

Supplemental Digital Content

Apathy and depressive symptoms in older people and incident myocardial infarction, stroke, and mortality: a systematic review and meta-analysis of individual participant data.

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Supplementary Methods 1. PROSPERO study protocol and amendments

Original protocol:

Title: Initiative on Cardiovascular disease Risk and Apathy (ICARA)

Jan Willem van Dalen, Lisa Eurelings, Willem A van Gool, Edo Richard, Eric P Moll van Charante, Gerben ter Riet

Citation:

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Review question(s):

Assessment of the association between symptoms of apathy (as measured with three apathy items of the 15-item Geriatric Depression Scale (GDS-15)) and risk of cardiovascular events, stroke events and all-cause mortality.

The three apathy items are:

- 1) "Have you dropped many of your activities and interests?"
- 2) "Do you prefer to stay at home, rather than going out and doing new things?" and
- 3) "Do you feel full of energy?".

Assessment of the association between symptoms of depression (as measured with the remaining GDS items) and risk of cardiovascular disease events, stroke events and all-cause mortality.

Searches:

The MEDLINE, EMBASE, and PsycINFO databases were searched using the OVID platform. No restrictions on language, publication year, or type of publication were applied. Relevant text words and search terms were used to find papers containing both data on any version of the Geriatric Depression Scale (GDS) and cardiovascular disease, including myocardial infarction, angina pectoris, peripheral arterial disease, stroke, and transient ischemic attack (TIA). Additionally, the reference lists of selected papers were screened and authors of potentially eligible studies that were known by the authors were approached.

Types of study to be included:

All longitudinal studies involving study populations representative of the general older community-dwelling population with a mean age of ≥ 65 years are eligible.

Condition or domain being studied:

In a large cohort of community-dwelling older individuals, symptoms of apathy, as measured with three apathy items from the GDS-15, have been found to significantly increase the risk of incident cardiovascular disease (Eurelings et al., International Journal of Geriatric Psychiatry 2014;29:454-463). These findings strengthen earlier cross-sectional associations between symptoms of apathy and a history of cardiovascular disease, stroke and cardiovascular risk factors (Ligthart et al., Archives of General Psychiatry 2012;69:363-642; van der Mast et al., International Journal of Geriatric Psychiatry 2008;23:266-271). To ascertain the predictive value of symptoms of apathy, external validation is needed in other cohorts with comparable study populations. Therefore, the aim of this study is to examine the association between symptoms of apathy and the risk of cardiovascular disease events, stroke events and all-cause mortality, using pooled data from several different longitudinal cohort studies in community dwelling older individuals. In addition, the relation between symptoms of depression, as measured with the remaining items of the GDS, and the occurrence of cardiovascular disease events, stroke events and all-cause mortality will be assessed.

Participants/ population:

Populations consisting of community-dwelling older individuals or study populations representative of the community dwelling older population with a mean age of ≥ 65 years were eligible for inclusion. Studies had to employ a GDS version including the three apathy items and investigate subsequent cardiovascular disease and/or mortality.

Studies in individuals that were selected on the basis of being frail, having a specific (cardiovascular) disease, cardiovascular risk factors or a specific cardiovascular risk profile were excluded. Studies entirely consisting of disabled, hospitalized or institutionalized individuals and studies in caregivers of diseased individuals were also excluded. However, if part of the study population met the eligibility criteria, the study was considered eligible.

To ascertain generalizability of findings to the general older population, we did not include control populations of case-control studies. Finally, only studies with a sample size of more than 100 were included.

Intervention(s), exposure(s):

Several factor analyses have shown that an apathy sub-domain can be identified from three items within the GDS-15. Symptoms of apathy, as measured with these three items, have been found to predict the occurrence of cardiovascular events, in contrast to symptoms of depression, as measured with the remaining 12 items.

The three GDS items identified as representing apathy are:

- 1) "Have you dropped many of your activities and interests?"
- 2) "Do you prefer to stay at home, rather than going out and doing new things?" and
- 3) "Do you feel full of energy?"

Comparator(s)/ control:

Participants with 2 or more symptoms of apathy according to the three apathy items from the GDS-15 (GDS-3A \geq 2) will be compared to those with 1 or 0 symptoms of apathy (GDS-3A $<$ 2). Participants with symptoms of depression, defined as 2 or more symptoms of the 12 remaining items of the GDS-15 (GDS-12D \geq 2), will be compared to those with 1 or 0 symptoms of depression (GDS-12D $<$ 2).

Outcome(s)**Primary outcomes:**

Cardiovascular disease events, stroke events and mortality.

No restrictions were applied regarding length of follow-up. Regarding cardiovascular and stroke events, if dates of events are available, hazard ratio's will be calculated. If no dates are available, odds ratio's will be calculated, stratifying the analyses by length of follow-up. Regarding mortality, only hazard ratio's will be calculated.

Secondary outcomes:

None

Data extraction, (selection and coding):

Studies will be assessed for eligibility by screening of titles and abstracts by two independent reviewers. From the selected reports, study cohorts will be identified. Each study cohort will subsequently be assessed for eligibility independently by both reviewers. Discrepancies in the selection process will be resolved by consensus. If consensus cannot be reached, an independent consultant will be available. References of selected articles will be screened for additional eligible studies.

Risk of bias (quality) assessment:

Assessment of risk of bias and data quality will be performed in accordance to the MOOSE criteria, the IPD specific recommendations of the Cochrane Handbook (chapter 18) and the additional recommendations by Riley et al. (BMJ 2010;340:c221). The influence of bias will be assessed in sensitivity-analyses. Discrepancies in individual study data will be resolved in consultation with the specific study collaborators.

Strategy for data synthesis

The data will be analyzed on the level of individual participants. A quantitative synthesis is planned. Separate analyses will be performed for incident stroke and other incident cardiovascular disease. If dates of events are available, time-to-event analyses will

be performed. If no dates are available, logistic regression analyses will be performed stratifying by length of follow-up, and presented as separate results. Regarding mortality, only a time-to-event analysis will be performed. All analyses will be adjusted for age and gender. In case of between-study heterogeneity, which is to be expected amongst others due to different ethnic backgrounds of study populations and the different age distributions of studies, random effects models will be deployed. If statistically feasible, we will opt for a one-stage analysis approach.

Analysis of subgroups or subsets

Subgroup analyses:

- Since a history of cardiovascular disease and stroke may confound the relationship between symptoms of apathy/depression and incident cardiovascular disease/mortality, subgroup analyses will be performed in participants without a history of cardiovascular disease or stroke.
- Since functional impairment may confound the relationship between symptoms of apathy/depression and incident cardiovascular disease/mortality, the main analyses will focus on non-institutionalized older individuals. However, if data are also available on institutionalized participants we will perform a subgroup-analysis in this group. This subgroup analysis is dependent on information available across the participating cohort studies.
- In older participants, symptoms of apathy may more often be part of normal aging and less related to underlying pathology than in younger individuals. In addition, in the oldest old participants a survival effect regarding cardiovascular disease incidence may play a role. It will therefore be assessed whether any differential effects of symptoms of apathy and depression on cardiovascular disease and mortality risk exist for the youngest and oldest old.
- Since neuropsychiatric symptoms are known to be influenced by gender, it will be explored whether symptoms of apathy/depression are differently related to mortality/cardiovascular disease risk for men and women.
- In addition, depending upon the received data, the analyses on incident cardiovascular disease and mortality risk will be repeated using the 6 “Withdrawal– Apathy– Lack of Vigor” items of the GDS-30 (as described by Adams (Gerontologist 2001;41:768-777)) as a measure of apathy symptoms. The remaining 24 items will then be used to measure symptoms of depression.

Sensitivity analyses:

- To assess whether results are robust against recall-bias related to neuropsychiatric symptoms, a sensitivity analysis will be performed excluding all studies with self-reported cardiovascular events.
- As a sensitivity analysis, a more specific cut-off of GDS-12D=5 will be used in addition to the sensitive cut-off of GDS-12D=2. Depending upon the data that will be received, the above stated analyses may be adapted and additional analyses may be performed.

Dissemination plans:

On completion of the review, a paper will be submitted to a peer reviewed journal.

Contact details for further information:

Mr van Dalen
Department of Neurology
Room H2-235
Academic Medical Center
Meibergdreef 9
1105 AZ, Amsterdam
j.vandalen@amc.nl

Organisational affiliation of the review:

Academic Medical Center
www.amc.nl

Review team:

Mr Jan Willem van Dalen, Academic Medical Center, department of Neurology
Dr Lisa Eurelings, Academic Medical Center, department of Neurology
Professor Willem A van Gool, Academic Medical Center, department of Neurology
Dr Edo Richard, Academic Medical Center, department of Neurology
Dr Eric P Moll van Charante, Academic Medical Center, department of General Practice
Dr Gerben ter Riet, Academic Medical Center, department of General Practice

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Amendments to original protocol:

Primary outcomes:

- Time to first occurrence of myocardial infarction has been analyzed to represent cardiovascular disease (CVD). This was done because the robustness of this outcome enhances comparability across studies and avoids misclassification of disease status and time of occurrence that may coincide with less robust cardiovascular outcomes such as angina pectoris and peripheral arterial disease.

Strategy for data synthesis:

- Separate logistic analyses, performed to include studies without time to event data for myocardial infarction or stroke, were adjusted for duration of follow-up rather than stratified because periods of follow-up varied considerably among studies. To minimize the risk of confounding of associations by previous vascular disease, analyses were adjusted for a history of myocardial infarction and/or stroke. These analyses were conceived after the results of the initial analyses were known (i.e. not prespecified).

Intervention(s), exposure(s):

- To compare with our previous analyses,¹ analyses have been added for participants with isolated symptoms of apathy (GDS-3A \geq 2 compared to GDS-3A $<$ 2 in participants with GDS-12D $<$ 2) and participants with isolated symptoms of depression (GDS-12D \geq 2 compared to GDS-12D $<$ 2 in participants with GDS-3A $<$ 2).

Sensitivity analyses:

Additional analyses:

- In the original protocol, the cut-off definitions for the analysis with a more specific cut-off point for depressive symptoms should have read GDS-12D \geq 5 and GDS-12D \geq 2 rather than GDS-12D=5 and GDS-12D=2.
- Definition of isolated apathy and depressive symptoms as endorsing \geq 2 items on their respective subscales, without endorsement of any of the items on the other subscale. This analysis was conceived after the results of the initial analyses were known.
- Separate analysis of stroke including transient ischemic attack (TIA). This analysis was conceived after the results of the initial analyses were known.
- Separate analysis of a composite outcome of future myocardial infarction, angina pectoris and/or peripheral arterial disease. This analysis was conceived after the results of the initial analyses were known.
- Separate analysis on cardiovascular mortality (defined as International Classification of Diseases (ICD) 9: 390-459; ICD-10: I00-I99) and non-cardiovascular mortality (other causes of death, i.e. all other ICD-codes). These analyses were conceived after the results of the initial analyses were known.
- Separate analyses for each primary outcome were performed in subgroups, comparing higher versus lower risk of bias, for each bias criterion assessed. These analyses were conceived after results of the initial analyses were known.

1. Eurelings LS, Ligthart SA, van Dalen JW, Moll van Charante EP, van Gool WA, Richard E. Apathy is an independent risk factor for incident cardiovascular disease in the older individual: a population-based cohort study. *Int J Geriatr Psychiatry*. 2014;29(5):454-463

Supplementary Methods 2. Full search strategy

Using the OVID platform on Tuesday September 3rd 2013:

Medline: 368
 Embase: 831
 PsycINFO: 444
 Total: 1643
 After removal of duplicates (n=393): 1250

Medline

# ▲	Searches	Results	Search Type
1	angina pectoris.mp. or exp Angina Pectoris/	51235	Advanced
2	peripheral arterial disease.mp. or exp Peripheral Arterial Disease/	6630	Advanced
3	myocardial infarction.mp. or exp Myocardial Infarction/	193414	Advanced
4	exp Stroke/ or stroke.mp.	194684	Advanced
5	transient ischemic attack.mp. or exp Ischemic Attack, Transient/	20225	Advanced
6	cardiovascular disease.mp. or exp Cardiovascular Diseases/	1886481	Advanced
7	exp Risk Factors/ and exp Cardiovascular Diseases/	158732	Advanced
8	cardiovascular risk.mp.	40894	Advanced
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	1948165	Advanced
10	geriatric depression scale.mp.	2070	Advanced
11	GDS.mp.	1998	Advanced
12	GDS-15.mp.	236	Advanced
13	GDS-30.mp.	38	Advanced
14	10 or 11 or 12 or 13	3068	Advanced
15	9 and 14	368	Advanced

Embase:

# ▲	Searches	Results	Search Type
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1	angina pectoris.mp. or exp angina pectoris/	87174	Advanced
2	peripheral arterial disease.mp. or exp peripheral occlusive artery disease/	128297	Advanced
3	myocardial infarction.mp. or exp heart infarction/	309884	Advanced
4	stroke.mp. or exp cerebrovascular accident/	275429	Advanced
5	transient ischemic attack.mp. or exp transient ischemic attack/	25472	Advanced
6	cardiovascular disease.mp. or exp cardiovascular disease/	3140266	Advanced
7	cardiovascular risk.mp. or exp cardiovascular risk/	136647	Advanced
8	1 or 2 or 3 or 4 or 5 or 6 or 7	3229634	Advanced
9	geriatric depression scale.mp. or exp Geriatric Depression Scale/	3350	Advanced
10	GDS.mp.	2923	Advanced
11	GDS-15.mp.	320	Advanced
12	GDS-30.mp.	49	Advanced
13	9 or 10 or 11 or 12	4735	Advanced
14	8 and 13	831	Advanced

PsychINFO:

#	▲ Searches	Results	Search Type
1	angina pectoris.mp. or exp Angina Pectoris/	451	Advanced
2	exp Cardiovascular Disorders/ or peripheral arterial disease.mp.	40208	Advanced
3	myocardial infarction.mp. or exp Myocardial Infarctions/	3502	Advanced
4	exp Cerebral Ischemia/ or exp Cerebrovascular Accidents/ or stroke.mp.	21584	Advanced
5	transient ischemic attack.mp.	358	Advanced
6	exp Risk Factors/ and exp Cardiovascular Disorders/	4189	Advanced
7	cardiovascular risk.mp.	2145	Advanced
8	1 or 2 or 3 or 4 or 5 or 6 or 7	47273	Advanced
9	geriatric depression scale.mp.	5094	Advanced
10	GDS.mp.	1179	Advanced
11	GDS-15.mp.	168	Advanced

12 GDS-30.mp.
13 9 or 10 or 11 or 12
14 8 and 13

30 Advanced
5372 Advanced
444 Advanced

Supplementary Methods 3. Description of requested participant-level data and methods used to check individual participant data integrity

The following participant-level data were requested: sex, birth date or age at Geriatric Depression Scale (GDS) administration, all individual GDS items and date of GDS administration, cardiovascular disease and stroke occurring before GDS administration, cardiovascular disease events (specified as myocardial infarction, angina pectoris and peripheral arterial disease), stroke, and transient ischemic attacks (TIA) occurring after GDS administration, dates of cardiovascular and stroke/TIA events occurring after GDS administration, mortality with date of death and cause of death.

IPD from all studies were pooled after the following standard checks were performed: 1) verification of data completeness and amount of missing data; 2) evaluation of data validity (e.g. order of dates, conflicting event variables, agreement of data across multiple visits); 3) evaluation of data consistency (within multiple datasets and if possible with published reports (e.g. cross-check of the number of individuals for whom IPD were provided for each study with the number of included individuals reported in published reports)). Data issues were resolved in close collaboration with the study investigators and there were no major issues that could not be resolved after consultation with the study investigators.

Supplementary Methods 4. Details regarding harmonization of vascular variables and R code for main analyses

Details regarding harmonization of vascular variables

- *History of myocardial infarction and/or stroke variable:*

If a history of stroke excluding transient ischemic attack (TIA) was not available to create the composite variable history of myocardial infarction and/or stroke, a history of stroke including TIA was used instead (if available). This was the case for the HIMS, InveCe.Ab, MrMs OS, SLAS1, SLAS2, and SOF study (see Supplementary Table 1 for the study abbreviations).

- *Incident myocardial infarction and stroke variables:*

If the provided myocardial infarction and/or stroke variables did not (systematically) include fatal events, fatal events occurring within the follow-up period of vascular events of the particular study were added based on the primary cause of death according to the International Classification of Diseases (ICD) codes as described below. For the ILSA and BFC80+ studies ICD codes were not available, but causes of death were provided and used to include fatal myocardial and stroke events. For the EAS and Trelong studies fatal events were not systematically registered and causes of death were not available.

- The following ICD codes were used to add fatal myocardial infarction events:

- ICD-9: 410
- ICD-10: I21 and I22

- The following ICD codes were used to add fatal stroke events:

- ICD-9: 431, 432, 433, 434, and 436
- ICD-10: I61, I62, I63, I64, I65, and I66

- *Time-to-event analyses:*

If exact event dates were unavailable but the period in which the event occurred was known and no longer than 1 year these events were included in the time-to-event analyses using the middle of the follow-up period to estimate the event date. This was the case for events in the L85+, EAS, and MAS study.

R code for main analyses

Package: coxme

R-code: Apathy may be substituted for depression, isolated apathy, or isolated depression. Cvhistory represents a dichotomized history of myocardial infarction and/or stroke. Dichotomous variables are coded as 0/1 for not present/present or female/male.

Model 1: `coxme (Surv(censor_time,outcome)~apathy+(apathy|study))`

Model 2: `coxme (Surv(censor_time,outcome)~apathy+sex+age+(age|study)+(sex|study)+(apathy|study))`

Model 3: `coxme (Surv(censor_time,outcome)~apathy+sex+age+cvhistory+(age|study)+(sex|study)+(cvhistory|study)+(apathy|study))`

Supplementary Table 1. Additional characteristics of study samples included in ICARA

Study	Sample ^a	Selected population?	Assessment methods		Unknown status for time-to-event analysis (% , N/total N)		
			MI	Stroke	MI	Stroke	Mortality
BELFRAIL Study (BFC80+), Belgium	F/M ≥80 years, recruitment by general practitioners. Two practices included all eligible patients. The remaining 27 practices included a maximum of 3 consecutive patients during a 3-week interval repeated five times so that every practice included a maximum of 15 patients. Exclusion criteria: (1) dementia (MMSE score<15/30); (2) in palliative care (3) medical emergency.	age selection	questionnaire filled out by general practitioner	13.0 65/499	10.8 54/499	0 0/499	
Canadian Study on Health and Aging (CSHA), Canada	F/M ≥65 years, random sampling, stratified by age, from computerized records of provincial universal health insurance plans and an aggregate list based on election and other municipal records. Exclusion criteria: (1) individuals from the Yukon and North West Territories, Indian reserves and military units; (2) life-threatening illness; (3) not fluent in either English or French.	-	NA	NA	NA	10.4 157/1514	
Einstein Aging Study (EAS), USA	F/M ≥70 years, systematic recruitment from population lists of Medicare recipients (1998-2004) or Bronx County registered voters (2004-2014). Exclusion criteria: (1) visual or auditory impairments; (2) active psychiatric symptomatology; (3) non-ambulatory status.	-	self-report or through family member	50.7 976/1924	50.1 964/1924	0.2 4/1924	
Health In Men Study (HIMS), Australia	M ≥65-79 years, from intervention group of a randomized controlled trial of screening for abdominal aortic aneurysms. Random sampling from electoral roll, leading to inclusion of Australian citizens only. Exclusion criteria: none.	sex selection	Western Australian Data Linkage System	0 0/5519	0.3 18/5519	0 0/5519	
Health, Well-Being and Aging Study - Brazil (SABE - Brazil)	F/M ≥60 years, sample consists of two segments: (1) probabilistic sample of 1568 individuals, stratified by age and sex, (2) 575 individuals living in the districts where previous interviews were conducted. The latter segment was recruited to compensate for mortality in the population >75 years to achieve the desired number of interviews in this age group. Exclusion criteria: none.	-	NA	self-report	NA	NA ^b 9.3 173/1863	

Supplementary Table 1. Additional characteristics of study samples included in ICARA (continued)

Study	Sample ^a	Selected population?	Assessment methods		Unknown status for time-to-event analysis (% , n/total N)		
			MI	Stroke	MI	Stroke	Mortality
Hertfordshire Cohort Study (HCS), England	F/M born in Hertfordshire, England, during 1920-1930 and still living in the east or north-west districts of Hertfordshire who could be traced and were willing to participate. Exclusion criteria: none.	selected inhabitants	NA	NA	NA	NA	0.9 8/882
Hong Kong Old Old Study (HKOOS), China	F/M ≥70 years, random sampling, stratified by age and sex, from the Old Age Allowance Scheme. Exclusion criteria: none.	-	NA	NA	NA	NA	5.4 83/1540
Insufficienza Cardiaca negli Anziani Residenti a Dicomano Study (ICARe Dicomano), Italy	F/M ≥65 years, all eligible individuals recorded in city registry office. Exclusion criteria: none.	-	NA	NA	NA	NA	0 0/634
Intervention project on cerebrovascular diseases and dementia in the Ebersberg district (INVADE), Germany	F/M ≥55 years, all members of a specific health insurance company, living in single district. Exclusion criteria: none.	selection of members of health insurance company	hospital discharge diagnoses based on information of the health insurance company		0 (0/3837)	0 (0/3837)	0 (0/3837)
Invecchiamento Cerebrale in Abbiategrasso Study (InveCe.Ab), Italy	F/M 70-74 years, recruitment via public presentation of study to eligible individuals identified through municipal registry. If individuals did not volunteer to participate during the meeting a letter was sent with a confirmed appointment date and contact by phone. Exclusion criteria: none.	volunteer selection	self-report during geriatric evaluation and contact with primary care physician for doubtful cases		NA ^b	16.1 203/1262	0 0/1262
Italian Longitudinal Study on Aging (ILSA), Italy	F/M 65-84 years, random sampling from the electoral rolls, stratified by five years of age and sex using the equal allocation strategy. Exclusion criteria: none.	-	Interview, Rose questionnaire, ECG, neurological examination and medical records		6.5 218/3342	6.5 216/3342	6.5 217/3342

Supplementary Table 1. Additional characteristics of study samples included in ICARA (continued)

Study	Sample ^a	Selected population?	Assessment methods		Unknown status for time-to-event analysis (% , n/total N)		
			MI	Stroke	MI	Stroke	Mortality
Leiden 85-Plus Study (L85+), Netherlands	All individuals living in single city, reaching 85 th birthday within one month before start of study. Exclusion criteria: none.	age selection	medical records from primary physician and ECG		0.4 2/445	0 0/445	0 0/445
Mr. Os and Ms. Os Study (MrMs OS), China	F/M ≥65 years, recruitment of volunteers via advertisements in community centers and housing estates and public presentations. Exclusion criteria: (1) unable to walk without assistance; (2) bilateral hip replacement.	volunteer selection	information of the Clinical Management System database of the Hong Kong Hospital Authority		0 1/3998	0 0/3998	0 0/3998
Osservatorio Geriatrico Regione Campania Study (OGC), Italy	F/M ≥65 years, random sample, stratified by age, sex, and size of urban unit, from the electoral rolls. Exclusion criteria: none.	-	NA	NA	NA	NA	0 0/1250
Outcomes of Sleep Disorders in Older Men Study (MrOS Sleep), USA	M ≥65 years, who actively participated in the MrOS study. Exclusion criteria MrOS: (1) inability to walk without assistance from another person; (2) bilateral hip replacements; (3) inability to provide self-reported data. Exclusion criteria MrOS Sleep: (1) sleeping with a continuous positive airway pressure or bilevel positive airway pressure mask in the last 3 months; (2) sleeping with a mouthpiece in the last 3 months; (3) having an open tracheostomy; (4) using oxygen therapy during sleep in the last 3 months.	sex selection	four-monthly self-report with central adjudication via medical records and supporting documentation		1.8 55/3130	1.8 56/3130	3.2 101/3130
Selenium and Cognitive Decline Study (SCDS), China	F/M ≥65 years, recruitment by door-to-door census in selected areas based on selenium levels. Exclusion criteria: (1) hearing problems.	selected areas	NA	NA	NA	NA	1.3 23/1735
Singapore Longitudinal Ageing Study I (SLAS I), Singapore	F/M ≥55 years, recruitment by door-to-door census in South-east region of Singapore. Exclusion criteria: (1) those mentally or physically unable to give informed consent or to complete the interview (e.g. stroke, aphasia, profound dementia).	-	NA	NA	NA	NA	0 0/2789

Supplementary Table 1. Additional characteristics of study samples included in ICARA (continued)

Study	Sample ^a	Selected population?	Assessment methods		Unknown status for time-to-event analysis (% , n/total N)		
			MI	Stroke	MI	Stroke	Mortality
Singapore Longitudinal Ageing Study II (SLAS II), Singapore	F/M ≥55 years, recruitment by door-to-door census in South-central and South-west region of Singapore. Exclusion criteria: (1) those mentally or physically unable to give informed consent or to complete the interview (e.g. stroke, aphasia, profound dementia).	-	NA	NA	NA	NA	0 0/3263
Study of Osteoporotic Fractures (SOF), USA	F ≥65 years, recruitment by mailings to age-eligible women identified from community-based listings. Exclusion criteria: (1) bilateral hip replacement; (2) unable to walk without assistance.	sex selection	self-report	NA	NA ^b	NA	0 0/6591
Sydney Memory and Ageing Study (MAS), Australia	F/M 70-90 years, random sampling from the electoral rolls. Exclusion criteria: (1) dementia, psychotic symptoms, schizophrenia or bipolar disorder, multiple sclerosis, motor neuron disease, developmental disability, progressive malignancy; (2) any medical or psychological conditions that may have prevented completing assessments; (3) MMSE score of <24 adjusted for age, education; (4) English insufficient to complete psychometric assessment	-	self-report	NA ^b	13.6 140/1033	0 0/1033	
Treviso Longeva Study (Trelong), Italy	F/M ≥70 years, systematic random sampling from residents lists in the Registry Office of the Municipality. Exclusion criteria: none.	-	self-report or in case of cognitive impairment caregiver information and review of hospital records	NA ^b	NA ^b	0 0/575	

Abbreviations: ICARA, Initiative on Cardiovascular disease Risk and Apathy; F, females; M, males; MI, myocardial infarction; NA, not applicable; ECG, electrocardiography; MMSE, Mini-Mental State Examination.

Study design: all studies concern prospective cohorts, except the INVADE study. This is a non-randomized controlled trial to reduce the incidence of stroke and dementia by systematic identification and evidence-based treatment of vascular risk factors. Only data from the intervention arm was available for inclusion in this meta-analysis.

^a Study samples included in the meta-analyses consist of community-dwelling individuals with an available apathy and/or depression score.

^b No time-to-event data due to unavailability of event dates. Event data are used in a logistic regression sensitivity analyses as described in Supplementary Table 3.

Supplementary Table 2. Sensitivity analysis for the associations of apathy and depressive symptoms with subsequent stroke including transient ischemic attack

<i>Stroke including transient ischemic attack*</i>						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	1191/13930	1.66 (1.38-1.99)	1191/13930	1.50 (1.25-1.81)	1191/13905	1.44 (1.20-1.72)
Apathy, isolated ^b	809/10011	1.64 (1.42-1.90)	809/10011	1.47 (1.27-1.70)	809/9993	1.41 (1.22-1.64)
Depression ^c	1188/13924	1.53 (1.30-1.79)	1188/13924	1.45 (1.23-1.70)	1188/13899	1.40 (1.21-1.61)
Depression, isolated ^d	629/9159	1.35 (1.10-1.66)	629/9159	1.31 (1.06-1.61)	629/9144	1.27 (1.03-1.56)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥ 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1).

^c Depressive symptoms: a score of ≥ 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1).

^e Unadjusted.

^f Adjusted for baseline age and sex.

^g Adjusted for baseline age, sex, and history of myocardial infarction and/or stroke.

* Studies included in analysis: Model 1, 2, and 3: BFC80+, HIMS, MAS, MrMs Os, MrOS Sleep.

Supplementary Table 3. Sensitivity analysis for the associations of apathy and depressive symptoms with subsequent myocardial infarction and stroke using logistic regression analysis

Myocardial infarction*						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	OR (95% CI)	Events(n)/ Total (n)	OR (95% CI)	Events(n)/ Total (n)	OR (95% CI)
Apathy ^a	1723/29759	1.44 (1.23-1.68)	1723/29759	1.32 (1.13-1.54)	1710/29409	1.21 (1.08-1.34)
Apathy, isolated ^b	1217/21070	1.49 (1.28-1.74)	1217/21070	1.34 (1.18-1.52)	1209/20848	1.23 (1.08-1.40)
Depression ^c	1713/29554	1.18 (0.97-1.44)	1713/29554	1.15 (0.95-1.39)	1700/29205	1.08 (0.91-1.27)
Depression, isolated ^d	992/20043	1.23 (1.03-1.46)	992/20043	1.20 (1.00-1.43)	981/19804	1.10 (0.92-1.32)
Stroke**						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	OR (95% CI)	Events(n)/ Total (n)	OR (95% CI)	Events(n)/ Total (n)	OR (95% CI)
Apathy ^a	1599/24590	1.52 (1.31-1.77)	1599/24590	1.36 (1.17-1.59)	1446/23219	1.30 (1.10-1.53)
Apathy, isolated ^b	1002/16638	1.54 (1.33-1.77)	1002/16638	1.34 (1.11-1.62)	925/15880	1.28 (1.11-1.48)
Depression ^c	1571/24345	1.33 (1.11-1.59)	1571/24345	1.29 (1.09-1.52)	1427/23021	1.25 (1.04-1.51)
Depression, isolated ^d	867/16294	1.18 (0.99-1.40)	867/16294	1.15 (0.96-1.36)	759/15252	1.10 (0.89-1.37)

Abbreviations: OR, odds ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥ 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1).

^c Depressive symptoms: a score of ≥ 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1).

^e Unadjusted.

^f Adjusted for baseline age, sex, and follow-up time of study.

^g Adjusted for baseline age, sex, follow-up time of study, and history of myocardial infarction and/or stroke.

* Studies included in analysis: Model 1 and 2: BFC80+, EAS, HIMS, ILSA, INVADE, Invece.Ab, L85+, MAS, MrMs Os, MrOS Sleep, SOF, Trelong; Model 3: BFC80+, EAS, HIMS, ILSA, INVADE, Invece.Ab, L85+, MAS, MrMs Os, MrOS Sleep, SOF (unavailable history of myocardial infarction and/or stroke for the other study).

** Studies included in analysis: Model 1 and 2: BFC80+, EAS, HIMS, ILSA, INVADE, Invece.Ab, L85+, MAS, MrMs Os, MrOS Sleep, SABE, Trelong; Model 3: BFC80+, EAS, HIMS, ILSA, INVADE, Invece.Ab, L85+, MAS, MrMs Os, MrOS Sleep (unavailable history of myocardial infarction and/or stroke for the other studies).

Supplementary Table 4. Sensitivity analysis for the associations of apathy and depressive symptoms with subsequent myocardial infarction and stroke (depressive symptoms defined as GDS-12D \geq 5)

Myocardial infarction*						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	1213/21326	1.41 (1.25-1.58)	1213/21326	1.29 (1.15-1.45)	1211/21290	1.21 (1.08-1.36)
Apathy, isolated ^b	1090/18979	1.40 (1.24-1.59)	1090/18979	1.27 (1.12-1.44)	1088/18946	1.20 (1.06-1.36)
Depression ^c	1204/21129	1.24 (0.92-1.69)	1204/21129	1.26 (0.95-1.67)	1202/21094	1.21 (0.92-1.58)
Depression, isolated ^d	682/13870	1.13 (0.73-1.76)	682/13870	1.25 (0.81-1.93)	681/13852	1.19 (0.77-1.84)
Stroke**						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	1449/23284	1.62 (1.40-1.87)	1449/23284	1.43 (1.23-1.67)	1449/23232	1.37 (1.18-1.59)
Apathy, isolated ^b	1262/20807	1.66 (1.47-1.87)	1262/20807	1.46 (1.28-1.67)	1262/20758	1.40 (1.23-1.60)
Depression ^c	1430/23086	1.42 (1.06-1.90)	1430/23086	1.37 (1.02-1.83)	1430/23035	1.30 (0.97-1.73)
Depression, isolated ^d	762/15291	1.38 (0.98-1.94)	762/15291	1.42 (1.01-1.99)	762/15263	1.35 (0.96-1.89)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥ 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥ 2 on the GDS-3A in participants with ≤ 4 depressive symptoms (GDS-12D ≤ 4).

^c Depressive symptoms: a score of ≥ 5 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥ 5 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1).

^e Unadjusted.

^f Adjusted for baseline age and sex.

^g Adjusted for baseline age, sex, and history of myocardial infarction and/or stroke.

* Studies included in analysis: Model 1, 2, and 3: BFC80+, EAS, HIMS, ILSA, INVADE, L85+, MrMs Os, MrOS Sleep.

** Studies included in analysis: Model 1, 2, and 3: BFC80+, EAS, HIMS, ILSA, INVADE, InveCe.Ab, L85+, MAS, MrMs Os, MrOS Sleep.

Supplementary Table 5. Sensitivity analysis for the associations of isolated apathy and depressive symptoms with subsequent myocardial infarction and stroke (GDS-3A \geq 2 in individuals with GDS-12D=0 and GDS-12D \geq 2 in individuals with GDS-3A=0 respectively)

<i>Myocardial infarction*</i>						
	Model 1 ^e		Model 2 ^f		Model 3 ^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	1213/21326	1.41 (1.25-1.58)	1213/21326	1.29 (1.15-1.45)	1211/21290	1.21 (1.08-1.36)
Apathy, isolated ^b	599/9987	1.37 (1.14-1.63)	599/9987	1.23 (1.03-1.48)	598/9974	1.20 (1.00-1.43)
Depression ^c	1204/21129	1.14 (0.94-1.37)	1204/21129	1.11 (0.92-1.34)	1202/21094	1.08 (0.91-1.29)
Depression, isolated ^d	316/6615	0.87 (0.59-1.26)	316/6615	0.88 (0.61-1.28)	315/6605	0.87 (0.60-1.27)
<i>Stroke**</i>						
	Model 1 ^e		Model 2 ^f		Model 3 ^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	1449/23284	1.62 (1.40-1.87)	1449/23284	1.43 (1.23-1.67)	1449/23232	1.37 (1.18-1.59)
Apathy, isolated ^b	614/11057	1.40 (1.17-1.68)	614/11057	1.22 (1.02-1.47)	614/11036	1.19 (0.99-1.42)
Depression ^c	1430/23086	1.46 (1.26-1.70)	1430/23086	1.39 (1.20-1.61)	1430/23035	1.36 (1.18-1.56)
Depression, isolated ^d	357/7416	1.36 (1.01-1.81)	357/7416	1.34 (1.00-1.79)	357/7405	1.31 (0.98-1.75)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of \geq 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of \geq 2 on the GDS-3A in participants without depressive symptoms (GDS-12D=0).

^c Depressive symptoms: a score of \geq 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of \geq 2 on the GDS-12D in participants without apathy symptoms (GDS-3A=0).

^e Unadjusted.

^f Adjusted for baseline age and sex.

^g Adjusted for baseline age, sex, and history of myocardial infarction and/or stroke.

* Studies included in analysis: Model 1, 2, and 3: BFC80+, EAS, HIMS, ILSA, INVADE, L85+, MrMs Os, MrOS Sleep.

** Studies included in analysis: Model 1, 2, and 3: BFC80+, EAS, HIMS, ILSA, INVADE, InveCe.Ab, L85+, MAS, MrMs Os, MrOS Sleep.

Supplementary Table 6. Sensitivity analysis for the associations of apathy and depressive symptoms with the composite endpoint of myocardial infarction, angina pectoris and/or peripheral arterial disease

Composite endpoint myocardial infarction, angina pectoris and/or peripheral arterial disease*						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	OR (95% CI)	Events(n)/ Total (n)	OR (95% CI)	Events(n)/ Total (n)	OR (95% CI)
Apathy ^a	1919/14146	1.42 (1.17-1.73)	1919/14146	1.36 (1.13-1.65)	1917/14130	1.33 (1.20-1.49)
Apathy, isolated ^b	1275/8663	1.45 (1.27-1.66)	1275/8663	1.35 (1.18-1.54)	1273/8653	1.26 (1.10-1.45)
Depression ^c	1903/13951	1.10 (0.83-1.45)	1903/13951	1.11 (0.86-1.45)	1901/13935	1.08 (0.85-1.37)
Depression, isolated ^d	1008/9472	1.07 (0.89-1.27)	1008/9472	1.06 (0.88-1.26)	1007/9463	1.00 (0.84-1.20)

Abbreviations: OR, odds ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥ 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1).

^c Depressive symptoms: a score of ≥ 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1).

^e Unadjusted.

^f Adjusted for baseline age, sex, and follow-up time of study.

^g Adjusted for baseline age, sex, follow-up time of study, and history of myocardial infarction and/or stroke.

* Studies included in analysis: Model 1, 2, and 3: BFC80+, HIMS, ILSA, Invece.Ab, MrMs Os.

Supplementary Table 7. Sensitivity analysis for the associations of apathy and depressive symptoms with all-cause mortality (depressive symptoms defined as GDS-12D≥5)

All-cause mortality*						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	15615/46802	1.75 (1.63-1.87)	15612/46796	1.52 (1.44-1.61)	11984/38898	1.47 (1.38-1.56)
Apathy, isolated ^b	12878/40737	1.74 (1.66-1.82)	12875/40732	1.49 (1.43-1.55)	10420/35215	1.44 (1.37-1.51)
Depression ^c	15268/45877	1.68 (1.51-1.86)	15265/45871	1.61 (1.48-1.75)	11861/38691	1.61 (1.45-1.79)
Depression, isolated ^d	8774/31647	1.58 (1.38-1.81)	8771/31642	1.56 (1.40-1.74)	7042/27380	1.55 (1.37-1.76)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥2 on the GDS-3A in participants with ≤4 depressive symptoms (GDS-12D≤4).

^c Depressive symptoms: a score of ≥5 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥5 on the GDS-12D in participants with ≤1 apathy symptoms (GDS-3A≤1).

^e Unadjusted.

^f Adjusted for baseline age and sex.

^g Adjusted for baseline age, sex, and history of myocardial infarction and/or stroke.

* Studies included in analysis: Model 1 and 2: BFC80+, CSHA, EAS, HCS, HIMS, HKOOS, ICARe Dicomano (apathy analysis only because of unavailable depression scores), ILSA, INVADE, InveCe.Ab, L85+, MAS, MrMs Os, MrOs Sleep, OGC, SABE-Brazil, SLAS1, SLAS2, SCDS, SOF, Trelong; Model 3: BFC80+, EAS, HIMS, ILSA, INVADE, InveCe.Ab, L85+, MAS, MrMs Os, MrOs Sleep, SCDS, SLAS1, SLAS2, SOF (unavailable history of myocardial infarction and/or stroke for the other studies).

Supplementary Table 8. Sensitivity analysis for the associations of isolated apathy and depressive symptoms with all-cause mortality (GDS-3A \geq 2 in individuals with GDS-12D=0 and GDS-12D \geq 2 in individuals with GDS-3A=0 respectively)

	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/	HR (95% CI)	Events(n)/	HR (95% CI)	Events(n)/	HR (95% CI)
	Total (n)		Total (n)		Total (n)	
Apathy ^a	15615/46802	1.75 (1.63-1.87)	15612/46796	1.52 (1.44-1.61)	11984/38898	1.47 (1.38-1.56)
Apathy, isolated ^b	6172/21765	1.75 (1.65-1.86)	6172/21764	1.45 (1.37-1.54)	5290/19499	1.41 (1.32-1.51)
Depression ^c	15268/45877	1.55 (1.43-1.67)	15265/45871	1.46 (1.37-1.56)	11861/38691	1.44 (1.35-1.53)
Depression, isolated ^d	4129/17523	1.29 (1.15-1.46)	4128/17521	1.25 (1.12-1.39)	3391/15498	1.32 (1.20-1.46)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of \geq 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of \geq 2 on the GDS-3A in participants without depressive symptoms (GDS-12D=0).

^c Depressive symptoms: a score of \geq 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of \geq 2 on the GDS-12D in participants without apathy symptoms (GDS-3A=0).

^e Unadjusted.

^f Adjusted for baseline age and sex.

^g Adjusted for baseline age, sex, and history of myocardial infarction and/or stroke.

* Studies included in analysis: Model 1 and 2: BFC80+, CSHA, EAS, HCS, HIMS, HKOOS, ICARe Dicomano (apathy analysis only because of unavailable depression scores), ILSA, INVADE, InveCe.Ab, L85+, MAS, MrMs Os, MrOS Sleep, OGC, SABE-Brazil, SLAS1, SLAS2, SCDS, SOF, Trelong; Model 3: BFC80+, EAS, HIMS, ILSA, INVADE, InveCe.Ab, L85+, MAS, MrMs Os, MrOs Sleep, SCDS, SLAS1, SLAS2, SOF (unavailable history of myocardial infarction and/or stroke for the other studies).

Supplementary Table 9. Analysis for the associations of apathy and depressive symptoms with cardiovascular- and non-cardiovascular mortality

Cardiovascular mortality*						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	3764/27559	1.67 (1.45-1.92)	3763/27554	1.45 (1.27-1.66)	2847/21706	1.38 (1.16-1.66)
Apathy, isolated ^b	2481/18844	1.87 (1.68-2.08)	2481/18843	1.56 (1.41-1.73)	2066/16088	1.50 (1.36-1.66)
Depression ^c	3672/26831	1.48 (1.32-1.67)	3671/26826	1.41 (1.27-1.56)	2845/21692	1.33 (1.18-1.51)
Depression, isolated ^d	2190/18324	1.39 (1.20-1.62)	2189/18320	1.32 (1.18-1.48)	1704/15060	1.27 (1.11-1.45)
Non-cardiovascular mortality*						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	6673/27559	1.67 (1.53-1.83)	6672/27554	1.48 (1.38-1.58)	5178/21706	1.45 (1.34-1.57)
Apathy, isolated ^b	4238/18844	1.62 (1.51-1.74)	4238/18843	1.38 (1.28-1.48)	3606/16088	1.36 (1.27-1.47)
Depression ^c	6535/26831	1.52 (1.34-1.73)	6534/26826	1.48 (1.32-1.65)	5170/21692	1.50 (1.35-1.66)
Depression, isolated ^d	3972/18324	1.32 (1.17-1.50)	3971/18320	1.32 (1.19-1.45)	3222/15060	1.39 (1.27-1.52)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥ 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1).

^c Depressive symptoms: a score of ≥ 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1).

^e Unadjusted.

^f Adjusted for baseline age and sex.

^g Adjusted for baseline age, sex, and history of myocardial infarction and/or stroke.

* Cardiovascular mortality: fatal cardiovascular events as the primary cause of death (ninth version of the International Classification of Diseases (ICD-9): 390-459; tenth version of the International Classification of Diseases (ICD-10): I00-I99). Non-cardiovascular mortality: other causes (all other ICD-codes). Studies included in analysis: Model 1 and 2: CSHA, HCS, HIMS, HKOOS, ICARe Dicomano (apathy analysis only because of unavailable depression scores), InveCe.Ab, L85+, MAS, MrMs Os, MrOS Sleep, SABE-Brazil, SOF; Model 3: HIMS, InveCe.Ab, L85+, MAS, MrMs Os, MrOs Sleep, SOF (unavailable history of myocardial infarction and/or stroke for the other studies).

Supplementary Table 10. Sub group analysis for the associations of apathy and depressive symptoms with myocardial infarction based on age tertiles.

Myocardial infarction* <72 years						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	151/6778	1.25 (0.88-1.77)	151/6778	1.24 (0.87-1.76)	151/6766	1.14 (0.80-1.62)
Apathy, isolated ^b	105/4621	1.13 (0.71-1.82)	105/4621	1.11 (0.70-1.76)	105/4614	1.02 (0.64-1.62)
Depression ^c	151/6738	1.00 (0.69-1.45)	151/6738	1.08 (0.75-1.56)	151/6726	1.00 (0.69-1.45)
Depression, isolated ^d	103/4853	0.92 (0.48-1.77)	103/4853	1.00 (0.55-1.82)	103/4847	0.95 (0.51-1.74)
Myocardial infarction* 72-77 years						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	478/7681	1.27 (1.05-1.53)	478/7681	1.26 (1.05-1.52)	478/7675	1.19 (0.98-1.43)
Apathy, isolated ^b	353/5417	1.28 (1.02-1.61)	353/5417	1.26 (1.01-1.59)	353/5413	1.21 (0.96-1.52)
Depression ^c	474/7622	1.14 (0.92-1.43)	474/7622	1.17 (0.94-1.45)	474/7617	1.09 (0.88-1.35)
Depression, isolated ^d	292/5107	1.04 (0.74-1.45)	292/5107	1.08 (0.78-1.49)	292/5105	1.03 (0.75-1.42)
Myocardial infarction* >77 years						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	584/6867	1.37 (1.16-1.61)	584/6867	1.33 (1.13-1.57)	582/6849	1.27 (1.07-1.50)
Apathy, isolated ^b	403/4429	1.48 (1.20-1.81)	403/4429	1.40 (1.15-1.72)	401/4419	1.34 (1.09-1.64)
Depression ^c	579/6769	1.09 (0.81-1.46)	579/6769	1.12 (0.84-1.49)	577/6751	1.10 (0.82-1.47)
Depression, isolated ^d	287/3910	1.34 (0.99-1.83)	287/3910	1.33 (0.98-1.81)	286/3900	1.33 (0.98-1.81)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥ 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1).

^c Depressive symptoms: a score of ≥ 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1).

^e Unadjusted.

^f Adjusted for baseline age and sex.

^g Adjusted for baseline age, sex, and history of myocardial infarction and/or stroke.

* Studies included in analysis: Model 1, 2, and 3: BFC80+, EAS, HIMS, ILSA, INVADE, L85+, MrMs Os, MrOS Sleep.

Supplementary Table 11. Sub group analysis for the associations of apathy and depressive symptoms with stroke based on age tertiles.

Stroke* <72 years						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	222/7221	1.19 (0.75-1.87)	222/7221	1.22 (0.83-1.78)	222/7209	1.17 (0.81-1.70)
Apathy, isolated ^b	132/4941	1.11 (0.74-1.67)	132/4941	1.03 (0.68-1.56)	132/4934	0.99 (0.66-1.51)
Depression ^c	218/7181	1.56 (1.18-2.06)	218/7181	1.62 (1.22-2.16)	218/7169	1.57 (1.18-2.10)
Depression, isolated ^d	149/5252	1.45 (1.03-2.06)	149/5252	1.58 (1.09-2.28)	149/5246	1.54 (1.06-2.23)
Stroke* 72-77 years						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	530/8718	1.67 (1.40-2.00)	530/8718	1.65 (1.39-1.97)	530/8702	1.58 (1.32-1.88)
Apathy, isolated ^b	351/6170	1.62 (1.30-2.03)	351/6170	1.59 (1.27-1.98)	351/6157	1.53 (1.23-1.92)
Depression ^c	527/8660	1.45 (1.19-1.76)	527/8660	1.48 (1.23-1.79)	527/8645	1.39 (1.15-1.69)
Depression, isolated ^d	290/5908	1.28 (0.95-1.74)	290/5908	1.32 (0.97-1.79)	290/5900	1.27 (0.94-1.71)
Stroke* >77 years						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	697/7345	1.45 (1.18-1.77)	697/7345	1.42 (1.16-1.74)	697/7321	1.36 (1.11-1.66)
Apathy, isolated ^b	445/4817	1.40 (1.15-1.70)	445/4817	1.34 (1.11-1.63)	445/4801	1.29 (1.06-1.57)
Depression ^c	685/7245	1.31 (1.05-1.64)	685/7245	1.31 (1.05-1.62)	685/7221	1.29 (1.06-1.58)
Depression, isolated ^d	323/4131	1.01 (0.75-1.36)	323/4131	1.00 (0.74-1.35)	323/4117	0.99 (0.73-1.34)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥ 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1).

^c Depressive symptoms: a score of ≥ 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1).

^e Unadjusted.

^f Adjusted for baseline age and sex.

^g Adjusted for baseline age, sex, and history of myocardial infarction and/or stroke.

* Studies included in analysis: Model 1, 2, and 3: BFC80+, EAS, HIMS, ILSA, INVADE, InveCe.Ab, L85+, MAS, MrMs Os, MrOS Sleep.

Supplementary Table 12. Sub group analysis for the associations of apathy and depressive symptoms with mortality based on age tertiles.

All-cause mortality* <72 years						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	2371/15829	1,61 (1,43-1,80)	2371/15829	1,64 (1,44-1,87)	1587/13196	1,52 (1,27-1,83)
Apathy, isolated ^b	2317/15476	1,33 (1,21-1,46)	2317/15476	1,43 (1,31-1,57)	1575/13156	1,35 (1,21-1,51)
Depression ^c	1435/10926	1,42 (1,23-1,63)	1435/10926	1,38 (1,16-1,63)	1034/9586	1,36 (1,07-1,74)
Depression, isolated ^d	1569/12263	1,10 (0,98-1,24)	1569/12263	1,20 (1,07-1,35)	1095/10591	1,20 (1,04-1,39)
All-cause mortality* 72-77 years						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	5141/16660	1.65 (1.56-1.76)	5141/16660	1.65 (1.55-1.75)	4171/14350	1.58 (1.48-1.69)
Apathy, isolated ^b	3164/11370	1.56 (1.44-1.70)	3164/11370	1.52 (1.4-1.650)	2817/10424	1.48 (1.36-1.61)
Depression ^c	5043/16388	1.49 (1.36-1.62)	5043/16388	1.52 (1.41-1.65)	4135/14288	1.48 (1.35-1.63)
Depression, isolated ^d	3051/11316	1.31 (1.18-1.46)	3051/11316	1.33 (1.21-1.47)	2612/10137	1.34 (1.20-1.49)
All-cause mortality* >77 years						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	8100/14307	1.50 (1.40-1.60)	8100/14307	1.44 (1.34-1.53)	6226/11352	1.42 (1.32-1.52)
Apathy, isolated ^b	4599/8822	1.59 (1.49-1.69)	4599/8822	1.45 (1.36-1.54)	3882/7566	1.42 (1.33-1.53)
Depression ^c	7905/14007	1.42 (1.30-1.55)	7905/14007	1.43 (1.32-1.54)	6151/11247	1.44 (1.33-1.56)
Depression, isolated ^d	4151/8063	1.40 (1.28-1.55)	4151/8063	1.40 (1.29-1.52)	3335/6652	1.45 (1.33-1.57)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥ 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1).

^c Depressive symptoms: a score of ≥ 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1).

^e Unadjusted.

^f Adjusted for baseline age and sex.

^g Adjusted for baseline age, sex, and history of myocardial infarction and/or stroke.

* Studies included in analysis: Model 1 and 2: BFC80+, CSHA, EAS, HCS, HIMS, HKOOS, ICARe Dicomano (apathy analysis only because of unavailable depression scores), ILSA, INVADE, InveCe.Ab, L85+, MAS, MrMs Os, MrOs Sleep, OGC, SABE-Brazil, SLAS1, SLAS2, SCDS, SOF, Trelong; Model 3: BFC80+, EAS, HIMS, ILSA, INVADE, InveCe.Ab, L85+, MAS, MrMs Os, MrOs Sleep, SCDS, SLAS1, SLAS2, SOF (unavailable history of myocardial infarction and/or stroke for the other studies).

Supplementary Table 13. Analysis for the associations of apathy and depressive symptoms with subsequent myocardial infarction and stroke in individuals without a myocardial infarction and/or stroke history

Myocardial infarction*				
	Model 1^e		Model 2^f	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	872/18179	1.34 (1.17-1.54)	872/18179	1.21 (1.06-1.40)
Apathy, isolated ^b	630/12532	1.44 (1.18-1.75)	630/12532	1.25 (1.05-1.48)
Depression ^c	866/18013	1.11 (0.90-1.36)	866/18013	1.07 (0.88-1.31)
Depression, isolated ^d	522/12155	1.18 (0.93-1.49)	522/12155	1.16 (0.92-1.47)
Stroke**				
	Model 1^e		Model 2^f	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	1067/19860	1.64 (1.45-1.87)	1067/19860	1.44 (1.25-1.66)
Apathy, isolated ^b	708/13798	1.54 (1.31-1.80)	708/13798	1.35 (1.15-1.58)
Depression ^c	1053/19693	1.43 (1.25-1.65)	1053/19693	1.33 (1.15-1.54)
Depression, isolated ^d	587/13398	1.13 (0.84-1.53)	587/13398	1.09 (0.79-1.49)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥ 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1).

^c Depressive symptoms: a score of ≥ 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1).

^e Unadjusted.

^f Adjusted for baseline age and sex.

* Studies included in analysis: Model 1, 2: BFC80+, EAS, HIMS, ILSA, INVADE, L85+, MrMs Os, MrOS Sleep.

** Studies included in analysis: Model 1, 2: BFC80+, EAS, HIMS, ILSA, INVADE, InveCe.Ab, L85+, MAS, MrMs Os, MrOS Sleep.

Supplementary Table 14. Analysis for the associations of apathy and depressive symptoms with all-cause mortality in individuals without a myocardial infarction and/or stroke history

	Model 1^e		Model 2^f	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	9727/33956	1.69 (1.56-1.83)	9727/33956	1.47 (1.37-1.57)
Apathy, isolated ^b	6425/24471	1.68 (1.59-1.78)	6425/24471	1.43 (1.35-1.52)
Depression ^c	9632/33782	1.57 (1.43-1.72)	9632/33782	1.44 (1.35-1.53)
Depression, isolated ^d	5991/24531	1.40 (1.31-1.50)	5991/24531	1.34 (1.25-1.43)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥ 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1).

^c Depressive symptoms: a score of ≥ 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1).

^e Unadjusted.

^f Adjusted for baseline age and sex.

* Studies included in analysis: Model 1 and 2: BFC80+, EAS, HIMS, ILSA, INVADE, InveCe.Ab, L85+, MAS, MrMs Os, MrOS Sleep, SCDS, SLAS1, SLAS2, SOF.

Supplementary Table 15. Sensitivity analysis for the associations of apathy and depressive symptoms with subsequent myocardial infarction and stroke comparing studies with an observational and experimental design

Myocardial infarction*						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Observational						
Apathy ^a	1127/17525	1.42 (1.26-1.60)	1127/17525	1.30 (1.15-1.47)	1125/17508	1.23 (1.09-1.39)
Apathy, isolated ^b	794/11583	1.49 (1.27-1.74)	794/11583	1.34 (1.15-1.56)	792/11573	1.27 (1.10-1.48)
Depression ^c	1116/17332	1.18 (0.97-1.43)	1116/17332	1.16 (0.96-1.40)	1114/17315	1.13 (0.95-1.34)
Depression, isolated ^d	638/11656	1.22 (0.98-1.50)	638/11656	1.22 (0.98-1.50)	637/11646	1.19 (0.96-1.46)
Experimental						
Apathy ^a	86/3801	1.33 (0.87-2.04)	86/3801	1.14 (0.74-1.75)	86/3782	1.06 (0.69-1.63)
Apathy, isolated ^b	67/2884	1.30 (0.80-2.12)	67/2884	1.09 (0.66-1.79)	67/2873	1.02 (0.62-1.69)
Depression ^c	88/3797	0.88 (0.52-1.47)	88/3797	0.81 (0.48-1.36)	88/3779	0.77 (0.46-1.30)
Depression, isolated ^d	44/2214	0.49 (0.15-1.59)	44/2214	0.50 (0.15-1.62)	44/2206	0.48 (0.15-1.56)
Stroke**						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Observational						
Apathy ^a	1249/19483	1.61 (1.37-1.90)	1249/19483	1.45 (1.22-1.72)	1249/19450	1.37 (1.16-1.63)
Apathy, isolated ^b	797/13044	1.61 (1.38-1.87)	797/13044	1.42 (1.22-1.65)	797/13019	1.36 (1.17-1.58)
Depression ^c	1232/19289	1.39 (1.16-1.67)	1232/19289	1.35 (1.13-1.62)	1232/19256	1.32 (1.12-1.55)
Depression, isolated ^d	668/13077	1.24 (1.02-1.50)	668/13077	1.20 (0.99-1.46)	668/13057	1.17 (0.96-1.42)
Experimental						
Apathy ^a	200/3801	1.60 (1.21-2.11)	200/3801	1.29 (0.97-1.71)	200/3782	1.26 (0.95-1.67)
Apathy, isolated ^b	131/2884	1.39 (0.98-1.98)	131/2884	1.14 (0.80-1.63)	131/2873	1.12 (0.79-1.60)
Depression ^c	198/3797	1.69 (1.26-2.28)	198/3797	1.46 (1.08-1.97)	198/3779	1.45 (1.07-1.95)
Depression, isolated ^d	94/2214	1.40 (0.81-2.39)	94/2214	1.32 (0.77-2.26)	94/2206	1.31 (0.77-2.26)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥ 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1).

^c Depressive symptoms: a score of ≥ 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1).

^e Unadjusted.

^f Adjusted for baseline age and sex.

^g Adjusted for baseline age, sex, and history of myocardial infarction and/or stroke.

* Studies included in analysis: Observational: Model 1, 2, and 3: BFC80+, EAS, HIMS, ILSA, L85+, MrMs Os, MrOS Sleep. Experimental: Model 1, 2, and 3: INVADE.

** Studies Included in analysis: Observational: Model 1, 2, and 3: BFC80+, EAS, HIMS, ILSA, InveCe.Ab, L85+, MAS, MrMs Os, MrOS Sleep. Experimental: Model 1, 2, and 3: INVADE.

Supplementary Table 16. Sensitivity analysis for the associations of apathy and depressive symptoms with all-cause mortality comparing studies with an observational and experimental design

<i>Mortality*</i>						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Observational						
Apathy ^a	14745/43001	1.73 (1.62-1.85)	14742/42995	1.52 (1.43-1.60)	11122/35116	1.45 (1.36-1.55)
Apathy, isolated ^b	8611/28235	1.72 (1.64-1.81)	8611/28234	1.46 (1.39-1.53)	7150/24703	1.43 (1.36-1.51)
Depression ^c	14407/42080	1.54 (1.42-1.67)	14404/42074	1.46 (1.37-1.57)	11007/34912	1.44 (1.35-1.54)
Depression, isolated ^d	8400/29433	1.39 (1.28-1.52)	8397/29428	1.34 (1.25-1.43)	6670/25174	1.37 (1.29-1.46)
Experimental						
Apathy ^a	870/3801	2.03 (1.78-2.33)	870/3801	1.64 (1.43-1.88)	862/3782	1.59 (1.39-1.83)
Apathy, isolated ^b	587/2884	1.81 (1.54-2.13)	587/2884	1.52 (1.29-1.79)	583/2873	1.47 (1.24-1.73)
Depression ^c	861/3797	1.63 (1.41-1.88)	861/3797	1.39 (1.20-1.61)	854/3779	1.37 (1.18-1.59)
Depression, isolated ^d	374/2214	1.18 (0.88-1.57)	374/2214	1.15 (0.86-1.53)	372/2206	1.12 (0.84-1.50)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥ 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1).

^c Depressive symptoms: a score of ≥ 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1).

^e Unadjusted.

^f Adjusted for baseline age and sex.

^g Adjusted for baseline age, sex, and history of myocardial infarction and/or stroke.

* Studies included in analysis: Observational: Model 1 and 2: BFC80+, CSHA, EAS, HCS, HIMS, HKOOS, ICARe Dicomano (apathy analysis only because of unavailable depression scores), ILSA, InveCe.Ab, L85+, MAS, MrMs Os, MrOS Sleep, OGC, SABE-Brazil, SLAS1, SLAS2, SCDS, SOF, Trelong; model 3: BFC80+, EAS, HIMS, ILSA, InveCe.Ab, L85+, MAS, MrMs Os, MrOs Sleep, SCDS, SLAS1, SLAS2, SOF (unavailable history of myocardial infarction and/or stroke for the other studies). Experimental: Model 1, 2, and 3: INVADE

Supplementary Table 17. Sensitivity analysis for the associations of apathy and depressive symptoms with subsequent myocardial infarction and stroke comparing general and selected study populations

Myocardial infarction*						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
General						
Apathy ^a	140/4061	1.34 (0.95-1.90)	140/4061	1.38 (0.97-1.96)	140/4061	1.31 (0.92-1.86)
Apathy, isolated ^b	68/2000	2.21 (1.32-3.70)	68/2000	2.19 (1.30-3.69)	68/2000	2.05 (1.21-3.48)
Depression ^c	129/3873	0.99 (0.70-1.39)	129/3873	1.06 (0.74-1.50)	129/3873	1.01 (0.71-1.45)
Depression, isolated ^d	82/2644	1.13 (0.72-1.77)	82/2644	1.20 (0.76-1.88)	82/2644	1.18 (0.75-1.85)
Selected						
Apathy ^a	1073/17266	1.42 (1.25-1.60)	1073/17266	1.27 (1.12-1.44)	1071/17230	1.20 (1.06-1.35)
Apathy, isolated ^b	793/12467	1.40 (1.21-1.63)	793/12467	1.26 (1.08-1.46)	791/12446	1.19 (1.03-1.39)
Depression ^c	1075/17256	1.19 (0.97-1.46)	1075/17256	1.13 (0.91-1.40)	1073/17221	1.09 (0.89-1.34)
Depression, isolated ^d	600/11226	1.19 (0.94-1.50)	600/11226	1.17 (0.92-1.47)	599/11208	1.13 (0.90-1.43)
Stroke**						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
General						
Apathy ^a	198/4965	1.52 (1.14-2.02)	198/4965	1.43 (1.06-1.91)	198/4951	1.32 (0.98-1.77)
Apathy, isolated ^b	90/2762	1.21 (0.74-1.96)	90/2762	1.04 (0.63-1.70)	90/2749	1.00 (0.61-1.65)
Depression ^c	184/4777	1.36 (1.00-1.84)	184/4777	1.34 (0.98-1.83)	184/4763	1.28 (0.94-1.75)
Depression, isolated ^d	110/3127	1.16 (0.79-1.70)	110/3127	1.09 (0.74-1.62)	110/3118	1.06 (0.72-1.57)
Selected						
Apathy ^a	1251/18319	1.63 (1.38-1.93)	1251/18319	1.44 (1.20-1.72)	1251/18281	1.38 (1.16-1.64)
Apathy, isolated ^b	838/13166	1.61 (1.39-1.85)	838/13166	1.41 (1.22-1.63)	838/13143	1.36 (1.18-1.57)
Depression ^c	1246/18309	1.49 (1.26-1.76)	1246/18309	1.41 (1.19-1.66)	1246/18272	1.38 (1.20-1.60)
Depression, isolated ^d	652/12164	1.28 (1.05-1.58)	652/12164	1.26 (1.03-1.54)	652/12145	1.23 (1.00-1.50)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥ 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1).

^c Depressive symptoms: a score of ≥ 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1).

^e Unadjusted.

^f Adjusted for baseline age and sex.

^g Adjusted for baseline age, sex, and history of myocardial infarction and/or stroke.

* Studies included in analysis: General: Model 1, 2, and 3: ILSA and EAS. Selected: Model 1, 2, and 3: BFC80+, HIMS, INVADE, L85+, MrMs Os, MrOS Sleep.

** Studies included in analysis: General: Model 1, 2, and 3: ILSA, MAS and EAS. Selected: Model 1, 2, and 3: BFC80+, HIMS, INVADE, InveCe.Ab, L85+, MrMs Os, MrOS Sleep.

Supplementary Table 18. Sensitivity analysis for the associations of apathy and depressive symptoms with all-cause mortality comparing general and selected study populations

<i>Mortality*</i>						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
General						
Apathy ^a	5948/19075	1.78 (1.63-1.94)	5945/19069	1.56 (1.46-1.66)	2688/12094	1.52 (1.40-1.66)
Apathy, isolated ^b	2508/11111	1.80 (1.64-1.98)	2508/11110	1.50 (1.36-1.64)	1327/8319	1.54 (1.35-1.76)
Depression ^c	5619/18168	1.58 (1.39-1.79)	5616/18162	1.47 (1.33-1.63)	2582/11904	1.52 (1.40-1.65)
Depression, isolated ^d	3014/12992	1.46 (1.25-1.71)	3011/12987	1.35 (1.20-1.52)	1550/9450	1.48 (1.33-1.65)
Selected						
Apathy ^a	9667/27727	1.70 (1.53-1.88)	9667/27727	1.49 (1.38-1.62)	9296/26804	1.44 (1.33-1.56)
Apathy, isolated ^b	6690/20008	1.69 (1.58-1.80)	6690/20008	1.45 (1.38-1.53)	6406/19257	1.42 (1.34-1.50)
Depression ^c	9649/27709	1.54 (1.41-1.69)	9649/27709	1.46 (1.34-1.59)	9279/26787	1.41 (1.30-1.52)
Depression, isolated ^d	5760/18655	1.38 (1.29-1.49)	5760/18655	1.35 (1.26-1.44)	5492/17930	1.32 (1.23-1.42)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥ 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1).

^c Depressive symptoms: a score of ≥ 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1).

^e Unadjusted.

^f Adjusted for baseline age and sex.

^g Adjusted for baseline age, sex, and history of myocardial infarction and/or stroke.

* Studies included in analysis: General: Model 1 and 2 :CSHA, HKOOS, ICARe Dicomano (apathy analysis only because of unavailable depression scores), ILSA, MAS, OGC, SABE-Brazil, SLAS1, SLAS2, Trelong and EAS. Model 3: ILSA, MAS, SLAS1, SLAS2 and EAS (unavailable history of myocardial infarction and/or stroke for the other studies). Selected: Model 1 and 2: BFC80+, HCS, HIMS, INVADE, InveCe.Ab, L85+, MrMs Os, MrOS Sleep, SCDS, SOF. Model 3: BFC80+, HIMS, INVADE, InveCe.Ab, L85+, MrMs Os, MrOS Sleep, SCDS, SOF (unavailable history of myocardial infarction and/or stroke for the other studies).

Supplementary Table 19. Sensitivity analysis for the associations of apathy and depressive symptoms with subsequent myocardial infarction and stroke comparing studies with assessment of events by self-report only and other methods

Myocardial infarction*						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Other methods						
Apathy ^a	1191/20378	1.39 (1.24-1.57)	1191/20378	1.27 (1.13-1.43)	1189/20342	1.20 (1.06-1.35)
Apathy, isolated ^b	843/13739	1.42 (1.23-1.65)	843/13739	1.28 (1.11-1.48)	841/13718	1.22 (1.05-1.41)
Depression ^c	1182/20181	1.15 (0.95-1.39)	1182/20181	1.12 (0.93-1.35)	1180/20146	1.09 (0.91-1.30)
Depression, isolated ^d	672/13228	1.17 (0.95-1.44)	672/13228	1.17 (0.95-1.44)	671/13210	1.14 (0.92-1.40)
Self-report only						
Apathy ^a	22/948	2.53 (1.09-5.86)	22/948	2.58 (1.11-5.99)	22/948	2.25 (0.96-5.28)
Apathy, isolated ^b	18/728	3.24 (1.29-8.17)	18/728	3.17 (1.25-8.01)	18/728	2.90 (1.13-7.42)
Depression ^c	22/948	0.85 (0.29-2.52)	22/948	0.93 (0.31-2.76)	22/948	0.88 (0.29-2.61)
Depression, isolated ^d	10/642	0.98 (0.12-7.76)	10/642	1.03 (0.13-8.11)	10/642	1.05 (0.13-8.30)
Stroke**						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Other methods						
Apathy ^a	1383/20374	1.64 (1.42-1.90)	1383/20374	1.46 (1.25-1.71)	1383/20335	1.40 (1.20-1.63)
Apathy, isolated ^b	876/13731	1.57 (1.36-1.80)	876/13731	1.38 (1.19-1.59)	876/13707	1.33 (1.16-1.53)
Depression ^c	1364/20177	1.54 (1.34-1.76)	1364/20177	1.46 (1.27-1.67)	1364/20139	1.42 (1.26-1.61)
Depression, isolated ^d	721/13227	1.27 (1.05-1.53)	721/13227	1.24 (1.03-1.49)	721/13206	1.21 (1.00-1.46)
Self-report only						
Apathy ^a	66/2910	1.39 (0.83-2.32)	66/2910	1.30 (0.77-2.18)	66/2897	1.15 (0.68-1.94)
Apathy, isolated ^b	52/2197	1.52 (0.83-2.77)	52/2197	1.46 (0.79-2.70)	52/2185	1.29 (0.70-2.39)
Depression ^c	66/2909	0.54 (0.12-2.47)	66/2909	0.54 (0.12-2.37)	66/2896	0.49 (0.10-2.31)
Depression, isolated ^d	41/2064	0.93 (0.37-2.34)	41/2064	0.89 (0.35-2.29)	41/2057	0.82 (0.32-2.13)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥ 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1).

^c Depressive symptoms: a score of ≥ 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1).

^e Unadjusted.

^f Adjusted for baseline age and sex.

^g Adjusted for baseline age, sex, and history of myocardial infarction and/or stroke.

* Studies included in analysis: Other methods: Model 1, 2, and 3: BFC80+, HIMS, ILSA, INVADE, L85+, MrMs Os, MrOS Sleep. Self-report: Model 1, 2, and 3: EAS.

** Included in analysis: Other methods: Model 1, 2, and 3: BFC80+, HIMS, ILSA, INVADE, L85+, MrMs Os, MrOS Sleep. Self-report: Model 1, 2, and 3: EAS, InveCe.Ab, MAS.

Supplementary Table 20. Sensitivity analysis for the associations of apathy and depressive symptoms with subsequent myocardial infarction and stroke comparing studies with a lower and higher percentage unknown status than the median percentage

<i>Myocardial infarction*</i>						
	Model 1 ^e		Model 2 ^f		Model 3 ^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Lower (<1.1%)						
Apathy ^a	832/13758	1.41 (1.22-1.62)	832/13758	1.26 (1.10-1.45)	830/13735	1.18 (1.03-1.36)
Apathy, isolated ^b	588/9607	1.33 (1.12-1.57)	588/9607	1.19 (1.00-1.41)	586/9593	1.12 (0.95-1.33)
Depression ^c	834/13747	1.34 (1.14-1.58)	834/13747	1.28 (1.08-1.51)	832/13725	1.22 (1.05-1.42)
Depression, isolated ^d	444/8790	1.18 (0.91-1.52)	444/8790	1.16 (0.90-1.50)	443/8780	1.13 (0.87-1.45)
Higher (>1.1%)						
Apathy ^a	381/7568	1.40 (1.14-1.73)	381/7568	1.33 (1.08-1.65)	381/7555	1.28 (1.03-1.58)
Apathy, isolated ^b	273/4860	1.81 (1.40-2.34)	273/4860	1.66 (1.27-2.15)	273/4853	1.58 (1.22-2.06)
Depression ^c	370/7382	0.94 (0.73-1.21)	370/7382	0.95 (0.75-1.21)	370/7369	0.93 (0.74-1.19)
Depression, isolated ^d	238/5080	1.15 (0.81-1.63)	238/5080	1.19 (0.86-1.65)	238/5072	1.19 (0.86-1.64)
Stroke**						
	Model 1 ^e		Model 2 ^f		Model 3 ^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Lower (<4.2%)						
Apathy ^a	1212/16815	1.65 (1.40-1.96)	1212/16815	1.45 (1.20-1.74)	1212/16791	1.39 (1.16-1.66)
Apathy, isolated ^b	812/12177	1.61 (1.39-1.86)	812/12177	1.41 (1.22-1.63)	812/12162	1.36 (1.17-1.57)
Depression ^c	1207/16805	1.57 (1.35-1.82)	1207/16805	1.46 (1.25-1.70)	1207/16782	1.43 (1.25-1.63)
Depression, isolated ^d	626/10951	1.32 (1.07-1.63)	626/10951	1.29 (1.05-1.59)	626/10940	1.26 (1.02-1.55)
Higher (>4.2%)						
Apathy ^a	237/6469	1.49 (1.14-1.94)	237/6469	1.39 (1.06-1.81)	237/6441	1.28 (0.98-1.68)
Apathy, isolated ^b	116/3751	1.27 (0.82-1.98)	116/3751	1.10 (0.71-1.71)	116/3730	1.03 (0.66-1.60)
Depression ^c	223/6281	1.26 (0.96-1.67)	223/6281	1.25 (0.95-1.65)	223/6253	1.20 (0.91-1.59)
Depression, isolated ^d	136/4340	1.07 (0.74-1.55)	136/4340	1.05 (0.73-1.51)	136/4323	1.01 (0.70-1.45)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥ 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1).

^c Depressive symptoms: a score of ≥ 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1).

^e Unadjusted.

^f Adjusted for baseline age and sex.

^g Adjusted for baseline age, sex, and history of myocardial infarction and/or stroke.

* Studies included in analysis: <1.1%: Model 1, 2, and 3: HIMS, INVADE, L85+, MrMs Os. >1.1%: Model 1,2, and 3: BFC80+, EAS, ILSA, MrOS Sleep.

** Studies included in analysis: <4.2%: Model 1, 2, and 3: HIMS, INVADE, L85+, MrMs Os, MrOS Sleep. >4.2%: Model 1, 2, and 3: BFC80+, EAS, InveCe.Ab, ILSA, MAS.

Supplementary Table 21. Sensitivity analysis for the associations of apathy and depressive symptoms with all-cause mortality comparing studies with a percentage unknown status equal to or higher than the median percentage

<i>Mortality*</i>	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
<i>Equal (0.0%)</i>						
Apathy ^a	9864/31653	1.80 (1.62-2.00)	9864/31653	1.54 (1.42-1.68)	8638/29128	1.46 (1.34-1.60)
Apathy, isolated ^b	6283/22362	1.75 (1.65-1.85)	6283/22362	1.48 (1.40-1.56)	5946/21645	1.45 (1.36-1.53)
Depression ^c	9667/30999	1.59 (1.44-1.76)	9667/30999	1.47 (1.35-1.60)	8619/29109	1.41 (1.30-1.54)
Depression, isolated ^d	5671/22153	1.42 (1.31-1.53)	5671/22153	1.34 (1.26-1.43)	5243/21212	1.34 (1.25-1.44)
<i>Higher (>0.0%)</i>						
Apathy ^a	5751/15149	1.69 (1.58-1.81)	5748/15143	1.51 (1.43-1.60)	3346/9770	1.48 (1.38-1.58)
Apathy, isolated ^b	2915/8757	1.69 (1.56-1.84)	2915/8756	1.43 (1.32-1.56)	1787/5931	1.40 (1.27-1.56)
Depression ^c	5601/14878	1.49 (1.32-1.67)	5598/14872	1.45 (1.31-1.59)	3242/9582	1.49 (1.38-1.61)
Depression, isolated ^d	3103/9494	1.33 (1.15-1.53)	3100/9489	1.32 (1.17-1.48)	1799/6168	1.41 (1.26-1.57)

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Apathy symptoms: a score of ≥ 2 on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

^b Isolated apathy symptoms: a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1).

^c Depressive symptoms: a score of ≥ 2 on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

^d Isolated depressive symptoms: a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1).

^e Unadjusted.

^f Adjusted for baseline age and sex.

^g Adjusted for baseline age, sex, and history of myocardial infarction and/or stroke.

* Studies included in analysis: 0.0%: Model 1 and 2: BFC80+, HIMS, ICARe Dicomano (apathy analysis only because of unavailable depression scores), INVADE, InveCe.Ab, L85+, MAS, MrMs Os, OGC, SLAS1, SLAS2, SOF, Trelong. Model 3: BFC80+, HIMS, INVADE, InveCe.Ab, L85+, MAS, MrMs Os, SLAS1, SLAS2, SOF (unavailable history of myocardial infarction and/or stroke for the other studies). >0.0%: Model 1 and 2: CSHA, EAS, HCS, HKOOS, ILSA, MrOS Sleep, SCDS, SABE-Brazil. Model 3: EAS, ILSA, MrOS Sleep, SCDS (unavailable history of myocardial infarction and/or stroke for the other studies).

Supplementary Table 22. Analysis for the associations of apathy and depressive symptoms with subsequent myocardial infarction, stroke and mortality using continuous symptom scores

Myocardial infarction*						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	1213/21326	1.20 (1.13-1.27)	1213/21326	1.14 (1.08-1.21)	1211/21290	1.11 (1.04-1.17)
Apathy, isolated ^b	861/14467	1.20 (1.12-1.29)	861/14467	1.13 (1.06-1.22)	859/14446	1.10 (1.03-1.18)
Depression ^c	1204/21129	1.04 (0.99-1.09)	1204/21129	1.04 (1.00-1.09)	1202/21094	1.03 (0.99-1.08)
Depression, isolated ^d	682/13870	1.05 (0.99-1.11)	682/13870	1.06 (1.00-1.12)	681/13852	1.05 (0.99-1.11)
Stroke**						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	1449/23284	1.27 (1.16-1.38)	1449/23284	1.18 (1.08-1.29)	1449/23232	1.15 (1.05-1.26)
Apathy, isolated ^b	928/15928	1.26 (1.18-1.36)	928/15928	1.15 (1.06-1.25)	928/15892	1.13 (1.04-1.23)
Depression ^c	1430/23086	1.07 (1.02-1.12)	1430/23086	1.06 (1.01-1.11)	1430/23035	1.05 (1.00-1.10)
Depression, isolated ^d	762/15291	1.06 (1.01-1.11)	762/15291	1.06 (1.01-1.11)	762/15263	1.04 (1.00-1.09)
All-cause mortality***						
	Model 1^e		Model 2^f		Model 3^g	
	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)	Events(n)/ Total (n)	HR (95% CI)
Apathy ^a	15615/46802	1.37 (1.31-1.43)	15612/46796	1.27 (1.23-1.31)	11984/38898	1.24 (1.20-1.28)
Apathy, isolated ^b	9198/31119	1.35 (1.29-1.40)	9198/31118	1.23 (1.20-1.26)	7733/27576	1.22 (1.19-1.25)
Depression ^c	15268/45877	1.10 (1.09-1.12)	15265/45871	1.10 (1.08-1.11)	11861/38691	1.09 (1.07-1.11)
Depression, isolated ^d	8774/31647	1.10 (1.08-1.12)	8771/31642	1.09 (1.07-1.11)	7042/27380	1.10 (1.07-1.12)

Abbreviations: HR, hazard ratio; CI, confidence interval.

a Apathy symptoms: score on the 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-3A) and any depression score.

b Isolated apathy symptoms: score on the GDS-3A in participants with ≤1 depressive symptoms (GDS-12D≤1).

c Depressive symptoms: score on the 12-item depression subscale of the 15-item Geriatric Depression Scale (GDS-12D) and any apathy score.

d Isolated depressive symptoms: score on the GDS-12D in participants with ≤1 apathy symptoms (GDS-3A≤1).

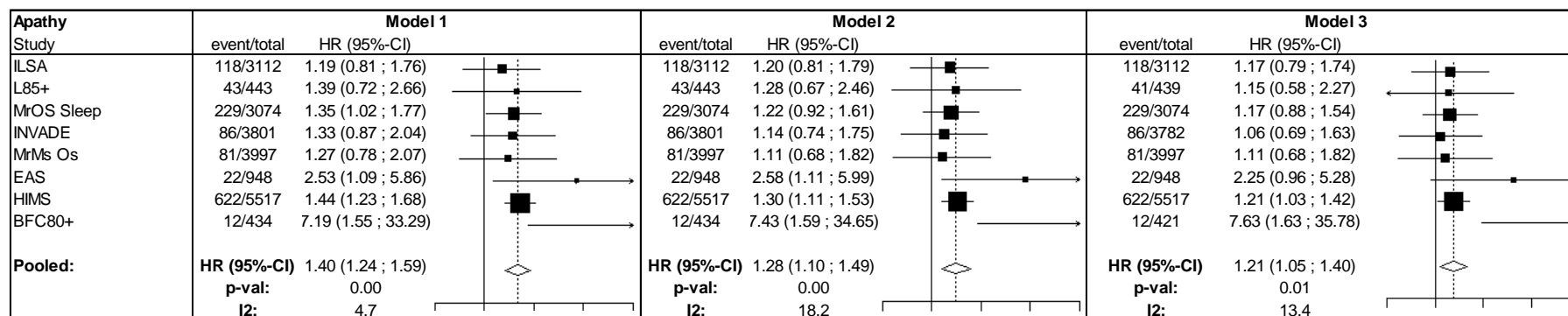
e Unadjusted.

f Adjusted for baseline age and sex.

g Adjusted for baseline age, sex, and history of myocardial infarction and/or stroke. * Studies included in analysis: Model 1, 2, and 3: BFC80+, EAS, HIMS, ILSA, INVADE, L85+, MrMs Os, MrOS Sleep. ** Studies included in analysis: Model 1, 2, and 3: BFC80+, EAS, HIMS, ILSA, INVADE, InveCe.Ab, L85+, MAS, MrMs Os, MrOS Sleep.

*** Studies included in analysis: Model 1 and 2: BFC80+, CSHA, EAS, HCS, HIMS, HKOOS, ICARe Dicomano (apathy analysis only because of unavailable depression scores), ILSA, INVADE, InveCe.Ab, L85+, MAS, MrMs Os, MrOS Sleep, OGC, SABE-Brazil, SLAS1, SLAS2, SCDS, SOF, Trelong; Model 3: BFC80+, EAS, HIMS, ILSA, INVADE, InveCe.Ab, L85+, MAS, MrMs Os, MrOS Sleep, SCDS, SLAS1, SLAS2, SOF (unavailable history of myocardial infarction and/or stroke for the other studies)

Supplementary Figures 1A-D. Forest plots for the associations of apathy and depressive symptoms with subsequent myocardial infarction per study



Supplementary Figure 1A Hazard ratios for myocardial infarction per study for apathy symptoms (a score of ≥ 2 on the GDS-3A and any depression score). HRs calculated per study using fixed effect Cox regression. Pooled HR and 95% value calculated using inverse-variance weighted DerSimonian and Laird random effects meta-analysis of separate study estimates (these differ from HRs obtained in one-stage analyses).

Model 1: HR for myocardial infarction for apathy symptoms, Model 2: adjusted for age and sex, Model 3: additionally adjusted for history of myocardial infarction and/or stroke.

Abbreviations: GDS-3A, 3-item apathy subscale of the 15-item Geriatric Depression Scale; HR, hazard ratio; 95%-CI, 95% confidence intervals

Isolated apathy Study	Model 1			Model 2			Model 3		
	event/total	HR (95%-CI)		event/total	HR (95%-CI)		event/total	HR (95%-CI)	
ILSA	50/1272	1.95 (1.02 ; 3.74)		50/1272	1.89 (0.98 ; 3.67)		50/1272	1.81 (0.93 ; 3.52)	
L85+	30/334	1.81 (0.80 ; 4.07)		30/334	1.70 (0.76 ; 3.84)		28/331	1.48 (0.63 ; 3.52)	
MrOS Sleep	197/2587	1.61 (1.18 ; 2.18)		197/2587	1.43 (1.05 ; 1.96)		197/2587	1.38 (1.01 ; 1.88)	
INVADE	67/2884	1.30 (0.80 ; 2.12)		67/2884	1.09 (0.66 ; 1.79)		67/2873	1.02 (0.62 ; 1.69)	
MrMs Os	40/2104	1.25 (0.55 ; 2.82)		40/2104	1.07 (0.47 ; 2.43)		40/2104	1.06 (0.47 ; 2.41)	
EAS	18/728	3.24 (1.29 ; 8.17)		18/728	3.17 (1.25 ; 8.01)		18/728	2.90 (1.13 ; 7.42)	
HIMS	451/4285	1.32 (1.09 ; 1.59)		451/4285	1.19 (0.99 ; 1.44)		451/4285	1.13 (0.93 ; 1.37)	
BFC80+	8/273	6.03 (1.17 ; 31.07)		8/273	6.06 (1.17 ; 31.4)		8/266	7.45 (1.44 ; 38.64)	
Pooled:	HR (95%-CI)	1.52 (1.26 ; 1.84)		HR (95%-CI)	1.41 (1.13 ; 1.76)		HR (95%-CI)	1.35 (1.07 ; 1.71)	
	p-val:	0.00		p-val:	0.00		p-val:	0.01	
	I2:	19.1		I2:	32.8		I2:	37.2	

Supplementary Figure 1B Hazard ratios for myocardial infarction per study for isolated apathy symptoms (a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1)). HRs calculated per study using fixed effect Cox regression. Pooled HR and 95% value calculated using inverse-variance weighted DerSimonian and Laird random effects meta-analysis of separate study estimates (these differ from HRs obtained in one-stage analyses). Model 1: HR for myocardial infarction for isolated apathy symptoms, Model 2: adjusted for age and sex, Model 3: additionally adjusted for history of myocardial infarction and/or stroke.

Abbreviations: GDS-3A, 3-item apathy subscale of the 15-item Geriatric Depression Scale; GDS-12D, 12-item depression subscale of the 15-item Geriatric Depression Scale; HR, hazard ratio; 95%-CI, 95% confidence intervals.

Depression Study	Model 1			Model 2			Model 3		
	event/total	HR (95%-CI)		event/total	HR (95%-CI)		event/total	HR (95%-CI)	
ILSA	107/2925	0.97 (0.66 ; 1.42)		107/2925	1.02 (0.69 ; 1.51)		107/2925	1.00 (0.68 ; 1.49)	
L85+	43/443	1.43 (0.74 ; 2.74)		43/443	1.50 (0.78 ; 2.87)		41/439	1.62 (0.84 ; 3.13)	
MrOS Sleep	229/3075	0.97 (0.67 ; 1.41)		229/3075	0.90 (0.62 ; 1.32)		229/3075	0.87 (0.59 ; 1.26)	
INVADE	88/3797	0.88 (0.52 ; 1.47)		88/3797	0.81 (0.48 ; 1.36)		88/3779	0.77 (0.46 ; 1.30)	
MrMs Os	81/3997	1.16 (0.75 ; 1.79)		81/3997	1.16 (0.75 ; 1.80)		81/3997	1.16 (0.75 ; 1.80)	
EAS	22/948	0.85 (0.29 ; 2.52)		22/948	0.93 (0.31 ; 2.76)		22/948	0.88 (0.29 ; 2.61)	
HIMS	622/5510	1.48 (1.24 ; 1.76)		622/5510	1.40 (1.18 ; 1.68)		622/5510	1.30 (1.08 ; 1.55)	
BFC80+	12/434	0.99 (0.29 ; 3.37)		12/434	1.01 (0.29 ; 3.48)		12/421	1.03 (0.30 ; 3.54)	
Pooled:	HR (95%-CI)	1.16 (0.96 ; 1.39)		HR (95%-CI)	1.15 (0.97 ; 1.36)		HR (95%-CI)	1.12 (0.95 ; 1.31)	
	p-val:	0.12		p-val:	0.12		p-val:	0.17	
	I²:	27.8		I²:	20.6		I²:	12.3	

Supplementary Figure 1C Hazard ratios for myocardial infarction per study for depressive symptoms (a score of ≥ 2 on the GDS-12D and any apathy score). HRs calculated per study using fixed effect Cox regression. Pooled HR and 95% value calculated using inverse-variance weighted DerSimonian and Laird random effects meta-analysis of separate study estimates (these differ from HRs obtained in one-stage analyses).

Model 1: HR for myocardial infarction for depressive symptoms, Model 2: adjusted for age and sex, Model 3: additionally adjusted for history of myocardial infarction and/or stroke.

Abbreviations: GDS-12D, 12-item depression subscale of the 15-item Geriatric Depression Scale; HR, hazard ratio; 95%-CI, 95% confidence intervals.

Isolated depression Study	Model 1			Model 2			Model 3		
	event/total	HR (95%-CI)		event/total	HR (95%-CI)		event/total	HR (95%-CI)	
ILSA	72/2002	1.14 (0.71 ; 1.81)		72/2002	1.19 (0.74 ; 1.91)		72/2002	1.17 (0.72 ; 1.88)	
L85+	30/331	1.85 (0.82 ; 4.16)		30/331	2.15 (0.95 ; 4.87)		29/329	2.28 (1.00 ; 5.19)	
MrOS Sleep	153/2173	1.35 (0.78 ; 2.33)		153/2173	1.28 (0.74 ; 2.22)		153/2173	1.24 (0.71 ; 2.15)	
INVADE	44/2214	0.49 (0.15 ; 1.59)		44/2214	0.50 (0.15 ; 1.62)		44/2206	0.48 (0.15 ; 1.56)	
MrMs Os	59/3102	1.12 (0.67 ; 1.87)		59/3102	1.14 (0.68 ; 1.90)		59/3102	1.14 (0.68 ; 1.92)	
EAS	10/642	0.98 (0.12 ; 7.76)		10/642	1.03 (0.13 ; 8.11)		10/642	1.05 (0.13 ; 8.30)	
HIMS	311/3143	1.26 (0.91 ; 1.75)		311/3143	1.21 (0.87 ; 1.68)		311/3143	1.15 (0.83 ; 1.60)	
BFC80+	3/263	∞		3/263	∞		3/255	∞	
Pooled:	HR (95%-CI)	1.21 (0.99 ; 1.49)		HR (95%-CI)	1.21 (0.98 ; 1.49)		HR (95%-CI)	1.18 (0.96 ; 1.46)	
	p-val:	0.07		p-val:	0.07		p-val:	0.11	
	I²:	0.0		I²:	0.0		I²:	0.0	

Supplementary Figure 1D Hazard ratios for myocardial infarction per study for isolated depressive symptoms (a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1)). HRs calculated per study using fixed effect Cox regression. Pooled HR and 95% value calculated using inverse-variance weighted DerSimonian and Laird random effects meta-analysis of separate study estimates (these differ from HRs obtained in one-stage analyses).

Model 1: HR for myocardial infarction for isolated depressive symptoms, Model 2: adjusted for age and sex, Model 3: additionally adjusted for history of myocardial infarction and/or stroke.

Abbreviations: GDS-3A, 3-item apathy subscale of the 15-item Geriatric Depression Scale; GDS-12D, 12-item depression subscale of the 15-item Geriatric Depression Scale; HR, hazard ratio; 95%-CI, 95% confidence intervals; ∞, inestimable within study.

Supplementary Figures 2A-D. Forest plots for the associations of apathy and depressive symptoms with subsequent stroke per study

Apathy Study	Model 1			Model 2			Model 3		
	event/total	HR (95%-CI)		event/total	HR (95%-CI)		event/total	HR (95%-CI)	
ILSA	146/3114	1.48 (1.06 ; 2.06)		146/3114	1.40 (0.99 ; 1.97)		146/3112	1.30 (0.92 ; 1.83)	
L85+	45/445	1.49 (0.79 ; 2.80)		45/445	1.46 (0.78 ; 2.76)		45/440	1.33 (0.71 ; 2.52)	
MrOS Sleep	194/3073	1.35 (1.00 ; 1.82)		194/3073	1.16 (0.85 ; 1.56)		194/3073	1.12 (0.83 ; 1.52)	
MAS	15/891	1.81 (0.64 ; 5.07)		15/891	1.43 (0.50 ; 4.10)		15/879	1.40 (0.49 ; 4.04)	
INVADE	200/3801	1.60 (1.21 ; 2.11)		200/3801	1.29 (0.97 ; 1.71)		200/3782	1.26 (0.95 ; 1.67)	
MrMs Os	173/3997	1.52 (1.10 ; 2.10)		173/3997	1.38 (1.00 ; 1.91)		173/3997	1.35 (0.98 ; 1.88)	
EAS	37/960	1.64 (0.85 ; 3.15)		37/960	1.61 (0.84 ; 3.09)		37/960	1.39 (0.72 ; 2.71)	
HIMS	600/5499	2.03 (1.73 ; 2.39)		600/5499	1.82 (1.55 ; 2.15)		600/5499	1.71 (1.45 ; 2.02)	
InveCe.Ab	14/1059	∞		14/1059	∞		14/1058	∞	
BFC80+	25/445	1.73 (0.79 ; 3.80)		25/445	1.79 (0.81 ; 3.95)		25/432	1.74 (0.78 ; 3.86)	
Pooled:	HR (95%-CI)	1.71 (1.54 ; 1.91)		HR (95%-CI)	1.49 (1.32 ; 1.69)		HR (95%-CI)	1.45 (1.30 ; 1.61)	
	p-val:	0.00		p-val:	0.00		p-val:	0.00	
	I²:	0.0		I²:	10.2		I²:	0.0	

Supplementary Figure 2A Hazard ratios for stroke per study for apathy symptoms (a score of ≥ 2 on the GDS-3A and any depression score). HRs calculated per study using fixed effect Cox regression. Pooled HR and 95% value calculated using inverse-variance weighted DerSimonian and Laird random effects meta-analysis of separate study estimates (these differ from HRs obtained in one-stage analyses).

Model 1: HR for stroke for apathy symptoms, Model 2: adjusted for age and sex, Model 3: additionally adjusted for history of myocardial infarction and/or stroke.

Abbreviations: GDS-3A, 3-item apathy subscale of the 15-item Geriatric Depression Scale; HR, hazard ratio; 95%-CI, 95% confidence intervals; ∞, inestimable within study.

Isolated apathy Study	Model 1			Model 2			Model 3		
	event/total	HR (95%-CI)		event/total	HR (95%-CI)		event/total	HR (95%-CI)	
ILSA	50/1274	0.70 (0.28 ; 1.75)	←	50/1274	0.59 (0.23 ; 1.51)	←	50/1272	0.58 (0.23 ; 1.49)	←
L85+	36/335	1.26 (0.55 ; 2.87)	←	36/335	1.26 (0.55 ; 2.87)	←	36/331	1.14 (0.50 ; 2.62)	←
MrOS Sleep	158/2583	1.51 (1.07 ; 2.13)	←	158/2583	1.29 (0.91 ; 1.83)	←	158/2583	1.25 (0.88 ; 1.77)	←
MAS	15/753	2.20 (0.78 ; 6.19)	→	15/753	1.70 (0.59 ; 4.90)	←	15/742	1.65 (0.57 ; 4.79)	←
INVADE	131/2884	1.39 (0.98 ; 1.98)	←	131/2884	1.14 (0.80 ; 1.63)	←	131/2873	1.12 (0.79 ; 1.60)	←
MrMs Os	77/2104	1.83 (1.08 ; 3.10)	←	77/2104	1.60 (0.94 ; 2.73)	←	77/2104	1.59 (0.93 ; 2.71)	←
EAS	25/735	1.58 (0.68 ; 3.65)	←	25/735	1.57 (0.68 ; 3.65)	←	25/735	1.40 (0.59 ; 3.31)	←
HIMS	410/4271	1.72 (1.41 ; 2.09)	←	410/4271	1.52 (1.25 ; 1.85)	←	410/4271	1.46 (1.19 ; 1.77)	←
InveCe.Ab	12/709	∞	←	12/709	∞	←	12/708	∞	←
BFC80+	14/280	1.80 (0.63 ; 5.19)	←	14/280	1.90 (0.65 ; 5.53)	←	14/273	1.87 (0.63 ; 5.55)	←
Pooled:	HR (95%-CI)	1.59 (1.39 ; 1.83)		HR (95%-CI)	1.39 (1.21 ; 1.60)		HR (95%-CI)	1.34 (1.17 ; 1.54)	
	p-val:	0.00		p-val:	0.00		p-val:	0.00	
	I²:	0.0		I²:	0.0		I²:	0.0	

Supplementary Figure 2B Hazard ratios for stroke per study for isolated apathy symptoms (a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1)). HRs calculated per study using fixed effect Cox regression. Pooled HR and 95% value calculated using inverse-variance weighted DerSimonian and Laird random effects meta-analysis of separate study estimates (these differ from HRs obtained in one-stage analyses). Model 1: HR for stroke for isolated apathy symptoms, Model 2: adjusted for age and sex, Model 3: additionally adjusted for history of myocardial infarction and/or stroke.

Abbreviations: GDS-3A, 3-item apathy subscale of the 15-item Geriatric Depression Scale; GDS-12D, 12-item depression subscale of the 15-item Geriatric Depression Scale; HR, hazard ratio; 95%-CI, 95% confidence intervals; ∞, inestimable within study.

Depression Study	Model 1			Model 2			Model 3		
	event/total	HR (95%-CI)		event/total	HR (95%-CI)		event/total	HR (95%-CI)	
ILSA	132/2927	1.38 (0.97 ; 1.96)		132/2927	1.39 (0.97 ; 1.99)		132/2925	1.33 (0.93 ; 1.91)	
L85+	45/445	0.81 (0.39 ; 1.68)		45/445	0.82 (0.40 ; 1.71)		45/440	0.84 (0.40 ; 1.74)	
MrOS Sleep	194/3074	1.35 (0.94 ; 1.95)		194/3074	1.22 (0.85 ; 1.75)		194/3074	1.18 (0.82 ; 1.70)	
MAS	15/891	∞		15/891	∞		15/879	∞	
INVADE	198/3797	1.69 (1.26 ; 2.28)		198/3797	1.46 (1.08 ; 1.97)		198/3779	1.45 (1.07 ; 1.95)	
MrMs Os	173/3997	1.41 (1.05 ; 1.91)		173/3997	1.39 (1.03 ; 1.88)		173/3997	1.36 (1.01 ; 1.84)	
EAS	37/959	1.75 (0.88 ; 3.49)		37/959	1.72 (0.86 ; 3.42)		37/959	1.62 (0.81 ; 3.25)	
HIMS	597/5492	1.81 (1.52 ; 2.16)		597/5492	1.71 (1.44 ; 2.04)		597/5492	1.60 (1.34 ; 1.90)	
InveCe.Ab	14/1059	0.33 (0.07 ; 1.48)		14/1059	0.32 (0.07 ; 1.45)		14/1058	0.31 (0.07 ; 1.39)	
BFC80+	25/445	1.35 (0.61 ; 2.98)		25/445	1.37 (0.62 ; 3.04)		25/432	1.40 (0.63 ; 3.09)	
Pooled:	HR (95%-CI)	1.50 (1.29 ; 1.75)		HR (95%-CI)	1.44 (1.25 ; 1.66)		HR (95%-CI)	1.43 (1.27 ; 1.60)	
	p-val:	0.00		p-val:	0.00		p-val:	0.00	
	I²:	25.6		I²:	16.5		I²:	0.0	

Supplementary Figure 2C Hazard ratios for stroke per study for depressive symptoms (a score of ≥ 2 on the GDS-12D and any apathy score). HRs calculated per study using fixed effect Cox regression. Pooled HR and 95% value calculated using inverse-variance weighted DerSimonian and Laird random effects meta-analysis of separate study estimates (these differ from HRs obtained in one-stage analyses).

Model 1: HR for stroke for depressive symptoms, Model 2: adjusted for age and sex, Model 3: additionally adjusted for history of myocardial infarction and/or stroke.

Abbreviations: GDS-12D, 12-item depression subscale of the 15-item Geriatric Depression Scale; HR, hazard ratio; 95%-CI, 95% confidence intervals; ∞ , inestimable within study.

Isolated depression Study	Model 1			Model 2			Model 3		
	event/total	HR (95%-CI)		event/total	HR (95%-CI)		event/total	HR (95%-CI)	
ILSA	83/2006	1.08 (0.70 ; 1.66)		83/2006	1.07 (0.69 ; 1.66)		83/2004	1.05 (0.68 ; 1.64)	
L85+	31/332	0.35 (0.08 ; 1.47)		31/332	0.35 (0.08 ; 1.46)		31/329	0.38 (0.09 ; 1.59)	
MrOS Sleep	129/2169	1.90 (1.12 ; 3.20)		129/2169	1.80 (1.06 ; 3.04)		129/2169	1.74 (1.03 ; 2.95)	
MAS	6/473	∞		6/473	∞		6/466	∞	
INVADE	94/2214	1.40 (0.81 ; 2.39)		94/2214	1.32 (0.77 ; 2.26)		94/2206	1.31 (0.77 ; 2.26)	
MrMs Os	120/3102	1.47 (1.03 ; 2.11)		120/3102	1.47 (1.03 ; 2.11)		120/3102	1.44 (1.00 ; 2.06)	
EAS	21/648	1.82 (0.61 ; 5.43)		21/648	1.75 (0.58 ; 5.23)		21/648	1.61 (0.52 ; 4.95)	
HIMS	252/3134	1.17 (0.80 ; 1.70)		252/3134	1.11 (0.76 ; 1.62)		252/3134	1.08 (0.74 ; 1.57)	
InveCe.Ab	14/943	0.45 (0.10 ; 2.00)		14/943	0.45 (0.10 ; 2.03)		14/943	0.43 (0.10 ; 1.91)	
BFC80+	12/270	1.33 (0.40 ; 4.40)		12/270	1.31 (0.39 ; 4.36)		12/262	1.32 (0.39 ; 4.43)	
Pooled:	HR (95%-CI)	1.30 (1.08 ; 1.56)		HR (95%-CI)	1.27 (1.05 ; 1.52)		HR (95%-CI)	1.24 (1.03 ; 1.49)	
	p-val:	0.01		p-val:	0.01		p-val:	0.02	
	I²:	1.1		I²:	0.0		I²:	0.0	

Supplementary Figure 2D Hazard ratios for stroke per study for isolated depressive symptoms (a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1)). HRs calculated per study using fixed effect Cox regression. Pooled HR and 95% value calculated using inverse-variance weighted DerSimonian and Laird random effects meta-analysis of separate study estimates (these differ from HRs obtained in one-stage analyses). Model 1: HR for stroke for isolated depressive symptoms, Model 2: adjusted for age and sex, Model 3: additionally adjusted for history of myocardial infarction and/or stroke.

Abbreviations: GDS-3A, 3-item apathy subscale of the 15-item Geriatric Depression Scale; GDS-12D, 12-item depression subscale of the 15-item Geriatric Depression Scale; HR, hazard ratio; 95%-CI, 95% confidence intervals; ∞, inestimable within study.

Supplementary Figures 3A-D. Forest plots for the associations of apathy and depressive symptoms with all-cause mortality per study

Apathy Study	Model 1			Model 2			Model 3		
	event/total	HR (95%-CI)	forest plot	event/total	HR (95%-CI)	forest plot	event/total	HR (95%-CI)	forest plot
ILSA	1256/3114	1.77 (1.58 ; 1.98)		1256/3114	1.61 (1.43 ; 1.80)		1255/3112	1.55 (1.38 ; 1.74)	
L85+	424/445	1.31 (1.06 ; 1.63)		424/445	1.29 (1.04 ; 1.61)		419/440	1.23 (0.99 ; 1.54)	
MrOS Sleep	1055/3028	1.84 (1.62 ; 2.08)		1055/3028	1.49 (1.31 ; 1.69)		1055/3028	1.44 (1.27 ; 1.63)	
MAS	235/1030	1.80 (1.39 ; 2.34)		235/1030	1.45 (1.11 ; 1.89)		233/1017	1.43 (1.10 ; 1.87)	
SABE - Brazil	813/1689	1.42 (1.21 ; 1.67)		813/1689	1.40 (1.19 ; 1.64)		-	-	
INVADE	870/3801	2.03 (1.78 ; 2.33)		870/3801	1.64 (1.43 ; 1.88)		862/3782	1.59 (1.39 ; 1.83)	
MrMs Os	970/3998	1.32 (1.14 ; 1.52)		970/3998	1.20 (1.04 ; 1.38)		970/3998	1.19 (1.03 ; 1.37)	
OCG	658/1250	1.85 (1.58 ; 2.17)		658/1250	1.59 (1.35 ; 1.87)		-	-	
SLAS I	327/2788	1.80 (1.32 ; 2.47)		327/2788	1.63 (1.19 ; 2.23)		326/2784	1.56 (1.14 ; 2.16)	
SLAS II	142/3263	4.13 (2.29 ; 7.47)		142/3263	2.63 (1.44 ; 4.79)		142/3261	2.50 (1.37 ; 4.56)	
HCS	350/874	1.70 (1.34 ; 2.16)		350/874	1.65 (1.30 ; 2.09)		-	-	
EAS	732/1920	1.60 (1.38 ; 1.85)		732/1920	1.53 (1.32 ; 1.77)		732/1920	1.48 (1.28 ; 1.71)	
HKOOS	712/1457	1.50 (1.27 ; 1.77)		712/1457	1.31 (1.11 ; 1.55)		-	-	
HIMS	1651/5517	1.97 (1.79 ; 2.18)		1651/5517	1.74 (1.58 ; 1.92)		1651/5517	1.68 (1.52 ; 1.86)	
InveCe.Ab	45/1262	1.46 (0.65 ; 3.26)		45/1262	1.66 (0.73 ; 3.79)		45/1260	1.70 (0.75 ; 3.88)	
CSHA	529/1355	1.97 (1.66 ; 2.34)		526/1349	1.70 (1.43 ; 2.02)		-	-	
ICARe Dicomano	177/634	1.74 (1.28 ; 2.35)		177/634	1.36 (0.99 ; 1.88)		-	-	
SCDS	304/1712	1.56 (1.24 ; 1.97)		304/1712	1.36 (1.08 ; 1.73)		304/1710	1.36 (1.08 ; 1.72)	
BFC80+	201/499	1.58 (1.20 ; 2.08)		201/499	1.43 (1.08 ; 1.88)		196/481	1.43 (1.08 ; 1.90)	
SOF	3797/6591	1.81 (1.69 ; 1.94)		3797/6591	1.49 (1.39 ; 1.60)		3794/6588	1.44 (1.34 ; 1.54)	
Trelong	367/575	2.21 (1.80 ; 2.71)	367/575	1.93 (1.55 ; 2.40)	-	-			
Pooled:	HR (95%-CI)	1.73 (1.62 ; 1.85)	HR (95%-CI)	1.52 (1.44 ; 1.60)	HR (95%-CI)	1.46 (1.38 ; 1.56)			
	p-val:	0.00	p-val:	0.00	p-val:	0.00			
	I²:	68.2	I²:	48.4	I²:	46.7			

Supplementary Figure 3A Hazard ratios for mortality per study for apathy symptoms (a score of ≥ 2 on the GDS-3A and any depression score). HRs calculated per study using fixed effect Cox regression. Pooled HR and 95% value calculated using inverse-variance weighted DerSimonian and Laird random effects meta-analysis of separate study estimates (these differ from HRs obtained in one-stage analyses).

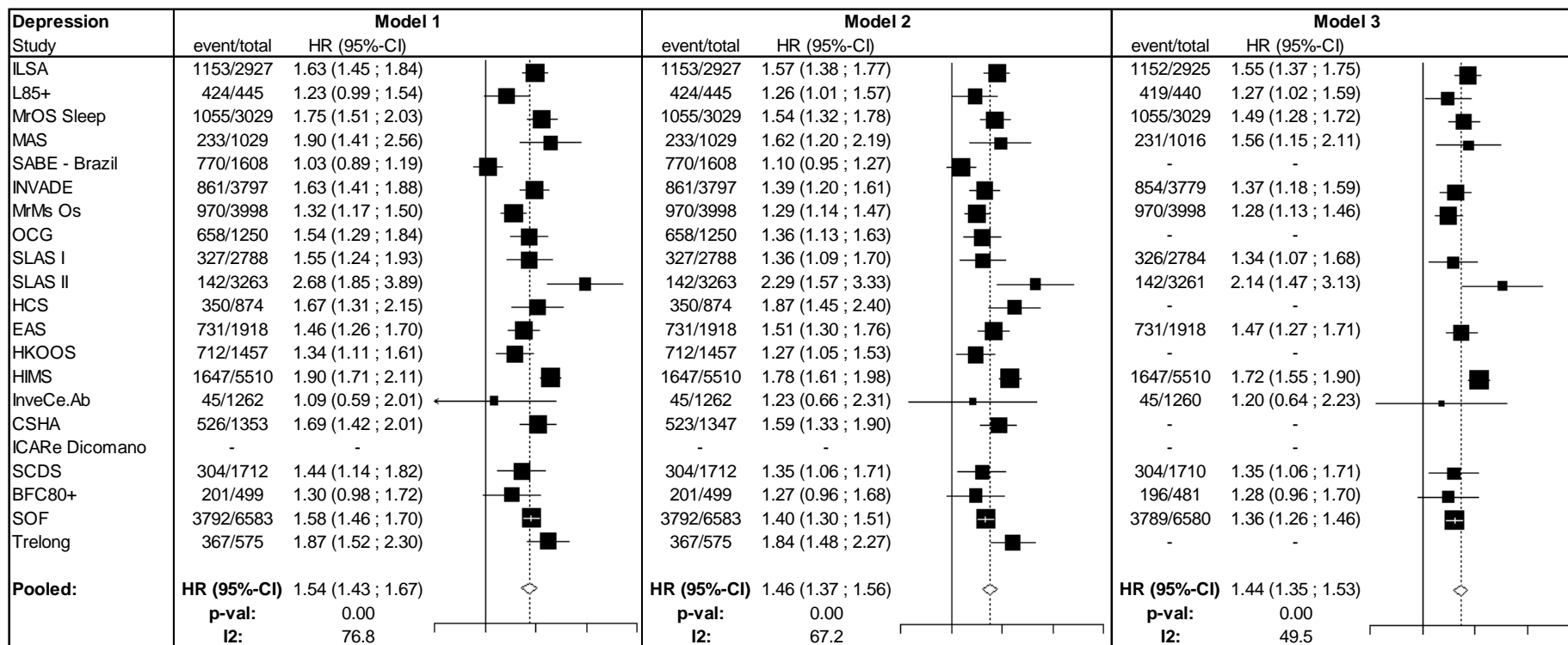
Model 1: HR for mortality for apathy symptoms, Model 2: adjusted for age and sex, Model 3: additionally adjusted for history of myocardial infarction and/or stroke.

Abbreviations: GDS-3A, 3-item apathy subscale of the 15-item Geriatric Depression Scale; HR, hazard ratio; 95%-CI, 95% confidence intervals

Isolated apathy Study	Model 1			Model 2			Model 3		
	event/total	HR (95%-CI)		event/total	HR (95%-CI)		event/total	HR (95%-CI)	
ILSA	404/1274	1.82 (1.44 ; 2.31)		404/1274	1.62 (1.28 ; 2.06)		403/1272	1.60 (1.26 ; 2.04)	
L85+	317/335	1.44 (1.09 ; 1.90)		317/335	1.48 (1.12 ; 1.96)		313/331	1.39 (1.04 ; 1.85)	
MrOS Sleep	827/2561	1.70 (1.46 ; 1.97)		827/2561	1.36 (1.17 ; 1.58)		827/2561	1.33 (1.14 ; 1.54)	
MAS	176/864	1.93 (1.43 ; 2.60)		176/864	1.52 (1.12 ; 2.05)		174/852	1.49 (1.09 ; 2.02)	
SABE - Brazil	404/858	1.65 (1.20 ; 2.26)		404/858	1.39 (1.01 ; 1.91)		-	-	
INVADE	587/2884	1.81 (1.54 ; 2.13)		587/2884	1.52 (1.29 ; 1.79)		583/2873	1.47 (1.24 ; 1.73)	
MrMs Os	452/2105	1.30 (1.02 ; 1.66)		452/2105	1.12 (0.88 ; 1.42)		452/2105	1.11 (0.87 ; 1.42)	
OCG	158/367	1.55 (1.12 ; 2.15)		158/367	1.24 (0.89 ; 1.73)		-	-	
SLAS I	197/1944	2.16 (1.14 ; 4.08)		197/1944	2.01 (1.06 ; 3.80)		197/1942	1.94 (1.03 ; 3.68)	
SLAS II	104/2898	3.00 (0.95 ; 9.48)		104/2898	1.66 (0.52 ; 5.29)		104/2896	1.50 (0.47 ; 4.80)	
HCS	269/720	1.44 (1.05 ; 1.98)		269/720	1.36 (0.98 ; 1.87)		-	-	
EAS	449/1357	1.64 (1.36 ; 1.99)		449/1357	1.49 (1.23 ; 1.80)		449/1357	1.45 (1.19 ; 1.76)	
HKOOS	136/309	1.34 (0.95 ; 1.87)		136/309	1.17 (0.83 ; 1.66)		-	-	
HIMS	1112/4285	1.72 (1.53 ; 1.94)		1112/4285	1.51 (1.34 ; 1.70)		1112/4285	1.47 (1.31 ; 1.66)	
InveCe.Ab	29/845	2.61 (0.62 ; 11.01)		29/845	3.12 (0.74 ; 13.22)		29/843	3.62 (0.84 ; 15.54)	
CSHA	318/937	2.04 (1.62 ; 2.57)		318/936	1.58 (1.25 ; 2.00)		-	-	
ICARe Dicomano	-	-		-	-		-	-	
SCDS	108/741	1.27 (0.86 ; 1.88)		108/741	1.20 (0.81 ; 1.79)		108/741	1.20 (0.81 ; 1.79)	
BFC80+	116/313	1.74 (1.20 ; 2.53)		116/313	1.65 (1.14 ; 2.40)		112/302	1.68 (1.15 ; 2.46)	
SOF	2873/5219	1.82 (1.67 ; 1.98)		2873/5219	1.49 (1.36 ; 1.62)		2870/5216	1.44 (1.32 ; 1.58)	
Trelong	162/303	2.10 (1.48 ; 2.99)		162/303	1.39 (0.95 ; 2.04)		-	-	
Pooled:	HR (95%-CI)	1.72 (1.63 ; 1.81)		HR (95%-CI)	1.46 (1.39 ; 1.53)		HR (95%-CI)	1.44 (1.36 ; 1.51)	
	p-val:	0.00		p-val:	0.00		p-val:	0.00	
	I²:	9.3		I²:	0.0		I²:	0.0	

Supplementary Figure 3B Hazard ratios for mortality per study for isolated apathy symptoms (a score of ≥ 2 on the GDS-3A in participants with ≤ 1 depressive symptoms (GDS-12D ≤ 1)). HRs calculated per study using fixed effect Cox regression. Pooled HR and 95% value calculated using inverse-variance weighted DerSimonian and Laird random effects meta-analysis of separate study estimates (these differ from HRs obtained in one-stage analyses). Model 1: HR for mortality for isolated apathy symptoms, Model 2: adjusted for age and sex, Model 3: additionally adjusted for history of myocardial infarction and/or stroke.

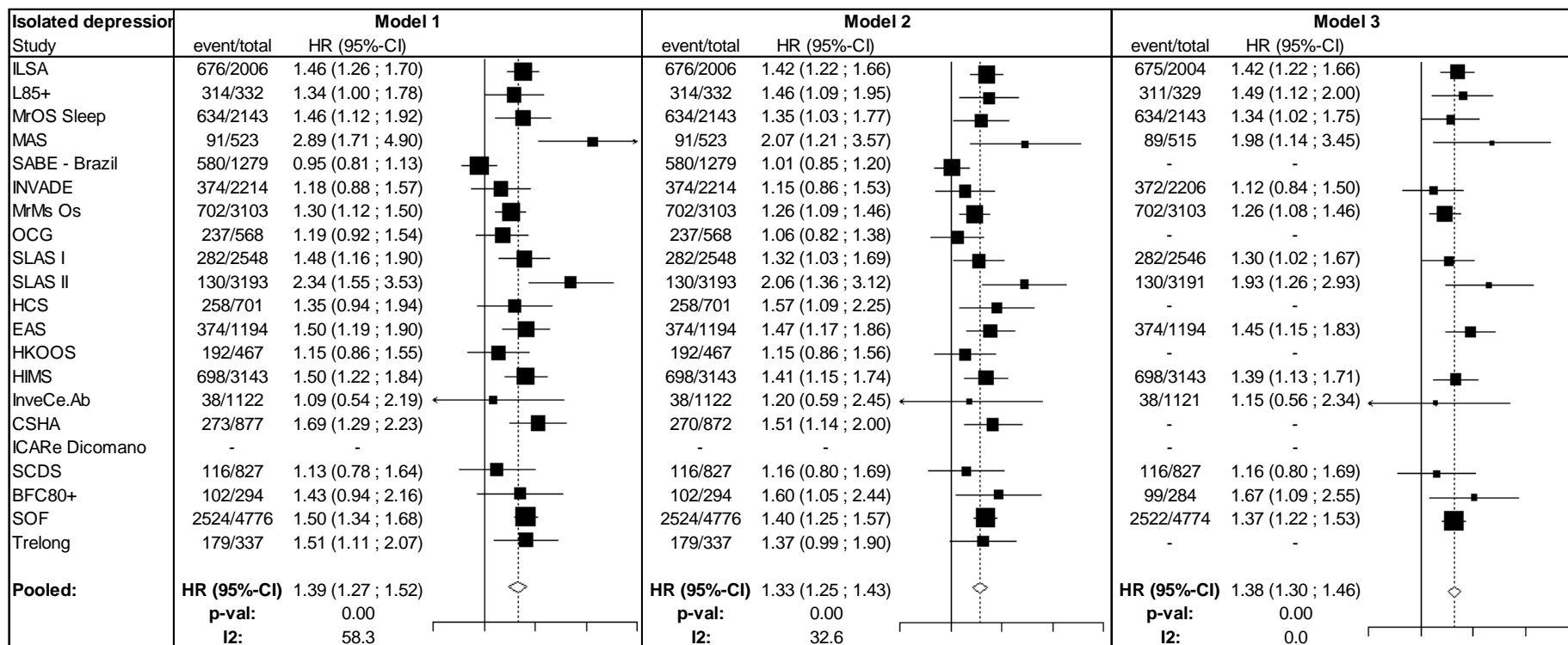
Abbreviations: GDS-3A, 3-item apathy subscale of the 15-item Geriatric Depression Scale; GDS-12D, 12-item depression subscale of the 15-item Geriatric Depression Scale; HR, hazard ratio; 95%-CI, 95% confidence intervals.



Supplementary Figure 3C Hazard ratios for mortality per study for depressive symptoms (a score of ≥ 2 on the GDS-12D and any apathy score). HRs calculated per study using fixed effect Cox regression. Pooled HR and 95% value calculated using inverse-variance weighted DerSimonian and Laird random effects meta-analysis of separate study estimates (these differ from HRs obtained in one-stage analyses).

Model 1: HR for mortality for depressive symptoms, Model 2: adjusted for age and sex, Model 3: additionally adjusted for history of myocardial infarction and/or stroke.

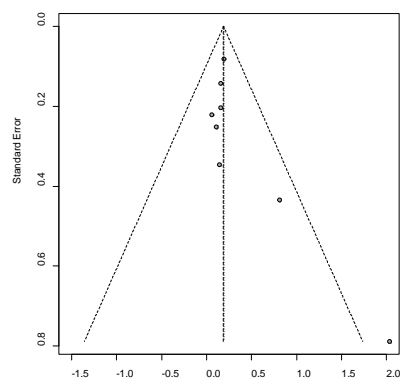
Abbreviations: GDS-12D, 12-item depression subscale of the 15-item Geriatric Depression Scale; HR, hazard ratio; 95%-CI, 95% confidence intervals.



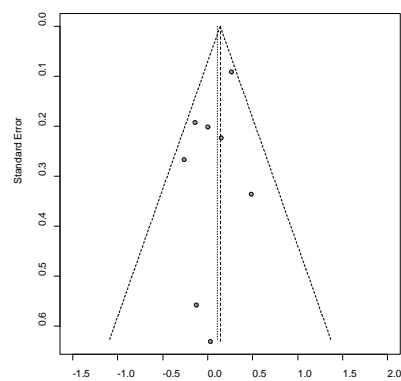
Supplementary Figure 3D Hazard ratios for mortality per study for isolated depressive symptoms (a score of ≥ 2 on the GDS-12D in participants with ≤ 1 apathy symptoms (GDS-3A ≤ 1)). HRs calculated per study using fixed effect Cox regression. Pooled HR and 95% value calculated using inverse-variance weighted DerSimonian and Laird random effects meta-analysis of separate study estimates (these differ from HRs obtained in one-stage analyses). Model 1: HR for mortality for isolated depressive symptoms, Model 2: adjusted for age and sex, Model 3: additionally adjusted for history of myocardial infarction and/or stroke.

Abbreviations: GDS-3A, 3-item apathy subscale of the 15-item Geriatric Depression Scale; GDS-12D, 12-item depression subscale of the 15-item Geriatric Depression Scale; HR, hazard ratio; 95%-CI, 95% confidence intervals.

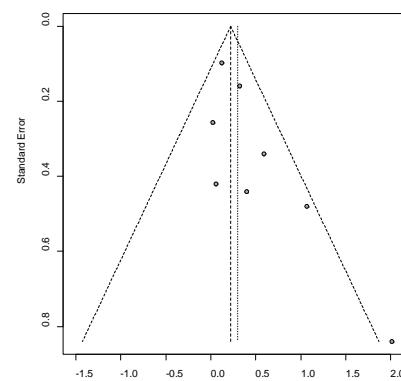
Supplementary Figures 4A-D. Funnel plots for the maximally adjusted associations of apathy and depressive symptoms with subsequent myocardial infarction



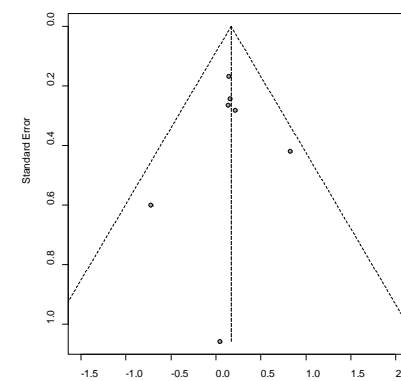
A



B



C

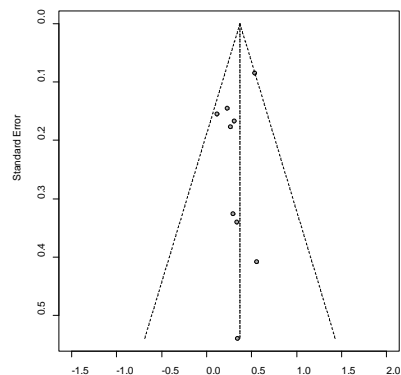


D

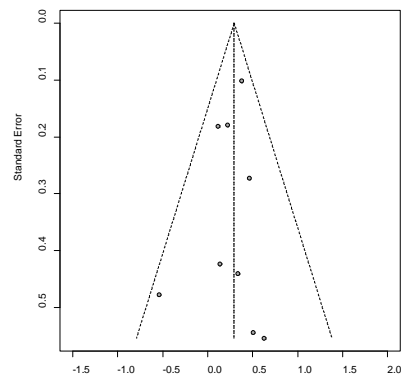
Supplementary Figures 4 A-D Hazard ratios for myocardial infarction per study for apathy symptoms (A), isolated apathy symptoms (B), depressive symptoms (C) and isolated depressive symptoms (D). HRs calculated per study using fixed effect Cox regression. Pooled HR and 95% value calculated using inverse-variance weighted DerSimonian and Laird random effects meta-analysis of separate study estimates (these differ from HRs obtained in one-stage analyses).

All analyses are adjusted for age, sex, history of myocardial infarction and/or stroke.

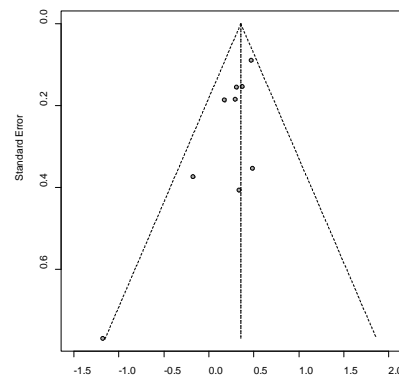
Supplementary Figures 5A-D. Funnel plots for the maximally adjusted associations of apathy and depressive symptoms with subsequent stroke



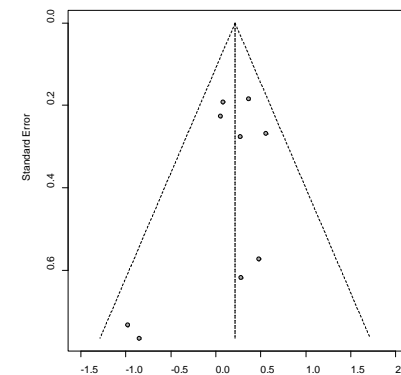
A



B



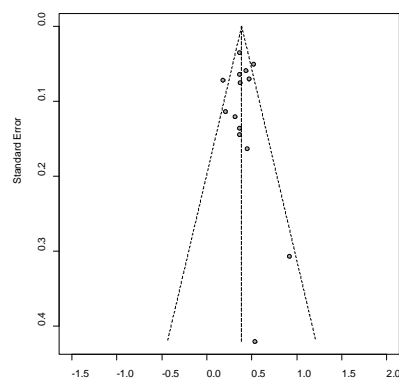
C



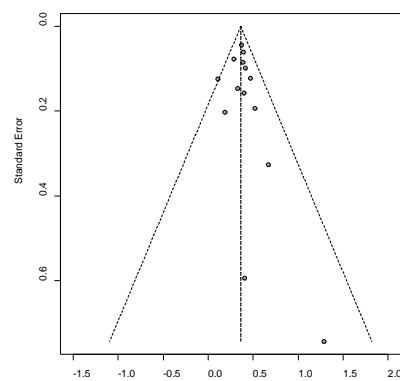
D

Supplementary Figures 5 Hazard ratios for stroke per study for apathy symptoms (A), isolated apathy symptoms (B), depressive symptoms (C) and isolated depressive symptoms (D) HRs calculated per study using fixed effect Cox regression. Pooled HR and 95% value calculated using inverse-variance weighted DerSimonian and Laird random effects meta-analysis of separate study estimates (these differ from HRs obtained in one-stage analyses). All analyses are adjusted for age, sex, history of myocardial infarction and/or stroke.

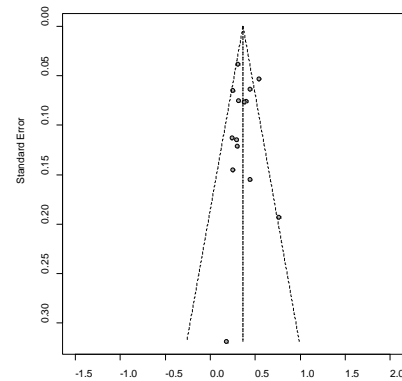
Supplementary Figures 6A-D. Funnel plots for the maximally adjusted associations of apathy and depressive symptoms with subsequent mortality



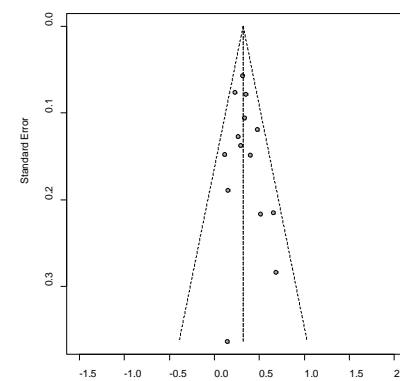
A



B



C



D

Supplementary Figures 6 Hazard ratios for mortality per study for apathy symptoms (A), isolated apathy symptoms (B), depressive symptoms (C) and isolated depressive symptoms (D) HRs calculated per study using fixed effect Cox regression. Pooled HR and 95% value calculated using inverse-variance weighted DerSimonian and Laird random effects meta-analysis of separate study estimates (these differ from HRs obtained in one-stage analyses). All analyses are adjusted for age, sex, history of myocardial infarction and/or stroke.

Supplementary Results 1. Details on provided Geriatric Depression Scale data

Study	GDS version
BFC80+	15-item Geriatric Depression Scale
CSHA	15-item Geriatric Depression Scale
EAS	15-item Geriatric Depression Scale
HIMS	15-item Geriatric Depression Scale
SABE - Brazil	15-item Geriatric Depression Scale
HCS	15-item Geriatric Depression Scale
HKOOS	15-item Geriatric Depression Scale
ICARe Dicomano	30-item Geriatric Depression Scale
INVADE	15-item Geriatric Depression Scale
InveCe.Ab	15-item Geriatric Depression Scale
ILSA	30-item Geriatric Depression Scale
L85+	15-item Geriatric Depression Scale
MrMs OS	15-item Geriatric Depression Scale
OGC	30-item Geriatric Depression Scale
MrOS Sleep	15-item Geriatric Depression Scale
SCDS	30-item Geriatric Depression Scale
SLAS I	15-item Geriatric Depression Scale
SLAS II	15-item Geriatric Depression Scale
SOF	15-item Geriatric Depression Scale
MAS	15-item Geriatric Depression Scale
Trelong	15-item Geriatric Depression Scale

Note 1. Due to time constraint in digitalizing individual Geriatric Depression Scale (GDS) items from paper case record forms, the ICARe Dicomano study could provide data on the 3 apathy items only within the original time frame of this meta-analysis and did not contribute data on the 12 depression items.

Note 2. In the MAS study the 15-item Geriatric Depression Scale (GDS-15) was used with a slightly modified version of item 9 (“Do you prefer to stay home at night rather than go out and do new things?”) instead of the more common one (“Do you prefer to stay at home rather than going out and doing new things?”).¹ In order to determine whether this would affect classification of depression, a statistical analysis was carried out on two data sets from the same sample, one with the GDS-15 containing the version used in MAS, and the other with the more common version. Using the same cut-point for depression (score ≥ 6) the results showed a high level of agreement between the two classifications (kappa = .931) with a total of only 4 false positives, and no false negatives, out of a sample of 354.¹

1. Brink TL. Geriatric Depression and Hypochondriasis - Incidence, Interaction, Assessment and Treatment. *Psychotherapy: Theory, Research & Practice*.1982;19(4):506-511

Supplementary Results 2. Assessment of availability bias

The 31 non-participating studies were smaller than the 21 study samples that were included in ICARA (mean number of individuals per study 1695 and 2268 respectively). Furthermore, individuals of non-participating studies were slightly older (mean of the reported mean age non-participating studies (n=24 studies, not obtainable from the literature for 7 non-participating studies): 76.7 years ; included study samples (n=21): 75.2 years) and more often female (mean proportion of females non-participating studies (n=31): 57.7%; included study samples (n=21): 52.1%).