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

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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...
1 | BACKGROUND

The neurodegenerative process in Alzheimer’s disease (AD) starts long before clinical diagnosis 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. 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. 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. 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 psychotic disorders); and (2) persist for ≥6 months (to increase the likelihood that they are secondary to neurodegenerative disease rather than life stressors).

MBI comprises five core domains of NPS including affective dysregulation, impulse dyscontrol, social inappropriateness, psychotic symptoms, and apathy. Apathy, characterized by decreased interest, initiative, and emotional reactivity, is one of the most common, stable, and persistent NPS. Apathy in AD is associated with lower quality of life, poorer health, greater caregiver distress and burden, and higher mortality. Apathy can also present in prodromal disease and is associated with incident dementia, amyloid beta (Aβ), and tau. 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, MBI-apathy may be a robust marker for prognosticating incident dementia. 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.
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 $\chi^2$ 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 $= 76.2 \pm 8.84$ vs. $72.9 \pm 9.82$, $P < 0.001$) and had a higher proportion of males (65% vs. 37.4%, $P < 0.001$), White
### TABLE 1 Characteristics of participants

| Characteristics         | No-NPS (N=3578) | MBI-apathy (N=354) | P-value |
|-------------------------|-----------------|--------------------|---------|
| Age                     |                 |                    |         |
| Mean (SD)               | 72.9 (9.82)     | 76.2 (8.84)        | <0.001  |
| 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  |
| Median [min, max]       | 16.0 [100, 29.0] | 16.0 [200, 26.0]   |         |
| Sex                     |                 |                    |         |
| Male                    | 1337 (37.4%)    | 230 (65.0%)        | <0.001  |
| Female                  | 2241 (62.6%)    | 124 (35.0%)        |         |
| Race                    |                 |                    |         |
| White                   | 2745 (76.7%)    | 302 (85.3%)        | <0.001  |
| 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  |
| MCI                     | 478 (13.4%)     | 207 (58.5%)        |         |
| APOE genotype           |                 |                    |         |
| ε3                      | 2016 (56.3%)    | 187 (52.8%)        | 0.182   |
| 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.

Participants (85.3% vs. 76.7%, P < 0.001), and MCI (58.5% vs. 13.4%, P < 0.0001). 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 (χ² = 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 (χ² = 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      | NC (n = 3247) | Reference   |         |
| diagnosis               | 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 NPS-apathy. The NPS-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 NPS-apathy (P < 0.0001). The unadjusted 5-year dementia-free survival probability for the no-NPS group was 87.3% (95% CI: 86.2–88.3), while for the NPS-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 (χ² = 0.051, P = 0.821). Cox regressions demonstrated significant main effects with a greater progression rate in NPS-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
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.

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.
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

| 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) | 2.01 (1.04, 3.87) | p=0.293 | 2.6 (1.2, 5.6) | p=0.015 |
| ε4            | 2.79 (2.16, 3.61) | 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

**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.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{29,30} While comorbidity 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{23,38-40} and region-specific neurodegenerative markers\textsuperscript{5,41,42} in combination with AD genetic risk\textsuperscript{43,44} to explore further if MBI-apathy is an independent risk factor or an early disease marker.\textsuperscript{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).\textsuperscript{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.\textsuperscript{5} 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.\textsuperscript{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. 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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