Supplementary Online Content

van Dalen JW, van Wanrooij LL, van Charante EPM, Brayne C, van Gool WA, Richard E. Association of apathy with risk of incident dementia: a systematic review and meta-analysis. *JAMA Psychiatry*. Published online July 18, 2018. doi:10.1001/jamapsychiatry.2018.1877

This supplementary material has been provided by the authors to give readers additional information about their work.

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Set	Search Statement
1.	Apathy.mp. or exp Apathy/
2.	"apathy scale".mp.
3.	"apathy evaluation scale".mp.
4.	"Neuropsychiatric Inventory".mp.
5.	exp Alzheimer Disease/ or alzheimer*.mp. or exp dementia/ or dementia.mp.
6.	hazard.mp.
7.	incident.mp.
8.	predict*.mp.
9.	exp Risk Factors/ or risk.mp. or exp Risk/
10.	6 or 7 or 8 or 9
11.	1 or 2 or 3 or 4
12.	5 and 10 and 11
13.	Apathy.mp. or exp APATHY/
14.	"Apathy scale".mp.
15.	"apathy evaluation scale".mp.
16.	"Neuropsychiatric Inventory".mp.
17.	"Lille Apathy Rating Scale".mp.
18.	exp ALZHEIMER'S DISEASE/ or Alzheimer*.mp. or exp dementia/ or dementia.mp
19.	risk.mp. or exp RISK FACTORS/
20.	hazard.mp.
21.	incident.mp.
22.	predict*.mp.
23.	13 or 14 or 15 or 16 or 17
24.	19 or 20 or 21 or 22
25.	18 and 23 and 24
26.	apathy.mp. or exp apathy/
27.	"apathy scale".mp.
28.	"apathy evaluation scale".mp.
29.	"Neuropsychiatric Inventory".mp.
30.	"Lille Apathy Rating Scale".mp.
31.	exp Alzheimer disease/ or alzheimer*.mp. or exp dementia/ or dementia.mp
32.	exp risk/ or risk.mp. or exp risk factor/
33.	hazard.mp.
34.	incident.mp.
35.	predict*.mp.
36.	26 or 27 or 28 or 29 or 30
37.	32 or 33 or 34 or 35
38.	31 and 36 and 37
39.	12 or 25 or 38
40.	remove duplicates from 39

eTable 1. Full search conducted through OVID in Medline, Embase and PsychINFO databases. Search terms can appear multiple times, each time optimized for another database.

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General information:
Author, year, cohort nationality, population description, number of participants, % female, study objectives, recruitment procedure, inclusion/exclusion criteria, % excluded
Apathy & dementia:
Criteria, overall number and %, follow-up duration, dementia definition & criteria, number and % incident dementia and/or Alzheimer's disease, number and % developing dementia and/or Alzheimer's disease with and without apathy, reported effect estimates for dementia and analysis characteristics
Other factors:
Information on demographic characteristics (if possible specific for apathy groups): age, sex, cognitive measures, depression, stroke history, activities of daily living

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eTable 2. Items on data extraction form

Sub-analysis	Rationale	Conception
High vs low age	Older patients have higher risk of both dementia and apathy	Predefined
Excluding vs not excluding depression	Patients with depression have higher risk of both dementia and apathy	Predefined
Long vs short FU	FU length must be sufficient for dementia to occur and may provide information on the mechanism of association	Predefined
High vs low bias scores	To assess the influence of bias on the overall results	Predefined
- High vs low representativeness bias	One of the highest scoring risk of bias categories	Post-hoc
- High vs low FU availability bias	One of the highest scoring risk of bias categories	Post-hoc
Meta-regression with age	Older patients have higher risk of both dementia and apathy	Predefined
Meta-regression with FU length	FU length must be sufficient for dementia to occur and may provide information on the mechanism of association	Predefined
Sensitivity analysis comparing aMCI and MCI subgroups	MCI and aMCI may have a different relation with apathy and dementia	Post-hoc
Sensitivity analysis comparing Alzheimer's disease to all-cause dementia as outcome	To assess whether results would have been different if all-cause dementia instead of AD data had been used	Post-hoc
Meta-regression of follow-up time, validated and custom definitions within MCI patients	Follow-up time explained most heterogeneity in the validated definition group. To assess consistency, this was also analysed in the custom definition group. Meta-regression of follow-up time and type of definition in the combined group provided insight in how much heterogeneity could be explained by the definition type accounting for follow-up time.	Post-hoc
Only for reported effect estimates:		
Adjusting vs not	Older patients have higher risk of both dementia and apathy	Pr

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adjusting for age		ed efi ne d
Adjusting vs not adjusting for cognition	Cognitive impairment is associated with both dementia risk and apathy	Pr ed efi ne d
Adjusting vs not adjusting for age and cognition	Combined adjustment for confounders deemed most important	Pr ed efi ne d
Excluding/adjusting for depression vs not excluding/adjusting for depression	Patients with depression have higher risk of both dementia and apathy	Pr ed efi ne d

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eTable 3. Sub-analyses and rationale. Abbreviations: FU: follow-up, aMCI: anamnestic mild cognitive impairment, MCI: mild cognitive impairment, AD: Alzheimer's disease

	Estimate AD	Estimate all-cause dementia
Ramakers 2010	OR: 0.67, 95%CI: 0.40–1.13	"essentially the same"
Peters 2013	HR: 0.58, 95%CI: 0.18-1.87	HR: 0.93, 95%CI: 0.43-2.02
Rosenberg 2013	HR: 1.16, 95%CI: 1.01-1.33	HR: 1.13, 95%CI: 1.00-1.28

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eTable 4. Estimates for AD and dementia compared within studies

Study (ref #)	Representative cohort	Control cohort	Exposure assessment	Outcome assessment	Outcome exclusion	Analysis adjustment	FU length	FU availability	NOS score
Bartolini 2005 (22)	A (1)	A (1)	C (0)	A (1)	A (1)	B (1)	C (0)	A (1)	6
Burke 2016 (23)	A (1)	A (1)	A (1)	A (1)	A (1)	A (2)	A (1)	C (0)	8
Chan 2011	C (0)	A (1)	A (1)	A (1)	A (1)	A (2)	B (1)	C (0)	7
Brodaty 2012	C (0)	A (1)	A (1)	A (1)	A (1)	C (0)	B (1)	B (1)	6
Teng 2007 (24)	C (0)	A (1)	B (0)	B (0)	A (1)	C (0)	A (1)	C (0)	3
Chilovi 2009 (25)	A (1)	A (1)	A (1)	A (1)	A (1)	A (2)	B (1)	B (1)	9
Ramakers 2010 (18)	A (1)	A (1)	C (0)	A (1)	A (1)	A (2)	A (1)	B (1)	8
Van der Linde 2011	C (0)	A (1)	B (0)	B (0)	A (1)	A (2)	B (1)	C (0)	5
Richard 2012 (13)	B (0)	A (1)	C (0)	A (1)	A (1)	A (2)	A (1)	B (1)	7
Somme 2013 (26)	C (0)	A (1)	A (1)	A (1)	A (1)	B (1)	A (1)	C (0)	6
Rosenberg 2013 (27)	A (1)	A (1)	A (1)	B (0)	A (1)	A (2)	B (1)	C (0)	7
Sobow 2014 (28)	B (0)	A (1)	A (1)	B (0)	A (1)	B (1)	B (1)	B (1)	6
Pink 2015 (29)	B (0)	A (1)	A (1)	A (1)	A (1)	A (2)	A (1)	B (1)	8
Robert 2008 (30)	C (0)	A (1)	A (1)	A (1)	A (1)	A (2)	B (1)	B (1)	8
Palmer 2010 (31)	C (0)	A (1)	A (1)	A (1)	A (1)	B (1)	B (1)	B (1)	7
Peters 2013 (17)	C (0)	A (1)	A (1)	A (1)	A (1)	A (2)	B (1)	C (0)	7
Total/max score	5/16	16/16	11/16	13/16	16/16	24/32	15/16	9/16	

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eTable 5. Bias assessment overview. Risk of bias table. For each category, A indicates low risk of bias, B indicates intermediate risk of bias, and C high risk of bias or insufficient information available on the subject. Scores obtained per category are in parentheses. For most categories, A scores 1 point, B and C no points. For “Analysis adjustment” A scores 2 points and B 1 point. For follow-up length and availability, both category A and B score 1 point. Reasons for scores are detailed in etable 3. Abbreviations: Ref #: reference number, max: maximum, NOS: Newcastle-Ottawa Scale for bias assessment in cohort studies

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	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration outcome was not present at start of the study	Comparability of cohorts based on design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up cohorts
Bartolini	A: memory clinic patients without objectifiable cognitive impairment	A: same community	C: motivational items chosen from depression scale	A: memory clinic diagnosis	B: step-wise logistic regression controls for BDI score and trail making test B	A: single clinical assessment after 1 year	C: 1 year follow-up	A: complete follow-up
Burke	A: memory clinic patients without objectifiable cognitive impairment	A: same community	A: NPI-Q administered by health professional	A: memory clinic diagnosis	A: controls for sex, age, race, Hispanic origin, family history of dementia	A: yearly screening	A: 8.4 year follow-up (mean 4.0 years)	C: 87% lost to follow-up
Chan	C: mixed sample of volunteers and random recruits	A: same community	A: NPI administered to informant	A: expert psychiatrist evaluation	A: controls for age, sex, MMSE and education	A: single measurement at 2 years	B: 2 year follow-up	C: not described
Brodaty	C: only data for mixed population reported	A: same community	A: NPI administered to informant	A: comprehensive neuropsychological assessment	C: study does not control for confounders	A: single measurement at 2 years	B: 2 year follow-up	B: 21% lost to follow-up
Teng	C: % in-/excluded not reported	A: same community	B: NPI, caregiver report, not detailed whether supervised	A: memory clinic diagnosis	C: study does not control for confounders	B: screening at follow-up visits, not clearly described	A: maximum 5.5 years (mean 2.0 years)	C: not described
Chilovi	A: diagnosis at memory clinic	A: same community	A: Clinical diagnosis according to Marin's apathy criteria	A: comprehensive clinical assessment	A: adjusted for age, Barthel index, ADAS-cog and depression (DSM-IV)	A: single clinical assessment after 2 years	B: 2 year follow-up (mean 2 years)	B: 4% lost to follow-up
Ramakers	A: diagnosis at memory clinic	A: same community	C: subitems of depression scale	A: memory clinic diagnosis	A: adjusted for age, education and sex	A: assessment after 2, 5 and 10 years (not for all subjects, minimum 2 years)	A: >88% eligible for 5 year follow-up (mean 5.4 years)	B: 15% lost to follow-up (excluding mortality) with reasons given

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eTable 6. Detailed bias assessment table based on the Newcastle-Ottawa rating scale for observational cohort studies. Studies were scored in according to standardized criteria. For the total score, every category scored A (or B or higher in case of follow-up length) was worth one point. The comparability of the cohort on basis of design or analysis could score a maximum of 2 points if both the major confounders of age and cognition were controlled for. NPI-Q: neuropsychiatric inventory Q, NPI: neuropsychiatric inventory, BDI: Beck's Depression Inventory, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders IV

	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration outcome was not present at start of the study	Comparability of cohorts based on design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up cohorts
Vd Linde	C: MMSE score <27 in screened poulation sample	A: same community	B: GMS-AGECAT algorithm: not apathy specific	A: GMS-AGECAT algorithm	A: controls for age, sex, education, social class, MMSE, subjective and objective memory and ADL	B: single GMS-AGECAT measurement at 2 years equivalent to DSM-IV	B: 2 year follow-up	C: 38% lost to follow-up
Richard	B: memory clinic diagnosis from world wide database, depressive symptoms excluded	A: same community	C: subitems of depression scale	A: memory clinic diagnosis	A: controls for age, education, sex and MMSE score	A: biannual or yearly clinical/cognitive assessment	A: maximum 5.2 years (mean 2.7 years)	B: 4% lost to follow-up
Somme	C: % in-/excluded not reported	A: same community	A: NPI administered by neuropsychologist	A: neurological examination	B: controls for MMSE	A: yearly assessment	A: 10 year follow-up (mean 3.5 years)	C: not described
Rosenberg	A: MCI diagnosis at memory clinic	A: same community	A: NPI-Q administered by health professional	A: memory clinic diagnosis	A: controls for age, Afro-American race, Hispanic ethnicity, CDR, and MMSE	B: screening at follow-up visits, timing of screening not described	B: median follow-up 1.58 years, inter quartile range: 1.08-2.09	C: 51% lost to follow-up
Sobow	B: Definition of MCI: clinical dementia rating scale = 0.5	A: same community	A: NPI administered by neuropsychologist	A: memory clinic diagnosis	B: backward logistic regression controls sex, BMI, and BMI change	B: dementia defined as CDR score >0.5 after 2 years	B: 2 year follow-up	B: 14% lost to follow-up
Pink	B: Screened population cohort	A: same community	A: NPI-Q administered by trained professional	A: clinical diagnosis after screening	A: controls for age, sex, education and	A: 15-monthly assessment	A: median follow-up 3.0 years,	B: 15% lost to follow-up

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					medical comorbidity		inter quartile range: 2.5-5.3 years	

eTable 6 continued. Detailed bias assessment table based on the Newcastle-Ottawa rating scale for observational cohort studies. Studies were scored in according to standardized criteria. For the total score, every category scored A (or B or higher in case of follow-up length) was worth one point. The comparability of the cohort on basis of design or analysis could score a maximum of 2 points if both the major confounders of age and cognition were controlled for. NPI: neuropsychiatric inventory, NPI-Q: neuropsychiatric inventory Q, MMSE: mini-mental state examination, CDR: clinical dementia rating, BMI: body mass index

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	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration outcome was not present at start of the study	Comparability of cohorts based on design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up cohorts
Robert	C: MCI according to own diagnostic criteria, similar to amnestic MCI	A: same community	A: apathy inventory caregiver interview	A: memory clinic diagnosis	A: controls for age, sex and educational level	A: biannual assessment	B: 3 year follow-up (mean not reported)	B: 10.3% lost to follow-up
Palmer	C: % in-/excluded not reported	A: same community	A: NPI and psychiatric diagnosis	A: memory clinic diagnosis	B: controls for age, gender, education MMSE and depression but only 15 events	A: yearly assessment	B: 4 year follow-up (mean 1.4 years)	B: 24% lost to follow-up, similar baseline characteristics except lower instrumental ADL
Peters	C: % in-/excluded not reported & screened population cohort	A: same community	A: NPI-Q administered by trained professional	A: comprehensive clinical assessment	A: controls for age, education, APOE4 and 3MS	A: single 18-month assessment	B: 3 year follow-up (mean 3.3 years)	C: 51% not included in analysis due to incomplete baseline or loss to follow-up

eTable 6 continued. Detailed bias assessment table based on the Newcastle-Ottawa rating scale for observational cohort studies. Studies were scored in according to standardized criteria. For the total score, every category scored A (or B or higher in case of follow-up length) was worth one point. The comparability of the cohort on basis of design or analysis could score a maximum of 2 points if both the major confounders of age and cognition were controlled for. NPI: neuropsychiatric inventory, NPI-Q: neuropsychiatric inventory Q, MMSE: mini-mental state examination, APOE4: apolipoprotein E allele E4, CDR: clinical dementia rating, BMI: body mass index, 3MS: modified mini-mental state examination,

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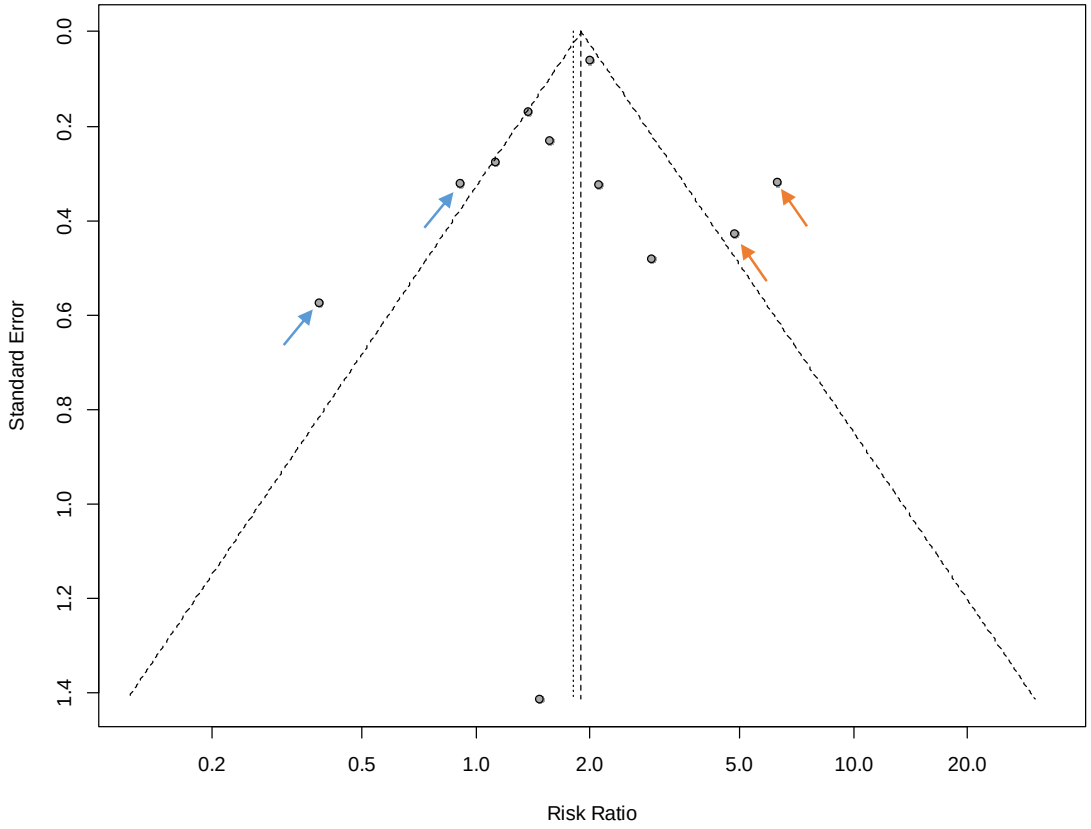
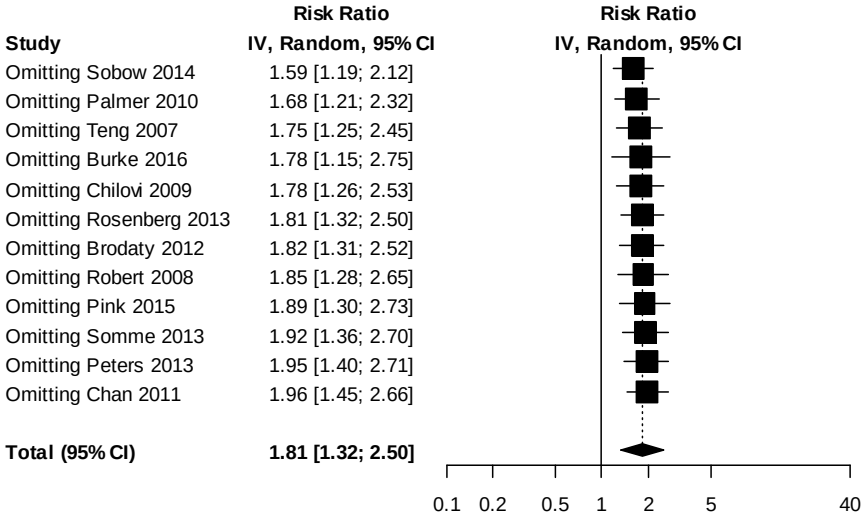


eFigure 1. Funnel plot for the overall analyses of studies using validated instruments to measure apathy. The left vertical bar represents the random-effects estimate with 95% confidence intervals, the right vertical bar represents the fixed-effects estimate. The studies with larger than expected effect estimates are those by Sobow et al.(28) and Palmer et al.(31) (red arrows), the studies with lower than expected effect estimates those by Chan et al. and Peters et al (blue arrows).



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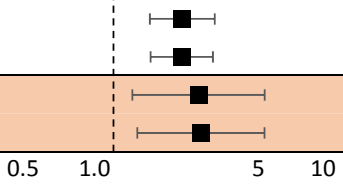
eFigure 2. Forest plot of leave-one-out analysis. Depicting the range of overall estimates of the pooled relative risks omitting each study once. RR: Relative Risk, 95%-CI: 95% confidence interval

	RR	95%CI	I2	Subgroup estimate
RR outcome AD	1.82	1.33-2.51	75	
RR outcome dementia	1.81	1.32-2.50	76	
HR outcome AD	2.40	1.29-4.49	90	
HR outcome dementia	2.39	1.27-4.51	90	



eFigure 3. sensitivity analysis with AD instead of dementia as preferential outcome

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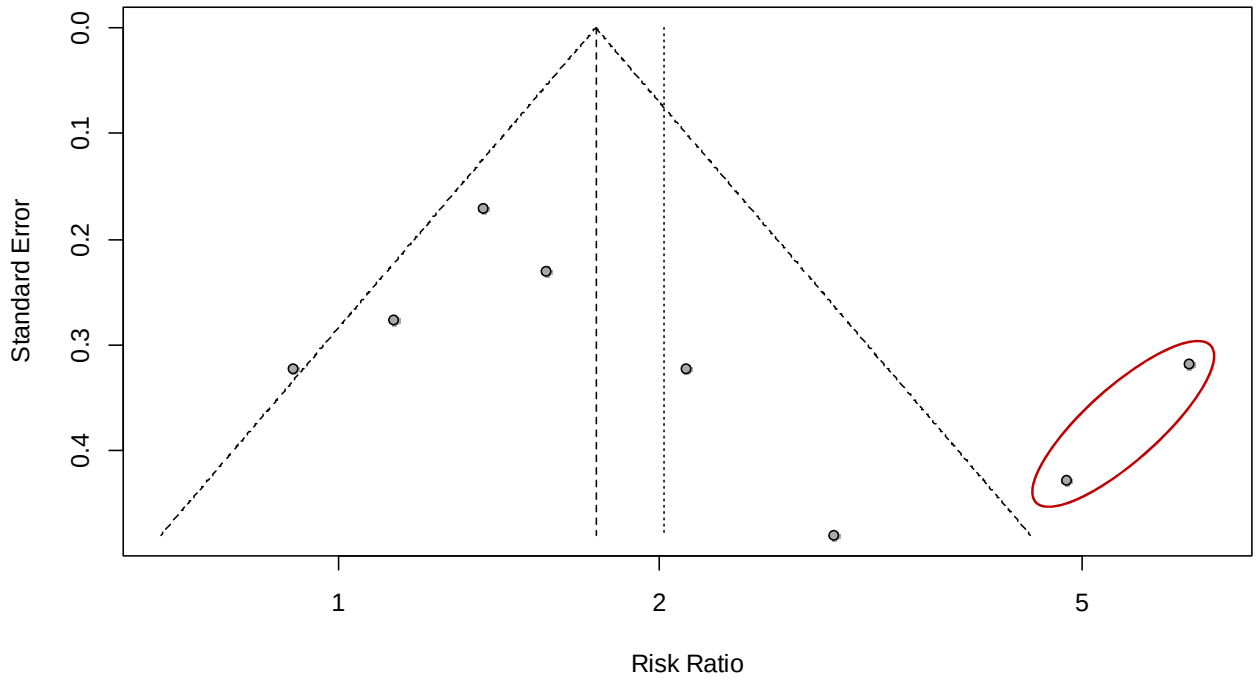

eFigure 4. Funnel plot for the relative risks reported in studies in the Mild Cognitive Impairment subgroup. Only studies using validated apathy scales are included. The left vertical bar represents the fixed-effects estimate with confidence intervals based on 1.96 standard deviations. The right vertical bar marks the random-effects estimate. The outlying studies with higher than expected risk ratios by Sobow et al.(28) and Palmer et al(31) (red circle) and the lower standard errors of studies with lower risk ratios suggests some publication bias.

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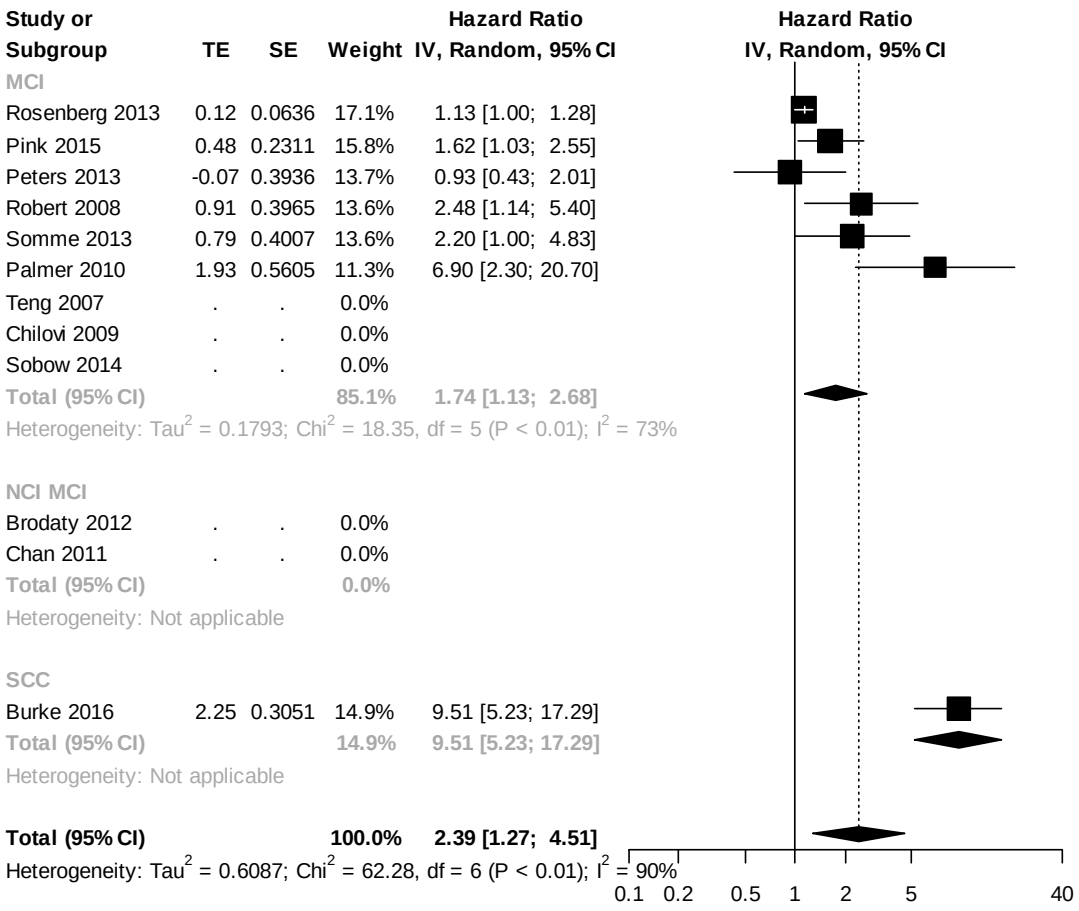

eFigure 5. Overall and subgroup analyses of HRs in Mild Cognitive Impairment in studies using recommended validated measures to diagnose apathy. Abbreviations: CIND: cognitive impairment no dementia, MCI: mild cognitive impairment, SCC: subjective cognitive impairment, TE: natural log of effect size, SE: standard error of ES, HR: hazard ratio, 95%-CI: 95% confidence interval

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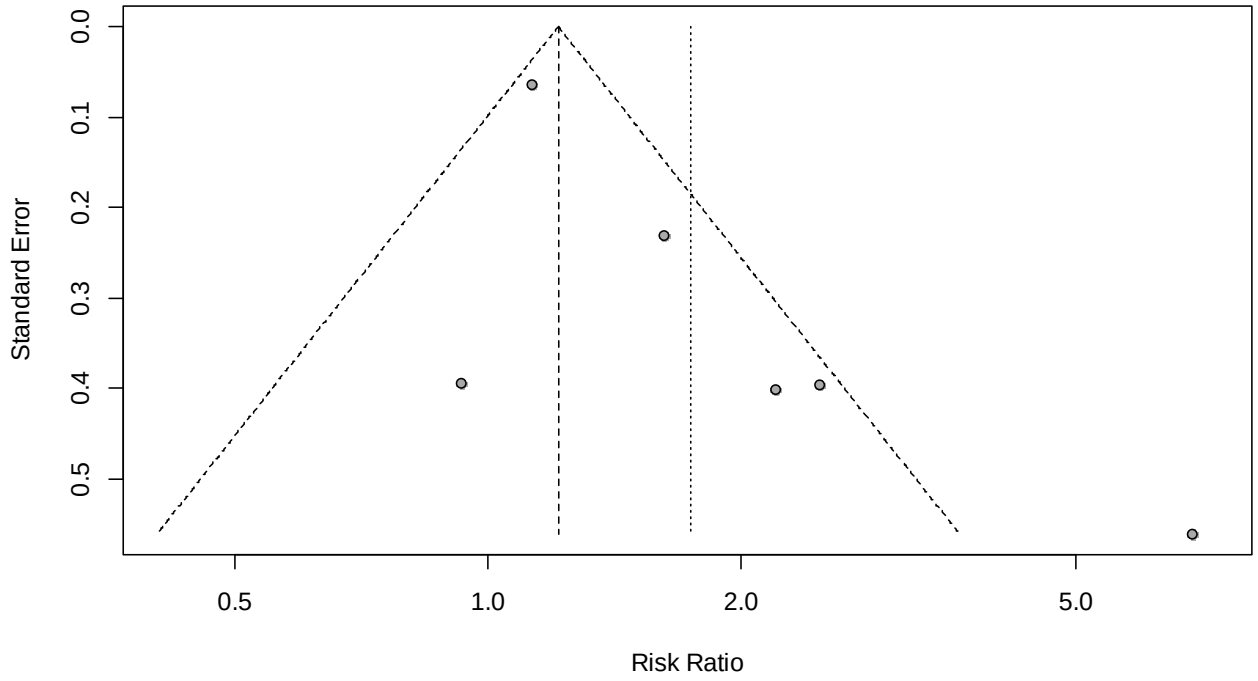

eFigure 6. Funnel plot of hazard ratios reported in studies. Only studies using validated recommended apathy scales are included. The left vertical bar represents the fixed-effects estimate with 95% confidence intervals. The right vertical bar marks the random-effects estimate. The distribution of studies (nearly all higher than the overall random-effects estimate, with studies with a lower standard error finding less effects) suggests an overrepresentation of studies reporting a significant association between apathy and dementia incidence.

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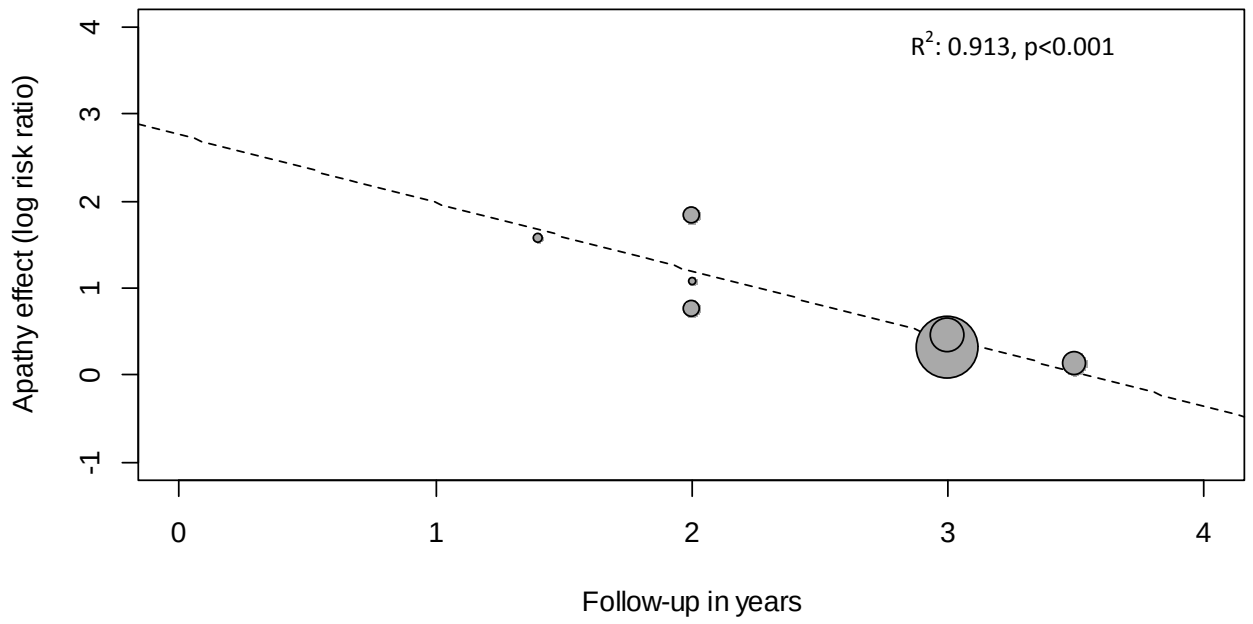

eFigure 7. Meta-regression of risk ratios for developing dementia in Mild Cognitive Impairment patients with apathy relative to mean follow-up duration in years. Only studies using validated apathy scales are included (n=7). Each bubble represents a study and bubble size represents the sample size of the study. The regression line shows a trend of declining risk with longer follow-up time. R^2 represents the proportion of heterogeneity explained by the regression

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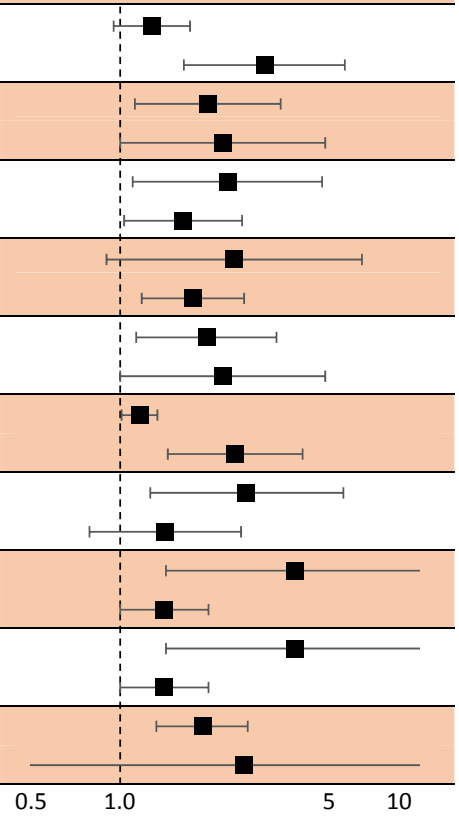
Subgroup	Studies	HR	95%CI	I2	Subgroup estimate
Age high	Rosenberg, Pink, Peters	1.19	0.96-1.48	22	
Age low	Robert, Palmer, Somme	3.03	1.63-5.61	34	
Adjusting for age	Rosenberg, Pink, Robert, Palmer	1.68	1.05-2.70	75	
Not adjusting for age	Somme	2.20	1.00-4.83	-	
Adjusting for cognition	Rosenberg, Robert, Palmer, Somme, Peters	1.85	1.04-3.31	76	
Not adjusting for cognition	Pink	1.62	1.03-2.55	-	
Adjusting for age and cognition	Rosenberg, Robert, Palmer	1.81	0.91-3.63	79	
Not adjusting for age and cognition	Pink, Somme	1.75	1.18-2.59	0	
Low bias	Rosenberg, Pink, Robert, Palmer, Peters	1.68	1.05-2.70	75	
High bias	Somme	2.20	1.00-4.83	-	
Low representativenss bias	Rosenberg	1.13	1.00-1.28	-	
High representativeness bias	Pink, Robert, Somme, Palmer	2.41	1.44-4.06	49.6	
Low FU availability bias	Pink, Robert, Palmer	2.64	1.26-5.55	66	
High FU availability bias	Rosenberg, Somme	1.21	0.86-1.71	33	
Excluding depression	Robert, Palmer	3.83	1.42-10.33	35	
Not excluding depression	Rosenberg, Pink, Somme, Peters	1.30	0.97-1.73	41	
Excluding or adjusting for depression	Robert, Palmer	3.83	1.42-10.33	55	
Not excluding or adjusting for depression	Rosenberg, Pink, Somme, Peters	1.30	0.97-1.73	41	
Long FU	Pink, Robert, Somme, Peters	1.67	1.16-2.41	19	
Short FU	Rosenberg, Palmer	2.59	0.46-14.77	90	



eFigure 8. Subgroup analyses in Mild Cognitive Impairment patients based on reported maximally adjusted hazard ratios. Only studies using validated apathy scales are included. FU: follow-up, RR: relative risk, 95%CI: 95% confidence interval

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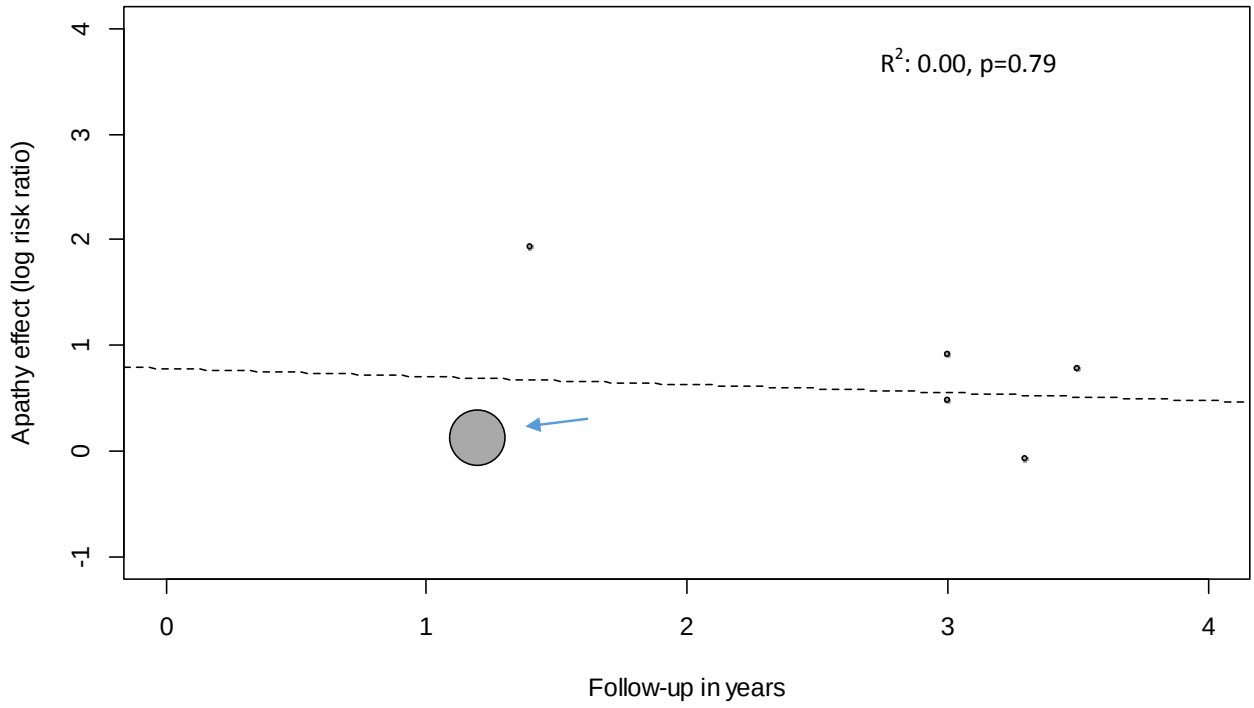
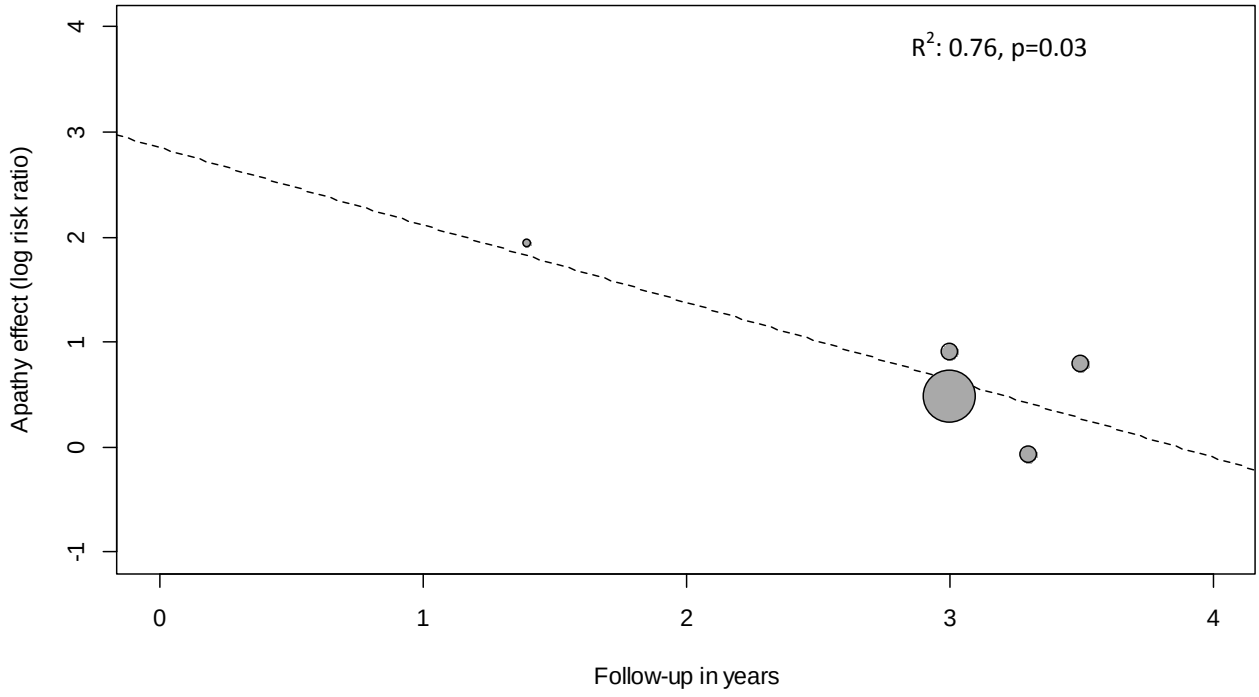


eFigure 9. Meta-regression of reported hazard ratios for Mild Cognitive Impairment patients with apathy relative to follow-up duration in years. Only studies using validated recommended apathy scales are included. Each bubble represents a study and bubble size represents the sample size of the study. The regression line shows no association between the follow-up time in years and the size of the reported hazard ratios but seems to be dominated by Rosbenberg et al.(27) (blue arrow). R^2 represents the proportion of heterogeneity explained by the regression.



eFigure 10. Meta-regression of reported hazard ratios for Mild Cognitive Impairment patients with apathy relative to follow-up duration in years. In this meta-regression the study by Rosenberg et al.(27) identified in Figure 9 was omitted. Only studies using validated apathy scales are included. Each bubble represents a study and bubble size represents the sample size of the study. The regression line suggests decreasing hazard ratio with longer follow-up. R^2 represents the proportion of heterogeneity explained by the regression.

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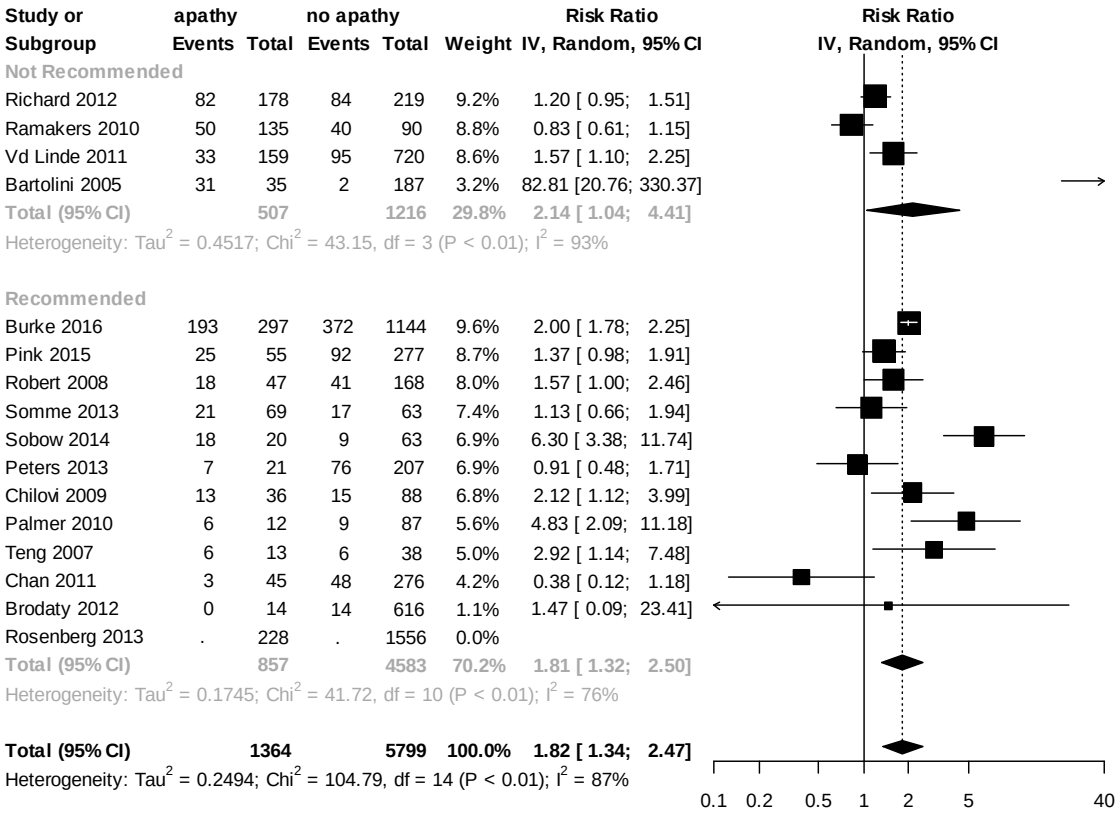

eFigure 11. Forest plot of calculated Risk Ratio analysis of studies using validated recommended and custom definitions of apathy. 95%-CI: 95% confidence interval

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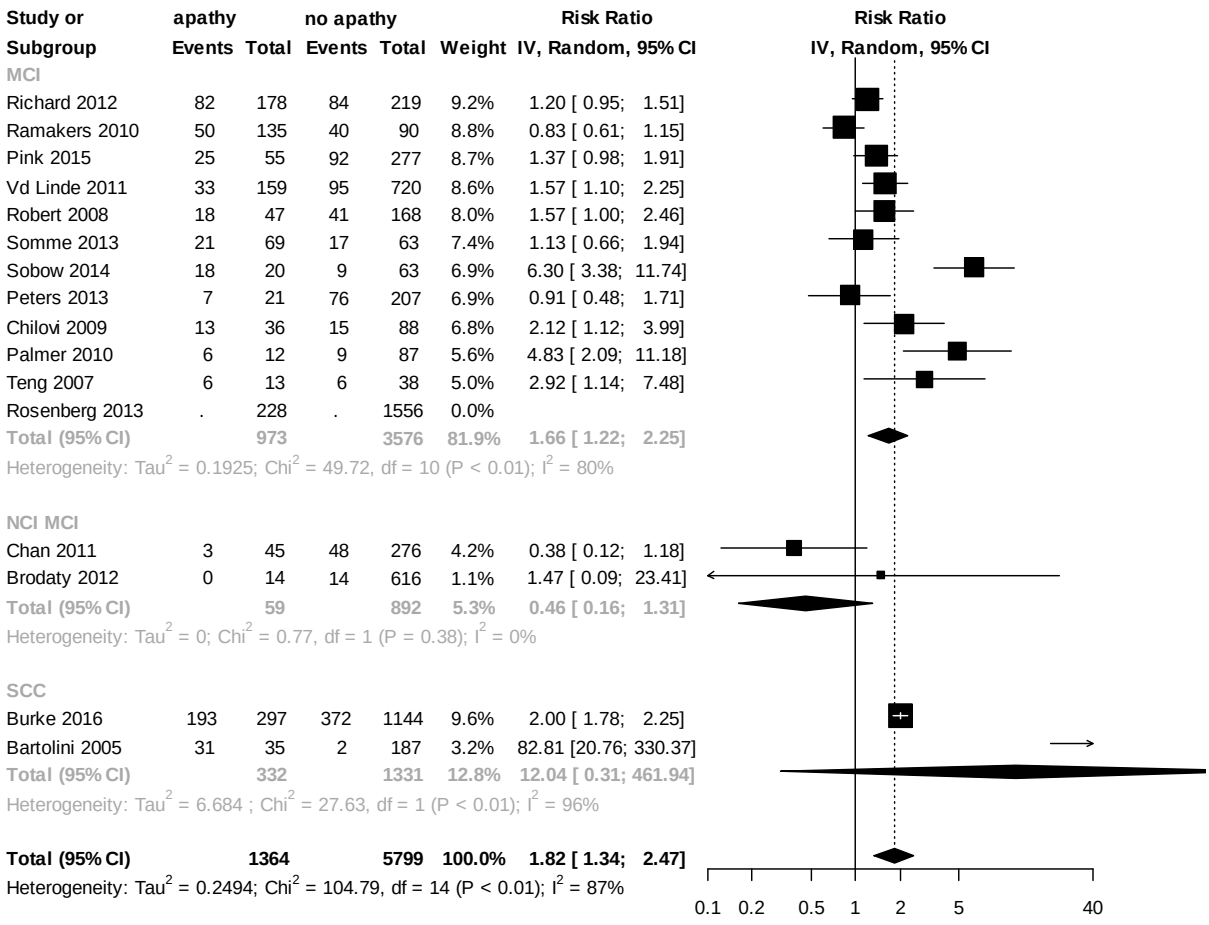

eFigure 12. Forest plot for relative risk of developing dementia including studies using validated and custom apathy according to subgroups based on diagnosis. Abbreviations: CIND: cognitive impairment no dementia, MCI: mild cognitive impairment, NCI MCI: mixed normal cognition and MCI, SCC: subjective cognitive impairment, RR: relative risk, 95%-CI: 95% confidence interval

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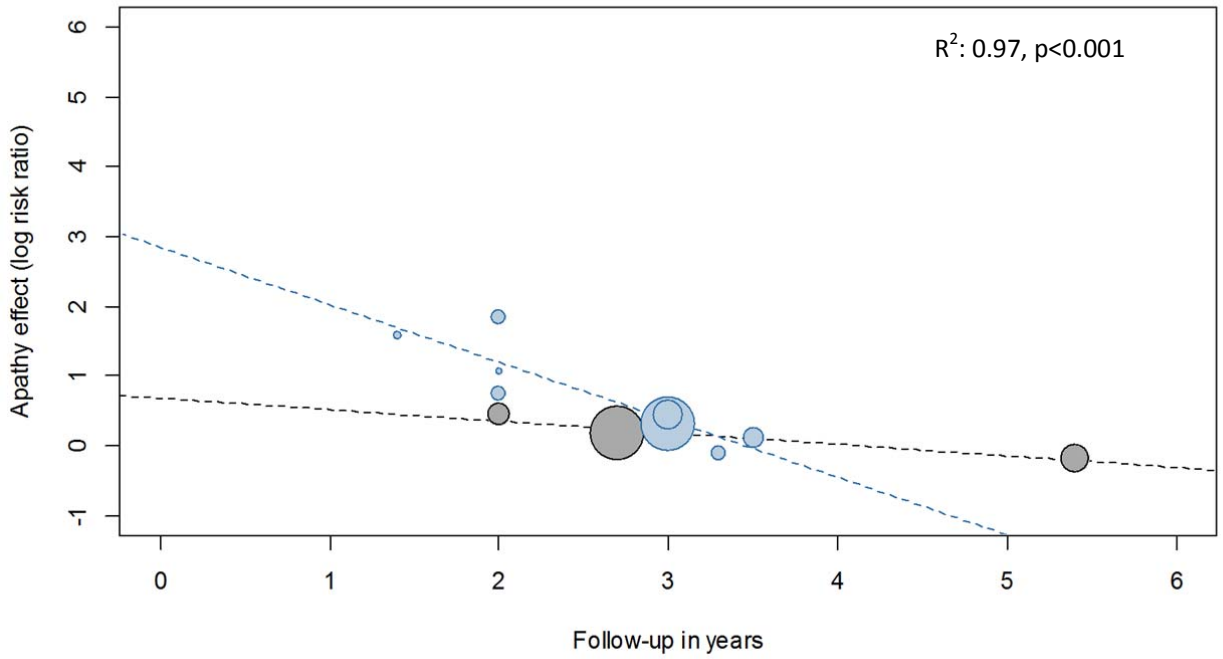

eFigure 13. Meta-regression of log risk ratio of dementia for patients with apathy in studies using recommended (blue) and custom (grey) definitions over follow-up time (years). Plots of separate meta-regressions overlaid. Combined meta-regression with follow-up time and definition type with their interaction explained 95% of heterogeneity in study estimates.

	Log RR	95%CI	p-value
Intercept	0.69	0.19;1.19	0.01
FU-time	-0.17	-0.30;-0.03	0.02
Recommended definition	2.16	1.10;3.22	<0.001
FU-time*Recommended definition	-0.67	-1.02;-0.30	<0.001

Explained I^2: 97%
Residual I^2: 10%

eFigure 14. Meta-regression results of the log risk ratio for dementia in participants with apathy predicted by FU-time, apathy definition type and their interaction

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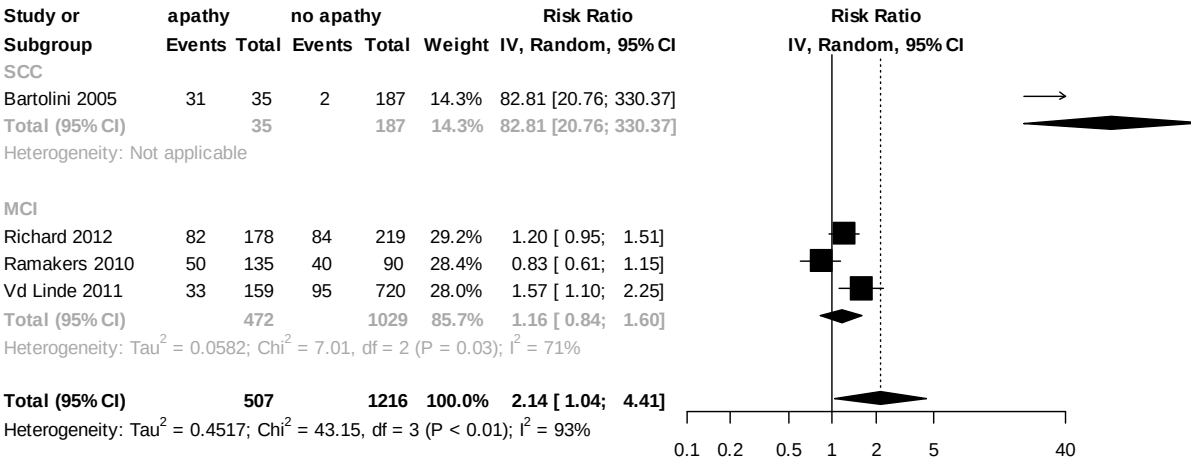

eFigure 15. Overall and subgroup analyses of RR in MCI and SCC patients for studies using custom definitions of apathy. MCI: mild cognitive impairment, SCC: subjective cognitive impairment, 95%-CI: 95% confidence interval

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