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ABSTRACT

Background

Cerebral white matter hyperintensities (WMH), detected *in vivo* with magnetic resonance imaging (MRI), are commonly used to assess cerebrovascular burden in cognitive impairment. However, the association between WMH and cognition is not consistent the across literature. The present review examines evidence from published longitudinal studies.

Methods

We reviewed the PubMed data base from January 1990 to March 2013 and included studies investigating the association of WMH with 1) the risk of dementia in the general population, 2) the risk of conversion to dementia in the mild cognitive impairment (MCI) population, and 3) cognitive decline in the general population.

Results

WMH were associated with all types of dementia in the general population, but not in MCI patients. Results are discrepant for global decline.

Conclusion

WMH appear to be early predictors of the risk of dementia, but this association appears to be modulated by cognitive reserve, age and the spatial distribution of lesions. There are however some limits in the use of WMH as a marker of vascular burden. In addition to their ischemic origin, WMH may be the result of co-occurring morbidity. Further research is needed to elucidate to what extent, WMH actually reflect vascular risk to evaluate the likely efficacy of interventions specifically targeting WMH reduction.

Introduction

Alzheimer's disease (AD), defined as a neurodegenerative process, is usually considered the most common form of dementia, followed by vascular dementia (VaD), related to cerebral vascular lesions (ischemic, or hemorrhagic, or single or multiples infarcts) . However, in autopsy series, an overlap between the pathological characteristics of AD (tangles and neuritic plaques) and vascular pathology has frequently been observed in demented subjects (Ince, 2001; Schneider et al., 2007; Snowdon et al., 1997), thus making it difficult to clinically differentiate the two entities. Moreover, epidemiological and clinical studies in the last two decades have suggested that the underlying biological characteristics of the two disorders may be interdependent such that increased vascular risk factors (diabetes, hypertension, dyslipidemia, cardiopathies, lifestyle) are also risk factors for AD (Silvestrini et al., 2012; Tolppanen et al., 2012). While to date no imaging study has compared the frequency of vascular disorder and AD in cohorts with dementia, longitudinal community-based postmortem brain series suggest that a mixed pathological basis occurs in over 60% of cases (Ince, 2001; Schneider et al., 2007). Moreover, given the insensitivity of standard neuropathological analyses to microvascular disease, this is likely to be an underestimation.

The dichotomization between pure neurodegenerative and pure vascular forms of dementia is therefore currently being questioned, and a reformulation of the diagnostic criteria for AD has been proposed (McKhann et al., 2011). It is still not clear whether vascular lesions are directly involved in the development of AD, or

whether they may lower the burden of AD pathology necessary to produce clinical symptoms of dementia (Esiri et al., 1999; Godin et al., 2010; van der Flier et al., 2004). Estimating the contribution of cerebrovascular disease in cognitive decline is important for the understanding of the etiology of dementia, and because vascular risk factors represent modifiable factors and potential therapeutic targets (Valenzuela et al., 2012). Progress in neuroimaging has provided relevant means to estimate *in vivo* cerebrovascular burden, accumulated throughout life. Pathology in small cerebral arteries, which cannot be imaged directly, is typically measured by cerebral white matter hyperintensities (WMH) appearing as hyperintense areas on T2 weighted magnetic resonance imaging (MRI) scans (including FLAIR) and are commonly found in the elderly (Ylikoski et al., 1995). Pathological correlates of these hyperintense areas include myelin pallor, loss of myelin and axons, and mild gliosis (Fazekas et al., 1993; Gouw et al., 2011). Such lesions may cause cognitive impairment by disrupting cortical connections mediated by specific white matter tracts (Smith et al., 2011). The etiology of WMH is still not fully understood, but WMH are thought to mainly result from pathological changes in small vessels (Pantoni and Garcia, 1997; Roman et al., 2002) leading to chronic hypoperfusion of white matter and disruption of the blood-brain barrier with leakage of plasma into white matter (O'Sullivan et al., 2002; Topakian et al., 2010).

WMH could represent a non-invasive method to assess vascular risk in epidemiologic studies, or as a surrogate marker in clinical trials (Richard et al., 2010; Schmidt et al., 2012). Numerous studies have investigated the association between WMH and cognition, with conflicting results. The present review examines evidence from published longitudinal studies assessing the relationship between WMH and 1) risk of

dementia in the general population, 2) risk of transition from mild cognitive impairment (MCI) to dementia and 3) cognitive decline without dementia in the general population.

Methods

Study selection for the review

We reviewed the PubMed data base from January 1990 to March 2013. A combination of search strategies using MeSH terms and other search terms (keyword search) were used. In summary, the search covered the following terms: white matter, periventricular, subcortical, leukoaraiosis, dementia, cognition, MRI, and longitudinal studies. The detailed search strategy is reported in the Appendix. Reference lists of relevant articles were also examined.

In this review, we included studies with assessment of WMH at baseline and with longitudinal data on cognition. We retained studies investigating the association of WMH with 1) the risk of dementia in the general population, 2) the risk of conversion to dementia in the MCI population, and 3) cognitive decline in the general population. We reviewed titles and abstracts of identified articles which were published in English. For those potentially meeting the inclusion criteria, the full paper was reviewed. If several publications were found for the same cohort and the same outcome, we retained the study with the longest follow-up, or the highest number of participants if duration of follow-up was similar.

From the selected studies, information relating to the following characteristics was collected: number of participants, mean age, duration of follow-up, quantification method of WMH, outcome definition (all types of dementia versus AD, VaD, mixed

dementia (MD), and others; neuropsychological tests used to assess cognitive decline), and number of events observed during the follow-up period. Hazards Ratio (HR), Odds Ratio (OR), and adjustment variables were extracted when available.

Results

Selected studies

Overall 824 references were initially identified from the initial searches. Studies with cross-sectional data on cognition or with MRI at the end of follow-up instead of at baseline were not included. Studies on WMH in high risk subjects such as patients with monogenic cerebrovascular disease (CADASIL), vascular risk, stroke or depression were excluded, as well as studies on the association of WMH with cognitive decline in already demented or MCI individuals. Finally, duplicates (De Groot et al., 2002; Ikram et al., 2010; Kuller et al., 2005; Rosano et al., 2007; Vermeer et al., 2003) were also discarded. After the initial screening, 23 articles were retrieved for full text review. We included one additional paper (Bombois et al., 2008) from the hand search of the reference list of these 23 articles. We finally included 24 articles.

WMH and risk of dementia in the general population

Results from the five population-based studies investigating the association between WMH and the risk of dementia are shown in Table 1. Overall, the association was significant for all types of dementia, and a meta-analysis (Debette and Markus, 2010) carried out on three of these five studies (Debette et al., 2010; Kuller et al., 2003; Prins et al., 2004) provided an HR of 2.9 (1.3-6.3). Two studies distinguished

between periventricular and deep (or subcortical) WMH (PWMH and DWMH respectively): Prins et al. showed that the association with risk of dementia was significant for PWMH only, whereas Meguro et al. found that these locations were both significantly associated with risk of dementia. Kuller et al. and Meguro et al. reported specific significant associations between WMH and risk of dementia other than AD. While Meguro et al. found no association with AD, Kuller et al. showed a slightly lower than for VaD and mixed dementia, but significant HR (1.5 (1.17-1.99)) in the association between WMH and risk of AD, which is in agreement with other studies (Brickman et al., 2012; Debette et al., 2010; Prins et al., 2005) in which AD cases were the most frequent.

WMH and risk of dementia in MCI subjects

Results from studies investigating the association between WMH and the risk of dementia in MCI patients are shown in Table 2. Nine of the 12 studies assessed the relationship between WMH and risk of all types of dementia; all finding no significant association (Bombois et al., 2008; Clerici et al., 2012; DeCarli et al., 2004; Devine et al., 2013; Geroldi et al., 2006; Kantarci et al., 2009; Korf et al., 2004; Smith et al., 2008; Tapiola et al., 2008). Three studies (Defrancesco et al., 2013; Staekenborg et al., 2009; van Straaten et al., 2008) investigated the specific relationship between WMH and risk of AD: total WMH load was not significantly associated with risk of AD in any of these studies, and of the two studies (Staekenborg et al., 2009; van Straaten et al., 2008) distinguishing between PWMH and DWMH, only one (van Straaten et al., 2008) showed a significant association between PWMH and risk of AD. Conversely, total WMH load (Bombois et al., 2008; Staekenborg et al., 2009),

and PWMH and DWMH (Staekenborg et al., 2009) were significantly associated with risk of dementia other than AD.

WMH and cognitive decline in the general population

Results from studies investigating the association between WMH and cognitive decline in the general population are shown in Table 3. Among studies testing the relationship between WMH and global cognitive decline, results were discrepant: five studies (Godin et al., 2010; Inaba et al., 2011; Prins et al., 2005; Silbert et al., 2009; Smith et al., 2008) found a significant association, while the other 2 did not (Debette et al., 2010; Kuller et al., 1998). Among studies with positive results, studies distinguishing between PWMH and DWMH showed significant associations between PWMH and global cognitive decline (Godin et al., 2010; Prins et al., 2005; Silbert et al., 2009), while negative results were reported for DWMH (Godin et al., 2010; Prins et al., 2005). Regarding specific cognitive domains, a significant association was found for PWMH and decline in processing speed and executive functions (Prins et al., 2005), but not reaching significance for verbal fluency and memory (Christensen et al., 2009; Prins et al., 2005). Conversely, Christensen et al. did not find a significant association between WMH and processing speed. However, little cognitive change is observed in this sample, in which participants are relatively young and have high levels of education. The neuropsychological tests used in these studies are, however, too limited in scope to conclude domain specific effects, and further research is required using functional imaging to ensure persons with WMH process information in the same way as those without.

Discussion

In this review, we examined the extent to which WMH may predict dementia or cognitive decline in both the general population and in MCI patients. Overall WMH load appears to be a significant predictor of all types of dementia in the general population, but not in MCI patients. This may of course partly reflect the inadequacy of MCI criteria. The association between WMH and risk of VaD or mixed dementia seems to be the most consistent irrespective of the population. Regarding cognitive decline, results are discrepant for global decline, but suggest the possibility of a specific relationship between WMH and decline in executive functions and processing speed, supporting findings from cross-sectional studies (Murray et al., 2010; Tullberg et al., 2004).

The findings of this review show above all that the strength of the relationship between WMH and cognition varies according to the population and the cognitive dimension under consideration. As adequate estimations of reliability between visual scale ratings and automatic methods of WMH quantification have been reported (Olsson et al., 2013; Valdes Hernandez Mdel et al., 2013) it is unlikely that heterogeneity in the different WMH measurement methods over the different studies constitutes a significant cause of inconsistency. A number of alternative hypotheses may be postulated to explain the differences between studies:

1) The relationship between WMH and cognition is confounded by cognitive reserve

People may differ in their capacity to compensate for the deleterious effect of WMH, as has already been observed for some people with extensive AD histopathology (senile plaques and neurofibrillary tangles) who did not exhibit cognitive impairment before death (Bennett et al., 2003). The concept of "cognitive reserve" has been proposed to explain how neurodegenerative changes that are similar in nature and extent, may give rise to considerable variation in terms of cognitive consequences (Stern, 2002). This may be defined as individual ability to make flexible and efficient use of available neuronal networks or active reserve (Steffener and Stern, 2012), and differential capacity of the brain itself to cope with pathology or passive reserve. Although one study did not find direct evidence to support the cognitive reserve hypothesis (Christensen et al., 2009), several others support the notion that reserve may influence the relationship between WMH and some cognitive domains (Brickman et al., 2011; Dufouil et al., 2003; Murray et al., 2011; Nebes et al., 2006; Saczynski et al., 2008; Vemuri et al., 2011) and in dementia (Skoog et al., 2012) . The latter study was, however, cross-sectional (Skoog et al., 2012), and used head size as a proxy of cognitive reserve, which is assumed to reflect the passive model. Moreover, WMH were estimated with CT scans which are less sensitive than MRI in detecting WMH. In the Esprit Study (Ritchie et al., 2004), a cohort of people aged 65 years and over recruited from the electoral rolls in Montpellier (France), a significant interaction was found between WMH and education (a proxy of the active model of cognitive reserve); severe WMH significantly increasing the risk of developing MCI and dementia over a 7-year period in low educated participants, while subjects with

higher education level were seen to be more likely to be resilient to the deleterious effects of severe WMH (Mortamais et al., 2013a).

Cognitive reserve could indeed balance the negative impact of pathological brain burden such as that of WMH on late life cognitive ability, acting through both protective and compensatory mechanisms. On the other hand, greater head size (Coffey et al., 1999), stronger myelination and more richly connected fiber tracts were observed in the white matter of highly educated people (Teipel et al., 2009), suggesting a link between the active and passive models. How cognitive reserve is implemented is still unclear, but this hypothesis suggests several avenues for dementia prevention. Inconsistencies between observations of the association between WMH and cognitive decline have to date not taken into account the notion of cognitive reserve, although most have adjusted by education, which is, however, a poor proxy for active reserve only.

2) The risk conferred by WMH may vary across the life-span with "vulnerability windows" determined by age and comorbidity

The observations obtained to date suggest that WMH are poor predictors of transition to dementia once cognitive impairment is present. The prevalence of WMH increases with advancing age (Ylikoski et al., 1995) and it has been suggested that their relationship with vascular risk factors becomes less clear (Breteler et al., 1994; O'Sullivan et al., 2003; van Dijk et al., 2008). As observed for the pathological features of AD (Haroutunian et al., 2008; Savva et al., 2009), the importance of WMH in cognitive decline may change with advancing age. The few studies which have

examined the relationship between WMH and cognition in the oldest old (Firbank et al., 2012; Skoog et al., 1998) have indeed found no association in terms of either prevalence or incidence of dementia. This could reflect the fact that WMH accumulation stands out in younger subjects where it is less frequent, but at higher ages is indistinguishable from 'normal' ageing-related cumulation not related to neurodegenerative disease.

These findings suggest that the association between increasing WMH volume and cognitive deterioration is less apparent with advancing age either due to loss of effect or masked by comorbidities which constitute risk factors in themselves.

3) WMH location may differentially determine risk

The assumption of much research in this area is that the impact on cognitive functioning is largely determined by the extent of WMH damage, whereas as is the case for other types of brain lesion, localization may be a more important factor. WMH may cause cognitive impairment by disrupting cortical connections that are mediated by specific white matter tracts (Smith et al., 2011). For instance, the strong association found between WMH and executive functioning would appear to be principally due to the presence of WMH in the frontal lobes (Chen et al., 2006), prefrontal cortex and their associated cortical-cortical and cortical-subcortical connectivity (Brickman et al., 2006). As noted in the above review, periventricular WMH seem to better anticipate both dementia and cognitive impairment than deep WMH. Findings concerning this categorization remain controversial, and as De Carli

et al. (2005) have pointed out, may simply reflect the capacity of these two locations to reflect total WMH volume.

Independently of periventricular or subcortical locations, conflicting results have been reported concerning the extent and spatial distribution of WMH in different brain regions in patients with MCI or dementia. While some studies did not find a particular regional distribution of WMH in AD (Chen et al., 2006; Gootjes et al., 2004; Holland et al., 2008), others found significantly higher WMH in parietal and posterior regions in AD (Brickman et al., 2012; Yoshita et al., 2006). In both MCI and normal ageing white matter deterioration shows antero-posterior progression (Artero et al., 2004; Gao et al., 2011). The association between WMH in the parietal and posterior regions with the risk of MCI or dementia could be thus confounded by total WMH load. In the Esprit study, we observed that total WMH volume and percentage of WMH in the temporal region were the best predictors of progression to MCI and dementia. Specifically, severe total WMH load with a high proportion of hyperintensities in the temporal region was significantly associated with the risk of developing MCI or dementia (Mortamais et al., 2013b). The association between WMH and risk of MCI/dementia therefore appears to depend on both the extent and location of WMH, and further research is needed to determine which particular white matter structure in the temporal region is involved. This particular spatial distribution was observed in healthy subjects, before the onset of clinical symptoms, and may therefore facilitate the detection of patients at risk of MCI or dementia.

4) The impact of WMH on cognition is determined by other concurrent structural brain changes in aging and in AD

If the link between atrophy and HSB seems independent of age (Appelman et al., 2009), it is not yet clear whether they are independent of other common risk factors, including vascular risk factors. In addition, their pathophysiological processes may be interdependent: ischemia due to cerebrovascular disease indeed damages the axons which correspond to cortical neurons and may be the cause of neuronal loss by retrograde degeneration. Whatever are the mechanisms that link brain atrophy and WMH, it seems necessary to consider the overall atrophy as potential confounding factor in studies investigating the relationship between cognition and WMH, in order to determine the specific impact of WMH regardless of this parameter which is also related to age and concomitant with WMH.

Furthermore, the fact that brain regions where WMH cluster in people who will develop cognitive deterioration colocalize to the distribution of AD pathology (Braak and Braak, 1991), and that the associations between WMH and cognition persist after adjusting for vascular risk factors (Bombois et al., 2008; Godin et al., 2010; Inaba et al., 2011; Kuller et al., 2003) suggests that, in addition to its ischemic origin, WMH may have other etiologies. Other potential mechanisms have been suggested such as Wallerian degeneration that occurs secondary to neuronal loss (Leys et al., 1991), or amyloid angiopathy (Chen et al., 2006). Alternatively, microvascular white matter disease may impair amyloid clearance and contribute consequently to β-amyloid deposition in AD (Grimmer et al., 2012).

Other studies have, however, found no relationship between WMH and progression of AD-specific pathology (Lo and Jagust, 2012). Moreover, the association between WMH and cognition is not affected when adjusted for hippocampal volume or medial temporal lobe atrophy (Bombois et al., 2008; Brickman et al., 2012; Mortamais et al.,

2013b; Silbert et al., 2009), hallmarks of neurodegeneration in AD on MRI, suggesting that the vascular contribution to dementia does exist and is probably additive with AD pathology (Godin et al., 2010; van der Flier et al., 2004).

Conclusion

WMH appear to be early predictors of dementia. However, the strength of the association between WMH and cognition appears to be modulated by cognitive reserve, age and the spatial distribution of lesions. These factors should be taken into account in epidemiological studies investigating the contribution of vascular risk with WMH in dementia, or in clinical trials using WMH as surrogate marker.

There are however some limits in the use of WMH as a marker of vascular burden. In addition to their ischemic origin, WMH may be the result of co-occurring morbidity. Further research is needed to disentangle the possible etiologies of WMH, in order to elucidate to what extent WMH actually reflect vascular risk and hence evaluate the likely efficacy of interventions specifically targeting WMH reduction.

Appendix

The search strategy was carried out in two steps with the PubMed Advanced Search Builder.

1) First step

((((white matter) OR periventricular) OR subcortical) OR leukoaraiosis[MeSH Terms]) AND (((((dementia[MeSH Terms]) OR alzheimer disease[MeSH Terms]) OR cognition[MeSH Terms]) OR cognition disorders[MeSH Terms])) AND (imaging, magnetic resonance[MeSH Terms]) AND ((((((longitudinal studies[MeSH Terms]) OR cohort studies[MeSH Terms]) OR follow up studies[MeSH Terms]) OR prospective studies[MeSH Terms]) OR risk factors[MeSH Terms])) AND ("1990/01/01"[Date - Publication] : "2013/03/01"[Date - Publication]).

Results: 759 publications.

2) Second step

This second step was carried out in order to select the more recent studies which

MeSH Terms are not yet registered in PubMed (in process).

((white matter lesions[Title/Abstract]) OR (white matter hyperintensity[Title/Abstract])) AND (dementia[Title/Abstract]) AND ("2012/01/01"[Date - Publication] : "2013/03/01"[Date - Publication]).

Results: 65 publications.

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Table 1. Association between WMH and risk of dementia in the general population. Prospective studies, with assessment of WMH at baseline.

Study **Sample size (n)** **Mean age**	**Follow-up period**	**WMH quantification methods**	**Incident dementia**	**Results** **Hazards Ratio (HR (95%CI)) and Odds Ratio (OR (95%CI)). When non specified, HR and OR are given for all types of dementia**
Cardiovascular Health Study (Kuller et al., 2003) **n=3375** **≥ 65 years old**	Not available	Semi-quantitative (grade ranges 0 to 9). Dichotomization (> 3 vs. ≤3).	n=480 (criteria not specified) -52 VaD -76 MD -330 AD	HR=1.7 (1.36-2.10) for WMH>3. HR=2.1 (1.36-3.11) for VaD+MD and WMH>3. HR=1.5 (1.17-1.99) for AD and WMH>3. *Adjustment on age, sex, race, education, baseline cognition, apoe4 genotype, ventricular grade, infarcts on MRI, vascular risks factors, stroke, subclinical disease.*
Rotterdam Scan Study (Prins et al., 2004) **n=1077** **72.2 years old**	5.2 years	Semi-quantitative for PWMH (grade ranges 0 to 9) and quantitative for DWMH. Continuous.	n=45 (DSM-IIIR) -6 VaD -34 AD -5 others	HR=1.42 (1.04-1.94) for PWMH per SD increment. NS for DWMH. *Adjustment on age, sex, infarcts on MRI, and brain atrophy.*
Framingham Offspring Study (Debette et al., 2010) **n=2013** **62 years old**	5.9 years	Quantitative. Continuous + dichotomization : « EXT-WMH »= WMH> (mean volume in a specific age group+ 1 SD)	n=11(DSM-IV) -3 VaD -7 AD -1 other	HR=1.97 (1.16-3.35) for increasing WMH. HR=2.75 (0.74-10.19) for « EXT-WMH ». *Adjustment on age, sex, and infarcts on MRI.*
Meta-analysis from the 3 previous studies (Debette and Markus, 2010)				HR=2.9 (1.3-6.3). Test for heterogeneity: p=0.001, I^2=85.1%.
Osaki –Tajiri Project (Meguro et al., 2007) **n=204**	5 years	Semi-quantitative (4 grades) for PWMH and DWMH. Continuous	n=28 (DSM-IV and CDR1+) -17 AD	NS for AD. For VaD :

≥ 65 years old			-5 VaD -2 DBL -4 others	OR=4.14 (p<0.005) for PWMH OR=4.04, 3.27 (p<0.05) for DWMH right and left.
Washington Heights/inwood Columbia Aging Project (WHICAP) (Brickman et al., 2012) **n=503** **79,7 years old**	3.4 years	Quantitative Continuous per cerebral lobes (frontal, parietal, temporal and occipital).	n=46 (DSM-IIIR) -45 AD -1 DLB	HR=1.20 (1.01-1.43) for WMH in the parietal lobe per 1ml increment. NS in the others lobes. *Adjustment on age, sex, apoe4 genotype, education, hippocampal volume, and ethnicity.*

Abbreviations : WMH, white matter hyperintensities ; VaD, vascular dementia; AD, Alzheimer's disease; MD, mixed dementia; apoe, apolipoprotein E; PWMH, periventricular white matter hyperintensities; DWMH, deep white matter hyperintensities; SD, standard deviation; NS, no significant; DLB, dementia with Lewy bodies.

Table 2. Association between WMH and risk of dementia in MCI patients. Prospective studies, with assessment of WMH at baseline.

Study (MCI subjects) **Sample size (n)** **Mean age**	**Follow-up period**	**WMH quantification methods**	**Incident dementia**	**Results** **Hazards Ratio (HR (95%CI)) and Odds Ratio (OR (95%CI)). When non specified, HR and OR are given for all types of dementia**
Patients from the Huddinge University Hospital, Sweden (Korf et al., 2004) **n=75** **63 years old**	2.8 years	Semi-quantitative (Wahlund Scale). Continuous	n=37 (DSM-IV) -34 AD -3 VaD	HR=1.00 (0.93-1.08) per unit WMH *Univariate analysis*
Patients from memory disorder clinics, California. (DeCarli et al., 2004) **n=52** **72.8 years**	3.1 years	Quantitative. Dichotomization : "high" WMH volume if greater than the 75th percentile	n=17 (CDR≥1.0) -10 AD -2 VaD -4 MD -1 other	HR=0.73 (0.35-1.54) *Adjustement on age, sex, education, cortical gray matter, hippocampal volume, lacunes.*
Patients from a memory clinic at Brescia, Italy. (Geroldi et al., 2006) **n=52** **70 years old**	1.3 years	Semi-quantitative (ARWMC Scale total Score). Dichotomization: severe WMH if total score >6 or any regional score>2.	n=11 (DSM-IV) -7 AD -1 VaD -3 DLB	OR=2.9 (0.7-11.4) *Univariate analysis*
subjects of a Finnish study (general population) (Tapiola et al., 2008) **n=60** **Between 63 and 81 years old**	2.8 years	Semi-quantitative (Wahlund Scale). Continuous.	n=13 (DSM-IV) -9 AD -3 VaD -1 MD	HR=1.01 (0.89-1.14) per unit WMH. *Univariate analysis.*

General population (Smith et al., 2008) **n=156** **72.3 years old**	6.4 years	Quantitative. (WMH volume/ intracranial volume)*100. Dichotomization: severe WMH >(mean % + 1 SD).	n=54 (DSM-IV) -45 AD	HR=1.26 (0.61-2.59) *Univariate analysis.*
Patients from a ''memory clinic '' in Lille, France (Bombois et al., 2008) **n=170** **68.1 years old**	3.8 years	Semi-quantitative. (Sheltens Scale). Continuous	n=67 (DSM-IV) -29 AD -19 DBL -8 MD -7 VaD -4 others	HR=1.01 (0.97-1.05) per unit WMH HR=1.14 (1.06-1.24) for VaD and MD per unit WMH *Adjustment on age, sex, education, MTLA, vascular risk factors, baseline cognition.*
Patients from a clinical trial (van Straaten et al., 2008) **n=152** **72.4 years old**	3 years	Semi-quantitative (Sheltens Scale). Continuous	n=55 (NINCDS-ADRDA) -55 AD	HR=1.59 (1.24-2.05) per unit PWMH HR=1.02 (0.97-1.08) per unit DWMH HR=1.03(0.99-1.06) per unit total WMH *Adjustment on age and education*
Patients from a ''memory clinic '' of Vrije Universiteit (Staekenborg et al., 2009) **n=152** **69.9 years old**	2.0 years	Semi-quantitative (Sheltens scale). Dichotomization: - < vs ≥6 for total WMH - < vs ≥3 for PWMH - < vs ≥4 for DWMH	n=72 (NINCDS-ADRDA) -56 AD -7 VaD -5 DBL -7 others	For AD: HR=1.2 (0.7-2.2) for total WMH HR=1.1 (0.7-2.0) for PWMH HR=1.3 (0.8-2.3) for DWMH For others types of dementia : HR=5.8 (1.2-26.6) for total WMH HR=6.5 (1.4-29.8) for PWMH HR=5.7 (1.2-26.7) for DWMH *Adjustment on age and sex*
Patients from the ''Mayo Clinic Alzheimer's Disease Research Center'' (Kantarci	2.1 years	Quantitative. Dichotomization : WMH> and WMH≤	n=75 (DSM-III) -57 AD -15 DBL	HR=0.75 (0.42-1.35) *Adjustment on age, sex and education.*

et al., 2009) **n=151** **77 years old**		(mean volume+ 1 SD)	-3 others	
Patients from the ‘’Center for Research and Treatment of Cognitive Dysfunction, Milan University ’’ **(Clerici et al., 2012)** **n=245** **74.1 years old**	2.4 years	Semi-quantitative (ARWM Scale total Score). Dichotomization : No WMH (ARWMC score=0) vs. presence of WMH	n=129 (DSM-IV) -88 AD -13 DBL -12 VaD -16 others	HR=0.8 (0.6-1.2) for total WMH HR=0.8 (0.6-1.2) for PWMH HR=1.4 (0.9-2.1) for DWMH *Adjustment on age, sex and education.*
Patients from the ’’University Clinic of Innsbruck’’ **(Defrancesco et al., 2013)** **n=60** **73.6 year old**	1.5 years	Semi-quantitative (Fazekas and Sheltens scales). Continuous.	n=31 (ICD-10 criteria.) -31 AD	No association.
Patients from the National Health Service Memory Clinic in North Essex, UK **(Devine et al., 2013)** **n=129** **72.2 years old**	5 years	Semi-quantitative (Wahlund scale). Dichotomization: ’’ low WMH’’ if score between 0 -3, ’’ High WMH’’ if score between 4 and 24.	n=66 (criteria not specified) -39 AD	HR=1.18 (0.47-2.98) *Adjustment on age, sex, type of MCI (amnesic and non-amnesic), baseline cognition*.

Abbreviations : WMH, white matter hyperintensities ; VaD, vascular dementia; AD, Alzheimer’s disease; MD, mixed dementia; apoe, apolipoprotein E; PWMH, periventricular white matter hyperintensities; DWMH, deep white matter hyperintensities; SD, standard deviation; NS, no significant; DLB, dementia with Lewy bodies; ARWMC, Age-Related White Matter Changes.

Table 3. Association between WMH and cognitive decline in the general population. Prospective studies, with assessment of WMH at baseline.

Study **Sample size (n)** **Mean age**	**Follow-up period**	**WMH quantification methods**	**Cognitive decline evaluation**	**Results**
Cardiovascular Health Study (Kuller et al., 1998) **n=3469** **≥ 65 years old**	3-7 years	Semi-quantitative (grade ranges 0 to 9). Dichotomization (> 3 vs. ≤3)	Global decline (3MSE)	OR=1.4 (1.1-1.9) for a 3MSE score<80 at years 5 to 6. OR=1.20 (0.98-1.47) for a 3MSE score decrease ≤ 5. *Adjustment on age, education, sex, low 3MSE at years 5 to 6, apoe 4 genotype infarcts, clinical and subclinical CVD at baseline, high ventricular volume, High sulci width, ethnicity.*
Rotterdam Scan Study (Prins et al., 2005) **n=832** **71 years old**	5.2 years	Semi-quantitative pour PWMH (grade ranges 0 to 9). Quantitative for DWMH. PWMH et DWMH : variables continuous.	Global decline (MMSE) + Processing speed, executive functions and (Stroop Test, Letter-Digit Substitution Task, Verbal Fluency Test, 15-word verbal learning test).	Per SD increment - Decrease of 0.035 (0.003-0.066) point/year in MMSE score for PWMH -Significant decline for Stroop naming Test and Letter Digit Substitution Test for PWMH, (Processing speed, executive functions). No association with DWMH. *Adjustment on age, sex, education and the interaction of age with time.*
General population (Smith et al., 2008) **n=67** **71.2 years old**	5.1 years	Quantitative. (WMH volume/ intracranial volume)*100. Dichotomization: severe WMH > (mean % + 1 SD).	Global decline: conversion to MCI (CDR=0.5) n=26	HR=3.30 (1.33-8.22) for severe WMH *adjustment on apoe 4 genotype, age, sex, education, smoking, CDR sum of boxes*
Oregon Brain Aging (Silbert et al., 2009) **n=98** **≥ 65 years old**	9.5 years	Quantitative. Continuous.	Global decline: conversion to persistent cognitive impairment (CDR≥0.5 for 2 consecutive follow-up). n=53	HR=1.04 (1.00-1.07) for increasing total WMH HR=1.06 (1.01-1.10) for increasing PWMH *Adjustment on age, hypertension, MMSE, APOE 4 genotype, intracranial and hippocampal volume.*

PATH Through Life Project (Christensen et al., 2009) **n=416** **62.6 years old**	4 years	Quantitative (WMH volume/ white matter)*100. Continuous	Processing speed (SDMT) Memory (California Verbal Learning Test: immediate and delayed recall)	Linear Regression Models Predicting 4-year change in SDMT score: β=0.07, p=0.86 Predicting 4-year change in immediate recall score: β=0.02, p=0.89 Predicting 4-year change in delayed recall score: β=0.21, p=0.13 *Adjustment on age, sex, education, baseline score, brain atrophy, intracranial volume.*
3C-Dijon MRI study (Godin et al., 2010) **n=1701** **72.3 years old**	4 years	Quantitative. Continuous.	Global decline assessed with several tests: MMSE, BVRT, IST, TMT part B. Moderate decline: n=224 Severe decline: n=46 (including incident dementia)	Per SD increment. 1) Severe decline OR=1.2 (1.1-1.5) for total WMH OR=1.4 (1.0-2.1) for PWMH No association with DWMH 2) Moderate decline: no association. *Adjustment on age, sex, education, hypertension, history of cardiovascular disease, diabetes, MMSE score, hypercholesterolemia, apoe 4 genotype, intracranial volume.*
Framingham Offspring Study (Debette et al., 2010) **n=1344** **62 years old**	6.2 years	Quantitative. Continuous + dichotomization : « EXT-WMH » = WMH > (mean volume in a specific age group+ 1 SD)	Global decline : conversion to MCI (n=93) and to amnesic MCI (n=93)	MCI : OR=1.09 (0.85-1.39) for increasing WMH OR=1.35 (0.71-2.56) for EXT-WMH Amnesic MCI: OR=1.22 (0.96-1.56) for increasing WMH OR=1.64 (0.93-2.89) for EXT-WMH *Adjustment on age, sex, education, duration of follow-up, brain infarcts.*
Honolulu-Asia aging study (Inaba et al., 2011) **n=267** **Between 74 and 95 years old.** **Men only.**	5 years	Semi-quantitative (grade ranges 1 to 9). Dichotomization: presence of WMH (grade 3-9, 38.2%), absence of WMH (grade 1-2, 61.8%)	Decline = decrease in CASI score ≥(12+1 SD)	OR=1.97 (1.08-3.61) *Adjustment on age, education, apoe 4 genotype, infarcts, baseline CASI score, hypertension.*

Abbreviations : WMH, white matter hyperintensities ; VaD, vascular dementia; AD, Alzheimer's disease; MD, mixed dementia; apoe, apolipoprotein E; PWMH, periventricular white matter hyperintensities; DWMH, deep white matter hyperintensities; SD, standard deviation; NS, non significant; DLB, dementia with Lewy bodies; ARWMC, Age-Related White Matter Changes; MMSE, Mini Mental State Examination; 3MSE, modified Mini-Mental State Examination; BVRT, Benton Visual Retention Test; IST, Isaacs Set Test;TMT, Trail Making Test; CASI, Cognitive Abilities Screening Instrument; SDMT, Symbol-Digit Modalities Test.