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### Vascular factors in dementia and apathy

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# CHAPTER 5

## **LOW-GRADE INFLAMMATION DIFFERENTIATES BETWEEN SYMPTOMS OF APATHY AND DEPRESSION IN COMMUNITY-DWELLING OLDER INDIVIDUALS**

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## **ABSTRACT**

### **Background**

Systemic low-grade inflammation has repeatedly been associated with depression in old age, but the relationship with apathy is less clear. The present study assessed whether C-reactive protein (CRP) is differentially associated with symptoms of apathy and depression.

### **Methods**

A population-based cohort study was carried-out. At baseline and after two and four years of follow-up, CRP levels were assessed and symptoms of apathy and depression were measured using the 15-item Geriatric Depression Scale. Logistic regression analysis was used to investigate the cross-sectional and longitudinal associations of CRP with symptoms of apathy and depression.

### **Results**

Two thousand forty-seven community-dwelling participants (70-78 years) without a history of cardiovascular disease or stroke were studied. A cross-sectional association was found between CRP and apathy symptoms at three time points (odds ratio [OR] per natural log unit increase in CRP: baseline visit=1.40, 95% CI=1.12-1.75; two-year follow-up visit=1.62, 95% CI=1.17-2.25; four-year follow-up visit=1.51, 95% CI=1.03-2.21). This did not change after adjustment for demographics and depressive symptoms, and was slightly attenuated after adjustment for cardiovascular risk factors. No cross-sectional association was found with depressive symptoms. Baseline CRP did not predict incident apathy or depressive symptoms during four years of follow-up.

### **Conclusions**

Increased CRP levels are associated with apathy symptoms but not with depressive symptoms. This suggests a differential effect of inflammation on apathy and depression. In older persons, symptoms of apathy may be a behavioral manifestation of concurrent low-grade inflammation.

## INTRODUCTION

Apathy and depression are common in community-dwelling older individuals<sup>1-3</sup> and both conditions have been associated with several adverse outcomes, including cognitive and functional impairment.<sup>4-6</sup> Although apathy, which is primarily defined as a disorder of motivation,<sup>7</sup> can occur as a symptom of depression, it can also occur independently as an isolated syndrome. Apathy can be discriminated from depression by lack of motivation in the absence of dysphoric symptoms, such as a depressed mood, guilt, hopelessness, and helplessness.<sup>8</sup> Differentiating apathy from depression is clinically relevant, because management and prognosis differ,<sup>9</sup> and because both conditions appear to be differentially associated with future cardiovascular disease. Recently, symptoms of apathy were found to be an independent risk factor for incident cardiovascular disease in community-dwelling older individuals, whereas depressive symptoms were not.<sup>10</sup> This may reflect different underlying etiologies of both conditions, and, in particular, may indicate the involvement of vascular factors in the development of apathy.<sup>1,2</sup>

Cardiovascular disease is often accompanied by a chronic, low-grade systemic inflammatory reaction. C-reactive protein (CRP), a sensitive systemic marker of inflammation, has been associated with the initiation and progression of atherosclerosis and with an increased risk of cardiovascular events.<sup>11,12</sup> Especially CRP levels >3 mg/L are associated with a high risk of future cardiovascular events, but even those with 1 to 3 mg/L are at moderate risk.<sup>11</sup> Systemic inflammation has also been hypothesized to foment 'sickness behavior', referring to a cluster of adaptive behavioral symptoms including somnolence, loss of energy, malaise, and diminished interest in activities,<sup>13</sup> that overlap with symptoms of apathy. In this manner, low-grade inflammation associated with atherosclerosis may manifest as apathy-like symptoms.

Elevated levels of CRP have been associated with depression.<sup>14,15</sup> However, because apathy and depression may be confused due to overlapping clinical features,<sup>9</sup> this association may be confounded by symptoms of apathy. Whether mild to moderate elevations in CRP are associated with symptoms of apathy is unclear due to conflicting findings.<sup>16,17</sup> An association between apathy symptoms and increased CRP levels may point in the direction of a mechanistic explanation for the independent association of apathy symptoms with incident cardiovascular events that was reported previously.<sup>10</sup> Symptoms of apathy could be a behavioral manifestation of the low-grade inflammatory reaction associated with underlying atherosclerosis, a process that in itself may lead to an increased risk of future vascular events.

In the present study, we assessed whether CRP is differentially associated with present or future symptoms of apathy and depression. Given the increased risk of incident cardiovascular disease associated with symptoms of apathy, we hypothesized that increased CRP levels would be associated with both present and future apathy symptoms.

## METHODS

### Participants

The study sample was drawn from the ongoing Prevention of Dementia by Intensive Vascular Care (preDIVA) trial (ISRCTN29711771). This is a cluster-randomized controlled trial with a follow-up of six years to assess the efficacy of nurse-led intensive vascular care on the prevention or postponement of dementia and disability in a primary health care population. Mortality, cognitive decline, depression, and vascular events (including myocardial infarction, peripheral arterial disease, angina pectoris, and stroke) are secondary outcomes. Between May 2006 and March 2009, 3533 community-dwelling older individuals aged 70-78 were included. All eligible individuals in 116 general practitioner (GP) practices were invited, resulting in a participation rate of 53.3%. The non-respondents did not differ substantially from the study participants.<sup>2</sup> The Medical Ethics Committee of the Academic Medical Center in Amsterdam has approved the study and all participants signed informed consent before enrolment. A detailed description of the preDIVA study design has been published elsewhere.<sup>18</sup> For the present analyses the population is considered as a cohort, irrespective of randomization group.

### Assessment of symptoms of apathy and depression

At baseline and after two and four years of follow-up, symptoms of apathy and depression were assessed using the 15-item Geriatric Depression Scale (GDS-15) (range from 0-15, higher scores indicate worse functioning), which is a widely used self-administered depression screening measure.<sup>19</sup> Participants were requested to fill out the questionnaire at home before visiting a practice nurse. During the visit, the practice nurse ran through the questionnaire to check whether the participant had completed all items and to help in case of any questions. In line with previous factor analyses,<sup>2</sup> an apathy score was calculated using the sum of three apathy-items (GDS-3A; range 0-3 points, higher scores indicating more apathy). These items are: (1) Have you dropped many of your activities and interests?; (2) Do you prefer to stay at home, rather than going out and doing new things?; and (3) Do you feel full of energy? Face validity of this 3-item apathy subscale was established by an expert team of psychiatrists, behavioral neurologists, and neuropsychologists who consented on the same three GDS-15 items as representing apathy symptoms, while being unaware of the factor analyses results.<sup>1</sup> The remaining 12 items were considered to represent depressive symptoms and were summed to calculate a depression score (GDS-12D; range 0-12 points, higher scores indicating more depressive symptoms). Symptoms of apathy and depression were defined as  $GDS-3A \geq 2$  and  $GDS-12D \geq 2$ , respectively. Participants with  $>2$  items missing on the GDS-12D and/or  $>1$  on the GDS-3A were excluded from the analysis.

## Assessment of C-reactive protein

At all three visits, serum CRP levels were determined in local laboratories affiliated with the GP practices using immunoturbidimetric assays (Beckman Coulter Olympus AU2700, Siemens Advia 2400, Roche Cobas 6000, and Roche Modular P800). Because CRP values above 10 mg/L mostly indicate active inter-current infection, rather than a low-grade inflammatory reaction associated with cardiovascular disease risk, individuals with CRP values higher than 10 mg/L were removed from the analysis.<sup>11</sup>

## Other measurements

At baseline, data on socio-demographic features (age, sex, and level of education) were obtained for all individuals. Presence of a history of cardiovascular disease (including myocardial infarction, peripheral arterial disease, and angina pectoris) or stroke was evaluated by interview with a practice nurse in combination with simultaneous review of the GP's electronic medical records. At baseline and after two and four years follow-up, data on cardiovascular risk factors were recorded: blood pressure, diabetes mellitus (DM), cholesterol, body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), and smoking (current versus never/former). Cognitive function was assessed with the Mini-Mental State Examination (MMSE) (range from 0-30, higher scores indicating better functioning).<sup>20</sup>

## Statistical analysis

To correct for possible confounding of the association between low-grade inflammation and symptoms of apathy/depression by previous cardiovascular disease or stroke (since symptoms of apathy and depression can occur as a direct consequence of a stroke lesion, or as a result from disability caused by previous vascular disease), we excluded individuals with a history of cardiovascular disease or stroke from the primary analyses.<sup>10</sup> However, using a sensitivity framework, all analyses were repeated including these participants.

CRP values were skewed to the right and were natural log transformed (ln-CRP) after adding 1 to all CRP values to avoid excessive separation of values. Logistic regression analysis was used to analyze the cross-sectional and longitudinal associations of ln-CRP (independent variable) with symptoms of apathy and depression (dependent variables). Because of the transformation, odds ratios (OR) represent OR per natural log unit increase in CRP (natural logarithmic base≈2.72). Separate analyses were performed for apathy symptoms (GDS-3A≥2) and depressive symptoms (GDS-12D≥2). Three separate cross-sectional analyses were performed using the baseline, the two-year, and the four-year follow-up data on CRP and GDS-3A/GDS-12D scores. In the longitudinal analysis,

the association between baseline CRP and incident symptoms of apathy and depression after four years of follow-up was assessed, restricting the analysis to participants who did not have baseline symptoms of apathy or depression ( $GDS-3A \leq 1$  and  $GDS-12D \leq 1$ ). As a sensitivity analysis, the association between baseline CRP and incident symptoms of apathy and depression after two years of follow-up was also assessed.

All cross-sectional analyses were adjusted for demographic characteristics (age at the respective visit, sex, and level of education (<7, 7-12, and >12 years)) and additionally for cardiovascular risk factors at the respective visit (hypertension (systolic blood pressure (SBP)  $\geq 160$  mmHg), dyslipidemia (total cholesterol  $\geq 251$  mg/dL), current smoking, BMI  $\geq 30$  kg/m<sup>2</sup>, and DM). The longitudinal analyses were adjusted for baseline demographics and additionally for baseline cardiovascular risk factors. Furthermore, to assess the effect of CRP on apathy symptoms independent of co-morbid depressive symptoms and the effect of CRP on depressive symptoms independent of co-morbid apathy symptoms, all apathy analyses were adjusted for GDS-12D score and all depression analyses for GDS-3A score. The data were analyzed with SPSS statistical software, version 20.0 (IBM Corp., Armonk, NY).

## RESULTS

### Study population

Of the 3533 participants that completed the preDIVA baseline assessment, 2259 had no history of cardiovascular disease or stroke (Figure 1). Of these, 78 refused blood sampling resulting in 2047 participants with a baseline CRP  $\leq 10$  mg/L who were available for inclusion in the cross-sectional analysis using baseline data. Of the 2259 participants without a history of cardiovascular disease or stroke, 1813 and 1457 participants completed the two- and four year follow-up visit respectively. At both visits, the most frequently occurring reasons for drop-out were withdrawal on own request and relocation. Of the participants that did attend the two- and four year follow-up visit, respectively 835 and 841 refused blood sampling, resulting in respectively 899 and 566 participants with a CRP level  $\leq 10$  mg/L who were available for analysis. Both after two and four years of follow-up, there were no major differences with respect to important baseline characteristics between participants with an available CRP measurement and those without (i.e. those who did not attend the follow-up visit and those who did attend the follow-up visit but refused blood sampling) (see supplementary table S1). For the longitudinal analysis on incident symptoms of apathy and depression after four years, 1015 participants with a baseline CRP  $\leq 10$  mg/L and without symptoms of apathy or depression at baseline were studied. For the analysis of incident symptoms of apathy and depression after two years of follow-up, the number of studied participants was 1264.

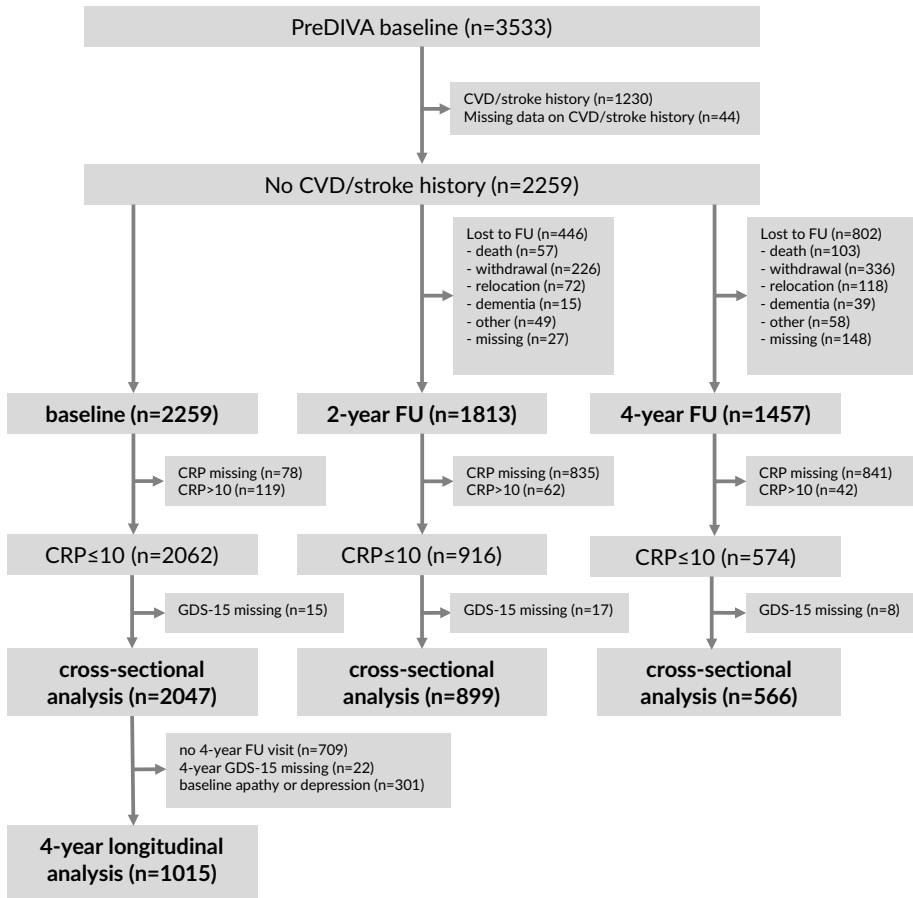


Figure 1. Flowchart of selection of study participants. Missing items on the 15-item Geriatric Depression Scale (GDS-15): >2 items missing on the Geriatric Depression Scale-12D and/or >1 item missing on the Geriatric Depression Scale-3A. CVD, cardiovascular disease; FU, follow-up; CRP, C-reactive protein (in mg/L).

Baseline characteristics are summarized in table 1 for the total study population (n=2047) and separately for participants with apathy symptoms (n=329 (16.1%)) and depressive symptoms (n=321 (15.7%)). The baseline median CRP concentration was 2.0 mg/L (interquartile range (IQR) 1.0-3.0) in the total study sample. At the two-year follow-up assessment (n=899), apathy symptoms were present in 145 (16.1%) participants and depressive symptoms in 142 (15.8%) participants. At the four-year follow-up visit (n=566), these numbers were 110 (19.4%) and 89 (15.7%), respectively. The median CRP concentration was 2.0 mg/L (IQR 1.0-3.0) after two years of follow-up and 1.7 mg/L (IQR 1.0-3.3) after four years of follow-up.

**Table 1. Baseline characteristics of all participants without cardiovascular disease/stroke and according to symptoms of apathy and depression**

Characteristic	Total study population (n=2047)	Apathy symptoms (GDS-3A≥2) (n=329)	Depressive symptoms (GDS-12D≥2) (n=321)
<b>Demographics</b>			
Mean age (years) (SD)	74.2 (2.5)	74.8 (2.5)	74.4 (2.3)
Male sex, n (%)	804 (39.3)	108 (32.8)	105 (32.7)
<b>Educational level<sup>a</sup></b>			
Low (<7 years), n (%)	469 (23.1)	111 (33.9)	101 (32.1)
Intermediate (7-12 years), n (%)	1296 (63.9)	184 (56.3)	188 (59.7)
High (>12 years), n (%)	262 (12.9)	32 (9.8)	26 (8.3)
White, n (%) <sup>b</sup>	1967 (98.0)	316 (96.9)	308 (97.5)
<b>Cardiovascular risk factors</b>			
Diabetes Mellitus, n (%)	321 (15.7)	67 (20.4)	57 (17.8)
BMI≥30 kg/m <sup>2</sup> , n (%) <sup>c</sup>	457 (22.3)	99 (30.1)	83 (25.9)
Current smoking, n (%) <sup>d</sup>	240 (11.7)	58 (17.6)	54 (16.8)
Systolic blood pressure≥160 mmHg, n (%) <sup>d</sup>	836 (40.9)	153 (46.5)	130 (40.5)
Total cholesterol≥251 mg/dL, n (%) <sup>e</sup>	352 (17.2)	64 (19.5)	67 (20.9)
<b>Inflammation measure</b>			
Median CRP mg/L (IQR)	2.0 (1.0-3.0)	2.0 (1.0-1.4)	2.0 (1.0-3.0)
<b>Neuropsychiatric measures</b>			
Median GDS-15 (IQR)	1 (0-2)	3 (1-5)	3 (1-5)
Median GDS-3A (IQR)	0 (0-1)	2 (2-3)	1 (0-2)
Median GDS-12D (IQR)	0 (0-1)	1 (0-3)	2 (3-4)
Mean MMSE score (SD)	28.2 (1.7)	27.9 (1.7)	27.9 (2.0)

SD = standard deviation; BMI = body mass index; CRP = C-reactive protein; IQR = interquartile range; 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; MMSE = Mini-Mental State Examination.

<sup>a</sup> Missing data for total sample, participants with apathy symptoms and participants with depressive symptoms respectively: n=20, n=2, n=6. Percentages do not add up to 100 because of rounding. <sup>b</sup> Missing data for n=39, n=3, n=5. <sup>c</sup> Missing data for n=1, n=0, n=0. <sup>d</sup> Missing data for n=2, n=0, n=0. <sup>e</sup> Missing data for n=4, n=1, n=0.

## Cross-sectional associations

CRP level was cross-sectionally associated with symptoms of apathy at all visits (OR baseline visit=1.40, 95% CI=1.12-1.75; two-year follow-up visit=1.62, 95% CI=1.17-2.25; four-year follow-up visit=1.51, 95% CI=1.03-2.21) (table 2). This did not change importantly after adjustment for demographic characteristics. Additional adjustment for cardiovascular risk factors and GDS-12D score did not affect the association found at two and four years of follow-up (OR two-year follow-up visit =1.54, 95% CI=1.05-2.26; OR four-year follow-up visit=1.71, 95% CI=1.08-2.69), but led to slight attenuation of the association at the baseline visit (OR=1.26, 95% CI=0.97-1.63). This attenuation was

Table 2. Cross-sectional associations between CRP and symptoms of apathy and depression<sup>a</sup>

	Total number of subjects (n) Subjects with symptoms (n)	Model 1 <sup>b</sup>		Model 2 <sup>c</sup>		Model 3 <sup>d</sup>	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Apathy symptoms (GDS-3A≥2)	baseline n=2047 n=329	1.40 (1.12–1.75)	.003	1.32 <sup>e</sup> (1.05–1.66)	.016	1.26 <sup>f</sup> (0.97–1.63)	.083
	2-year visit n=899 n=145	1.62 (1.17–2.25)	.004	1.50 <sup>g</sup> (1.07–2.11)	.018	1.54 <sup>h</sup> (1.05–2.26)	.029
	4-year visit n=566 n=110	1.51 (1.03–2.21)	.036	1.48 <sup>i</sup> (1.00–2.19)	.049	1.71 <sup>j</sup> (1.08–2.69)	.021
Depressive symptoms (GDS-12D≥2)	baseline n=2047 n=321	1.09 (0.87–1.37)	.458	1.04 <sup>e</sup> (0.83–1.32)	.722	0.89 <sup>f</sup> (0.69–1.16)	.397
	2-year visit n=899 n=142	1.09 (0.78–1.52)	.632	1.03 <sup>g</sup> (0.73–1.45)	.865	0.89 <sup>h</sup> (0.60–1.31)	.548
	4-year visit n=566 n=89	1.01 (0.66–1.56)	.956	0.98 <sup>i</sup> (0.62–1.52)	.911	0.80 <sup>j</sup> (0.48–1.33)	.388

CRP = C-reactive protein; 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.

<sup>a</sup> Logistic regression analysis for natural log-transformed C-reactive protein (CRP) in subjects without a history of cardiovascular disease/stroke and with CRP ≤ 10 mg/L.

<sup>b</sup> Unadjusted.

<sup>c</sup> Adjusted for demographics: age at respective visit, sex, educational level (<7 years, 7–12 years, >12 years).

<sup>d</sup> Adjusted for demographics, cardiovascular risk factors (systolic blood pressure (SBP) ≥ 160 mmHg, total cholesterol ≥ 251 mg/dL, current smoking, body mass index (BMI) ≥ 30 kg/m<sup>2</sup>, and presence of diabetes mellitus), GDS-12D score (apathy analysis) and GDS-3A score (depression analysis).

<sup>e</sup> Missing data for 20 participants.

<sup>f</sup> Missing data for 29 participants.

<sup>g</sup> Missing data for 10 participants.

<sup>h</sup> Missing data for 37 participants.

<sup>i</sup> Missing data for 7 participants.

<sup>j</sup> Missing data for 40 participants.

largely due to adjustment for BMI. No associations were found between CRP level and depressive symptoms (table 2).

## Longitudinal associations

Table 3 shows the results of the longitudinal analysis for participants free of symptoms of apathy and depression at baseline. Baseline CRP level did not predict incident symptoms of apathy (OR=1.20, 95% CI=0.81–1.78) or incident depressive symptoms (OR=1.10, 95% CI=0.73–1.64) after four years of follow-up. In addition, baseline CRP level was not associated with incident apathy or depressive symptoms after two years of follow-up (see supplementary table S2).

Repeating the cross-sectional and longitudinal analyses including all participants with a history of cardiovascular disease or stroke (n=1230) and with missing data on this variable (n=44) did not change any of the conclusions.

Table 3. Longitudinal associations between baseline CRP and incident symptoms of apathy and depression after four years of follow-up<sup>a</sup> (n=1015)

	Subjects with incident symptoms (n)	Model 1 <sup>b</sup>		Model 2 <sup>c</sup>		Model 3 <sup>d</sup>	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Incident apathy symptoms (GDS-3A $\geq$ 2)	104	1.20 (0.81–1.78)	.360	1.22 <sup>e</sup> (0.82–1.81)	.334	1.10 <sup>f</sup> (0.71–1.70)	.673
Incident depressive symptoms (GDS-12D $\geq$ 2)	100	1.10 (0.73–1.64)	.658	1.05 <sup>e</sup> (0.70–1.59)	.817	0.98 <sup>f</sup> (0.62–1.53)	.916

CRP = C-reactive protein; 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.

<sup>a</sup> Logistic regression analysis for natural log-transformed baseline C-reactive protein (CRP) in subjects with baseline CRP $\leq$ 10 mg/L, without baseline apathy and depressive symptoms, and without a history of cardiovascular disease/stroke.

<sup>b</sup> Unadjusted.

<sup>c</sup> Adjusted for baseline demographics: age, sex, educational level (<7 years, 7–12 years, >12 years).

<sup>d</sup> Adjusted for baseline demographics, baseline cardiovascular risk factors (systolic blood pressure (SBP)  $\geq$ 160 mmHg, total cholesterol $\geq$ 251 mg/dL, current smoking, body mass index (BMI)  $\geq$ 30 kg/m<sup>2</sup>, and presence of diabetes mellitus), GDS-12D score (apathy analysis) and GDS-3A score (depression analysis) at four years of follow-up.

<sup>e</sup> Missing data for 8 participants.

<sup>f</sup> Missing data for 15 participants.

## DISCUSSION

In the present study in community dwelling older individuals, a cross-sectional association was found between CRP level and symptoms of apathy at multiple points in time during follow-up. No cross-sectional association was found with depressive symptoms. Also, baseline CRP-level did not predict incident symptoms of apathy or depression after two or four years of follow-up.

The results of this study suggest a concurrent relationship between CRP levels as a marker of low-grade inflammation and symptoms of apathy. These symptoms may be a behavioral manifestation of a chronic low-grade inflammatory process. The finding that CRP levels did not predict incident apathy symptoms after two or four years of follow-up could reflect that the relationship between increased CRP levels and apathy symptoms is merely concomitant. This is consistent with the 'sickness behavior' hypothesis, which proposes presence of apathy-like symptoms at the time of systemic inflammation.<sup>13</sup> However, in spite of the clinical similarities between apathy and sickness behavior, the overlap between both conditions may only be partial. Sickness behavior represents a cytokine-induced adaptive response to infection which is normally fully reversible when the pathogen has been eliminated.<sup>13</sup> Apathy on the other hand may be a maladaptive, potentially non-reversible response induced by chronic low-grade inflammation. Another reason for not finding a longitudinal association between increased CRP levels and

apathy symptoms could be selective drop-out of participants, given that the most frequently occurring reasons for drop-out were withdrawal on own request and relocation. Part of the participants that withdrew from the study could have been too apathetic to attend a follow-up visit and some of the participants who did not attend the follow-up visit due to relocation could have been institutionalized due to cardiovascular disease, which is associated with both increased CRP levels<sup>11</sup> and apathy symptoms.<sup>1,2,10</sup>

Symptoms of apathy have been found to significantly increase the risk of future cardiovascular events, and mediation analyses have revealed that part of this association can be explained by the mediating effect of smoking, physical inactivity, and DM.<sup>10,21</sup> However, the majority of the effect of apathy symptoms on incident cardiovascular disease is caused by other, yet unknown, factors.<sup>21</sup> If symptoms of apathy are indeed a behavioral manifestation of underlying low-grade inflammation associated with atherosclerosis, this may be an additional explanation why these symptoms are predictive for future cardiovascular events. The finding that no association was observed with depressive symptoms may indicate a differential effect of inflammation on the development of symptoms of apathy and depression. This lends further support to the concept of apathy and depression as being separate clinical constructs, although often co-occurring.

The results of this study are in line with previous findings of an association between CRP level and apathy in elderly women with cognitive impairment.<sup>17</sup> Similarly, an association between apathy and level of tumor necrosis factor alpha (TNF- $\alpha$ ) or its soluble receptors, as markers of inflammation, has been reported in two studies in elderly individuals with cognitive impairment.<sup>22,23</sup> In a population-based cohort study of older individuals, CRP was specifically associated with worse performance on information processing speed and attention and executive functioning,<sup>24</sup> which are frequent neuropsychological correlates of apathy.<sup>4,5</sup> Importantly, these associations were independent of depressive symptoms. Similar findings were observed in a study of older individuals with cardiovascular disease.<sup>25</sup> Our results are in contrast with earlier findings from the Leiden 85-Plus Study in which no cross-sectional association with either symptoms of apathy or depression was found and higher baseline CRP levels increased the risk of depression.<sup>16</sup> These discrepancies may partly be due to the different study populations, most notably the substantially higher age of the participants of the Leiden 85-Plus Study. CRP has been shown to display different characteristics depending on the age of the population studied. For example, elevated levels of CRP have been associated with an increased risk of future cognitive decline in mid- and early late-life, but are associated with less cognitive decline in the very old.<sup>26</sup> We did not observe any association between raised CRP levels and depressive symptoms, in contrast to findings of meta-analyses indicating that increased CRP levels are associated with both present and future depression.<sup>14,15</sup> Several explanations may account for this. First, in the meta-analysis of longitudinal studies, the effect was only modest<sup>15</sup> and the strongest associations have

been observed in clinically depressed patient samples as opposed to community-based samples.<sup>14</sup> The degree of depressive symptoms in the current population-based sample may not have been sufficient to detect such an association. Second, the effect sizes differed substantially across individual studies,<sup>14</sup> and part of this heterogeneity may be due to confounding by apathy, since several studies used depression assessment instruments containing apathy items. Recent studies indicate that inflammation predominantly induces vegetative symptoms such as fatigue and loss of energy, rather than affective symptoms such as disturbances in mood and feelings of guilt or worthlessness.<sup>27,28</sup>

Strengths of this study include its large sample size and longitudinal design. Earlier studies on the association between apathy and markers of inflammation have predominantly been performed in relatively small samples. The population-based design increases the generalizability of our findings. Some limitations to the present study should also be noted. Because an extensive clinical examination of apathy and depression was not part of the preDIVA study protocol, formal diagnoses of depression and apathy according to clinical guidelines could not be established. Although the three apathy items from the GDS-15 have a sensitivity of 69% and specificity of 85% when compared to the Apathy Scale,<sup>1</sup> it is not clear how these symptoms relate to apathy as an independent syndrome. The three items do not cover all three areas (reduced goal-directed behavior, goal-directed cognitive activity, and emotions) of the consensus diagnostic criteria as described by Robert et al.<sup>7</sup> It is therefore important to note that the use of the GDS-3A implies that only the association between low-grade inflammation and *symptoms* representing apathy, as a behavioral dimension rather than a discrete syndrome, can be examined. The same applies to the measurement of depressive symptoms in the current study. The percentages of participants with symptoms of apathy and depression were fairly similar at baseline and also over time, potentially indicating co-morbidity between both conditions. One could therefore argue that the association between increased CRP levels and apathy symptoms was mainly driven by concomitant depressive symptoms. However, this association remained after adjustment for GDS-12D scores, indicating an effect of CRP on apathy symptoms, independent of depressive symptoms. Although participants without a CRP measurement did not differ substantially at baseline from those with a CRP measurement, it is possible that missing CRP at follow-up is not the result of missing completely at random. Extensive co-morbidity, age, socio-economic status, and, as mentioned above, even the presence of apathy or depression are potential reasons for missing the laboratory assessment, which may have introduced sampling bias. We were not able to adjust for inflammatory co-morbidities, such as rheumatoid arthritis and malignancies, but since individuals with these conditions generally have CRP levels > 10 mg/L<sup>29</sup> and were thus excluded from this study, it is unlikely that this has led to substantial residual confounding. Finally, although CRP is frequently used as an indicator of systemic inflammation, other, more direct markers of inflamma-

tion, such as interleukin-1 and TNF- $\alpha$ , may better indicate inflammation, and are the main pro-inflammatory cytokines involved in 'sickness behavior'.<sup>13</sup> The use of CRP as the only measure of inflammation in the present study may therefore have led to an underestimation of the associations.

In conclusion, in this large sample of community-dwelling older individuals, we found a concurrent relationship between low-grade inflammation and symptoms of apathy. Apathy symptoms may be a behavioral manifestation of concomitant underlying low-grade inflammation. The absence of a relation with depressive symptoms may indicate a differential effect of inflammation on apathy and depression and underlines the importance of discriminating between both conditions.

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## REFERENCES

1. van der Mast RC, Vinkers DJ, Stek ML, et al. Vascular disease and apathy in old age. The Leiden 85-Plus Study. *Int J Geriatr Psychiatry*. 2008;23(3):266-271.
2. Ligthart SA, Richard E, Fransen NL, et al. Association of vascular factors with apathy in community-dwelling elderly individuals. *Arch Gen Psychiatry*. 2012;69(6):636-642.
3. Luppá M, Sikorski C, Luck T, et al. Age- and gender-specific prevalence of depression in latest-life--systematic review and meta-analysis. *J Affect Disord*. 2012;136(3):212-221.
4. Brodaty H, Sachdev PS, Withall A, Altendorf A, Valenzuela MJ, Lorentz L. Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke - the Sydney Stroke Study. *Psychol Med*. 2005;35(12):1707-1716.
5. van Reekum R, Stuss DT, Ostrander L. Apathy: why care? *J Neuropsychiatry Clin Neurosci*. 2005;17(1):7-19.
6. Wilkins VM, Kiosses D, Ravdin LD. Late-life depression with comorbid cognitive impairment and disability: nonpharmacological interventions. *Clin Interv Aging*. 2010;5:323-331.
7. Robert P, Onyike CU, Leentjens AF, et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry*. 2009;24(2):98-104.
8. Marin RS, Firinciogullari S, Biedrzycki RC. The sources of convergence between measures of apathy and depression. *J Affect Disord*. 1993;28(1):7-14.
9. Fones CS. Distinguishing apathy syndromes from vascular depression. *Arch Gen Psychiatry*. 1998;55(9):844-845.
10. Eurelings LS, Ligthart SA, van Dalen JW, Moll van Charante EP, van Gool WA, Richard E. Apathy is an independent risk factor for incident cardiovascular disease in the older individual: a population-based cohort study. *Int J Geriatr Psychiatry*. 2014;29(5):454-463.
11. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation*. 2003;107(3):363-369.
12. Bisoendial RJ, Boekholdt SM, Vergeer M, Stroes ES, Kastelein JJ. C-reactive protein is a mediator of cardiovascular disease. *Eur Heart J*. 2010;31(17):2087-2091.
13. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008;9(1):46-56.
14. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med*. 2009;71(2):171-186.
15. Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. *J Affect Disord*. 2013;150(3):736-744.
16. Maas DW, van der Mast RC, de Craen AJ. Increased C-reactive protein is not associated with apathy: the Leiden 85-Plus Study. *Int J Geriatr Psychiatry*. 2009;24(11):1177-1184.
17. Hall JR, Johnson LA, Vo HT, Barber RC, Winter S, O'Bryant SE. Biomarkers and depressive symptoms in older women with and without cognitive impairment. *JBBB*. 2012;2:276-281.
18. Richard E, Van den Heuvel E, Moll van Charante EP, et al. Prevention of dementia by intensive vascular care (PreDIVA): a cluster-randomized trial in progress. *Alzheimer Dis Assoc Disord*. 2009;23(3):198-204.

19. Lesher EL, Berryhill JS. Validation of the Geriatric Depression Scale--Short Form among inpatients. *J Clin Psychol*. 1994;50(2):256-260.
20. 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.
21. Eurelings LS, Jaccard J, Moll van Charante EP, et al. The mediating role of cardiovascular risk factors in the relationship between symptoms of apathy and incident cardiovascular disease in community-dwelling older individuals. *Int Psychogeriatr*. 2016;28(4):669-679.
22. Hall JR, Vo HT, Johnson LA, Winter S, Barber RC, O'Bryant SE. Biomarkers and depressive symptoms in a sample of cognitively intact and Alzheimer's Disease elderly males. *NM*. 2011;2:306-312.
23. Guimarães HC, Caramelli P, de Paula França E, Afonso MPD, Fialho PPA, Teixeira AL. Serum levels of soluble TNF- $\alpha$  receptors but not BDNF are associated with apathy symptoms in mild Alzheimer's disease and amnesic mild cognitive impairment. *Dem Neuropsychol*. 2013;7:298-303.
24. Heringa SM, van den Berg E, Reijmer YD, et al. Markers of low-grade inflammation and endothelial dysfunction are related to reduced information processing speed and executive functioning in an older population - the Hoorn Study. *Psychoneuroendocrinology*. 2014;40:108-118.
25. Hoth KF, Haley AP, Gunstad J, et al. Elevated C-reactive protein is related to cognitive decline in older adults with cardiovascular disease. *J Am Geriatr Soc*. 2008;56(10):1898-1903.
26. Lima TA, Adler AL, Minett T, et al. C-reactive protein, APOE genotype and longitudinal cognitive change in an older population. *Age Ageing*. 2014;43(2):289-292.
27. Duijvis HE, Vogelzangs N, Kupper N, de Jonge P, Penninx BW. Differential association of somatic and cognitive symptoms of depression and anxiety with inflammation: findings from the Netherlands Study of Depression and Anxiety (NESDA). *Psychoneuroendocrinology*. 2013;38(9):1573-1585.
28. Inagaki M, Akechi T, Okuyama T, et al. Associations of interleukin-6 with vegetative but not affective depressive symptoms in terminally ill cancer patients. *Support Care Cancer*. 2013;21(8):2097-2106.
29. Allin KH, Nordestgaard BG. Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. *Crit Rev Clin Lab Sci*. 2011;48(4):155-170.

## SUPPLEMENTARY MATERIAL

Table S1. Baseline characteristics of participants with and without an available CRP measurement

Characteristic	With 2-year CRP (n=978)	Without 2-year CRP (n=1281)	P	With 4-year CRP (n=616)	Without 4-year CRP (n=1643)	P
<b>Demographics</b>						
Mean age (years) (SD)	74.1 (2.4)	74.3 (2.5)	.043	74.0 (2.4)	74.3 (2.5)	.015
Male sex, n (%)	378 (38.7)	517 (40.4)	.411	235 (38.1)	660 (40.2)	.382
Educational level <sup>a</sup>			.526			.052
Low (<7 years), n (%)	233 (24.0)	292 (23.0)		116 (19.0)	409 (25.1)	
Intermediate (7-12 years), n (%)	614 (63.4)	810 (63.8)		418 (68.5)	1006 (61.8)	
High (>12 years), n (%)	122 (12.6)	167 (13.2)		76 (12.5)	213 (13.1)	
<b>Inflammation measure</b>						
Median CRP mg/L (IQR) <sup>b</sup>	2.0 (1.0-4.0)	2.0 (1.0-4.0)	.045	2.0 (1.0-4.0)	2.0 (1.0-4.0)	.935
<b>Neuropsychiatric measures</b>						
Apathy symptoms (GDS-3A $\geq$ 2), n (%) <sup>c</sup>	160 (16.4)	210 (16.5)	.978	104 (16.9)	266 (16.3)	.703
Depressive symptoms (GDS-12D $\geq$ 2), n (%) <sup>d</sup>	141 (14.5)	214 (16.8)	.147	83 (13.5)	272 (16.6)	.072

CRP = C-reactive protein; SD = standard deviation; IQR = interquartile range; 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. P values from Student's t-test and Mann-Whitney U test for continuous variables, chi-squared test for binary variables, and chi-squared test for trend for ordinal variables. <sup>a</sup> Missing data for 21 participants. <sup>b</sup> Missing data for 78 participants. <sup>c</sup> Missing data for 10 participants. <sup>d</sup> Missing data for 12 participants.

Table S2. Longitudinal associations between baseline CRP and incident symptoms of apathy and depression after two years of follow-up<sup>a</sup> (n=1264)

	Subjects with incident symptoms (n)	Model 1 <sup>b</sup>		Model 2 <sup>c</sup>		Model 3 <sup>d</sup>	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Incident apathy symptoms (GDS-3A $\geq$ 2)	110	1.45 (1.00-2.11)	.048	1.31 <sup>e</sup> (0.89-1.92)	.170	1.12 <sup>f</sup> (0.74-1.70)	.597
Incident depressive symptoms (GDS-12D $\geq$ 2)	111	1.40 (0.97-2.03)	.075	1.30 <sup>e</sup> (0.89-1.89)	.178	1.21 <sup>f</sup> (0.80-1.83)	.358

CRP = C-reactive protein; 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.

<sup>a</sup> Logistic regression analysis for natural log-transformed baseline C-reactive protein (CRP) in subjects with baseline CRP $\leq$ 10 mg/L, without baseline apathy and depressive symptoms, and without a history of cardiovascular disease/stroke.

<sup>b</sup> Unadjusted.

<sup>c</sup> Adjusted for baseline demographics: age, sex, educational level (<7 years, 7-12 years, >12 years).

<sup>d</sup> Adjusted for baseline demographics, baseline cardiovascular risk factors (systolic blood pressure (SBP)  $\geq$ 160 mmHg, total cholesterol $\geq$ 251 mg/dL, current smoking, body mass index (BMI)  $\geq$ 30 kg/m<sup>2</sup>, and presence of diabetes mellitus), GDS-12D score (apathy analysis) and GDS-3A score (depression analysis) at two years of follow-up.

<sup>e</sup> Missing data for 10 participants.

<sup>f</sup> Missing data for 18 participants.