

# 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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**Background:** Previous findings suggest that apathy symptoms independently of depressive symptoms measured using the Geriatric Depression Scale (GDS) are associated with cardiovascular disease (CVD) in older individuals.

**Aims:** To study whether apathy and depressive symptoms in older people are associated with future CVD, stroke, and mortality using individual patient-data meta-analysis.

**Methods:** Medline, Embase, and PsycInfo databases up to September 3, 2013, were systematically searched without language restrictions. We sought prospective studies with older (mean age  $\geq 65$  years) community-dwelling populations in which the GDS was employed and subsequent stroke and/or CVD were recorded to provide individual participant data. Apathy symptoms were defined as the three apathy-related subitems of the GDS, with depressive symptoms the remaining items. We used myocardial infarction (MI), stroke, and all-cause mortality as main outcomes. Analyses were adjusted for age, sex, and MI/stroke history. An adaptation of the Newcastle–Ottawa scale was used to evaluate bias. Hazard ratios were calculated using one-stage random-effect Cox regression models.

**Results:** Of the 52 eligible studies, 21 (40.4%) were included, comprising 47,625 older people (mean age [standard deviation] 74 [7.4] years), over a median follow-up of 8.8 years. Participants with apathy symptoms had a 21% higher risk of MI (95% confidence interval [CI] 1.08–1.36), a 37% higher risk of stroke (95% CI 1.18–1.59), and a 47% higher risk of all-cause mortality (95% CI 1.38–1.56). Participants with depressive symptoms had a comparably higher risk of stroke (HR 1.36, 95% CI 1.18–1.56) and all-cause mortality (HR 1.44, 95% CI 1.35–1.53), but not of MI (HR 1.08, 95% CI 0.91–1.29). Associations for isolated apathy and isolated depressive symptoms were comparable. Sensitivity analyses according to risk of bias yielded similar results.

**Conclusion:** Our findings stress the clinical importance of recognizing apathy independently of depressive symptoms, and could help physicians identify persons at increased risk of vascular disease.

**Keywords:** apathy, older people, depression, cardiovascular disease, meta-analysis, stroke, myocardial infarction

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## Introduction

A number of meta-analyses have reported that depression in older people is associated with an increased risk of cardiovascular disease (CVD).<sup>1–4</sup> From a clinical point of view, it is important that specific symptom clusters within depression might be differentially related to incident CVD.<sup>5–7</sup> One such symptom cluster is apathy, generally defined

as disrupted motivation, resulting in reduced goal-driven behavior, cognition, and emotion, although exact definitions vary. We found that in community-dwelling older people, a cluster of three motivational symptoms related to apathy within the 15-item Geriatric Depression Scale (GDS15)<sup>8–10</sup> was associated with an increased risk of incident CVD. There was no such association for the 12 remaining symptoms within the GDS15.<sup>11</sup>

This finding corroborated previously reported associations of apathy symptoms with a history of stroke, CVD, and concurrent cardiovascular (CV) risk factors.<sup>8,12</sup> These findings are consistent with the “vascular apathy” hypothesis, which supposes vascular factors play an important role in the etiology of apathy in later life.<sup>12</sup> Apathy symptoms can occur in both the context of depression and independently as an isolated syndrome of disturbed motivation,<sup>13</sup> reportedly occurring in around 10%–20% of community-dwelling older people.<sup>8,14–16</sup> However, apathy currently receives little prominence in diagnostic practice. Determining whether community-dwelling older people with apathy symptoms have an increased risk of CV events is important, since these individuals may be disinclined to engage actively in healthy behavior and be easily overlooked in general practice, because of a tendency to withdraw from medical care due to the nature of the condition.

To corroborate our findings regarding the relation between incident CVD and apathy symptoms, external validation is essential. For this purpose, the Initiative on Cardiovascular Disease Risk and Apathy (ICARA) was set up, which aimed to study the independent relationships of apathy and depressive symptoms with myocardial infarction (MI), stroke, and mortality risk, by pooling data from longitudinal cohort studies in community-dwelling older people worldwide. Given our previous findings and the vascular apathy hypothesis, we hypothesized that apathy and depressive symptoms would be independently and differentially associated with MI, stroke, and mortality risk.

## Methods

We conducted a participant-data meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses of Individual Participant Data (PRISMA-IPD) guidelines and the recommendations made by Riley et al for conducting IPD analyses.<sup>17,18</sup> The IPD protocol was registered in the PROSPERO database ([http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42014013087#.VWSK447tBc](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014013087#.VWSK447tBc), [Supplementary materials](#)). This study was judged exempt from review by

the Amsterdam Academic Medical Center Medical Ethics Committee.

## Search strategy and selection criteria

Using the Ovid platform, we searched the Medline, Embase, and PsycInfo databases up to and including September 3, 2013. We did not apply any language restrictions or restrictions on publication type or year. The full search strategy is described in the [Supplementary material](#). In short, we used relevant keywords to search for longitudinal studies employing any version of the GDS and containing longitudinal data on CVD (including peripheral arterial disease [PAD], angina pectoris, and MI) and/or stroke (including transient ischemic attack [TIA]). Furthermore, we screened the bibliographies of selected papers and contacted investigators of a potentially eligible study known through acquaintance.

We included published original research papers that studied samples of community-dwelling older people (mean age  $\geq 65$  years) representative of the general population, employed a GDS version in which the three apathy items previously identified through several principal-component analyses were included,<sup>8,9</sup> and investigated occurrence of stroke and/or CVD. There were no restrictions regarding duration of follow-up. Studies that included both community-dwelling and institutionalized participants were eligible only if they were able to distinguish between the two. We tried to maximize representation for the general population by excluding studies that selected participants based on frailty, disability, CV-risk profile, or any specific disease. We also excluded case-control studies, since the control groups of these studies are likely to form a particular selection, rather than a cohort representative of the general population. To balance the required demands of reference screening, study coordination, and data harmonization with the relevance of the data contribution we excluded dissertations, conference abstracts and studies with a sample size  $\leq 100$ .

Titles and abstracts of identified papers were screened independently by two reviewers (LE, JWD). Full texts of selected articles were retrieved and papers reporting on the same single study collated. Studies were assessed for eligibility independently by both reviewers. Discrepancies were resolved by consensus. A third reviewer was available for consultation where agreement could not be reached (ER). For studies that were cross-sectional but otherwise eligible, PubMed and the Internet were searched for any indication of longitudinal follow-up being available for the study population in question. If so, studies were considered eligible.

Authors of eligible studies were invited to contribute data for our analyses. A reminder was sent after 1 month.

## Data, definitions, and statistics

The variables requested and methods used to check data integrity are described in the [Supplementary materials](#). Unless reported there, all statistical analyses were prespecified.

### Apathy and depressive symptoms

We defined apathy symptoms as a score  $\geq 2$  on the three apathy items of the GDS15 apathy subscale (GDS3A): “Have you dropped many of your activities and interests?”, “Do you prefer to stay at home, rather than going out and doing new things?”, and “Do you feel full of energy?” (reverse-coded).<sup>8,9</sup> These items have been reported to have a sensitivity of 69% and a specificity of 85% to detect apathy based on the customary cutoff ( $>13$ ) of the 14-item apathy scale in older adults.<sup>12</sup> We defined depressive symptoms as a score  $\geq 2$  on the 12 remaining items of the GDS15 (GDS12D). For studies employing GDS versions with  $>15$  items, we selected the appropriate three and 12 items. We performed separate analyses for apathy symptoms, isolated apathy symptoms (concurrent GDS3A  $\geq 2$  and GDS12D  $\leq 1$ ), depressive symptoms, and isolated depressive symptoms (concurrent GDS12D  $\geq 2$  and GDS3A  $\leq 1$ ). These cutoffs were based on analyses in previous studies.<sup>11</sup> We conducted sensitivity analyses in which the more specific  $\geq 5$  cutoff for GDS12D depressive symptoms was used and isolated symptoms were defined as a score  $\geq 2$  on one subscale and a score of 0 on the other. We excluded individuals with more than one missing item on the GDS3A and/or more than two missing items on the GDS12D from the analyses. Post hoc, a sensitivity analysis was performed with apathy and depressive scores as continuous predictors.

### Outcomes

We used time to first fatal or nonfatal MI, first fatal or nonfatal stroke (TIA excluded), and mortality as primary outcomes. Regarding MI and stroke events, these could be both first ever (i.e. incident) or recurrent. Mixed-model Cox proportional-hazard regression was used to calculate hazard ratios (HRs). Mixed-model logistic regression analyses were used to repeat the primary analyses on MI and stroke with the inclusion of studies in which dates of events were unavailable. A sensitivity analysis was conducted, including TIA. Finally, in order to compare results with those of our previous studies, a composite CVD outcome comprising

myocardial infarction (MI), angina pectoris (AP) and peripheral arterial disease (PAD) was analyzed.<sup>11</sup> Because an exact date of onset may be difficult to establish in cases of AP and PAD, these analyses were performed using logistic regression models. Subanalyses were conducted for CV mortality (primary CV cause of death according to the ICD9 [390–459] or -10 [I00–I99]) and non-CV mortality (all other causes) separately. A detailed description of how vascular variables were harmonized is provided in the [Supplementary material](#). To assess how HRs differed among studies, we plotted and pooled the separate results of fixed-effect Cox analyses in each study for all primary outcomes, using inverse variance-weighted DerSimonian and Laird random-effect models. To quantify heterogeneity,  $I^2$  statistics were used.

### Confounders and interaction

Three models were assessed for each outcome. Model 1 was unadjusted, model 2 adjusted for age and sex (in logistic regression additionally for study follow-up duration), and model 3 additionally adjusted for history of MI and/or stroke, because these may be confounders in the relationship of apathy and depressive symptoms with each outcome.<sup>11</sup> Interaction analyses were performed to evaluate possible moderation by age, sex, and history of MI and/or stroke. To examine the effect of age on the observed relations in more detail, we performed subgroup analyses within tertiles based on age. Furthermore, subgroup analyses were performed in individuals without a history of MI and/or stroke to facilitate comparison with our previous analyses.<sup>11</sup>

### Statistical analysis

Random-effect Cox proportional-hazard regression analyses were performed in R (version 3.2) using the Coxme package.<sup>19,20</sup> Overall HRs for the IPD meta-analyses were calculated using a one-stage random-effect model, with independent random slopes in each study for each predictor to account for clustering of participants (ie, clusters based on study).<sup>21</sup> For binary logistic regression analyses, similar models were used, employing the Lme4 package.<sup>22</sup> The R codes used are described in more detail in the [Supplementary material](#). Statistical analyses were two-tailed, and significance was set at  $\alpha=0.05$ . We plotted and pooled HRs within individual studies using the Meta package.<sup>23</sup>

### Bias assessment

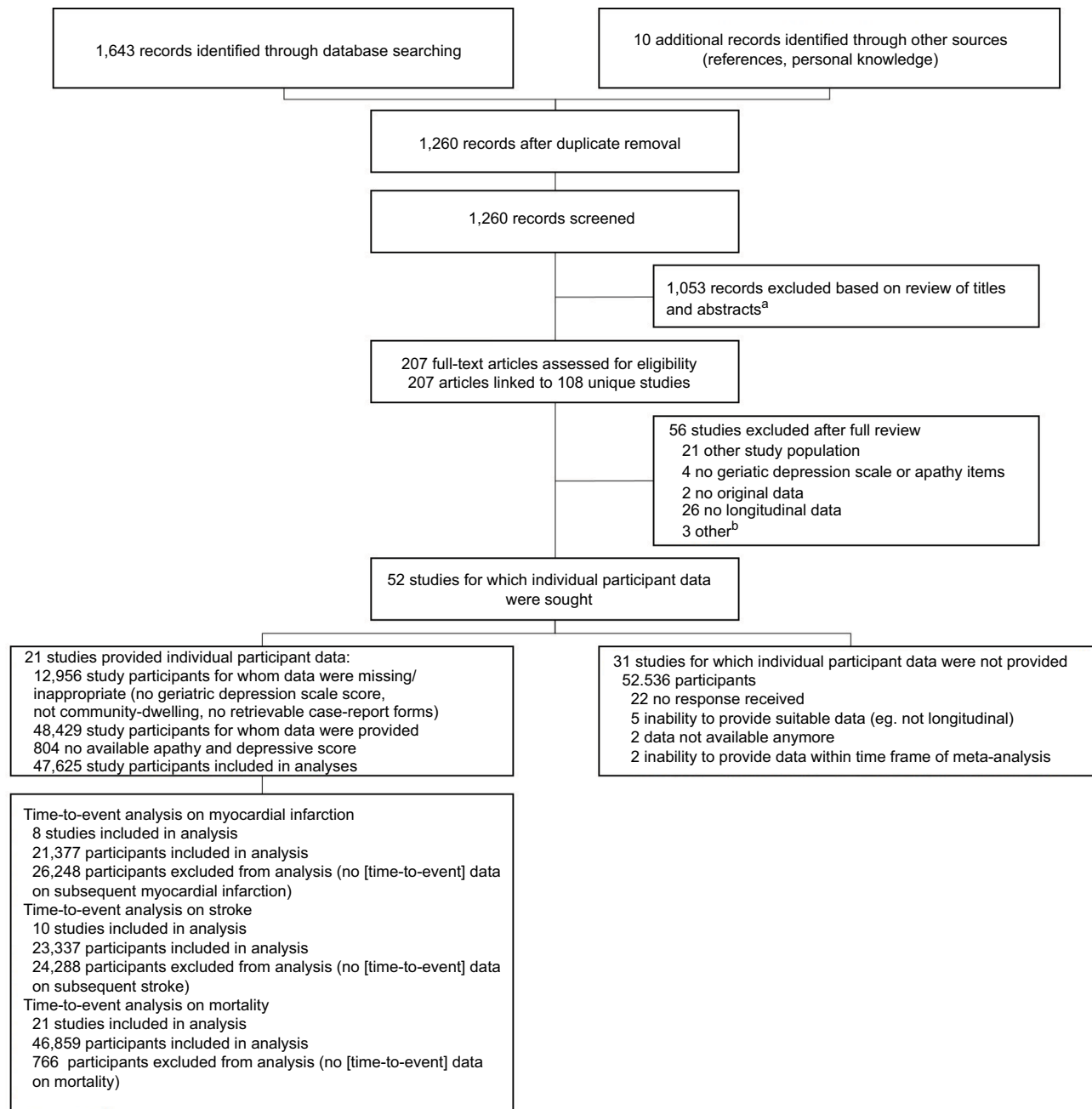
We assessed availability bias by comparing distributions of age, sex, and population sizes of participating and nonparticipating

pating studies. Risk of bias was evaluated per study using an adapted version of the Newcastle–Ottawa quality-assessment scale for cohort studies,<sup>24</sup> based on the following characteristics: method of outcome assessment for MI and stroke (self-report only vs other methods); proportion with missing status with regard to occurrence of MI, stroke, and mortality (lower vs higher than the median proportion for that outcome); study design (observational vs experimental); and selected vs general populations according to independent evaluation by two reviewers (LE, JWD), with selection based on age ( $\geq 80$

years only), sex, and/or recruitment strategy (specific sample types) (Table S1). Discrepancies were resolved by consensus and consultation with a third author (WAG) if necessary. Sensitivity analyses comparing studies with lower vs higher risk of bias were performed for each primary outcome for each criterion.

## Results

Search results are depicted in Figure 1. A total of 21 (40.4% of eligible) studies participated,<sup>25–45</sup> comprising data from



**Figure 1** PRISMA diagram of study selection.

**Notes:** <sup>a</sup>Dissertation/conference abstract,  $\leq 100$  study participants, no longitudinal data, case-control study, no original data, no geriatric depression scale or geriatric depression scale version without apathy items; <sup>b</sup>one dissertation, one study with  $\leq 100$  participants, and full text not available for one study.

48,429 community-dwelling older people. One study used a slightly modified apathy item on the GDS15. Another study could only provide data on apathy, not on the depression items of the GDS15 ([Supplementary material](#)). After excluding participants with neither apathy nor depression scores ( $n=804$ ), the final sample consisted of 47,625 older (mean age  $74\pm 7.4$  [range 53–105] years) community-dwelling people (51.5% women). The median follow-up for mortality was 8.8 years, yielding 360,306 person-years in total. In total, 31.1% (14,788 of 47,566) of participants had apathy symptoms, 32.4% (15,093 of 46,624) depressive symptoms, 13.8% (6,541 of 47,243) isolated apathy symptoms, 15.3% (7,169 of 46,947) isolated depressive symptoms, and 16.7% (7,911 of 47,276) both. Table 1 describes the general characteristics of the individual study and total ICARA samples. [Table S1](#) describes details on study design, in/exclusion criteria, recruitment strategy, and MI and stroke assessment.

## Outcomes

Time-to-event data were available for stroke in ten ( $n=23,337$ ) and for MI in eight ( $n=21,377$ ) studies. MI occurred in 5.7% (1,217) and stroke in 6.2% (1,452) of individuals. For participants with and without apathy symptoms, average 5-year risk was 27% vs 16.3% for mortality, 6% vs 3.9% for MI, and 7.4% vs 4.2% for stroke, respectively. Average 5-year risk comparing participants with and without depressive symptoms was 24.7% vs 17.3% for mortality, 4.5% vs 4.6% for MI, and 6.4% vs 4.8% for depressive symptoms, respectively. Data on fatal and nonfatal events were provided by all except two studies, which only supplied data on nonfatal events.<sup>27,45</sup> No violations of the proportional-hazard assumption were identified through evaluation of survival curves and Schönfeld residuals. Adjusted for age, sex, and history of MI and/or stroke, presence of apathy symptoms increased the hazard of future MI by 21% (HR 1.21, 95% confidence interval [CI] 1.08–1.36) and future stroke by 37% (HR 1.37, 95% CI 1.18–1.59) (Table 2). Depressive symptoms similarly increased the hazard of future stroke by 36% (HR 1.36, 95% CI 1.18–1.56), but increased the hazard of MI less substantially by 8%, with CIs overlapping 0 (HR 1.08, 95% CI 0.91–1.29). Results for isolated apathy and isolated depressive symptoms were comparable to those for apathy and depressive symptoms, respectively.

Sensitivity analyses including TIA in analyses of stroke gave similar results ([Table S2](#)). Results of analyses using logistic regression instead of Cox regression models (allowing for four additional studies for MI and two for stroke) were also comparable ([Table S3](#)). The association between stroke

and depressive symptoms was slightly attenuated when the GDS12D  $\geq 5$  cutoff for depressive symptoms was applied. A stricter definition for isolated symptoms (0 points on the other subscale) slightly attenuated the association for isolated apathy symptoms with future MI and stroke ([Tables S4](#) and [S5](#)). The hazard for the composite outcome of occurrence of MI, AP, and/or PAD was 33% (95% CI 1.20–1.49) higher for participants with apathy symptoms compared to those without and 8% for participants with depressive symptoms, with CIs overlapping 0 (95% CI 0.85–1.37) ([Table S6](#)).

Time-to-event data with regard to all-cause mortality were provided by all studies ( $n=46,859$ ). During follow-up, 33.3% (15,626) of participants died. In the fully adjusted models, both apathy symptoms (HR 1.47, 95% CI 1.38–1.56) and depressive symptoms (HR 1.44, 95% CI 1.35–1.53) increased the hazard of mortality by nearly 50% (Table 2). Associations for isolated apathy and depressive symptom were similar.

Sensitivity analyses using the stricter isolated symptom definition and those using the GDS12D  $\geq 5$  cutoff for depressive symptoms gave comparable results regarding mortality ([Tables S7](#) and [S8](#)). ICD codes regarding cause of death were provided by 12 studies. HRs for apathy and depressive symptoms seemed slightly higher for non-CV (apathy HR 1.45 [95% CI 1.34–1.57]; depressive HR 1.50 [95% CI 1.35–1.66]) compared to CV mortality (apathy HR 1.38 [95% CI 1.16–1.66]; depressive HR 1.33 [95% CI 1.18–1.51]), and CIs of the estimates overlapped ([Table S9](#)).

When apathy symptoms were explored as categorical predictors, a dose–response relationship between increasing apathy scores and increasing HRs was found for all outcomes (Figure 2). Pooled analyses of HRs in individual studies gave similar results to the one-stage approach (summarized in Table 3, forest plots in [Figures S1–S3](#)). Heterogeneity was low in analyses of MI (apathy  $I^2=13\%$ , depressive  $I^2=12\%$ , isolated apathy  $I^2=37\%$ , isolated depressive  $I^2=0$ ), low in analyses of stroke (all  $I^2=0$ ), and moderate in analyses of mortality for overall symptoms (apathy  $I^2=47\%$ , depressive  $I^2=50\%$ ), while low for isolated symptoms (both  $I^2=0$ ). Funnel plots of these analyses showed no indication of publication bias ([Figures S4–S6](#)).

## Interaction

We observed interactions between age and (isolated) depressive symptoms (HR 0.98, 95% CI 0.96–0.99; isolated symptoms, HR 0.97, 95% CI 0.94–0.99) in their relationship with stroke. This suggests that the relation between (isolated) depressive symptoms and future stroke is stronger in younger participants. These interactions were consistently present

**Table 1** Characteristics of total ICARA population and individual study samples included in ICARA<sup>a</sup>

Study	Region	GDS-examination date	Participants, n	Age, mean (SD), years	Women, n/total (%)
<b>Total ICARA population</b>		1990–2014	47,625	74 (7.4)	24,544/47,625 (51.5)
<b>Median (IQR) across studies</b>			1,735 (958–3,303)	74.4 (72.2–78.3)	56.6% (48.6%–61.2%)
BELFRAIL study (BFC80+) <sup>25</sup>	Belgium	2008–2009	499	84 (3.5)	302/499 (60.5)
Canadian Study on Health and Aging (CSHA) <sup>26</sup>	Canada	1995–1997	1,514	82.5 (6.7)	874/1,514 (57.7)
Einstein Aging Study (EAS) <sup>27</sup>	USA	1998–2014	1,924	78.2 (5.4)	1,189/1,924 (61.8)
Health in Men Study (HIMS) <sup>28</sup>	Australia	2001–2004	5,519	76.8 (3.7)	0/5,519 (0)
Health, Well-Being, and Aging Study – Brazil (SABE) <sup>29</sup>	Brazil	2000	1,863	72.1 (7.8)	1,094/1,863 (58.7)
Hertfordshire Cohort Study (HCS) <sup>30</sup>	England	1995–1996	882	68.4 (2.8)	340/882 (38.5)
Hong Kong Old-Old Study (HKOOS) <sup>31</sup>	China	1991–1992	1,540	77.8 (6.2)	693/1,540 (45)
Insufficienza Cardiaca negli Anziani Residenti a Dicomano study (ICARe Dicomano) <sup>32</sup>	Italy	1995–1996	634	73.7 (6.4)	374/634 (59)
Intervention Project on Cerebrovascular Diseases and Dementia in the Ebersberg District (INVADE) <sup>33</sup>	Germany	2001–2003	3,837	67.1 (7.7)	2,256/3,857 (58.8)
Invecchiamento Cerebrale in Abbiategrasso study (InveCe.Ab) <sup>34</sup>	Italy	2009–2011	1,262	72.2 (1.3)	680/1,262 (53.9)
Italian Longitudinal Study on Aging (ILSA) <sup>35</sup>	Italy	1992–1993	3,342	74.4 (5.6)	1,578/3,342 (47.2)
Leiden 85-Plus study (L85+) <sup>36</sup>	the Netherlands	1997–1999	445	85 (0)	275/445 (61.8)
Mr Os and Ms Os study (MrMs Os) <sup>37</sup>	China	2001–2003	3,998	72.3 (5.2)	1,999/3,998 (50)
Osservatorio Geriatrico Regione Campania study (OGC) <sup>38</sup>	Italy	1990–1991	1,250	74.1 (6.3)	707/1,250 (56.6)
Outcomes of Sleep Disorders in Older Men study (MrOS Sleep) <sup>39</sup>	USA	2003–2005	3,130	76.4 (5.6)	0/3,130 (0)
Selenium and Cognitive Decline Study (SCDS) <sup>40</sup>	China	2006–2007	1,735	73.8 (5.3)	926/1,735 (53.4)
Singapore Longitudinal Ageing Study I (SLAS I) <sup>41</sup>	Singapore	2003–2005	2,789	66.0 (7.7)	1,760/2,789 (63.1)
Singapore Longitudinal Ageing Study II (SLAS II) <sup>42</sup>	Singapore	2008–2013	3,263	67.0 (7.9)	2,041/3,263 (62.5)
Study of Osteoporotic Fractures (SOF) <sup>43</sup>	USA	1991–1994	6,591	76.7 (4.8)	6,591/6,591 (100.0)
Sydney Memory and Ageing Study (MAS) <sup>44</sup>	Australia	2005–2007	1,033	78.3 (4.8)	569/1,033 (55.1)
Treviso Longeva study (Trelong) <sup>45</sup>	Italy	2003–2004	575	82.3 (7.7)	296/575 (51.5)

**Notes:** <sup>a</sup>Study samples included in the meta-analyses consisted of community-dwelling individuals with an available apathy and/or depression score. All samples population-based. <sup>b</sup>Numbers concern only studies included in time-to-event analysis. <sup>c</sup>Study included in time-to-event analysis and logistic regression analysis. <sup>d</sup>Study included in logistic regression analysis only. <sup>e</sup>If a history of stroke excluding TIA was not available to create the composite variable history of MI and/or stroke, a history of stroke including TIA was used instead if available. <sup>f</sup>Due to time constraints in digitalizing individual GDS items from paper case-record forms, the ICARe Dicomano study provided data on the GDS3A items only within the time frame of this meta-analysis. <sup>g</sup>Median of mortality follow-up calculated excluding deceased individuals. Number of participants with missing data within each study sample: age – CSHA 6; baseline apathy score – CSHA 2, HIMS 2, ILSA 13, INVADE 36, MAS 3, MrOS Sleep 1, SABE-Brazil 1, SLAS I 1; baseline depression score – CSHA 4, EAS 2, HIMS 9, ICARe Dicomano 634 (not available [NA]), ILSA 213, INVADE 40, MAS 4, SABE 86, SLAS I 1, SOF 8; history of MI and/or stroke – BFC80+ 18, CSHA 1,514 (NA), HCS 882 (NA), HKOOS 1,540 (NA), ICARe Dicomano 634 (NA), ILSA 2, INVADE 19, InveCe.Ab 2, L85+ 5, MAS 13, OGC 1,250 (NA), SABE-1,863 (NA), SCDS 2, SLAS I 4, SLAS2 2, SOF 3, Trelong 575 (NA); subsequent MI – BFC80+ 65 (time to event [TTE] and logistic [L]), CSHA 1,514 (NA), EAS 976 (TTE + L), HCS 882 (NA), HKOOS 1,540 (NA), ICARe Dicomano 634 (NA), ILSA 218 (TTE + L), InveCe.Ab 188 (L), L85+ 2 (TTE + L), MAS 140 (L), MrMs Os 1 (TTE + L), MrOS Sleep 55 (TTE + L), OGC 1,250 (NA), SABE 1,863 (NA), SCDS 1,735 (NA), SLAS1 2,789 (NA), SLAS2 3,263 (NA), SOF 404 (L), Trelong 275 (L); subsequent stroke – BFC80+ 54 (TTE + L), CSHA 1,514 (NA), EAS 964 (TTE+L), HCS 882 (NA), HIMS 18 (TTE + L), HKOOS 1,540 (NA), ICARe Dicomano 634 (NA), ILSA 216 (TTE + L), InveCe.Ab 203 (TTE + L), MAS 140 (TTE + L), MrMs Os 1 (TTE + L), MrOS Sleep 56 (TTE + L), OGC 1,250 (NA), SCDS 1,735 (NA), SABE 843 (L), SLAS1 2,789 (NA), SLAS2 3,263 (NA), SOF 6,591 (NA), Trelong 275 (L); number deceased – CSHA 1,57, EAS 4, HCS 8, HKOOS 83, ILSA 217, MrOS Sleep 101, SABE 173, SCDS23.

**Abbreviations:** GDS, Geriatric Depression Scale; MI, myocardial infarction; TIA, transient ischemic attack; ICARA, Initiative on Cardiovascular Disease Risk and Apathy.

across studies ( $I^2=0$ ). Interaction effects between age and both apathy and depressive symptoms (both HRs 0.99, 95% CI 0.98–0.99) were present for mortality, suggesting the relationships were stronger in younger individuals. These interactions were also consistent across studies (apathy symptoms,  $I^2=32.4%$ ; depressive symptoms,  $I^2=22.9%$ ). Inclusion of these interaction terms into the fully adjusted models did not meaningfully alter any of the conclusions (data not

shown). In subgroup analyses within tertiles based on age (<72, 72–77, >77 years), the relationship between apathy and both MI and stroke was stronger in older subgroups. The relationship between depressive symptoms and stroke appeared stronger in younger subgroups (Tables S10–S12). Subanalyses in participants without a history of MI and/or stroke gave results similar to the main analyses (Tables S13 and S14).

Baseline apathy symptoms (GDS3A $\geq 2$ ), n/total (%)	Baseline depressive symptoms (GDS12D $\geq 2$ ), n/total (%)	History of MI and/or stroke, n/total (%)	Subsequent MI, n/total (%)	Subsequent stroke, n/total (%)	Deceased, n/total (%)	Follow-up mortality, median (IQR), years <sup>g</sup>
14,788/47,566 (31.1)	15,093/46,624 (32.4)	4,987/39,297 (12.7)	1,217/21,377 (5.7) <sup>b</sup>	1,452/23,337 (6.2) <sup>b</sup>	15,626/46,859 (33.3)	8.8 (5.3–10.9)
31.8% (21.4%–42.2%)	31.3% (21.1%–47.3%)	13.6% (7.7%–18.2%)	3.3% (2.3%–9.1%) <sup>b</sup>	5% (3.4%–7.3%) <sup>b</sup>	38.1% (22.8%–48.6%)	8.5 (5–11.2)
205/499 (41.1)	186/499 (37.3)	89/481 (18.5)	12/434 (2.8) <sup>c</sup>	25/445 (5.6) <sup>c</sup>	201/499 (40.3)	5.1 (5–5.3)
540/1,512 (35.7)	486/1,510 (32.2)	–	–	–	529/1,357 (39)	5 (4.7–5.2)
727/1,924 (37.8)	562/1,922 (29.2)	348/1,924 (18.1)	22/948 (2.3) <sup>c</sup>	37/960 (3.9) <sup>c</sup>	732/1,920 (38.1)	8 (0–16)
2,372/5,517 (43)	1,223/5,510 (22.2)	1,010/5,519 (18.3) <sup>e</sup>	623/5,519 (11.3) <sup>c</sup>	600/5,501 (10.9) <sup>c</sup>	1,653/5,519 (30)	7.4 (6.7–8.1)
379/1,862 (20.4)	824/1,777 (46.4)	–	–	138/1,020 (13.5) <sup>d</sup>	814/1,690 (48.2)	10.7 (10.4–10.9)
175/882 (19.8)	154/882 (17.5)	–	–	–	350/874 (40)	15.1 (14.7–15.4)
1,050/1,540 (68.2)	1,210/1,540 (78.6)	–	–	–	712/1,457 (48.9)	4.7 (3–10.2)
189/634 (29.8)	–	–	–	–	177/634 (27.9)	8.5 (8.3–8.5)
1,571/3,801 (41.3)	880/3,797 (23.2)	276/3,818 (7.2)	89/3,837 (2.3) <sup>c</sup>	202/3,837 (5.3) <sup>c</sup>	876/3,837 (22.8)	11.2 (10.1–11.6)
140/1,262 (11.1)	417/1,262 (33)	171/1,260 (13.6) <sup>e</sup>	17/1,074 (1.6) <sup>d</sup>	14/1,059 (1.3) <sup>c</sup>	45/1,262 (3.6)	2.2 (2.1–2.3)
1,059/3,329 (31.8)	1,767/3,129 (56.5)	405/3,340 (12.1)	118/3,124 (3.8) <sup>c</sup>	147/3,126 (4.7) <sup>c</sup>	1,258/3,125 (40.3)	8.1 (3.6–8.5)
113/445 (25.4)	110/445 (24.7)	69/440 (15.7)	43/443 (9.7) <sup>c</sup>	45/445 (10.1) <sup>c</sup>	424/445 (95.3)	13.5 (12.9–13.9)
895/3,998 (22.4)	1,893/3,998 (47.3)	545/3,998 (13.6) <sup>e</sup>	81/3,997 (2) <sup>c</sup>	173/3,997 (4.3) <sup>c</sup>	970/3,998 (24.3)	11.3 (10.7–11.8)
682/1,250 (54.6)	883/1,250 (70.6)	–	–	–	658/1,250 (52.6)	12.2 (12.2–12.2)
928/3,129 (29.7)	503/3,130 (16.1)	625/3,130 (20)	229/3,075(7.4) <sup>c</sup>	194/3,074 (6.3) <sup>c</sup>	1,055/3,029 (34.8)	9.5 (9.3–9.8)
901/1,735 (51.9)	988/1,735 (56.9)	90/1,733 (5.2)	–	–	304/1,712 (17.8)	4.5 (4.5–4.5)
239/2,788 (8.6)	844/2,788 (30.3)	188/2,785 (6.8) <sup>e</sup>	–	–	327/2,789 (11.7)	9.9 (9–10.6)
70/3,263 (2.1)	365/3,263 (11.2)	253/3,261 (7.8) <sup>e</sup>	–	–	142/3,263 (4.4)	3.6 (2.5–5)
1,811/6,591 (27.5)	1,364/6,583 (20.7)	767/6,588 (11.6) <sup>e</sup>	463/6,187 (7.5) <sup>d</sup>	–	3,797/6,591 (57.6)	15.7 (13.5–16.5)
504/1,030 (48.9)	162/1,029 (15.7)	151/1,020 (14.8)	27/893 (3) <sup>d</sup>	15/893 (1.7) <sup>c</sup>	235/1,033 (22.7)	7 (5.8–7.1)
238/575 (41.1)	272/575 (47.3)	–	11/300 (3.7) <sup>d</sup>	16/300 (5.3) <sup>d</sup>	367/575 (63.8)	10.4 (10.1–10.8)

## Risk of bias

Overall, studies that did not participate in ICARA (n=31) were smaller than those included (n=21), had slightly older study populations, and included relatively more women ([Supplementary material](#)). Sensitivity analyses comparing studies with higher versus lower risk of bias generally did not give any substantial deviations from the main analysis results, with association magnitudes being similar ([Tables S15–S21](#)). However, the evidence was poor in some categorizations, due to substantially smaller sample sizes (eg, experimental study designs [[Table S15](#)], self-reported outcomes [[Table S19](#)], and high percentage of missing outcomes [[Table S20](#)]). Sensitivity analyses with apathy and depressive-symptom scores as continuous predictors ([Table S22](#)) showed similar results: in models adjusted for age, sex, and history of MI and/or stroke, the hazard for participants with apathy symptoms for future MI increased, with an 11% per point increase (HR 1.11, 95%

CI 1.04–1.17), for stroke with a 15% per point increase (HR 1.15, 95% CI 1.05–1.26), and for mortality with a 24% per point increase (HR 1.24, 95% CI 1.20–1.28). Associations were comparable for isolated apathy symptoms. Depressive symptoms gave a 5% increase per point for future stroke (HR 1.05, 95% CI 1.00–1.10) and 9% for mortality (HR 1.09, 95% CI 1.07–1.11). The hazard of MI increased less substantially, by 3% per point increase, with CIs overlapping 0 (HR 1.03, 95% CI 0.99–1.08).

## Availability of data

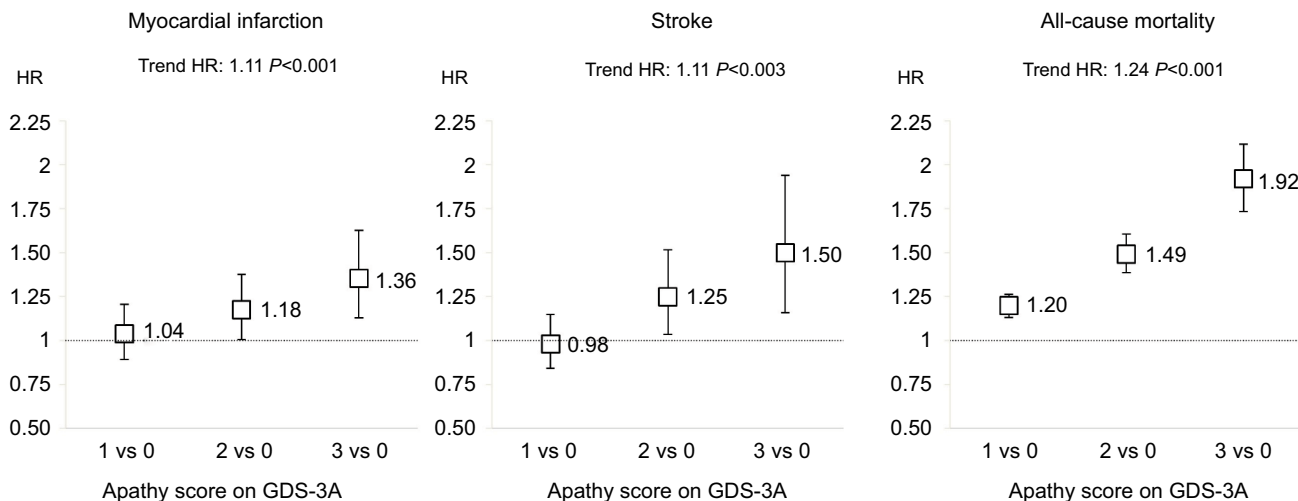
The data used in this paper are available from each individual participating study. However, restrictions apply to the availability of these data, which are not publicly available and were used under license for the current study. Data are however available from the authors upon reasonable request and with the permission of each individual study included.

**Table 2** Associations of apathy and depressive symptoms with subsequent myocardial infarction, stroke, and all-cause mortality

Myocardial infarction*						
	Model 1 <sup>e</sup>		Model 2 <sup>f</sup>		Model 3 <sup>g</sup>	
	Events/total, n	HR (95% CI)	Events/total, n	HR (95% CI)	Events/total, n	HR (95% CI)
Apathy <sup>a</sup>	1,213/21,326	1.41 (1.25–1.58)	1,213/21,326	1.29 (1.15–1.45)	1,211/21,290	1.21 (1.08–1.36)
Apathy, isolated <sup>b</sup>	861/14,467	1.46 (1.26–1.69)	861/14,467	1.31 (1.13–1.51)	859/14,446	1.24 (1.08–1.44)
Depression <sup>c</sup>	1,204/21,129	1.14 (0.94–1.37)	1,204/21,129	1.11 (0.92–1.34)	1,202/21,094	1.08 (0.91–1.29)
Depression, isolated <sup>d</sup>	682/13,870	1.17 (0.95–1.44)	682/13,870	1.17 (0.95–1.44)	681/13,852	1.14 (0.93–1.40)
Stroke**						
	Model 1 <sup>e</sup>		Model 2 <sup>f</sup>		Model 3 <sup>g</sup>	
	Events/total, n	HR (95% CI)	Events/total, n	HR (95% CI)	Events/total, n	HR (95% CI)
Apathy <sup>a</sup>	1,449/23,284	1.62 (1.40–1.87)	1,449/23,284	1.43 (1.23–1.67)	1,449/23,232	1.37 (1.18–1.59)
Apathy, isolated <sup>b</sup>	928/15,928	1.57 (1.37–1.80)	928/15,928	1.38 (1.2–1.58)	928/15,892	1.33 (1.15–1.52)
Depression <sup>c</sup>	1,430/23,086	1.46 (1.26–1.70)	1,430/23,086	1.39 (1.20–1.61)	1,430/23,035	1.36 (1.18–1.56)
Depression, isolated <sup>d</sup>	762/15,291	1.25 (1.04–1.50)	762/15,291	1.22 (1.01–1.46)	762/15,263	1.18 (0.99–1.42)
All-cause mortality***						
	Model 1 <sup>e</sup>		Model 2 <sup>f</sup>		Model 3 <sup>g</sup>	
	Events/total, n	HR (95% CI)	Events/total, n	HR (95% CI)	Events/total, n	HR (95% CI)
Apathy <sup>a</sup>	15,615/46,802	1.75 (1.63–1.87)	15,612/46,796	1.52 (1.44–1.61)	11,984/38,898	1.47 (1.38–1.56)
Apathy, isolated <sup>b</sup>	9,198/31,119	1.73 (1.65–1.82)	9,198/31,118	1.46 (1.40–1.53)	7,733/27,576	1.44 (1.36–1.51)
Depression <sup>c</sup>	15,268/45,877	1.55 (1.43–1.67)	15,265/45,871	1.46 (1.37–1.56)	11,861/38,691	1.44 (1.35–1.53)
Depression, isolated <sup>d</sup>	8,774/31,647	1.38 (1.27–1.50)	8,771/31,642	1.33 (1.25–1.42)	7,042/27,380	1.36 (1.28–1.44)

**Notes:** <sup>a</sup>Score ≥2 on the three-item apathy subscale of the Geriatric Depression Scale (GDS3A) and any depression score; <sup>b</sup>score ≥2 on the GDS3A in participants with one or no depressive symptoms; <sup>c</sup>score ≥2 on the 12-item depression subscale of the GDS (GDS12D) and any apathy score; <sup>d</sup>score ≥2 on the GDS12D in participants with one or no apathy symptoms; <sup>e</sup>unadjusted; <sup>f</sup>adjusted for baseline age and sex; <sup>g</sup>adjusted for baseline age, sex, and history of myocardial infarction and/or stroke. Included in analysis: \*models 1–3 – BFC80+, EAS, HIMS, ILSA, INVADE, L85+, MrMs Os, MrOs Sleep; \*\*models 1–3 – BFC80+, EAS, HIMS, ILSA, INVADE, InveCe.Ab, L85+, MAS, MrMs Os, MrOs Sleep; \*\*\*models 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, 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).

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



**Figure 2** HRs for myocardial infarction, stroke, and all-cause mortality by apathy score in individuals without depressive symptoms.

**Notes:** Results from Cox proportional-hazard analyses with GDS3A score as predictor adjusted for baseline age, sex, and history of myocardial infarction and/or stroke in individuals without depressive symptoms (GDS12 score ≤1).

**Abbreviation:** GDS, Geriatric Depression Scale.

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**Table 3** Two-stage analyses of associations of apathy and depressive symptoms with subsequent myocardial infarction, stroke, and all-cause mortality

	Myocardial infarction*					
	Model 1 <sup>e</sup>		Model 2 <sup>f</sup>		Model 3 <sup>g</sup>	
	HR (95% CI)	I <sup>2</sup>	HR (95% CI)	I <sup>2</sup>	HR (95% CI)	I <sup>2</sup>
Apathy <sup>a</sup>	1.40 (1.24–1.59)	5	1.28 (1.10–1.49)	18	1.21 (1.05–1.40)	13
Apathy, isolated <sup>b</sup>	1.52 (1.26–1.84)	19	1.41 (1.13–1.76)	33	1.35 (1.07–1.71)	37
Depression <sup>c</sup>	1.16 (0.96–1.39)	28	1.15 (0.97–1.36)	21	1.12 (0.95–1.31)	12
Depression, isolated <sup>d</sup>	1.21 (0.99–1.49)	0	1.21 (0.98–1.49)	0	1.18 (0.96–1.46)	0
	Stroke**					
	Model 1 <sup>e</sup>		Model 2 <sup>f</sup>		Model 3 <sup>g</sup>	
	HR (95% CI)	I <sup>2</sup>	HR (95% CI)	I <sup>2</sup>	HR (95% CI)	I <sup>2</sup>
Apathy <sup>a</sup>	1.71 (1.54–1.91)	0	1.49 (1.32–1.69)	10	1.45 (1.3–1.61)	0
Apathy, isolated <sup>b</sup>	1.59 (1.39–1.83)	0	1.39 (1.21–1.60)	0	1.34 (1.17–1.54)	0
Depression <sup>c</sup>	1.55 (1.29–1.75)	26	1.44 (1.25–1.66)	17	1.43 (1.27–1.60)	0
Depression, isolated <sup>d</sup>	1.3 (1.08–1.56)	1	1.27 (1.05–1.52)	0	1.24 (1.03–1.49)	0
	All-cause mortality***					
	Model 1 <sup>e</sup>		Model 2 <sup>f</sup>		Model 3 <sup>g</sup>	
	HR (95% CI)	I <sup>2</sup>	HR (95% CI)	I <sup>2</sup>	HR (95% CI)	I <sup>2</sup>
Apathy <sup>a</sup>	1.73 (1.62–1.85)	68	1.52 (1.44–1.60)	48	1.46 (1.38–1.56)	47
Apathy, isolated <sup>b</sup>	1.72 (1.63–1.81)	9	1.46 (1.39–1.53)	0	1.44 (1.36–1.51)	0
Depression <sup>c</sup>	1.54 (1.43–1.67)	77	1.46 (1.37–1.56)	67	1.44 (1.35–1.53)	50
Depression, isolated <sup>d</sup>	1.39 (1.27–1.52)	58	1.33 (1.25–1.43)	32	1.38 (1.3–1.46)	0

**Notes:** Results from two-stage analyses by pooling results of Cox proportional-hazard analyses within individual studies using DerSimonian and Laird random-effect models (forest plots in Figures S1–S3). <sup>a</sup>Score  $\geq 2$  on the three-item apathy subscale of the Geriatric Depression Scale (GDS3A) and any depression score; <sup>b</sup>score  $\geq 2$  on the GDS3A in participants with one or no depressive symptoms; <sup>c</sup>score  $\geq 2$  on the 12-item depression subscale of the GDS (GDS12D) and any apathy score; <sup>d</sup>score  $\geq 2$  on the GDS12D in participants with one or no apathy symptoms; <sup>e</sup>unadjusted; <sup>f</sup>adjusted for baseline age and sex; <sup>g</sup>adjusted for baseline age, sex, and history of myocardial infarction and/or stroke. Included in analysis: \*models 1–3 – BFC80+, EAS, HIMS, ILSA, INVADE, L85+, MrMs Os, MrOs Sleep; \*\*models 1–3 – BFC80+, EAS, HIMS, ILSA, INVADE, InveCe.Ab, L85+, MAS, MrMs Os, MrOs Sleep; \*\*\*models 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). **Abbreviation:** GDS, Geriatric Depression Scale

## Discussion

In this IPD meta-analysis of a large sample of community-dwelling older people, we found that apathy symptoms, irrespectively of concurrent depressive symptoms, were associated with a higher risk of MI, stroke, and all-cause CV and non-CV mortality. Depressive symptoms were related to a similarly increased risk of stroke and mortality outcomes, but not of MI. These observed associations were independent of age, sex, and history of MI/stroke.

The current study has several strengths. Large-scale meta-analysis of IP data is considered the “gold standard” for meta-analyses,<sup>18</sup> reducing the potential for ecological bias compared to meta-analyses synthesizing individual study results.<sup>46</sup> An assortment of studies were included with regard to country of origin and demographic characteristics, increasing the generalizability of our findings. The risk of publication bias seems limited, given that none of the included studies originally aimed to assess the association between apathy symptoms and vascular outcomes or mortality. Nevertheless, publication bias of the relationship between depression and

CVD could have indirectly influenced our results. Funnel plots of within-study associations, however, suggested the risk of publication bias playing a role in our findings is low. One-stage analyses were performed, which are recommended above two-stage methods, since their statistical approach is more exact, have more power for detection of interaction, and allow for better control of confounding and accounting for heterogeneity by allowing controlling for covariates at both the participant and study level.<sup>21,46</sup> Finally, the data were extensively explored in a range of sensitivity and interaction analyses.

Although it may be considered a limitation that the apathy and depression subscales have not been validated against a clinical diagnosis,<sup>10</sup> the intention of our study was not to formally diagnose apathy and/or depression, but rather to explore whether degrees of apathy and depressive symptoms were differentially associated with future vascular disease and mortality. It is important to note that our results pertain to the symptoms in the GDS15, and may not be generalizable to all depressive and apathy symptoms in a clinical interview.

We could not adjust for all potential confounders, including (chronic) vascular comorbidity, functional and cognitive impairment, socioeconomic status, and education, potentially leading to residual confounding. However, adjustment for some of these characteristics could have led to overadjustment, since they could also function as mediators. We tried to reduce the risk that individuals with severe cognitive and functional impairment were included in our analyses by excluding institutionalized individuals. In addition, several studies have found associations of apathy in older people with adverse outcomes independently of disability and cognition.<sup>11,16,47</sup>

Although we were able to acquire IPD for a large number of older people, more than half the eligible studies did not participate. These studies seemed to have slightly different population characteristics, suggesting that not including their data may have had some impact on our results. Non-participating studies were smaller, had more women, and slightly older populations. Since older age was a mediator of the associations with apathy symptoms, inclusion of these older cohorts could have decreased the magnitude of the unadjusted associations. Furthermore, although we incorporated studies from all over the world, more variety in population provenance may have allowed investigation into how geography affects these relations, since it has been shown that the exact construct of apathy symptoms within the GDS may differ among cultures.<sup>48</sup> Finally, since we did not have longitudinal data regarding the development of apathy and depressive symptoms over time, we cannot ascertain whether their stability has an influence on the risk of subsequent unfavorable clinical outcomes.

That apathy symptoms in this IPD meta-analysis were associated with subsequent MI (and also PA and PAD) independently of depressive symptoms corroborates our previous report of a specific association for apathy symptoms with an increased risk of CVD<sup>11</sup> and concurs with the vascular apathy hypothesis.<sup>12</sup> This IPD meta-analysis is (to our knowledge) the first to study the association between apathy symptoms and subsequent MI systematically. Previous studies assessing the reverse association consistently reported that a history of vascular disease predicted greater apathy, but not depression scores.<sup>12,49</sup> That apathy symptoms are specifically associated with future MI is in line with findings in other studies that suggest that motivation-related somatic rather than mood-related depressive symptoms are related to adverse CV outcomes in older individuals.<sup>6,50,51</sup> We found no association between depressive symptoms and future MI, which may be

contrary to results of several traditional meta-analyses.<sup>1-4</sup> However, since no discrimination was made between apathy and depressive symptomatology in these studies, it is possible that those associations were at least partly driven by apathy.

Both apathy and depressive symptoms were associated with an approximately 37%-higher risk of future stroke. This is contrary to our previous single-cohort study, in which no associations between either apathy or depressive symptoms and higher future stroke risk were found.<sup>11</sup> This discrepancy can most likely be explained by the far greater statistical power of the current analysis. In addition, the present study population was slightly younger on average, and both our own results and the previous literature suggest that the relationship between depressive symptoms and future stroke is stronger in younger people.<sup>52,53</sup> The association of depressive symptoms with future stroke is in line with several meta-analyses that – although not distinguishing between apathy and depressive symptoms – have shown that depression and somewhat less so depressive symptoms are independent risk factors for stroke, increasing the risk by 20%–45%.<sup>52-55</sup>

We found an approximately 45% higher hazard for both apathy and depressive symptoms with all-cause mortality. A similarly increased risk of mortality in people with depression has been demonstrated by several studies.<sup>56-59</sup> Studies that have examined the relation between apathy symptoms and mortality in general community-dwelling older populations are sparse, employed different methods of apathy assessment, and mostly studied specific populations, eg, those with frailty, heart disease, or dementia.<sup>60-64</sup>

The mechanisms by which apathy and depressive symptoms are related to future adverse vascular outcomes are unknown. Conceivably, both causal and noncausal effects play a role. Deleterious health behaviors and CV-risk factors may be induced by apathy and depression and thus partly mediate the reported associations with unfavorable outcomes.<sup>65-70</sup> Other mediators may also be of influence, eg, reduced compliance with CV-risk management.<sup>70</sup> Alternatively, the observed associations may be due to a common etiology underlying vascular disease, apathy, and depressive symptoms. It is imaginable that apathy and/or depressive symptoms are markers of underlying subclinical (cerebral) atherosclerosis, which is a strong risk factor for vascular events.<sup>70</sup> Previous studies have associated apathy and depressive symptoms with the presence of white-matter lesions in older individuals, also without clinical depression.<sup>71-75</sup> Although our previous research suggests that the relation-

ship between apathy symptoms and future vascular events is independent of CV-risk factors,<sup>11,67</sup> conceivably apathy symptoms reflect cerebrovascular damage by long-standing elevated CV risk, eg, midlife hypertension. If apathy is indeed a marker of cerebrovascular damage, such risk factors could be considered confounders underlying the relation between apathy and incident disease. Furthermore, although apathy predicts future vascular events independently of vascular event history, vascular events are a risk factor for apathy. This suggests that the temporal relationship between apathy and vascular events could be bidirectional, corresponding with previous findings that apathy symptoms can also be preceded by CVD.<sup>12</sup>

Our finding that symptoms of apathy gave an approximately 20% increased hazard of MI, while depressive symptoms did not seem clearly to increase this hazard, may have several explanations. Apathy symptoms may be more specific markers of underlying cerebrovascular disease, as suggested by the stronger relation with incident stroke, and thus more strongly associated with other incident vascular disease. Alternatively, apathy symptoms may be more sensitive to prodromal CV disease, since individuals with poor CV condition may tend to be less outgoing and feel less energetic. The relationship among apathy and depressive symptoms and mortality may be mediated by the increased occurrence of major vascular events, including MI and stroke, which are among the most important causes of death worldwide.<sup>76</sup> Alternatively, both types of symptoms could be manifestations of other underlying conditions that give a higher risk of mortality.

The dose-response relationship between apathy symptoms and subsequent stroke, MI and mortality, independent of depressive symptoms, together with previous analyses suggesting that apathy predicts CVD over and above the presence of CV-risk factors,<sup>67</sup> stress that recognition of apathy symptoms in older people is important, regardless of depressive symptoms. Although apathy symptoms may manifest themselves in the context of depression, our research adds to the expanding body of evidence highlighting apathy as an important standalone syndrome.<sup>8,12,49,67,77–81</sup> Distinct associations were found between apathy symptoms and a number of patient-important CV outcomes, including MI, AP, and PAD. Participants with two or more apathy symptoms had a 20%–30%-increased risk of these outcomes, independently of concurrent depressive symptoms. Individuals with a maximum apathy score (10.6% of our study population) had an 88% increased hazard of mortality. These findings imply that more attention on recognizing, detecting, and managing

apathy in general practice is warranted. This is especially relevant, since patients with apathy are less likely to engage actively in CV-risk prevention and health care.<sup>82</sup>

It is also important to recognize apathy as an entity distinct from depression, since treatment with selective serotonin-reuptake inhibitors (SSRIs) has not only been found to be ineffective but could also potentially aggravate apathy.<sup>83–85</sup> Given the common and potentially serious side effects of SSRI treatment in older people, this is especially undesirable.<sup>86,87</sup> If treatment of symptoms could mitigate the increased risks, based on the risks in the symptom-free populations and fully adjusted models, successful apathy treatment could decrease the absolute 5-year risks for these individuals from 4.7% to 3.9% for MI and from 5.8% to 4.2% for stroke. Depressive-symptom treatment would decrease these risks by 5.0% to 4.6% for MI and from 6.5% to 4.8% for stroke. Increased awareness of apathy in research settings is instrumental in elucidating its specific etiological role in CV disease and increasing the knowledge of its clinical correlates.

In conclusion, this IPD meta-analysis provides substantial evidence that apathy symptoms in community-dwelling older people are associated with an increased risk of future stroke, MI, and mortality, independently of concurrent depressive symptoms. It suggests depressive symptoms are associated with a similarly increased risk of stroke and mortality, but not substantially of MI. These independent associations between apathy symptoms and patient-important outcomes stress the necessity of recognizing apathy in older people independently of depressive symptoms. Future studies may investigate whether these associations are specific for apathy symptoms according to the GDS or also apply similarly to apathy and depressive symptoms according to other scales. Future research could evaluate the effects of change in the presence of these symptoms over time, aim at unraveling the mechanisms underlying their associations with adverse outcomes in later life, and examine whether interventions can prevent or reduce their occurrence and clinical consequences.

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## ICARA participating studies

Australia – Health in Men Study, Sydney Memory and Ageing Study; Belgium – BELFRAIL Study; Brazil – Health, Well-Being, and Aging Study; Canada – Canadian Study on Health and Aging; China – Hong Kong Old-Old Study, Mr Os and Ms Os Study, Selenium and Cognitive Decline Study; Germany – Intervention Project on Cerebrovascular Diseases and Dementia in the Ebersberg District; Italy – Insufficienza Cardiaca negli Anziani Residenti a Dicomano Study, Invecchiamento Cerebrale in Abbiategrasso Study, Italian Longitudinal Study on Aging, Osservatorio Geriatrico Regione Campania Study, Treviso Longeva (Trelong) Study; Singapore – Singapore Longitudinal Ageing Study I, Singapore Longitudinal Ageing Study II; the Netherlands – Leiden 85-Plus Study; UK – Hertfordshire Cohort Study; USA – Einstein Aging Study; Outcomes of Sleep Disorders in Older Men Study; Study of Osteoporotic Fractures.

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## Author contributions

All authors read and approved the final manuscript and were responsible for the study concept and design, acquisition/analysis/interpretation of data, critical revision of the manuscript for important intellectual content, administrative/technical/material support, and agreed to be accountable for all aspects of the work. LSME and JWD were responsible for drafting the manuscript and statistical analysis, and EPMC, ER, and WAG for study supervision. JWD had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Disclosure

The authors report no conflicts of interest in this work.

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