Vascular risk factors for depression and apathy

Wouts, Lonneke

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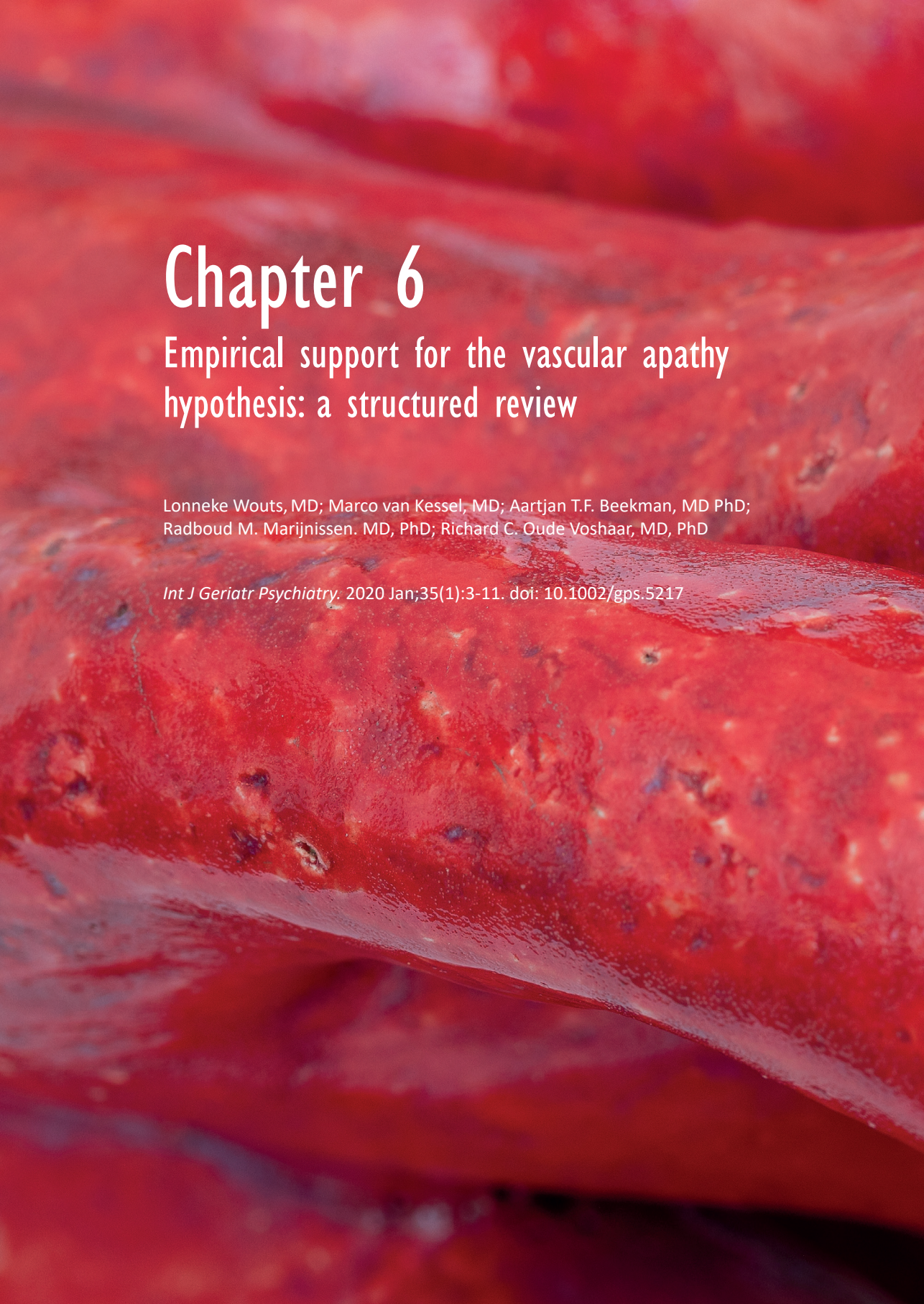

Chapter 6

Empirical support for the vascular apathy hypothesis: a structured review

Lonneke Wouts, MD; Marco van Kessel, MD; Aartjan T.F. Beekman, MD PhD; Radboud M. Marijnissen. MD, PhD; Richard C. Oude Voshaar, MD, PhD

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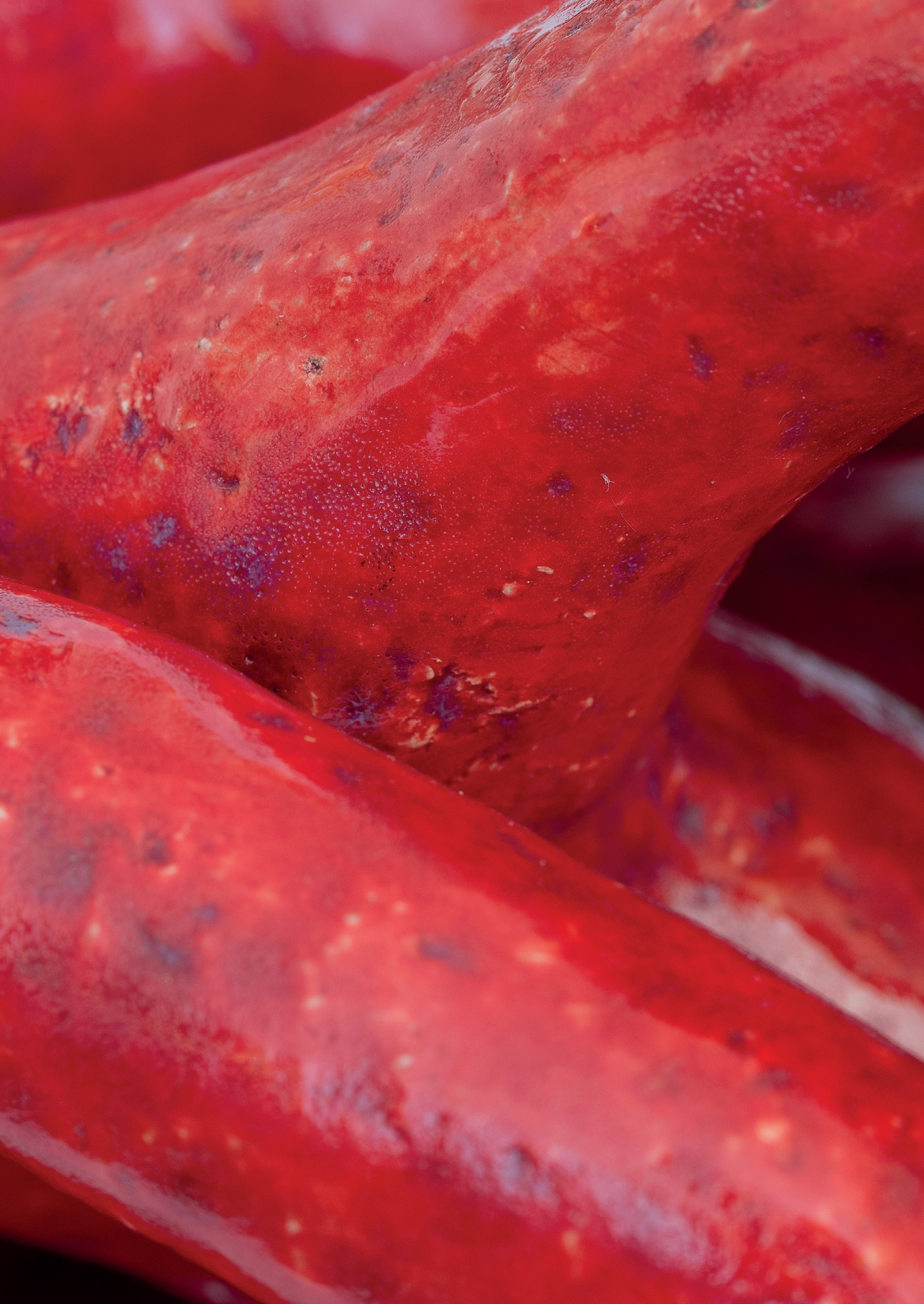


Abstract

Objectives

A systematic review of the relationship between subclinical small vessel disease (SSVD) in the general population and apathy to examine the hypothesis that apathy has a vascular basis.

Methods

We searched for studies on associations between apathy and SSVD, operationalized as white matter hyperintensities (WMH) or white matter diffusivity changes, lacunar infarcts, cerebral microbleeds, decreasing cortical thickness, and perivascular spaces, while also peripheral proxies for SSVD were considered, operationalized as ankle brachial pressure index (ABI), intima media thickness, arterial stiffness, cardio-femoral pulse wave velocity, hypertension or cardiovascular disease. Only eligible retrospective and prospective observational studies conducted in the general population were included.

Results

The 14 studies eligible for review examined the associations between apathy and hypertension (3), ABI (1), arterial stiffness (1), cardiovascular disease (2), WMH (3), white matter diffusivity (2), cerebral microbleeds (1), or cortical thickness (3). Arterial stiffness and white matter diffusivity were not related to apathy, while the associations with cortical thickness were contradictory. Cross-sectional studies in the general population did find evidence of apathy being associated with WMH, CM, cardiovascular disease, hypertension and ABI and cardiovascular disease was prospectively associated with apathy. The methodologies of the studies reviewed were too heterogeneous to perform meta-analyses.

Conclusions

Although more prospective evidence is needed and vascular depression needs to be controlled for, cardiovascular disease, hypertension and ABI as proxies for SSVD, and WMH and cerebral microbleeds as direct measures of SSVD have been found to be associated with apathy in the general population, supporting the hypothesis of vascular apathy.

Introduction

Apathy, or diminished motivation, has traditionally been regarded as a symptom of psychiatric and neurological disorders, such as major depressive disorder [1] and Parkinson's disease [2]. Apathy has increasingly come to be regarded as an independent syndrome for which diagnostic criteria have been proposed in a consensus paper [3 4]. With its prevalence in the general population (≥50 years) being estimated at 23.7% [5], the impact of apathy on both individuals and the society is extensive. The apathy syndrome negatively affects motivational decision making [6] and is associated with functional decline [5], reduced engagement in activities of daily living, and a poorer quality of life [7]. Understandably, apathy is very distressing for family and other caregivers [8].

The hypothesis of vascular apathy assumes a relationship between the generally widespread cerebrovascular damage caused by small vessel disease (SVD) and apathy [9 10]. Whether cerebrovascular damage due to small vessel disease, is associated with apathy, -even in the general population without prior knowledge of cerebrovascular damage-, is the main subject of this study.

Various brain circuits play a role in planning, motivation and, auto activation, among which are the frontal regions with their projections to prefrontal regions and the basal ganglia, the parietal regions, and the anterior cingulate [11]. The vascular apathy hypothesis then supposes that SVD can cause apathy by damaging these tracts. However, the relationship between vascular disease and apathy could well be bidirectional: a recent systematic review and meta-analysis showed that apathy increases the risk of myocardial infarction by 21 %, stroke by 37%, and even mortality by 47% [12]. In the populations evaluated, these risks might additionally or alternatively be raised due to the participants' adverse health behaviours and low adherence to treatment regimens for vascular disease [13 14 15]. Moreover, apathy and vascular disease might have a shared aetiology [16], while apathy could well be a marker of subclinical SVD (SSVD) [14].

Early evidence for the vascular apathy hypothesis was reported in studies in clinical samples with established cerebrovascular disease (e.g. vascular dementia and stroke), where apathy appeared related to the general effect (or severity) of cerebrovascular damage given that, associations with specific cerebral circuitries and regions were inconsistent [17 18]. Particularly the stroke subtype of SVD (lacunar infarcts and white matter hyperintensities) was found to be related to apathy in several other studies, independent of depression [19 20 21].

Indirect and also contradictory evidence came from research into late-life depression, where chronicity of late-life depression was found to be associated with the severity of the risk factors for cerebrovascular disease and apathy [22]. Still, although the presence of apathy was predicted by vascular factors in several elderly depressed populations [23], other studies found no such associations [24 12]. Moreover, depression itself could be related to vascular factors, as the so-called vascular depression hypothesis postulates [25] which

complicates the interpretation of findings pertaining to vascular apathy in depressed populations.

Other indirect evidence seems to support the existence of vascular apathy in that a negative interaction was observed between neuroticism and cerebrovascular risk factors in the prediction of depression, suggesting that apathy caused by SSVD might attenuate the depressogenic effect of neuroticism [10 26].

Obviously, more convincing and direct evidence of vascular apathy could come from research investigating the apathy-SSVD relationship in the general population, given that cerebral SVD develops from a subclinical condition, increasing the risk on overt cerebrovascular disease [27 28 29 30], where, although still subclinical, SSVD might cause subtle signs and symptoms, like mild disturbances in gait, cognitive functioning and mood [27],

The aim of the present systematic review is to examine all the evidence supporting an association between SSVD and apathy in the general population, while also considering findings of associations between proxies of SSVD and apathy.

Methods

Literature search process

All eligible articles were found using Ovid-all resources (which include the Cochrane Library, EMBASE, MEDLINE, and PSYCHINFO), limits: English, humans. The search terms were vascular apathy, and apathy combined with deep white matter hyperintensities (DWMH), white matter hyperintensities (WMH), cerebrovascular disease (not stroke) (CV disease), lacunar infarcts, cerebral microbleeds, cortical thickness, perivascular spaces, ankle brachial pressure index (ABI), intima media thickness (IMT), arterial stiffness, cardio-femoral pulse wave velocity (CFPWV), hypertension, cardiovascular disease and cerebrovascular risk factors (CVRF). Duplicates were removed.

The search was conducted on the 27th of June, 2018 by the first author (LW) and checked by the second author (MvK). Differences in findings were analyzed and discrepancies were discussed between both authors (LW and MvK) and when no consensus could be reached, a third author (RM) was asked to make the final judgment. Two more eligible articles were identified while preparing a speech on apathy using the search terms “apathy” and “dementia” [31 32]. On inspection these two studies also reported on the general population or populations with minimal cognitive impairment (MCI), which is why we included them in our review.

Articles were included when 1. apathy was assessed by any kind of relevant instrument; 2. SSVD was based on either neuroimaging, considered a direct measure of SSVD or peripheral measures of atherosclerosis, considered as proxies for SSVD; 3. studies reported on observational epidemiological research, and 4. were performed in the general

population. This implies that studies in broad patient groups or the general population including those with minimally cognitively impaired patients were included in the review. Studies were excluded i. when the language was not English and ii. when the studies concerned specific populations, such as post-stroke patients, patients with dementia (including vascular dementia), with Parkinson's disease or major depression.

Study quality

The quality of the case control, cross-sectional and longitudinal studies selected for review was judged against specific criteria for design and methodology. We used an adapted version of the evaluation scale for cross-sectional (not case-control) studies originally developed by Kuijpers et al.[33] (online supplementary file 1). For case-control and longitudinal studies we used scales based on the Newcastle-Ottawa scale [34] (online supplementary file 2). Overall quality of a study was considered high when it attained at least 60% of the maximum score [35].

Evaluation of the quality of apathy scales

The apathy evaluation scale (AES) and the apathy subscale of the neuropsychiatric inventory (NPI) were considered of high quality [36 37]. The 3 apathy items of the geriatric depression scale (GDS-3A) are validated by comparison with the apathy scale (sensitivity 69% and specificity 85% [29 38]). The apathy scale (an abbreviated version of the AES) and therefore also the apathy items of the GDS were not granted the highest quality status in our evaluation based on the review by Clarke et al., 2011 [37]. Clinician- or informant-based information was considered of higher quality than self-reported in the older population where individuals may have been suffering from MCI [39].

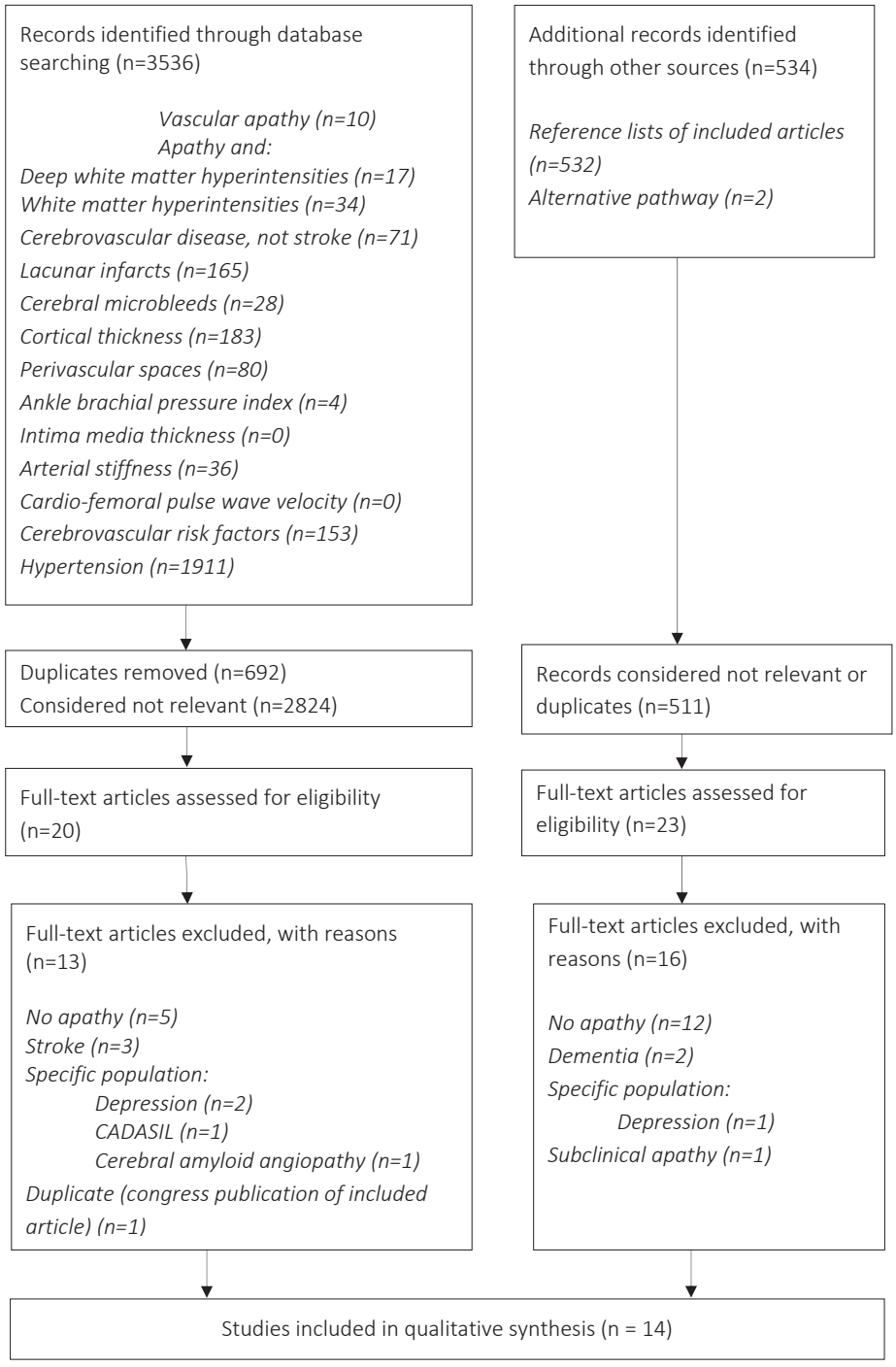
Evaluation of the quality of SSVD assessment

SSVD on neuroimaging was operationalized as WMH, silent lacunar infarcts, cerebral microbleeds, or decreased cortical thickness on MRI scans [27]. Diffusion tensor imaging (DTI) studies the diffusivity of water molecules in white matter as a model of the connectivity of this tissue and its markers (fractional anisotropy and diffusivity) are associated with SVD [40].

Peripheral measures of atherosclerosis were operationalized as the ABI, IMT, and/or CFPWV. Although the ABI and CFPWV are measures of large artery atherosclerosis [41], we considered both measures proxies for SSVD as large artery and small vessel disease are closely related [42]. Cardiovascular disease was included as an SSVD proxy, since it can lead to haemodynamic changes affecting the small vessels [42]. Finally, being the strongest risk factor for SSVD, hypertension was also taken as an SSVD proxy [27 43].

Studies were awarded an extra point was if SSVD proxies were measured rather than mentioned in an interview or derived from information provided by general practitioners. Self-reported SSVD was categorized as "low quality".

Figure 1. Flow chart of the inclusion of studies



Results

The results of the search strategy are shown in the flow chart depicted in Figure 1. No relevant studies published before 1990 were found. Of the 14 studies included in the review, one study reported on both peripheral proxies as well as direct measures of SSVD [30], four studies on peripheral proxies of SSVD only [9 29 43 44], and finally nine studies on direct measures of SSVD only [31 32 45 46 47 48 49 50 51].

SSVD and apathy

In Table 1 the five studies that used peripheral proxies for SSVD are listed and details and results described. A meta-analysis of the results was not possible, because the research designs, SSVD proxies, and methods of ascertaining apathy that had been used differed too widely.

Table 1. Studies with peripheral proxies for Subclinical small vessel disease

Author year	Population Study design Number of participants	Proxy for subclinical small vessel disease	Apathy instrument	Results	Quality
Van der Mast et al., 2008	General population, >85 years, Longitudinal, 500	CVP†	GDS-3A‡	Mean number of CVP†: apathy 1.04 (0.11) versus no apathy 0.77 (0.05); p=0.02 CVP† and increase in apathy : 0.05 (0.02); p=0.007	High (9/9)
Yao et al., 2009	General population, Cross-sectional, 222	Diastolic blood pressure	Apathy scale	Diastolic blood pressure: OR§ 1.055 (1.014-1.098); p=0.009	High (10/16)
Suga-wara et al., 2011	General population, Cross-sectional, 860	ABI¶	Apathy scale	ABI¶: beta-0.071 (t value-2.039); p<0.05 Systolic blood pressure: beta-0.056 (t value -1.420); p=0.156	High (6/9)
Ligthart et al., 2012	General population, Cross-sectional, 3534	Cerebro-vascular risk factors	GDS-3A‡	CVP† and apathy 1.28 (1.09-1.52); p=0.004 Systolic blood pressure is associated with apathy	High (12/16)
Van Sloten et al., 2016	General population, Cross-sectional, 2058	Arterial stiffness	GDS-3A‡	Arterial stiffness: OR§ 1.07 (0.96-1.19)	High (11/16)

Legend: † CVP: cardiovascular pathologies; ‡ GDS-3A: three apathy items of the geriatric depression scale; § OR: odds ratio; ¶ABI: ankle brachial index. High quality: ≥60% of the maximum score.

Three studies examined associations between hypertension and apathy [9 30 43], two of which found a significant link with systolic blood pressure [9 43], and the other with the diastolic (but not systolic) blood pressure [30]. This latter study [30] also examined the association between WMH and apathy by neuroimaging, of which the results are presented in section '*Neuroimaging and apathy*'.

In their large-scale study, Ligthart et al. [9] found an odds ratio (OR) of 1.28 in their participants with cardiovascular disease (1.09-1.52; p=0.004). The number of cardiovascular pathologies in another large and prospective study [29] was found to be associated with apathy at baseline and with incident apathy during follow-up.

Finally, ABI was associated with apathy [43], but arterial stiffness (CFPWV) was not [44].

Neuroimaging and apathy

The ten studies using MRI or DTI are presented in Table 2.

Of the three studies examining the association between WMH and apathy, the two cross-sectional studies found a significant association [30 48] whereas the (smaller) case-control study did not [49]. Again, a meta-analysis and quantitative estimation of the WMH and apathy association was not possible, because of the large differences in the studies' research designs, the methods of ascertaining WMH (number or volume), and apathy scales used. It needs to be noted here, that with 4354 participants the study by Van Grool et al. [48] would have largely outweighed the findings of the other studies in any meta-analysis, since the other studies had much smaller samples.

Mean white matter diffusivity (MD) was associated with apathy in specific areas in the small-scale study by Cacciari et al. [45], but not in the study by Moonen et al. [50]. Other DTI measures (fractional anisotropy (FA); axial diffusivity (AD) and radial diffusivity (RD) were not associated with apathy [50].

Evaluating the data of 802 participants, Xu et al. [51] found the participants who had suffered a single cerebral microbleed to show significantly more apathy than participants without cerebral microbleeds.

Of the three studies examining looking at cortical thickness and apathy, two studies found an association between apathy and a reduced thickness of the temporal lobe [31 32]. No associations were reported for apathy and the entorhinal cortex, the orbitofrontal cortex, or the middle frontal gyrus [47], while no association or even an inverse association was found between apathy and the anterior cingulate [32 47]. However, in a model in which apathy was adjusted for depressive symptom severity, apathy was found to be associated with a more rapid reduction of the anterior cingulate cortex during follow-up [47].

Discussion

Main findings

The results of our review indeed support the hypothesis that SSVD is related with apathy. More specifically, as peripheral proxies for SSVD, hypertension and cardiovascular disease were consistently found to be associated with apathy [9 29 30 43]. With the only study examining ABI finding a significant association with apathy while another single study focusing on arterial stiffness did not [43 44], the results with respect to other peripheral measures of atherosclerosis were inconclusive. Apathy was, however, also linked to cerebral microbleeds [51] and WMH load [30 48]. SSVD was related to white matter diffusivity; however a direct association between white matter diffusivity and apathy has not been established yet [45 50]. The evidence on the relationship between cortical thickness and apathy is inconclusive [31 32 47].

Hypertension, cardiovascular disease, white matter hyperintensities and apathy

Both systolic and diastolic blood pressure were associated with apathy [9 30 43], while associations between white matter hyperintensities and apathy (and cerebral microbleeds and apathy) were found in large-scale and high-quality studies [30 48 51]. Although Delrieu et al.[49] did not find any such evidence, their study may have been underpowered. Finally, cardiovascular disease was firmly associated with apathy, not only cross-sectionally but also longitudinally [9 29].

Although its aetiology is not fully understood, WMH reflects ischaemic arteriolosclerosis in the brain [27] and is related to congenital heart disease, hypertension, carotid blood flow, diabetes and cardiovascular health [52]. WMH may then be seen as consequence of chronic hypoperfusion as well as impaired cerebrovascular reactivity. Nonetheless, blood-brain-barrier leakage and myelin-remodeling problems could play a role [53]. The relation between hypertension, cardiovascular disease and WMH could be limited blood flow to the brain and/or arterial stiffness [52 53 54].

How SSVD can lead to apathy is not yet fully understood. Destruction of limbic or reward pathways are considered as a potential cause. Indeed, apathy was found to be associated with impaired connectivity of limbic association tracts in patients with clinical SVD [55]. The results of the DTI studies of white matter connectivity and apathy in SSVD, however, were not conclusive [45 50].

Cortical thinning, SSVD and apathy

The contradictory findings regarding the relationship between cortical thickness and apathy might be due to other mechanisms than SSVD leading to cortical thinning. Cortical thickness and WMH are associated, but they are not interchangeable [56 57]. Cortical thinning in the parietal lobes, anterior insula and caudate nuclei bilateral is related to WMH, but widespread cortical thinning is related to normal aging as well as early

Alzheimer's disease [56 57 58]. In the frontal regions, the temporal regions, and the anterior cingulate, all areas which have been studied specifically, cortical thinning could be caused by aging as well as Alzheimer's disease. Our review has shown that associations in the general population between apathy and the WMH-related regions of cortical thinning (parietal lobes, anterior insula and caudate nuclei) have not been studied yet. This is a consideration for future research, more than it is a counterargument for an association between SSVD and apathy.

The vascular apathy hypothesis and the vascular depression hypothesis

Depression can be a confounder when looking for the relationship between vascular disease and apathy, since apathy may be a symptom of depression (anhedonia), while it has also been related to vascular disease [25 59].

Of the fourteen studies we reviewed, twelve controlled for depression [9 29 30 31 32 43 44 45 47 49 50 51]. In three of these latter studies the GDS was used as a measure of both apathy and depression [9 29 44] and in five articles [31 32 47 49 50] the GDS was used as a measure of depression, including the three apathy items of this scale. Since these GDS apathy items show a low sensitivity and a high specificity as a measure of apathy in older populations [38] correction for depression measured by the GDS may imply that apathy was also corrected for, attenuating the SSVD-apathy association. If depression was overcorrected for in these studies, the associations between SSVD and apathy may also have been stronger than the statistics now show.

On the other hand the role of apathy in the vascular depression hypothesis is often not accounted for in research while it may potentially act as a confounder. In patients with clinical SVD, apathy was associated with reduced white matter integrity, while depression was not, when apathy was controlled for [19 21]. Arguably, with the emerging evidence for the vascular apathy hypothesis one may wonder whether in research of the vascular depression hypothesis apathy was and is adequately corrected for.

Limitations:

As stated, most of the research we reviewed was cross-sectional, preventing us from establishing whether SSVD precedes apathy, while we were also unable to determine whether more SSVD leads to higher levels of apathy. An alternative explanation for an apathy-SSVD or an SSVD-apathy relationship in cross-sectional designs is that apathy leads to poorer cardiovascular outcomes due to differences in health behaviours [14]. Does an association between CVRF and apathy then reflect the concept of vascular apathy our does it (partially) reflect differences in health behaviours that are caused by apathy? Nevertheless, the findings of an increase in the incidence of apathy with more cardiovascular pathologies [29] points towards CVRF as an aetiological factor in apathy (and not only the reverse mechanism).

Another methodological issue is the use of many different proxies for SSVD. The use of a broad array of SSVD proxies has negative consequences for the comparability of the research and precludes meta-analysis to estimate the magnitude of associations found. Nonetheless, generalizability increases when increasing levels of apathy are associated with widely different proxies for SSVD.

Finally, of the many different apathy scales that were employed, the AES and the NPI apathy subscale were the only tools that are well-validated [36 37], which is why we cannot rule out that the use of the other apathy scales may have negatively affected the quality of the results reported.

Conclusion

The studies published to date show that WMH, cerebral microbleeds, cardiovascular disease, hypertension and ABI are associated with apathy in the general population. However, as most studies were cross-sectional in nature, the directions of the associations remain unclear and might be reciprocal/bidirectional. Finally, although the hypothesis of vascular apathy is supported by the available literature, more prospective evidence is needed.

Table 2. Studies using Magnetic Resonance Imaging or Diffusion Tensor imaging

Author Year	Population Study design Number of participants	MRI† DTI‡	Proxy for subclinical small vessel disease	Apathy instrument	Results	Quality
Yao et al., 2009	General population Cross-sectional 222	MRI†	Silent infarction Deep WMH§	Apathy scale	WMH§: odds ratio 1.826 (1.129-2.953) for apathy per grade WMH§; p=0.014	High (10/16)
Cacciari et al., 2010	MCI¶ patient Cross-sectional 20	DTI‡	Mean diffusivity of white matter (20 pixels)	Italian dementia apathy interview and rating	Mean diffusivity of white matter is associated with apathy 4 areas	Not high (6/16)
Naka-mura et al, 2013 (55)	MCI¶ patients Cross-sectional 516	MRI†	vascularMCI¶ : ≥5 lacunar infarcts and white matter lesions	Clinical assessment of spontaneity	vascularMCI¶ was associated with apathy, more strongly than other MCI¶	Not high (8/16)
Za-hodne et al, 2013	MCI¶ patients Longitudinal 334	MRI†	Cortical thickness	Neuropsychiatric Inventory apathy scale	Entorhinal cortex: rate of change: 0.001 (0.001) Orbitofrontal cortex: rate of change:-6e-4 (0.001) Middle frontal gyrus: rate of change: 14.5e-4(0.001) Anterior cingulate cortex: rate of change:-0.002 (0.001); p<0.1; model corrected for depression: p=0.025	High (7/9)
Grool et al, 2014	General population Cross-sectional 4354	MRI†	WMH§ (total and region) Total brain volume	GDS-3A††	Total WMH§ volume: 1.07 (1.02-1.13); p=0.008 (model 2)	High (11/16)
Dono-van et al, 2014	General population Cross-sectional and (partly) longitudinal 812	MRI†	Cortical thickness	Neuropsychiatric inventory apathy scale	Bilateral average cortical thickness and apathy over time; beta 0.35 (0.29-0.41); p<0.0001	High (11/16)

Author Year	Population Study design Number of participants	MRI† DTI‡	Proxy for subclinical small vessel disease	Apathy instrument	Results	Quality
Guercio et al, 2015B	General population Cross-sectional 66	MRI†	Cortical thickness	Apathy evaluation scale	Inferior temporal cortex: beta 18.07 (6.45-29.70); p=0.004 Anterior cingulate cortex: beta-10.03 (-19.38—0.068); p=0.04	Not high (7/16)
Delrieu et al, 2015	MCI patients Case-control 65	MRI† and FDG-PET‡‡	Brain volume WMH§ volume Reduced glucose metabolism	Neuropsychiatric inventory apathy scale	WMH§ and no apathy versus apathy 0.9 (0.5) versus 0.5 (0.1); p=0.678	High (6/9)
Moonen et al, 2017	General population Cross-sectional 195	MRI† and DTI‡	Fractial anisotropy Mean Diffusivity Axial diffusivity Radial diffusivity	Apathy scale	Fractial anisotropy: 0.62 (-0.04-1.028); p=0.07 (model 3)	High (10/16)
Xu et al., 2017	General population Cross-sectional 802	MRI†	Cerebral microbleeds	Neuropsychiatric Inventory apathy scale	No cerebral microbleed versus one : 0.04 (0.39) versus 0.25 (1.44); p=0.02	High (11/16)

Legend: † MRI: magnetic resonance imaging; ‡ DTI: diffusion tensor imaging; § WMH: white matter hyperintensities; ¶ MCI: minimal cognitive impairment; †† GDS-3A: three apathy items of the geriatric depression scale; ‡‡ FDG-PET: fludeoglucose positron-emission tomography. High quality: ≥60% of the maximum score.

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