

Mobility and falls—relation to urinary incontinence

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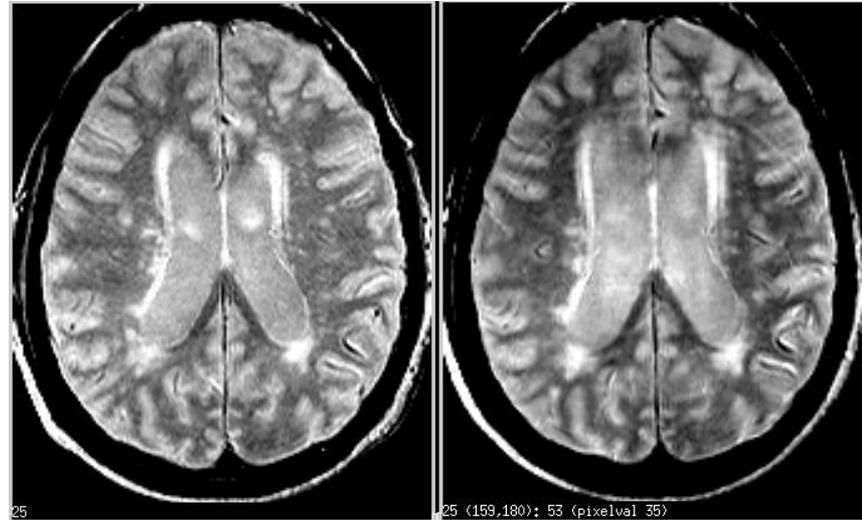
Other financial relationships: None

Conflicts of interest: None

A traditional neurologist's perspective on the relation of mobility to UI

- Urge I-Bifrontal syndrome → bilateral frontal lesions-e.g. NPH, glioma → small-steps, poor balance, shuffling gait, ↓ executive fn, apathy
- Mixed-combination OI&UI-Cervical, thoracic cord lesion → spastic paraparesis
- Overflow I-lesions of Conus Medullaris (CM) & nerves—loss of circuitry for bladder control-
CM lesions → flaccid paraparesis
- Functional I—Mobility disorder, AD, etc

PDWI from 85y/o male
with severe gait-
balance impairment



What is microvascular disease?

Comparison of stroke and some characteristics of white matter hyperintensity lesions-i.e. brain microvascular disease

<i>Characteristic</i>	<i>Stroke (large artery)</i>	<i>White matter hyperintensities</i>
Onset/progression	Sudden/brief if any	Ill-Defined/gradual over years
Manifestations	Focal neurologic deficit	Functional limitations
Location	Vascular distribution	Grow from head/tail-lateral ventricles
Size	Stroke (cm) → lacune (mm)	< 1 mm
Vessel	Large-to-small artery	Arteriolar
Pathophysiology	Ischemic	Unclear

Note: there may be infarction because of small vessel disease that has onset/progression and manifestations that are similar to large artery stroke. ^aModified from White *et al*⁶⁸ with permission of Elsevier.

What is prevalence of WMH?

- Rotterdam study, population-based, 65-84 yrs-Sample, 1115s =**27%**
- Helsinki Aging Brain Study population-based, mean age=71.5 yrs, **39%**
- Cardiovascular Health Study (large U.S.) population- based **87%**
- Atherosclerosis Risk in Communities Study (large U.S.) population-based **86%**
- WMH is **commonly encountered** in population-based studies with **definition of case** likely explaining difference in prevalence among studies

CT/MRI Rating Scale for WMH

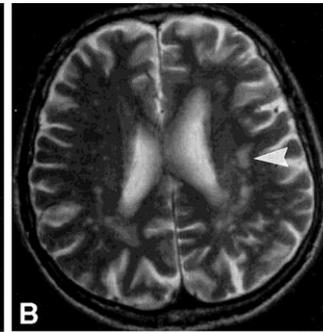
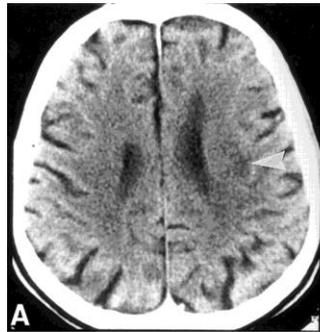
Wahlund et al-Stroke, 2001, 32:1318-22

Rating Scale

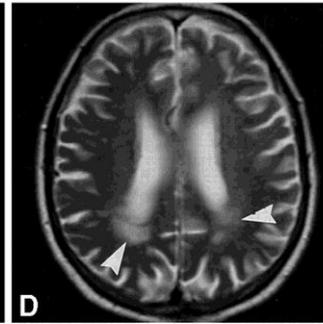
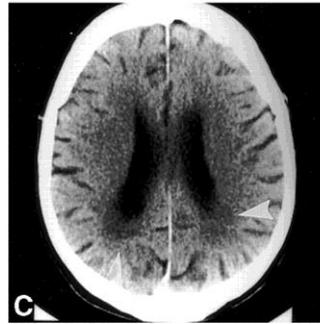
CT

MRI

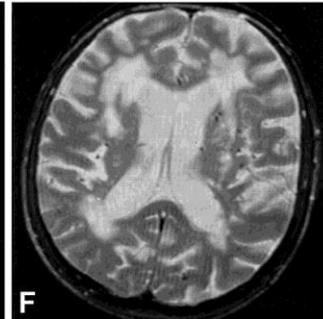
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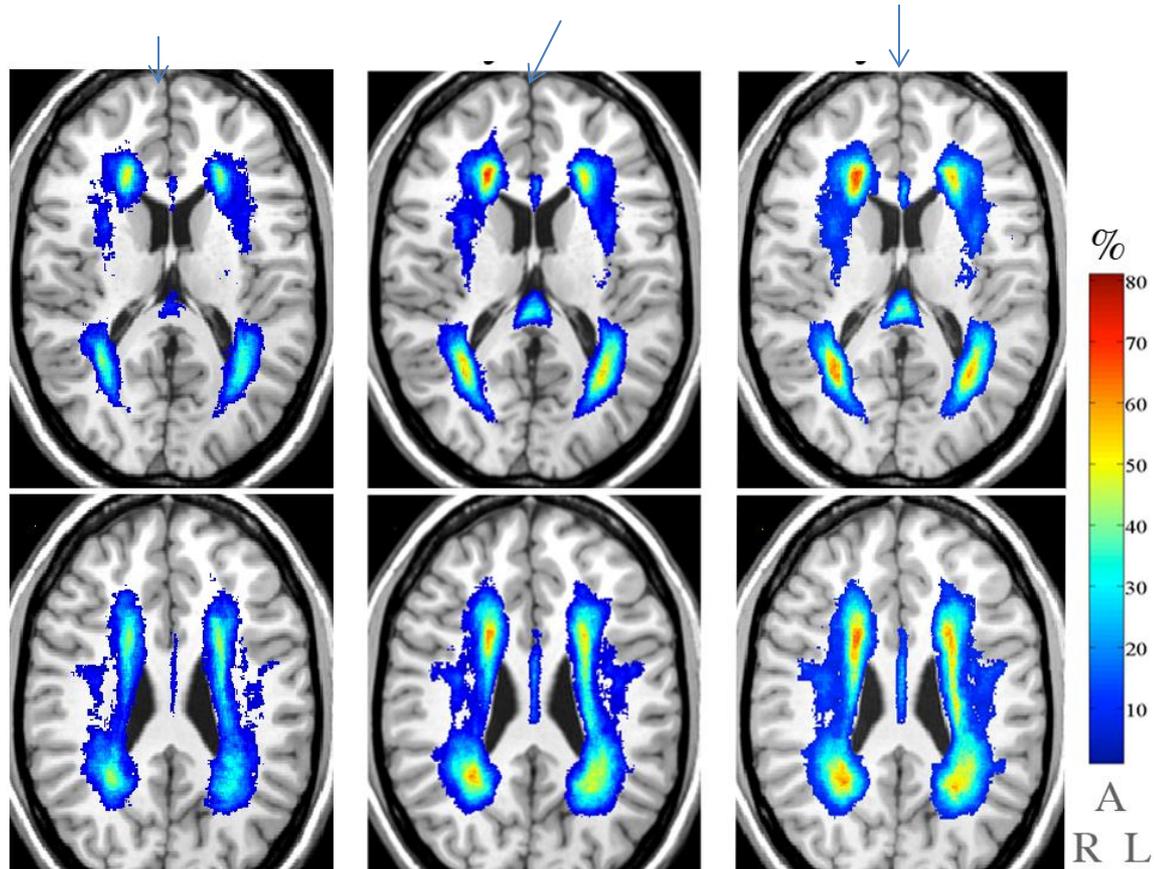
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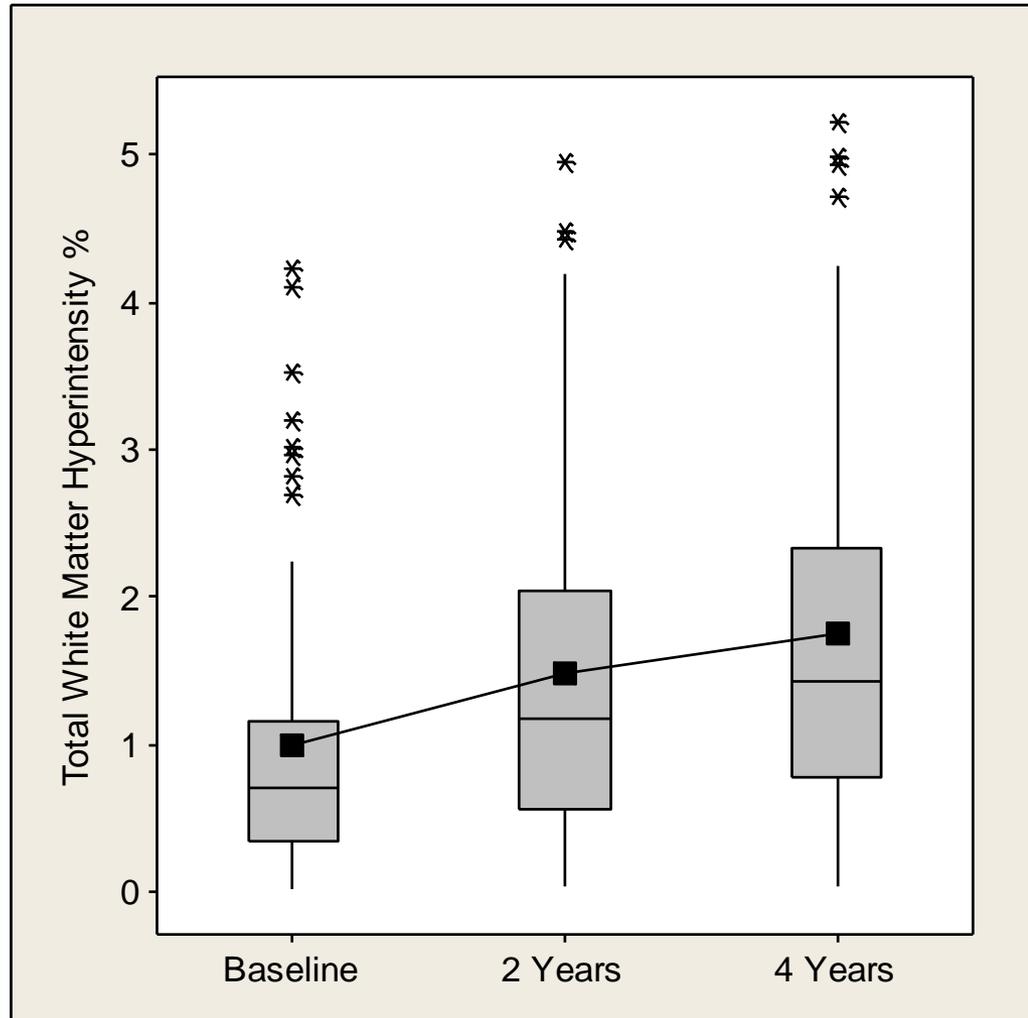
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Location & frequency of WMHs in 67 subjects for whom MRI data for all 3 time-points were available (rows): WMHs (in color) are overlaid on grayscale slice (0.87 mm-thickness). Columns: 2 slices separated by 12.2 millimeters. Corona Radiata is prime site of WMHs.



Accrual of White Matter Hyperintensity (WMH) (% ICCV)



Boxplots showing the total White Matter Hyperintensity (% ICCV) at 3 time points of the study. The bottom of the box represents the first quartile, while the top represents the third quartile. The box portion represents the middle 50% of observations (inter-quartile range). The line drawn through the middle of the box represents the median while square in the box represents the mean. The whiskers (lines extending from the box) indicate the lowest and highest values in the data set (excluding outliers) while outliers, are represented by asterisks. A value is considered an outlier if it is outside of the box by more than 1.5 times the inter-quartile range.

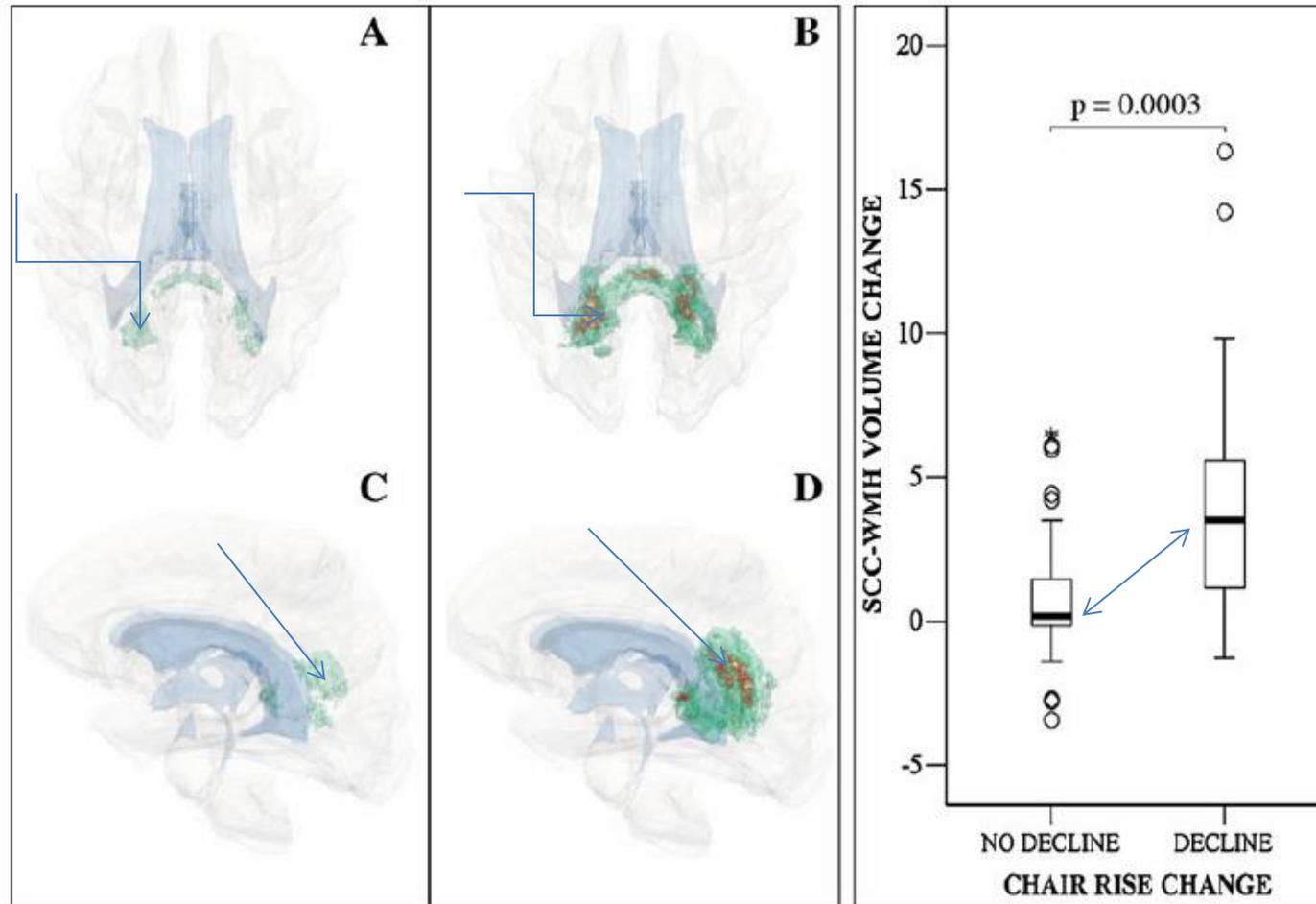
What is pathophysiology of WMH?

- Van Swieten et al - 19 brains, link $\uparrow T_2$ WM signal to demyelination, astrocytic gliosis
- Fazekas— \uparrow severity of T_2 WM signal linked to \uparrow severity of tissue damage
- Thickened walls-small arteries
- WMH pathology—gliosis, myelin loss-- non-specific changes
- Diffusion tensor imaging (DTI) measures integrity of brain microstructure; is sensitive to early white matter damage

Hypothesis relating anatomic – pathology to mobility

- Cerebellum, thalamus & basal ganglia integrate & facilitate function of sensorimotor cortex
- Mobility controlled by a bilateral network (i.e., pre-supplementary motor cortex linked to sensori-visual cortex) connected by peri-ventricular WM
- Occurrence of WMH in periventricular WM & corpus callosum disrupts sensorimotor integration
- Mobility → time-dependent requires fast responses
- WM lesions (WMH) damage sensory-motor processing supporting mobility → impaired mobility

r-WMH volume change in Splenium Corpus Callosum (SCC) vs. chair rise change over 2 years



Baseline relationship of t-WMH to r-WMH and mobility

- Strong correlations between total WMH (t-WMH) and regional WMH (r-WMH)
- Correlation coefficients ranged from 0.5 to 0.9 for 8 of 10 structures (others-0.2 & 0.3)
- r-WMH, Splenium of Corpus Callosum was best predictor of mobility but tWMH almost as good
- Using logistic regression, 1% \uparrow t-WMH = 2.4X's > chance of gait velocity < 0.69m/s

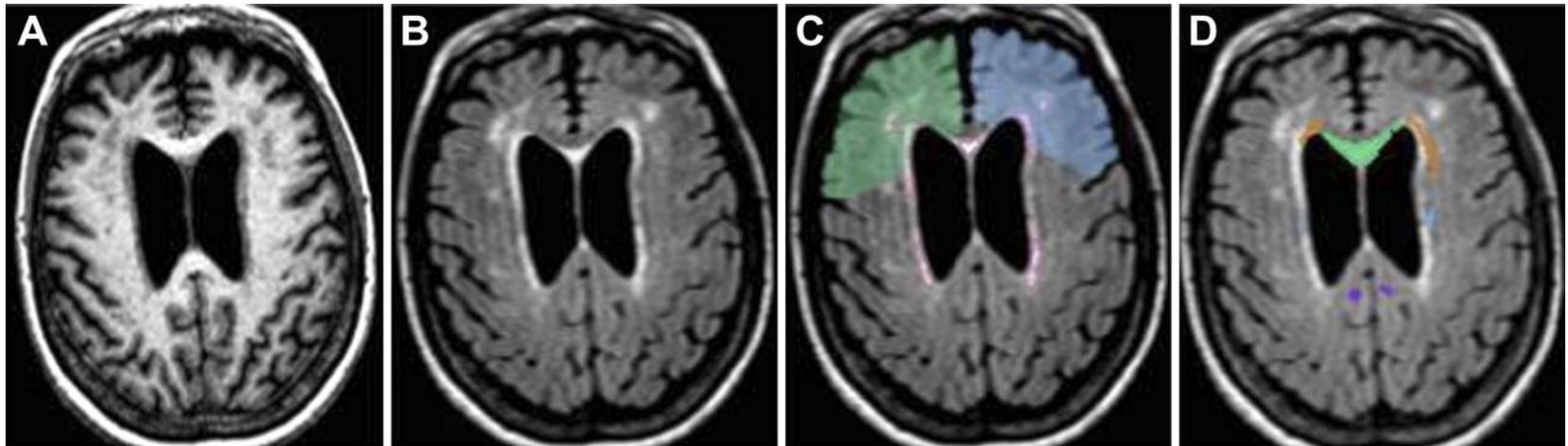
PET/fMRI and urinary function

- Forebrain control/integration of urinary function has been studied using PET & fMRI
- Medial prefrontal ctx-Ascending input through thalamus, insula & lat prefrontal ctx. → integration of sensory input → controls voiding
- Mid cingulate/adj supplementary motor area-perception of sensory input preparatory motor responses
- Subcortical input through parahippocampal-limbic (affective input)
- Ascending afferent input through periaqueductal gray and descending motor control through pontine micturition center
- There have been some effort to study connectivity of above neuronal regions but this data is weak and incomplete by comparison
- Need to delineate key white matter structures responsible for urinary function

UI and WMH

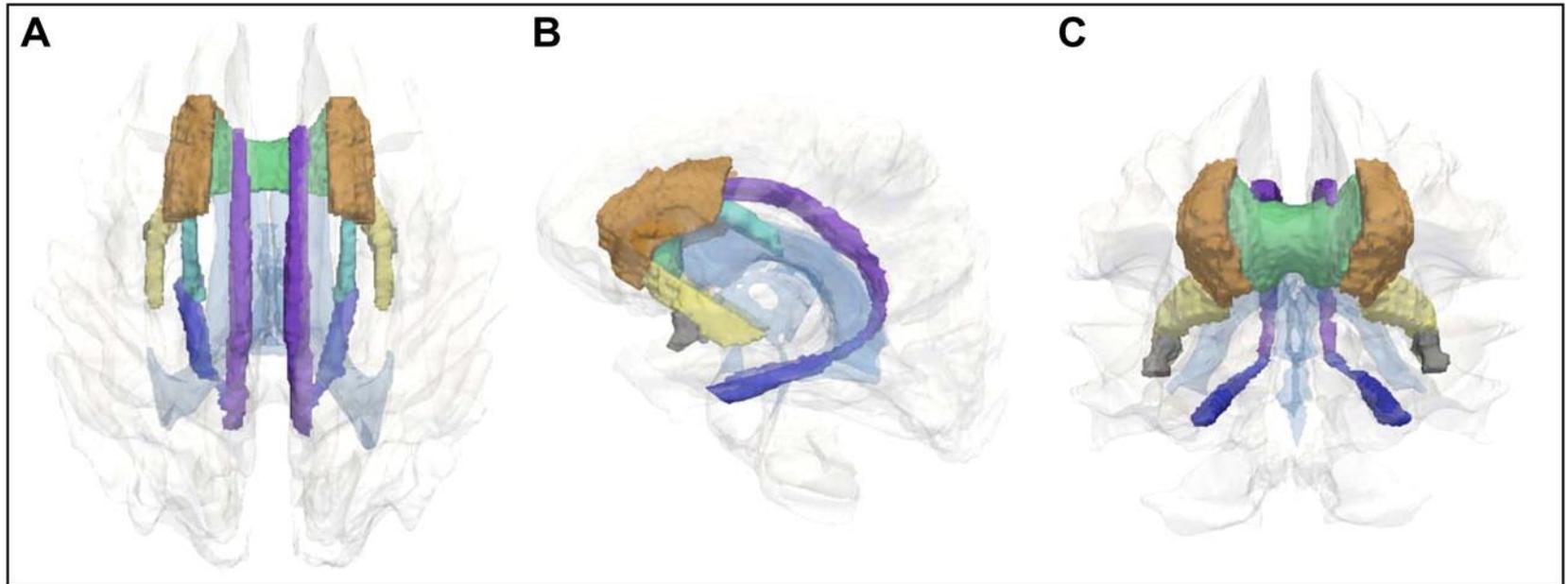
- Sixty-two (64%) of the participants were incontinent, mostly with urgency (37; 60%) and moderate – severe symptoms (36; 58%).
- Incontinent individuals were more likely to be women with worse scores for depression and mobility.
- WMH located in right inferior frontal regions predicted UI severity, with no significant relationship with incontinence type, bother, or functional impact.
- As regards WM tracts, WMH within regions normally occupied by the anterior corona radiata predicted severity and degree of bother, cingulate gyrus predicted incontinence and severity, whereas cingulate (hippocampal portion) and superior fronto-occipital fasciculus predicted severity.
- Suggest a central role for cingulum in bladder control c/w fMRI data
- Location of above WM tracts overlaps/abuts those supporting mobility—tightening relationship

Example of magnetic resonance series and regions of interest (ROIs) used in the study: (A) MPRAGE, (B) FLAIR, and (C) frontal left (blue) and right (green) ROIs overlaid to a FLAIR image on which the areas of white matter (WM) hyperintensity are outlined in red (output of the segmentation method); (D) a FLAIR image overlaid with some of the selected WM tracts-based ROIs, namely, genu of the corpus callosum (green), anterior corona radiata (orange-brown), cingulum/cingulate gyrus (purple), superior fronto-occipital fasciculus (light blue).



**George A. Kuchel et al. J Gerontol A Biol Sci Med Sci
2009;64A:902-909**

**Three-dimensional (3D) models of the seven white matter (WM) tracts selected for analysis:
Top (A), side (B), and frontal (C) views of a 3D reconstruction of the human brain are
presented with ventricles (faint blue) and total brain WM (white/gray) shown in transparency.**



**George A. Kuchel et al. J Gerontol A Biol Sci Med Sci
2009;64A:902-909**

White Matter and UI

- Presence of WMH in right inferior frontal regions and selected WM tracts predicts incontinence, incontinence severity, and degree of bother
- a critical role for the cingulum in bladder control, while also suggesting potential involvement of other nearby WM tracts such as anterior corona radiata and superior fronto-occipital fasciculus .

Hypertension treatment and white matter lesion (WML) progression over 5 years-

Verhaaren BF et. al. Hypertension 2013; 61: 1354-1359

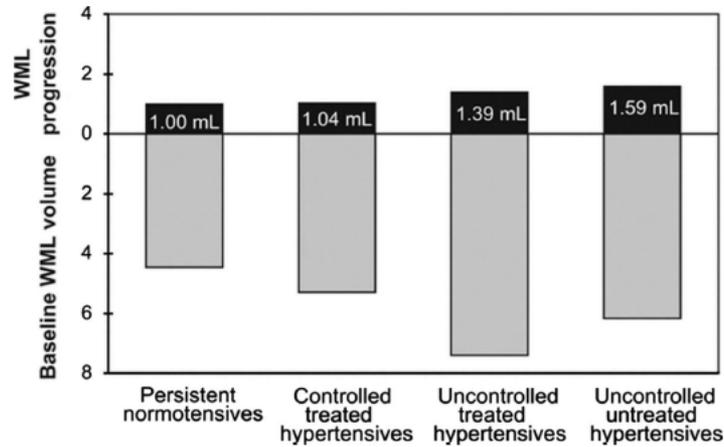
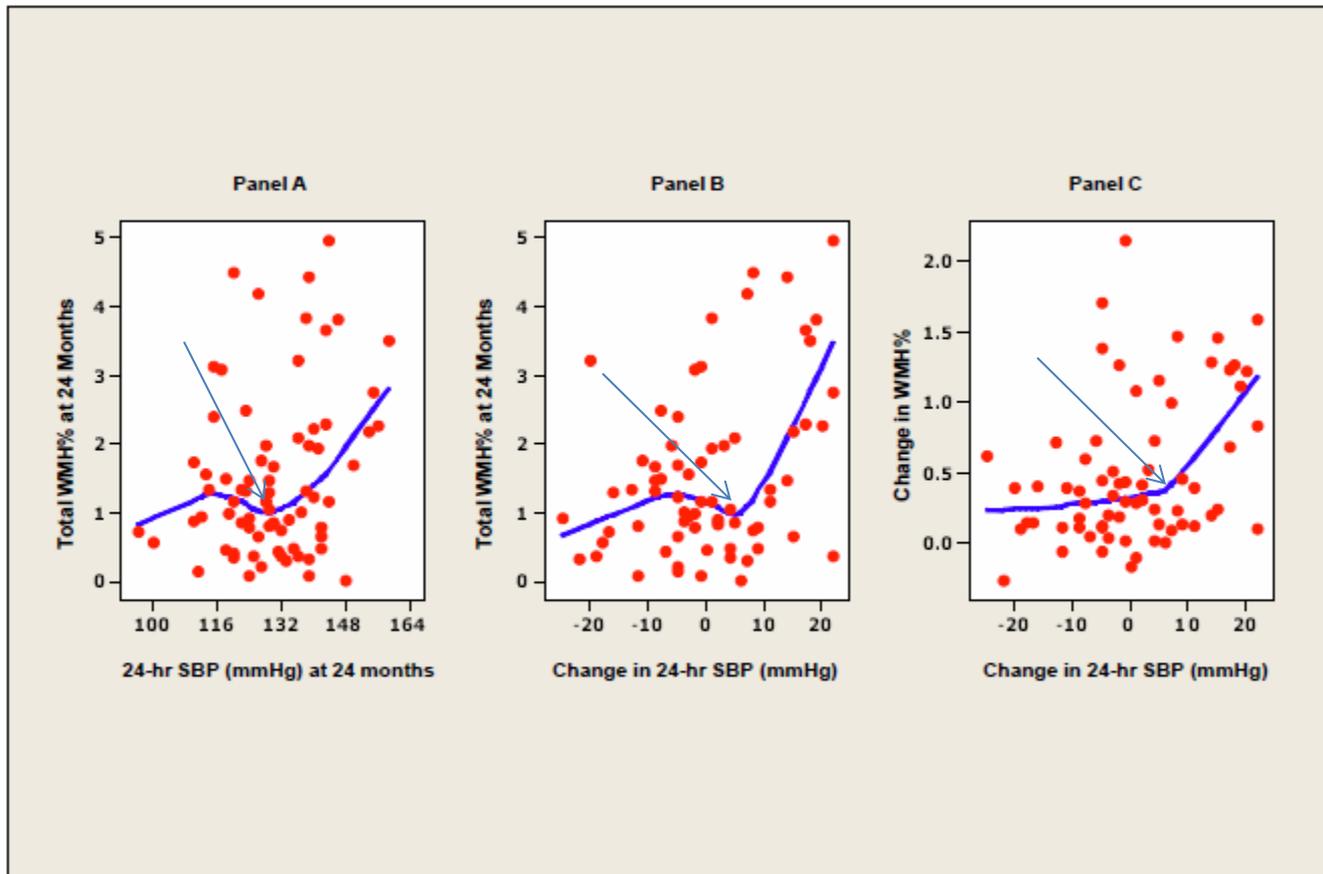


Figure 3. Mean white matter hyperintensity progression in mL (95% confidence interval; black bars) on top of the baseline white matter lesion volume (gray bars) for four blood pressure categories.

24-hr systolic BP at 2 yrs is linked to WMH (absolute WMH/BP & change)

From- White ,Wolfson, et. al., Circulation: 124:2312-9, 2011



WMH and mobility measures at 24 months using 24hSBP cut point of 135 mmHg

Table 3. White Matter Lesion Volume and Functional Parameters at 24 months According to 24-hour Blood Pressure Cut-Points Above and Below 135 mmHg

	<u>24-HOUR AMBULATORY BLOOD PRESSURE</u>		P-value
	<135 mmHg (n = 28)	≥ 135 mmHg (n = 45)	
24-hour Systolic BP (mmHg)	122.0 ± 1.3	142.9 ± 1.2	< 0.001
Total WMH (%)	1.26 ± 0.15	1.96 ± 0.26	0.03
Change in WMH (%)*	0.43 ± 0.07	0.62 ± 0.10	0.100
Mobility assessments			
Tinetti Gait	11.5 ± 0.2	11.0 ± 0.3	0.184
Stair descent time (sec)	5.8 ± 0.4	6.8 ± 0.4	0.023
Maximal gait velocity (m/s)	2.5 ± 0.1	2.2 ± 0.1	0.051
Walk time (sec)	2.9 ± 0.1	3.5 ± 0.2	0.003

INtensive versus Standard Ambulatory Blood Pressure Lowering to Prevent Functional DeclIne in The ElderLy (*INFINITY*)

- 3-year clinical trial comparing intensive to standard BP control using ambulatory BP monitoring to guide treatment - 200 subjects ≥ 75 yrs
- Different treatment goals but similar treatment algorithms & meds
Standard = 24-hour systolic BP mean of < 145 mmHg
Intensive = 24-hour systolic BP mean of ≤ 130 mmHg
- Outcomes assessed at baseline, 18 months & 36 months
- Measures of mobility - gait speed, stair ascent/descent, changing and maintaining body position, supine-to-sit, sit-to-stand, functional reach, and maintenance of 3 stance postures
- Measures of executive functioning & process speed- Trail Making-B, Stroop Color-Word Test, California Computerized Assessment Package, simple & sequential reaction time
- Urinary incontinence measured by validated questionnaires
- Measures of WM Integrity-WMH volume, Diffusion Tensor Imaging-FA, AD

Intensive versus Standard Ambulatory Blood Pressure Reduction to Lessen Functional Decline NIH/NIA R01-AG 022092-10 Principal Investigators: William B. White, MD and Leslie Wolfson, MD, University of Connecticut School of Medicine

August 2016

- Eligible based on phone screen: 446
- Consent Visit Completed:354 No Consent Visit: 92
- Consented: 340
- Randomized:199, Excluded after consent: 141
- Has not achieved goal: 16 At goal:154
- (another 16 met goal and later withdrew) Withdrawn: 29
- Month 1 Visit Completed:191
- Month 6 Visit Completed:158
- Month 12 Visit Completed: 170
- Month 18 Visit Completed:141
- Month 24 Visit Completed: 114
- Month 30 Visit Completed: 89
- Month 36 Visit Completed: 68

Knowledge gaps--questions to be addressed

- Prevalence of UI due to WMH
- Define white matter pathways serving urinary function—Use of Diffusion Tensor Imaging
- Relation of symptoms to site of damage
- Define relationship between UI and WMH
- Define pathophysiology of WMH-?ischemic, other
- Define relation between UI and vascular disease risk factors
- Prevention trials