

Hypertension and White Matter Damage Worsen Cognition in Presymptomatic Genetic Frontotemporal Dementia: A GENFI Study

Nol Swaddiwudhipong^{1,2}, P Simon Jones¹, Arabella Bouzigues³, Lucy L. Russell³, Phoebe H. Foster³, Eve Ferry-Bolder³, John C. van Swieten⁴, Lize Jiskoot⁴, Harro Seelaar⁴, Raquel Sánchez-Valle⁵, Robert Laforce^{6,7}, Caroline Graff^{8,9}, Daniela Galimberti^{10,11}, Rik Vandenberghe^{12,13}, Alexandre de Mendonça¹⁴, Giuseppe di Fede¹⁵, Isabel Santana¹⁶, Alexander Gerhard^{17,18}, Johannes Levin^{19,20}, Benedetta Nacmias²¹, Markus Otto²², Maxime Bertoux²³, Thibaud Lebouvier²⁴, Simon Ducharme^{25,26}, Chris R. Butler^{27,28}, Isabelle Le Ber^{29,30}, Elizabeth Finger³¹, Maria Carmela Tartaglia³², Mario Masellis³³, Matthis Synofzik^{34,35}, Fermin Moreno^{36,37}, Barbara Borroni³⁸, Jonathan D Rohrer³, James Rowe^{1,2}, and Kamen Tsvetanov¹ for The Genetic Frontotemporal dementia Initiative (GENFI)

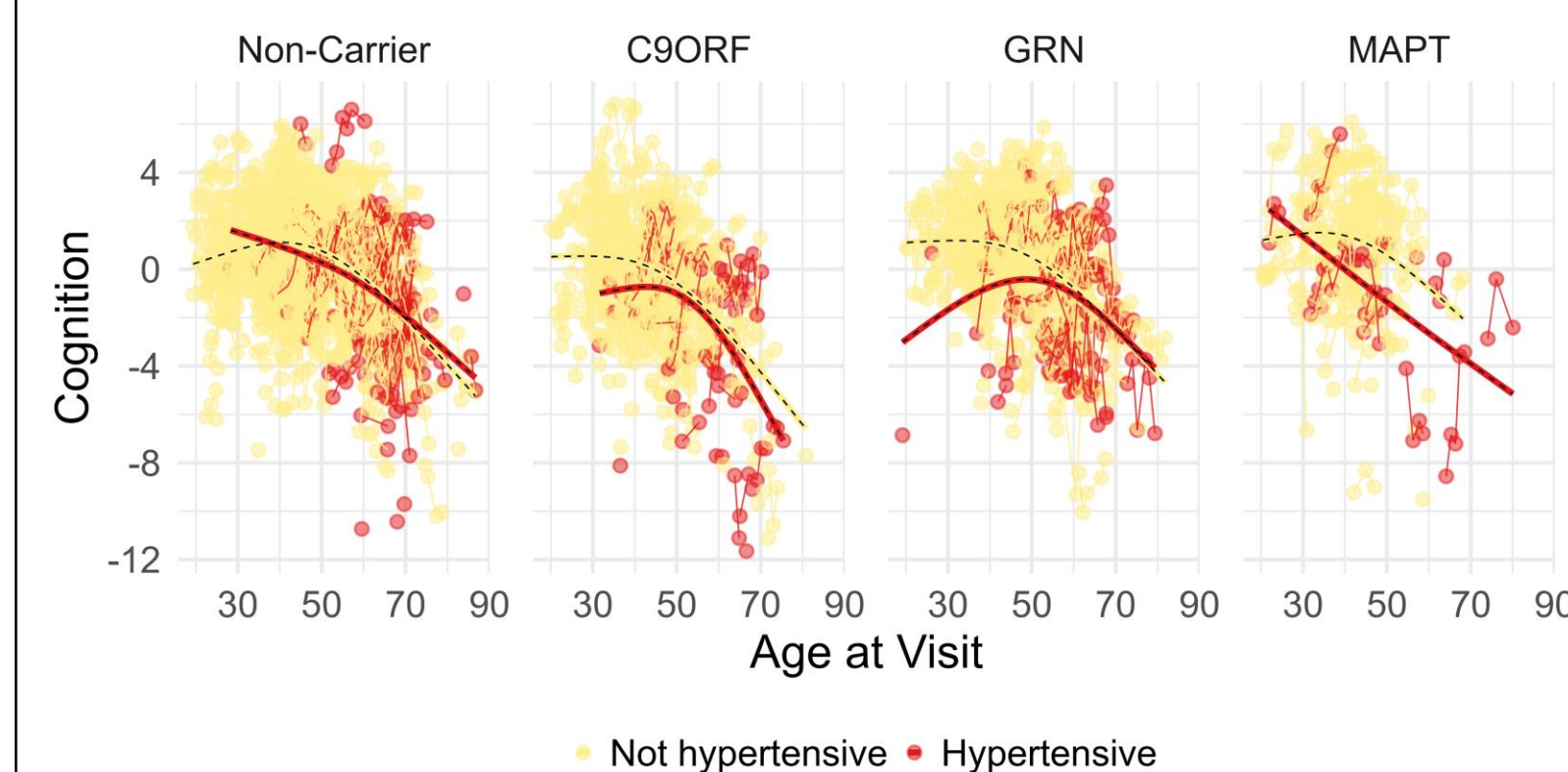
¹Department of Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom, ²Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom, ³Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, United Kingdom, ⁴Department of Neurology, Erasmus Medical Centre, Rotterdam, Netherlands, ⁵Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Spain, ⁶Clinique Interdisciplinaire de Mémoire, Département des Sciences Neurologiques, CHU de Québec, Québec, QC, Canada, ⁷Faculté de Médecine, Université Laval, Québec, QC, Canada, ⁸Department of Neurobiology, Karolinska Institutet, Solna, Sweden, ⁹Unit for Hereditary Dementias, Theme Inflammation and Aging, Karolinska University Hospital, Solna, Sweden, ¹⁰Fondazione Ca' Granda, IRCCS Ospedale Policlinico, Milan, Italy, ¹¹University of Milan, Centro Dino Ferrari, Milan, Italy, ¹²Laboratory for Cognitive Neurology, Department of Neurosciences, Leuven Brain Institute, KU Leuven, Leuven, Belgium, ¹³Neurology Service, University Hospitals Leuven, Leuven, Belgium, ¹⁴Faculty of Medicine, University of Lisbon, Lisbon, Portugal, ¹⁵Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ¹⁶University Hospital of Coimbra (HUC), Neurology Service, Faculty of Medicine, University of Coimbra, Coimbra, Portugal, ¹⁷Division of Neuroscience and Experimental Psychology, Wolfson Molecular Imaging Centre, University of Manchester, Manchester, United Kingdom, ¹⁸Departments of Geriatric Medicine and Nuclear Medicine, University of Duisburg-Essen, Essen, Germany, ¹⁹Department of Neurology, Ludwig-Maximilians Universität München, Munich, Germany, ²⁰German Center for Neurodegenerative Diseases (DZNE), Munich Cluster of Systems Neurology (SyNergy), Munich, Germany, ²¹Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy, ²²Department of Neurology, University of Ulm, Ulm, Germany, ²³Inserm 1172; CHU, CNR-MAJ, Labex Distalz, LiCEND, Lille, France, ²⁴Univ Lille; Inserm 1172; CHU, CNR-MAJ, Labex Distalz, LiCEND, Lille, France, ²⁵Department of Psychiatry, McGill University Health Centre, McGill University, Quebec, QC, Canada, ²⁶McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Quebec, QC, Canada, ²⁷Nuffield Department of Clinical Neurosciences, Medical Sciences Division, University of Oxford, Oxford, United Kingdom, ²⁸Department of Brain Sciences, Imperial College London, London, United Kingdom, ²⁹Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP – Hôpital Pitié-Salpêtrière, Paris, France, ³⁰Centre de référence des démences rares ou précoces, IM2A, Département de Neurologie, AP-HP – Hôpital Pitié-Salpêtrière, Paris, France, ³¹Department of Clinical Neurological Sciences, University of Western Ontario, London, ON, Canada, ³²Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, ON, Canada, ³³Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, University of Toronto, Toronto, ON, Canada, ³⁴Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research and Center of, University of Tübingen, Tübingen, Germany, ³⁵Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany, ³⁶Cognitive Disorders Unit, Department of Neurology, Donostia University Hospital, San Sebastian, Spain, ³⁷Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Spain, ³⁸Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy.

Summary Our study suggests that hypertension and white matter damage contribute to cognitive impairment in presymptomatic genetic frontotemporal dementia. This highlights hypertension as a potential modifiable risk factor and points to PSMD as a candidate biomarker of vascular contributions to cognitive vulnerability.

Introduction

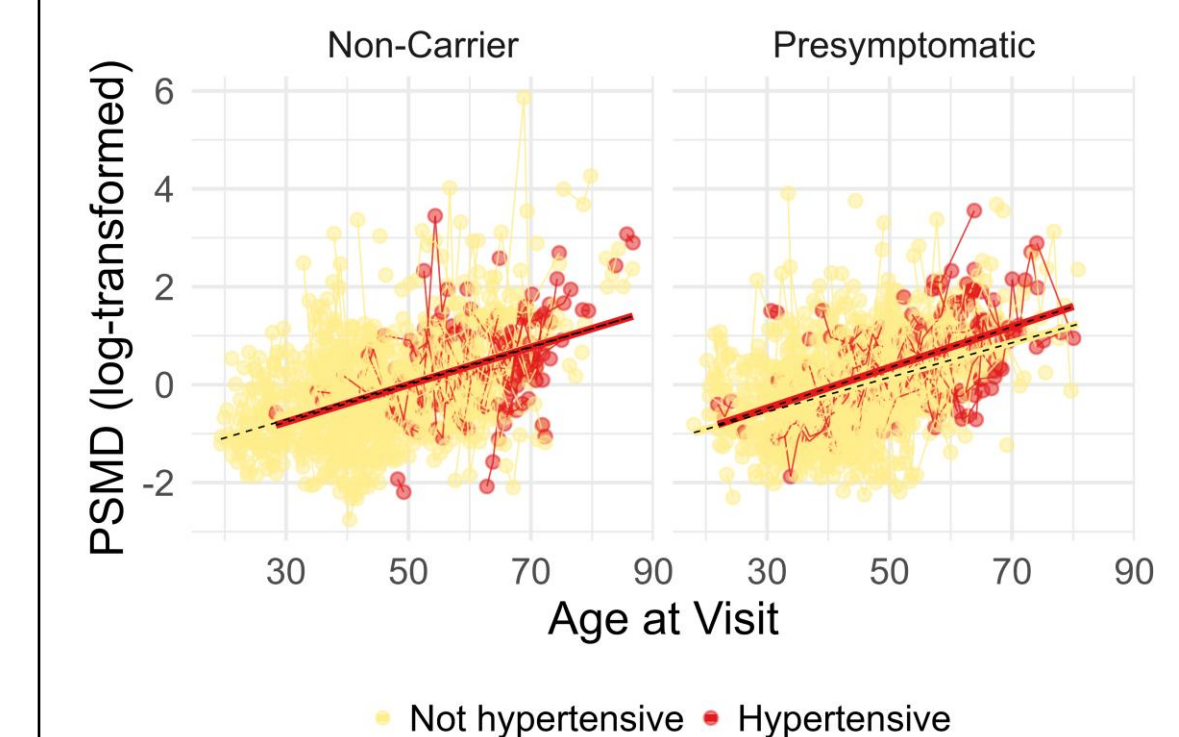
- The Genetic Frontotemporal Dementia Initiative (GENFI) includes families with autosomal-dominant frontotemporal dementia (FTD) mutations (*C9orf72*, *GRN*, and *MAPT*), enabling the study of presymptomatic carriers and within-family comparison with non-carriers.
- Hypertension affects white-matter integrity (1) and increases dementia risk (2), but its role in presymptomatic FTD is unclear.
- Studying this may reveal early modifiable vascular risk factors for disease progression.

Hypertension exacerbates cognitive impairment in presymptomatic carriers



The interaction between baseline hypertension and carrier status was associated with poorer cognition in the overall carrier cohort ($p = 0.02$) and the *C9orf72* subgroup ($p = 0.02$).

Hypertension correlates with increased white matter damage in presymptomatic carriers

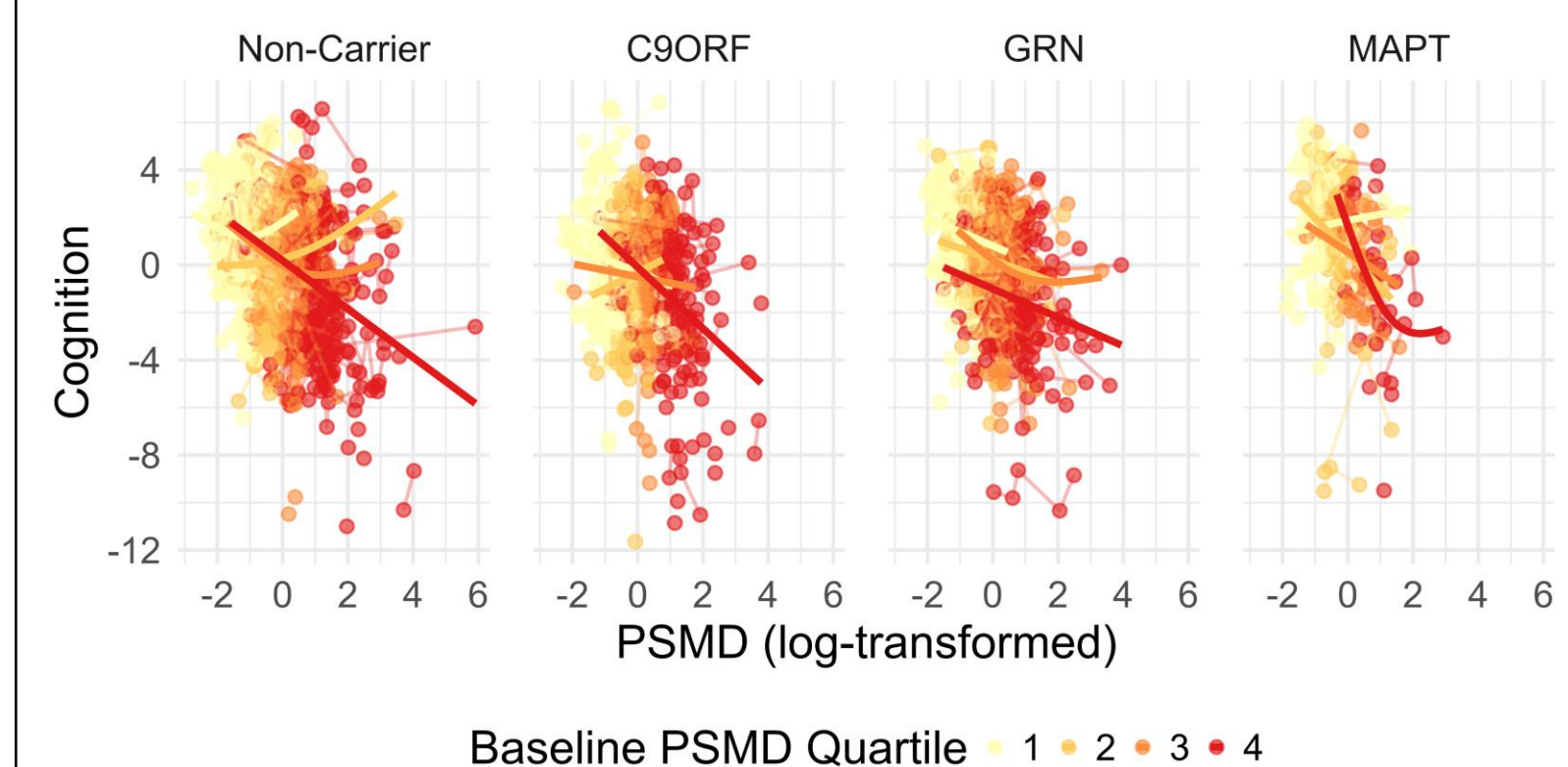


The interaction between baseline hypertension and carrier status was associated with higher PSMD in presymptomatic gene carriers ($p=0.02$).

Methods

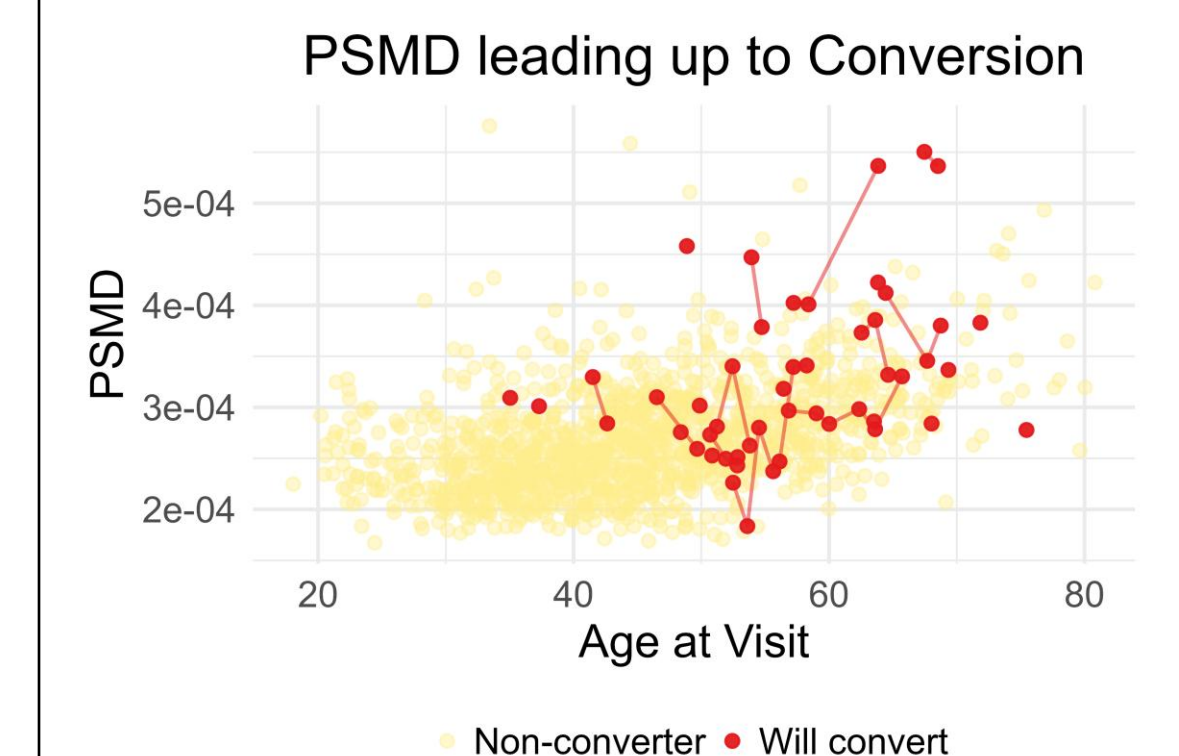
- Cognitive function was summarised using the single principal component ("Cognition") from 18 cognitive tests.
- Diffuse microstructural damage was quantified using Peak Width of Skeletonised Mean Diffusivity (PSMD), calculated as the difference between the 95th and 5th percentiles of mean diffusivity values within the white-matter skeleton, following a previously described automated tool (3).
- Regression models tested associations between Cognition, white matter integrity and genetic status across FTD genes.

Global white matter damage is associated with cognitive decline in presymptomatic carriers



Interactions between *baseline PSMD × time from baseline × GRN carrier status* ($p=0.02$) and *longitudinal PSMD change × MAPT carrier status* ($p<0.001$) were associated with greater longitudinal cognitive decline.

Higher PSMD is associated with an increased hazard of conversion to symptomatic dementia



Using a Cox proportional hazards model adjusted for age, higher PSMD predicted an increased hazard of conversion to symptomatic dementia ($p = 0.04$).

References

- de Leeuw F-E, de Groot JC, Oudkerk M, Witteman JCM, Hofman A, van Gijn J, et al. Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain*. 2002 Apr 1;125(4):765–72.
- Ou YN, Tan CC, Shen XN, Xu W, Hou XH, Dong Q, et al. Blood Pressure and Risks of Cognitive Impairment and Dementia. *Hypertension*. 2020 July;76(1):217–25.
- Baykara E, Gesierich B, Adam R, Tuladhar AM, Biesbroek JM, Koek HL, et al. A Novel Imaging Marker for Small Vessel Disease Based on Skeletonization of White Matter Tracts and Diffusion Histograms. *Ann Neurol*. 2016;80(4):581–92.

