Neuroimaging Biomarkers Moderate the Association between Demographic Risk and Dementia Rating Scale across Neurodegenerative Diseases: The Sunnybrook Dementia Study

Shraddha Sapkota[1], Joel Ramirez[1], Mario Masellis[1,2], Sandra E. Black[1,2]

[1]Sunnybrook Research Institute, Toronto, Canada; [2]Department of Medicine (Neurology), University of Toronto, Toronto, Canada

INTRODUCTION

- A large spectrum of pathologies in the aging brain in combination with cardiovascular risk have led to an increased prevalence and diagnosis of mixed neurodegenerative diseases (combinations of proteinopathies and vasculopathies) in late life[1].
- Risk scores to quantitatively differentiate neurodegenerative patients and at-risk adults for cognitive impairment present an alternative risk assessment tool for individually tailored intervention programs and/or preventative measures. Previous studies have proposed risk scores to predict dementia incidence and cognitive decline using multiple domains[2].
- **Research Goal:** To develop a novel multimodal, integrative method to examine the synergistic influence of established demographic risk factors (age, sex, education), neuroimaging biomarkers (ventricular atrophy), and markers of small vessel disease (whitematter hyperintensity, lacunes) to predict performance and change on the dementia rating scale (DRS) across neurodegenerative diseases.

RESEARCH QUESTIONS (RQ)

- **RQ 1:** Do higher **(a)** ventricular atrophy, markers of small vessel disease, and **(b)** demographic risk predict lower DRS performance and steeper decline across neurodegenerative diseases?
- **RQ 2:** Do ventricular atrophy and markers of small vessel disease moderate or mediate the association between demographic risk and DRS performance and change across neurodegenerative diseases?

METHOD

- **Participants:** Diagnosed patients and cognitively normal older adults (*n* = 833) tested every year for ~3 years (Wave 1 = baseline, Wave 2 = first follow-up, Wave 3 = second follow-up) from the Sunnybrook Dementia Study (SDS) (***Table 1***). The participants represented:
  - Normal Controls (NC), Alzheimer's disease (AD), Mild Cognitive Impairment (MCI), Vascular Cognitive Impairment (VCI), Parkinson's disease-Lewy body dementia (PD-LBD), Frontotemporal Lobar Degeneration (FTLD), and mixed vascular/neurodegenerative diseases.
- **Dementia Rating Scale (DRS):** 36 tasks with high reliability and validity[3,4]. Total = 144.
  - Attention (8 items-37 points); Initiation-Preservation (11 items-37 points); Construction (6 items-6 points); Conceptualization (6 items-39 points); Memory (5 items-25 points).
- **Magnetic Resonance Imaging (MRI) derived volumetrics:**
  - Ventricular volume, whitematter hyperintensity (WMH), and lacunes (***Figures 1-3***) were obtained from validated pipelines: Semi-Automated Brain Region Extraction (SABRE)[5] and Lesion Explorer[6].

STATISITICAL ANALYSES

- **DRS Latent Growth Model:** Latent growth model of change over ~3 years.
- **Demographic Risk Score (RS) Calculation:** Age [0 ≤ 70 years (mean age), 1 > 70 years] + sex [0 = male, 1 = female] + education [0 > 14 years (mean education), 1 ≤ 14 years]
- **Statistical Analyses:** Latent growth model of change and regression analyses in Mplus 7.
  Models tested:
  - **RQ 1a:** Neuroimaging risk biomarkers (ventricular volume, WMH, lacunes) on DRS performance and change
  - **RQ1b:** Demographic RS on DRS performance and change
  - **RQ 2:** Demographic RS as moderated and mediated by neuroimaging risk (ventricular volume, WMH, lacunes,) on DRS performance and change

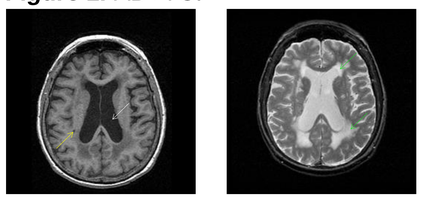
Table 1. **Baseline Characteristics**

Characteristics	
n	Wave 1 = 833; Wave 2 = 514; Wave 3 = 300
Age (years)	70.47 (9.40)
Education (years)	14.11 (3.73)
Sex (M/F)	394/439

Note. Values are mean (standard deviation). *n* = Total number. Exclusionary criteria applied.

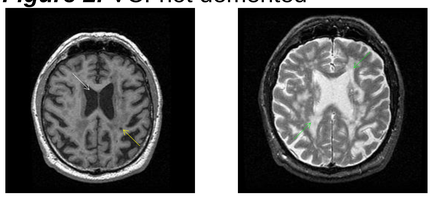
RESULTS

Figure 1. AD+VCI



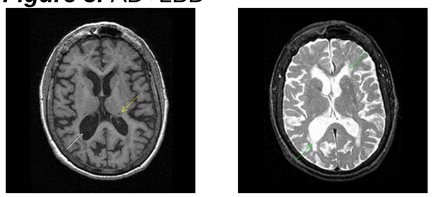
78 years old, female,15 years education

Figure 2. VCI-not demented



68 years old, male, 12 years education

Figure 3. AD+LBD



76 years old, female, 10 years of education

Note. white arrow = enlarged ventricles; yellow arrow = lacune; green arrow = WMH.

- **DRS Latent Growth Model:** Random intercept and random slope best represented the DRS growth model over three years (AIC = 12980.56; BIC = 13018.08; $X^2(df)$ = 1.499(1), p = .221; *RMSEA* (90% CI) = .025 (.000-.101); *CFI* = .999; and *SRMR* = .031).
- **RQ 1a:** All three neuroimaging biomarkers predicted DRS performance. First, larger ventricular volume predicted poorer DRS performance (β = -2.77; SE = 0.027; p < .001), and steeper 3-year decline (β = -1.07; SE = 0.22; p < .001). Second, higher WMH (β = -1.37, SE = 0.56, p = .014) and higher lacunes (β = -32.00, SE = 14.61, p = .028) predicted poorer DRS baseline performance.
- **RQ 1b:** Higher demographic RS predicted poorer DRS baseline performance (β = -1.46, SE = 0.65, p = .024) and less decline over 3 years (β = 0.99, SE = 0.48, p = .038).
- **RQ 2:** Neuroimaging biomarkers moderated the association between demographic RS and DRS performance. Specifically, higher demographic RS predicted poorer DRS performance in those with low ventricular volume (β = -1.81, SE = 0.74, p = .015) (***Figure 4***), low WMH (β = -2.22, SE = 0.79, p = .005) (***Figure 5***), and low lacunes (β = -1.66, SE = 0.74, p = .025). Higher demographic RS predicted less DRS decline for those with low ventricular volume (β = 1.13, SE = 0.53, p = .034) (***Figure 4***) and high WMH (β = 1.71, SE = 0.71, p = .016). We did not observe any mediation effects.

Figure 4.

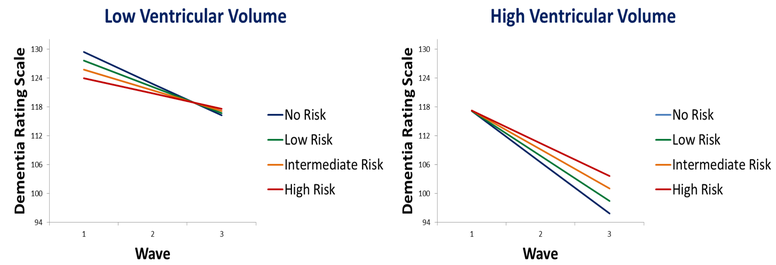
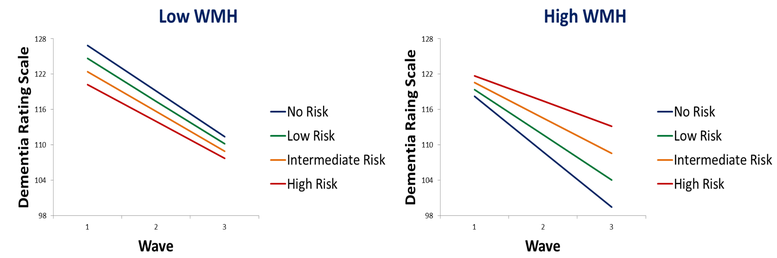


Figure 5.



DISCUSSION

- Ventricular atrophy and markers of small vessel disease moderated the association between demographic risk and the DRS performance. As expected, adults with high demographic RS had low DRS performance at baseline but were declining at a slower rate than their counterparts who start with a high DRS performance (potentially higher cognitive reserve) and rapidly decline. This association is only present in those with high WMH and low ventricular volume at baseline suggesting differential influence on the DRS performance over time.
- Given the inherent complexity of dementia that includes multiple pathological entities (i.e., FTLD, AD+LBD) in addition to small vessel disease and brain atrophy, investigation of mixed vascular/neurodegenerative diseases is warranted. Innovative methodological approaches may aid in identifying potential complex and dynamic mechanisms underlying multifaceted clinical phenotypes across neurodegenerative diseases.

REFERENCES

[1] Schneider & Bennett. (2010). *Stroke, 41,* S144-S146.
[2] Anstey et al. (2014). *PLoS One, 9,* e86141.
[3] Green et al. (1995). *The Journal of Neuropsychiatry and Clinical Neurosciences, 7,* 357-360.
[4] Vitaliano et al. (2004). *Journal of Chronic Disease, 37,* 743-753.
[5] Dade et al. (2004). *Neuroimage, 22,* 1492-1502.
[6] Ramirez et al. (2011). *Neuroimage, 54,* 963-973.

ACKNOWLEDGEMENTS

We gratefully acknowledge support from (1) the Canadian Institutes of Health Research to SEB and MM and (2) the Alzheimer's Society of Canada/Canadian Consortium on Neurodegeneration in Aging Postdoctoral Fellowship to SS. We thank our participants and their families for their time and contribution.