Modifiable dementia risk factor associations with ATN biomarkers: Findings from the European Prevention of Alzheimer's Dementia study

Eddy Roccati[1], Aidan Bindoff[1], Jessica Collins[1], Joshua Eastgate[1], Jay Borchard[1], Jane Alty[1,2], Anna King[1], James Vickers[1], Margherita Carboni[3], Chad Logan[4], EPAD Consortium[5] | eddy.roccati@utas.edu.au | @eddy_roccati | utas.edu.au/wicking

1: Wicking Dementia Research and Education Centre, University of Tasmania 2: Royal Hobart Hospital, Hobart, Tasmania, Australia 3: Roche Diagnostics International Ltd, Rotkreuz, Zug, Switzerland 4: Roche Diagnostics GmbH, Penzberg, Germany 5: Radiology and Nuclear Medicine, Universiteit Amsterdam, Netherlands

1. Background

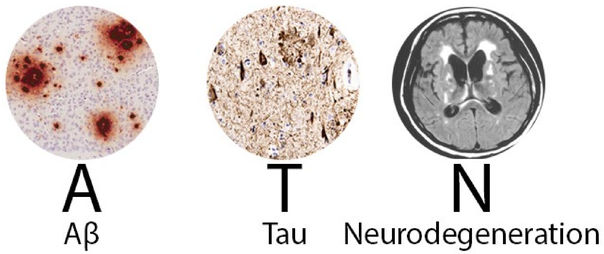

Figure 1: AT(N) criteria, defining a biological continuum for AD

- We now have a discrete AT(N) profile for Alzheimer's disease hallmark biomarkers: amyloid β (A), p-tau (T) and neurodegeneration (N)[1]
- There is also strong evidence that targeting modifiable risk factors can maintain and improve cognitive function, as well as reducing risk for Alzheimer's disease (AD) and other forms of dementia[2]
- Despite evidence of a biologically defined AD continuum and modifiable risk amelioration, there is a paucity of studies investigating modifiable risk factors with respect to AT(N) biomarkers
- The aim of this study was to investigate how modifiable risk factors relate to the three hallmark AT(N) biomarkers of AD

2. Methods

- Participants were drawn from the European Prevention of Alzheimer's Dementia (EPAD): a prospective, multicentre, pan-European cohort study[3]
- Eligible participants underwent clinical and neurological assessments, brain magnetic resonance imaging, cerebrospinal fluid (CSF) collection, neuropsychological assessment and completed a variety of demographic, clinical, medical history and lifestyle surveys for 10 binary modifiable risk variables
- Data were analysed via the NeuroToolKit Application (NTKApp, BetaVersion, 2022) via the AD Workbench (ADDI)
- Generalized additive models with penalized regression splines were used to model the associations between modifiable risk factor adherence and AT(N) biological criterion: A (CSF amyloid-β 42 [Aβ42 pg/mL]); T (CSF phosphorylated-tau 181 [p-tau 181 pg/mL]); N (total hippocampal volume [mm^3])

3. Results I

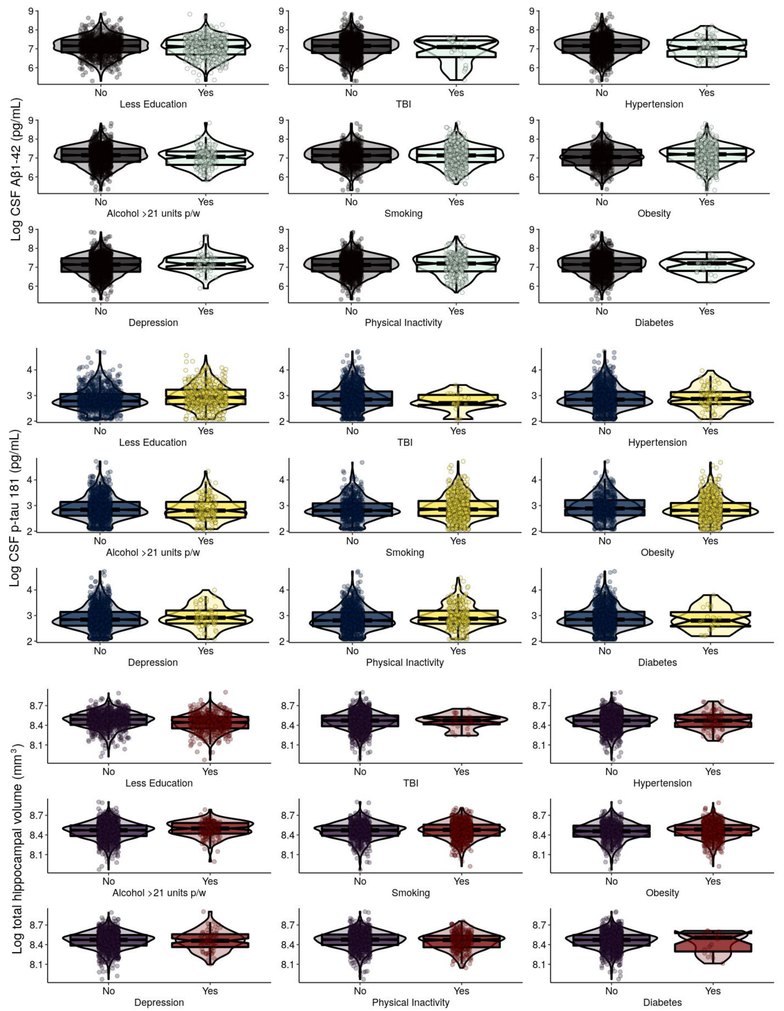

Figure 2: Levels of log transformed CSF Aβ1-42 (pg/mL), CSF p-tau 181 (pg/mL) and total hippocampal volume (mm3) of EPAD participants grouped by adherence to modifiable risk factors

4. Results II

		Female	Male	Total	p-value
N (%)		821 (56%)	653 (44%)	1474	
Age at baseline in years (SD)		65.5 (7.2)	66.7 (7.4)	66.0 (7.3)	<0.001
Education in years (SD)		14.1 (3.7)	14.7 (3.8)	14.4 (3.7)	0.004
MMSE (SD)		28.4 (1.9)	28.4 (2)	28.4 (1.9)	0.809
APOE ε4 genotype					0.211
	e2e2	2 (0.3%)	2 (0.3%)	4 (0.3%)	
	e2e3	60 (7.8%)	57 (9.6%)	117 (8.6%)	
	e3e3	410 (53.2%)	304 (51.1%)	714 (52.3%)	
	e2e4	18 (2.3%)	17 (2.9%)	35 (2.6%)	
	e3e4	249 (32.3%)	186 (31.3%)	435 (31.9%)	
	e4e4	31 (4%)	29 (4.9%)	60 (4.4%)	
A: CSF Aβ1-42 pg/mL (SD)		1427.7 (798.9)	1325.8 (669.7)	1382.6 (745.9)	0.016
T: CSF p-tau 181 pg/mL (SD)		20.0 (11.1)	20.0 (11)	20.0 (11.1)	0.977
N: THV mm^3 (SD)		4591 (767.3)	4896.2 (823.9)	4724.8 (806.8)	

Table 1: Demographic statistics for included EPAD participants (n = 821)

- The most commonly reported risk factors were obesity (59.3%), smoking (53.9%), less education (34.4%), physical inactivity (21.5%) and alcohol consumption (12.4%)
- A total of 338 (22.9%) participants reported adhering to zero risk factors, 340 (23.1%) reported one, 440 (29.9%) reported two, 272 (18.5%) reported three, 79 (5.4%) reported four and 5 (0.3%) reported five
  - **A :** TBI significantly associated with increased CSF Aβ1-42 (pg/mL)
  - **T :** BMI significantly positively associated with CSF p-tau 181 (pg/mL)
  - **N :** Education and BMI both significantly associated with THV (mm^3)

4. Conclusions

- Modifiable risk factors of less education, less exercise, TBI and higher BMI were all significantly associated with increased AD biomarker burden
- Our results support previous studies identifying associations between modifiable risk factors and AD
- This suggests early intervention strategies focused on education and lifestyle factors and improvements in prevention and treatment of TBI may modify risk profiles associated with cognitive decline.

References

1: Jack Jr CR, Bennett DA, Blennow K, et al. Nia-aa research framework: Toward a biological definition of Alzheimer's disease. Alzheimer's & Dementia. 2018;14(4):535-562. 2: Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the lancet commission. The Lancet. 3: Solomon A, Kivipelto M, Molinuevo JL, Tom B, Ritchie CW. European prevention of Alzheimer's dementia longitudinal cohort study (epad lcs): Study protocol.

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- MC is a full-time employee of Roche Diagnostics International Ltd, Rotkreuz, Switzerland and holds shares in F. Hoffman-La Roche. CL is a full-time employee of Roche Diagnostics GmbH, Penzberg, Germany. ELECSYS is a trademark of Roche. All other authors declare they have no competing interests.