



Gut Bacterial Metabolite Imidazole Propionate Exacerbates Alzheimer's Disease Pathology

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Alzheimer's disease and related dementias (ADRD) are a global burden:

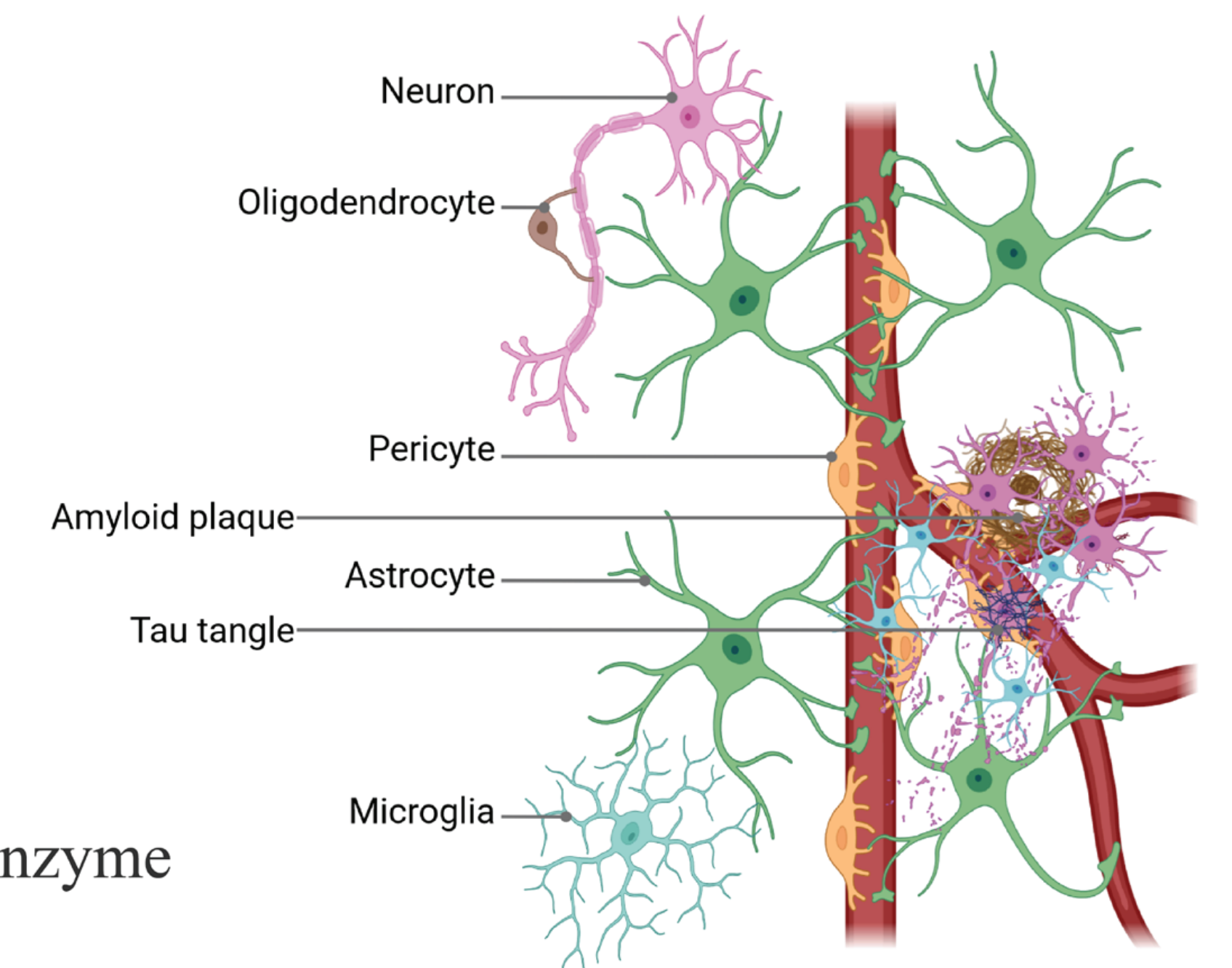
- AD is a debilitating, progressive neurocognitive decline characterized by **amyloid- β depositions**, **tau tangles** and **neuroinflammation**
- Globally there are **55-57 Million individuals** living with dementia in 2026
- There are 10 Million new cases each year, averaging to **1 dementia diagnosis every 3.2 seconds**
- Currently there is **no known cure** or effective prophylaxis for AD

Imidazole propionate (ImP) is associated with negative health outcomes

- Untargeted metabolomic studies reveal strong associations between ImP and ADRD comorbidities and all cause **mortality**
- Circulating ImP levels in plasma range between **0nM to 2000nM in humans** worldwide, **>50nM** is often associated with metabolic diseases such as **cardiovascular disease**, **type 2 diabetes**, **metabolic dysfunction-associated steatohepatitis** etc.

ImP a **bacterially produced** metabolite

- Dietary **Histidine** is transformed by the liver and some gut bacteria into **Urocanate**, which is then converted to ImP by the bacterial enzyme Urocanate reductase (UrdA, EC:1.3.99.33)
- Several gut bacteria such as *eggerthella lenta*, *Sutterella wadsworthensis*, *Holdemania filiformis* etc. express UrdA



Plasma ImP levels are associated with Age and Cognitive decline

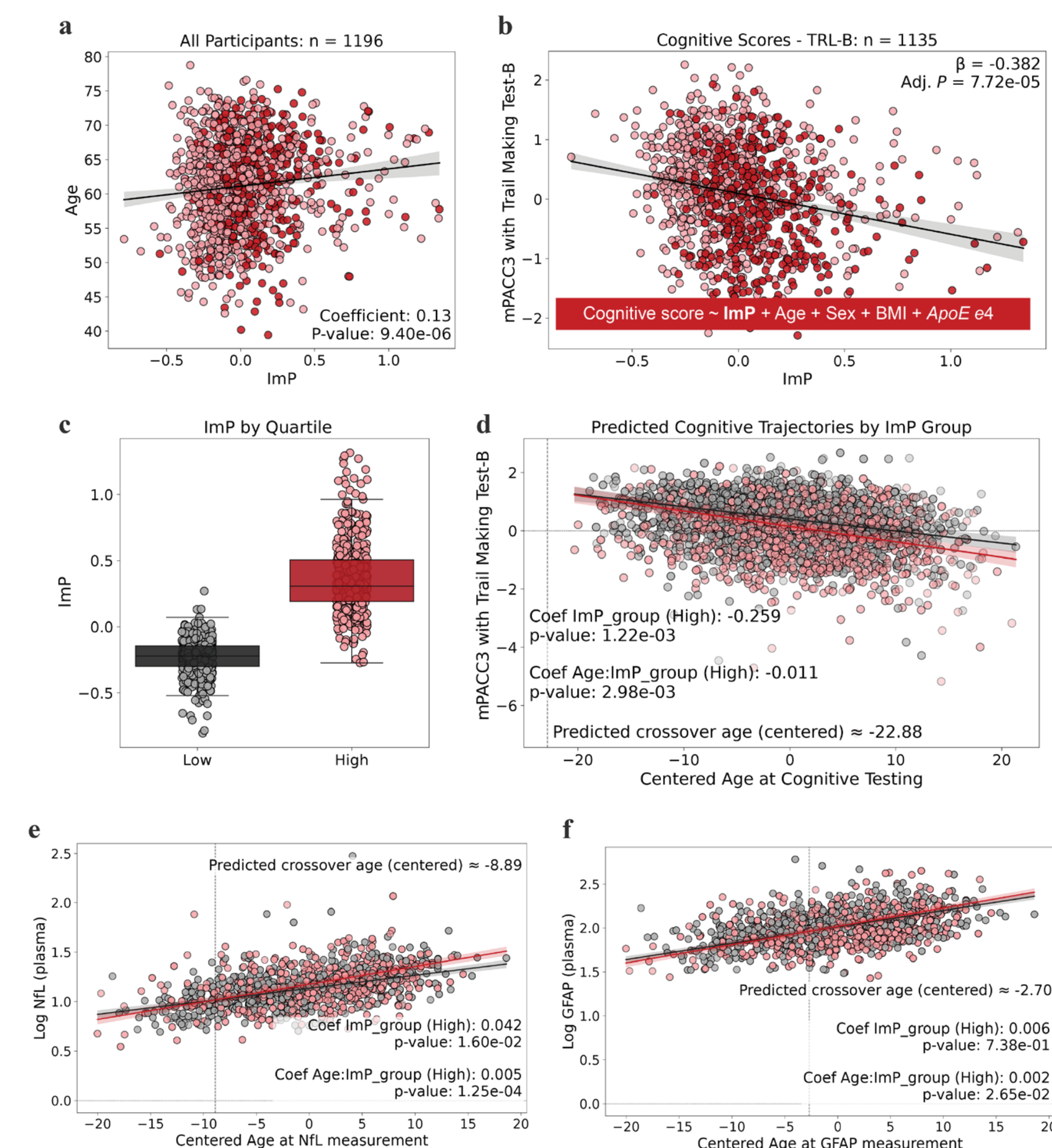


Figure 1. ImP is associated with age and cognitive decline. **a**, Plasma ImP is associated with Age. **b**, Plasma ImP is cross-sectionally associated with cognitive scores. **c**, Distributions of Low (<25%) and High (>75%) quartiles of participants by ImP levels. **d**, High ImP participants experience a steeper cognitive decline ≈ 22.88 years earlier than Low ImP individuals. **e**, High ImP levels predict steeper increase in neurodegeneration marker NFL ≈ 8.89 years earlier than Low ImP participants. **f**, High ImP levels predict a moderate increase in reactive astroglial marker GFAP ≈ 2.7 years earlier than low ImP counterparts.

Putative ImP producing bacteria are associated with cognitive decline

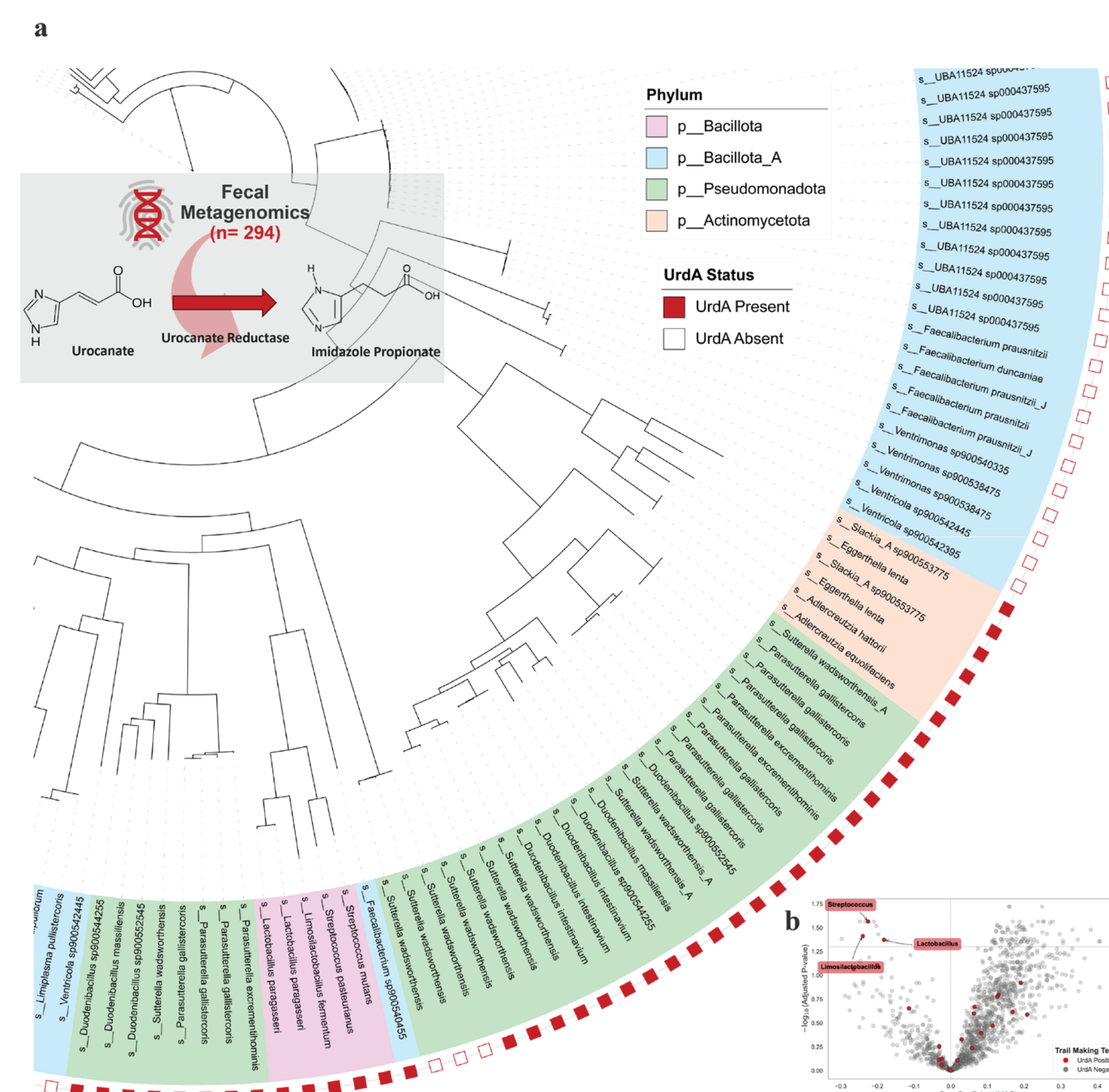


Figure 2. Fecal metagenomics identified putative ImP producers to be associated with cognitive decline. **a**, Shotgun metagenomic sequencing identified ≈ 50 bacteria that encode UrdA in their genomes, from the Wisconsin ADRC's MARS cohort. **b**, Abundances of 3 ImP producing bacterial taxa are negatively associated with cognitive scores.

Takeaway 2: Metagenomic sequencing revealed multiple putative ImP producers that are negatively associated with cognitive scores. However, causality needs to be explored...

ImP can cross the Blood-brain barrier and exacerbate AD histopathology in mice

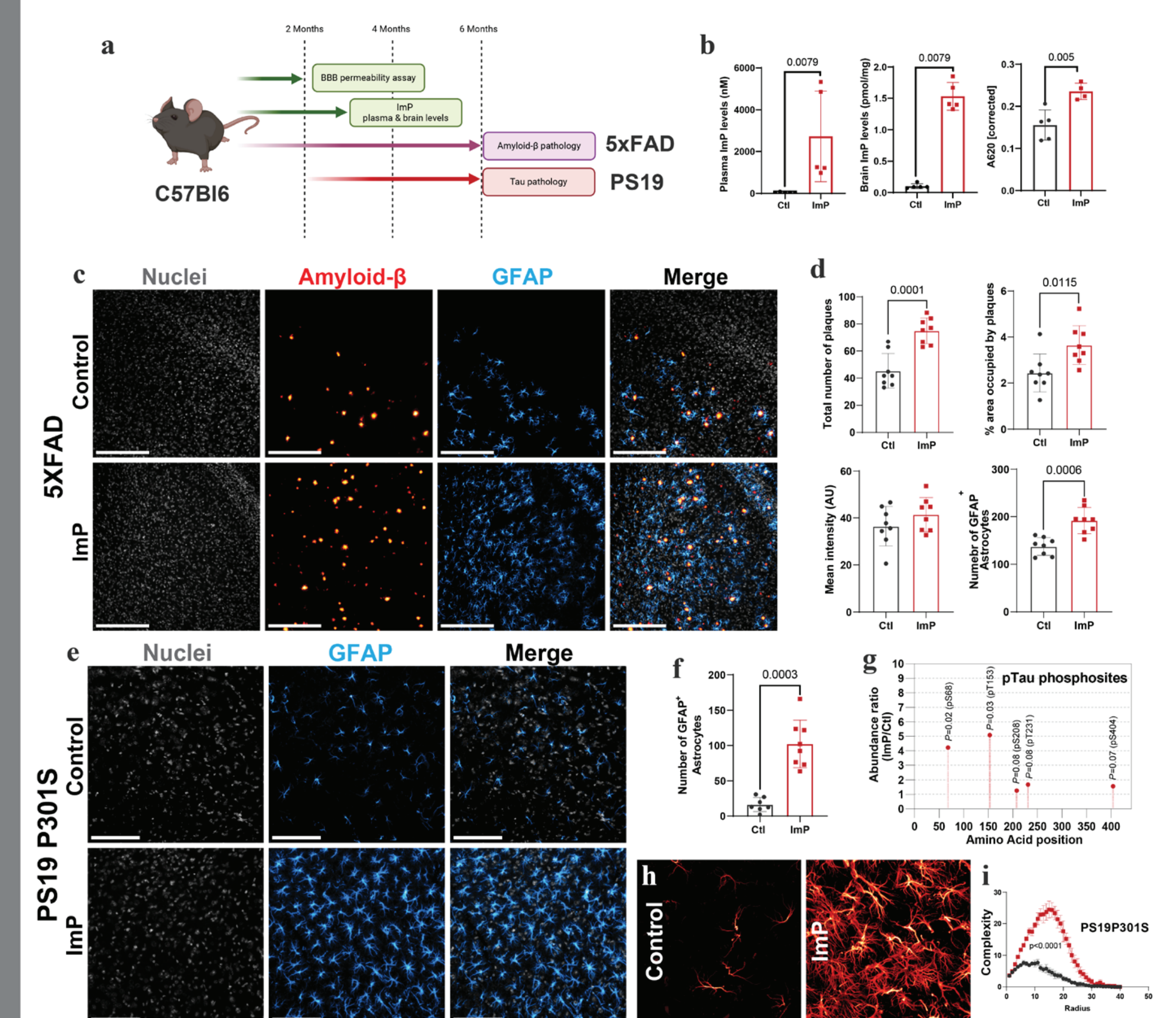


Figure 3. Chronic ImP exposure exacerbates ADRD histopathology. **a**, Study design. **b**, ImP treatment increases plasma ImP, which can then penetrate the BBB. **c, d**, 5xFAD mice exposed to ImP show increased amyloid plaques and GFAP⁺ astrocytes. **e, f, g, h** and **i**, PS19P301S mice exposed to ImP show increased reactive gliosis and Tau hyperphosphorylation.

Takeaway 3: Controlling for chronic ImP exposure in pre-clinical animal models of ADRD identified a causal role of ImP in worsened neuropathology.

Acknowledgements



Takeaway 1: ImP is associated to ADRD phenotypes cross-sectionally and longitudinally.