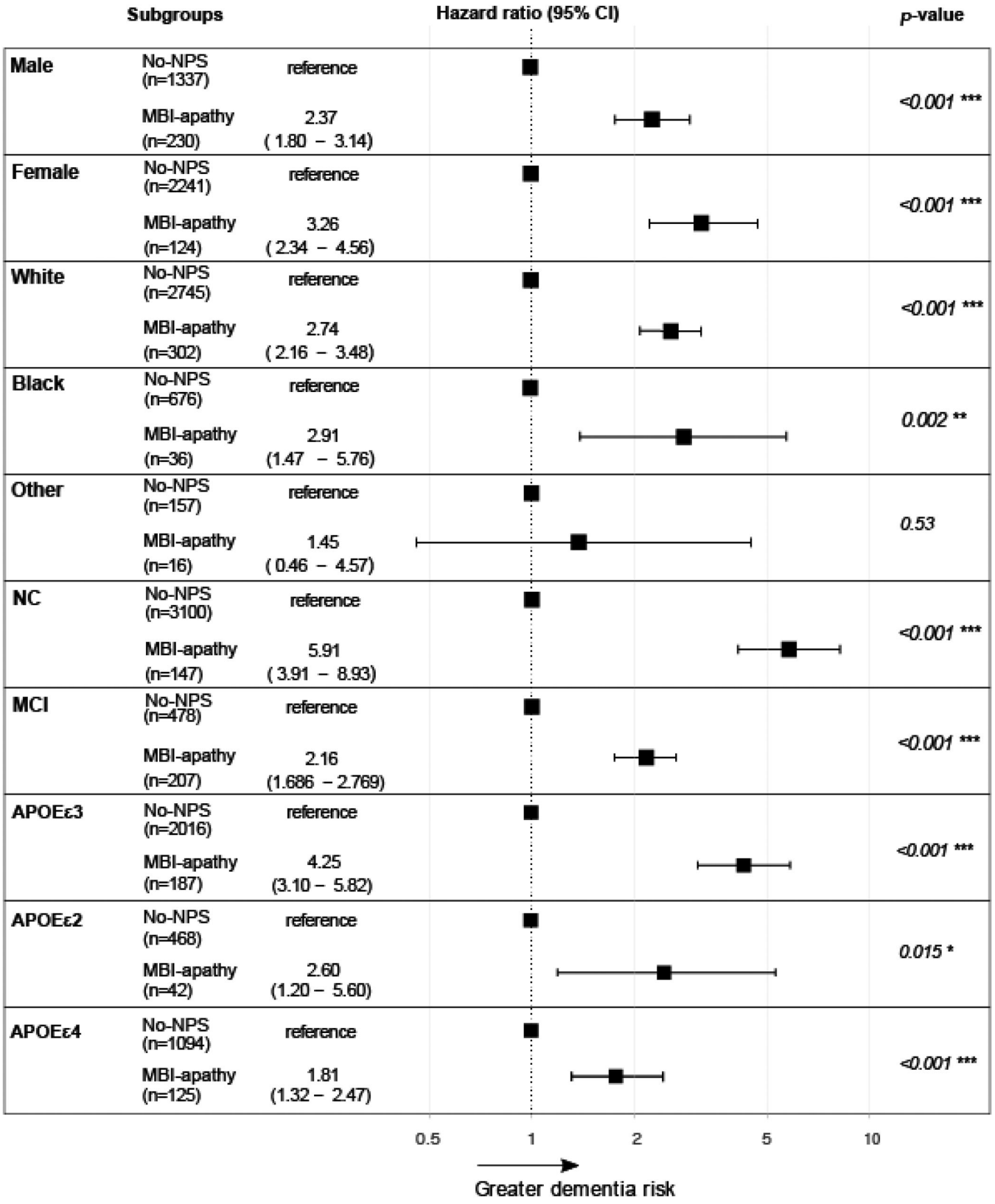

FIGURE 2 Interaction between MBI-apathy and sex, race, clinical cognitive diagnosis, and *APOE* genotype on dementia risk as represented by a forest plot which shows the hazard ratio and 95% confidence intervals. *APOE*, apolipoprotein E; CI, confidence interval; MBI, mild behavioral impairment; MCI, mild cognitive impairment; NPS, neuropsychiatric symptoms; NC, normal cognition. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

TABLE 2 Hazard ratio and 95% confidence intervals associated with variables considered in the Cox regression analyses with incident dementia diagnosis as the outcome variable

Factor	Subgroup	HR (95% CI)	*P*-value
NPS group	No-NPS (n = 3578)	Reference	
	MBI-apathy (n = 354)	2.69 (2.15–3.36)	<0.001***
Age	(n = 3932)	1.06 (1.05–1.08)	<0.001***
Years of education	(n = 3932)	0.96 (0.93–0.99)	0.01
Sex	Male (n = 1567)	Reference	
	Female (n = 2365)	1.06 (0.86–1.30)	0.614
Race	White (n = 3042)	Reference	
	Black (n = 712)	0.57 (0.47–0.77)	<0.001
	Other (n = 173)	0.77 (0.46–1.30)	0.328
Clinical cognitive diagnosis	NC (n = 3247)	Reference	
	MCI (n = 685)	10.97 (8.71–13.82)	<0.001
APOE genotype	ε3 (n = 2203)	Reference	
	ε2 (n = 510)	0.66 (0.45–0.97)	<0.05
	ε4 (n = 1219)	2.10 (1.70–2.60)	<0.001***

Abbreviations: *APOE*, apolipoprotein E; CI, confidence interval; HR, hazard ratio; MBI, mild behavioral impairment; MCI, mild cognitive impairment; NPS, neuropsychiatric symptoms; NC, normal cognition. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

had greater progression to dementia compared to no-apathy in both NC and MCI, the contribution of apathy to dementia was greater in NC (HR = 5.34, 95% CI: 3.64–7.82) than in MCI (HR = 2.23, 95% CI: 1.81–2.75), interaction $P < 0.001$. Significant interaction effects were observed for *APOE* genotype (Table S4 in supporting information). While MBI-apathy had greater progression rate to dementia compared to no-apathy for two of the three *APOE* genotypes, the contribution of apathy to dementia risk was greater for ε3 (HR = 3.93, 95% CI: 3.01–5.14) versus ε4 (HR = 1.97, 95% CI: 1.51–2.59), interaction $P < 0.001$; and ε3 (HR = 3.93, 95% CI: 3.01–5.14) versus ε2 (HR = 1.8, 95% CI: 0.92–3.52), interaction $P = 0.033$; but not ε2 (HR = 1.8, 95% CI: 0.92–3.52) versus ε4 (HR = 1.97, 95% CI: 1.51–2.59), interaction $P = 0.804$.

3.3 | Secondary analysis of differences in dementia incidence between NPI-apathy and no-NPS

Sample characteristics are described in Table S5 in supporting information. The sample comprised 5842 individuals with no NPS prior to dementia diagnosis and 1445 with NPI-apathy. The NPI-apathy group differed from the no-NPS group with respect to years of education ($P < 0.001$), sex ($P < 0.001$), race ($P < 0.001$), cognitive diagnosis ($P < 0.001$), and *APOE* genotype ($P < 0.001$).

The KM survival curves demonstrated that compared to no-NPS, dementia-free survival was lower in NPI-apathy ($P < 0.0001$). The unadjusted 5-year dementia-free survival probability for the no-NPS group was 87.3% (95% CI: 86.2.1–88.3), while for the NPI-apathy group it was 50.9% (95% CI: 47.8–54.2; Figure S3C). Proportional hazards assumptions were tested using Schoenfeld residuals; assumptions were not violated ($\chi^2 = 0.051$, $P = 0.821$). Cox regressions demonstrated significant main effects with a greater progression rate in NPI-apathy compared to the no-NPS reference group (adjusted HR = 1.80, 95% CI: 1.59–2.04, $P < 0.001$; Table S6 in supporting information).

4 | DISCUSSION

In this study of dementia-free older adults, we explored dementia risk associated with the apathy domain of MBI. We investigated

(A)

Clinical cognitive diagnosis	No-NPS	MBI-apathy	Effect of apathy within the strata of clinical cognitive diagnosis
	HR (95% CI) *p*-value	HR (95% CI) *p*-value	HR (95% CI) *p*-value
NC	1 (Reference)	5.91 (3.91, 8.93) $p<0.001$	5.91 (3.91, 8.93) $p<0.001$
MCI	13.81 (10.66, 17.89) $p<0.001$	29.83 (22.27, 39.96) $p<0.001$	2.16 (1.69, 2.77) $p<0.001$
Multiplicative interaction test:		HR=2.73, 95%CI:1.69-4.42, $p<0.001$	

(B)

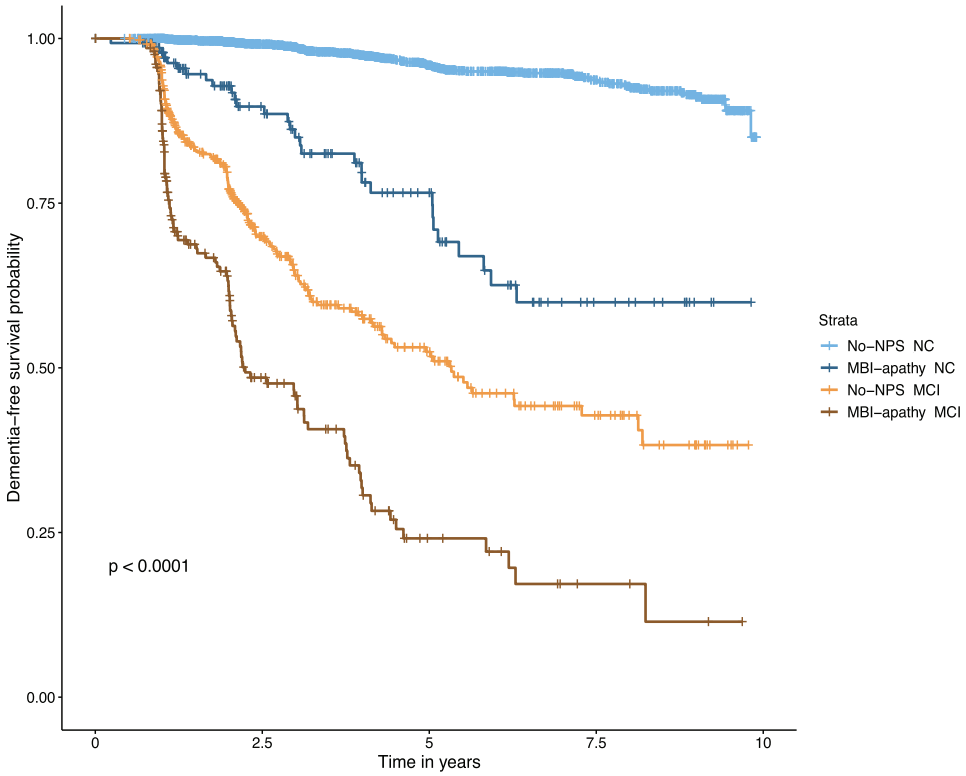

FIGURE 3 A, Interaction effects between NPS group and cognitive diagnosis. B, Kaplan–Meier dementia-free survival probability of individuals with no NPS and individuals with MBI-apathy stratified by cognitive status. CI, confidence interval; HR, hazard ratio; MBI, mild behavioral impairment; MCI, mild cognitive impairment; NPS, neuropsychiatric symptoms; NC, normal cognition

the rates of progression to dementia in individuals with MBI-apathy, relative to those with no apathy and no NPS and effect modification by cognitive diagnosis and *APOE* genotype. We also investigated the rate of progression to dementia using a more conventional approach to apathy, assessed at a single time point, without consideration of past psychiatric history. MBI-apathy had a 2.69- and 2.61-fold greater progression rate to dementia compared to no-NPS and no-apathy, respectively, while NPI-apathy had a 1.80-fold greater progression rate to dementia compared to no-NPS. These findings suggest that there is greater incidence of dementia when apathy is both persistent and emergent, supporting the utility of these two cardinal MBI criteria when applied to apathy. Baseline cognitive status was an important moderator of progression to dementia, with different HRs for NC and MCI. With prevalences in our sample of 4.5% in NC and 30.2% in MCI, MBI-apathy represents a substantial at-risk group for dementia. *APOE* genotype was another important moderator, as our findings revealed different HRs among *APOE* carriers.

(A)

APOE genotype	No-NPS	MBI-apathy	Effect of apathy within the strata of APOE genotype
	HR (95% CI) *p*-value	HR (95% CI) *p*-value	HR (95% CI) *p*-value
ε3	1 (Reference)	4.25 (3.1, 5.82) $p<0.001$	4.25 (3.1, 5.82) $p<0.001$
ε2	0.77 (0.48, 1.25) $p=0.293$	2.01 (1.04, 3.87) $p=0.037$	2.6 (1.2, 5.6) $p=0.015$
ε4	2.79 (2.16, 3.61) $p<0.001$	5.05 (3.63, 7.03) $p<0.001$	1.81 (1.32, 2.47) $p<0.001$
Multiplicative interaction test:		ε3 vs. ε2: HR=1.64, 95%CI:0.72-3.73, $p=0.24$ ε3 vs. ε4: HR=2.35, 95%CI:1.53-3.61, $p<0.001$ ε2 vs. ε4: HR=1.44, 95%CI:0.63-3.26, $p=0.39$	

(B)

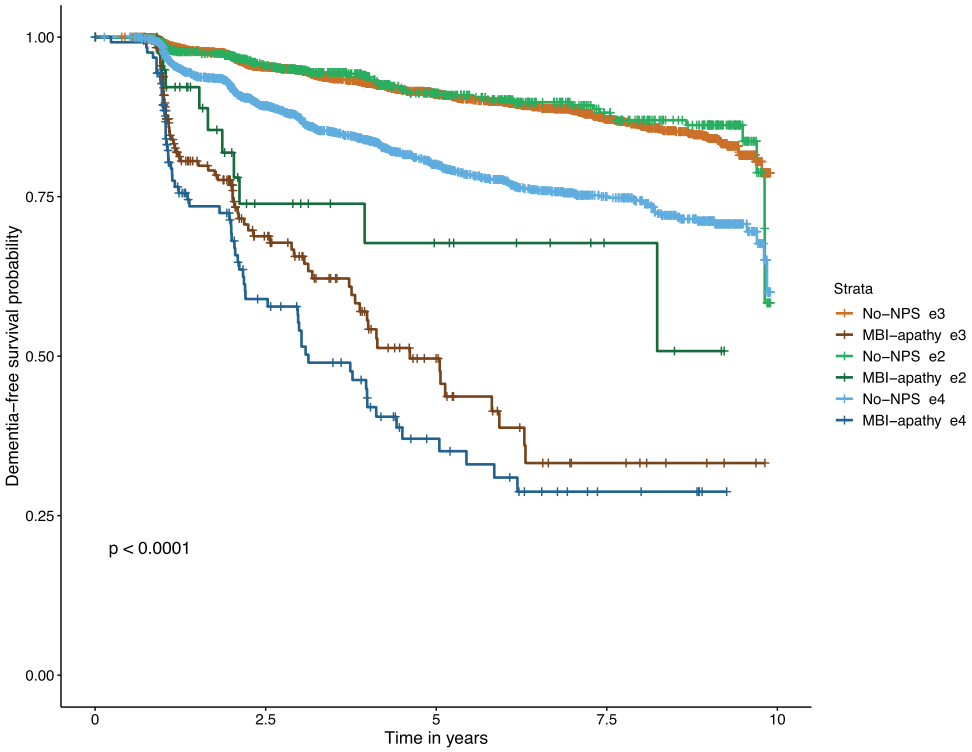

FIGURE 4 A, Interaction effects between NPS status and *APOE* genotype; B, Kaplan–Meier dementia-free survival probability of individuals with no NPS and individuals with MBI-apathy stratified by *APOE* genotype. *APOE*, apolipoprotein E; CI, confidence interval; HR, hazard ratio; MBI, mild behavioral impairment; NPS, neuropsychiatric symptoms

4.1 | Apathy and cognitive status

In MCI, HR for incident dementia for MBI-apathy was 2.16 compared to no-NPS and 2.23 compared to no-apathy. In NC, relative rates were significantly higher, with HRs of 5.91 compared to no-NPS and 5.34 compared to no-apathy. This finding might be explained by progression along the cognitive spectrum. In MCI, MBI-apathy may be one of several risk factors for progression contributing relatively less than it does in NC where there may be fewer comorbid risk factors. Thus, MBI-apathy appears to be of particular concern, especially in NC.

Studies in both NC and MCI participants have demonstrated an association between apathy and incident cognitive decline and dementia. However, no previous work has operationalized apathy using the more conservative MBI classification approach, which offers greater

specificity. A previous systematic review and meta-analysis in NC revealed greater apathy-associated rates of incident dementia, with a pooled HR of 3.42 from three included studies.[21] Similarly, in MCI, meta-analysis demonstrated greater apathy-associated rates of incident dementia, with a pooled HR of 1.54 from 11 included studies.[22] The relatively higher HR in NC versus MCI from these meta-analyses is consistent with our findings, in which individuals with both NC and MCI were included, allowing for direct comparisons between cognitive groups. Of note, the HRs in our study are higher than the pooled estimates in the meta-analyses. These differences may arise from application of the MBI symptom emergence and persistence criteria, increasing signal and reducing noise when defining the at-risk group. This has previously been demonstrated in samples of NC, subjective cognitive impairment, and MCI, where applying MBI criteria demonstrated better specificity for AD detection and dementia prognostication compared to conventional approaches to assessing NPS.[2,23] Nonetheless, these findings have implications for the importance of behavioral symptoms in predicting future dementia prior to cognitive symptom onset, offering a window of opportunity for treatment at an early stage of the disease.

4.2 | *APOE* and effect modification

Effect modification was observed for *APOE* genotype. While MBI-apathy was associated with higher risk for dementia in all genotypes, the association was strongest in *APOE* ε3 carriers and the difference between *APOE* ε3 and *APOE* ε4 carriers was statistically significant. Possibly, the risk conferred by MBI-apathy is relatively less in the *APOE* ε4 group because progression is driven by additional pathways related to the *APOE* ε4 allele unrelated to apathy. Secondary analyses between MBI-apathy and no-apathy were similar.

The current evidence base suggests that *APOE* ε2 is associated with a lower dementia risk than *APOE* ε3 and *APOE* ε4.[24-27] *APOE* ε2 carriers are 0.2 times less likely to develop AD dementia, whereas *APOE* ε4 carrier risk is five times greater, compared to *APOE* ε3 homozygotes.[24,28] We also found that risk of dementia progression among *APOE* ε2 carriers was significantly lower than *APOE* ε3 carriers. Our primary results show that *APOE* ε2 carriers without NPS have the lowest risk for developing dementia compared to *APOE* ε3 carriers. Further, while *APOE* ε2 carriers with MBI-apathy had a higher risk than the *APOE* ε3 no-NPS reference group, due to the contribution of MBI to risk, they still demonstrated the lowest risk among their *APOE* MBI-apathy counterparts and lower risk than the *APOE* ε4 no-NPS group. Until present, little was known about the interaction between *APOE* genotype and NPS in determining risk, especially in NC. Studies in MCI have examined such interactions, finding that co-occurrence of *APOE* ε4 and apathy posed the greatest risk for incident dementia.[29,30] While concomitance of the aforementioned risk marker is associated with greater dementia risk, a systematic review and meta-analysis investigating the relationship between *APOE* and affective symptoms in MCI and AD dementia found no evidence that *APOE* ε4 carriership is associated with the presence of apathy.[31] The lack of an association may be the result of capturing apathy with more liberal conventional approaches versus the more conservative MBI approach used for our study. Our research suggests that we cannot underappreciate the clinical value of identifying and monitoring highly prevalent behavioral symptoms in prodromal AD.

Compared to *APOE* ε4, fewer studies have investigated the role of *APOE* ε2 in MCI and AD samples with apathy, and no studies assessing the interaction between *APOE* ε2 and apathy on incident dementia were found. Generally, *APOE* ε2 in MCI and AD is neuroprotective. In a study examining the influence of *APOE* genotype on cognition and neuroimaging features among NC and MCI adults, *APOE* ε2 was protective with respect to changes in immediate memory, executive function, and hippocampal volume during progression from NC to MCI.[32] Furthermore, across the AD spectrum from NC to AD, *APOE* ε2 carriers have shown less Aβ deposition, less cortical thinning, less hippocampal atrophy, slower cognitive decline, and later symptom onset compared to non-carriers.[25,33-37] Together, these results suggest that the neuroprotective role of *APOE* ε2 might extend beyond reducing the risk for AD dementia as it may also contribute to the structural and functional preservation of aging brains while also enhancing pathological resistance during the prodromal stages of AD.[27] Thus, in addition to exploring *APOE* ε4 interactions, these results lend importance to the investigation of *APOE* ε2 interactions with novel and previously identified risk factors for AD dementia, potentially leading to more targeted study of mechanistic and physiological brain differences between *APOE* genotypes.

4.3 | Limitations

Despite the novelty of exploring the MBI-apathy domain and all *APOE* genotypes in a large dementia-free sample, several limitations are worth consideration. First, NACC participants may not be fully representative of community samples. The high education level and lack of racial diversity raise questions about the generalizability of results. Second, we investigated the associations between MBI-apathy status and dementia incidence but cannot assume causation. Future studies may benefit from investigating AD biomarkers[23,38-40] and region-specific neurodegenerative markers[5,41,42] in combination with AD genetic risk[43,44] to explore further if MBI-apathy is an independent risk factor or an early disease marker.[45] Future studies may benefit from investigating apathy severity, to provide a more complete understanding of this association. Lastly, our findings are limited to the use of the NPI-Q to measure apathy, as opposed to the MBI checklist (MBI-C).[46,47] The MBI-C was developed specifically for dementia prognostication in functionally independent community-dwelling older adults and queries apathy subdomains consistent with syndromic apathy criteria.[8] In a study evaluating the performance of the NPI-Q and MBI-C to measure NPS in memory clinic patients with subjective cognitive decline, MCI, and dementia, apathy was identified in 59.9% of participants using the MBI-C and 43.9% using the NPI-Q.[47] The broader syndromic apathy framework, as detected by the MBI-C, may therefore yield greater sensitivity and give rise to higher apathy

prevalence compared to the NPI-Q.[47] Future studies could use this scale and explore the MBI-C-apathy score as both a continuous and categorical variable to better understand associated risk.

5 | CONCLUSIONS

MBI-apathy has greater dementia incidence than both no-NPS and no-apathy. More conventionally measured apathy (NPI-apathy) also had greater dementia incidence than no-NPS, but relatively less than MBI-apathy. Thus, even in older adults without cognitive impairment, apathy, especially later-life emergent and persistent apathy, is associated with significantly greater dementia incidence. MBI-apathy also conferred greater risk in NC than in MCI, highlighting the importance of incorporating baseline cognitive status when assessing behavioral risk. Additionally, more precise risk estimates for each cognitive category can be generated by including *APOE* genotype in modeling. Identifying individuals at greater risk prior to dementia onset provides earlier opportunity for both pharmacological and non-pharmacological interventions, improving the chance of changing outcomes.

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CONFLICTS OF INTEREST

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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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