

Population-Based Continuous Reference Curves for Plasma p-tau-217, BD-Tau, and Novel Biomarker Ratios



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Background

Biomarkers to detect the pathological hallmarks of Alzheimer's disease (AD) include:

- Amyloid-associated tau phosphorylation preceding neurofibrillary tangle formation

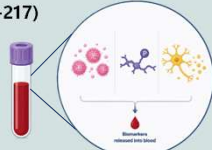
Biomarker: Phosphorylated tau 217 (p-tau-217)

- Neuronal injury and neurodegeneration

Biomarker: Brain Derived Tau (BD-Tau)

- Amyloid Beta plaque formation

Biomarker: Amyloid Beta 42 (Aβ42)



This study aims to create valid reference curves for standardized interpretation of p-tau-217, BD-Tau, and ratios for p-tau-217/BD-Tau and p-tau-217/Aβ42.

Methods

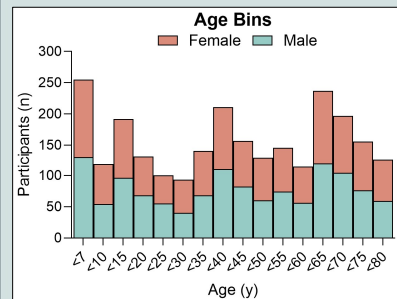


Figure 1. Distribution of CHMS participants by age and sex. n=2500 participants from Cycle 5 collected in 2016/2017. The sex distribution of participants was equal, with n=1,250 (50%) males and females.

- 2500 samples were analyzed from the Canadian Health Measures Survey (CHMS) Biobank to create reference curves
- CHMS = National epidemiological study that gathers information on health of Canadians ages 3 to 79 years old¹
- Analysis performed on Quanterix Simoa HD-X analyzer using ALZpath p-tau-217 Advantage Plus, BD-Tau Advantage Plus, and Neurology 4-plex E assays
- Continuous reference curves are created using generalized additive models for location, scale, and shape (GAMLSS) to define age-specific percentiles²

Conclusions

- Significant age partitions were discovered for all markers
- Significant sex differences were observed for all markers except for the p-tau-217/BD-Tau ratio

Age-specific reference curves will provide an important foundation for interpreting plasma biomarkers of AD and support their integration into future neurodegeneration research and clinical studies.

Continuous Reference Curves

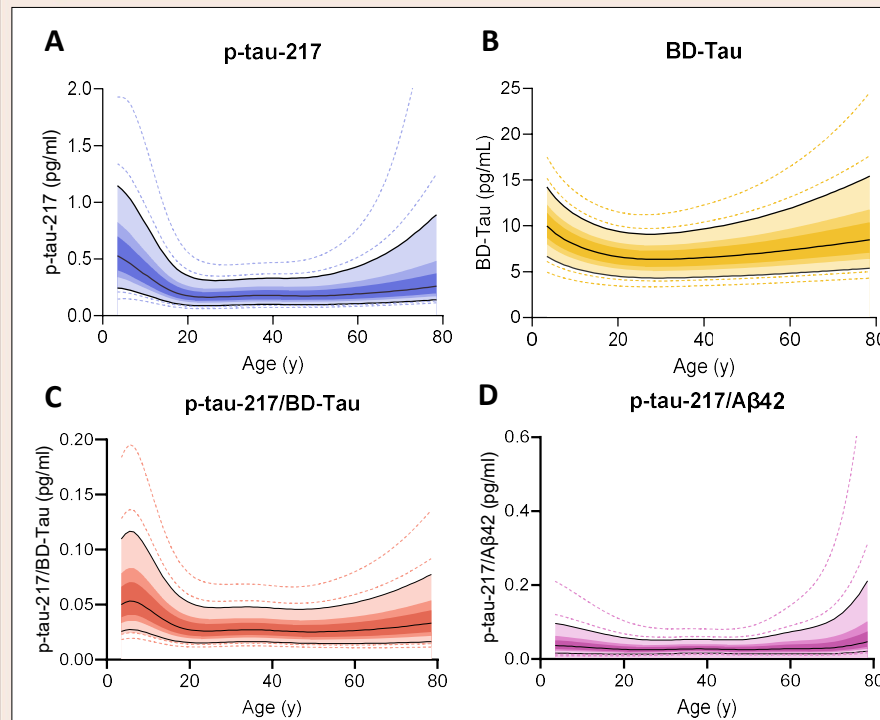


Figure 2. Continuous reference curves for plasma p-tau-217 (A), BD-Tau (B), p-tau-217/BD-Tau (C), and p-tau-217/Aβ42 (D). Produced using n=2500 CHMS participants and GAMLSS regression to determine smoothed percentiles. Displayed percentiles include 1st (lowest dotted line), 3rd (second lowest dotted line), 5th (lowest solid line and first shaded gradation from bottom), 15th (second shaded gradation from bottom), 25th (third shaded gradation from bottom), 50th (central solid line), 75th (fourth shaded gradation from bottom), 85th (fifth shaded gradation from bottom), 95th (upper solid line and end of shaded gradations), 97th (second highest dotted line), and 99th (highest dotted line), with the shaded region indicating the reference interval from the 5th to the 95th percentile.

Sex-Specific Reference Intervals

- Sex effects were assessed in evenly distributed age bins for all biomarkers (3-19, 20-39, 40-59, and 60-79 years old) using the Harris and Boyd method³, followed by validation with simple linear regression
- p-tau-217 was associated with sex in age bins from 3 to 79 years
- BD-Tau was associated with sex in age bins from 3 to 59 years
- The p-tau-217/Aβ42 ratio was associated with sex in age bins from 20 to 39 years
- Apparent divergence in older adults (p-tau-217/Aβ42 ratio) may reflect increased variability at older ages and should be further explored

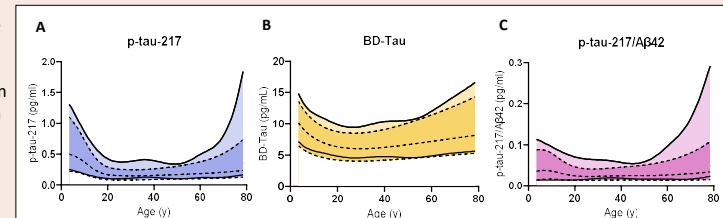


Figure 3. Sex specific continuous reference intervals for plasma p-tau-217 (A), BD-Tau (B), and p-tau-217/Aβ42 (C). Produced using n=2,050 CHMS participants and GAMLSS regression to determine smoothed percentiles. Females are displayed with dashed lines (n=1,009) and males are displayed with solid lines (n=1,041), the 5th, 50th, and 95th percentiles are displayed.

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References:
1. Muggeo V TF, Eilers P, Sciarra M, Attanasio M. Multiple smoothing parameters selection in additive regression quantiles. *Statistical Modelling*. 2020. 2. Halaschek-Wiener J, Tindale LC, Collins JA, et al. The Super-Seniors Study: Phenotypic characterization of a healthy 85+ population. *PLoS One*. 2018. 3. Harris EK, Boyd JC. On dividing reference data into subgroups to produce separate reference ranges. *Clinical Chemistry*. 1990.



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