Am J of Geriatric Psychiatry 31:3 (2023) 183–194

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ajgponline.org

Clinical Review Article

Strengths and Weaknesses of the Vascular Apathy Hypothesis: A Narrative Review

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ARTICLE INFO

Article history:
Received July, 6 2022
Revised September, 12 2022
Accepted September, 27 2022

Key Words:
Apathy
cerebral small vessel disease
white matter hyperintensities

ABSTRACT

The vascular apathy hypothesis states that cerebral small vessel disease (CSVD) can cause apathy, even when no other symptoms of CSVD are present. In order to examine this hypothesis, the objectives of this narrative review are to evaluate the evidence for a pathophysiological mechanism linking CSVD to apathy and to examine whether CSVD can be a sole cause of apathy. The nature of the CSVD-apathy relationship was evaluated using the Bradford Hill criteria as a method for research on the distinction between association and causation. Pathological, neuroimaging, and behavioral studies show that CSVD can cause lesions in the reward network, which causes an apathy syndrome. Studies in healthy older individuals, stroke patients and cognitively impaired persons consistently show an association between CSVD markers and apathy, although studies in older persons suffering from depression are inconclusive. A biological gradient is confirmed, as well as a temporal relationship, although the evidence for the latter is still weak. The specificity of this causal relationship is low given there often are other contributing factors in CSVD patients with apathy, particularly depression and cognitive deterioration. Differentiating between vascular apathy and other apathy syndromes on the basis of clinical features is not yet possible, while in-depth knowledge about differences in the prognosis and efficacy of treatment options for apathy caused by CSVD and other apathy syndromes is lacking. Since we cannot differentiate between etiologically different apathy syndromes as yet, it is premature to use the term vascular apathy which would suggest a distinct clinical apathy syndrome. (Am J Geriatr Psychiatry 2023; 31:183–194)

Abbreviations: WMH, White matter hyperintensities; CSVD, Cerebral small vessel disease

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https://doi.org/10.1016/j.jagp.2022.09.016

Highlights

- **What is the primary question addressed by this study?**
  Can cerebral small vessel disease (CSVD) cause apathy, even when no other symptoms of CSVD are present yet?
- **What is the main finding of this study?**
  A causal relationship between CSVD and apathy was established, but the specificity of this relationship is low.
- **What is the meaning of the finding?**
  When a CSVD patient presents with apathy we recommend looking for other contributing factors, such as depression or cognitive deterioration.

INTRODUCTION

As a clinical syndrome, apathy is characterized by diminished motivation, leading to a reduction in emotions, thoughts, and initiative to perform activities.[1] Cerebral small vessel disease (CSVD), an atherosclerotic disease of the brain causing ischemic changes in the surrounding brain tissue, is suspected to be a cause of this frequent and disabling syndrome.[2,3] Neuroimaging markers of CSVD include white matter hyperintensities (WMH), cerebral microbleeds, lacunar infarcts, and visible perivascular spaces. Clinically, CVSD is associated with several symptoms and consequences, in particular cognitive impairment, problems with gait and balance, and a higher incidence of depression, stroke, dementia, disability, and death.[4] The vascular apathy hypothesis states that CSVD can be a sole cause of apathy, even in the absence of other symptoms of CSVD.[5-7]

Apathy is seen in 2%−6% of the general population, with its prevalence increasing with age.[8] Also the prevalence of CSVD increases with age, from 5% in people aged 50 years to almost 100% in those older than 90 years.[9] In CSVD populations 52% had severe apathy (based on the Apathy Scale and a median cut-off of 3).[10] Given these high prevalence rates, the vascular apathy hypothesis is particularly relevant for older populations, even more so considering the often more profound consequences of apathy such as aggravated functional impairment,[11] reduced quality of life,[3] high caregiver burden,[12,13] and a raised risk of incident cardiovascular disease, stroke, and mortality[14] and dementia.[15]

Although attractive as a hypothesis, many questions remain unanswered. Questions that remain are whether CSVD is a true causal factor for apathy and whether it can be a sole cause of apathy. Furthermore, the term 'vascular apathy' suggests a distinguishable clinical syndrome, but is that claim truly supported by the evidence?

This information is not only relevant for researchers, but also for clinicians. Researchers need a clear overview on what we do and what we do not know to help devise relevant research designs to fill in the gaps in our knowledge. Clinicians need this information to decide on how to interpret symptoms of patients presenting with apathy and signs of CSVD on imaging and to decide on what information and advice to give to these patients and their relatives and/or caregivers.

Objectives

The objective of the present narrative review article is twofold. We sought to gather and evaluate the evidence suggesting a pathophysiological mechanism linking CSVD and apathy and to examine whether the hypothesis that CSVD can be a sole cause of apathy has been substantiated.

METHODS

In order to be able to distinguish between association and causation, we tested the evidence using the Bradford Hill criteria,[16,17] which are summarized in Table 1. No single criterion can prove causation, but each criterion adds to the credibility of causation.

In order to establish whether CSVD can cause apathy, we searched the literature for evidence on the *plausibility* and the *strength* of associations.

In addition, we assessed whether there is a *biological gradient*, we evaluated data on the *temporality* of associations and the *consistency* and *coherence* of the

TABLE 1. Bradford-Hill Criteria for Causation

Criterion	Description
Plausibility	There is a rational, logical basis for an association.
Strength	The association is strong.
Temporality	The cause precedes the effect.
Biological gradient	There is a dose-response relationship.
Consistency	The association is established in multiple observations in different populations under different circumstances.
Specificity	The outcome is best predicted by one primary factor.
Coherence	The association is coherent with other knowledge.
Experimental evidence	The association is confirmed in experimental designs.
Analogy	An analogue phenomenon in another area is already accepted.

findings. Our second objective, to determine if CSVD can be a sole cause of apathy, was evaluated using the *specificity*-criterion.

We performed various searches to identify relevant research work (see supplementary material for each specific research question). 'White matter hyperintensities', 'lacunar infarcts', 'cerebral microbleeds', 'cortical thickness' and 'perivascular spaces' were included in the search criteria for 'cerebral small vessel disease'. When we searched for a combination of cerebral small vessel disease and apathy, we also included 'vascular apathy' as a search term. Searches were performed in PUBMED, English language, on December the 9, 2021. Abstracts of all articles were checked for relevance by the first author (LW). For some of the research questions recent (structured) reviews and meta-analyses were available. Information on other more recent research work which was not included in these (structured) reviews or meta-analyses was added when relevant to the argumentation.

For the *plausibility*-criterion we looked into the pathophysiological mechanisms that would link CSVD to apathy, thus supporting a causal relationship. To establish the *strength* of the association we looked into the odds ratios (OR), standard mean differences (SMD) and (clinical) significance of associations between CSVD biomarkers and apathy measures. A *biological gradient* was established if the level of CSVD was associated with the level of apathy. The *temporality*-criterion was fulfilled if the CSVD-apathy association was established in prospective studies. The *consistency* was based on the diversity of populations and circumstances in which the association was established and on the validity of the methods used to assess CSVD and apathy. Moreover, we established if these findings were *coherent* with results from other areas of research.

In our context *specificity* is established when the outcome (apathy) is best predicted by this one primary factor (CSVD). Hence, we looked at other important risk-factors for apathy and to what extent these could have influenced the results of studies assessing the CSVD-apathy association.

The criterion of *experimental evidence* cannot be evaluated since no cure for CSVD is yet established. Bradford-Hill stated that the criterion of *analogy* can provide some circumstantial additional support,[16] but it is not a core criterion for causation and we chose not to use it as evidence in this narrative review.

RESULTS

Plausibility

What pathophysiological mechanisms would link CSVD to apathy? In CSVD the small perforating arterioles, the capillaries and probably the venules of the brain are dysfunctioning, causing lesions. WMH, cerebral microbleeds, lacunar infarcts and perivascular spaces are biomarkers of CSVD, visible on neuroimaging.[18] It concerns a whole-brain disease and the lesions it causes are probably more dynamic than earlier thought: regions without visible lesions on neuroimaging can actually dysfunction, while regions with visible lesions sometimes regenerate.[4] In general though, it is a progressive disease.[4,18] Also, although upon pathological examination of the brains of CSVD patients not all radiological lesions seem to represent actual lesions, most do.[19] Furthermore, an increasing total CSVD burden or progression of WMH load does seem to reflect progression in CSVD severity.[18,20] It is therefore plausible that radiologically observed CSVD manifests as pathological lesions in the brain and that these lesions can hinder brain circuitries.

Imaging studies across patient populations (including populations of patients with neurodegenerative diseases, acquired brain injury, psychiatric disorders or Parkinson's disease) have related apathy to white matter lesions in the frontal, striatal and anterior cingulate pathways, to basal ganglia lesions and

to lesions in the parietal pathways.[21–23] Pathway analyses revealed that network disruption mediated the relationship between CSVD markers and apathy.[24] But how do lesions in these pathways lead to apathy?

Diffusion tensor imaging and functional imaging studies in humans have shown that effort-based decision making tasks are related to the frontal and striatal regions, including the medial orbitofrontal cortex, the anterior cingulate cortex (ACC) and the basal ganglia including the ventral striatum.[25] Connectivity in these pathways, which together are called the reward network, was reduced in CSVD patients with apathy (and connectivity was not reduced in motor or visual networks).[26] The link between this reward network and apathy would then be as follows: when, at the functional level, the process of effort-based decision making is disturbed, we see an apathy syndrome at the clinical level. And indeed, when behavioral paradigms were applied in CSVD patients, those with apathetic symptoms were less responsive to rewards and less inclined to investing efforts.[27,28]

The plausibility of a pathophysiological link between CSVD and apathy has thus been convincingly demonstrated.

Strength and Biological Gradient

What information do we have on the strength of a CSVD-apathy relationship and does the severity of CSVD predict the level of apathy?

In a recent meta-analysis of apathy studies including healthy individuals, persons with cognitive deficits and/or stroke, larger WMH volumes were significantly associated with apathy, with an OR of 1.41 (95% CI 1.05−1.89) and a standard mean difference (SMD) in apathy scores on the Apathy Evaluation Scale (AES)[29] between WMH severities (low or high) of 0.38 (95% CI 0.15−0.61).[30] In a large diffusion tensor imaging (DTI) study CSVD patients were significantly more apathetic than healthy controls, with the microstructural white matter changes in the CSVD sample showing a strong relationship with apathy.[10] In older adults receiving treatment for depression evidence of an WMH-apathy association was less consistent than in the populations referred to earlier (healthy older adults and older adults with cognitive impairment and/or stroke). One study did find an association,[31] one did not,[32] and in a severely depressed population the WMH-apathy association was established in participants with late-onset depression only.[33]

Other CSVD biomarkers than WMH could not be systematically analyzed, due to the large heterogeneity with respect to CSVD biomarkers, apathy scales and research designs across studies. In those investigating the association between lacunes and apathy, some reported confirmatory[34,35] and some negative results.[26,36]

As to subcortical infarcts, most studies supported a clinically significant association with apathy, but because of the heterogeneity in their designs the strength of the association remains unclear. Finally, no evidence was found to suggest that microbleeds or perivascular spaces are associated with apathy.[26,36–38]

While most research uses WMH as a biomarker of CSVD, this might not be the best index since CSVD causes widespread disruptions in cerebral connections. Given that CSVD concerns a whole- brain disease, studies focusing on a particular type of MRI finding (for instance only WMH) might thus miss the larger picture, where the use of a composite score -which combines information on CSVD neuroimaging biomarkers- might be more informative.[4,20] A high total CSVD burden raised the odds of having apathy in poststroke patients (OR 3.61; 95% CI 1.34 −9.68)[39] and in a CSVD sample apathy was associated with the total CSVD burden (R^2 = 0.332; t = 4.134; p <0.00).[40]

Numerous studies only examined whether CSVD markers such as WMH predicted apathy, without looking for evidence of a dose-response effect.[10,26,31,32,36,37,41-49] The studies that did do so are summarized here to evaluate the support for a biological gradient. In healthy older adults the WMH grade was found to correlate with apathy.[50] In geriatric outpatients WMH volume was related to apathy.[51] In a study of Alzheimer's disease patients WMH volume was not related to apathy as measured by NPI score,[52] while in a small study in patients with probable Alzheimer's disease frontal WMH volume was related to apathy.[53] In patients diagnosed with subcortical vascular cognitive impairment each additional lacuna and higher WMH volumes were both related to the severity of apathy,[35] while in another cohort of subcortical vascular patients with mixed cognitive status higher lacunar volume in WMH was related to the presence of apathy.[34]

In stroke patients the periventricular white matter hyperintensity score and the number of pontine infarcts were associated with apathy,[54] while a gradient between total CSVD burden and risk of apathy was established in another cohort of stroke patients.[39] Finally, the extent of the total CSVD burden predicted apathy in CSVD patients.[40]

In two cohort-studies of SVD patients white matter connectivity measures were significantly associated with apathy, while WMH volume or the number of lacunar infarcts (when depression and cognition were corrected for) were not, suggesting it might be *large-scale* white matter network disruption specifically which is associated with apathy.[24,26]

Although, all in all, we can safely conclude that there is a dose-response relationship between CSVD and apathy in a diversity of populations, these results could do with replication. And particularly the association between the total CSVD burden and the severity of apathy needs further looking into, since this might be a more accurate biomarker for underlying network disruption.

Temporality

Prospective studies supporting an association between CSVD at baseline and apathy at follow-up, or between CSVD progression and changes in apathy scores over time, add credibility to a causal relationship. Neuroimaging studies assessing frontal subcortical atrophy or WMH within 24 hours of a stroke found an association with apathy at 3−6 months of follow-up,[37,54,55] barring a small scale study.[36] A study in which neuroimaging was conducted 3 months poststroke and apathy assessed the next year also found no evidence of an association.[39] A study comparing baseline WMH volumes and apathy severity scores after 5 years in otherwise healthy individuals also found no evidence linking baseline WMH values to changes in apathy.[56] A study aiming to compare the differences in the course of neuropsychiatric symptoms between patients with Alzheimer's disease and vascular dementia patients with WMH and lacunar infarcts on neuroimaging, found a higher level of apathy and a significant increase in apathy in the latter group, which was not related to cognitive decline.[57] The baseline WMH volumes of depressed patients receiving electric convulsive treatment (ECT) did not predict apathy post-ECT but remaining depressive symptomatology and apathy at baseline did.[32]

All in all, the temporal relationship between CSVD and apathy has some empirical support but this is thus far limited to stroke patients. Of note is that all these studies looked at the association between baseline WMH and apathy at follow-up. Studies investigating the progression of CSVD or WMH over time and its relation to changes in apathy were still lacking.

Consistency

Are the reported associations between (markers of) CSVD and apathy consistent across a diversity of populations and contexts? Mostly, the evidence was obtained in healthy (older) adults and individuals with cognitive deficits and/or stroke.[7,30] The few studies that specifically studied the WMH-apathy association in individuals with Parkinson's disease showed that apathy was predicted by WMH integrity[58] and that apathy severity was associated with WMH severity.[59] In depression, or after depression, findings are inconsistent. No association was found in older adults stills showing apathy following ECT for depression,[32] but in depressed age peers who showed remaining symptoms of apathy after treatment with citalopram an association was found with white matter (and anterior cingulate) volumes,[31] while WMH correlated with apathy in older adults with severe late-onset depression,[33] but not in those with severe early-onset depression. Possible explanations for these inconsistencies will be discussed in the *Specificity* section.

The age range and demographic characteristics of study populations were diverse. The majority of studies looked at adults and often at older adults, including community-dwelling individuals and/or (mildly or severely) functionally impaired inpatients or outpatients. Study participants resided in European, North-American and Asian countries, no data were available on residents of South- and Central-America, Africa and Australia. Overall, the WMH-apathy association was consistent across the study populations. Associations between other neuroimaging markers or the total CSVD burden and apathy have received less broad attention as yet.

We next looked at measurement instruments for either CSVD or apathy and whether associations were consistent regardless of the techniques applied.

CSVD was mainly investigated using magnetic resonance imaging, diffusion tensor imaging or positron emission tomography scans, with which WMH, lacunes (number or volumes), subcortical infarcts, microbleeds, perivascular spaces or total CSVD burden were assessed.[20] Studies measuring WMH,[30] WMH network connectivity[24,26] and total CSVD burden consistently showed associations with apathy.[39,40] Studies focusing on other neuroimaging markers of CSVD were scarce or showed inconsistent results.

The studies involved used a diversity of apathy scales, but most widely used and validated, i.e., the AES,[8,24,31,37,39,54] the apathy scale (AS),[32,33,47,50,53,55,60] the apathy scale of the Neuropsychiatric Inventory[35,40,42 44,45,48,49,52,57,61] and the 3A scale of the Geriatric Depression Scale (GDS 3A).[10,26,46,62,63] We could not establish a pattern demonstrating that one scale yielded different results regarding the CSVD-apathy association than other scales. It is known, however, that in cognitively impaired persons self-reported apathy is not as reliable as clinician of informant rated indices.[8] Since evidence of a CSVD-apathy association was obtained in different populations, and not exclusively in individuals with cognitive impairment, and since many of these latter studies used clinician or informant rated scales, it is not likely that this (significantly) influenced the results.

Coherence

Is the causal relationship between CSVD and apathy coherent with knowledge from other sources of information?

In rats, damage to the mediofrontal pathways disturbs effort-based decision making: rather than seeking large rewards at the expense of great effort, they were more likely to choose smaller rewards demanding less effort.[64]

In humans, apathy is a common symptom following bilateral anterior cingulotomy, a procedure for therapy resistant severe chronic pain in which the ACC is cleaved,[65] and also frequently mentioned in case-reports of brain damage of the ACC.[66] Apathy was also noted in a study of 114 patients with iatrogenic brain damage due to radiotherapy of the whole brain for primitive cerebral neoplasia, where the level of apathy depended on the cumulative doses of radiotherapy and was associated with the extent of the white matter damage.[67]

Hence, we conclude a causal relationship between CSVD and apathy is coherent with knowledge from other areas of research.

Specificity

To evaluate the specificity of the CSVD-apathy association we will look at other relevant risk-factors for apathy and if these could have confounded the results.

Particularly in older populations, physical and motor disabilities, a diminished level of consciousness (as seen in delirium), substance use (for instance use of antipsychotics or benzodiazepines) or major changes in the patients environment are well-established and highly relevant risk-factors for apathetic behavior.[68–72] These are ruled out in the diagnostic criteria for apathy,[1] but most epidemiological research, especially in the general population, uses apathy rating scales rather than a broader clinical assessment.[7] Of the 27 studies on the CSVD-apathy association which we assessed for this narrative review only 9 controlled for the use of sedatives,[31,32,34,35,40,44,45,48,49] the other studies did not or to a limited extent (i.e., only antidepressants), and only 8 controlled for physical impairment.[35,36,37,40,47,49,54,57]

In the brain, motivation, initiative and execution, -which are diminished in the apathy syndrome-, involve generating and weighing options, reaching a decision, generating arousal and acting, where the ability to anticipate, desire and like the outcome acts as a reward system and self-stimulating feedback loop.[73] Besides the various brain areas forming the reward network[74] also multiple neurotransmitter systems that can be affected by neurodegeneration, such as the dopamine and serotonin systems, play a role in these processes.[22,73] And not only the reward network, but also the salience network, -a network that processes emotional information and activates other networks to respond-, is associated with apathy and particularly in depression this network might be functionally affected.[23,75,76]

Depressive disorder is a frequent and relevant risk-factor for apathy, with apathy in late-life depression posing a risk for treatment resistance and often persevering, particularly in those with residual depressive symptoms.[32,71]

Except for a few studies of the CSVD-apathy relationship which only partially corrected for the presence of a depressive disorder,[26,52] all studies considered in this narrative review acknowledged, assessed and corrected for this possible confounder.

There is yet another highly relevant pathway causing apathy in late-life: cognitive impairment.[68,71] Apathy in late-life, particularly in those with depression as well, is associated with cognitive impairment and dementia.[15,77,78] In all studies on the CSVD-apathy relationship evaluated here, cognitive impairment was assessed and corrected for, although in some studies only to a limited extent (i.e., exclusion of participants with severe cognitive dysfunction).[26,39]

Furthermore, not only CSVD but also large vessel ischemic or hemorrhagic stroke has been shown to be associated with apathy.[38] Could large vessel stroke act as a confounder the studies under review? This is not very likely, since only two studies did not report on the presence of stroke,[24,42] four studies included stroke patients only,[36,37,39,41] while all the other studies excluded participants with a history of stroke[31,32,33,40,45,46,51] or with signs of large vessel stroke on neuroimaging.[10,26,34,35,43,44,47–50,52–54,57]

In conclusion, the majority of the studies on the CSVD-apathy association might be confounded by the use of (sedative) medication or physical impairment, which is a weakness in the body of evidence supporting this relationship.

While the presence of depressive disorder, cognitive impairment and stroke are well controlled for in most studies, particularly in old-age these risk-factors often co-occur with CSVD and might still contribute in causing an apathy syndrome in the individual. And indeed, in individuals with apathetic behavior showing CSVD on neuroimaging there was not seldom an interplay between cognitive impairment, depressive disorder and apathy.[48,71,78] Hence, the specificity of the causal relationship between CSVD and apathy is low.

DISCUSSION

CSVD and Apathy: A Causal Relationship?

In conclusion, there is evidence that not only shows an association between WMH as a biomarker of CSVD and apathy but also supports a causal relationship between CSVD and apathy. Nevertheless, the evidence of a temporal and dose-response relationship is still weak and would benefit from prospective studies investigating the relationship between total CSVD burden (or WMH) change and change in apathy severity, most preferably in or comparing different, well-characterized populations.

Better still would be if imaging techniques were applied, -such as DTI-, that provide information on the disruption of networks, in prospective studies on apathy and apathy severity, since not only the volume of WMH or total CSVD burden, but also the *location of the damage* due to WMH or CSVD might be a determining factor in the extent of network destruction in the brain.

Vascular Apathy: A Distinct Clinical Syndrome?

Although there is evidence to support that CSVD can be a cause and possibly a sole cause of an apathy syndrome, this does not mean that use of the term ´vascular apathy´ as a subcategory of the more generic term ´apathy syndrome´ is applicable to clinical practice. One of the objectives of this narrative review was to establish if we can say that vascular apathy is a clinical syndrome in its own right, i.e., a combination of symptoms resulting from a single cause or so commonly occurring together as to constitute a distinct clinical picture?

First, can we make unequivocal distinctions between vascular apathy and other clinical presentations of CSVD? It is not too difficult to discriminate between vascular apathy and Binswanger's disease,[79] vascular parkinsonism[80] and subcortical vascular dementia,[81] since patients with these conditions present with other distinctive symptoms (gait disturbances in vascular parkinsonism), more symptoms (not only apathy, but also gait disturbances, MCI and bladder dysfunction in Binswanger's disease), or more and more severe symptoms (severe cognitive impairment affecting overall daily functioning in subcortical vascular dementia). However, subcortical MCI and the depressive-executive subtype of depression are more difficult to discriminate from vascular apathy. Neuropsychological testing will help to establish subcortical MCI, as in MCI one of the cognitive domains is affected, -in *subcortical* MCI often semantic memory, executive/attentional functioning, visuospatial functioning or perceptual skills[81] - without problems in daily functioning.

When only apathetic symptoms are present the criteria for a depressive disorder are not met (DSM-5; 2013). Still, discriminating between apathy as part of a depressive disorder, or apathy as an independent syndrome remains difficult in individuals coping with a depressive disorder, since anhedonia, loss of interest, indecisiveness and psychomotor retardation are symptoms that characterize both disorders[82] (see Table 2). Interestingly, in a CSVD study investigating the process of effort-based decision making, a high resistance to efforts and a low response to rewards was seen in the patients with apathy, while the depressed CSVD patients showed a different decision-making pattern, with a higher decision making boundary, reflecting a need for more information before making a decision.[28] In the future behavioral tests might help to discriminate between apathetic and depressed CSVD patients, but to date these new behavioral paradigms have only been applied in apathy studies.[25]

Moreover, to our knowledge no studies have been performed that compared clinical symptoms of apathy in CSVD patients to clinical symptoms of apathy in other populations. And, given that currently there is no convincing evidence to suggest that vascular apathy is *clinically* distinct from apathy due to other causes both are diagnosed according to the same consensus criteria.[1]

Moreover, when CSVD is identified as the likely cause of apathy, this does not alter the treatment since no specific other options have been developed. Monitoring both systolic and diastolic blood pressure should be

TABLE 2. Overlapping and Distinguishing Symptoms Between Apathy and Depression

Apathy Diagnostic Criteria (2018)	Depression Diagnostic Criteria (DSM-5)
(A) A quantitative reduction of goal-directed activity (behavioural, cognitive, emotional or social) in comparison to the patient's previous level of functioning. (B) Symptoms of at least 2 of the 3 following dimensions for at least 4 weeks. (C) These symptoms cause clinically significant impairment in functioning. (D)The symptoms are not solely attributable to physical or motor disabilities, a diminished level of consciousness, substance use or major changes in the patient's environment.	(A)The individual must be experiencing five or more symptoms during the same 2-week period and at least one of the symptoms should be either (1) depressed mood or (2) loss of interest or pleasure (core criteria). (B) Collectively, these symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. (C)These symptoms must not be caused by a somatic condition or use of medication or drugs. (D)These symptoms must not be caused by another psychiatric disorder. (E) No manic or hypomanic episodes
Overlapping symptoms	
B1 BEHAVIOUR AND COGNITION: reduced general level of activity; diminished persistence of activity; less interest or slow in making choices; less interest in external issues; less interest in own health and image.	2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day. 5. A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down). 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day.
B2 EMOTION: less spontaneous emotion; fewer emotional reactions to the environment; less concern about the impact of actions/feelings on others; less empathy; less use of verbal or physical expressions	2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
B3 SOCIAL INTERACTION: less spontaneous social initiative; less environmentally stimulated social interaction; decreased interest in interactions with family members; less verbal interaction; being more homebound	5. A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down).
Distinguishing symptoms	
	1. Depressed mood most of the day, nearly every day. 3. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day. 4. Insomnia or hypersomnia nearly every day. 6. Fatigue or loss of energy nearly every day. 7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day. 9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

emphasized,[83] while physical activity, occupational therapy and/or cognitive interventions are the non-pharmacological treatments of choice.[84] The evidence for the efficacy of pharmacological interventions is still weak and confined to specific populations, and for CSVD related-apathy no such evidence exists.[85,86]

Further, often CSVD will not be the sole cause of apathy. According to the diagnostic criteria[1] sedative medication, physical impairment and important psychosocial changes that induce apathetic behavior should be ruled out before diagnosing an apathy syndrome, but even then, other causes of apathy, -in particular neurodegenerative processes and depression-, often co-occur with CSVD.[48,71,78,]

In conclusion, based on our review of the literature we can argue that the use of the term vascular apathy is justified by the evidence that CSVD is a cause of apathy. Furthermore, apathy in CSVD patients can often be distinguished from other clinical syndromes which are associated with CSVD.

However, there are no data to support that vascular apathy is different from other apathy syndromes in clinical presentation or treatment options and it accordingly does not qualify as a distinct clinical syndrome. The term *vascular apathy* would at this moment merely refer to the probable cause of the apathy and not to a clinically different syndrome. Further, since CSVD may often not be the sole cause of apathy and in clinical practice one cannot always be certain about which of several contributing factors is the most important, we recommend using the non-specific term *apathy syndrome* for the time being.

LIMITATIONS

The Bradford-Hill criteria which were used to evaluate the causal relationship between CSVD and apathy were not intended as a "check-list" of criteria, but as criteria to consider when distinguishing between association or causation.[16] We aimed to stay true to this way of thinking. In our opinion, a narrative review better suited this purpose than a structured review or meta-analysis would, since in a narrative review a broader scope of evidence and arguments can be presented and more emphasis is put on the process of weighing of evidence and arguments.

The main limitation of this choice -the other side of the coin- is that in narrative review literature searches are not performed twice, the included studies are not as thoroughly weighed on quality by two authors as they would be in a structured review and data are not pooled as in a meta-analysis.

Furthermore, we limited the sources of information to published articles, it would have been interesting to gather expert opinions, for instance by means of the Delphi method.

Another limitation comes with applying the Bradford-Hill criteria to the CSVD-apathy association: there are no experimental data, only observational data[87] to support a causality claim.

CONCLUSION

Consistent pathophysiological evidence linking CSVD and apathy makes it plausible that CSVD can cause apathy. This causal relationship is supported by the evidence on the strength and biological gradient of the CSVD-apathy associations obtained in a diversity of populations, although the evidence for a temporal relationship is still weak. Given that there are often other factors in patients with CSVD that may cause or contribute to apathy, the specificity of the causal relationship can be said to be low. It is premature to speak of vascular apathy as if referring to a distinct clinical apathy syndrome, since differentiation between apathy syndromes on the basis of clinical features is unfeasible, while in-depth knowledge about differences in the prognosis and efficacy of dedicated treatment for apathy caused by CSVD and other apathy syndromes is lacking.

AUTHORS CONTRIBUTIONS

Lonneke Wouts was responsible for the design of the work in co-operation with the other authors, for the search and analysis of the literature reviewed, for the interpretation of the results, for the first draft and the following revisions according to the input of the other authors and for the final approval. She agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

Radboud Marijnissen, Richard Oude Voshaar and Aartjan Beekman were responsible for the design in co-operation with Lonneke Wouts, for the interpretation of the results of the literature reviewed, for critically revising the

first draft and also the following revisions for important intellectual content and for the final approval of the version to be published. They agree to be accountable for all aspects of the work and to ensure that questions to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

DATA STATEMENT

The data has not been previously presented orally or by poster at scientific meetings.

DISCLOSURES

The authors report no conflicts with any product mentioned or concept discussed in this article.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jagp.2022.09.016.

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