ORIGINAL ARTICLE

Association of Vascular Factors With Apathy in Community-Dwelling Elderly Individuals

Suzanne A. Ligthart, MD; Edo Richard, MD, PhD; Nina L. Fransen, BSc; Lisa S. M. Eurelings, MD; Leo Beem, PhD†; Piet Eikelenboom, MD, PhD; Willem A. van Gool, MD, PhD; Eric P. Moll van Charante, MD, PhD

Context: Apathy in community-dwelling elderly individuals has been associated with a history of stroke and other cardiovascular disease.

Objective: To assess the relationship between symptoms of apathy and cardiovascular risk factors or disease (stroke or other) in a large sample of elderly people aged 70 to 78 years without depression or dementia.

Design: Cross-sectional data analysis within an ongoing cluster-randomized, open, multicenter trial.

Setting: The Netherlands, general community.

Participants: We studied 3534 elderly individuals without dementia who were included in the Prevention of Dementia by Intensive Vascular Care trial.

Main Outcome Measures: Symptoms of apathy, assessed with 3 items from the 15-item Geriatric Depression Scale, in participants with few or no depressive symptoms.

Results: The median age of participants was 74.3 years. Principal components analysis of the Geriatric Depression Scale confirmed a separate factor for the apathy items (Geriatric Depression Scale–3A). Two or more symptoms of apathy were present in 699 participants (19.9%), of whom 372 (53.2%) were without depressive symptoms (Geriatric Depression Scale–12D score <2). Ordinal regression analysis showed that increasing apathy in the absence of depressive symptoms was associated with a history of stroke (odds ratio, 1.79; 95% CI, 1.38-2.31) and cardiovascular disease other than stroke (1.28; 1.09-1.52). Exploratory analysis among 1889 participants free from stroke and other cardiovascular disease revealed an association between apathy score and the following cardiovascular risk factors: systolic blood pressure ($P=.03$), body mass index ($P=.002$), type 2 diabetes mellitus ($P=.07$), and C-reactive protein ($P<.001$).

Conclusions: Symptoms indicative of apathy are common in community-dwelling nondemented older people who are free from depression. The independent association of stroke, other cardiovascular disease, and cardiovascular risk factors with symptoms of apathy suggests a causal role of vascular factors.

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Defined as an impairment of motivation, apathy is operationalized as diminished goal-oriented behavior and cognition.[1,2] It is a very common symptom in several neuropsychiatric diseases, including dementia, stroke, depression, Parkinson disease, and schizophrenia,[3] but it is also observed in otherwise healthy elderly persons.[4,5] Apathy is associated with poor treatment response and negative outcomes, such as functional loss and caregiver distress.[3,6] Several risk factors for apathy in older people have been reported, such as advancing age, an increasing number of health conditions, lower income, current depression, and cognitive and functional impairment.[4,7-9]

So far, only a few studies[4,5,8,10,11] have described the prevalence of apathy in community-dwelling populations without overt neuropsychiatric diseases. Depending on the inclusion criteria and instruments used, it was found to range from 1% to 27%. Recently, it has been suggested that apathy is associated with cardiovascular pathologic features: for community-dwelling elderly individuals with apathy, a history of cardiovascular disease (CVD; eg, myocardial infarction, peripheral arterial disease, or stroke reported by their general practitioner [GP] and by electrocardiogram assessments) was present more often than for controls.[11] Moreover, elderly individuals with CVD more often developed apathy, but not depression, during follow-up.[11]

Author Affiliations: Departments of General Practice (Drs Ligthart, Beem, and Moll van Charante) and Neurology (Drs Richard, Eurelings, Eikelenboom, and van Gool and Ms Fransen), Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands. †Deceased.

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Recognition of apathy and the underlying mechanisms could lead to better understanding of this condition that may represent a construct that is distinct from depression in some participants. A different prognosis and different therapeutic options may apply for apathy. We aimed to assess the prevalence of apathy symptoms in a large cohort of community-dwelling elderly people, and we analyze the association between apathy and a history of stroke or other CVD. In addition, we explore the independent effect of vascular risk factors on apathy in participants without depressive symptoms and without a history of any CVD.

METHODS

PARTICIPANTS

From May 1, 2006, through March 31, 2009, a total of 3534 community-dwelling elderly individuals in the Netherlands were included for participation in the Prevention of Dementia by Intensive Vascular Care (PREDIVA) trial.[12] This cluster-randomized controlled trial with a 6-year follow-up is designed to assess the effects of nurse-led, intensive vascular care on the prevention or postponement of dementia and disability in a primary health care population. Cardiovascular events and depression are secondary outcomes. The background, methods, randomization, and projected follow-up of the PREDIVA trial have been previously described.[12] In short, all patients in participating primary health care centers aged 70 to 78 years, without a diagnosis of dementia and able to visit their primary care practice, were eligible for this study. Patients with a condition likely to hinder successful long-term follow-up (eg, terminal illness, alcoholism, or living abroad for the main part of the year) were excluded by their GP (11.2% of total population). Patients were invited by a letter from the researchers and their own GP as well as a reminder and a telephone call from the nurse practitioner, after which 53.3% signed informed consent. After baseline assessments, GP practices were randomized to standard care or intensive vascular care. In the intervention group, a nurse-led intervention aimed at cardiovascular risk factors was provided that is based on current national guidelines. This includes lifestyle advice, smoking cessation programs, and diet counseling. Cardiovascular medication adherence is addressed and, if indicated, GPs initiate or improve medical treatment of hypertension, dyslipidemia, type 2 diabetes mellitus (T2DM), and the use of thrombocyte aggregation inhibitors or anticoagulants.

The PREDIVA study was approved by the medical ethics committee of the Academic Medical Center, Amsterdam.

BASELINE ASSESSMENT

During the PREDIVA baseline assessments, data were collected on demographic characteristics, cardiovascular risk factors (blood pressure, body mass index [calculated as weight in kilograms divided by height in meters squared], lipid spectrum, C-reactive protein [CRP], smoking habits, and fasting blood glucose/T2DM), and history of CVD, categorized as stroke/transient ischemic attack (TIA) or other CVD (including myocardial infarction, angina pectoris, and peripheral arterial disease). Medical history and current medication use were cross-checked with the electronic medical records of the GPs if necessary. In the Netherlands, more than 98% of the population is registered with a GP. All GPs participating in the PREDIVA study use electronic medical records, which are connected to the local pharmacies to enable close monitoring of prescriptions. Cognitive function was assessed using the Mini-Mental State Examination (MMSE).[13] Disability was measured using the Academic Medical Center Linear Disability Score (ALDS).[14]

ASSESSMENT OF APATHY AND DEPRESSIVE SYMPTOMS

At baseline, the 15-item Geriatric Depression Scale (GDS-15) was administered to all participants to screen for depressive symptoms.[15] Previous research has shown that the GDS-15, also referred to as the short form of the originally developed GDS-30, has 3 dimensions: general depressive affect (7 items), life satisfaction (4 items), and withdrawal (3 items).[16] One remaining item on problems with memory did not load on any factor in the principal components analysis. The subscale on withdrawal, also described as "apathy," contains the following items: (1) Have you dropped many of your activities and interests? (2) Do you prefer to stay at home rather than to go out and do new things? (3) Do you feel full of energy? Van der Mast et al[11] reported a sensitivity of 69% and a specificity of 85% for this subscale compared with the 14-item Apathy Scale of Starkstein et al[17] in participants 85 years or older. The same 3 items were identified also as part of the 6 "WAV items" within the GDS-30 (withdrawal, apathy, and [lack of] vigor), along with 3 other items outside the GDS-15, and were preserved in a confirmatory factor analysis.[7,18]

We conducted an exploratory factor analysis to verify the validity of this construct within the PREDIVA data. Using principal components analysis with varimax rotation (Kaiser normalization), a 3-component structure was found, with all 3 apathy items loading on the same factor, along with the item on memory. When solutions were chosen with more components, the 3 apathy items retained their projection onto 1 component.

On the basis of these findings, 2 subscales were discerned within the GDS-15: one for apathy symptoms (GDS-3A; range, 0-3 points, with higher scores indicating more apathy) and one for depression (GDS-12D; range, 0-12 points, with higher scores indicating more symptoms of depression/dissatisfaction with life). Apathy was analyzed ordinally. To allow for comparison with previously published data, the presence of apathy symptoms was also dichotomized as 2 or 3 points on the GDS-3A vs 0 or 1 points. The prevalence of depressive symptoms was operationalized as 2 or more points on the GDS-12D.[11]

STATISTICAL ANALYSIS

Data were analyzed using SPSS statistical software, version 18.0 (SPSS Inc). For univariate analyses, the χ^2 statistic was used for independence for nominal variables, Kruskal-Wallis was used for ordinal variables, and 1-way analysis of variance was used for continuous variables.

Multiple imputations using the Markov chain Monte Carlo method were executed to replace missing data with plausible values. In view of the ordinal nature of apathy scores from 0 to 3, ordinal regression analysis was performed with GDS-3A as the dependent variable to analyze the cross-sectional relation of CVD with an increasing apathy score. Separate analyses were performed in participants with few or no depressive symptoms (GDS-12D score <2) and participants with depressive symptoms (GDS-12D score ≥ 2). Separate analyses of participants who did not have depressive symptoms allow us to assess the relation between isolated symptoms of apathy and cardiovascular risk factors, which is hypothesized to be different from symptoms of apathy in the presence of depressive symptoms. The association of symptoms of apathy and a history of

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Table 1. Baseline Characteristics of 3534 Participants in the PREDIVA Study

Characteristic	Value
Demographic	
Male sex, No. (%)	1609 (45.5)
Age, median (IQR), y	74.3 (4.1)
Educational level ≤6 y, No. (%)[a]	837 (23.9)
Neuropsychiatric measures[b]	
MMSE, median (IQR)	28 (27-29)
GDS-15, median (IQR)	1 (0-2)
GDS-12D, median (IQR)	0 (0-1)
GDS-3A, median (IQR)	0 (0-1)
GDS-12D score ≥2 points, No. (%)	658 (18.7)
GDS-3A score ≥2 points, No. (%)	699 (19.9)
Medical history, No. (%)	
Type 2 diabetes mellitus	647 (18.3)
Cardiovascular disease[c]	1045 (29.8)
Stroke[d]	346 (9.9)

Abbreviations: GDS-15, 15-item Geriatric Depression Scale; GDS-3A, 3-item apathy subscale of the GDS-15; GDS-12D, 12-item depression subscale of the GDS-15; IQR, interquartile range; MMSE, Mini-Mental State Examination; PREDIVA, Prevention of Dementia by Intensive Vascular Care.

[a] Data were missing for 35 participants.

[b] Twenty-eight participants had more than 3 items missing on GDS-15 (>2 on the GDS-12D and/or >1 on the GDS-3A). The GDS-3A is derived from the GDS-15, using 3 items on apathy (withdrawal); the GDS-12D comprises all remaining nonapathy items of the GDS-15.

[c] Data were missing for 24 participants.

[d] Data were missing for 48 participants.

stroke (yes/no) and "other CVD" (yes/no) was investigated with ordinal regression analysis. Because symptoms of apathy are influenced by demographic characteristics, cognitive status, and other comorbidities, 3 models are presented. Model 1 shows the crude associations. In model 2, demographic characteristics (age, sex, and educational level) are controlled for. Model 3 shows these associations controlled for cognitive status using the MMSE score and controlled for the number of nonvascular prescriptions as a proxy for other comorbidities in addition to the demographic characteristics.[4,19] A direct effect of stroke due to structural brain damage can contribute to the pathophysiological features of apathy after stroke. Therefore, stroke and other CVD are analyzed separately.

Although the ALDS may correct for disability resulting from previous stroke or CVD, it was not included in the model because apathy is reported to cause disability, leading to potential overcorrection for functional decline. Nevertheless, a separate analysis with the ALDS as an independent covariate was performed to evaluate this effect.

The relationship of vascular risk factors with apathy, including blood pressure, T2DM, obesity, smoking, and hypercholesterolemia, was further explored in participants without symptoms of depression and CVD or stroke/TIA in their medical history, both with and without correction for demographic characteristics (age, sex, and educational level). This exploratory analysis was aimed at evaluating the associations with vascular risk factors independent of the CVD and stroke/TIA that may result from these risk factors.

RESULTS

Table 1 shows the baseline characteristics for the PREDIVA study population (N=3534). The median age was 74.3 years; 54.5% of participants were female and 97.9% were white. A history of all-cause CVD (stroke and/or other CVD) was present in 35.2% of the participants. Twenty-eight participants (<1%) had more than 3 items missing on the GDS-15 (>2 on the GDS-12 and/or >1 on the GDS-3) and were excluded from the analysis. The median GDS-15 score was 1 (6.3% had a score ≥6), and 699 of 3506 participants (19.9%) had a score of 2 or 3 points on the GDS-3A. In participants with few or no symptoms of depression on the GDS-12D, 372 (10.6%) scored positive on at least 2 apathy items. The median MMSE score was 28 (interquartile range, 27-29).

Results of univariate analysis of GDS-3A for participants with few or no depressive symptoms (GDS-12D score <2) are shown in **Table 2**. Within this group (n=2848), a history of stroke/TIA or other CVD was increasingly present with higher apathy scores. Higher apathy scores were associated with low educational level (≤6 years), higher age, more prescriptions for nonvascular conditions, and lower MMSE scores.

Missing data ranged from zero missing (for sex and age) to 131 missing (3.7%; for CRP). The Markov chain Monte Carlo procedure yielded 5 subsets of imputed data. The pooled results of multivariate ordinal regression analysis for participants without depressive symptoms are given in **Table 3**. Model 1 shows the unadjusted association, model 2 shows the association when adjusted for demographic characteristics (age, sex, and educational level), and model 3 shows the association when adjusted for demographic characteristics, MMSE score, and the number of nonvascular prescriptions. Odds ratios represent the effect of change in 1 unit of the predictors on the apathy score odds, with the ratio being the same for each of the cumulative probabilities in the proportional odds model. In participants without depression, a history of stroke/TIA and a history of other CVD were both significantly associated with increasing apathy scores. An additional adjustment for disability using the ALDS yielded slightly lower odds ratios for the effects of a history of stroke/TIA and other CVD (1.65; 95% CI, 1.28-2.14; and 1.21; 1.02-1.44, respectively), but their contribution in the model retained significance ($P < .001$ and $P = .03$, respectively). In participants with depressive symptoms (GDS-12D score ≥2) (n=658), there was no significant association of apathy with stroke/TIA (fully adjusted model: odds ratio, 1.16; 95% CI, 0.81-1.67; $P = .42$) or other CVD (fully adjusted model: 1.08; 0.80-1.46; $P = .63$). A similar analysis excluding all participants who had reported a history of stroke/TIA had no important effect on the odds ratios in the remaining model of either group or on their significance (difference in odds ratio for all independent variables, <4%).

The Figure shows that the prevalence of T2DM, increasing systolic blood pressure, body mass index, and CRP are associated with increasing severity of apathy in 1889 participants free from CVD and symptoms of depression (GDS-12D score <2) (T2DM: $P = .07$; systolic blood pressure: $P = .03$; body mass index: $P = .002$; and CRP: $P < .001$). No association with apathy was found for current smoking and increasing diastolic blood pressure (current smoking: $P = .17$; diastolic blood pressure: $P = .38$). Also, no association was found for high-density lipoprotein, low-density lipoprotein, or total cholesterol level (data not shown). In a mul-

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Table 2. Demographic and Clinical Characteristics by Apathy Score in Univariate Analysis for 2848 Participants Without Depressive Symptoms (GDS-12D Score <2)

Variable	GDS-3A Score, No. (%)				Overall[a]	*P* Value
	0	1	2	3		
Total	1695 (59.5)	781 (27.4)	296 (10.4)	76 (2.7)	**2848** (100)	
Demographic characteristic						
Male sex	806 (47.6)	383 (49.0)	125 (42.2)	35 (46.1)	**1349** (47.4)	.25[b]
Educational level <6 y[c]	316 (18.8)	194 (25.1)	87 (29.6)	21 (28.0)	**618** (21.9)	<.001[b]
Mean age, y	74.11	74.37	74.79	75.27	74.28	<.001[d]
Mean MMSE score	28.29	28.18	28.01	28.00	28.23	.009[e]
Nonvascular prescriptions[f]	1.52	1.78	2.13	2.84	1.69	<.001[e]
Cardiovascular history						
CVD[g]	428 (25.3)	233 (29.8)	105 (35.5)	32 (42.1)	**798** (28.0)	<.001[b]
Stroke[h]	108 (6.4)	63 (8.1)	43 (14.5)	13 (17.1)	**227** (8.0)	<.001[b]

Abbreviations: CVD, cardiovascular disease; 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; MMSE, Mini-Mental State Examination.
[a] Data were missing for 28 participants on the GDS-3A or GDS-12D.
[b] χ^2 Test.
[c] Data were missing for 26 participants.
[d] One-way analysis of variance.
[e] Kruskal-Wallis test.
[f] Number of different prescriptions.
[g] Data were missing for 21 participants.
[h] Data were missing for 38 participants.

Table 3. Ordinal Logistic Regression With Apathy Score as the Dependent Variable for 2848 Participants Without Depressive Symptoms (GDS-12 Score <2)[a]

Characteristic	Model 1		Model 2		Model 3	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
CVD, excluding stroke	1.39 (1.18-1.63)	<.001	1.37 (1.16-1.61)	<.001	1.28 (1.09-1.52)	.004
Stroke	1.80 (1.40-2.33)	<.001	1.84 (1.42-2.38)	<.001	1.79 (1.38-2.31)	<.001

Abbreviations: CVD, cardiovascular disease; GDS-12, 12-item subscale of the 15-item Geriatric Depression Scale; OR, odds ratio.
[a] Odds ratios are given for every point increase in the apathy score (possible score, 0-3). Model 1 is unadjusted; model 2 is adjusted for age, sex, and educational level; and model 3 is adjusted for age, sex, educational level, Mini-Mental State Examination score, and number of nonvascular prescriptions.

tivariate model adjusted for age, sex, and educational level, these associations were slightly attenuated (T2DM: $P=.08$; systolic blood pressure: $P=.05$; body mass index: $P=.02$; CRP: $P<.001$; current smoking: $P=.02$; and total cholesterol level: $P=.86$).

COMMENT

Our findings demonstrate that symptoms of apathy are common in community-dwelling elderly individuals without dementia or symptoms of depression and that apathy symptoms are associated with a history of stroke/TIA and other CVD. In elderly people with depressive symptoms, these associations were not found. Increasing apathy scores were also associated with cardiovascular risk factors, including T2DM, systolic blood pressure, obesity, and CRP in participants free from CVD, stroke/TIA, and depression.

Our finding that symptoms of apathy are prevalent in 20% of otherwise healthy community-dwelling elderly individuals is in agreement with other reports (20%-27%),[5,10,11] although some found much lower rates (1%-6%),[4,8] reflecting a lack of agreement on the definition of apathy. In 2009, consensus diagnostic criteria were developed by Robert et al[20] to facilitate further research on the nosological position of apathy, both as an independent construct and in relation to other neuropsychiatric disorders. For this diagnosis, 2 of 3 dimensions of apathy (reduced goal-directed behavior, goal-directed cognitive activity, and emotions) must be present for a minimum of 4 weeks, and there should be functional impairments caused by apathy. A criterion standard for measuring apathy is, however, not yet available. In our large population-based study, symptoms of apathy and depression were assessed with the GDS-15 rather than by a specific apathy scale or clinical interviews.

Despite this limitation, the GDS-3A items have repeatedly been shown to represent apathy or withdrawal, as discussed in the "Methods" section. In addition to a comparison with the apathy scale, the face validity of these items was confirmed by consensus among 17 professionals unaware of the factor analysis.[11] In our exploratory factor analysis, we found a separate factor for these 3 items as well, in accordance with these previous findings and strengthening the hypothesis that these items represent a distinct cluster of symptoms.

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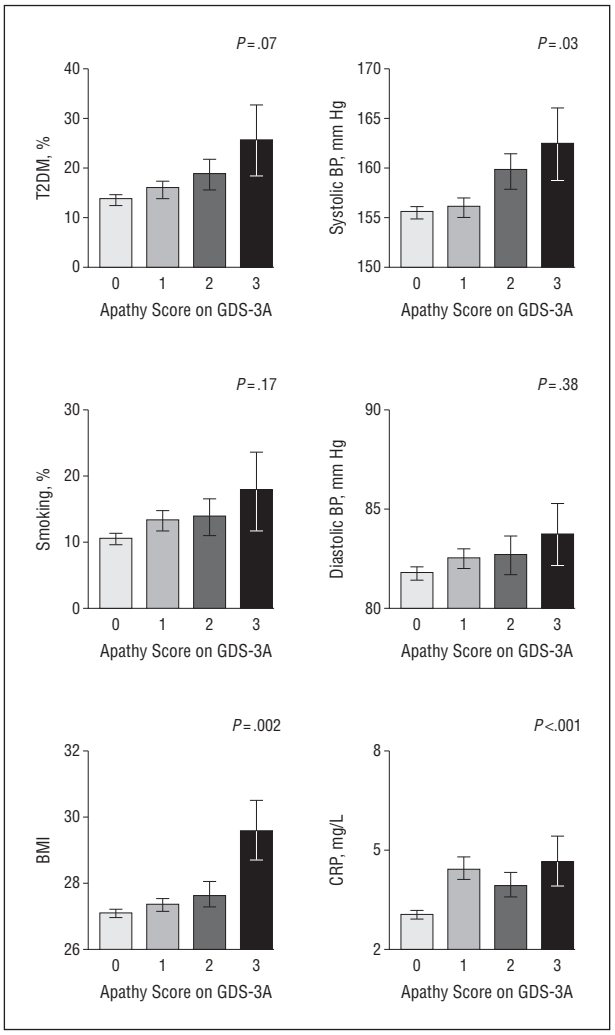

Figure. Cardiovascular risk factors by apathy score in participants without cardiovascular disease or stroke and without depressive symptoms (Geriatric Depression Scale–12D score <2) (n=1889). Error bars indicate standard error. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CRP, C-reactive protein; GDS-3A, 3-item apathy subscale of the 15-item Geriatric Depression Scale; and T2DM, type 2 diabetes mellitus.

A cross-sectional relationship between increasing age and apathy was described previously,[10] as well as a progression of apathy prevalence with increasing age during follow-up.[4,11] Lower baseline MMSE scores among otherwise healthy community-dwelling elderly individuals with apathy were reported previously,[10] although others found no association with changes in apathy scores after 5 years of follow-up.[4] A lower baseline level of education in relation to apathy in the general population has been reported before in 1 study.[21]

Our finding that apathy is associated with a history of stroke/TIA and other CVD in an unselected population aged 70 to 78 years is consistent with a previous report by van der Mast et al[11] in a sample of 85-year-old community-dwelling elderly, in which they found that older people with apathy had more cardiovascular pathologic features (both including and excluding stroke) compared with study participants without apathy. In addition, vascular disease at baseline predisposed to apathy but not depression during 5 years of follow-up. Consistent with our findings, peripheral arterial disease, as measured by a lower ankle-brachial index, was recently found to be an independent risk factor for apathy in a community-dwelling population.[21] It was recently shown that healthy elderly individuals with apathy more often have deep white matter lesions than those without,[5] whereas progression of deep white matter lesions was not associated with development of depressive symptoms among older people at risk of CVD.[22] A relation of specific anatomical locations of cerebral infarcts and deep white matter lesions with apathy has been suggested. Especially, lesions in the basal ganglia and frontosubcortical lesions have been reported to be associated with apathy, although never in an unselected population-based sample such as ours.[3,23,24] Because we did not perform neuroimaging, we do not know whether specific lesion localizations are associated with apathy in our sample.

To overcome the potential bias that apathy after stroke is attributable to direct brain damage, we analyzed the association of apathy with cardiovascular risk factors in participants who had never had a stroke or TIA. This analysis also showed a strong correlation of symptoms of apathy with vascular risk factors. This refutes the possibility that the association of apathy with CVD is driven by direct brain damage as a consequence of (classic) stroke alone and suggests that other forms of brain damage may play a role—for example, slowly progressive white matter changes or clinically "silent" subcortical ischemic lesions.

The association of apathy with hypertension, T2DM, obesity, and CRP in elderly who are free from stroke/TIA, CVD, and depressive symptoms in our cohort (**Figure**) lends further support for a possible causal role of vascular factors. It is interesting to see consistency in their increase with apathy score, suggesting a "dose-effect" relation, although some of these relations may be confounded by, for instance, adherence to prescribed treatment.

Similar to our findings, other studies on apathy in nondemented community-dwelling elderly found no relation between depressive symptoms and CVD, deep white matter lesions, or cardiovascular risk factors.[5,11,21] A recent publication from the Rotterdam study concluded that atherosclerosis does not appear to increase the risk of incident depression in older adults.[25] In fact, hypotheses on the role of vascular factors in depression may be confounded by the concept of apathy—that is, when psychometric instruments to assess depression that include several items on apathy are used, patients can be misdiagnosed as depressive on the basis of a high score on apathy items. The consistent relation between age and apathy within nondepressed elderly in our study suggests a pathophysiological mechanism that is different from depression. Since the "vascular depression" hypothesis was coined in 1997, it has been noted that older patients with depressive disorders and vascular or cerebrovascular disease have different symptoms, with more prominent apathy and lack of insight and less feelings of guilt, supporting the hypothesis of different pathophysiological mechanisms underlying depression in the elderly.[26,27] In this context, it might be appropriate to conclude that, in addition to the concept of "vascular depression," there are possibly a significant

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number of older people without depressed mood who have "vascular apathy."

The *DSM-IV* allows the diagnosis of depression in the absence of a depressed mood, provided that symptoms of loss of interest or anhedonia are present. This may in part explain the high frequency of co-occurrence of depression and apathy.[2] Indeed, this may have caused misclassification of patients with apathy (with no or few dysphoric symptoms) as having a depressive syndrome.[7,28,29] If so, this could have important consequences for clinical practice. Characterizing a patient as apathetic instead of depressed will have consequences for treatment and prognosis.

One of the strengths of this study is the large, unselected general population and the limited number of exclusion criteria (mainly dementia and short life expectancy), increasing the external validity and minimizing potential selection bias. Because the study was not primarily designed to measure apathy but does include depression as a secondary outcome, apathy was measured with the GDS-3A as part of the GDS-15. Although several apathy scales are available, as yet no consensus has been reached on the optimal set of instruments for use in unselected and disease-specific neuropsychiatric populations.[30] The recently published consensus criteria on apathy are a welcome contribution to this field, and we hope they will help guide future research on this subject.[20]

Most participants were white, and there might be a selection of the "worried well" regarding the preventive nature of the study, although our sample does not seem very different from the overall Dutch population. Among 7 of the PREDIVA health care centers, the age and sex of participants (n=900) vs nonparticipants (n=689) were compared and showed that the latter were slightly older (mean, 74.6 vs 74.3 years; $P=.02$) and there were slightly more women (58.8% vs 54.5%; $P=.09$). In the Dutch "Doetinchem cohort study" (n=4520; 2003-2007), 18% to 28% of participants aged 65 to 75 were reported to be obese (body mass index >30) vs 24% in our population.[31] The number of smokers among our participants (13.3%) is similar to that of the Dutch population in general of the same age (12%-15%),[32] providing further credibility to the external validity of our findings.

Our findings are based on a secondary analysis of baseline data of the PREDIVA study. There are some limitations with respect to parameters of depletion and frailty. The overall score on the ALDS in our population is high, indicating little disability. It is likely that the frailest participants in the population do not participate in the PREDIVA study because they were excluded by their GP. By screening for cognitive impairment with the use of the MMSE and Visual Association Test, we aimed to exclude participants with imminent dementia. This does not exclude the possibility of subtle cognitive impairment in some of the participants but, considering the design, setting, and size of this study, this screening is adequate.

The present findings warrant further research into the relationship of cardiovascular risk factors and atherosclerotic disease with symptoms of apathy and depression. The influence of these symptoms on frailty or handicap (and vice versa) could be important in understanding the effect of apathy and depression on functional impairment. Further longitudinal studies could contribute to our knowledge on the natural course of symptoms of apathy, potential ways of preventing apathy (and associated disability), and the potential misclassification of persons who are apathetic rather than depressed.

In conclusion, symptoms of apathy appear to be highly prevalent in the healthy, community-dwelling elderly population. The strong association between symptoms of apathy and a history of stroke/TIA, other CVD, and cardiovascular risk factors among community-dwelling elderly participants who are free from depressive symptoms and dementia is suggestive of an important contribution of vascular factors in the etiology of apathy.

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Correspondence: Suzanne A. Ligthart, Department of General Practice, Academic Medical Center, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, the Netherlands (s.a.ligthart@amc.nl).
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REFERENCES

1. Marin RS. Apathy: a neuropsychiatric syndrome. *J Neuropsychiatry Clin Neurosci.* 1991;3(3):243-254.
2. Starkstein SE, Leentjens AF. The nosological position of apathy in clinical practice. *J Neurol Neurosurg Psychiatry.* 2008;79(10):1088-1092.
3. van Reekum R, Stuss DT, Ostrander L. Apathy: why care? *J Neuropsychiatry Clin Neurosci.* 2005;17(1):7-19.
4. Brodaty H, Altendorf A, Withall A, Sachdev P. Do people become more apathetic as they grow older? a longitudinal study in healthy individuals. *Int Psychogeriatr.* 2010;22(3):426-436.
5. Yao H, Takashima Y, Mori T, Uchino A, Hashimoto M, Yuzuriha T, Miwa Y, Sasaguri T. Hypertension and white-matter lesions are independently associated with apathetic behavior in healthy elderly subjects: the Sefuri brain MRI study. *Hypertens Res.* 2009;32(7):586-590.
6. Brodaty H, Sachdev PS, Withall A, Altendorf A, Valenzuela MJ, Lorentz L. Frequency and clinical, neuropsychological and neuroimaging correlates of apathy

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following stroke—the Sydney Stroke Study. *Psychol Med*. 2005;35(12):1707-1716.
7. Adams KB. Depressive symptoms, depletion, or developmental change? withdrawal, apathy, and lack of vigor in the Geriatric Depression Scale. *Gerontologist*. 2001;41(6):768-777.
8. Onyike CU, Sheppard JM, Tschanz JT, Norton MC, Green RC, Steinberg M, Welsh-Bohmer KA, Breitner JC, Lyketsos CG. Epidemiology of apathy in older adults: the Cache County Study. *Am J Geriatr Psychiatry*. 2007;15(5):365-375.
9. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA*. 2002;288(12):1475-1483.
10. Clarke DE, Ko JY, Lyketsos C, Rebok GW, Eaton WW. Apathy and cognitive and functional decline in community-dwelling older adults: results from the Baltimore ECA longitudinal study. *Int Psychogeriatr*. 2010;22(5):819-829.
11. van der Mast RC, Vinkers DJ, Stek ML, Bek MC, Westendorp RG, Gussekloo J, de Craen AJ. Vascular disease and apathy in old age: the Leiden 85-Plus Study. *Int J Geriatr Psychiatry*. 2008;23(3):266-271.
12. Richard E, Van den Heuvel E, Moll van Charante EP, Achthoven L, Vermeulen M, Bindels PJ, van Gool WA. Prevention of Dementia by Intensive Vascular Care (PREDIVA): a cluster-randomized trial in progress. *Alzheimer Dis Assoc Disord*. 2009;23(3):198-204.
13. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12(3):189-198.
14. Holman R, Lindeboom R, Vermeulen M, de Haan RJ. The AMC Linear Disability Score project in a population requiring residential care: psychometric properties. *Health Qual Life Outcomes*. 2004;2:42. doi:10.1186/1477-7525-2-42.
15. Lesher EL, Berryhill JS. Validation of the Geriatric Depression Scale–Short Form among inpatients. *J Clin Psychol*. 1994;50(2):256-260.
16. Mitchell J, Mathews HF, Yesavage JA. A multidimensional examination of depression among the elderly. *Res Aging*. 1993;15:198-219.
17. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 1992;4(2):134-139.
18. Adams KB, Matto HC, Sanders S. Confirmatory factor analysis of the geriatric depression scale. *Gerontologist*. 2004;44(6):818-826.
19. Agostini JV, Han L, Tinetti ME. The relationship between number of medications and weight loss or impaired balance in older adults. *J Am Geriatr Soc*. 2004; 52(10):1719-1723.
20. Robert P, Onyike CU, Leentjens AF, Dujardin K, Aalten P, Starkstein S, Verhey FR, Yessavage J, Clement JP, Drapier D, Bayle F, Benoit M, Boyer P, Lorca PM, Thibaut F, Gauthier S, Grossberg G, Vellas B, Byrne J. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry*. 2009;24(2):98-104.
21. Sugawara N, Yasui-Furukori N, Umeda T, Kaneda A, Sato Y, Takahashi I, Matsuzaka M, Danjo K, Nakaji S, Kaneko S. Ankle brachial pressure index as a marker of apathy in a community-dwelling population. *Int J Geriatr Psychiatry*. 2011; 26(4):409-414.
22. Versluis CE, van der Mast RC, van Buchem MA, Bollen EL, Blauw GJ, Eekhof JA, van der Wee NJ, de Craen AJ; PROSPER Study. Progression of cerebral white matter lesions is not associated with development of depressive symptoms in elderly subjects at risk of cardiovascular disease: the PROSPER Study. *Int J Geriatr Psychiatry*. 2006;21(4):375-381.
23. Takashima Y, Yao H, Koga H, Endo K, Matsumoto T, Uchino A, Sadanaga-Akiyoshi F, Yuzuriha T, Kuroda Y. Frontal lobe dysfunction caused by multiple lacunar infarction in community-dwelling elderly subjects. *J Neurol Sci*. 2003; 214(1-2):37-41.
24. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cereb Cortex*. 2006;16(7):916-928.
25. Newson RS, Hek K, Luijendijk HJ, Hofman A, Witteman JC, Tiemeier H. Atherosclerosis and incident depression in late life. *Arch Gen Psychiatry*. 2010;67 (11):1144-1151.
26. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. "Vascular depression" hypothesis. *Arch Gen Psychiatry*. 1997;54(10):915-922.
27. Alexopoulos GS. Depression in the elderly. *Lancet*. 2005;365:1961-1970.
28. Marin RS, Firinciogullari S, Biedrzycki RC. The sources of convergence between measures of apathy and depression. *J Affect Disord*. 1993;28(2):117-124.
29. Levy ML, Cummings JL, Fairbanks LA, Masterman D, Miller BL, Craig AH, Paulsen JS, Litvan I. Apathy is not depression. *J Neuropsychiatry Clin Neurosci*. 1998; 10(3):314-319.
30. Clarke DE, Ko JY, Kuhl EA, van Reekum R, Salvador R, Marin RS. Are the available apathy measures reliable and valid? a review of the psychometric evidence. *J Psychosom Res*. 2011;70(1):73-97.
31. Blokstra A, Picavet HSJ, Verschuren WMM. *The Doetinchem Cohort Study 4th Measurement 2003-2007 [(in Dutch]*. Bilthoven, the Netherlands: National Institute of Public Health and the Environment (RIVM); 2010. Report No. 260401007/2010.
32. Hoeymans N, Melse JM, Schoenmaker CG. *Report of the Dutch 2010 Public Health Status and Forecasts Report: Health and Its Determinants [in Dutch]*. Bilthoven, the Netherlands: National Institute of Public Health and the Environment (RIVM); 2010. Report No. 270061006.

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