Perspective

White matter hyperintensity burden in elderly cohort studies. The Sunnybrook Dementia Study, Alzheimer Disease Neuroimaging Initiative, and Three-City Study

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Abstract

Given the recent acknowledgement of the complex mixed pathologies that contribute to the clinical expression of dementia, various cohort studies have aimed to examine Alzheimer’s disease and cerebrovascular disease as comorbid pathologies, with neuroimaging playing a central role in these studies. Using white matter hyperintensities (WMH) as a biomarker of cerebrovascular disease, we compared WMH burden between the Sunnybrook Dementia Study, the Alzheimer’s Disease Neuroimaging Initiative (ADNI1), the Three-City Study, and various other studies around the world. Based on our findings, it was evident that ADNI1 had minimal WMH burden relative to other large studies that examine aging and dementia. This low WMH burden in ADNI1 may be considered as both an advantage, representing a relatively “pure” sample with little confounding vasculopathy, and a disadvantage, as it limits generalizability to “real-world” patient populations with mixed pathologies and to nondemented groups with baseline vascular disease. We explore possible reasons for this distinction, including management of vascular risk factors, gaps in diagnostic criteria, and future directions for clinical research.

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Keywords: Alzheimer’s disease; Cerebrovascular disease; Aging; White matter hyperintensities; Dementia; Elderly cohort; Population studies

1. Introduction

Dementia affects approximately 44 million people worldwide according to current estimates, a number that is predicted to more than triple to 135 million by 2050 [1]. As Alzheimer’s disease (AD) and vascular cognitive disorders are the top two leading primary causes of dementia [2], recent studies examining the contribution of modifiable risk factors for dementia have acknowledged cerebrovascular pathology as a primary concern [3–6], with neuroimaging playing a central role in many of these studies [7]. As most dementia cases are mixed pathologies with some vascular component [8], many present studies have increased their...
focus toward understanding the role of vasculopathy, vascular brain injury, and the management of vascular risk factors [9,10], in the context of AD pathophysiology [11–13].

As recently defined by an international consensus process, white matter hyperintensities (WMH) of presumed vascular origin, visible on structural magnetic resonance imaging (MRI), are commonly used markers of cerebrovascular disease [7]. Clinico-pathologic correlations suggest WMH to be indicative of cerebral small vessel disease [7,14], potentially originating from ischemic tissue damage caused by arteriosclerosis [15,16], vasogenic edema induced by periventricular venous collagenosis [17,18], and cerebral amyloid angiopathy [19–21]. These imaging-based biomarkers of cerebral small vessel disease have been associated with increased age, vascular risk factors, mild cognitive impairment (MCI), and AD [22–24].

In this article, we chose to examine imaging markers of small vessel disease within three large neuroimaging studies: the Sunnybrook Dementia Study (SDS: Canada), the Alzheimer’s Disease Neuroimaging Initiative Phase 1 (ADNI1: mainly US), and the Three-City Study (3C: France). We examined these studies because (1) they were relatively contemporary, having been conducted around the same time, (2) the populations were sampled primarily from different countries, (3) the imaging acquisition protocols (at 1.5 tesla) were comparable, (4) WMH volumes were quantified using proton density and T2-weighted (T2) MRI sequences (i.e., non-FLAIR based), and (5) study samples were elderly, aged 50–90 years.

2. The Sunnybrook Dementia Study, Alzheimer’s Disease Neuroimaging Initiative, and Three-City Study

The SDS [25] is a prospective cohort study (1994–2014) conducted at the Sunnybrook Health Sciences Centre—University of Toronto, in Toronto, Canada (ClinicalTrials.gov NCT01800214). One goal of the SDS was to examine a real-world cohort of dementia patients and normal elderly (50–90 years old) and the potential impact of comorbid cerebral small vessel disease manifested primarily as covert lacunes and white matter lesions.

The ADNI1 [26] is a large multisite longitudinal brain imaging study based in the United States (53 sites) and Canada (5 sites). The first phase, ADNI1 (2004–2010), examined patients with AD, MCI, and normal elderly controls (NC), aged 55–90 years. The study’s primary objectives included the identification of biomarkers to identify AD at the earliest stage so that intervention, prevention, and treatment of dementia could be more effective (See Supplement 1 for additional details).

The 3C [27] is a multicenter, longitudinal population–based cohort study (1999–2012) conducted in three cities in France: Bordeaux, Dijon, and Montpellier. The goal of the 3C study was to examine the associations of vascular risk with dementia and cognitive impairment. Participants were randomly sampled from electoral rolls and aside from age (65–80 years), there were no exclusion criteria. The subsample examined in the present study included 1701 nondemented elderly with a mean mini-mental state examination (MMSE) of 28, suggesting a relatively normal sample. Unfortunately, stratification by cognitive status was not possible because diagnostic criteria for MCI were not implemented on entry into the 3C study.

3. WMH findings in dementia and the elderly: ADNI1, SDS, and 3C

To compare WMH volumes between SDS and ADNI1, we plotted head-size corrected WMH volumes by age to visually examine the distributions across the diagnoses (Dx; Fig. 1). To account for differences in disease severity for the AD groups, we only included patients with MMSE scores ≥20 (based on ADNI1 inclusion criteria). On visual inspection of the graphs displayed in Fig. 1, it was evident that there were very obvious differences in the distribution of WMH in these two cohort studies. Additionally, similar differences were demonstrated for all Dx groups within each sample, with the SDS samples exhibiting greater age-related WMH volumes compared with the ADNI1 samples.

As further demonstrated in Table 1, these differences can also be seen with group average and variability statistics, whereby the SDS sample displayed more variability and higher average WMH volumes across all Dx groups when compared with ADNI1 (all significant, P < .001, Table 1). Additionally, population-based data recently reported by the 3C group [28] were also included for relative comparison (Table 1). Based on these results, the vascular burden, indicated by WMH volumes, was much greater in the SDS and 3C samples than in the ADNI1 sample.

Additionally, because WMH volumes typically exhibit a nonnormal, often highly skewed distribution, the reporting of standard statistical measures for central tendency and spread may not be appropriate for proper visualization of the data. Given this phenomenon, we have also provided a breakdown of the proportional distributions by range of WMH in the SDS and ADNI1 samples. As shown in Fig. 2, compared with 22% in the SDS sample, 83% of the ADNI1 sample presented with less than 1 cc of WMH (dark green) across all Dx groups. Conversely, although over a third of the SDS sample had over 5 cc of WMH (warm colors: yellow, orange, and red), less than 3% of the ADNI1 sample had significant volumes of WMH. Although this could be due to a difference in the proportional representation of AD and MCI patients between the two studies, similar patterns are observed in the NC samples (albeit to a lesser degree). Interestingly, only the MCI and NC groups in ADNI1 had any subjects with WMHs exceeding the 20-cc mark (red), a proportional representation made up of three individuals (MCI: n = 2, NC: n = 1) who would be considered as statistical outliers for both groups. Overall, in contrast to the positively skewed distribution of WMH...
Fig. 1. Scatterplots showing the distribution of WMH volume by age for AD patients, MCI, and NC, comparing the ADNI1 (red circles) and the SDS (blue triangles). Head-size corrected WMH volumes are reported in cubic centimeters (cc). AD patients were also matched for disease severity using the MMSE. Dotted line represents the 10-cc cognitive threshold for WMHs originally proposed by Boone et al. [29]. Abbreviations: WMH, white matter hyperintensities; AD, Alzheimer’s disease; MCI, mild cognitive impairment; NC, normal elderly controls; ADNI1, Alzheimer’s Disease Neuroimaging Initiative; SDS, Sunnybrook Dementia Study; MMSE, mini-mental state examination.

4. Comparisons with other studies around the world

These graphs and descriptive statistics demonstrate that the ADNI1 multisite sample, obtained primarily from US sites, has significantly less burden of WMH on MRI compared with those obtained from the SDS tertiary memory clinic in Canada, and the 3C elderly population-based sample in France. Although these graphs and tables were generated from volumetrics obtained directly from the ADNI1 and SDS database tables, it would be prudent to look at how these results differ from some of the published reports from ADNI1, SDS, and 3C. Furthermore, an examination of publications from other similar elderly cohort studies around the world may provide additional insight into the visible small vessel disease burden in elderly and neurodegenerative clinical populations.

As shown in Table 2, the WMH volumes reported in recent publications of these first three groups were similar to our current results, with ADNI1 demonstrating the lowest WMH volumes compared with SDS and 3C publications. Specifically, ADNI1 published averages around ≤1 cc for all groups [32,33]; the SDS publications report average volumes in the range of 5–8 cc for dementia patients.
[24,34], and the 3C publications report volumes in the 4–5 cc range for its nondemented population-based sample [28,35,36].

Although we specifically selected these three studies based on their aforementioned similarities, there are several other large studies that have quantified WMH volumetrics which we can use for additional comparison (Table 2). Findings from the Leukoaraiosis and Disability Study [37], a European multicenter study which examined nondisabled elderly subjects with evidence of age-related white matter changes on MRI, report an average WMH volume of 20.2 cc ± 21.0 for their entire group and 6.4 cc ± 5.0 for the lowest grade group (i.e. Fazekas) [38]. Similarly, the Rotterdam Study, a Dutch population-based cohort study which examined stroke-free nondemented elderly subjects, recently reported an average white matter lesion volume of 3.7 cc ± 4.6 [39]. The Personality & Total Health Through Life longitudinal cohort study based in Australia, recently reported an average WMH volume of 4.8 cc ± 4.7 for their relatively young elderly cohort (60–64 years) [40]. The Clinical Research Center for Dementia of South Korea, a South Korean multisite elderly cohort study which examined patients with MCI or dementia, recently reported an average WMH volume of 10.8 cc ± 18.4 [41]. Thus, despite many of the potential differences in study protocols and image acquisitions between these studies, it would be reasonable to conclude that the visible small vessel disease burden in the SDS and 3C samples are within the range of typical real-world values.

Given these various reports from Asia and Australia to Europe and North America that have examined large elderly populations with and without dementia, the ADNI1 study...
Table 2
Comparison of WMH volumetric reports from the SDS, ADNI1, 3C, and elderly cohort studies

<table>
<thead>
<tr>
<th>Study Location</th>
<th>Study duration</th>
<th>Publication</th>
<th>Sample (n)</th>
<th>Age, y</th>
<th>Various</th>
<th>NC</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDS Canada</td>
<td>1994–2014</td>
<td>Current findings</td>
<td>NC (105), MCI (70), AD (212)</td>
<td>71.3 (8.6)</td>
<td>—</td>
<td>5.0 (8.4)</td>
<td>5.2 (7.1)</td>
<td>7.6 (9.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>McNeely et al. 2015</td>
<td>AD (234)</td>
<td>72.0 (9.0)</td>
<td>—</td>
<td>—</td>
<td>7.3 (9.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ramirez et al. 2014</td>
<td>NC (100), AD (265)</td>
<td>69.5 (8.0)*</td>
<td>—</td>
<td>2.5 (3.3)</td>
<td>—</td>
<td>5.4 (11.0)</td>
</tr>
<tr>
<td>ADNI1 N. America</td>
<td>2004–2010</td>
<td>Current findings</td>
<td>NC (216), MCI (347), AD (161)</td>
<td>75.0 (6.9)</td>
<td>—</td>
<td>0.7 (2.2)</td>
<td>0.8 (2.4)</td>
<td>1.0 (1.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carnmichael et al. 2010</td>
<td>NC (224), MCI (391), AD (189)</td>
<td>76.0 (6.9)</td>
<td>—</td>
<td>0.5 (1.1)</td>
<td>0.7 (1.2)</td>
<td>1.1 (2.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Barnes et al. 2013</td>
<td>NC (197), MCI (331), AD (146)</td>
<td>76.0 (5.1)*</td>
<td>—</td>
<td>0.3 (0.5)</td>
<td>0.3 (0.5)</td>
<td>0.4 (1.0)</td>
</tr>
<tr>
<td>3C France</td>
<td>1999–2012</td>
<td>Godin et al. 2010</td>
<td>Nondemented elderly (1701)</td>
<td>72.3 (4.1)</td>
<td>5.5 (4.9)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Godin et al. 2011</td>
<td>Nondemented elderly (1319)</td>
<td>72.0 (0.1)</td>
<td>5.3 (0.1)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Satizabal et al. 2012</td>
<td>Nondemented elderly (1771)</td>
<td>72.5 (4.1)</td>
<td>4.3 (3.7)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ADNI1 Germany</td>
<td>From 2001</td>
<td>Schmidt et al. 2010</td>
<td>Nondisabled elderly (380)</td>
<td>75.9 (5.1)</td>
<td>—</td>
<td>2.0 (21.0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verlinden et al. 2014</td>
<td>Nondemented elderly (2025)</td>
<td>59.9 (7.0)</td>
<td>2.0 (21.0)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PATH Australia</td>
<td>2001–2010</td>
<td>Chen et al. 2009</td>
<td>Community elderly (477)</td>
<td>62.6 (1.5)</td>
<td>4.9 (4.7)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CREDOS S. Korea</td>
<td>NC (105), MCI (70), AD (212)</td>
<td>72.1 (8.0)</td>
<td>10.8 (18.4)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Noh et al. 2014</td>
<td>NC and Dementia (352)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: WMH, white matter hyperintensities; SDS, Sunnybrook Dementia Study; ADNI1, Alzheimer’s Disease Neuroimaging Initiative; 3C, Three-City Study; Dx, diagnostic group; NC, normal elderly controls; MCI, mild cognitive impairment; AD, Alzheimer’s disease; LADIS, Leukoaraisis and Disibility Study; PATH, Personality & Total Health; CREDOS, Clinical Research Center for Dementia of South Korea; SD, standard deviation; IQR, interquartile range; SE, standard error.

NOTE. All data reported as mean (SD), unless otherwise marked.

*Based on reported NC data.

†Median (IQR).

‡Mean (SE).

appears to provide a rare opportunity to examine progression of early prodromal MCI to AD without the typical real-world confound of comorbid vasculopathy. As ADNI1 is the only elderly cohort study that reports an average WMH volume around ≤1 cc for both normal elderly and dementia patients, this may have important implications for the insights gained from ADNI1 results.

5. Gaps in the current diagnostic criteria?

When ADNI1 began in 2004, there were no guidelines in the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association clinical diagnostic criteria regarding WMH burden as observed on neuroimaging [42]. To account for significant vascular burden, ADNI1 applied an exclusion criteria threshold of ≤4 on the Hachinski ischemia scale [43]. Interestingly, the more recent National Institute on Aging-Alzheimer’s Association (NIA-AA) workgroups diagnostic criteria acknowledge the potential use of neuroimaging to evaluate the presence of WMH burden [44]. In contrast to the diagnosis of probable AD dementia, Section 5.2 of the NIA-AA criteria proposed a diagnosis of possible AD dementia in circumstances where patients have an etiologically mixed presentation. In particular, evidence of concomitant cerebrovascular disease, as indicated by “severe WMH burden,” would necessitate a diagnosis of possible AD. The primary difficulty with the etiologically mixed presentation criteria is that “severe” is a relative term, with no quantitative threshold for clinicians and researchers to follow (Fig. 3). In other words, at what point on the continuum does WMH burden transition from moderate to severe and consequently change a patient’s diagnosis from probable to possible AD dementia? Should this reliance on structural MRI for patient diagnostics be based on visual rating of WMH (e.g. Fazekas scale), or should it be based on a volumetric quantification method? Should there be a threshold for WMH burden before cognitive deficits are observed, as originally proposed by Boone and others in the 1990s [29,31]? Conversely, a recent proposal by the International Society for Vascular Behavioural and Cognitive Disorders outlined some recommendations regarding the diagnostic criteria for vascular cognitive disorders [45]. As the second most common single cause of dementia after AD, the diagnosis of vascular dementia (VaD) presents a significant challenge, particularly in light of the issues regarding the diagnosis of AD dementia with an etiologically mixed presentation. The publication outlines some of the issues related to the interaction between vascular and neurodegenerative processes and the complications when discerning AD-type pathology from VaD, as these two pathologies often co-exist. Furthermore, as the term “dementia” has become increasingly synonymous with the term “Alzheimer’s disease,” when a patient presents with significant WMH burden, that patient is more likely to be diagnosed as mixed AD, limiting the potential early detection of cognitive impairment due to vascular pathology.

Given the issues with the diagnostic criteria for AD, and the problems related to the overlapping neurodegenerative and vascular contributions to dementia, there are no agreed-on guidelines for how neuroimaging-based...
biomarkers should be used in dementia diagnostics. The lack of consensus-based criteria that specifically classify a mixed pathology dementia [46] may help to explain the differences between ADNI1 and other studies. Thus, in contrast to other more heterogeneous “real-world” clinical samples with a wider range of vascular burden in both demented and normal elderly populations, ADNI1 may represent a controlled “pure” sample, with little to no vascular comorbidity. Interestingly, despite the low vascular burden in the ADNI1 sample, baseline WMH burden was found to be associated with a decline in cognition, executive function, and semantic memory [32,47], suggesting that visible WMH may indeed be the tip of the iceberg of a more diffuse disease that is clinically relevant.

Although varying interpretations of the relevance of small vessel disease in applying diagnostic criteria between ADNI1 and other studies, thus, in contrast to other more heterogeneous “real-world” clinical samples with a wider range of vascular burden in both demented and normal elderly populations, ADNI1 may represent a controlled “pure” sample, with little to no vascular comorbidity. Interestingly, despite the low vascular burden in the ADNI1 sample, baseline WMH burden was found to be associated with a decline in cognition, executive function, and semantic memory [32,47], suggesting that visible WMH may indeed be the tip of the iceberg of a more diffuse disease that is clinically relevant.

Alternatively, the low WMH burden across the ADNI1 groups could represent a selection bias toward normal elderly and dementia volunteers who have very well-managed vascular risk factors when they came to academic centers for participation in such studies.

Results from a recent report by the Rotterdam Study [48], as well as similar reports from population-based studies in the United States [49–51], and the United Kingdom [52], suggest that recent increases in the administration of anti-thrombotics, anti-hypertensives, and lipid-lowering drugs have recently improved management of hypertension, obesity, and overall vascular health. Additional support for this comes from the Rotterdam Study’s neuroimaging results, where participants in the more recent subcohort (2005–2006) had significantly less WMH burden than those in the earlier subcohort (1995–1996), suggesting a decrease in cerebrovascular injury in the more recent sample. This decline in WMH burden was believed to be related to increased prosperity, education, and, more importantly, improved management of vascular risk factors [48,51–53].

In light of these recent positive reports, the low cerebrovascular burden in the ADNI1 sample may be evidence of a controlled sample with little to no overlapping vascular pathology and/or individuals with properly controlled management of their overall vascular health. Future studies examining the use of lipid lowering and anti-hypertensive medications in ADNI1 may provide further insight into this possibility. Most importantly, ADNI1, which is freely available, can be regarded as an important reference sample of clinically “pure” AD in a highly educated population, which can be used for comparison with other more representative “real-world” memory clinic samples and population studies.

6. Conclusion

Using WMH as a neuroimaging marker of cerebral small vessel disease, we found that the ADNI1 sample had a significantly lower burden relative to those reported in the SDS, the 3C, and various other elderly and dementia cohort studies around the world. Although this could be explained by uncertainty regarding what constitutes “severe” WMH burden in the diagnostic criteria, inclusion of participants whose vascular risk factors are well-controlled before and during the study, it is our view that ADNI1’s sample can be considered a relatively “pure,” filtered cohort of demented and nondemented elderly with little to no vascular burden—possibly the “cleanest” deeply endophenotyped elderly cohort acquired to date. There is no doubt that ADNI1 has already and will continue to yield critically
important insight into genetics, clinical, and progression patterns of sporadic AD that is relatively free of SVD.

In line with the continuing story of vascular contributions to dementia, there are studies currently underway in Canada which aim to directly assess the clinical impact of WMH burden in the context of neurodegeneration, aging, atherosclerosis, stroke, and dementia. The Medical Imaging Trial Network of Canada C6 (ClinicalTrials.gov NCT02330510) is a nationwide study measuring baseline amyloid uptake progression in patients with significant WMH burden to determine relationships with clinical, structural, and functional brain measures [54]. The Canadian Atherosclerosis Imaging Network is a pan-Canadian study examining carotid stenosis using 3D in vivo neck imaging, and end-organ brain disease through structural MRI, with the final goal of developing novel therapeutic interventions aimed at atherosclerosis [55,56]. The Ontario Neurodegenerative Disease Research Initiative is a multimodal observational study which is examining the interactions between various neurodegenerative diagnoses and contributions from small vessel disease copathology by looking for the early indicators, commonalities, and distinguishing characteristics in these diseases [57]. In addition, imaging analysis pipelines optimized for quantifying subtypes of small vessel disease have been developed for application in a number of these studies [58]. These multisite Canadian studies currently underway may provide additional insight into the complex neurodegenerative and vascular processes that lead to the clinical expression of dementia.

On this world stage of large, longitudinal, multicentre, multinational studies that are designed to help us understand the various neurologic disorders that plague our aging population, this balancing act between controlled scientific studies and those representing more real-world clinical populations presents a unique analytical challenge to the knowledge translation of “big data,” which has yet to be resolved. Understanding similarities and differences between pure and mixed vascular-AD dementia “big data” cohorts should yield important information that may eventually aid in the development of personalized therapeutics for AD dementia.

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Supplementary data

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References


