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White Matter Lesions and Brain Atrophy: More than Shared Risk Factors? A Systematic Review

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Key Words
Lacunar infarcts · White matter hyperintensities · Brain atrophy · Magnetic resonance imaging · Systematic reviews · Vascular risk factors

Abstract
Background: White matter lesions (WML) and brain atrophy are often found on MRI in the elderly. Shared vascular risk factors may be an explanation for their concomitance. However, disturbances of white matter integrity could also be involved in the pathogenesis of brain atrophy. Our objective was to systematically review studies that investigated the relation between WML and brain atrophy on MRI, and to investigate whether there is sufficient evidence to indicate that this relation is independent of shared risk factors. ***Methods:*** We searched PubMed for studies published in English between 1980 and October 2007, combining search terms for WML and brain atrophy. Articles that studied the relation between WML and brain atrophy were included if they met the following criteria: (1) original study, (2) MRI used for imaging, (3) assessment methods for WML and brain atrophy specified, and (4) a sample size of at least 20 participants. We recorded type and age of the study population, type and assessment of WML and brain atrophy, and variables for which adjustments were made in the analyses. ***Results:*** We identified 48 studies that met our inclusion criteria. A significant relation between WML and brain atrophy was found in 37 out of 48 studies. The source of the study population (e.g. clinic or population based) did not affect this relation. However, only 10 studies adjusted for shared risk factors, of which 9 found an association. ***Conclusions:*** The majority of studies found an association between WML and brain atrophy, but it is not yet clear if this association is independent of shared risk factors.

Introduction

In healthy individuals, global and regional brain volume decline starts at a slow rate in early adulthood and accelerates in older age [1–3]. The rate of this decline varies considerably among individuals [3]. This is of clinical importance since the extent and rate of progression of global and regional brain atrophy are associated with future cognitive deterioration and conversion to dementia [4–6].

Although brain atrophy may be caused by specific neurological diseases, it is often found on MRI in the el-

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derly without apparent neurological symptoms. Evidence has accumulated that vascular factors play an important role in the etiology of brain atrophy and development of dementia. These factors include hypertension [7, 8], hyperlipidemia [8], diabetes mellitus [9], obesity [10], large amounts of alcohol [11], and cigarette smoking [8, 9].

In addition to brain atrophy, the presence and severity of white matter lesions (WML) increase with age [12–14]. They too are associated with future cognitive decline and dementia [15–18]. Patients with subcortical vascular ischemic disease, which is characterized by substantial WML, show progressive cognitive impairment in specific domains and have a considerable risk of developing dementia [19, 20]. Furthermore, vascular risk factors, including hypertension [12, 14, 21–25], diabetes mellitus [26], obesity [27, 28], and smoking [14, 23], are also associated with WML.

More than 100 years ago, Alois Alzheimer and Otto Binswanger had already described the concomitant presence of subcortical vascular pathology and pronounced atrophy of the white matter with enormously enlarged ventricles in postmortem studies [29]. More recently, concomitant brain atrophy and WML have frequently been observed in elderly people on magnetic resonance imaging (MRI). However, it is unknown which factors may explain the co-occurrence of WML and brain atrophy. One possibility is that their coexistence may be explained by shared vascular risk factors or other shared factors associated with aging. Another possibility is that the disturbances of white matter integrity can contribute to the pathogenesis of brain atrophy by causing ischemic damage to axons, oligodendrocytes, and other glial cells [30].

In this study, we systematically reviewed available studies that investigated the relation between WML and global or regional brain atrophy on MRI to assess whether there is sufficient evidence to conclude that WML and brain atrophy are associated with each other independently of shared risk factors. Finally, we discussed the proposed mechanisms that could underlie the relation between WML and brain atrophy.

Methods

We searched PubMed for studies published in English between 1980 and October 2007. Since several synonyms exist for WML and brain atrophy, we made search terms for WML and brain atrophy and entered them as follows: ('search term for WML' AND 'search term for brain atrophy'). We combined this search with limits for language and publication date (fig. 1). The last search was performed on October 31st, 2007. Additional literature was obtained from reference lists of relevant articles.

Search term for white matter lesions:
('leukoaraiosis' [MeSH] OR leukoaraiosis [TIAB] OR leukoaraiosis [TIAB] OR white matter hyperintense [TIAB] OR white matter hyperintensity [TIAB] OR white matter hyperintensities [TIAB] OR white matter lesion [TIAB] OR white matter lesions [TIAB] OR white matter change [TIAB] OR white matter changes [TIAB] OR white matter abnormality [TIAB] OR white matter abnormalities [TIAB] OR white matter signal [TIAB] OR white matter signals [TIAB])
Search term for brain atrophy:
(((ventricle [TIAB] OR ventricles [TIAB] OR ventricular [TIAB] OR sulcus [TIAB] OR sulci [TIAB] OR sulcal [TIAB]) AND (enlargement [TIAB] OR size [TIAB] OR dilatation [TIAB] OR expansion [TIAB])) OR (('atrophy' [MeSH] OR atrophy [TIAB]) AND ('brain' [MeSH] OR brain [TIAB] OR cerebral [TIAB] OR hippocampus [TIAB] OR hippocampal [TIAB] OR cortical [TIAB] OR subcortical [TIAB] OR entorhinal cortex [TIAB] OR medial temporal lobe [TIAB])))
Limits
English [language] AND ('1980/01/01' [EDAT]: '2007/10/31' [EDAT])
[TIAB] = Title/Abstract; [MeSH] = Medical Subjects Heading; [EDAT] = Entry date, the date the citation was added to PubMed.

Fig. 1. Search terms and limits used for retrieval of relevant articles.

One investigator (A.P.A.A.) screened all titles and abstracts, and all full-text articles were evaluated by 2 investigators independently of each other (A.P.A.A. and L.G.E.). A consensus meeting was held for cases of disagreement. Since we used a broad search term, we expected a large number of irrelevant articles. Therefore, we defined the following exclusion criteria on the basis of which abstracts could be discarded: case reports and reviews, studies performed in a pediatric study population, and studies in which only computed tomography (CT) was used for imaging. Since we were interested in WML of possible ischemic origin, we also excluded studies that investigated hyperintensities on MRI with other known causes (hematological disorders, metabolic or toxic causes, non-infectious inflammatory or autoimmune diseases, infectious causes, genetic disorders, radiotherapy or chemotherapy, and head trauma).

For all potentially relevant articles, we retrieved the full-text version. Data was extracted from the articles if they met the following criteria: (1) the relation between WML and brain atrophy

was studied, (2) the report was published in English, (3) it was an original study, (4) MRI was used for imaging, (5) assessment methods for WML and brain atrophy were specified, and (6) a sample size of at least 20 participants per study group was defined.

For all relevant studies, we recorded the source population, the design (cross-sectional or longitudinal), the sample size, and the mean age of the participants. Next, we described the types of WML and measures of brain atrophy that were investigated and the methods that were used to assess WML and atrophy. Due to heterogeneity in the assessment of WML and brain atrophy, and due to variation in the units of measurements, it proved difficult to compare the measures of effect across studies quantitatively. Therefore, we decided to summarize the results qualitatively and recorded whether the relation between WML and measures of atrophy was statistically significant ($p < 0.05$). If different subtypes of WML or brain atrophy were investigated within 1 study, we recorded the results separately. Finally, we checked whether adjustments were made for potential shared risk factors in the analyses, and recorded the variables for which adjustments were made.

Results

Our search resulted in 689 articles. As expected, the majority of these articles were not relevant for this review because we used a broad search term. After screening of the titles and abstracts, we retrieved the full-text version of 145 articles. Of these, 41 met the inclusion criteria and 7 additional relevant articles were identified through reference lists of the included articles. The most important reason why articles were excluded was because WML and brain atrophy were both studied as the determinant or as the outcome of interest, but the relation between them was not investigated.

The source populations were very heterogeneous. However, the study populations in the individual studies were more homogeneous. As both WML and brain atrophy are associated with vascular disease and cognitive impairment, the majority of the original studies limited their study populations to either patients from one of these categories or to individuals from the general population. We classified the 48 included articles into 3 main categories to preserve the categorization made in the original studies: general population, subjects with cognitive impairment, and patients with vascular disease.

The general population category consisted of studies that investigated a community-dwelling population or studies that were performed in healthy controls or in patients without neurological or psychiatric disease. In the category of patients with cognitive impairment, study populations were included with (probable) Alzheimer's disease, mixed dementia or cognitive impairment without dementia. In 1 study, patients with Lewy body dementia were also included [31]. Studies investigating patients with vascular disease were further divided into a group of patients with vascular risk factors only and a group with clinically manifest cerebrovascular disease.

We also distinguished studies that investigated indicators of global brain atrophy from studies that investigated indicators of regional brain atrophy. Measures of global brain atrophy included total brain atrophy, cortical gray matter atrophy, white matter atrophy, and ventricular enlargement. The main measure of regional atrophy was medial temporal lobe atrophy (MTA), including atrophy of the hippocampus, amygdala, and entorhinal cortex.

Studies in which several study populations were investigated and studies reporting on the relation between WML and both global and regional brain atrophy were described in all relevant categories.

General Population

The characteristics and results of the 20 general population studies are summarized in table 1. There were 17 cross-sectional studies [9, 13, 22, 32–45], 2 longitudinal studies [46, 47] and 1 study is included twice in table 1, since both cross-sectional and longitudinal results were reported [48].

Thirteen studies involved a community-based study sample [9, 13, 22, 32, 33, 35, 37, 38, 41, 43, 45–47], while 5 studies involved healthy controls or hospital personnel [34, 36, 40, 44, 48]. Two studies included neurologically healthy patients with different amounts of WML [39, 42].

Of the 13 cross-sectional studies that investigated global atrophy, 10 found a significant relation between more WML and more global brain atrophy [9, 13, 32–39]. This relation was also observed in the 2 longitudinal studies investigating global atrophy [46, 47]. Of the 5 cross-sectional studies that examined regional brain atrophy, 3 studies found that WML were associated with more medial temporal lobe atrophy and with smaller hippocampal and amygdala volumes [40–42]. However, in the 2 other cross-sectional studies there was no association between WML and hippocampal atrophy [43], or hippocampal and entorhinal volumes [48]. Also, WML volume at baseline was not associated with the atrophy rates of the entorhinal cortex and hippocampus during follow-up [48].

Table 1. Studies investigating the relation between WML and brain atrophy in subjects from the general population

First author, year of publication	Study population	n	Age (mean ± SD)	WML	WML assessment	Atrophy	Atrophy assessment	Results	Significant relation	Adjustments
Cross-sectional studies – measures of global brain atrophy										
Mirsen 1991 [36]	healthy controls	45	70 ± 10	PVWML DWML	ordinal (0–1) ordinal (0–4)	sulcal widening ventricular enlargement sulcal widening ventricular enlargement	ordinal (0–5)	control subjects with PVWML showed more ventricular enlargement then those without	no yes no no	no
Agartz 1992 [44]	healthy adults	76	46 ± 18	PVWML DWML	ordinal (0–2)	sulcal widening ventricular enlargement sulcal widening ventricular enlargement	ordinal (1–3)	no association between WML and sulcal size or ventricular enlargement	no no no no	age
Breteler 1994 [33]	non-demented elderly	90	74 ± 6	total WML	ordinal (0–2)	ventricular volume	volumetric	WML associated with ventricular enlargement	yes	age and sex
Christiansen 1994 [45]	healthy volunteers	142	(21–80)	total WML	ordinal (0–11)	cerebral hemispheres ventricular volume	volumetric	no correlation between WML and size of the hemispheres or ventricles	no no	no
DeCarli 1995 [34]	healthy individuals	51	52 ± 20	total WML	volumetric	total brain volume ventricular volume	volumetric	WML associated with total brain atrophy and ventricular enlargement	yes yes	age
Ylikoski 1995 [38]	neurologically non-diseased elderly	128	72 (55–85)	PVWML DWML	ordinal (0–1)	sulcal widening ventricular enlargement sulcal widening ventricular enlargement	ordinal (0–3)	PVWML and DWML are associated with central brain atrophy	no yes no yes	age, sex, social class, MMSE, hypertension, diabetes, coronary heart disease, cardiac failure, cardiac arrhythmia, silent infarcts
Yue 1997 [13]	population-based	3,660	72 (65–95)	total WML	ordinal (0–9)	sulcal enlargement ventricular enlargement	ordinal (0–9)	WML were associated with ventricular enlargement	no yes	age, sex and race
Swan 2000 [22]	community-dwelling, white elderly men free of severe cognitive impairment	383	73 ± 3	total WML	volumetric	total brain volume	volumetric	only a marginal association between total brain volume and WML when treated as categorical variables (e.g., more or less than the median) was observed ($p < 0.11$)	no	no
Longstreth 2000 [9]	community-dwelling elderly without stroke or TIA	3,255	>65	total WML	ordinal (0–9)	sulcal widening ventricular enlargement	ordinal (0–9)	WML related to sulcal and ventricular size	yes yes	age, race, education, congestive heart failure, smoking, alcohol, use of insulin or anti/diabetic medication, albumin, use of estrogens, reader of the scan, clinic where scan was performed, season of the scan, abnormality on ECG, IMT, and stratified for sex
Mosley 2005 [32]	general population	1,538	63 ± 5	total WML	ordinal (0–9)	cortical atrophy ventricular enlargement	ordinal (0–9) ordinal (0–9)	WML correlated with cortical atrophy and ventricular enlargement	yes yes	no

Rossi 2006 [39]	neurologically healthy	133	57 ± 10	mainly anterior WML mainly posterior WML	ordinal (0–3)	frontal cortical gray matter cortical gray matter	volumetric	anterior WML (n = 39) associated with frontal atrophy, while posterior (n = 14) WML associated with more diffuse atrophy	yes yes	age and sex
Wen 2006 [37]	normal elderly	397	63 ± 1	PVWML DWML	volumetric	cortical gray matter ventricular size sulcal size cortical gray matter ventricular size sulcal size	volumetric	DWML correlated with cortical gray matter loss and ventricular and sulcal enlargement; PVWML correlated with cortical gray matter loss only	yes no no yes yes yes	sex
Ikram 2007 [35]	non-demented elderly	490	73 ± 8	total WML	volumetric	total brain volume gray matter volume white matter volume	volumetric	persons with WML had smaller brain volumes and less white matter volumes; gray matter did not decrease with increasing WML	yes no yes	age and sex
Cross-sectional studies – measures of regional brain atrophy										
O'Brien 1997 [40]	neurologically healthy volunteers	39	72	PVWML DWML	ordinal (0–3)	hippocampus	ordinal (0–3)	PVWML correlated with hippocampal atrophy	yes no	no
Korf 2004 [43]	population-based	543	82	total WML	ordinal (0–9)	hippocampus	volumetric	no significant difference in WML grade between individuals with and without hippocampus atrophy	no	age
van der Flier 2005 [42]	non-disabled elderly people	581	74 ± 5	total WML	ordinal (0–1)	MTA	ordinal (0–1)	correlation between the presence of severe WML and the presence of MTA	yes	no
den Heijer 2005 [41]	non-demented elderly	511	73 ± 8	PVWML DWML	ordinal (0–9) ordinal	hippocampus amygdala hippocampus amygdala	volumetric	persons with more WML had smaller hippocampal and amygdala volumes	yes no yes yes	age, sex, blood pressure, use of antihypertensive medication, cholesterol/HDL ratio, BMI and smoking
Du 2006 [48]	cognitively normal elderly	42	74 ± 8	total WML	volumetric	hippocampus entorhinal cortex	volumetric	WML volumes were not associated with volumes of entorhinal cortex and hippocampus	no no	age
Longitudinal studies – measures of global brain atrophy										
Enzinger 2005 [46]	subject without neuropsychiatric disease	201	60 ± 6	total WML	ordinal (0–3)	total brain volume	volumetric	WML score at baseline was associated with brain atrophy during follow-up	yes	brain volume at baseline, age and HbA_{1c}
Schmidt 2005 [47]	elderly without neuropsychiatric disease	329	60 ± 6	total WML	volumetric	total brain volume	volumetric	increasing WML volume was associated with brain parenchymal loss	yes	age, sex, education, BMI, hypertension, diabetes, cardiac disease and total cholesterol
Longitudinal studies – measures of regional brain atrophy										
Du 2006 [48]	cognitively normal elderly	42	74 ± 8	total WML	volumetric	hippocampus entorhinal cortex	volumetric	WML volumes at baseline had no effect on atrophy rates of entorhinal cortex and hippocampus	no no	age

Figures in parentheses are ranges. TIA = Transient ischemic attack; PVWML = periventricular WML; DWML = deep WML; MTA = medial temporal lobe atrophy; BMI = body mass index; ECG = electrocardiogram; HDL = high-density lipoprotein; IMT = intima-media thickness; MMSE = Mini-Mental State Examination.

Table 2. Studies investigating the relation between WML and brain atrophy in subjects with cognitive impairment

First author, year of publication	Study population	n	Age (mean ± SD)	WML	WML assessment	Atrophy	Atrophy assessment	Results	Significant relation	Adjustments
Cross-sectional studies – measures of global brain atrophy										
Mirsen 1991 [36]	AD	30	73 ± 7	PVWML DWML	ordinal (0–1) ordinal (0–4)	sulcal widening ventricular enlargement sulcal widening ventricular enlargement	ordinal (0–5)	no relation between PVWML and DWML with measures of atrophy	no no no no	no
Fazekas 1996 [50]	probable AD	30	65 ± 7	PVWML total WML	thickness volumetric	ventricular enlargement	volumetric	PVWML were associated with ventricular enlargement	yes no	no
Decarli 1996 [61]	probable AD	26	74 ± 7	PVWML DWML	ordinal (0–3)	brain volume ventricular volume brain volume ventricular volume	volumetric	no difference in brain or ventricular volumes between AD patients with (PVWML or DWML >2) or without WML (PVWML or DWML <2)	no no no no	no
Fein 2000 [51]	elderly subjects with lacunes and a spectrum of cognitive impairment/control group of subjects with probable AD/cognitively healthy controls	58/29/37	75	total WML	volumetric	cortical gray matter	volumetric	WML volume correlated with cortical gray matter atrophy in all subjects	yes	no
Hirono 2000 [62]	AD	76	76 ± 7	total WML	volumetric	total brain volume	volumetric	no association between WML volume and normalized brain volume	no	age, sex, education and duration of symptoms
Barber 2000 [31]	AD/Lewy body	25/27	77 ± 7	PVWML DWML	ordinal (0–5)	total brain volume ventricular volume total brain volume ventricular volume	volumetric	PVWML were related to ventricular dilatation in all subjects	yes yes no no	age
Mungas 2001 [52]	cognitively normal/cognitively impaired/demented elderly	90/37/30	74 ± 8	total WML	volumetric	cortical gray matter	volumetric	WML volume was associated with smaller cortical gray matter volume	yes	volume of lacunes
Bigler 2002 [49]	patients with AD, VaD, MCI, other neuropsychiatric disorders and normal controls	195	82 (67–97)	PVWML DWML	ordinal (0–3)	gray matter white matter gray matter white matter	volumetric	PVWML were associated with white matter volume loss	no yes no no	age
Capizzano 2004 [63]	probable AD	81	70 ± 8	total WML	volumetric	cortical gray matter	volumetric	WML related to cortical gray matter volume loss in the frontal, temporal, parietal and occipital lobes	yes	age, hypertension and MMSE
Tullberg 2004 [64]	CIND/demented	30/26	78 ± 9	frontal WML total WML	volumetric	cortical gray matter	volumetric	increased WML in the frontal region were associated with reduced frontal cortical gray matter in all subjects	yes yes	unknown
Du 2005 [60]	AD/mixed dementia	50/13	77 ± 6	total WML	volumetric	cortical gray matter	volumetric	WML related to cortical gray matter atrophy in all subjects	yes	age, sex, group effect and lacunes

Bracco 2005 [55]	probable AD	86	72 ± 7	total WML	ordinal (0–18)	cortical atrophy	ordinal (0–3)	no difference in cortical atrophy between groups of patients with different WML grade	no	no
Lunetta 2007 [58]	AD-affected individuals and their unaffected siblings	424	73 ± 9	total WML	ordinal (0–100)	cortical atrophy	ordinal (0–100)	WML correlated with cortical atrophy	yes	no
Cross-sectional studies – measures of regional brain atrophy										
Fein 2000 [51]	elderly subjects with lacunes and a spectrum of cognitive impairment/a control group of subjects with probable AD/cognitively healthy controls	58/29/37	75	total WML	volumetric	hippocampus	volumetric	WML volume did not correlate with hippocampal volume	no	no
Mungas 2001 [52]	cognitively normal/cognitively impaired/demented elderly	90/37/30	74 ± 8	total WML	volumetric	hippocampus	volumetric	WML volume was associated with hippocampal volume	yes	volume of lacunes
Bigler 2002 [49]	patients with AD, VaD, MCI, other neuropsychiatric disorders and normal controls	195	82 (67–97)	PVWML DWML	ordinal (0–0)	hippocampus	volumetric	WML did not correlate with hippocampal volume	no no	age
de Leeuw 2004 [65]	probable AD	179	68 ± 9	frontal WML temporal WML parieto-occ. WML infratentorial WML	ordinal (0–2)	MTA	ordinal (0–4)	WML in the frontal and parieto-occipital regions are related to more hippocampal atrophy	yes no yes no	age, sex, MMSE, hypertension and cortical atrophy
Du 2005 [60]	AD/mixed dementia	50/13	77 ± 6	total WML	volumetric	entorhinal cortex hippocampus	volumetric	WML are not related to hippocampal atrophy and EC atrophy in all subjects	no no	age, sex, group effect and lacunes
Korf 2005 [56]	probable AD	159	68 ± 9	total WML	ordinal (0–30)	MTA	ordinal (0–4)	more MTA in patients with WML compared to patients without WML	yes	age
van der Flier 2005 [57]	AD/MCI/elderly without memory impairment	41/20/28	74 ± 7	total WML	volumetric	MTA	volumetric	significant correlation between medial temporal lobe volume and WML volume	yes	no
van de Pol 2007 [53]	participants of a randomized double-blind placebo-controlled clinical trial of galantamine in MCI	896	70 ± 9	total WML	ordinal (0–30)	MTA	ordinal (0–4)	MTA was weakly associated with WML	yes	age and sex
Bombois 2007 [54]	MCI patients attending a memory clinic	170	68 (46–87)	PVWML DWML	ordinal	MTA	ordinal	age and MTA were independently associated with PVWML	yes no	age, gender, vascular risk factors (unspecified) and educational level

Table 2 (continued)

First author, year of publication	Study population	n	Age (mean ± SD)	WML	WML assessment	Atrophy	Atrophy assessment	Results	Significant relation	Adjustments
Lunetta 2007 [58]	AD-affected individuals and their unaffected siblings	424	73 ± 9	total WML	ordinal (0–100)	MTA	ordinal	WML correlated with MTA	yes	no
Staekenborg 2007 [59]	AD	111	70 ± 9	total WML	ordinal (0–3)	MTA	ordinal (0–4)	presence of MTA was associated with presence of WML	yes	no
Longitudinal studies – measures of regional brain atrophy										
de Leeuw 2006 [67]	AD	35	66 ± 9	PVWML	ordinal (0–1)	MTA	ordinal (0–4)	presence and progression of PVWML are associated with progression of MTA	yes no	age, sex, duration of follow-up, and blood pressure
				DWML						
van de Pol 2007 [66]	participants of a randomized double-blind placebo-controlled clinical trial of galantamine in MCI	323	69 ± 9	total WML	ordinal (0–30)	hippocampus	volumetric	baseline WML were not associated with rate of hippocampal atrophy	no	age and sex

Figures in parentheses are ranges. AD = Alzheimer's disease; VaD = vascular dementia; MCI = mild cognitive impairment; CIND = cognitively impaired/not demented; DWML = deep WML; MMSE = Mini-Mental State Examination; MTA = medial temporal lobe atrophy; parieto-occ. = parieto-occipital; PVWML = periventricular WML; EC = entorhinal cortex.

In 7 of the 20 general population studies, no adjustments were made for age [22, 32, 36, 37, 40, 42, 45]. Shared risk factors were only considered in 4 out of 20 studies [9, 38, 41, 47], all of which observed an association between WML and measures of brain atrophy.

Subjects with Cognitive Impairment

Nineteen cross-sectional studies [31, 36, 49–65] and 2 longitudinal studies [66, 67] were performed in patients with cognitive impairment. Characteristics and results of these studies are presented in table 2. In 5 studies [49, 51, 52, 58, 60], both global and regional brain atrophy were investigated, and therefore these studies are presented twice in table 2.

Study populations consisted of patients referred for evaluation of cognitive impairment or dementia [31, 36, 49, 50, 54–57, 59, 62, 63] or of patients who were recruited at specialized dementia centers [52, 60, 64, 65, 67]. Two studies were performed in MCI patients participating in a clinical trial [53, 66], one study was part of a large genetic study in AD patients and their non-demented siblings [58], and in the other study participants were selected because they met the criteria for probable AD and did or did not show severe WML on MRI [61]. Finally, 1 study was performed in a heterogeneous group of patients with lacunes and a spectrum of cognitive impairment, in patients with probable AD without lacunes, and a control group of individuals without cognitive impairment and without lacunes [51].

The relation between WML and global brain atrophy was assessed in 13 cross-sectional studies. In 9 of these, WML were associated with more global brain atrophy and with smaller cortical gray matter volumes [31, 49–52, 58, 60, 63, 64]. In the other 4 studies, these relations were not found [36, 55, 61, 62]. The relation between WML and measures of regional brain atrophy was investigated in 11 cross-sectional studies and in 2 longitudinal studies. A significant association between WML and atrophy of the hippocampus or medial temporal lobe was found in 7 cross-sectional studies [52–54, 56–59], although in 1 of these studies only periventricular WML, and not deep WML, were associated with medial temporal lobe atrophy [54]. In another cross-sectional study [65], a relation was found between WML in the frontal and parieto-occipital regions and more hippocampal atrophy. In 3 cross-sectional studies [49, 51, 60], no relation was found between total WML volume or WML ratings and volumes of the hippocampus or entorhinal cortex. In 1 longitudinal study, presence and progression of periventricular WML, but not deep WML, were associ-

ated with progression of medial temporal lobe atrophy [67]. In another longitudinal study, total WML volume at baseline was not associated with the rate of hippocampal atrophy [66].

In 10 studies, no adjustments were made for potential shared risk factors in the relation between WML and atrophy [36, 50–52, 55, 57–59, 61, 64]. Adjustments for age or sex were made in the remaining 11 studies. Three considered hypertension or blood pressure as a possible shared risk factor [63, 65, 67]. In 1 study [54], adjustments were made for vascular risk factors, without further specification. Therefore, although in the last 4 studies associations between WML and brain atrophy were found, it is unknown whether these associations are also independent of other vascular risk factors.

Patients with Vascular Risk Factors or Symptomatic Vascular Disease

The characteristics and results of the 4 studies [68–71] performed in patients with vascular risk factors are presented in table 3a and the characteristics and results of the 4 studies [72–75] performed in patients with symptomatic cerebrovascular disease are given in table 3b. Of these 8 studies, 5 examined the cross-sectional and 3 the longitudinal relation between WML and atrophy. Two cross-sectional studies [70, 72] examined global as well as regional atrophy. Furthermore, 1 study [74] reported the cross-sectional relation between WML and medial temporal lobe atrophy and the longitudinal relation between WML and ventricular enlargement.

The 4 studies that investigated a population with vascular risk factors recruited their patients from outpatient clinics [68–70] or from a trial on antihypertensive drugs [71]. The studies that investigated patients with manifest cerebrovascular disease included stroke survivors 3 months after discharge [72, 74], patients with a transient ischemic attack [75], and patients with a lacunar stroke [73].

In 2 cross-sectional studies performed in patients with vascular risk factors, associations were found between larger volumes of periventricular WML and more global brain atrophy and both sulcal and ventricular enlargement [68, 69]. However, in 2 other cross-sectional studies in hypertensive patients and normotensive controls, no associations between WML and total brain volume or hippocampal volume were found [70]. In a longitudinal study in hypertensive and normotensive elderly, there was no association between global atrophy rate and degree of WML at baseline, or change in WML severity during follow-up [71].

In the patients with stroke or TIA, cross-sectional associations were found between more WML and more cortical, central and medial temporal lobe atrophy [72–75]. The relation between WML and ventricular enlargement was also found in the longitudinal study [74].

In 3 studies [68, 71, 75], the analyses were adjusted for age. In 1 of these studies [75] there was an association between WML and brain atrophy after adjustment for systolic and diastolic blood pressure. However, there was no association between WML and brain atrophy in another study [71] in which adjustments were made for other vascular risk factors as well. In the remaining 5 studies, no adjustments were made for age, sex or other possible shared vascular risk factors [69, 70, 72–74].

Discussion

We included 48 articles that investigated the relation between WML and measures of global or regional brain atrophy. A significant relation between WML and global brain atrophy was found in 12 out of 15 general population studies, 9 out of 13 studies in patients with cognitive impairment and in 6 out of 8 studies performed in patients with vascular risk factors or symptomatic cerebrovascular disease. A significant relation between WML and medial temporal lobe atrophy – including atrophy of the hippocampus, amygdala, and entorhinal cortex – was found in 3 out of 6 general population studies, 9 out of 13 studies in patients with cognitive impairment, and in 2 out of 3 studies performed in patients with vascular risk factors or symptomatic cerebrovascular disease.

The clinical observation that WML and brain atrophy are often seen simultaneously on MRI is thus confirmed by the majority of the retrieved articles. However, most of the studies did not adjust for possible shared risk factors. Moreover, in 22 of the 48 studies no adjustments were made for age. From these studies, it is not possible to conclude that the relation between WML and brain atrophy is independent of age. When we look at all the studies that did adjust for age and other risk factors, 9 out of 10 studies found that WML were associated with measures of brain atrophy, providing at least some evidence that the relation is independent of shared risk factors [9, 38, 41, 47, 54, 63, 65, 67, 75].

Eight studies examined the longitudinal relation between WML and atrophy. Of these, 1 study did not adjust for age or other possible shared risk factors, 3 adjusted for age or age and sex, and 4 studies also adjusted for a small number of shared risk factors. Of the 7 longitudi-

Table 3a. Studies investigating the relation between WML and brain atrophy in subjects with vascular risk factors

First author, year of publication	Study population	n	Age (mean ± SD)	WML	WML assessment	Atrophy	Atrophy assessment	Results	Significant relation	Adjustments
Cross-sectional studies – measures of global brain atrophy										
Meguro 1992 [68]	patients with cerebrovascular risk factors without neurological abnormalities	52	72	PVWML	volumetric	global brain atrophy, ventricular enlargement	volumetric	WML related to global brain atrophy	yes yes	age and aortic arch calcification
Meguro 1993 [69]	patients with cerebrovascular risk factors without neurological abnormalities	52	(59–81)	PVWML	volumetric	global brain atrophy, sulcal enlargement, ventricular enlargement	volumetric	correlation between WML and brain atrophy and sulcal and ventricular enlargement	yes yes yes	no
Wiseman 2004 [70]	hypertensive subjects normotensive subjects	103 51	77 ± 4	PVWML basal ganglia WML total WML	ordinal (0–2) ordinal (0–30) ordinal (0–54)	whole brain	volumetric	no correlation between WML and total brain volume	no no no	no
Cross-sectional studies – measures of regional brain atrophy										
Wiseman 2004 [70]	hypertensive subjects normotensive subjects	103 51	77 ± 4	PVWML basal ganglia WML total WML	ordinal (0–2) ordinal (0–30) ordinal (0–54)	hippocampus	volumetric	no correlation between WML and hippocampal volume	no no no	no
Longitudinal studies – measures of regional brain atrophy										
Firbank 2007 [71]	hypertensive elderly normotensive elderly	68 27	77 ± 4 5 ± 2	total WML	volumetric	global brain atrophy	volumetric	no association between atrophy rate and either degree of WML at baseline, or change in WML severity	no	age, sex, smoking status, baseline glucose and cholesterol, baseline and change in WML and baseline and inter MRI blood pressure

Figures in parentheses are ranges. DWML = Deep WML; MTA = medial temporal lobe atrophy; PVWML = periventricular WML.

Table 3b. Studies investigating the relation between WML and brain atrophy in subjects with symptomatic vascular disease

First author, year of publication	Study population	n	Age (mean ± SD)	WML	WML assessment	Atrophy	Atrophy assessment	Results	Significant relation	Adjustments
Cross-sectional studies – measures of global brain atrophy										
Pohjasvaara 2000 [72]	post-stroke	337	70 ± 8	mean WML score	ordinal (0–3)	cortical brain atrophy central brain atrophy	ordinal (0–3)	mean WML score was higher in the patients having any moderate or severe cortical atrophy or any moderate or severe central atrophy	yes yes	no
Grau-Olivares 2007 [73]	patients with lacunar stroke with and without MCI	40	71 ± 12	total WML	ordinal (0–30)	gray matter atrophy	volumetric	in patients with MCI, total WML were correlated with frontal and temporal gray matter atrophy (not found in patients without MCI)	yes	no
Cross-sectional studies – measures of regional brain atrophy										
Pohjasvaara 2000 [72]	post-stroke	337	70 ± 8	mean WML score	ordinal (0–3)	MTA	ordinal (0–3)	mean WML score was higher in the patients with any moderate or severe medial temporal lobe atrophy	yes	no
Firbank 2007 [74]	stroke survivors without post-stroke dementia	79	80 ± 4	temporal parietal frontal occipital total WML	volumetric	MTA	ordinal (0–4)	MTA was correlated with both total and temporal WML	yes no no no yes	no
Longitudinal studies – measures of regional brain atrophy										
Walters 2003 [75]	patients with a first TIA without cognitive impairment	60	72 ± 7	total WML	ordinal (0–60)	total brain volume	volumetric	baseline WML were associated with progression of total brain atrophy	yes	age, systolic and diastolic blood pressure
Firbank 2007 [74]	stroke survivors without post-stroke dementia	41	80 ± 4	temporal parietal frontal occipital total WML	volumetric	ventricular enlargement	volumetric	total WML at baseline correlated with rate of ventricular enlargement	no no no no yes	no

Figures in parentheses are ranges. MTA = Medial temporal lobe atrophy.

nal studies that adjusted for age or other factors, 4 found that WML were significantly associated with progression of brain atrophy, whereas 3 did not find an association. Thus, from the existing longitudinal studies, we cannot conclude that WML are a risk factor for brain atrophy.

An interesting pattern was observed when we compared the results of studies investigating global atrophy with the results of studies investigating regional brain atrophy. The majority of studies found an association between WML and global brain atrophy, which remained in the majority of the studies after adjustment for age and vascular risk factors. This association was also present in the majority of the longitudinal studies. The studies that did not find an association between WML and global atrophy generally had smaller sample sizes and used less accurate rating scales, which may have resulted in a low power to detect a significant relationship. In comparison, the results from the studies investigating the association between WML and measures of regional brain atrophy were less consistent. Interestingly, from the 12 studies that adjusted for age or other factors, all 5 studies that used the MTA score found a significant association with WML, while the 7 studies that used volumetric measurements of the hippocampus did not, except for 1 study, find an association with WML. Since the MTA score not only visually assesses volume of the medial temporal lobe, but also volume of the temporal horn of the lateral ventricle and the choroid fissure, it is plausible that concomitant ventricular enlargement accounts for the observed association between WML and MTA score [76]. Support for this explanation comes from a study that found that the MTA score correlated better with the volume of the lateral ventricle than with the volume of the medial temporal lobe itself [77].

Several mechanisms have been proposed that may explain an association between WML and brain atrophy. One possible mechanism is loss of myelin, axons, and oligodendrocytes and other glial cells in the subcortical white matter as a result of ischemic damage due to the underlying small-vessel disease [30, 78]. The association of WML with cortical gray matter atrophy may possibly be explained by ischemic damage to the axons in the subcortical white matter leading to deafferentation of cortical-subcortical connections and subsequent cortical neurodegeneration [60]. Similar mechanisms have been proposed to explain the relation between WML and atrophy of the hippocampus and amygdala, and consequently the medial temporal lobe [41, 65]. Ischemia due to the cerebral small-vessel disease may well damage the axons in the white matter, which eventually could lead to shrinkage of the hippocampus as a result of Wallerian degeneration [79]. Another explanation that has been proposed is that an impaired autoregulation due to the microangiopathy in combination with the luminal narrowing reduces the cerebral blood flow [80]. Since the hippocampus and amygdala are sensitive to hypoxia and ischemia [81, 82], this ischemia may then lead to loss of the neurons in these brain structures [83].

Other observations that may support an association between WML and brain atrophy have come from studies in other neurological conditions, such as CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), multiple sclerosis [84], amyotrophic lateral sclerosis [85], and HIV [86]. Of these conditions, CADASIL is of particular interest, because the WML in that condition are also presumed to be due to vascular disease [87]. Apart from widespread WML and lacunar infarcts, brain atrophy is also a hallmark of this disease [88]. Furthermore, both hippocampal atrophy [89], subcortical atrophy [90], and global brain atrophy [91] are important predictors of cognitive performance in CADASIL patients. However, volume of WML was not associated with extent of hippocampal [89] or global brain atrophy [88, 90], although this can potentially be explained by the small sample sizes of studies in patients with CADASIL.

Given the plausible biological hypotheses, but inconsistent results, more research is warranted. Future studies should preferably assess WML as well as brain atrophy volumetrically. Visual rating scales are impeded by floor and ceiling effects and their reliability is often limited [92]. Volumetric measurements offer a more reliable, sensitive, and also objective alternative to visual rating scales [93]. However, in case volumetric assessment of WML in longitudinal studies is not feasible, at least dedicated longitudinal visual scales should be used [94]. In addition, quantitative measurements of WML and brain volumes should be normalized for head size [95]. This facilitates comparison between studies and also helps in overcoming the difficulty of interpreting the strength of the relation. Analyses on the association between WML and atrophy should at least take the effects of age and sex into account, but should also address shared vascular risk factors. Another factor that should be considered is the presence or number of lacunar infarcts. Lacunar infarcts are also considered to be caused by cerebral small-vessel disease and are also often found on MRI in the elderly [96–98]. In patients with Alzheimer's disease and mixed dementia, lacunar infarcts may be associated with subcorti-

cal brain atrophy [60, 99]. Furthermore, in studies that examine the association between WML and atrophy of the medial temporal lobe or structures herein, global brain atrophy should be taken into account to assess whether an association is explained by global brain atrophy. Finally, to properly address the issue of the directionality of the association between WML and brain atrophy, future studies should have a longitudinal design.

In conclusion, the majority of studies found an association between WML and global brain atrophy, but it is yet uncertain if this association is independent of shared risk factors. Further studies on the relation between WML and brain atrophy are therefore warranted and should make proper adjustments in the analysis, preferably be longitudinal in design, and use volumetric assessment of WML and brain atrophy.

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