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Association of Apathy With Risk of Incident Dementia
A Systematic Review and Meta-analysis

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IMPORTANCE Fear of dementia is pervasive in older people with cognitive concerns. Much research is devoted to finding prognostic markers for dementia risk. Studies suggest apathy in older people may be prodromal to dementia and could be a relevant, easily measurable predictor of increased dementia risk. However, evidence is fragmented and methods vary greatly between studies.

OBJECTIVE To systematically review and quantitatively synthesize the evidence for an association between apathy in dementia-free older individuals and incident dementia.

DATA SOURCES Two reviewers conducted a systematic search of Medline, Embase, and PsychINFO databases.

STUDY SELECTION Inclusion criteria were (1) prospective cohort studies, (2) in general populations or memory clinic patients without dementia, (3) with clear definitions of apathy and dementia, and (4) reporting on the association between apathy and incident dementia.

DATA EXTRACTION AND SYNTHESIS PRISMA and MOOSE guidelines were followed. Data were extracted by 1 reviewer and checked by a second.

MAIN OUTCOMES AND MEASURES Main outcomes were pooled crude risk ratios, maximally adjusted reported hazard ratios (HR), and odds ratios (OR) using DerSimonian-Laird random effects models.

RESULTS The mean age of the study populations ranged from 69.2 to 81.9 years (median, 71.6 years) and the percentage of women ranged from 35% to 70% (median, 53%). After screening 2031 titles and abstracts, 16 studies comprising 7365 participants were included. Apathy status was available for 7299 participants. Studies included populations with subjective cognitive concerns (n = 2), mild cognitive impairment (n = 11), cognitive impairment no dementia (n = 1), or mixed cognitive and no cognitive impairment (n = 2). Apathy was present in 1470 of 7299 participants (20.1%). Follow-up ranged from 1.2 to 5.4 years. In studies using validated apathy definitions (n = 12), the combined risk ratio of dementia for patients with apathy was 1.81 (95% CI, 1.32-2.50; I^2 = 76%; n = 12), the hazard ratio was 2.39 (95% CI, 1.27-4.51; I^2 = 90%; n = 7), and the odds ratio was 17.14 (95% CI, 1.91-154.0; I^2 = 60%; n = 2). Subgroup analyses, meta-regression, and individual study results suggested the association between apathy and dementia weakened with increasing follow-up time, age, and cognitive impairment. Meta-regression adjusting for apathy definition and follow-up time explained 95% of heterogeneity in mild cognitive impairment.

CONCLUSIONS AND RELEVANCE Apathy was associated with an approximately 2-fold increased risk of dementia in memory clinic patients. Moderate publication bias may have inflated some of these estimates. Apathy deserves more attention as a relevant, cheap, noninvasive, and easily measureable marker of increased risk of incident dementia with high clinical relevance, particularly because these vulnerable patients may forgo health care.

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Supplemental content

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Fear of dementia is common in patients presenting to memory clinics with cognitive concerns.[1] Although clinical evaluation can lead to a dementia diagnosis, patients often have milder conditions, including mild cognitive impairment (MCI) and isolated subjective cognitive concerns (SCC).[2-4] The annual progression from MCI to dementia in clinical settings is about 5% to 15%, while 20% to 25% of patients revert to normal cognition and functioning.[5] Patients with SCC have an increased risk (1.5- to 3-fold) of developing dementia compared with individuals without cognitive concerns, but most do not develop dementia in the near future.[3] However, fear of dementia is pervasive in patients with SCC or MCI,[1] and identifying those at increased risk is an important clinical concern.

Apart from memory loss and other cognitive disturbances, behavioral symptoms are common in most occurring forms of late-life dementia including Alzheimer disease (AD) and vascular dementia.[6] One of the most prevalent behavioral symptoms is apathy, estimated to affect almost half of patients.[7] Apathy is a disorder of motivation, manifesting itself as reduced interest, goal-directed cognition, and emotional expression.[8] Apart from dementia, apathy also occurs in MCI[9] and community-dwelling older people.[10] It has high clinical relevance because patients with apathy tend to withdraw from care and may escape clinicians' attention.[11-14] Apathy has been associated with incident dementia and could be useful as an easily assessable, low-cost, noninvasive marker of increased risk, which is relatively common and specific for future cognitive decline compared with other neuropsychiatric symptoms.[10,15-17] However, evidence is fragmented and apathy definitions vary greatly between studies.[10] We aimed to systematically review and meta-analyze the evidence from longitudinal cohorts for the association between apathy in older people and the risk of incident dementia.

Key Points

Questions What is the association between apathy in older people without dementia and incident dementia?

Findings In this systematic review and meta-analysis of 16 studies including 7365 patients, memory clinic patients with apathy had an approximately doubled risk of incident dementia, depending on age and cognitive function. Adjustment for apathy definition and duration of follow-up explained 95% of heterogeneity in patients with mild cognitive impairment; results seem generalizable to memory clinic populations.

Meaning Apathy is a relevant, noninvasive, cheap, and easily implementable prognostic factor prodromal to dementia. It has important clinical significance because patients are vulnerable and tend to withdraw from care, requiring an active caregiving approach from clinicians.

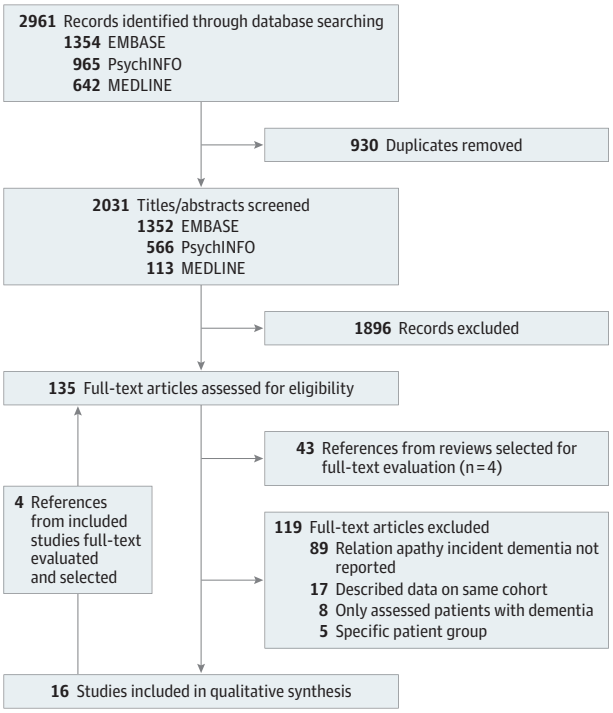
Methods

In this systematic review and meta-analysis following PRISMA and MOOSE guidelines,[18] we collated longitudinal cohort studies assessing apathy and subsequent incident dementia. Study populations could involve the general community-dwelling population or memory clinic patients. Studies concerning participants selected for specific medical conditions (eg, Down syndrome or frailty) or patients from care settings were excluded because such conditions may modify the association between apathy and incident dementia. Authors could use any diagnostic criteria to define apathy and dementia, provided definitions were clearly specified. Given the difficulties of retrospectively assessing whether apathy symptoms preceded dementia, only prospective cohort studies that diagnosed apathy in individuals without dementia were included. Randomized clinical trials were excluded because interventions provided may influence the association between apathy and incident dementia. There were no restrictions on publication year, language, or length of follow-up. There was no registered predefined review protocol.

Medline, Embase, and PsychINFO databases were searched from inception to October 2, 2017, and deduplicated using the OVID platform.[19] The full search is listed in eTable 1 in the Supplement. Search terms included apathy and commonly used apathy assessment instruments,[20] cross referenced with dementia or AD and terms referring to risk, incident, or prediction. Two investigators (L.vW. and J.W.vD.) independently screened titles and abstracts for (1) prospective longitudinal studies published in peer-reviewed journals; (2) in unselected community-dwelling populations or nondemented populations with cognitive concerns with or without cognitive impairment; (3) that clearly defined apathy and dementia diagnoses; and (4) that reported data regarding the association between apathy and incident dementia. Conflicts regarding inclusion were resolved by consensus. Full texts and bibliographies of included studies and relevant reviews were hand searched for additional studies. Data were extracted by 1 reviewer (J.W.vD.) and checked by a second (L.vW.) using a piloted standardized extraction form (eTable 2 in the Supplement) and assessed for risk of bias using an adapted version of the Newcastle-Ottawa quality assessment scale for cohort studies.[21]

Risk ratios (RR) and 95% confidence intervals for incident dementia were calculated per study using the number of dementia cases in the apathy and nonapathy groups. If unavailable, authors were approached to supplement these data.[22] If both AD and all-cause dementia were available,[23,24] all-cause dementia was used. A sensitivity analysis used AD as preferred outcome. Risk ratios, reported odds ratios (OR), and reported hazard ratios (HR) were pooled separately across studies. Random-effects Der Simonian-Laird models were used because of the heterogeneous study characteristics.[25] *P* values were 2-sided. For pooling reported effect sizes, maximally adjusted estimates were used. If these were overadjusted (<10 events per covariate), the most adjusted estimate without overadjustment was used. Studies using a validated recommended method to define apathy[20] and those using custom measurements were analyzed separately because the apathy construct may differ greatly between these categories. Heterogeneity was assessed using I^2 statistics.[25]

Figure 1. Flowchart of Search and Study Selection



Leave-one-out analyses were performed, in which every study was consecutively excluded once to assess its influence on the overall estimate. Subgroup and sensitivity analyses, including their rationale and whether they were predefined, are listed in eTable 3 in the Supplement. Meta-analyses were conducted in R (R Programming), using the meta and metafor packages.[26,27]

Results

From 2031 titles and abstracts, 15 studies were selected (**Figure 1**). Hand searching selected study bibliographies yielded 1 additional study.[28] Thus, 16 studies were included in the final synthesis.[15,22-24,28-39]

Table 1 provides an overview of the included studies. Fourteen concerned Western populations, one was a combined international population database,[15] and one was from China.[39] Four populations were derived from screened population-based cohorts[23,35,38,39] and 12 were from memory clinics. Study populations included SCC (n = 2),[29,30] MCI (n = 9),[15,22,24,31-35,38] amnestic MCI (n = 2),[28,36] cognitive impairment no dementia (n = 1),[23] and mixed patients with no cognitive impairment (NCI) and patients with MCI (n = 2).[37,39] The SCC studies excluded patients with abnormal neuropsychological test scores. Common exclusion criteria in MCI were psychiatric/somatic disorders possibly impairing cognition,[15,24,31,33,36,38] cerebrovascular disease or magnetic resonance imaging/computed tomography lesions,[24,28,31,33,36] and younger-onset MCI.[24,28,31] The median population sample size was 245.5 (range, 51-1821),[22,29,31] the median mean age was 71.6 years (range, 69.2-81.9 years),[23,28,29] and the median percentage of women was 53% (range; 35%-70.0%).[23,28,34]

Twelve studies defined apathy using a validated rating scale recommended to measure apathy[20] or a clinical diagnosis: 8 used any positive apathy score on the Neuropsychiatric Inventory informant (>0 of 12)[23,31,34,37,39] or questionnaire version (>0 of 3),[22,30,35] 1 used Neuropsychiatric Inventory informant score of greater than 2 of 12,[33] 1 used the standard Apathy Inventory cutoff (>2 in any dimension),[28] and 2 used standard clinical criteria.[32,36] Four studies used a custom apathy definition based on a general neuropsychiatric assessment tool or a minimum number of motivational subitems on a depression scale.[15,24,29,38] Overall, apathy at baseline was diagnosed in 1470 of 7299 participants (20.1%), prevalence ranging from 2.2% to 75% (median, 17.4%).[15,28,37]

Nine studies assessed AD as outcome (**Table 2**) using National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association[40] criteria (n = 7)[23,24,28-31,36] or a clinical diagnosis without further specification (n = 2).[15,22] Three studies also reported all-cause dementia[22-24]: 1 using a clinical diagnosis without specification,[22] 1 using *DSM-IV* criteria,[24,41] and 1 using *DSM-III-revised* criteria.[23,42] Seven studies assessed all-cause dementia only: 4 using *DSM-IV* criteria,[33,35,37,39] 1 using standard criteria per subtype,[32] 1 using a clinical dementia rating of at least 1,[34,43] and 1 using a comprehensive assessment score similar to a *DSM-III* diagnosis.[38]

Mean follow-up ranged from 1.2 to 5.4 years (median, 2.35).[15,23,24,31,32] Instead of a mean follow-up time, 6 studies only reported a period until reassessment, ranging from 1 to 3 years.[28,29,34] Overall, dementia occurred in 1953 of 7166 participants (27.3%) during follow-up, reported incidence ranging from 2.2% over 2 years to 41.8% over 1 year.[15,37] All studies except 1[22] reported the number of dementia cases for apathy and nonapathy groups separately. Calculated RRs ranged from 0.38 to 82.81.[24,29] Eight studies reported HRs,[15,22,23,28,30,33,35,44] 6 reported ORs,[24,29,32,34,38,39] and 2 did not report any measure of association for apathy and dementia.[31,37] Adjusted estimates ranged between 0.31 and3885 for ORs[24,29] and between 0.93 and 9.51 for HRs.[23,30] Most studies adjusted for the main confounders[10] of age (n = 11)[15,22-24,28,30,32,35,36,38,39] and baseline cognition (n = 10).[15,22,23,28,29,32,33,36] Four studies also reported unadjusted estimates,[15,24,30,38] ranging from an OR of 0.58 to an HR of 6.99.[24,30] Studies assessing both AD and all-cause dementia reported similar results for both outcomes (eTable 4 in the Supplement).[22-24]

eTable 5 in the Supplement lists study bias assessment scores and eTable 6 in the Supplement provides score motivations. The worst scoring categories were population representativeness, exposure assessment, and follow-up availability. Based on total Newcastle-Ottawa quality assessment scale score, 1 study had a relatively high bias risk[31] and 6 scored worse than average (<7 of 9 points).[29,31,33,34,37,38]

In studies using a recommended validated definition of apathy, the overall RR for developing dementia for patients with apathy (**Figure 2**) was 1.81 (95% CI, 1.32-2.50). Heterogeneity was high (I^2 = 76%). The funnel plot suggested low risk of publication bias (eFigure 1 in the Supplement). Leave-one-out

Table 1. Study Overview[a]

Source	Cohort Nationality	Setting	Population	Exclusion Criteria	No.	Age, Mean (SD), y	Female, No. (%)	Apathy Measure	Apathy Cases, No. (%)
Bartolini et al,[29] 2005	Italy	Memory clinic	SCC	Dementia, MCI, abnormal NP test scores	222	69.2 (4.8)	141 (64)	BDI[b]	35 (15.8)
Burke et al,[30] 2016	United States	Database of memory clinics	SCC	CDR >0, abnormal NP test scores	1567	71.2 (10.9)	988 (63)	NPI-Q	297 (18.9)
Chan et al,[39] 2011	China	CD sample and AR volunteers	NCI (35%); MCI (65%)	Age <60 y	321	77.3 (8.3)	225 (70)	NPI-i	45 (14.0)
Brodaty et al,[37] 2012	Australia	CD sample	NCI (63%); MCI (37%)	Inclusion, age 70-90 y; exclusion, MMSE<24, dementia, neurological disease, psychiatric/somatic disorders impairing cognition, developmental disability, malignancy, non-English, CI without SCC	630	78.2 (4.6)	346 (55)	NPI-i	14 (2.2)
Van der Linde et al,[38] 2013	United Kingdom	Population based	MCI (S)	Dementia, Parkinson disease, MMSE>26	879	56% ≥ 75[c]	927/1416 (65)	GMS-AGECAT	159 (18.1)
Pink et al,[35] 2015	United States	Population based	MCI	None reported	332	Median (IQR): 82.1 (77.7-85.0)	151 (45)	NPI-Q	55 (16.6)
Teng et al,[31] 2007	United States	Memory clinic	MCI	Age <50 y, neurological disease, CT/MRI lesions, psychiatric/somatic disorders impairing cognition	51	72.8 (7.2)	18 (35)	NPI-i	13 (25.5)
Vicini Chilovi et al,[32] 2009	Italy	Memory clinic	MCI	None reported	124	71.3 (7.7)	84 (68)	Clinical	36 (29.0)
Ramakers et al,[24] 2010	Netherlands	Memory clinic	MCI (GDS)	Age <56 y, cerebrovascular disease, brain trauma, psychiatric/somatic disorders impairing cognition	263	66.9 (7.7)	116 (44)	HAMD[b]	171 (75.0)
Richard et al,[15] 2012	International	Database of memory clinics	MCI (C)	Depression, MMSE<24, CDR not 0.5, neurological disease, psychiatric/somatic disorders impairing cognition, unstable medical condition	397	74.8 (7.5)	141 (36)	GDS-3A[b]	178 (44.8)
Somme et al,[33] 2013	Spain	Memory clinic	MCI	Neurodegenerative/cerebrovascular disease, acute psychiatric illness, severe comorbidities	132	69.8 (8.7)	62 (47)	NPI-i >2	69 (52.3)
Rosenberg et al,[23] 2013	United States	Database of memory clinics	MCI (C)	None reported	1821	75.3 (9.3)	920 (51)	NPI-Q	298 (16.7)
Sobów et al,[34] 2014	Poland	Memory clinic	MCI (NAW)	CDR not equal to 0.5	83	75.0 (1.9)	58 (70)	NPI-i	20 (24.1)
Robert et al,[28] 2008	France	Health clinic	aMCI (C)	Age <58 y, <4 y of education, MMSE <25, depression, MRI brain lesions	214	71.8 (5.4)	90 (42)	AI	47 (22.0)
Palmer et al,[36] 2010	Italy	Memory clinic	aMCI	Cerebrovascular disease, depression/somatic disorders possibly impairing cognition, MRI brain lesions	99	70.5 (6.6)	37 (37)	Clinical	12 (12.1)
Peters et al,[23] 2013	United States	Population based	CIND	CDR >0.5	230	81.9 (5.1)	115 (50)	NPI-i	21 (9.2)

Abbreviations: AI, Apathy Inventory; aMCI, amnestic mild cognitive impairment based on revised Peterson (Mayo Clinic) criteria; AR, actively responding; BDI, Beck Depression Inventory; CD, community dwelling; CDR, Clinical Dementia Rating; CIND, cognitive impairment no dementia; CT, computed tomography; GDS-3A, Geriatric Depression Scale 3 Apathy-related subitems; GMS-AGECAT, Geriatric Mental State Automated Geriatric Examination for Computer Assisted Taxonomy; HAMD, Hamilton rating scale for depression; MCI, mild cognitive impairment based on revised Peterson (Mayo Clinic) criteria; MCI (S), based on Stephan criteria; MCI (NAW), based on National Institute on Aging-Alzheimer Association workgroup; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NCI, no coginitive impairment; NP, neuropsychological; NPI-i, Neuropsychiatric Inventory for informants; NPI-Q, Neuropsychiatric Inventory Questionnaire for clinical informants; SCC, subjective cognitive concerns.

[a] Studies ordered by publication year within diagnostic group.

[b] Apathy measure based on subitems on a depression scale.

[c] Only a proportion of participants 75 years and older was available.

Table 2. Dementia Incidence and Association With Apathy

Source	Dementia	Criteria	Follow-up, Mean (SD), y	Dementia Incidence				Reported Association Apathy-Dementia		
				Overall, No. (%)	Apathy Group, No. (%)	No Apathy Group, No. (%)	Calculated RR (95% CI)	Crude (95% CI)	Adjusted (95% CI)	Adjustment
Bartolini et al,[29] 2005	AD	NINCDS	1[a]	33/222 (14.9)	31/35 (88.6)	2/187 (1.1)	82.81 (20.76-330.37)	NA	OR: 3885 (154-97902)[b]	Stepwise, depression (BDI), cognitive (TMT)
Burke et al,[30] 2016	AD	NINCDS	4.0 (0.6-8.8)[c]	565/1441 (39.2)	193/297 (65.0)	372/1144 (32.5)	2.00 (1.78-2.45)	HR: 6.99 (5.51-8.88)	HR: 9.51 (5.23-17.31)	Age, sex, race, Hispanic, ApE4, family history
Chan et al,[39] 2011	Dementia	*DSM-IV*, TR	2	51/321 (15.9)	3/45 (6.7)	48/276 (17.3)	0.38 (0.13-1.18)	NA	OR: 0.31 (0.09-1.13)	Age, sex, education, BL MMSE, depression, AbMB
Brodaty et al,[37] 2012	Dementia	*DSM-IV*	2	14/630 (2.2)	0/14 (0.0)	14/616 (2.2)	1.42 (0.09-22.69)	NA	NA	NA
Van der Linde et al,[38] 2013	Dementia	*DSM-III*	2	128/879 (14.6)	33/159 (20.8)	95/720 (13.2)	1.57 (1.10-2.49)	OR: 1.7 (1.1-2.7)	OR: 1.2 (0.7-1.9)[d]; OR: 1.0 (0.6-1.8)[e]	Age, sex, education, SOC, MMSE, SMC, OMC, ADL (BPS inst, emotional, stroke, MI, DM, SRH, smoking)[e]
Pink et al,[35] 2015	Dementia	*DSM-IV*	3.0 (2.5-5.3)[f]	117/332 (35.2)	25/55 (44.5)	92/277 (33.2)	1.34 (0.98-1.91)	NA	HR: 1.62 (1.03-2.54)	Age, sex, education, comorbidity
Teng et al,[31] 2007	AD	NINCDS	2.0 (1.2)	12/51 (23.5)	6/13 (46.2)	6/38 (15.8)	2.92 (1.14-7.48)	NA	NA	NA
Vicini Chilovi et al,[32] 2009	Dementia	NINCDS, VaD, LBD	2.0 (0.2)	28/124 (22.6)	13/36 (36.1)	15/88 (17.0)	2.12 (1.12-3.99)	NA	OR: 7.07 (1.9-25)	Age, depression (clinical diagnosis), ADL BI, Cognitive (ADAS)
Ramakers et al,[24] 2010	Dementia*	NINCDS and *DSM-IV*	5.4	90/225 (34.2)	50/135 (37.0)	40/90 (44.4)	0.83 (0.61-1.15)	OR: 0.58 (0.35-0.96)[b]	OR: 0.67 (0.40-1.13)[b]	Age, sex, education
Richard et al,[15] 2012	AD	Clinical	2.7 (1.0)	166/397 (41.8)	82/178 (46.1)	84/219 (38.4)	1.20 (0.95-1.51)	HR: 1.43 (0.86-2.38)[b]	HR: 1.85 (1.09-3.15)[b]	Age, sex, education; cognitive (MMSE)
Somme et al,[33] 2013	Dementia	*DSM-IV*	3.5 (2.9)	38/132 (28.0)	21/69 (30.4)	17/63 (27.0)	1.13 (0.66-1.94)	NA	HR: 2.20 (1.003-4.82)	cognitive (MMSE)
Rosenberg et al,[23] 2013	Dementia*	Clinical	1.2 (0.3)	527/1787 (29.5)	NA	NA	NA	NA	HR: 1.13 (1.00-1.28)	Age, sex, Hispanic race/ethnicity, cognitive (MMSE and CDR)
Sobów et al,[34] 2014	Dementia	CDR = 1	2[a]	27/83 (32.5)	18/20 (90)	9/63 (14.3)	6.30 (3.38-11.74)	NA	OR: 70.7 (5.6-699)	Backward, sex, BMI, dBMI
Robert et al,[28] 2008	AD	NINCDS	3[a]	59/215 (27.4)	18/47 (38.3)	41/168 (24.4)	1.57 (1.00-2.46)	NA	HR: 2.48 (1.14-5.37)	Age, sex, education, cognitive (FCSRT)
Palmer et al,[36] 2010	AD	NINCDS	1.4 (8.4)	15/99 (15.2)	6/12 (50)	9/87 (10.3)	4.83 (2.09-11.18)	HR: 4.6 (1.3-16.2)[d]	HR: 6.9 (2.3-20.6)[e]	Age, sex, education, depression (clinical diagnosis), cognitive (MMSE)[e]
Peters et al,[23] 2013	Dementia[b]	NINCDS and *DSM-IIIR*	3.3	83/228 (36.4)	7/21 (33.3)	76/207 (36.7)	0.91 (0.48-1.71)	NA	HR: 0.93 (0.43-2.02)	Age, education, ApE4, cognitive (3MS)

Abbreviations: 3MS, Modified Mini-Mental State Examination; AbMB, aberrant motor behavior; AD, Alzheimer Disease; ADAS, Alzheimer Disease Assessment Scale; ADL BI, Activities of Daily Living, Barthel Index; ApE4, Apolipoprotein allele ε4; BDI, Beck Depression Inventory score; BL, baseline; BMI, body mass index; BPS, other behavioral and psychological symptoms; CDR, Clinical Dementia Rating; dBMI, change in BMI; DM, diabetes mellitus; FCSRT, Free and Cued Selective Reminding Test; HR, hazard ratio; LBD, Lewy Body Dementia Standard Criteria; MI, myocardial infarction; MMSE, Mini-Mental State Examination; NINCDS, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association; OMC, objective memory impairment; OR, odds ratio; RR, risk ratio; SMC, subjective memory concerns; SOC, social class; SRH, self rated health; TMT, Trail Making Test; VaD, Vascular Dementia Standard Criteria (NINDS-AIREN).

[a] No mean follow-up but assessment for whole cohort at stated time.

[b] Study assessed both AD and all-cause dementia.

[c] Mean (minimum-maximum).

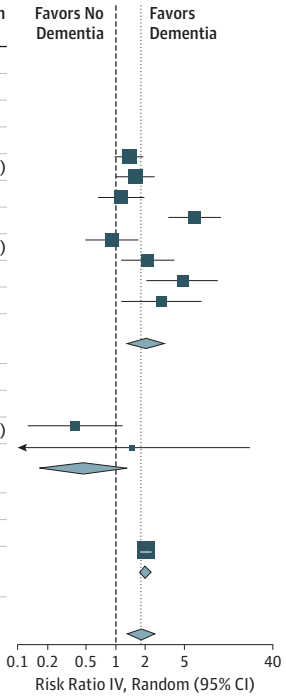
[d] Most adjusted estimate not overadjusted.

[e] Estimate considered overadjusted (<10 events per predictor).

[f] Median (interquartile range).

Figure 2. Forest Plot for Risk Ratio of Developing Dementia in Studies Using Recommended Validated Apathy Scales According to Subgroups Based on Diagnosis

Study or Subgroup	Apathy, No. Events	Apathy, No. Total	No Apathy, No. Events	No Apathy, No. Total	Weight IV, %	Risk Ratio Random (95% CI)
MCI						
Pink et al,[35] 2015	25	55	92	277	13.1	1.37 (0.98-1.91)
Robert et al,[28] 2008	18	47	41	168	11.8	1.57 (1.00-2.46)
Somme et al,[33] 2013	21	69	17	63	10.7	1.13 (0.66-1.94)
Sobow et al,[34] 2014	18	20	9	63	9.7	6.30 (3.38-11.74)
Peters et al,[23] 2013	7	21	76	207	9.6	0.91 (0.48-1.71)
Chilovi et al,[32] 2009	13	36	15	88	9.6	2.12 (1.12-3.99)
Palmer et al,[36] 2010	6	12	9	87	7.5	4.83 (2.09-11.18)
Teng et al,[31] 2007	6	13	6	38	6.6	2.92 (1.14-7.48)
Rosenberg et al,[22] 2013	NA	228	NA	1556	0.0	
Total (95% CI)		501		2547	78.5	2.02 (1.31-3.13)
Heterogeneity: $\tau^2 = 0.2953$; $\chi^2 = 32.41$, $df = 7$ ($P < .01$); $I^2 = 78\%$						
NCI MCI						
Chan et al,[39] 2011	3	45	48	276	5.3	0.38 (0.12-1.18)
Brodaty et al,[37] 2012	0	14	14	616	1.2	1.47 (0.09-23.41)
Total (95% CI)	NA	59	NA	892	6.5	0.46 (0.16-1.31)
Heterogeneity: $\tau^2 = 0$; $\chi^2 = 0.77$, $df = 1$ ($P = .38$); $I^2 = 0\%$						
SCC						
Burke et al,[30] 2016	193	297	372	1144	15.0	2.00 (1.78-2.25)
Total (95% CI)	NA	297	NA	1144	15.0	2.00 (1.78-2.25)
Heterogeneity: Not applicable						
Total (95% CI)	**NA**	**857**	**NA**	**4583**	**100.0**	**1.81 (1.32-2.50)**
Heterogeneity: $\tau^2 = 0.1745$; $\chi^2 = 41.72$, $df = 10$ ($P < .01$); $I^2 = 76\%$						



IV indicates inverse variance; MCI, mild cognitive impairment; NCI MCI, mixed normal cognition and MCI; SCC, subjective cognitive impairment.

analyses results (eFigure 2 in the Supplement) ranged from 1.59 (95% CI, 1.19-2.12; I^2 = 67%)[34] to 1.96 (95% CI, 1.45-2.66; I^2 = 73%).[23] Analyzing AD as preferential outcome gave similar results (eFigure 3 in the Supplement). Figure 2 lists results within diagnostic subgroups (SCC vs MCI and NCI and MCI). Owing to the small number of studies in other diagnostic groups, subanalyses were restricted to patients with MCI. The overall RR in patients with MCI was 2.02 (95% CI, 1.31-3.13; I^2 = 78%). Sensitivity analysis separating MCI, cognitive impairment no dementia, and anamnestic MCI subgroups gave similar results; therefore, they were analyzed as 1 diagnostic category. The funnel plot for RRs in patients with MCI suggests some publication bias (eFigure 4 in the Supplement). Leave-one-out analyses results ranged from 1.65 (95% CI, 1.18-2.31; I^2 = 58%)[34] to 2.22 (95% CI, 1.47-4.42; I^2 = 79%).[33]

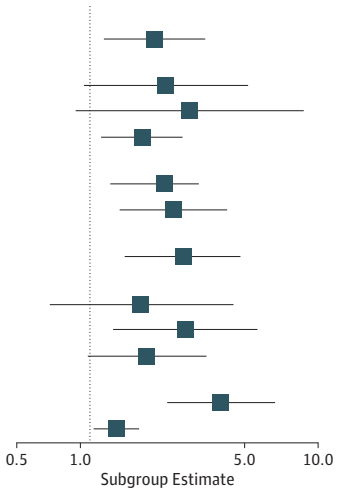
Pooling maximally adjusted HRs over all studies (eFigure 5 in the Supplement) gave a combined HR of 2.39 (95% CI, 1.27-4.51), with considerable heterogeneity (I^2 = 90%). Leave-one-out analyses results ranged from 1.74 (95% CI, 1.13-2.68),[30] to 2.80 (95% CI, 1.35-5.79).[23] In the MCI subgroup, the combined HR was 1.74 (95% CI, 1.13-2.68, I^2 = 73%) (eFigure 5 in the Supplement). Leave-one-out analysis results ranged from 1.44 (95% CI, 1.03-1.99; I^2 = 54%)[36] to 2.02 (95% CI, 1.13-2.68; I^2 = 59%).[23] The funnel plot suggested some publication bias (eFigure 6 in the Supplement). Pooling maximally adjusted ORs (n = 3) gave an overall estimate of 4.60 (95% CI, 0.26-80.20; I^2 = 89%). Estimates ranged from 1.48 (95% CI, 0.07-31.63; I^2 = 91%) to 17.14 (95% CI, 1.91-153.98; I^2 = 60%). The analyses pooling the ORs in MCI gave a combined OR of 17.14 (95% CI, 1.91-154.0; I^2 = 60%). Because ORs in MCI were only available for 2 studies,[32,34] no additional analyses were performed.

None of the subgroup pairs (**Figure 3**) were markedly different except for long follow-up (RR, 1.30; 95% CI, 1.04-1.63; I^2 = 0%) vs short follow-up (RR, 3.73; 95% CI, 2.17-6.42; I^2 = 53%). Meta-regression within MCI (eFigure 7 in the Supplement) showed a significant association between follow-up time and RR within studies (0.44 per year; 95% CI, 0.31-0.62; $P < .001$), accounting for an R^2 of 95% of heterogeneity. There was no association between age and RR (0.94 per year; 95% CI, 0.31-0.62; R^2 = 0%). Results of subgroup analyses for HRs in MCI (eFigure 8 in the Supplement) were comparable except for long vs short follow-up subgroup estimates being similar. Meta-regression showed no association between HRs and follow-up time (0.92 per year; 95% CI, 0.88-1.02; I^2 = 70%; R^2 = 0%) nor age (1.07 per year; 95% CI, 0.84-1.02; I^2 = 76%; R^2 = 0%). The meta-regression plot (eFigure 9 in the Supplement) suggested this disparity between RRs and HRs regarding follow-up time was largely owing to 1 study, unavailable for the RR analyses.[22] Omitting this study, there was a significant association between follow-up time and HR (0.48 per year; 95% CI, 0.25-0.93), explaining R^2 = 76% of heterogeneity (eFigure 10 in the Supplement).

Including studies using custom apathy definitions (eFigure 11 in the Supplement) gave an RR of 1.82 overall (95% CI, 1.34-2.47; I^2 = 87%) and of 1.66 within MCI (95% CI, 1.22-2.25; I^2 = 80%) (eFigure 12 in the Supplement). Meta-regression within MCI suggested R^2 = 97% of heterogeneity

Figure 3. Subgroup Analyses Within Mild Cognitive Impairment Patients Based on Risk Ratio

Subgroup	Studies	RR (95% CI)	I^2, %
Age low	Robert et al,[28] Somme et al,[33] Vincini Chilovi et al,[32] Palmer et al[36]	1.91 (1.15-3.17)	66
Age high	Pink et al,[35] Sobow et al,[34] Peters et al,[23] Teng et al[31]	2.13 (0.94-4.87	87
Low bias	Sommer et al,[33] Sobow et al,[34] Teng et al[31]	2.71 (0.87-8.51)	88
High bias	Pink et al,[35] Robert et al,[28] Vincini Chilovi et al,[32] Palmer et al,[36] Peters et al[23]	1.69 (1.12-2.53)	65
Low representativeness bias	Vincini Chilovi[32]	2.12 (1.23-2.97)	NA
High representativeness bias	Pink et al,[35] Robert et al,[28] Somme et al,[25] Sobow et al,[27] Palmer et al[36]	2.31 (1.35-3.96)	82
Low FU availability bias	Pink et al,[35] Robert et al,[28] Sobow et al,[27] Vincini Chilovi et al,[32] Palmer et al[36]	2.54 (1.42-4.53)	83
High FU availability bias	Sommer et al,[35] Teng et al[23]	1.67 (0.67-4.20)	66
Excluding depression	Robert et al,[20] Palmer et al,[29] Teng et al[23]	2.61 (1.27-5.37)	66
Not excluding depression	Pink et al,[28] Somme et al,[25] Sobow et al,[27] Vincini Chilovi et al,[32] Peters et al[17]	1.77 (0.98-3.21)	84
Short FU	Sobow et al,[34] Chilovi et al,[32] Palmer et al,[36] Teng et al[31]	3.73 (2.17-6.42)	53
High FU	Pink et al,[35] Robert et al,[28] Somme et al[33]	1.30 (1.04-1.63)	0



Only studies using validated apathy scales are included. FU indicates follow-up; RR, risk ratio.

could be explained by follow-up time, definition type (recommended vs custom), and their interaction, with I^2 = 10% heterogeneity remaining (eFigure 13 and 14 in the Supplement). The overall RR within studies using custom scales was 2.14 (95% CI, 1.04-4.41; I^2 = 93.0%) and within MCI was 1.16 (95% CI, 0.84-1.60; I^2 = 71%) (eFigure 15 in the Supplement). The small number of studies precluded subgroup analyses within this group.

Discussion

Apathy was consistently associated with an increased risk of incident dementia in patients with MCI and SCC in different settings and countries. However, heterogeneity was considerable. In MCI, the dementia risk was about double for patients with apathy and seemed higher for the short vs the long term, with meta-regression based on follow-up time explaining most heterogeneity. In SCC, the risk for patients with apathy may be as much as 2-fold to more than 7-fold higher, but data were too sparse for a reliable estimate. Results in mixed NCI-MCI populations are difficult to interpret owing to limited data on dementia development in both groups separately.

Subgroups of studies adjusting and not adjusting for age and cognition showed similar associations. This may be ecological fallacy. Within studies reporting both crude and adjusted estimates, adjustment for age and cognition increased the association of apathy with dementia, suggesting a stronger association in younger patients who are relatively cognitively intact. Concordantly, HRs seemed higher in SCC compared with MCI. Although usually considered an important confounder,[10] subgroup analyses showed no marked difference between studies including or excluding patients with depression. Apathy HRs seemed higher in studies controlling for depression, suggesting stronger associations in patients without depression, but group sizes were insufficient to allow firm conclusions. Regression with apathy definition type and follow-up duration together explained more than 95% of heterogeneity. Studies using custom apathy definitions found lower estimates. This may be attributable to measurement error, diluting associations. The diminishing association between apathy and dementia with longer follow-up suggests apathy is predominantly prodromal to dementia rather than a causal risk factor[10]; the risk regressing to the mean over time. However, selective dropout of patients with apathy may also have weakened long-term associations. There were insufficient data to assess the influence of apathy severity, although some studies using the NPI used low (Neuropsychiatric Inventory informant >0) and higher (Neuropsychiatric Inventory questionnaire >0; Neuropsychiatric Inventory informant >2) apathy severity thresholds.

Results seem generalizable to memory clinic populations. Patient demographics and proportions of patients with MCI developing dementia correspond to the literature.[3,5,45,46] The high dementia rate in SCC reported by Burke et al[30] may reflect the long follow-up. Poor scores regarding representativeness bias mainly resulted from unclear exclusion percentages or custom MCI definitions. Small groups made representativeness bias subgroup analyses uninformative. Although some studies used many exclusion criteria, exclusion percentages were generally acceptable. Results seem applicable to all-cause and AD dementia: individual study reports and sensitivity analyses showing similar results for both outcomes. This is not surprising given the mixed pathologies underlying clinical AD diagnoses in old age.[47] Because studies concerned memory clinic patients and/or individuals with cognitive symptoms, results may not be directly translatable to general community-dwelling older populations nor populations with comorbidity, preventing memory clinic consultation. Overall, validity seems high because most studies were conducted in clinical settings, using readily available and easily

measureable apathy criteria and standard dementia definitions. However, because rating scales were often informant-based, patient-informant associations and informants' expectations of normal behavior may have influenced apathy diagnoses, possibly mitigating the translatability of the results to the individual level.[6,48-50] Generalizability to non-Western cultures may also be limited: all but 1 study concerned Western populations, and the construct of behaviors considered apathetic may vary between cultures.[51]

Limitations

Our review has some limitations. First, reviewing the published literature may have introduced publication bias, leading to overestimation of the association between apathy and dementia. Most studies used the NPI, which measures 12 separate neuropsychiatric symptoms. Whether associations between dementia and these individual symptoms are reported and/or published may depend on their effect size. The extreme estimate by Bartolini et al[29] may exemplify the "winner's curse," ie, a newly discovered association often being inflated.[52] The lack of studies in SCC between 2005 and 2016 could indicate absence of replication efforts during this time but also that replication was unsuccessful and not published. However, funnel plots suggested that, overall, publication bias was limited. Second, because apathy and incident dementia are associated with study dropout,[13,53] the substantial attrition in some studies could have caused attrition bias, attenuating study estimates. Concordantly, studies with higher attrition bias risk seemed to report lower estimates. Third, ORs and RRs may give distorted results. Participants dropping out during follow-up should preferably be censored at the dropout time, not excluded or left in the denominator. With apathy being associated with dropout and mortality,[13,54] noncensoring could introduce bias, attenuating the association between apathy and dementia. Hazard ratios were therefore the most appropriate summary measure. However, these were unavailable for half of the studies. The different effect measures and the considerable heterogeneity preclude exact estimates of the association between apathy and incident dementia. However, the estimates were overall consistent. Fourth, combining population-based and clinical studies requires some consideration because these populations differ in sample representativeness, prevalence rates, and disease context, potentially influencing associations between apathy and dementia and generalizability.[55] Apathy prevalence and dementia risk estimates were similar in the 2 population-based MCI cohorts compared with memory clinic cohorts. However, inferences regarding mixed MCI-NCI populations are hampered by unclear generalizability and insufficient differentiated data, which may influence combined results. Finally, the value of the subgroup analyses is limited by the relatively small subgroups being easily dominated by single studies and the risk of type 1 error.

Conclusions

In conclusion, apathy was associated with an approximately 2-fold increased risk of dementia in memory clinic patients. The risk seems independent of concurrent depression, greater in the short term compared with the long term, and less strong with higher age and greater cognitive impairment. Withdrawal from activities and interests in older and/or more cognitively impaired individuals is less specific for underlying neuropathology, perhaps also reflecting changes in lifestyle and physical and mental ability. This suggests apathy is a particularly potent signal in relatively young and otherwise healthy individuals, in whom this behavior change is more easily noticed. Whether apathy, combined with other easily measureable clinical parameters, is a useful predictor on an individual level in clinical practice needs to be investigated in dedicated prognostic studies. The paucity of data on apathy in patients with SCC also warrants more research. Our results concur with findings that symptoms of apathy in community-dwelling older people increase the risk of cognitive decline and incident dementia.[16,56] These findings support the concept of mild behavioral impairment as a prodromal syndrome to dementia, with apathy possibly being among its most pervasive manifestations, which is potentially relevant for dementia trials.[57,58] However, many patients with apathy may not develop dementia, and the negative consequences of diagnoses without treatment options require consideration.[59,60] Results suggest apathy in older people deserves more attention as a prognostic factor. It is clinically relevant because older people with apathy represent a medically highly vulnerable group that tends to withdraw from care and may require active engagement from clinicians.[11-14,61] While much research is aimed at prognostic biomarkers based on advanced magnetic resonance imaging techniques or cerebrospinal fluid analyses, relatively simple measurement of neuropsychiatric symptoms merits consideration because it is less invasive, cheaper, and easier to implement on a broad scale.[62-64] For population and health care systems under financial constraint, taking apathy as a marker should be explored as a possible alternative to invasive and relatively expensive investigations.

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Concept and design: van Dalen, Moll van Charante, Brayne, Van Gool.
Acquisition, analysis, or interpretation of data: van Dalen, van Wanrooij, Moll van Charante, Richard.
Drafting of the manuscript: van Dalen.
Critical revision of the manuscript for important intellectual content: van Wanrooij, Moll van Charante, Brayne, Van Gool, Richard.
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Supervision: Moll van Charante, Brayne, Van Gool, Richard.

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