Australian National University

# Interrelationships among self-reported orthostatic hypotension, white matter hyperintensities and hippocampal volume in an 8-year longitudinal study of a young-old cohort

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# Areas of interest

Cardiovascular risk factors for cognitive decline, brain ageing, and dementia

- **Postural hypotension or orthostatic hypotension (OH)**

Definition: orthostatic hypotension as a SBP fall at least 20 mmHg and/or a DBP fall at least 10 mmHg within 3 min of standing. ‘head rush’ ‘dizzy spell’ more common in those with low blood pressure

- **Depressive symptoms**

Both cardiovascular risk factors, both have also been linked to brain structure and age-related brain changes

# Orthostatic hypotension (OH)

- Rapid change in blood pressure leads to rapid change in cerebral blood flow, loss of perfusion.
- Angelousi et al. 2014 Meta-analysis of 28 studies linked OH to coronary disease, heart failure, and arrhythmias. And overall mortality [pooled hazard ratio in random-effects model = 1.36 (1.13–1.63), P < 0.001)].
- OH is understudied as a risk factor for dementia and cognitive decline, but has been linked to increased cerebrovascular events and white matter hyperintensities (eg. Colloby et al, BJP, 2011).

# Late-life depression –OH, brain atrophy associations

## Depression is more prevalent in people with OH

- Cohort study: Irish Longitudinal Ageing Study (TILDA) reported association of symptomatic OH (SOH) and late-life depression (Regan et al, BMC 2013).
- Case-control study: compared 17 depressed and 17 non depressed and found OH more common in depressed (Richardson et al. AJGP 2007).

## Depressive symptoms and brain volumes

- Cohort study: WHICAP (n = 630) found increased WMH and reduced brain volume, smaller HC, associated with higher depressive symptoms (Geerlings et al, 2012, JAD).

# Hypotheses

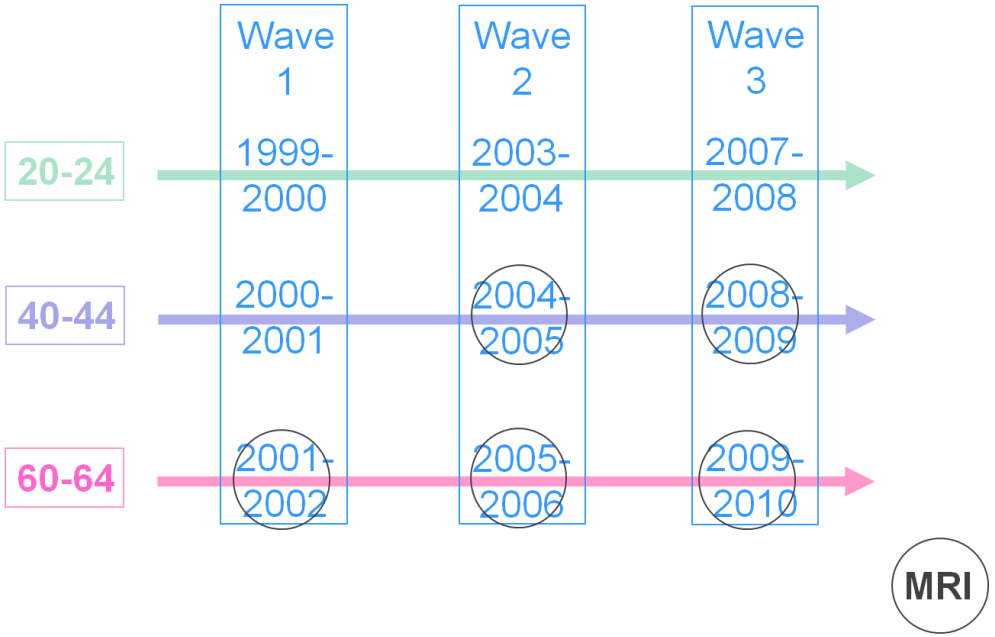
- OH is associated with increased WMH, and HC atrophy
- Depression is associated with increased WMH and HC atrophy
- Effects of OH are at least partly moderated by depression

Note: associations = cross-sectional

atrophy = longitudinal change

# PATH Through Life Study

- Random sample from the population of Canberra and Queanbeyan (N = 2551)
- Baseline age-range: 60-64
- Participants assessed every 4 years
- Measures include: socio-demographic, lifestyle, cognition, personality, employment, health, genetic, and more

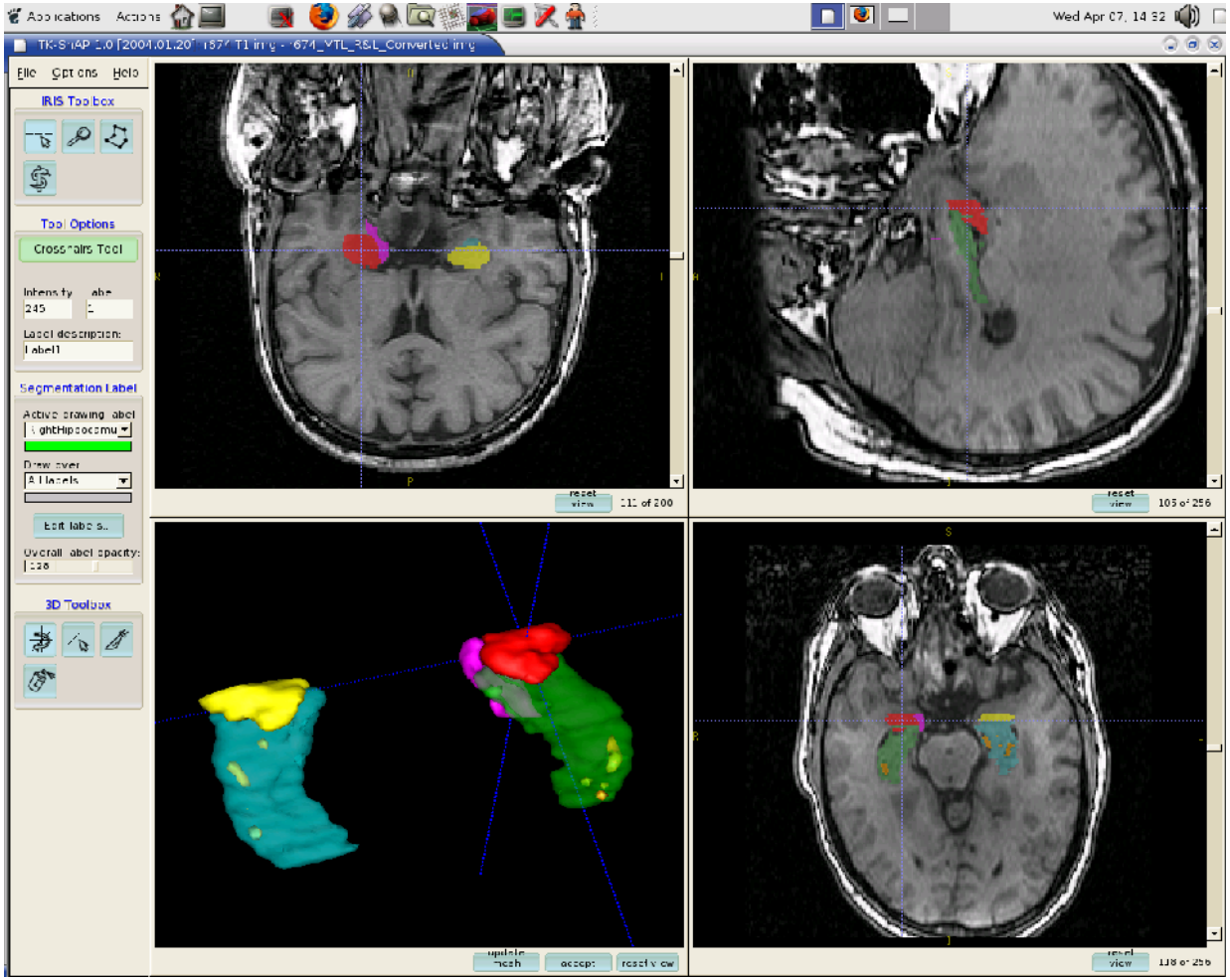


# Normative MRI substudy

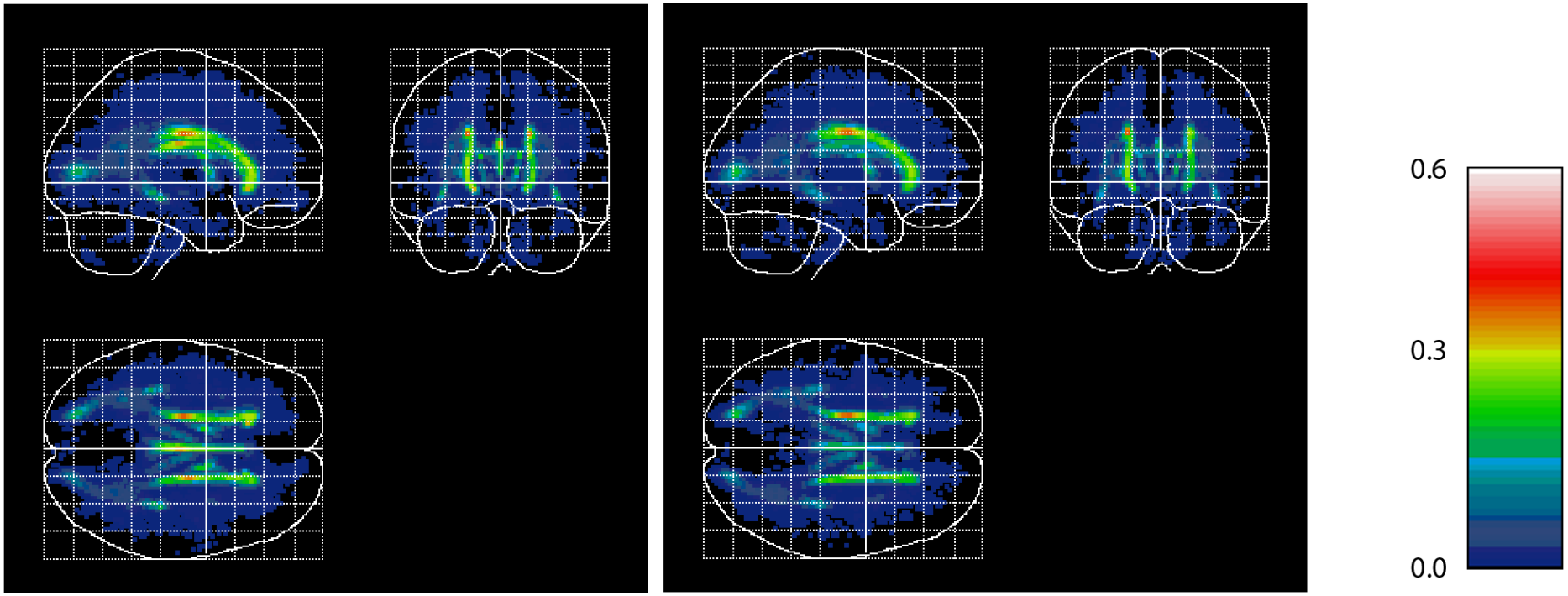
- All 60+ subjects eligible
- 2076 (81.5%) willing to participate
- 622 (30.0%) randomly invited for MRI
- 478 (76.8%) scans acquired Wave 1, 407 at Wave 2, 360 at Wave 3

MRI measures used in this study

- Hippocampal manually segmented
- Intracranial volume
- White matter, grey matter, CSF (SPM)
- White matter hyperintensity volume
- All normalised as appropriate




Maller, J.J., Reglade-Meslin, C., Anstey, K.J., Sachdev, P. (2006). Sex and symmetry differences in hippocampal volumetrics: Before and beyond the opening of the crus of the fornix. *Hippocampus,* 16(1), 80-90. (Volume in cubic mm)




a) Females

b) Males

Wen W, Sachdev P: The topography of white matter hyperintensities on brain MRI in middle-aged individuals. *Neuroimage* 2004, 22:144-54.

Abnormal signal intensities greater than 6 SDs above the mean white matter intensity were classified as WMH. Ie severe WMH

# Depression, OH, covariates

- Depressive symptoms measured by the Goldberg scale
- OH assessed at Waves 2 and 3 by the question:

  *"When getting up suddenly from a lying position, do you experience faintness, dizziness, light-headedness, nausea or blackout?"*

- Exclusion criteria : history of stroke, epilepsy, or clinical diagnosis of Dementia.
- Demographics : age, sex, education
- Objective blood pressure measures also taken

# Statistical analysis approach

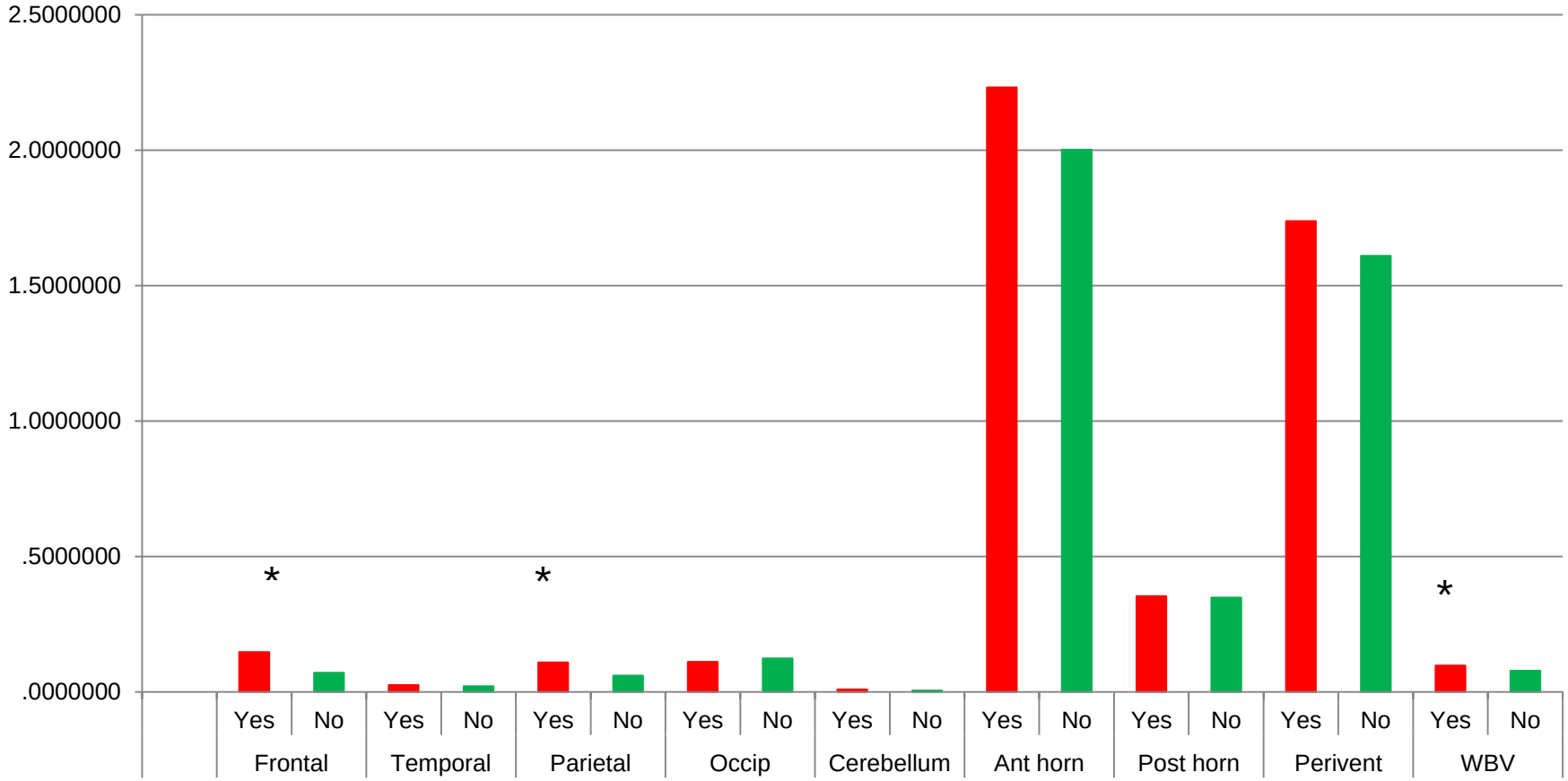
- Generalized linear models for cross-sectional analyses of Wave 2 WMH data
- Multi-level models for analysis of hippocampal volume change over 3 waves (8 years)
- Quadratic terms included in model to account for non-linear change in volumes
- Covariates  and OH included as fixed effects
- Models accounted for missing data

# Cross-sectional parameter estimates

| Region | OH W1 | Dep W2 |
|---|---|---|
| | *β* | *β* |
| Brain stem | | |
| Frontal lobes | **0.139**** | **0.038**** |
| Temporal lobes | 0.009 | 0.003 |
| Parietal lobes | **0.112*** | 0.023 |
| Occipital lobes | 0.037 | **0.039**** |
| Cerebellum | 0.007 | -0.003 |
| Anterior horn | 0.019 | 0.057 |
| Posterior horn | 0.235 | **0.265***** |
| Periventricular | 0.019 | 0.057 |
| Whole brain | **0.043*** | **0.009**** |

Generalized linear model adjusted for age, sex, education, smoking, alcohol, blood pressure,

## Mean volume of WMH at Wave 1 by Orthostatic hypertension status Wave 2 ($mm^3$)




Adjusted for age, sex, smoking, hypertension and years of education.
n for OH = 112, n for no OH = 294

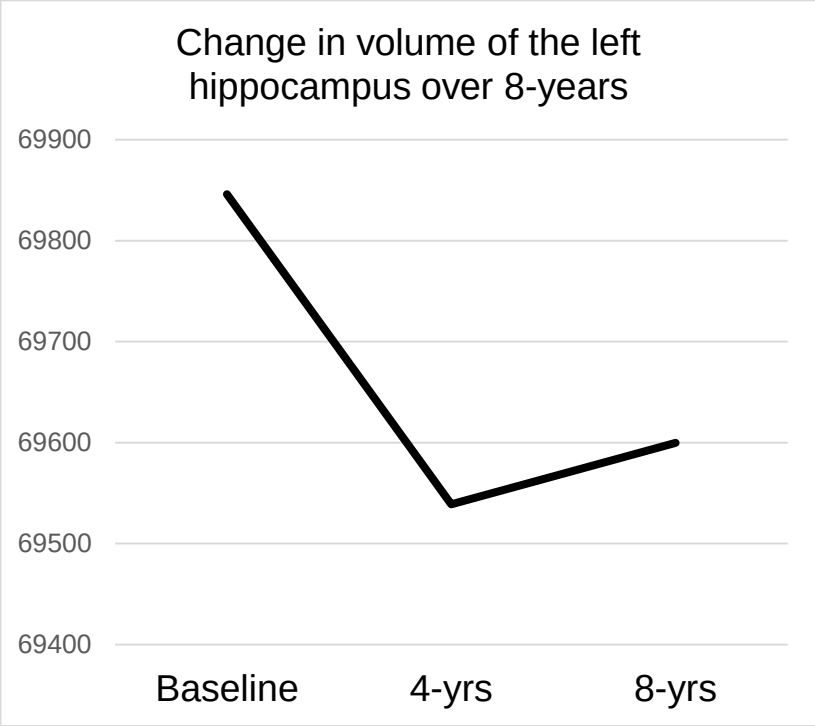
# Hippocampus associations

## Unadjusted associations among variables at Wave 2

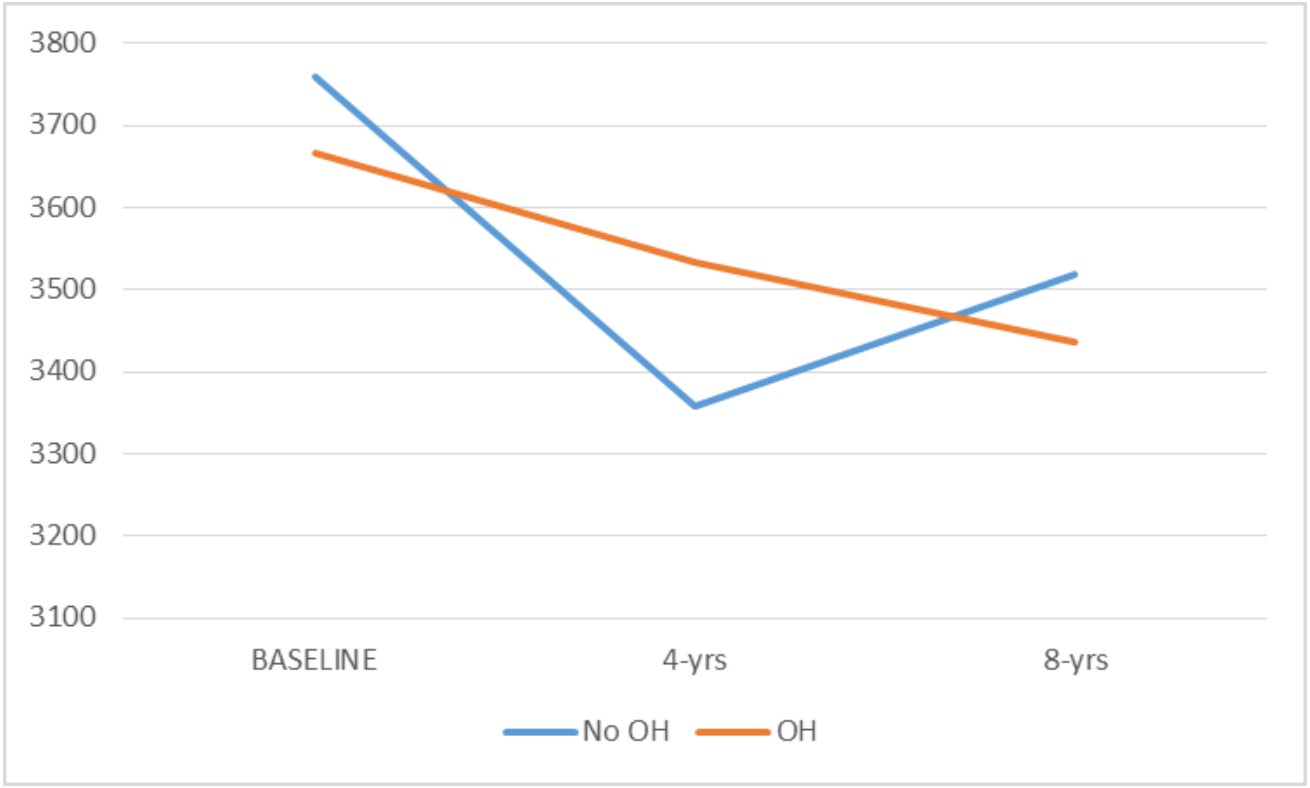
| | WBV | OH | Gender | Educ | Dep | Smoke | Hypert |
|---|---|---|---|---|---|---|---|
| L HC | .362** | .083 | -.239** | .139** | .022 | -.019 | .015 |
| R HC | .387** | .072 | -.309** | .151** | .036 | .000 | -.001 |

Hippocampal volumes not associated with OH or depressive symptoms in cross-sectional adjusted analyses

# Estimated change in HC volumes (linear mixed models) unadjusted

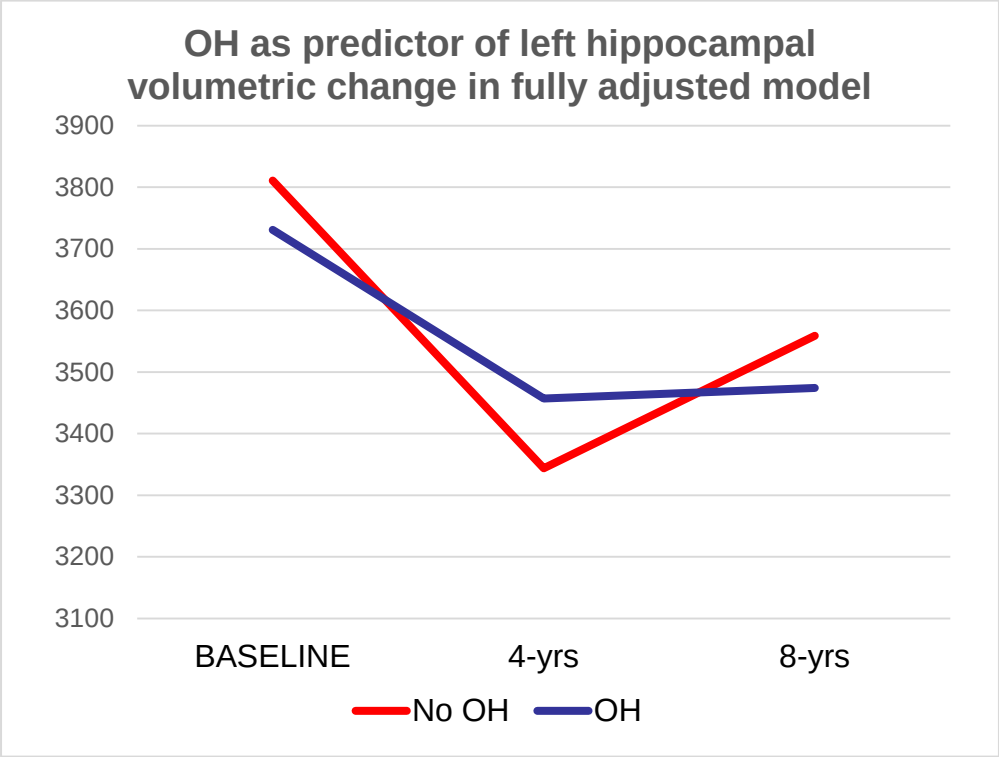


# OH predicting Left Hippocampal volume change over 8 years




OH x time, p = =.013; OH x time_sq, p =.012 . Non-OH group show no HC atrophy. Note adjusted for age, sex, education, smoking, diabetes, depression wave 1

# Fully adjusted analyses of OH predicting HC volume change




- **Time varying depressive symptoms fully attenuated the effect of OH on left hippocampal atrophy**

Covariates: Age, sex, years of education, alcohol consumption, smoking history, apoe-4, diabetes, BP meds , and depression medication

# Hypotheses and results

- OH is associated with more WMH Yes
- OH associated with HC volume No
- OH associated with HC atrophy Yes, in unadjusted analyses, and with covariates but not when time-varying depression included in model
- Depression is associated with more WMH Yes
- Depression associated with HC volume No
- Depression associated with HC atrophy Yes
- Effects of OH on HC atrophy are moderated by change in depressive symptoms over time

# Conclusion

- Both OH and depressive symptoms are vascular risk factors and are associated with WMH
- They also predicted HC atrophy (left only) where the effect of OH was explained by change in depressive symptoms
- Better measures needed to fully evaluated to better understand the independent versus interactive effects of these risk factors

# Strengths and limitations

- Longitudinal, normative neuroimaging data, controlled for many covariates, automated WMH data, narrow age-cohort design.
- Limitation of self-report of OH, – difficult for epidemiology to obtain objective measures.
- More waves of data would provide more reliable estimates of growth curves.
- Lack of clinical diagnosis of depression.

# General discussion

- General lack of epidemiological data on OH, yet increasing awareness that *variability* in blood pressure influences brain ageing and accumulation of neuropathology
- Strong reasons from cardiovascular literature and depression literature, to investigate OH and low blood pressure, as well as high blood pressure
- Predictors of change may differ from associations observed in cross-sectional studies
- Depression an important cardiovascular risk factor – complex nexus among depression, OH, cardiovascular disease and brain ageing

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