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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.


*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

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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]. Clinicopathologic 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 Heath 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 $\geq$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

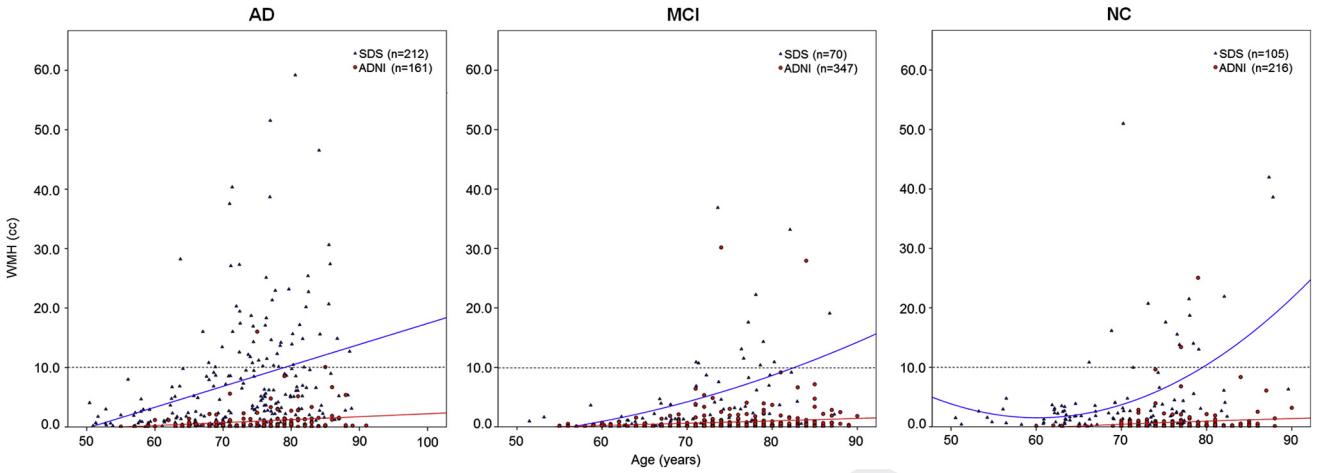


Fig. 1. Scatterplots showing the distribution of WMH volume by age for AD patients, MCI, and NC, comparing the ADNI1 (red circles) and the SDS (blue triangles). Head-size corrected WMH volumes are reported in cubic centimeters (cc). AD patients were also matched for disease severity using the MMSE. Dotted 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.

load in the SDS sample, the ADNI1 exhibited less of a skew, with a greater representation of subjects with minimal WMH burden across all Dx groups.

Finally, as changes to the brain's white matter are historically believed to be an age-related phenomenon, the question regarding the clinical meaningfulness of WMH often arises. Based on the threshold theory originally proposed by Boone et al. (1992) [29–31], we examined the data using a threshold value of 10 cc, above which the effect of WMH can be measured clinically (see dotted line on Fig. 1 and Supplement 3). Using this threshold as a benchmark, it is apparent that a quarter of the AD patients in the SDS presented with significant white matter disease. More importantly, the presence of clinically meaningful WMH in the SDS was not exclusive to AD patients, as both the MCI and NC groups had 17% and 13% of the samples, respectively, exceeding this threshold. In contrast, the ADNI1 had fewer subjects with WMH volumes beyond this threshold, providing a cleaner sample through which cognitive decline can be attributed primarily to AD pathology without confounding comorbid vasculopathy.

Table 1
MMSE, age, and WMH volumetrics by Dx group and study sample

| | MMSE (/30) | Age (y) | | WMH (cc) | |
|---|---|---|---|---|---|
| Study | Mean (SD) | Mean (SD) | Range | Mean (SD) | *P* |
| AD | | | | | |
| SDS, n = 212 | 24.5 (2.7) | 72.2 (8.9) | 50.4–88.9 | 7.6 (9.4) | *** |
| ADNI, n = 161 | 23.0 (2.1)* | 74.9 (7.6) | 55.0–91.0 | 1.0 (1.9) | |
| MCI | | | | | |
| SDS, n = 70 | 26.8 (2.2) | 71.6 (7.8) | 51.5–87.3 | 5.2 (7.1) | *** |
| ADNI, n = 347 | 27.0 (1.8)* | 74.6 (7.5) | 55.0–90.0 | 0.8 (2.4) | |
| NC | | | | | |
| SDS, n = 105 | 28.9 (1.0) | 69.5 (8.1) | 50.5–89.6 | 5.0 (8.4) | *** |
| ADNI, n = 216 | 29.0 (1.0)* | 75.9 (5.0) | 60.0–90.0 | 0.7 (2.2) | |
| 3C, n = 1701 | 27.7 (1.7) | 72.3 (4.1) | 65–80† | 5.5 (4.9) | — |

Abbreviations: MMSE, mini-mental state examination; WMH, white matter hyperintensities; Dx, diagnostic group; SD, standard deviation; AD, Alzheimer's disease; MCI, mild cognitive impairment; NC, normal elderly controls; ADNI1, Alzheimer's Disease Neuroimaging Initiative; SDS, Sunnybrook Dementia Study.

NOTE. ***$P < .001$ (Mann-Whitney U test).

*Mean (SD) reported by Carmichael et al. [32].

†Range based on reported group inclusion criteria.

## 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

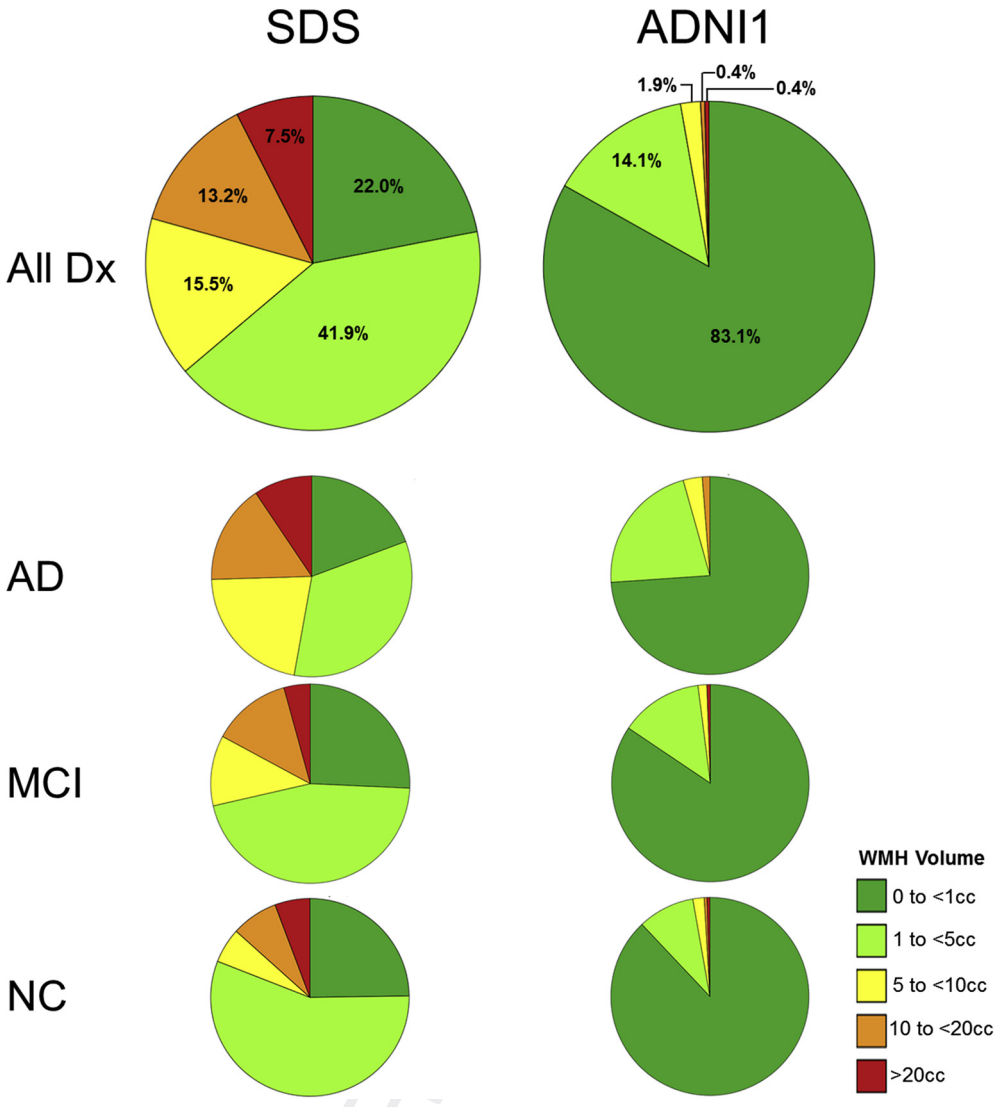


Fig. 2. Pie chart showing WMH volume ranges for the Sunnybrook Dementia Study (SDS) sample (left) and the Alzheimer's Disease Neuroimaging Initiative (ADNI1) sample (right). Abbreviations: WMH, white matter hyperintensities; ADNI1, Alzheimer's Disease Neuroimaging Initiative; SDS, Sunnybrook Dementia Study; AD, Alzheimer's disease; MCI, mild cognitive impairment; NC, normal elderly controls; Dx, diagnostic group.

[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

| Study | Location | Study duration | Publication | Sample (n) | Age, y | White matter hyperintensity (cc) by Dx | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Various | NC | MCI | AD |
| SDS | Canada | 1994–2014 | Current findings | NC (105), MCI (70), AD (212) | 71.3 (8.6) | — | 5.0 (8.4) | 5.2 (7.1) | 7.6 (9.4) |
| | | | McNeely et al. 2015 | AD (234) | 72.0 (9.0) | — | — | — | 7.3 (9.2) |
| | | | Ramirez et al. 2014 | NC (100), AD (265) | 69.5 (8.0)* | — | 2.5 (3.3)† | — | 5.4 (11.0)† |
| ADNI1 | N. America | 2004–2010 | Current findings | NC (216), MCI (347), AD (161) | 75.0 (6.9) | — | 0.7 (2.2) | 0.8 (2.4) | 1.0 (1.9) |
| | | | Carmichael et al. 2010 | NC (224), MCI (391), AD (189) | 76.0 (6.9) | — | 0.5 (1.1) | 0.7 (1.2) | 1.1 (2.0) |
| | | | Barnes et al. 2013 | NC (197), MCI (331), AD (146) | 76.0 (5.1)* | — | 0.3 (0.5)† | 0.3 (0.5)† | 0.4 (1.0)† |
| 3C | France | 1999–2012 | Godin et al. 2010 | Nondemented elderly (1701) | 72.3 (4.1) | 5.5 (4.9) | — | — | — |
| | | | Godin et al. 2011 | Nondemented elderly (1319) | 72.0 (0.1)‡ | 5.4 (0.1)‡ | — | — | — |
| | | | Satizabal et al. 2012 | Nondemented elderly (1771) | 72.5 (4.1) | 4.1 (3.7)† | — | — | — |
| LADIS | Europe | From 2001 | Schmidt et al. 2010 | Nondisabled elderly (340) | 73.9 (5.1) | 20.2 (21.0) | — | — | — |
| Rotterdam | Netherlands | 2005–2009 | Verlinden et al. 2014 | Nondemented elderly (2025) | 59.9 (7.0) | 3.7 (4.6) | — | — | — |
| PATH | Australia | 2001–2010 | Chen et al. 2009 | Community elderly (477) | 62.6 (1.5) | 4.9 (4.7) | — | — | — |
| CREDOS | S. Korea | 2000–2008 | Noh et al. 2014 | MCI and Dementia (352) | 72.1 (8.0) | 10.8 (18.4) | — | — | — |

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, Leukoaraiosis and Disability 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 $\leq$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 $\leq$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 coexist. 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

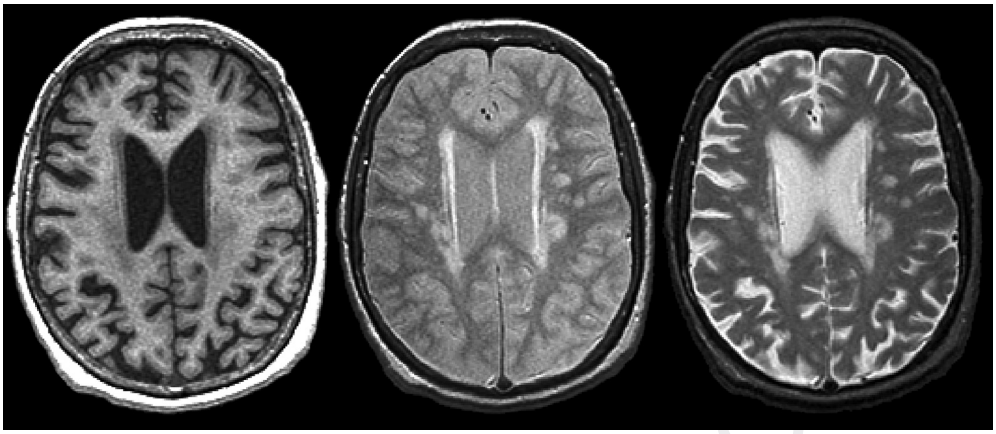

Fig. 3. Structural MRI (left = T1, middle = PD, and right = T2) of a 71-year-old woman living with Alzheimer's disease. Lesion analysis [58] revealed that she had 16 cc of WMH. Should this be considered moderate or severe WMH burden? Should this patient's diagnosis be probable or possible AD dementia? (See Supplement 2 for complete proton density images). Abbreviations: MRI, magnetic resonance imaging; PD, proton density; WMH, white matter hyperintensities; AD, Alzheimer's disease.

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 could explain the low WMH burden in ADNI1's AD and MCI groups, the low burden in the NC sample is less clearly explained. Although differences in education levels, imbalance in gender representation, or a larger proportion of apoE ε4 carriers could also partially explain the findings in ADNI1's AD and MCI groups, these demographic and genetic variables did not account for the low WMH's in the NC sample. 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 antithrombotics, 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

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2015.06.1886.

## References

[1] Alzheimer's Disease International. World Alzheimer Report 2014: Dementia and risk reduction: An analysis of protective and modifiable factors. London, UK: 2014.
[2] Fratiglioni L, Launer LJ, Andersen K, Breteler MM, Copeland JR, Dartigues JF, et al. Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000;54:S10–5.
[3] Black S, Iadecola C. Vascular cognitive impairment: Small vessels, big toll: Introduction. Stroke 2009;40:S38–9.
[4] Knopman DS. Cerebrovascular pathology in cognitive impairment: New (in)sights. Neurology 2012;78:1032–3.
[5] De la Torre JC. Detection, prevention, and pre-clinical treatment of Alzheimer's disease. J Alzheimers Dis 2014;:64–5.
[6] Portet F, Brickman AM, Stern Y, Scarmeas N, Muraskin J, Provenzano FA, et al. Metabolic syndrome and localization of white matter hyperintensities in the elderly population. Alzheimers Dement 2012;8:S88–951.
[7] Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013;12:822–38.
[8] Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007;69:2197–204.
[9] Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia: How to move forward? Neurology 2009;72:368–74.
[10] Mielke MM, Montine T, Khachaturian AS. Vascular diseases: one pathway toward new conceptual models of dementia. Alzheimers Dement 2012;8:S69–70.
[11] Deramecourt V, Slade JY, Oakley AE, Perry RH, Ince PG, Maurage CA, et al. Staging and natural history of cerebrovascular pathology in dementia. Neurology 2012;78:1043–50.
[12] Toledo JB, Arnold SE, Raible K, Brettschneider J, Xie SX, Grossman M, et al. Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. Brain 2013;136:2697–706.
[13] Moghekar A, Kraut M, Elkins W, Troncoso J, Zonderman AB, Resnick SM, et al. Cerebral white matter disease is associated with Alzheimer pathology in a prospective cohort. Alzheimers Dement 2012;8:S71–7.
[14] Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 2010; 9:689–701.
[15] Gouw AA, Seewann A, van der Flier WM, Barkhof F, Rozemuller AM, Scheltens P, et al. Heterogeneity of small vessel disease: A systematic review of MRI and histopathology correlations. J Neurol Neurosurg Psychiatry 2011;82:126–35.
[16] O'Sullivan M. Leukoaraiosis. Pract Neurol 2008;8:26–38.
[17] Black SE, Gao FQ, Bilbao J. Understanding white matter disease: Imaging-pathological correlations in vascular cognitive impairment. Stroke 2009;40:S48–52.
[18] Moody DM, Brown WR, Challa VR, Anderson RL. Periventricular venous collagenosis: Association with leukoaraiosis. Radiology 1995;194:469–76.
[19] Haglund M, Englund E. Cerebral amyloid angiopathy, white matter lesions and Alzheimer encephalopathy—a histopathological assessment. Dement Geriatr Cogn Disord 2002;14:161–6.
[20] Viswanathan A, Chabriat H. Cerebral microhemorrhage. Stroke 2006; 37:550–5.
[21] Smith EE, Eichler F. Cerebral amyloid angiopathy and lobar intracerebral hemorrhage. Arch Neurol 2006;63:148–51.
[22] Yoshita M, Fletcher E, Harvey D, Ortega M, Martinez O, Mungas DM, et al. Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD. Neurology 2006;67:2192–8.

[23] DeCarli C, Miller BL, Swan GE, Reed T, Wolf PA, Carmelli D. Cerebrovascular and brain morphologic correlates of mild cognitive impairment in the National Heart, Lung, and Blood Institute Twin Study. Arch Neurol 2001;58:643–7.

[24] Ramirez J, McNeely AA, Scott CJ, Stuss DT, Black SE. Subcortical hyperintensity volumetrics in Alzheimer's disease and normal elderly in the Sunnybrook Dementia Study: Correlations with atrophy, executive function, mental processing speed, and verbal memory. Alzheimers Res Ther 2014;6:49.

[25] The Sunnybrook Dementia Study n.d. Available from: www.brainlab.ca/sunnybrookdementiastudy (accessed March 19, 2015).

[26] Alzheimer's Disease Neuroimaging Initiative n.d. Available from: www.adni.loni.usc.edu (accessed March 19, 2015).

[27] The Three-City Study n.d. Available from: www.three-city-study.com (accessed March 19, 2015).

[28] Godin O, Tzourio C, Rouaud O, Zhu Y, Maillard P, Pasquier F, et al. Joint effect of white matter lesions and hippocampal volumes on severity of cognitive decline: The 3C-Dijon MRI study. J Alzheimers Dis 2010;20:453–63.

[29] Boone KB, Miller BL, Lesser IM, Mehringer CM, Hill-Gutierrez E, Goldberg MA, et al. Neuropsychological correlates of white-matter lesions in healthy elderly subjects. A threshold effect. Arch Neurol 1992;49:549–54.

[30] Albert M, Massaro J, Decarli C, Beiser A, Seshadri S, Wolf PA, et al. Profiles by sex of brain MRI and cognitive function in the Framingham Offspring Study. Alzheimer Dis Assoc Disord 2010;24:190–3.

[31] Decarli C, Murphy DG, Tranh M, Grady CL, Haxby JV, Gillette JA, et al. The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism of glucose in 51 healthy adults. Neurology 1995;45:2077–84.

[32] Carmichael O, Schwarz C, Drucker D, Fletcher E, Harvey D, Beckett L, et al. Longitudinal changes in white matter disease and cognition in the first year of the Alzheimer disease neuroimaging initiative. Arch Neurol 2010;67:1370–8.

[33] Barnes J, Carmichael OT, Leung KK, Schwarz C, Ridgway GR, Bartlett JW, et al. Vascular and Alzheimer's disease markers independently predict brain atrophy rate in Alzheimer's Disease Neuroimaging Initiative controls. Neurobiol Aging 2013;34:1996–2002.

[34] McNeely AA, Ramirez J, Nestor SM, Zhao J, Gao F, Kiss A, et al. Cholinergic subcortical hyperintensities in Alzheimer's disease patients from the Sunnybrook Dementia Study: Relationships with cognitive dysfunction and hippocampal atrophy. J Alzheimers Dis 2015;43:785–96.

[35] Godin O, Tzourio C, Maillard P, Mazoyer B, Dufouil C. Antihypertensive treatment and change in blood pressure are associated with the progression of white matter lesion volumes: The Three-City (3C)-Dijon Magnetic Resonance Imaging Study. Circulation 2011;123:266–73.

[36] Satizabal CL, Zhu YC, Mazoyer B, Dufouil C, Tzourio C. Circulating IL-6 and CRP are associated with MRI findings in the elderly: The 3C-Dijon Study. Neurology 2012;78:720–7.

[37] Pantoni L, Basile AM, Pracucci G, Asplund K, Bogousslavsky J, Chabriat H, et al. Impact of age-related cerebral white matter changes on the transition to disability—the LADIS study: Rationale, design and methodology. Neuroepidemiology 2005;24:51–62.

[38] Schmidt R, Ropele S, Ferro J, Madureira S, Verdelho A, Petrovic K, et al. Diffusion-weighted imaging and cognition in the leukoaraiosis and disability in the elderly study. Stroke 2010;41:e402–8.

[39] Verlinden VJ, van der Geest JN, de Groot M, Hofman A, Niessen WJ, van der Lugt A, et al. Structural and microstructural brain changes predict impairment in daily functioning. Am J Med 2014;127:1089–10962.

[40] Chen X, Wen W, Anstey KJ, Sachdev PS. Prevalence, incidence, and risk factors of lacunar infarcts in a community sample. Neurology 2009;73:266–72.

[41] Noh Y, Lee Y, Seo SW, Jeong JH, Choi SH, Back JH, et al. A new classification system for ischemia using a combination of deep and periventricular white matter hyperintensities. J Stroke Cerebrovasc Dis 2014;23:636–42.

[42] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS- ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984;34:939–44.

[43] Hachinski VC, Iliff LD, Zilhka E, DuBoulay GH, McAllister VL, Marshall J, et al. Cerebral blood flow in dementia. Arch Neurol 1975;32:632–7.

[44] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263–9.

[45] Sachdev P, Kalaria R, O'Brien J, Skoog I, Alladi S, Black SE, et al. Diagnostic criteria for vascular cognitive disorders: A VASCOG statement. Alzheimer Dis Assoc Disord 2014;28:206–18.

[46] Kling MA, Trojanowski JQ, Wolk DA, Lee VMY, Arnold SE. Vascular disease and dementias: Paradigm shifts to drive research in new directions. Alzheimers Dement 2013;9:76–92.

[47] Carmichael O, Mungas D, Beckett L, Harvey D, Tomaszewski Farias S, Reed B, et al. MRI predictors of cognitive change in a diverse and carefully characterized elderly population. Neurobiol Aging 2012;33:83–95.

[48] Larson EB, Langa KM. Aging and incidence of dementia: A critical question. Neurology 2012;78:1452–3.

[49] Langa KM, Larson EB, Karlawish JH, Cutler DM, Kabeto MU, Kim SY, et al. Trends in the prevalence and mortality of cognitive impairment in the United States: Is there evidence of a compression of cognitive morbidity? Alzheimers Dement 2008;4:134–44.

[50] Manton KC, Gu XL, Ukraintseva SV. Declining prevalence of dementia in the U.S. elderly population. Adv Gerontol 2005;16:30–7.

[51] Rocca WA, Petersen RC, Knopman DS, Hebert LE, Evans DA, Hall KS, et al. Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. Alzheimers Dement 2011;7:80–93.

[52] Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: Results of the Cognitive Function and Ageing Study I and II. Lancet 2013;382:1405–12.

[53] Schrijvers EMC, Verhaaren BFJ, Koudstaal PJ, Hofman A, Ikram MA, Breteler MMB. Is dementia incidence declining? Trends in dementia incidence since 1990 in the Rotterdam Study. Neurology 2012;78:1456–63.

[54] Medical Imaging Trial Network of Canada n.d. Available from: www.mitnec.org (accessed March 19, 2015).

[55] Tardif JC, Spence JD, Heinonen TM, Moody A, Pressacco J, Frayne R, et al. Atherosclerosis Imaging and the Canadian Atherosclerosis Imaging Network. Can J Cardiol 2013;29:297–303.

[56] Canadian Atherosclerosis Imaging Network n.d. Available from: www.canadianimagingnetwork.org (accessed March 19, 2015).

[57] Ontario Neurodegenerative Disease Research Initiative n.d. Available from: www.ondri.ca (accessed March 19, 2015).

[58] Ramirez J, Gibson E, Quddus A, Lobaugh NJ, Feinstein A, Levine B, et al. Lesion Explorer: A comprehensive segmentation and parcellation package to obtain regional volumetrics for subcortical hyperintensities and intracranial tissue. Neuroimage 2011;54:963–73.