Vascular factors in dementia and apathy
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CHAPTER 3

APATHY IS AN INDEPENDENT RISK FACTOR FOR INCIDENT CARDIOVASCULAR DISEASE IN THE OLDER INDIVIDUAL: A POPULATION-BASED COHORT STUDY

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ABSTRACT

Objective

Although depression is considered to be associated with cardiovascular disease (CVD), specifically symptoms of apathy have been strongly associated with a history of CVD in recent studies. In this study, we prospectively assess whether symptoms of apathy and depression are independent risk factors for incident CVD and stroke.

Methods

We carried out a prospective cohort study of 1810 community-dwelling older individuals (70-78 years) without a history of CVD or stroke. Symptoms of apathy and depression were assessed with the 15-item Geriatric Depression Scale. Incident CVD and stroke were assessed after 2 years follow-up. The associations of symptoms of apathy and depression with incident CVD and stroke were analyzed separately using logistic regression analysis.

Results

Symptoms of apathy and depression were present in 281 (15.5%) and 266 (14.7%) participants, respectively. Incident CVD occurred in 62 (3.5%) participants and stroke in 55 (3.1%) participants. Apathy was associated with incident CVD after adjustment for demographics and cardiovascular risk factors (odds ratio (OR)=2.60, 95% CI=1.46 - 4.65). Exclusion of subjects with depressive symptoms yielded a similar OR (2.94, 95% CI=1.45 - 5.96, n=1544). No association was found between depressive symptoms and incident CVD. Neither apathy symptoms nor depressive symptoms were associated with incident stroke.

Conclusions

Apathy, but not depression, is a strong, independent risk factor for incident CVD. It may be a marker of underlying vascular disease. By its nature, apathy may cause non-adherence to a healthy lifestyle, diminished activities, and possibly even withdrawal from clinical care aimed at improving vascular risk profiles.
INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide\(^1\) and is a major contributor to disability.\(^2\) Its incidence increases steeply with age, which emphasizes the need for prevention in older age groups.\(^3\) Symptoms of apathy and depression are also common in community-dwelling older individuals\(^4-7\) and both have been linked to cardiovascular disease and stroke.\(^4, 6, 8, 9\) Apathy, defined as an impairment in motivation,\(^10\) often occurs within the context of depression but can also exist independently, thus without symptoms of guilt, helplessness, hopelessness, and a negative mood.\(^11, 12\) It is important to distinguish apathy from depression because both conditions may have different underlying pathophysiology and thus require different treatments.\(^12, 13\)

The “vascular depression” hypothesis, formulated by Alexopoulos in 1997, proposes an etiologic role of vascular factors in the onset of depression in older individuals.\(^9\) In several cross-sectional studies, depression has indeed been associated with cardiovascular disease and stroke in older individuals,\(^14-16\) but most longitudinal studies were not able to confirm this.\(^17-19\)

Recently, in two cross-sectional studies, specifically symptoms of apathy, rather than depressive symptoms, have been strongly associated with a history of cardiovascular disease, stroke, and cardiovascular risk factors in community-dwelling older individuals.\(^4, 6\) In addition to these cross-sectional findings, van der Mast et al. found that older persons with vascular disease were at higher risk of developing apathy but not depression and coined the “vascular apathy” hypothesis.\(^4\)

If apathy is indeed a marker of underlying vascular disease, its presence may also indicate an increased risk of future vascular events, and recognition of these symptoms may be important to identify those individuals at increased risk. We therefore aimed to assess the specific contribution of both symptoms of apathy and depression to the prediction of the risk of incident cardiovascular disease and stroke in older persons. In line with the vascular apathy hypothesis, we hypothesized that apathy symptoms rather than depressive symptoms would be an independent risk factor for incident cardiovascular disease and stroke.

METHODS

Participants

Subjects were derived from the Prevention of Dementia by Intensive Vascular Care (preDIVA) trial (trial registration: isrctn.com, identifier: ISRCTN29711771). This is a Dutch ongoing, cluster-randomized trial carried out within primary care to assess the efficacy of a multi-component, nurse-led intervention aimed at vascular risk factors, with inci-
dent dementia and disability as primary endpoints. Secondary outcomes are mortality, cognitive decline, depression, incident stroke/transient ischemic attack (TIA), and incident cardiovascular disease (including myocardial infarction, angina pectoris, and peripheral arterial disease). The duration of the intervention and follow-up is 6 years. Exclusion criteria were a diagnosis of dementia and any condition that was assumed to impede a successful long term follow-up (e.g., metastatic malignancy and alcoholism). From May 2006 to March 2009, 3533 community-dwelling subjects aged 70-78 years were included. All eligible subjects in 116 general practitioner (GP) practices had been invited, yielding a participation rate of 53.3%. Ethical approval was obtained from the medical ethics committee of the Academic Medical Center, Amsterdam. Participants gave written informed consent before enrolment. Further details on the design of the preDIVA study are reported elsewhere.20

For the present analyses, the population is considered as a cohort, irrespective of randomization group. Because both apathy and depression may be a consequence of vascular disease,21-25 caused either directly through a stroke lesion,21,23 or indirectly through disability caused by vascular disease,26,27 we investigated the predictive value of these symptoms in subjects without previous cardiovascular disease or stroke. Participants with a history of cardiovascular disease or stroke or with missing data on this variable were therefore excluded from the analysis.

Assessment of symptoms of apathy and depression

At baseline, symptoms of apathy and depression were assessed with the 15-item Geriatric Depression Scale (GDS-15) (range from 0-15, higher scores equate with worse functioning), which is a widely used instrument by clinicians and researchers.28 Principal component analyses of the GDS-15 have repeatedly shown that three items representing apathy symptoms load on the same factor.6,29 These items are as follows: (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? Sensitivity and specificity for this subscale are 69% and 85%, respectively, compared with the 14-item Apathy Scale of Starkstein30 in subjects 85 years or older.4 An expert team of psychiatrists, behavioral neurologists, and neuropsychologists, unaware of the factor analyses, pointed out the same three GDS-15 items as representing apathy symptoms.4 A confirmatory factor analysis of the 30-item GDS identified these same three items as being part of a 6-item Withdrawal-Apathy-Vigor subscale.31

On the basis of these findings, we assessed apathy symptoms using these three items (GDS-3A; range 0-3 points, higher scores indicating more apathy). We considered the remaining 12 items to represent depressive symptoms (GDS-12D; range 0-12 points, higher scores indicating a stronger depressive tendency). Symptoms of apathy
and depression were defined as GDS-3A ≥2 and GDS-12D ≥2, respectively. This dichotomization allows for comparison with previously published studies.\textsuperscript{4, 6} In addition to the sensitive cut-off of GDS-12D ≥2, a more specific cut-off for depressive symptoms was also used (GDS-12D ≥5). When reporting depressive symptoms in the text, the sensitive cut-off of GDS-12D ≥2 was used unless stated otherwise.

**Assessment of cardiovascular disease and stroke**

At baseline, the presence of a history of cardiovascular disease (myocardial infarction, angina pectoris, and peripheral arterial disease) and stroke/TIA was assessed both by interview with a practice nurse and by consulting the electronic medical records (EMR) of the GP. Self-reported events had to be verified in the EMR. Data on cardiovascular risk factors (blood pressure, diabetes mellitus (DM), cholesterol, body mass index (calculated as weight in kilograms divided by height in meters squared), and smoking habits) were collected.

At the 2-year follow-up interview, assessment of incident stroke/TIA and cardiovascular disease (myocardial infarction, angina pectoris, and peripheral arterial disease) was conducted similarly to the assessment at baseline, that is, incident events were assessed by interview and by consulting the EMR of the GP. In addition, hospital discharge letters were checked.

To assess fatal incident cardiovascular disease and stroke, information on cause of death was collected from the EMR for participants that had died during follow-up. An expert panel of four independent senior specialists (Cardiology, Neurology, Psychiatry, and General Practice) classified the causes of death by consensus into mortality due to cardiovascular disease or stroke and mortality due to other causes. Cardiovascular and stroke mortality was determined to be either "probable" or "definite" by the panel. All cases of probable and definite cardiovascular and stroke mortality were included in the primary analysis.

**Other measurements**

Socio-demographic characteristics were obtained for all subjects at baseline. Current medication, cognitive function (Mini-Mental State Examination (MMSE) (range from 0 to 30, higher scores indicating better functioning)),\textsuperscript{32} level of physical activity (practicing sports, yes/no), and disability (Academic Medical Center Linear Disability Score (ALDS))\textsuperscript{33} were assessed both at baseline and after 2 years of follow-up. The ALDS is a generic linear handicap scale with a range from 0 to 100 where higher scores equate with better functioning. Medication use was derived from the EMR.
**Statistical analysis**

Participants with missing data on history of cardiovascular disease or stroke and/or with missing items on the GDS-15 (>2 on GDS-12D and/or >1 on GDS-3A) were excluded from the analyses. The Markov chain Monte Carlo multiple imputation method was performed on demographic variables, cardiovascular risk factors, ALDS, and current medication to replace missing data with plausible values. The dependent variables incident cardiovascular disease and stroke were not imputed. Univariate comparisons were performed using Student’s t-test and Mann-Whitney U (MW-U) test for continuous variables, chi-squared test for binary variables, and chi-squared test for trend for ordinal variables.

The association of symptoms of apathy and depression with incident cardiovascular disease and stroke was analyzed using logistic regression analysis with incident non-fatal and fatal cardiovascular disease and stroke as dependent variables. Because silent ischemic brain lesions might contribute to apathy symptoms and subjects affected by this may have an increased risk of clinically overt stroke, cardiac disease and stroke were analyzed as separate dependent variables. If participants suffered from incident stroke and cardiovascular disease, both events were analyzed separately. Separate analyses were performed for depressive symptoms most sensitively defined as GDS-12D ≥2 and with the more specific cut-off of ≥5. We used three models in the analyses. Model 1 is unadjusted. In model 2, analyses were adjusted for age, sex, and level of education (<7, 7-12, and >12 years), because apathy symptoms and vascular disease are influenced by demographics. In model 3, we additionally adjusted for baseline cardiovascular risk factors (systolic blood pressure ≥160 mmHg, BMI ≥30 kg/m2, total cholesterol ≥6.5 mmol/L, DM, current smoking, and not practicing sports). When reporting odds ratios (ORs) in the Results section, ORs of model 3 are reported unless stated otherwise. Cognitive decline, disability, and an increasing number of health conditions are all significantly related to apathy, and are known to be related to vascular disease outcomes. Therefore, in an exploratory fourth model, additional adjustments were made for cognitive status using the MMSE score, disability using the ALDS, and number of non-vascular prescriptions as a proxy for other comorbidities. All analyses have been repeated within the unimputed dataset. Data analyses were performed with SPSS statistical software, version 20.0 (IBM Corp., Armonk, NY).
RESULTS

Study population

Of the 3533 subjects included in preDIVA at baseline, 1802 participants had no history of cardiovascular disease or stroke and completed the 2-year follow-up interview (Figure 1). Of the 442 participants that were lost to follow-up at 2 years after randomization, 47 died within two years after randomization and 395 could not be followed-up after two years because of other reasons (e.g. withdrawal and relocation). Of the 47 deaths, 8 participants died of probable or definite cardiovascular disease or stroke and were added to the 1802 participants that completed the two year follow-up interview, resulting in a study population of 1810 participants.

Figure 1. Flowchart of selection of eligible study participants.

a Missing items on the 15-item Geriatric Depression Scale (GDS-15): >2 items missing on the Geriatric Depression Scale-12D and/or >1 item missing on the Geriatric Depression Scale-3A.

b Including probable and definite cardiovascular and stroke mortality.

c Subjects were older than participants included in study (mean (SD): 74.6 (2.5) versus 74.1 (2.5) years, p < 0.001) and less educated (<7 years: 30.1% versus 21.7%; 7-12 years: 58.7% versus 65.1%; >12 years: 11.1% versus 13.2%, p = 0.001). Gender did not differ significantly (male: 37.0% versus 40.3%, p = 0.22). CVD, cardiovascular disease.
Baseline characteristics

Baseline characteristics are shown in Table 1 for the entire study population (n=1810) and separately for symptom-free subjects (defined as subjects without apathy symptoms and without depressive symptoms) (n=1387 (76.6%)), subjects with apathy symptoms (n=281 (15.5%)), and subjects with depressive symptoms (n=266 (14.7%)). The percentages of the latter three categories do not add up to 100 due to overlap (124 (6.9%) individuals had both apathy and depressive symptoms).

Table 1. Baseline characteristics of all participants and according to symptoms of apathy and depression

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All n=1810</th>
<th>Symptom-free n=1387 (76.6)</th>
<th>Apathy symptoms(b) n=281 (15.5)</th>
<th>(p^d)</th>
<th>Depressive symptoms(c) n=266 (14.7)</th>
<th>(p^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>74.12 (2.45)</td>
<td>74.01 (2.45)</td>
<td>74.69 (2.43)</td>
<td>&lt;.001</td>
<td>74.31 (2.35)</td>
<td>.07</td>
</tr>
<tr>
<td>Male sex</td>
<td>729 (40.3)</td>
<td>575 (41.5)</td>
<td>99 (35.2)</td>
<td>.05</td>
<td>95 (35.7)</td>
<td>.08</td>
</tr>
<tr>
<td>Educational level</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>&lt;7 years</td>
<td>393 (21.7)</td>
<td>266 (19.2)</td>
<td>89 (31.7)</td>
<td>80 (30.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-12 years</td>
<td>1178 (65.1)</td>
<td>924 (66.6)</td>
<td>161 (57.3)</td>
<td>161 (60.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>239 (13.2)</td>
<td>197 (14.2)</td>
<td>31 (11.0)</td>
<td>25 (9.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>1770 (97.8)</td>
<td>1361 (98.1)</td>
<td>271 (96.4)</td>
<td>.08</td>
<td>258 (97.0)</td>
<td>.22</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP≥160 mmHg</td>
<td>733 (40.5)</td>
<td>543 (39.1)</td>
<td>133 (47.3)</td>
<td>.01</td>
<td>107 (40.2)</td>
<td>.74</td>
</tr>
<tr>
<td>Total cholesterol ≥6.5 mmol/L</td>
<td>317 (17.5)</td>
<td>232 (16.7)</td>
<td>57 (20.3)</td>
<td>.16</td>
<td>54 (20.3)</td>
<td>.15</td>
</tr>
<tr>
<td>BMI≥30 kg/m²</td>
<td>402 (22.2)</td>
<td>284 (20.5)</td>
<td>87 (31.0)</td>
<td>&lt;.001</td>
<td>72 (27.1)</td>
<td>.02</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>295 (16.3)</td>
<td>207 (14.9)</td>
<td>63 (22.4)</td>
<td>.002</td>
<td>53 (19.9)</td>
<td>.04</td>
</tr>
<tr>
<td>Current smoking</td>
<td>218 (12.0)</td>
<td>152 (11.0)</td>
<td>52 (18.5)</td>
<td>&lt;.001</td>
<td>41 (15.4)</td>
<td>.04</td>
</tr>
<tr>
<td>Not practicing sports</td>
<td>720 (39.8)</td>
<td>493 (35.6)</td>
<td>172 (61.2)</td>
<td>&lt;.001</td>
<td>131 (49.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MMSE, mean (SD)</td>
<td>28.27 (1.66)</td>
<td>28.35 (1.58)</td>
<td>28.04 (1.70)</td>
<td>.005</td>
<td>27.92 (1.98)</td>
<td>.002</td>
</tr>
<tr>
<td>ALDS, mean (SD)</td>
<td>87.65 (3.82)</td>
<td>88.26 (2.70)</td>
<td>84.89 (6.55)</td>
<td>&lt;.001</td>
<td>85.58 (6.36)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Number of non-vascular(d) prescriptions, mean (SD)</td>
<td>1.69 (1.93)</td>
<td>1.54 (1.82)</td>
<td>2.33 (2.24)</td>
<td>&lt;.001</td>
<td>2.29 (2.22)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

SD, standard deviation; SBP, systolic blood pressure; BMI, body mass index; MMSE, Mini-Mental State Examination; ALDS, Academic Medical Center Linear Disability Score.

\(a\) Values are numbers (percentages) unless stated otherwise. Before imputation missing value percentages were below 2% for demographics, cardiovascular risk factors, Mini-Mental State Examination (MMSE) score, and Academic Medical Center Linear Disability Score (ALDS). The missing value percentage of number of non-vascular prescriptions was 6.5%.

\(b\) Symptoms of apathy: Geriatric Depression Scale-3A≥2.

\(c\) Symptoms of depression: Geriatric Depression Scale-12D≥2.

\(d\) \(P\) value by T-test, Pearson \(\chi^2\) Test, \(\chi^2\) test for trend or Mann-Whitney U test, comparison with symptom-free group.
Subjects with apathy symptoms were significantly older than symptom-free subjects. In addition, subjects with apathy symptoms and those with depressive symptoms were more likely to have a lower level of education, lower baseline scores on MMSE and ALDS, and a higher number of non-vascular prescriptions, compared with symptom-free subjects. For both groups, associations were found with most cardiovascular risk factors, although for apathy symptoms, these seemed to be stronger.

The association of symptoms of apathy and depression with incident cardiovascular disease and stroke

Table 2 shows the association of symptoms of apathy and depression with incident cardiovascular disease and stroke. Incident cardiovascular disease occurred in 62 (3.5%) participants and incident stroke in 55 (3.1%) participants, of which respectively four (6.5%) and four (7.3%) were fatal. Three (0.2%) participants suffered both a non-fatal stroke and a non-fatal cardiovascular disease. Apathy symptoms were significantly associated with subsequent cardiovascular disease (odds ratio (OR) = 2.60, 95% CI = 1.46-4.65). This did not change importantly after additional adjustments for cognitive status, non-vascular comorbidity, and disability (OR = 2.70, 95% CI = 1.48-4.91). The ORs for incident cardiovascular disease for participants with depressive symptoms were lower than for participants with apathy symptoms and were not significant, irrespective of the cut-off for depressive symptoms (GDS-12D ≥2: OR = 1.55, 95% CI = 0.82-2.91; GDS-12D ≥5: OR = 1.56, 95% CI = 0.52-4.71). Symptoms of apathy and depression were not associated with incident stroke. Excluding three participants with probable (as opposed to definite) cardiovascular or stroke mortality from the analyses did not change these results.

On the basis of the results of these analyses, the association of apathy symptoms with incident cardiovascular disease and stroke was further explored. Because this association might have been confounded by comorbid depressive symptoms, an additional analysis was performed in subjects with a GDS-12D score ≤1 (n=1544 of whom 157 (10.2%) had apathy symptoms). The association between apathy symptoms and incident cardiovascular disease remained strong (OR = 2.94, 95% CI = 1.45-5.96). Additional adjustments for cognitive status, non-vascular comorbidity, and disability did not affect the results (OR = 3.02, 95% CI = 1.45-6.29). No association was found between apathy symptoms and incident stroke. Figure 2 shows the unadjusted relative risk of incident cardiovascular disease and stroke with increasing apathy score in this group. Repeating the analyses within the unimputed dataset did not affect any of the results mentioned earlier.
Table 2. Symptoms of apathy and depression and odds ratios for incident cardiovascular disease and stroke in participants without a history of cardiovascular disease or stroke (n=1810)a

<table>
<thead>
<tr>
<th>Incident cardiovascular disease (n=1777)b</th>
<th>All events (n)</th>
<th>Apathy/ depression and event (n)</th>
<th>Apathy/ depression and no event (n)</th>
<th>Model 1b OR (95% CI)</th>
<th>P</th>
<th>Model 2c OR (95% CI)</th>
<th>P</th>
<th>Model 3d OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis for symptoms of apathy (GDS-3A≥2), n=277</td>
<td>62</td>
<td>22</td>
<td>255</td>
<td>3.15 (1.84-5.39)</td>
<td>&lt;0.001</td>
<td>3.47 (2.00-6.02)</td>
<td>&lt;0.001</td>
<td>2.60 (1.46-4.65)</td>
<td>0.001</td>
</tr>
<tr>
<td>Analysis for symptoms of depression (GDS-12D≥2), n=263</td>
<td>62</td>
<td>14</td>
<td>249</td>
<td>1.72 (0.93-3.16)</td>
<td>0.08</td>
<td>1.80 (0.97-3.34)</td>
<td>0.06</td>
<td>1.55 (0.82-2.91)</td>
<td>0.18</td>
</tr>
<tr>
<td>Analysis for symptoms of depression (GDS-12D≥5), n=63</td>
<td>62</td>
<td>4</td>
<td>59</td>
<td>1.94 (0.68-5.51)</td>
<td>0.22</td>
<td>2.04 (0.71-5.89)</td>
<td>0.19</td>
<td>1.56 (0.52-4.71)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incident stroke (n=1782)f</th>
<th>All events (n)</th>
<th>Apathy/ depression and event (n)</th>
<th>Apathy/ depression and no event (n)</th>
<th>Model 1b OR (95% CI)</th>
<th>P</th>
<th>Model 2c OR (95% CI)</th>
<th>P</th>
<th>Model 3d OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis for symptoms of apathy (GDS-3A≥2), n=277</td>
<td>55</td>
<td>7</td>
<td>270</td>
<td>0.79 (0.35-1.76)</td>
<td>0.56</td>
<td>0.83 (0.55-1.26)</td>
<td>0.65</td>
<td>0.74 (0.32-1.69)</td>
<td>0.47</td>
</tr>
<tr>
<td>Analysis for symptoms of depression (GDS-12D≥2), n=265</td>
<td>55</td>
<td>12</td>
<td>253</td>
<td>1.63 (0.85-3.13)</td>
<td>0.15</td>
<td>1.77 (0.92-3.43)</td>
<td>0.09</td>
<td>1.74 (0.89-3.38)</td>
<td>0.10</td>
</tr>
<tr>
<td>Analysis for symptoms of depression (GDS-12D≥5), n=63</td>
<td>55</td>
<td>0</td>
<td>63</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; GDS-3A, 3-item apathy subscale of the 15-item Geriatric Depression Scale (GDS-15); GDS-12D, 12-item depression subscale of the GDS-15; n.a., not applicable.

a Odds ratios were computed using logistic regression analysis.
b Unadjusted.
c Adjusted for baseline demographics: age, sex, educational level (<7, 7-12, >12 years).
d Adjusted for baseline demographics and baseline cardiovascular risk factors: systolic blood pressure (SBP) ≥160 mmHg, total cholesterol ≥6.5 mmol/L, current smoking, not practicing sports, body mass index (BMI) ≥30 kg/m², and presence of diabetes mellitus.
e Data on incident cardiovascular disease were missing for 33 (1.8%) participants.
f Data on incident stroke were missing for 28 (1.5%) participants.
DISCUSSION

Here we show for the first time that symptoms of apathy are strongly associated with an increased risk of incident cardiovascular disease supporting the vascular apathy hypothesis. This association was independent of the presence of depressive symptoms and remained robust after adjustment for potential confounders, including demographics, cardiovascular risk factors, cognitive status, non-vascular comorbidity, and disability. In contrast, no association was found between depressive symptoms and incident cardiovascular disease. Figure 2 illustrates that increasing symptoms of apathy are associated with an increasing risk of incident cardiovascular disease. Neither apathy symptoms nor depressive symptoms were associated with incident stroke.

To our knowledge, this is the first study to examine whether symptoms of apathy are associated with an increased risk of incident cardiovascular disease or stroke. Previous studies have focused on depressive symptoms as a predictor of cardiovascular events and stroke. In a meta-analysis, depression, and to a lesser extent, depressive
symptoms, were found to be an independent risk factor for the onset of cardiovascular disease including stroke.\textsuperscript{43} Although individual prospective studies assessing the association of depression with stroke have reported inconsistent results, two meta-analyses reported that depression significantly increases the risk of stroke.\textsuperscript{44,45} An age-effect has been reported in one study, in which depressive symptoms were a risk factor for stroke in persons aged 65 years or younger, but not in the older individuals.\textsuperscript{46} The latter finding is consistent with the results from this present study in which no association was found between depressive symptoms and subsequent stroke in subjects aged 70 years and older.

Because of overlapping clinical features, including loss of interest and initiative, apathy may be confused with depression.\textsuperscript{47} Furthermore, instruments that assess depression frequently include several apathy items, which might lead to an overestimation of depression and misclassification of apathy as depression due to high scores on apathy items.\textsuperscript{11-13} The association of depression with cardiovascular disease and stroke previously reported might thus have been confounded by the presence of apathy. Apathy symptoms rather than depressive symptoms could be a marker of underlying vascular disease.

Longitudinal studies on apathy have been focusing on vascular factors preceding symptoms of apathy. The Leiden 85-plus study found that subjects with vascular disease were at higher risk of developing apathy, but not depression.\textsuperscript{4} In line with these findings, a lower ankle brachial pressure index, as a measure of atherosclerosis, was found to be an independent risk factor for apathy, but not for depression in a community-dwelling population.\textsuperscript{48} These findings also suggest an underlying vascular mechanism in the development of apathy.

However, no association was found between apathy symptoms and incident stroke in this present study. A possible explanation might be the occurrence of selective attrition since severe disability caused by stroke may have led to termination of study participation before reaching the two year follow-up interview in some participants. Another explanation might be that apathy is a behavioral manifestation of a low-grade inflammatory reaction (sickness behaviour),\textsuperscript{49} which may be more strongly associated with generalized cardiovascular disease than with stroke.\textsuperscript{50,51} This difference might be caused by the more heterogeneous etiology of stroke, including selective carotid artery disease, cerebral small vessel disease, and atrial fibrillation. To test this hypothesis, an exploratory analysis of C-reactive protein (CRP) as a marker of inflammation was performed. This showed that the baseline CRP levels in participants with baseline apathy symptoms (n=281) were significantly higher compared to control subjects without apathy symptoms (n=1529) (mean and standard deviation (SD): 5.08 (11.51) mg/L versus 3.29 (4.72) mg/L, \(p = 0.009\), MW-U test). Further supporting this hypothesis, the baseline CRP levels in participants with baseline apathy symptoms and incident stroke
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(n=7, mean (SD): 3.01 (2.36) mg/L) were lower than in subjects with baseline apathy symptoms and incident cardiovascular disease (n=22, mean (SD): 5.98 (8.43) mg/L). The difference did however not reach significance in this small number of subjects (p = 0.46, MW-U test).

PreDIVA is a large prospective population-based study with few exclusion criteria which minimizes potential selection bias and increases the external validity. In addition to self-report, ascertainment of incident cardiovascular disease and stroke was based on GP records that accurately keep track of important changes in health status, adding to its validity. Because of the preventive nature of the study, there may have been a selection of the "worried well". A comparison of age and sex between participants (n=900) and non-respondents (n=689) from a group of seven randomly chosen GP practices showed that the non-responders were slightly older (mean: 74.6 versus 74.3 years, p = 0.02) and there were slightly more women (58.8% versus 54.5%, p = 0.09). Comparison with the general Dutch population showed comparable prevalence of obesity and smoking, supporting the external validity of our findings. A limitation to this study is that preDIVA was not primarily designed to evaluate apathy and the study protocol did not allow for an extensive clinical examination of apathy. However, we were able to assess symptoms of apathy by using the GDS-3A as part of the GDS-15 and these three items have consistently shown to reflect apathy in several population-based studies.

To our knowledge, thus far, no reports are available on the diagnostic accuracy of the GDS-12D. Considering this limitation and the modest sensitivity of the GDS-3A, we did not aim for a formal diagnosis of either depression or apathy (as distinct diagnostic categories), but rather we wanted to explore associations between symptoms representing depressive or apathetic tendencies (as behavioral dimensions) and incident cardiovascular disease and stroke. Furthermore, a relatively short period of follow-up was deployed for this analysis. Despite this, the total number of events was reasonably high (117; 6.6% of the participants) and we did find a strong and robust association of apathy symptoms with incident cardiovascular disease. Future confirmation with longer follow-up and in different cohorts may strengthen this finding. The number of cardiovascular events in participants with depressive symptoms was however relatively small compared to the number of events in participants with apathy symptoms (14/263 (5.3%) and 22/277 (7.9%) respectively). This renders our finding on the absence of an association between depressive symptoms and incident cardiovascular disease prone to a type II error. Finally, because the present analysis was based on the information on incident cardiovascular disease and stroke at 2 years, no time-to-event analysis could be performed.

The results of this study indicate that it is important for clinicians to recognize symptoms of apathy as an independent risk factor for cardiovascular disease in older individuals without a history of cardiovascular disease or stroke. The OR of 2.94 is
comparable with the OR of other well-established cardiovascular risk factors, such as current smoking (OR 2.87), or diabetes mellitus (OR 2.37). Future research should focus on whether cardiovascular risk factor assessment and following treatment of cardiovascular risk factors can reduce the risk of incident cardiovascular disease in older persons with apathy symptoms and no previous cardiovascular disease or stroke. Early recognition of apathy symptoms with a simple instrument as the GDS may help to identify a vulnerable population at increased risk of incident cardiovascular disease. These older individuals would, on the basis of their negative history of cardiovascular disease and stroke only, otherwise not be eligible for prevention strategies and might even be prone to withdraw from clinical care because of the nature of apathy symptoms. In addition, apathy symptoms may lead to non-adherence to a healthy lifestyle and diminished activities, potentially adding to the clinical relevance of our observations.

CONCLUSION

Symptoms of apathy in older persons without a history of cardiovascular disease or stroke are highly prevalent and are strongly associated with incident cardiovascular disease. This association is independent from well-established cardiovascular risk factors and from the presence of depressive symptoms. Apathy can therefore be considered as an important risk factor for incipient cardiovascular disease. This underlines the need of recognition of apathy symptoms in older persons without previous cardiovascular disease or stroke, especially because the nature of these symptoms might lead to a tendency to withdraw from clinical care.

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