

# White matter hyperintensity burden in elderly cohort studies.

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

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## Background

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 (AD) and cerebrovascular disease as comorbid pathologies, with neuroimaging playing a central role in these studies.

## Objective

Using white matter hyperintensities (WMH) as a biomarker of cerebrovascular disease, we compared WMH burden between the Sunnybrook Dementia Study (SDS), the Alzheimer's Disease Neuroimaging Initiative (ADNI), the Three-City Study (3C), and various other studies around the world.

## Discussion

Based on our findings, it was evident that ADNI had minimal WMH burden relative to other large studies that examine aging and dementia.

This low WMH burden in ADNI 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.

Possible reasons for this distinction include a potential selection bias towards people with well managed vascular risk factors and gaps in diagnostic criteria.

## Results

Table 1: MMSE, Age, and WMH volumetrics by Dx group and study sample.

		MMSE (/30)		Age (years)		WMH (cc)		p
		Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	
AD	SDS (n=212)	24.5 (2.7)	50.4 - 88.9	72.2 (8.9)	50.4 - 88.9	7.6 (9.4)	0 - 100	***
	ADNI (n=161)	23.0 (2.1) <sup>†</sup>	51.5 - 87.3	74.9 (7.6)	51.5 - 87.3	1.0 (1.9)	0 - 100	***
MCI	SDS (n=70)	26.8 (2.2)	50.5 - 89.6	71.6 (7.8)	50.5 - 89.6	5.2 (7.1)	0 - 100	***
	ADNI (n=347)	27.0 (1.8) <sup>†</sup>	60.0 - 90.0	74.6 (7.5)	60.0 - 90.0	0.8 (2.4)	0 - 100	***
NC	SDS (n=105)	28.9 (1.0)	65 - 80 <sup>†</sup>	69.5 (8.1)	65 - 80 <sup>†</sup>	5.0 (8.4)	0 - 100	***
	ADNI (n=216)	29.0 (1.0) <sup>†</sup>	65 - 80 <sup>†</sup>	75.9 (5.0)	65 - 80 <sup>†</sup>	0.7 (2.2)	0 - 100	***
	3C (n=1701)	27.7 (1.7)	65 - 80 <sup>†</sup>	72.3 (4.1)	65 - 80 <sup>†</sup>	5.5 (4.9)	0 - 100	-

\*\*\* p<0.001 (Mann Whitney U)  
<sup>†</sup>Range: based on reported group inclusion criteria.  
<sup>‡</sup>Mean (SD) reported by Carmichael and colleagues [1].

WMH Volume Ranges for SDS & ADNI1 study samples

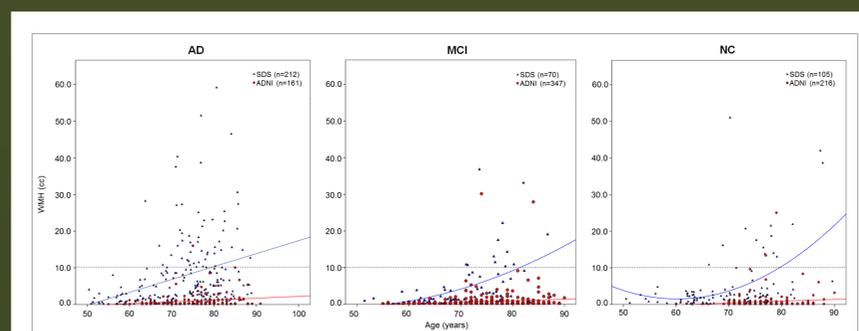


Fig. 1 Scatterplots showing the distribution of WMH volume by age for AD patients, MCI, and NC, comparing the ADNI1 (RED circles) and the SDS (BLUE triangles). Head-size corrected WMH volumes are reported in cubic centimeters (cc). AD patients were also matched for disease severity using the MMSE. Dotted line represents the 10cc cognitive threshold for WMHs originally proposed by Boone and colleagues [2].

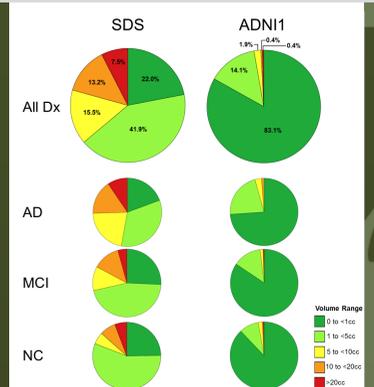
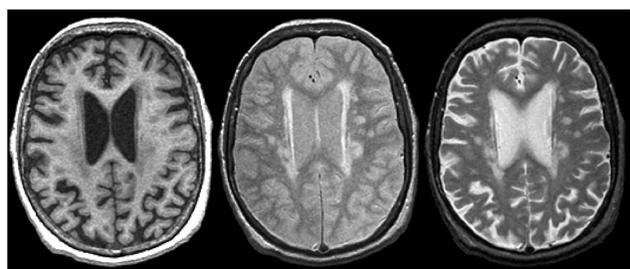


Fig. 2 Pie chart graphs showing WMH volume ranges for the Sunnybrook Dementia Study (SDS) (left) and the Alzheimer's Disease Neuroimaging Initiative (ADNI1) (right).



Gaps in diagnostic criteria: Probable vs. Possible AD?

Fig. 3 Structural MRI (left=T1, middle=PD, right=T2) of a 71 year old woman living with Alzheimer's disease. Lesion analysis revealed that she had 16cc of WMH. Should this be considered moderate or severe WMH burden? Should this patient's diagnosis be probable or possible AD dementia based on NIA-AA criteria [3]?

## Distributions of WMH by age in AD, MCI, and NC

Study	Location	Study Duration	Publication	Sample (n)	Age, y	White Matter Hyperintensity (cc) by Dx			
						Various	NC	MCI	AD
SDS	Canada	1994-2014	<b>Current findings</b>	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 (8.0)	-	-	7.3 (9.2)	
			Ramirez et al. 2014	NC (100), AD (265)	69.5 (8.0) <sup>c</sup>	2.5 (3.3) <sup>b</sup>	-	5.4 (11.0) <sup>b</sup>	
ADNI1	N. America	2004-2010	<b>Current findings</b>	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) <sup>c</sup>	0.3 (0.5) <sup>b</sup>	0.3 (0.5) <sup>b</sup>	0.4 (1.0) <sup>b</sup>	
3C	France	1999-2012	<b>Current findings</b>	Non-demented elderly (1701)	72.3 (4.1)	5.5 (4.9)	-	-	-
			Godin et al. 2010	Non-demented elderly (1319)	72.0 (0.1) <sup>b</sup>	5.4 (0.1) <sup>b</sup>	-	-	-
			Satizabal et al. 2012	Non-demented elderly (1771)	72.5 (4.1)	4.1 (3.7) <sup>b</sup>	-	-	-
LADIS	Europe	From 2001	Schmidt et al. 2010	Non-disabled elderly (340)	73.9 (5.1)	20.2 (21.0)	-	-	
Rotterdam	Netherlands	2005-2009	Verlinden et al. 2014	Non-demented 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)	-	-	

All data reported as Mean (SD), unless otherwise marked. <sup>a</sup> Median (IQR). <sup>b</sup> Mean (SE). <sup>c</sup> Based on reported NC data

Table 2: Comparison of WMH volumetric reports from various studies around the world

## Methods



### Sunnybrook Dementia Study (SDS: Canada)

- Prospective cohort study (1994-2014) conducted at Sunnybrook HSC, Toronto
- Real-world cohort of dementia patients and normal elderly (aged 50-90)



### Alzheimer's Disease Neuroimaging Initiative: Phase 1 (ADNI1: primarily USA)

- Large multi-site longitudinal brain imaging study (2004-2010) based in the US (53 sites) and Canada (5 sites)
- Patients with AD, mild cognitive impairment (MCI), and normal elderly controls (NC), aged 55-90



### Three-City Study (3C: France)

- Multi-center, longitudinal population-based cohort study (1999-2012) conducted in Bordeaux, Dijon, and Montpellier (France)
- Participants were randomly sampled from electoral rolls, no exclusion criteria except age (65-80)

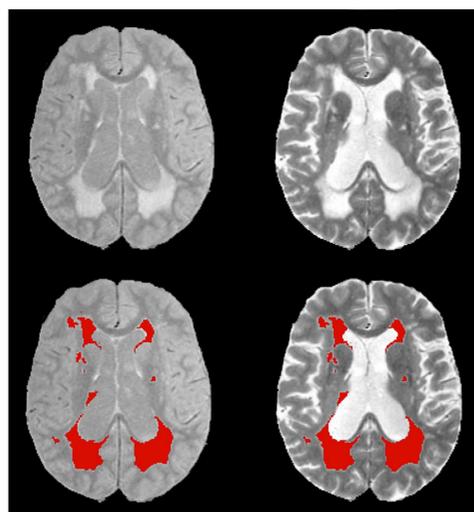


Fig. 4 Proton density (PD) and T2-weighted structural MRI showing white matter hyperintensities of presumed vascular origin (WMH) [15] segmentation in red. WMH volumetrics for SDS, ADNI1, and 3C were obtained from PD/T2-based segmentations.

Several other large studies were used for additional comparison demonstrating similar WMH results:

- Leukoaraiosis and Disability Study (LADIS) [4]
- Rotterdam Study [5]
- Personality & Total Health (PATH) Through Life [6]
- Clinical Research Center for Dementia of South Korea (CREDOS) [7]

### References

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- Wardlaw et al. (2013). *Lancet Neurol*.

### Main Study References

- SDS: [www.brainlab.ca/sunnybrookdementiastudy/](http://www.brainlab.ca/sunnybrookdementiastudy/); ClinicalTrials.gov NCT 01800214
- ADNI: [www.loni.ucla.edu/ADNI](http://www.loni.ucla.edu/ADNI)
- 3C: [www.three-city-study.com](http://www.three-city-study.com)

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