ARTICLE

Apathy and risk of probable incident dementia among community-dwelling older adults

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Abstract

Objective

To evaluate the association between baseline apathy and probable incident dementia in a population-based sample of community-dwelling older adults.

Methods

We studied 2,018 white and black community-dwelling older adults from the Health, Aging, and Body Composition (Health ABC) study. We measured apathy at year 6 (our study baseline) with the modified Apathy Evaluation Scale and divided participants into tertiles based on low, moderate, or severe apathy symptoms. Incident dementia was ascertained over 9 years by dementia medication use, hospital records, or clinically relevant cognitive decline on global cognition. We examined the association between apathy and probable incident dementia using a Cox proportional hazards model adjusting for demographics, cardiovascular risk factors, *APOE4* status, and depressed mood. We also evaluated the association between the apathy group and cognitive change (as measured by the modified Mini-Mental State Examination and Digit Symbol Substitution Test over 5 years) using linear mixed effects models.

Results

Over 9 years of follow-up, 381 participants developed probable dementia. Severe apathy was associated with an increased risk of dementia compared to low apathy (25% vs 14%) in unadjusted (hazard ratio [HR] 1.9, 95% confidence interval [CI] 1.5–2.5) and adjusted models (HR 1.7, 95% CI 1.3–2.2). Greater apathy was associated with worse cognitive score at baseline, but not rate of change over time.

Conclusion

In a diverse cohort of community-dwelling adults, apathy was associated with increased risk of developing probable dementia. This study provides novel evidence for apathy as a prodrome of dementia.

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Glossary

3MS = modified Mini-Mental State Examination; **CES-D** = Center for Epidemiologic Studies Depression Scale; **DSST** = Digit Symbol Substitution Test; **Health ABC** = Health, Aging, and Body Composition study; **HR** = hazard ratio; **MCI** = mild cognitive impairment; **NPS** = neuropsychiatric symptoms.

The prevalence of dementia is increasing[1] and there is growing interest in identifying preclinical markers of cognitive decline to better understand an individual's risk. Neuropsychiatric symptoms (NPS) are common across the spectrum of cognitive function in older adults, affecting up to half of patients with mild cognitive impairment (MCI) and nearly all patients with dementia over the course of their disease.[2–4] NPS have prognostic value in predicting accelerated disease progression[5] and functional decline.[6,7] In addition, both early-life[8,9] and late-life depression[10–12] have been established as important predictors of the incidence of dementia. Given the clinical relevance of NPS, experts have proposed the syndrome of mild behavioral impairment as an entity that precedes dementia onset.[13] However, few neuropsychiatric symptoms besides depression have been evaluated as independent predictors of cognitive decline in prospective studies.

Apathy, defined as decreased motivation and goal-directed behavior, is the most prevalent neuropsychiatric symptom among the dementia subtypes.[14] Apathy is correlated with depression but is a distinct entity with unique neuroanatomic correlates in the dorsolateral prefrontal cortex and associated subregions in the basal ganglia.[15,16] Despite some overlap in symptoms, appropriate diagnostic criteria can clinically separate apathy from depression.[17] Indeed, approximately one third of patients with dementia and apathy do not exhibit signs of comorbid depression.[18]

Previous cohort studies suggest that patients with MCI and apathy have a higher incident risk of dementia.[19–24] Apathy has therefore been flagged by the National Institute on Aging as a highly informative neuropsychiatric risk state.[25] However, existing studies have primarily been conducted in participants with preexisting MCI and are limited by small sample size,[19,20,22] short follow-up times,[19,20,23] or a lack of generalizability.[26] There are no large studies that have investigated apathy as an independent risk factor for or prodrome of dementia in a diverse sample of cognitively normal older adults. The goal of our study was to evaluate the hypothesis that apathy is a prodrome of incident dementia in a population-based sample of community-dwelling elders.

Methods

Standard protocol approvals, registrations, and patient consents

All participants signed a written informed consent, approved by the institutional review boards at each clinical site and the coordinating site. Full details of the Health, Aging, and Body Composition (Health ABC) study have been published.[27]

Population

We studied participants from the Health ABC study, a prospective cohort study of community-dwelling white and black older adults. The study was based in Memphis, Tennessee, and Pittsburgh, Pennsylvania, with the coordinating center in San Francisco, California. Potential participants were identified and contacted based on a random sample of Medicare-eligible adults (age 70–79) within predesignated zip codes. Participants were excluded if they had mobility or functional limitations, a life-threatening diagnosis such as cancer, or plans to leave the area within 3 years.

A total of 3,075 adults were enrolled from May 1997 to June 1998. For this study, we excluded participants who did not undergo a year 6 visit (456 participants), those who were identified to have dementia prior to our study baseline at year 6 (131 participants), and those who did not complete the apathy evaluation (465 participants). A total of 2,018 participants were included in our analytic cohort.

Measures

Apathy

We measured apathy with a modified version of the Apathy Evaluation Scale, a well-validated scale with the ability to discriminate apathy from depression and anxiety.[28] The 18-question Apathy Evaluation Scale was adapted to 5 questions based on expert consensus at the time of study design (table 1). Answers to questions were based on a Likert scale and scored between 0 ("Rarely or none of the time") and 3 ("Most or all of the time"). The total score ranges between 0 and 15, with 0 representing low apathy and 15 representing high apathy. Questions were administered by trained study staff at an in-person clinic visit using standardized scripts at year 6, our study baseline. We divided participants into tertiles based on the study sample, corresponding to low, moderate, or severe apathy.

Cognition

Participants underwent cognitive evaluation with the modified Mini-Mental State Examination (3MS) and the Digit Symbol Substitution Test (DSST) at years 5, 8, and 10. The 3MS assesses orientation, concentration, language, praxis, immediate memory, and delayed memory to yield a score between 0 and 100.[29] It is highly sensitive in detecting cognitive decline compared to other standard measurements.[30] The DSST assesses attention, processing speed, visuospatial function, and working memory.

Table 1 Questions and response options for the modified Apathy Evaluation Scale

Question	Response options
In the past 4 weeks, how often have you been interested in doing your usual activities?	• Most or all of the time • Much of the time • Some of the time • Rarely or none of the time • Don't know
In the past 4 weeks, how often have you been interested in leaving your home and going out?	• Most or all of the time • Much of the time • Some of the time • Rarely or none of the time • Don't know
In the past 4 weeks, how often have you been interested in getting together with friends and relatives?	• Most or all of the time • Much of the time • Some of the time • Rarely or none of the time • Don't know
Getting things done during the day is important to me.	• Most or all of the time • Much of the time • Some of the time • Rarely or none of the time • Don't know
Seeing a job through to the end is important to me.	• Most or all of the time • Much of the time • Some of the time • Rarely or none of the time • Don't know

Incident dementia

We determined incident dementia with a previously published algorithm incorporating dementia medication use, hospital records, or significant global cognitive decline.[31] Health ABC staff surveyed participants every 6 months regarding occurrence of hospitalizations, reviewed records associated with hospitalization, and recorded participants' home medications at each visit. The date of dementia incidence was defined as the first date that a participant met any of the following criteria: (1) occurrence of a hospitalization with dementia documented as a primary or secondary diagnosis; (2) identification of a prescription for a dementia medication (galantamine, memantine, donepezil, rivastigmine, or tacrine); or (3) clinically significant decline in cognition (>1.5 race-specific SD) from baseline to the last available cognitive score.

Other variables

Age, race, sex, and educational level were self-reported at baseline. Depressed mood was measured by the Center for Epidemiologic Studies Depression Scale (CES-D), a 20-item measure with a cutoff of 15 to identify severe depressive symptoms.[32] Hypertension was identified by self-report of diagnosis, use of any antihypertensive medication, or measured systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg. History of myocardial infarction, stroke, or TIA was determined by either a physician or self-reported diagnosis. Body mass index (kg/m^2) was calculated from direct height and weight measurements recorded at baseline. Participants self-reported use of cigarettes and alcohol. *APOE* genotype was determined by single nucleotide polymorphism analyses.

Statistical analysis

We used χ^2 tests and analysis of variance to evaluate whether participant characteristics differed between those reporting low, moderate, or severe apathy symptoms. To examine the association between apathy and probable incident dementia, we plotted Kaplan-Meier survival curves and computed Cox proportional hazards regression models. The time to event was calculated from baseline at year 6 until the date of dementia diagnosis during follow-up. Individuals without dementia were censored at the last available date of contact. We first analyzed the association between apathy and probable incident dementia (model 1) and then adjusted for demographics, education, history of myocardial infarction, history of stroke, hypertension, cigarette smoking, and *APOE4* status (model 2). In order to assess independence from depression, we then separately adjusted for depressed mood (model 3). We also tested for interactions between apathy tertile and sex, race, and *APOE4* status. To evaluate the robustness of our findings, we conducted sensitivity analyses excluding participants diagnosed with dementia only according to the neuropsychological testing criterion, participants with baseline depressed mood (CES-D score >15), and participants with baseline probable MCI.

Additional analyses were performed to evaluate change in cognition over time. We used linear mixed-effects regression models to investigate the association between apathy groups and change in cognition over follow-up from year 5 (the closest measurement to our study baseline) to year 10. Multivariable models were adjusted for demographics, education, history of myocardial infarction, history of stroke, hypertension, cigarette smoking, and depressed mood. All analyses were conducted in Stata (StataCorp, College Station, TX). Statistical significance was set at $p < 0.05$.

Data availability

Data not published within the article are available in a public repository. Anonymized data will be shared by request from any qualified investigator.

Results

Demographic characteristics are summarized in table 2. Of the 2,018 participants without dementia at baseline, the mean age was 73.9 years (SD 2.8). Approximately one third of participants were black (35.9%) and two thirds were white (64.1%). Slightly more than half (52.3%) of the cohort was female.

Table 2 Baseline characteristics of 2,018 older adults without dementia by apathy group

Characteristic	Low apathy (n = 768)	Moderate apathy (n = 742)	Severe apathy (n = 508)	*p* Value
Age, y	73.7 ± 2.8	73.9 ± 2.9	74.0 ± 2.8	0.40
Female	432 (41)	368 (35)	262 (24)	0.03
Race				<0.01
White	534 (41)	494 (38)	265 (21)	
Black	234 (32)	248 (34)	243 (34)	
Education, y	13.8 ± 2.9	13.3 ± 3.0	12.5 ± 4.4	<0.01
Alcohol use (>1 drink/day)	62 (41)	56 (37)	34 (22)	0.60
Tobacco use	48 (30)	56 (35)	57 (35)	0.01
Body mass index	26.9 ± 4.5	27.4 ± 4.5	27.7 ± 5.1	0.01
Depressed mood (CES-D ≥16)	44 (17)	85 (33)	126 (50)	<0.01
***APOE* ε4 positive**	205 (39)	176 (33)	143 (27)	0.15

Abbreviation: CES-D = Center for Epidemiologic Studies Depression Scale.
Values are mean ± SD or n (%).

Participants reported an average of 13.3 years (SD 3.4) of education. Participants were followed for a mean of 5.8 years (SD 3.0) until they were diagnosed with probable dementia or were censored. Participants who completed the apathy measure were more likely to be higher educated ($F = 44.4$, $p < 0.001$) and white (Pearson $\chi^2 = 37.0$, $p < 0.001$). There was no difference in likelihood of completion of the apathy measure by sex, *APOE4* status, or depressed mood.

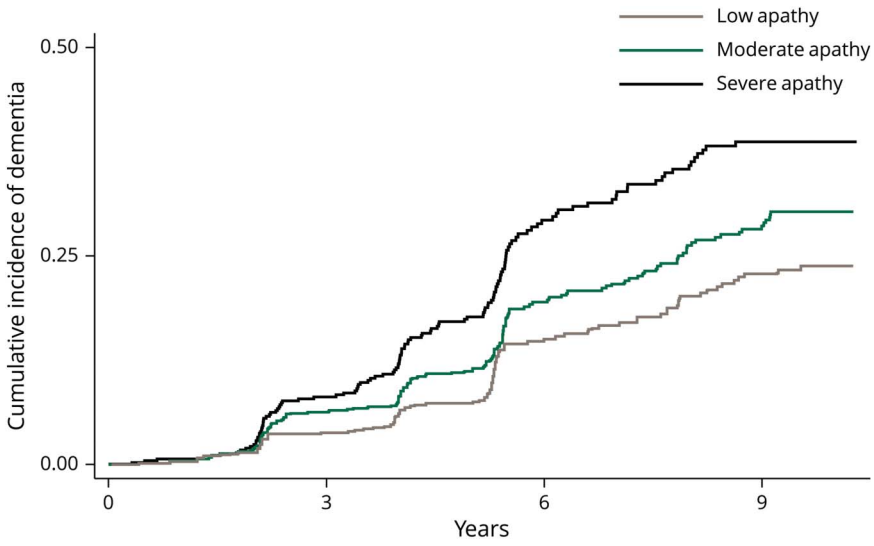
There were 768 (38%) participants in the low apathy group, 742 (37%) participants in the moderate apathy group, and 508 (25%) participants in the severe apathy group. Participants with greater apathy at baseline were significantly more likely to be male, black, and less educated. They were also more likely to have a higher body mass index and report a history of cigarette smoking. There were 255 participants in the cohort that met criteria for clinically depressed mood according to the CES-D. Half of these individuals (126/255) reported symptoms of severe apathy, compared to 33% (85/255) that reported moderate apathy and 17% (44/255) that reported low apathy.

Of 2,018 participants, 381 individuals developed probable dementia during the follow-up period. Twenty-nine (8%) were diagnosed by medication prescription only, 151 (40%) were diagnosed according to hospital records only, 56 (15%) were identified by a >1.5 SD change in the 3MS only, and 129 (34%) were diagnosed based on a combination of these findings. Participants developed dementia per our criteria an average of 4.6 years (SD 2.1) after the apathy assessment. In the severe apathy group, 25% of participants (127/509) developed probable incident dementia, compared to 14% (111/660) of those with low apathy. Kaplan-Meier survival curves by apathy group (figure 1) show that higher apathy was associated with higher risk of probable dementia in a graded fashion ($p < 0.0001$ by log-rank test). Table 3 summarizes the results of the Cox proportional hazards regression models. Compared to those with low apathy, participants with severe apathy were approximately twice as likely to develop probable dementia (hazard ratio [HR] 1.9, 95% CI 1.5–2.5, $p < 0.001$), an association that remained robust in the fully adjusted model (adjusted HR 1.8, 95% CI 1.3–2.3, $p < 0.001$). Participants reporting moderate apathy at baseline were 30% more likely to develop probable dementia compared to those with low apathy over the study period (HR 1.3, 95% CI 1.0–1.7, $p = 0.03$), but this association was no longer significant in the fully adjusted model (adjusted HR 1.3, CI 1.0–1.7, $p = 0.06$). There were no significant interactions between apathy group and sex, race, or *APOE4* status ($p > 0.05$ for all).

Additional analyses examined whether the apathy groups were associated with cognition. Compared to the low apathy group, the severe apathy group performed 1.6 points lower on the DSST (95% CI 0.2–2.9, $p = 0.029$) and 0.9 points lower on the 3MS at baseline (95% CI 0.1–1.6, $p = 0.019$) in fully adjusted linear regression models. However, there was no association observed between the apathy groups and change in cognition over time in unadjusted or adjusted linear mixed-effects regression models (figure 2, table 4).

We conducted additional sensitivity analyses. We repeated our Cox proportional hazard model sequentially excluding patients diagnosed with dementia only according to change in 3MS score (n = 56) or participants with baseline probable cognitive impairment (1.0–1.5 race-specific SD below the mean 3MS score). We also repeated analyses excluding the 258 patients with baseline depressed mood as measured by

Figure 1 Association between apathy and incident dementia among 2,018 older adults



Kaplan-Meier curves show dementia incidence over 9 years by apathy tertile ($p < 0.0001$ by log-rank test).

the CES-D. Results were very similar to our primary analyses and remained statistically significant.

Discussion

We found that community-dwelling older adults who report greater symptoms of apathy are approximately 80% more likely to develop probable dementia compared to those with few symptoms. Our study provides novel evidence for apathy as a prodrome of dementia.

Our findings are supported by prior studies showing that apathy increases the risk of probable dementia approximately twofold in individuals with MCI,[19–24] but extends this result to a population-based cohort of older adults without dementia. The majority of prior studies were conducted in patients sampled from memory clinics[21,33] or based on preexisting diagnoses of cognitive impairment.[13–16] These restrictions on patient cohorts and shorter follow-up time limits the ability to identify whether apathy was a prodromal symptom in the pathway of neurodegeneration, causal risk factor, or reaction to the diagnosis of dementia.[34] A prior meta-analysis suggested that apathy is prodromal because the association between apathy and dementia in patients with MCI diminished with longer follow-up, but this had not been rigorously evaluated.[35] The few existing studies in cognitively normal older adults had conflicting results regarding the risk of dementia conferred by apathy. One study found a 7-fold

Table 3 Risk of incident dementia by apathy tertile in a Cox proportional hazards model

Apathy tertile	N (% of total) with incident dementia	Hazard ratio (95% confidence interval)		
		Model 1	Model 2	Model 3
Low apathy	111/768 (14)	1 (Reference)	1 (Reference)	1 (Reference)
Moderate apathy	143/742 (19)	1.32 (1.02–1.69)	1.34 (1.03–1.74)	1.29 (0.99–1.69)
Severe apathy	127/508 (25)	1.91 (1.48–2.47)	1.91 (1.45–2.51)	1.77 (1.33–2.34)

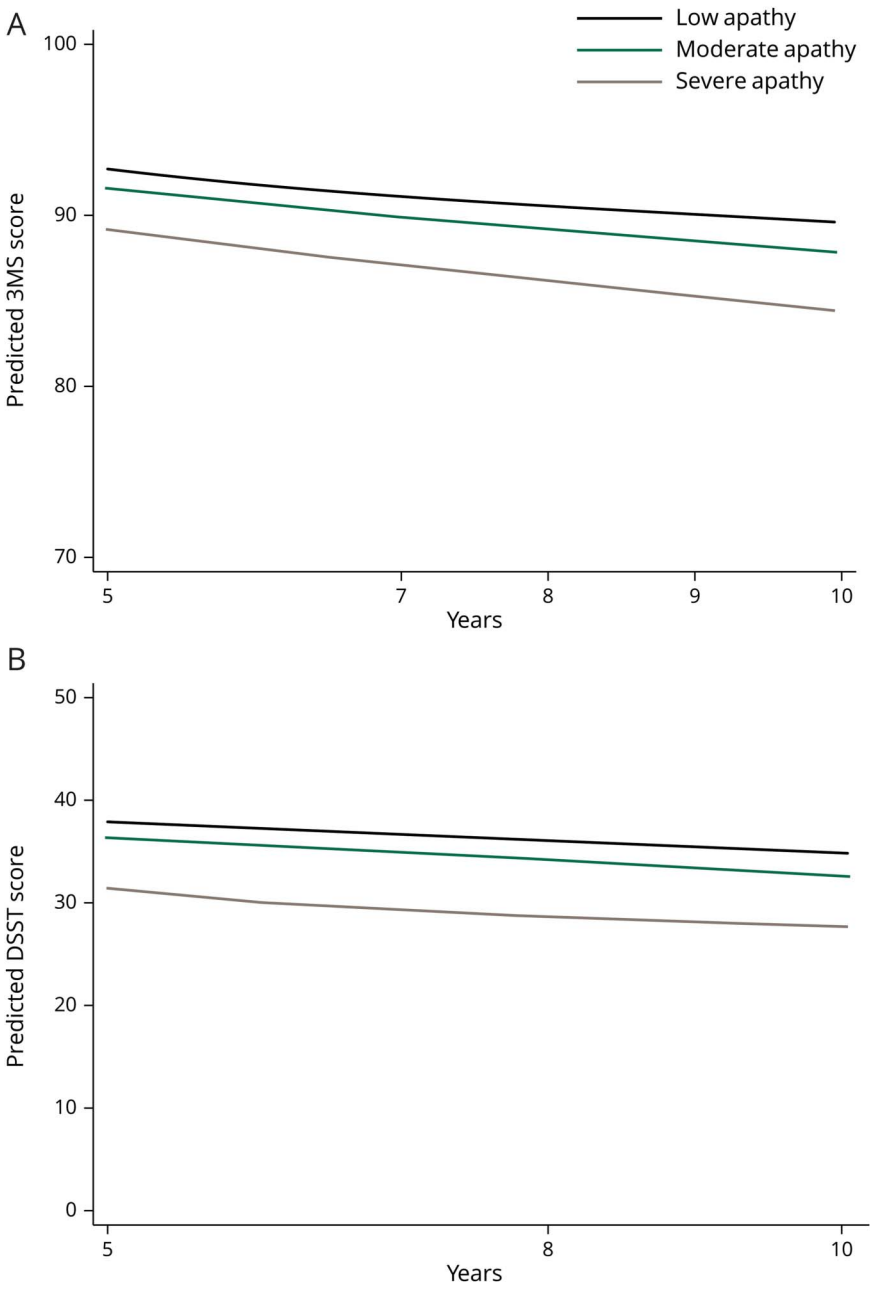
Model 1 is unadjusted. Model 2 is adjusted for demographics, education, history of myocardial infarction, history of stroke, hypertension, *APOE4* status, and cigarette smoking. Model 3 is adjusted in addition for depressed mood.

Table 4 Raw regression coefficients from the linear mixed model evaluating change over time in the modified Mini-Mental State Examination (3MS) and Digit Symbol Substitution Test (DSST) by apathy tertile

Apathy tertile	β (95% confidence interval)		
	Model 1	Model 2	Model 3
3MS			
Moderate	−0.23 (−0.72 to 0.25)	−0.17 (−0.67 to 0.33)	−0.10 (−0.60 to 0.41)
Severe	−0.54 (−1.10 to 0.01)	−0.26 (−0.85 to 0.32)	−0.09 (−0.70 to 0.51)
DSST			
Moderate	−0.26 (−0.90 to 0.39)	−0.35 (−1.00 to 0.31)	−0.24 (−0.90 to 0.42)
Severe	−0.44 (−1.19 to 0.32)	−0.57 (−1.35 to 0.20)	−0.32 (−1.12 to 0.49)

Model 1 is unadjusted. Model 2 is adjusted for demographics, education, myocardial infarction, history of stroke, hypertension, cigarette smoking, and *APOE4* status. Model 3 is adjusted in addition for depressed mood.

Figure 2 Modified Mini-Mental State Examination (3MS) and Digit Symbol Substitution Test (DSST) over time by apathy tertile, implied by linear mixed effects model



(A) 3MS. (B) DSST. Models included demographics, education, history of myocardial infarction, history of stroke, hypertension, cigarette smoking, *APOE4*, and depressed mood.

increase in the risk of Alzheimer dementia[26] and 2 others identified progression to MCI but not dementia over a short time frame.[19,36] In addition, existing studies were conducted in primarily white patients drawn from academic centers, whereas our study was 36% nonwhite and is more generalizable to the US population.

Our results support the hypothesis that apathy is a prodrome to dementia, which is in line with early studies evaluating the neurobiology of apathy in neurodegenerative conditions. In individuals with dementia, symptoms of apathy correlate with increased prefrontal tau and amyloid burden.[37,38] Neuroimaging studies also demonstrate that loss of white matter connectivity can contribute significantly to symptoms of apathy.[39,40] In adults with varied cognition, the posterior cingulate and inferior temporal cortex exhibit atrophy early in apathy development, with progression to involve the anterior cingulate, inferior frontal cortex, and insula.[41,42] There is conflicting evidence regarding the genetic underpinnings of apathy, with 2 studies finding an increased risk of apathy in *APOE4* carriers[43] and others finding no association.[44,45] In our cohort,

we did not find a significant interaction between *APOE4* status and apathy in predicting dementia. While it is possible that apathy also represents a causal risk factor for dementia, likely mediated by social withdrawal, our study adds to the growing body of evidence that it is a prodromal symptom.

In our study, apathy did not predict greater cognitive decline as measured by the 3MS and DSST, suggesting that apathy may be less helpful in predicting cognitive decline below the dementia threshold. However, prior studies found significant short-term cognitive decline after identification of apathy.[7] In our cohort, apathy was not measured until year 6 and we excluded participants who developed dementia prior to this, so the patients with more rapid cognitive decline were excluded from the analysis. Alternatively, prodromal apathy may represent selective vulnerability of frontal circuits that leads to changes less readily detectable on some cognitive tests. Individuals with dementia and apathy have previously been shown to have more impairment in multitasking, selective attention, and cognitive flexibility.[46] Our neuropsychological measures evaluated executive function, but are less likely to identify disinhibition, impaired judgement, and other behavioral changes that nonetheless significantly impact function. The presence of apathy is distressing to family and interferes substantially with activities of daily living, so this symptom may also increase the likelihood that a patient is diagnosed with dementia by a clinician even without a statistically significant difference in neuropsychological performance.

Strengths of our study include the diversity of our cohort, longer follow-up time in a sample of patients who are not cognitively impaired at baseline, and the ability to control for depressed mood and a number of cardiovascular risk factors. Our sample was less subject to referral bias that affects most studies conducted in memory clinics, but is subject to the healthy volunteer bias. However, population-based studies are particularly important when studying apathy, a symptom that may cause individuals to minimize contact with the health care system. Limitations include our use of an algorithm to diagnose dementia, which may not be as sensitive as an in-depth clinical evaluation and did not enable us to diagnose dementia subtypes. We did not have data available on hospital-acquired delirium to investigate how this could be associated with dementia. As delirium is a transient state and variably coded, surveillance of delirium is challenging using hospital data. Second, apathy was self-reported in this study in a population that may be experiencing behavioral changes with variable levels of insight. However, self-report is a common form of clinician assessment of behavioral symptoms and is more reliable in cognitively normal adults.[42] Sensitivity analyses excluding patients with baseline probable MCI showed no substantial difference in HRs. Third, the literature on depression as a predictor of dementia suggests that the timing of onset,[9] severity of symptoms,[12] and trajectory[47] are all important modifiers between depression and dementia risk. Our evaluation of these modifiers was limited by the lack of repeated evaluations or evaluation of symptoms earlier in life, though apathy is more likely to be a persistent state.[48,49]

We found that apathy is independently associated with increased risk of future probable dementia. As apathy is typically clinically apparent and highly distressing to family, a brief evaluation of apathy may be a helpful tool to identify older adults at increased risk of dementia. Neuroimaging and CSF biomarkers are promising new techniques in identifying prodromal dementia,[50] but they are currently under development and may not be available in underresourced health care systems. Future research is needed to further understand the neurobiology of apathy and the role of apathy screening in identifying individuals who would benefit from early reduction of modifiable risk factors or consideration for clinical trials.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Meredith A. Bock, MD	University of California, San Francisco	Designed and conceptualized study, analyzed the data, interpreted the data, drafted the manuscript for intellectual content
Amber Bahorik, PhD	University of California, San Francisco	Consulted on statistical analysis, revised the manuscript for intellectual content
Willa D. Brenowitz, PhD, MPH	University of California, San Francisco	Consulted on statistical analysis, revised the manuscript for intellectual content
Kristine Yaffe, MD	University of California, San Francisco; San Francisco Veterans Affairs Medical Center	Mentored study design process, interpreted the data, revised the manuscript for intellectual content

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