VALEURS DE RÉFÉRENCE DES BIOMARQUEURS SANGUINS DES MALADIES NEURODÉGÉNÉRATIVES BASÉES SUR LA COHORTE CONSTANCES

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Disclosures

	No, Nothing to disclose
x	Yes, please specify

Company / Name	Honoraria / Expense	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity Position	Employee	Other (Please specify)
Beckman Coulter	X	X						
Biogen	X							
Siemens	X							
Fujirebio	X	X						
Johnson & Johnson		X						
Lilly	X	X						
Sysmex		X						
Roche Diagnostics		X						

Blood biomarkers of Alzheimer's disease

Revue neurologique

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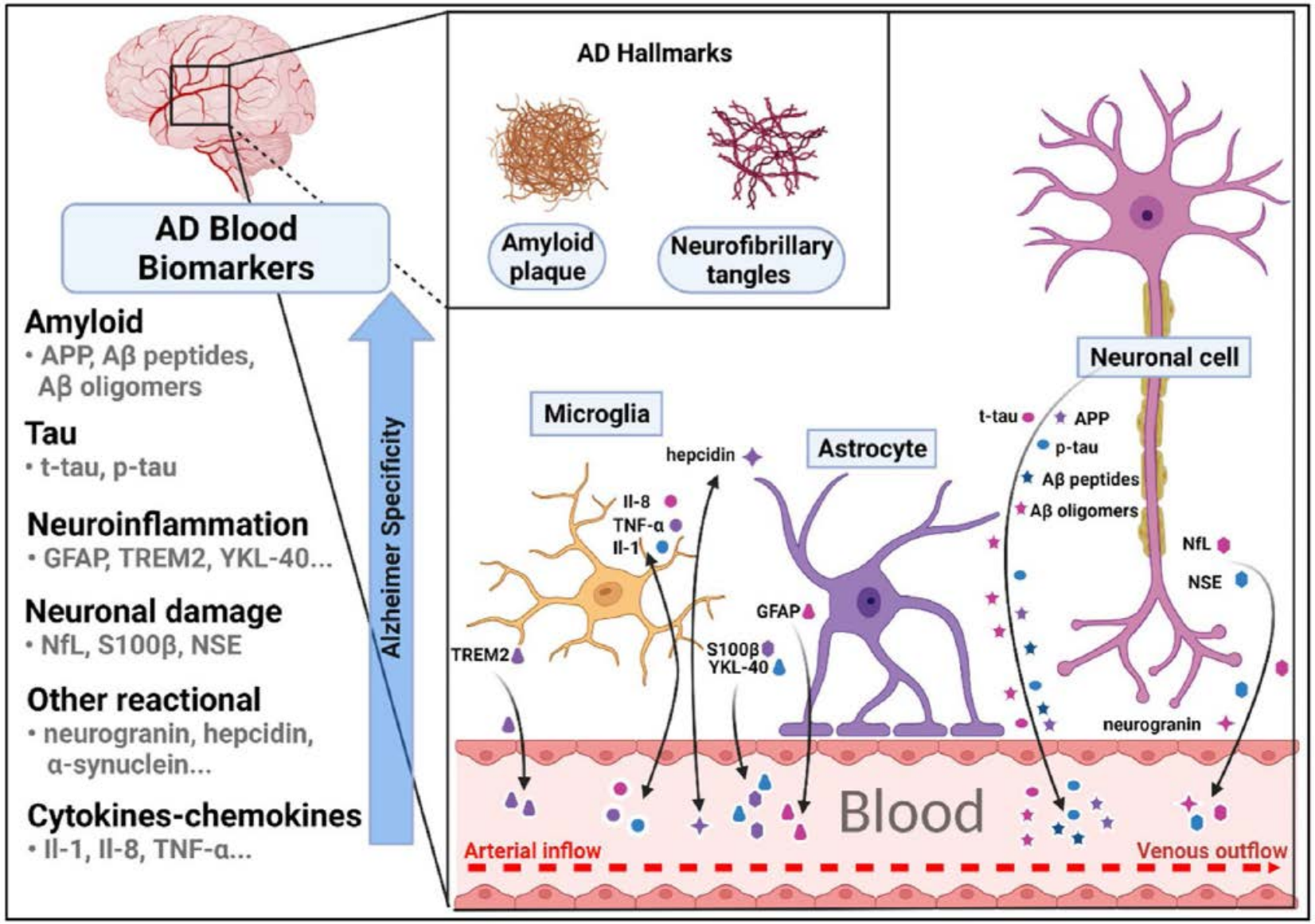
ELSEVIER

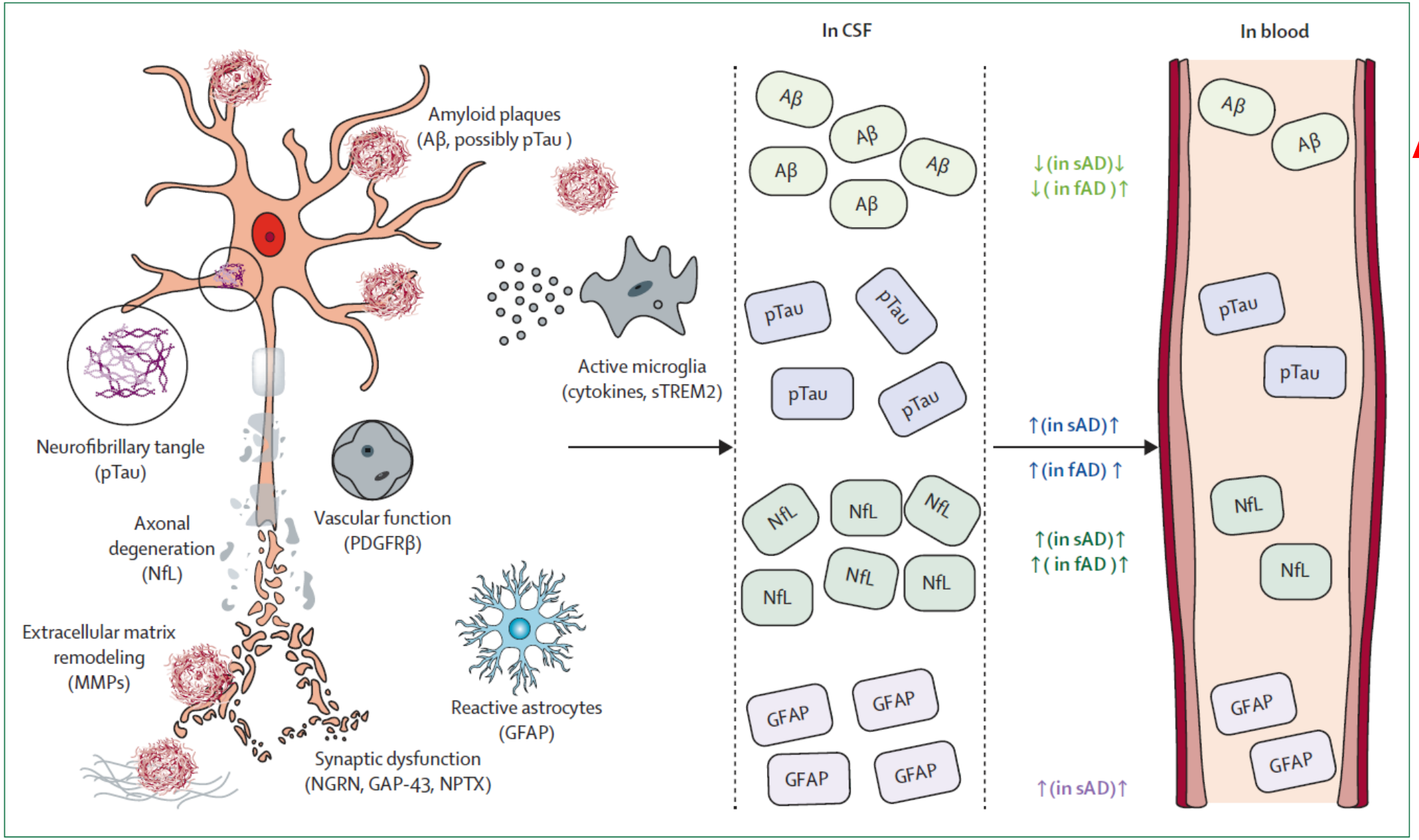
General review

Overview of the blood biomarkers in Alzheimer's disease: Promises and challenges

C. Delaby [a,b], C. Hirtz [a], S. Lehmann [a,*]



Blood biomarkers of Alzheimer's disease: clinical application



$A\beta_{42/40}$

pTau
181/217/231…

NfL

GFAP

Teunissen C *et al Lancet Neurol 2022*

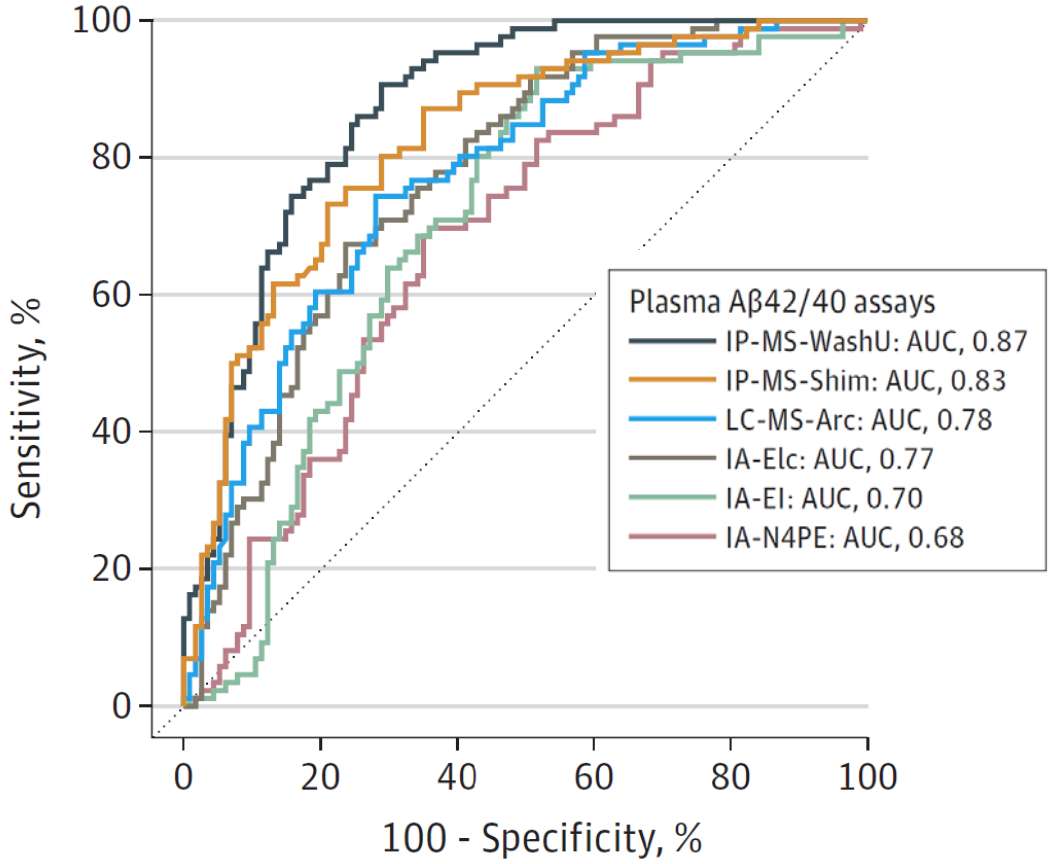
Blood amyloid and pTau biomarkers

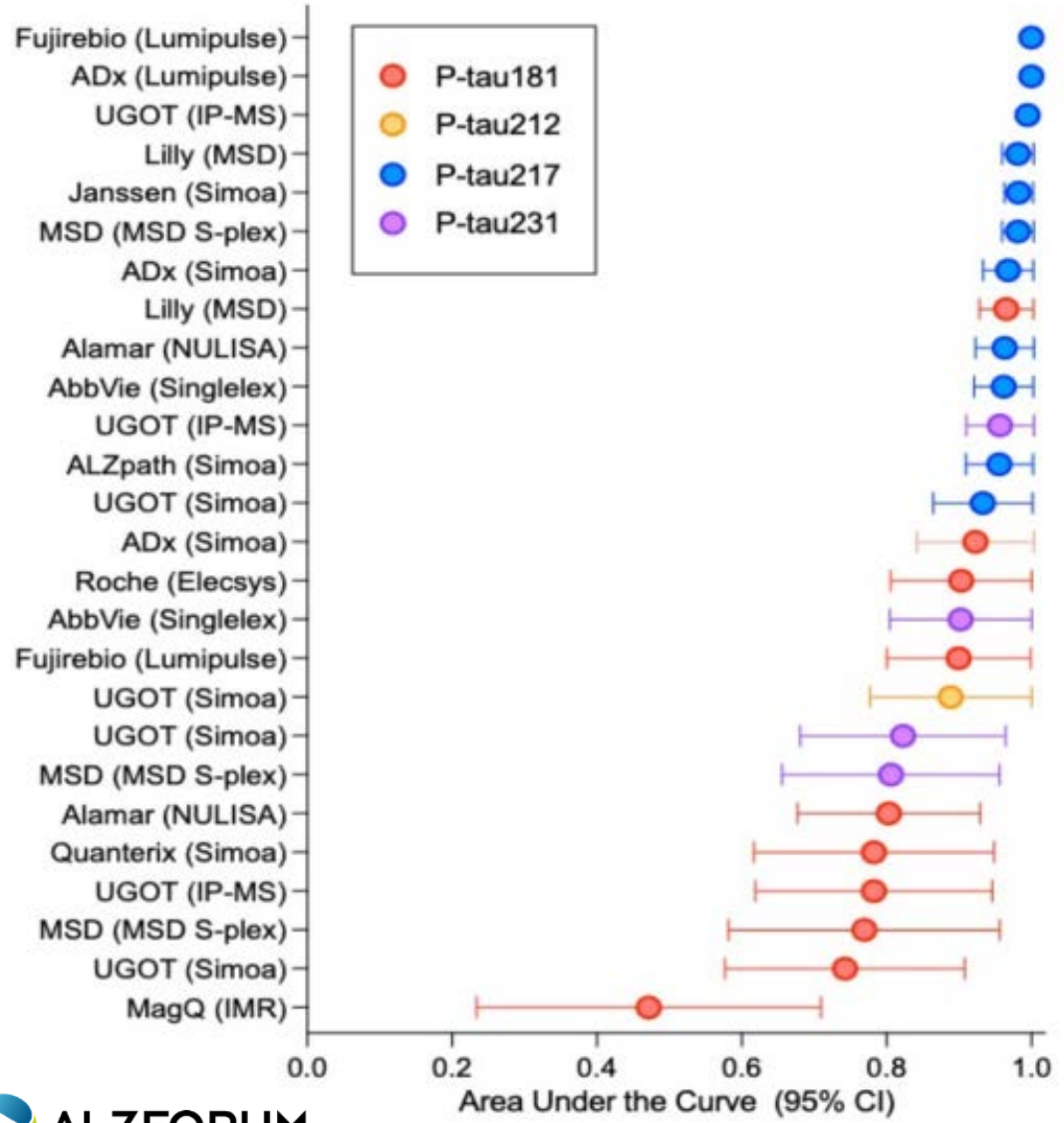
JAMA Neurology | Original Investigation

Head-to-Head Comparison of 8 Plasma Amyloid-β 42/40 Assays in Alzheimer Disease

Shorena Janelidze, PhD; Charlotte E. Teunissen, PhD; Henrik Zetterberg, MD, PhD; José Antonio Allué, PhD; Leticia Sarasa, PhD; Udo Eichenlaub, PhD; Tobias Bittner, PhD; Vitaliy Ovod, MSs; Inge M. W. Verberk, MSs; Kenji Toba, MD, PhD; Akinori Nakamura, MD, PhD; Randall J. Bateman, MD, PhD; Kaj Blennow, MD, PhD; Oskar Hansson, MD, PhD

(ROC) Analysis for Abnormal Cerebrospinal Fluid (CSF) Amyloid





ALZFORUM
NETWORKING FOR A CURE

pTau biomarkers and renal function

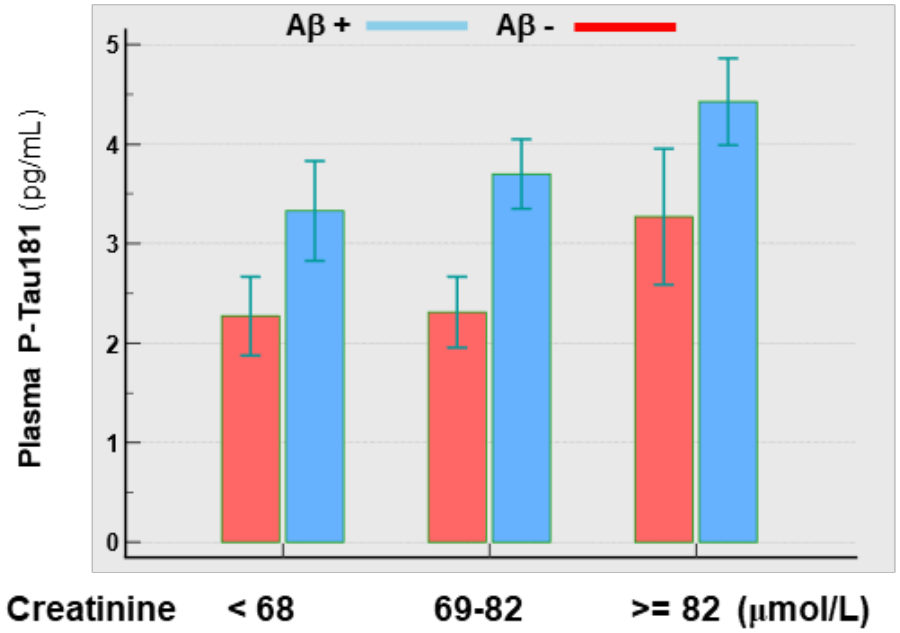
Neurodegeneration

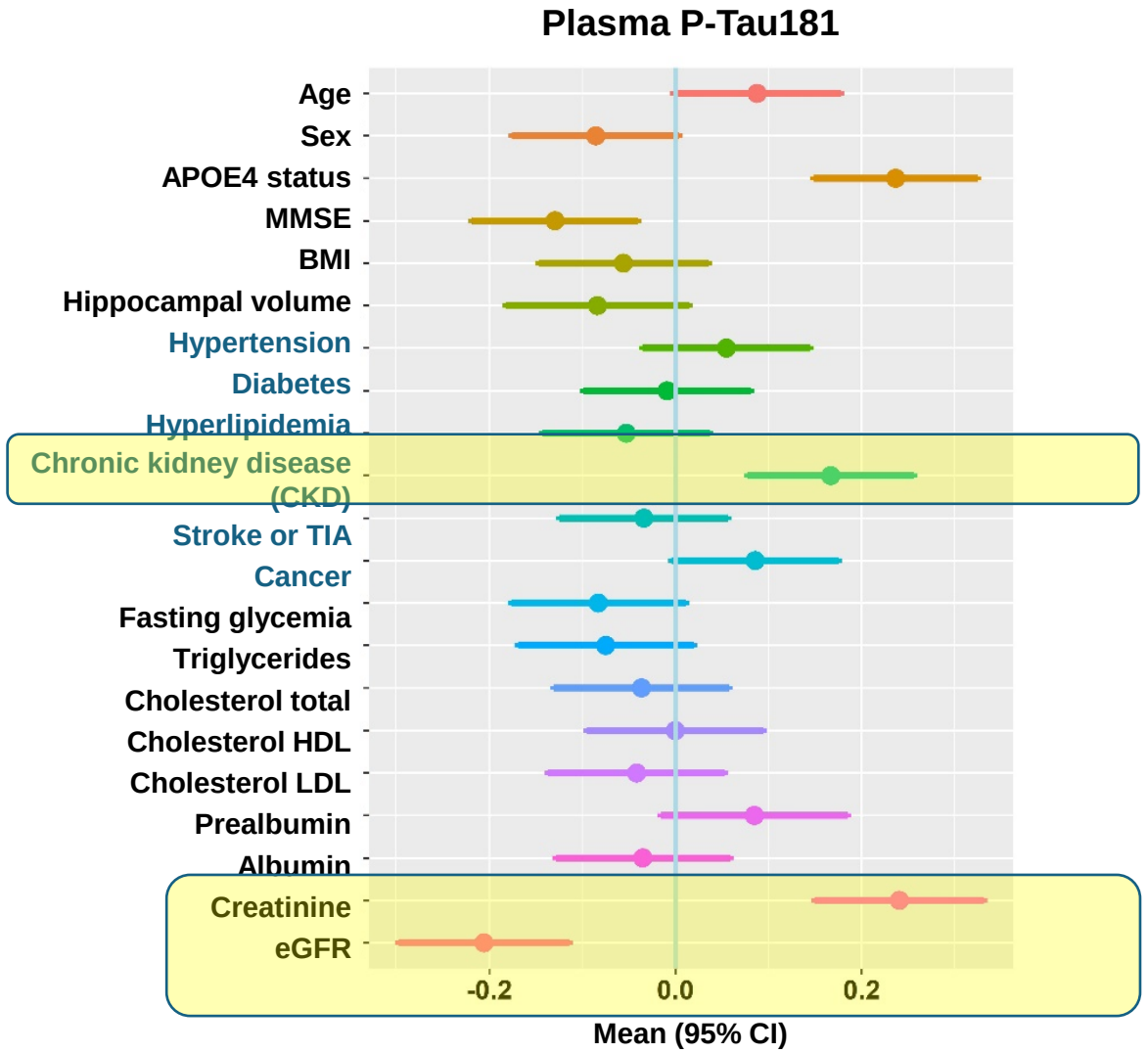
Original research

Plasma phosphorylated tau 181 predicts amyloid status and conversion to dementia stage dependent on renal function

Sylvain Lehmann ,[1] Susanna Schraen-Maschke,[2] Jean-Sébastien Vidal ,[3] Constance Delaby ,[1,4] Frédéric Blanc,[5] Claire Paquet,[6] Bernadette Allinquant,[7] Stéphanie Bombois,[2,8] Audrey Gabelle,[9] Olivier Hanon [3]

Lehmann S, *et al*. *J Neurol Neurosurg Psychiatry* 2023;**0**:1–9. doi:10.1136/jnnp-2022-330540





Association of blood biomarkers and renal function

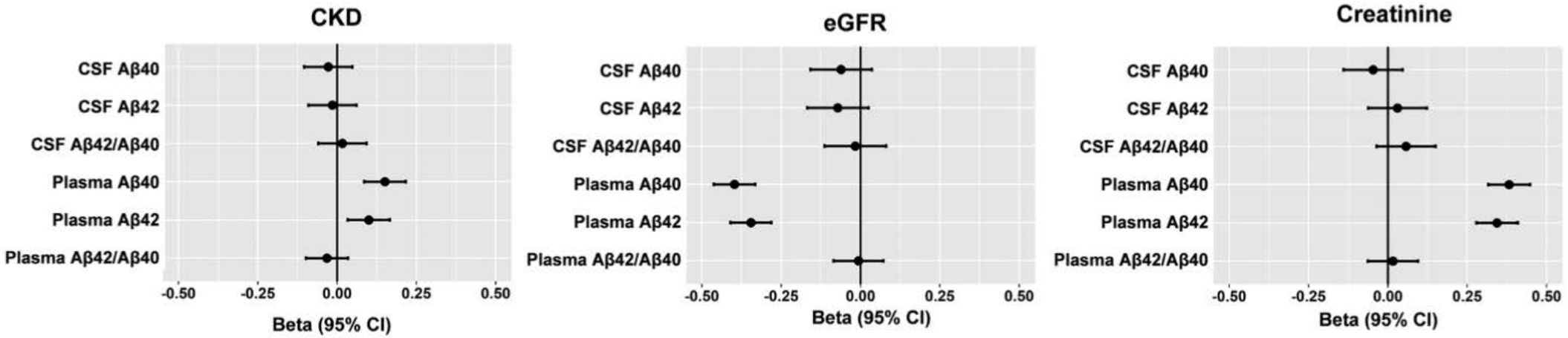
Received: 28 October 2022 | Revised: 17 December 2022 | Accepted: 22 December 2022

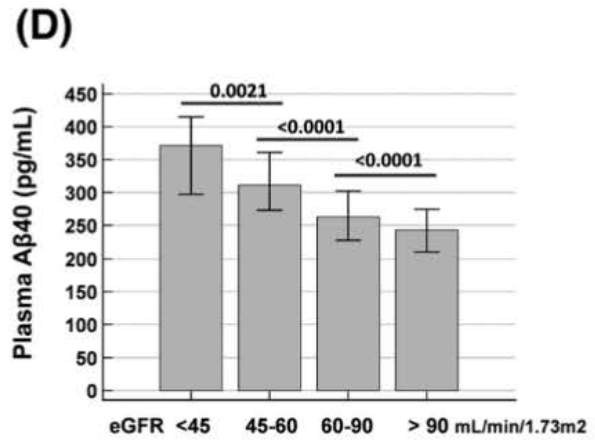
DOI: 10.1002/alz.12949

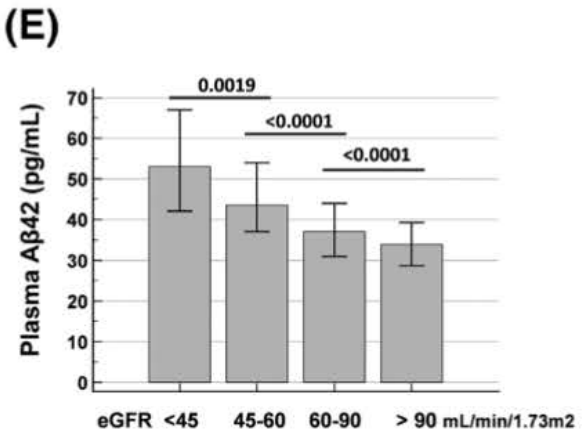
Alzheimer's & Dementia
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

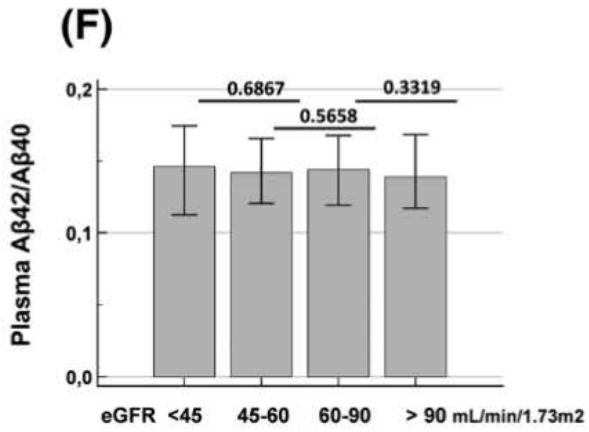
LETTER

Plasma Aβ42/Aβ40 ratio is independent of renal function







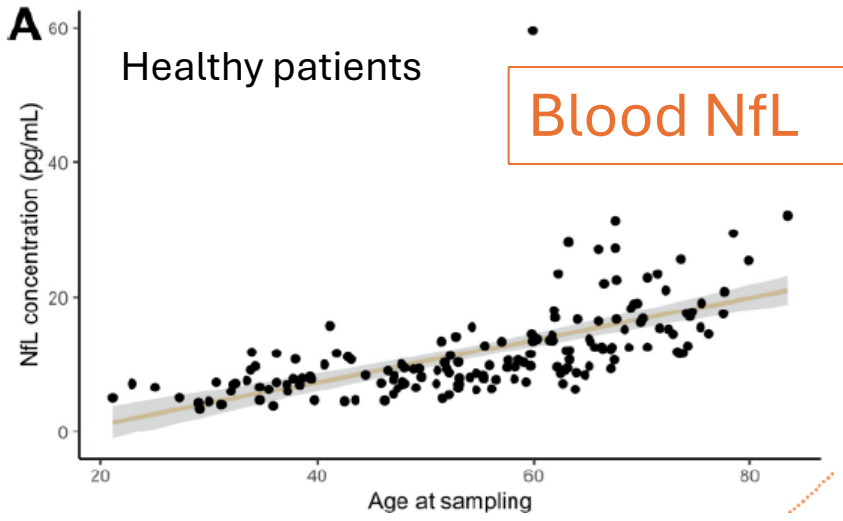


Neurofilament detection, application to multiple sclerosis (MS)

Serum Neurofilament Light: A Biomarker of Neuronal Damage in Multiple Sclerosis

Giulio Disanto, MD, PhD,[1] Christian Barro, MD,[2] Pascal Benkert, PhD,[3] Yvonne Naegelin, MD,[2] Sabine Schädelin, MSc,[3] Antonella Giardiello, MD,[1] Chiara Zecca, MD,[1] Kaj Blennow, PhD,[4] Henrik Zetterberg, PhD,[4,5] David Leppert, MD,[2] Ludwig Kappos, MD,[2] Claudio Gobbi, MD,[1] Jens Kuhle, MD, PhD,[2] and the Swiss Multiple Sclerosis Cohort Study Group

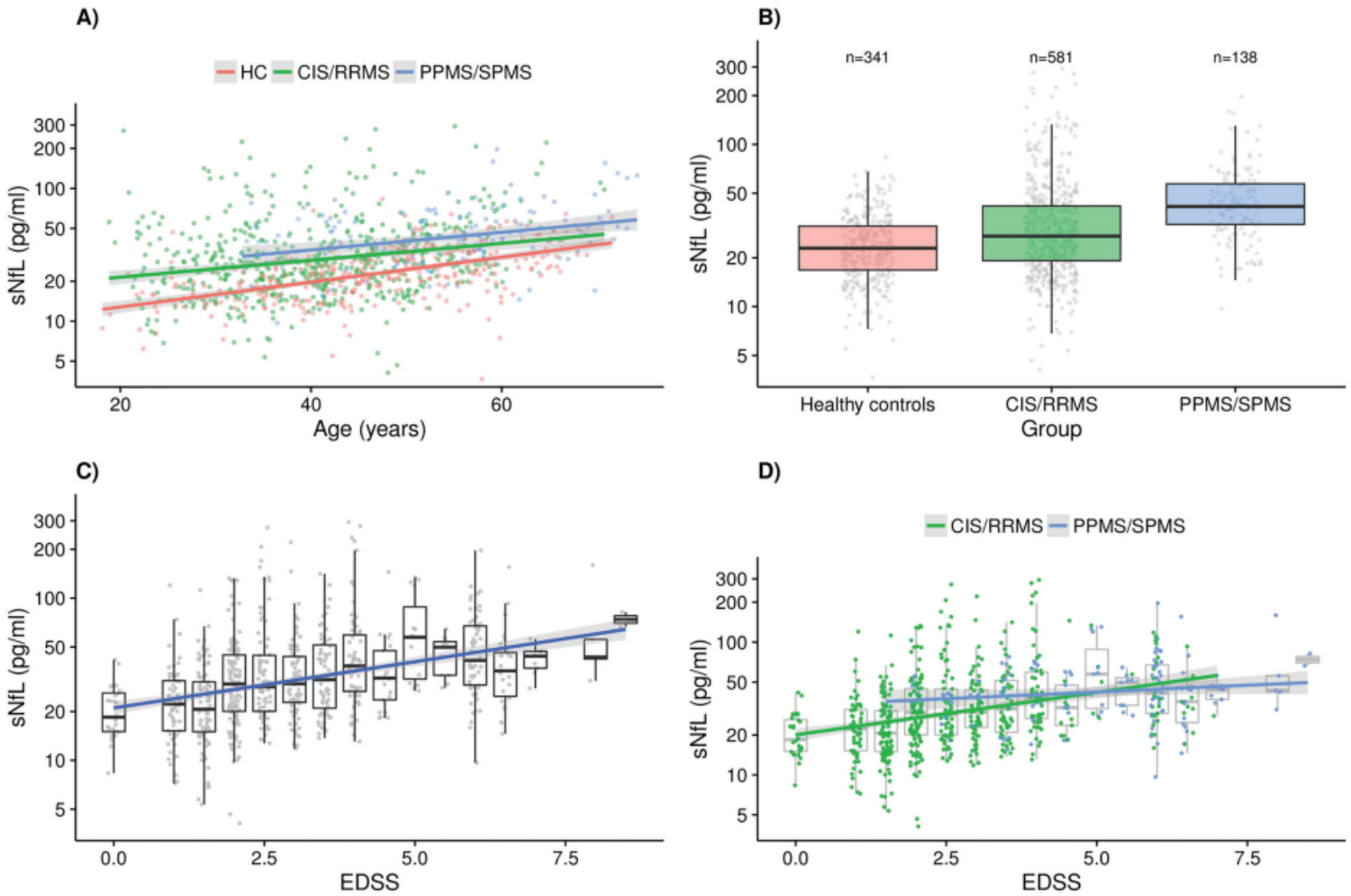
ANN NEUROL 2017;81:857–87



Saracino D et al, JNNP, 2021

Blood NfL

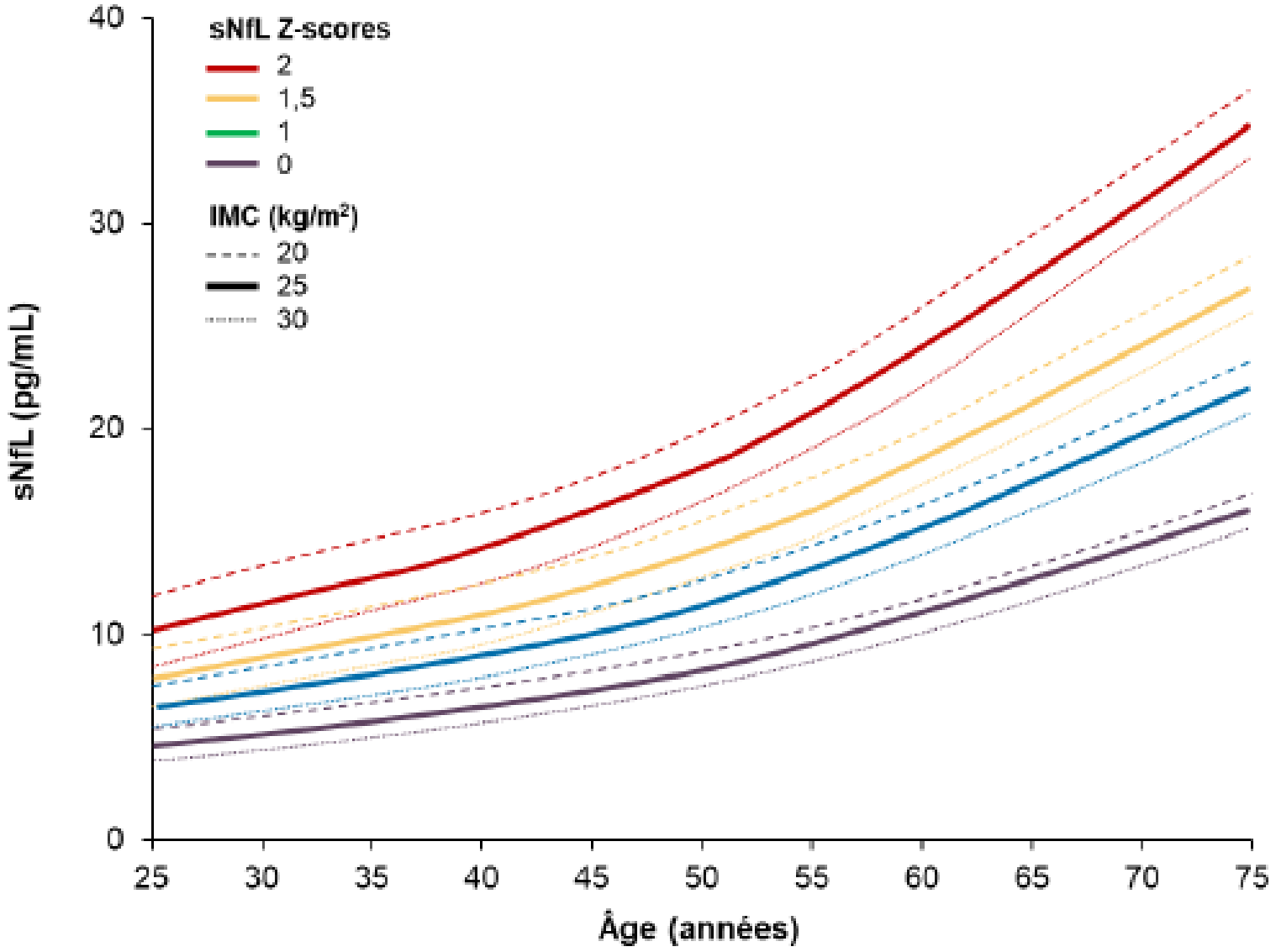
Age: +3%/year



Co-variables impacting NfL blood levels

AGE and BMI

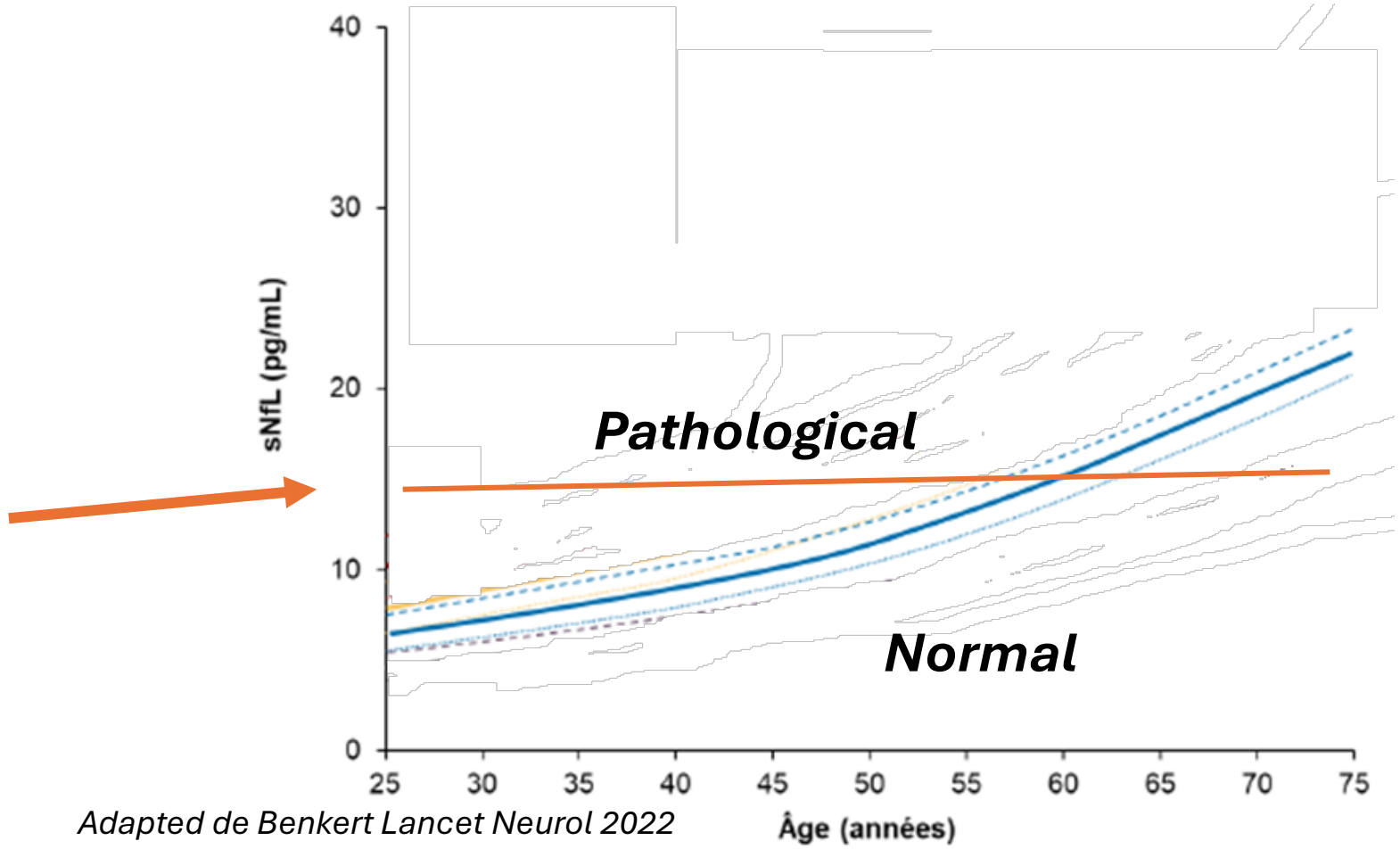
Benkert et al, Lancet Neurol 2022



Factors influencing NfL base values

Age: +3%/year

In order to use these biomarkers reliably, it is essential to know their normal values in the general population, so as to define the thresholds between **Normal and Pathological** at individual level.



Adapted de Benkert Lancet Neurol 2022

AXA INTERVAL projet (philanthropic funding)

PROJECT DESCRIPTION AND OBJECTIVES

- The main objective of our project is to establish reference values (ranges) for emerging blood biomarkers of Alzheimer's disease and related disorders: Aβ42 /40, pTau, NfL, GFAP.
- To achieve this, we rely on French epidemiological cohorts, made up of a representative sample combined with numerous socio-demographic and health data.

cohorte CONSTANCES

INVESTISSEMENTS D'AVENIR

Population cohorts

	Constances	3C
Age at inclusion	18-69 years old	+65 years old
Inclusion period	2012-2021	1999-2001
Selection frame	Public Health database (CNAV)	Electoral List
Centres	26 régions de France	3 centres: Montpellier, Bordeaux, Dijon
N	220 000	9294
Blood collection	2018-2021	1999-2001 (at baseline)
Follow-up	- Annual (postal, online) - Every 4 years (at the examination centre)	Up to 14 years
Selection	**Draw stratified over 24 strata** (age ([23–45[), [45–59[, [60–69[, and 70+], sex (male/female), BMI (<25, [25–30], ≥30)	**Draw stratified over 36 strata** (age ([65-70[;[70-75[; [75-80[;[80-85[; [85-90[; ≥90 years), sex, and BMI
N included	**4890**	**483**

CONSTANCES

Selection of participant in the Population cohorts

Constances
4885 participants

3C
483 participants

Excluded at the time of collection:
Neurodegenerative diseases (n=41)
MMSe <24 (n=46)

Excluded at the time of collection:
Neurodegenerative diseases (n=23)
MMSe <24 (n=24)

5234 participants

- **Missing biomarker data (n=3)**
- **Missing data on covariates (n=101)**
- **Biomarker values < LLOQ (n=5)**
- **Outliers (n=2)**

5123 participants

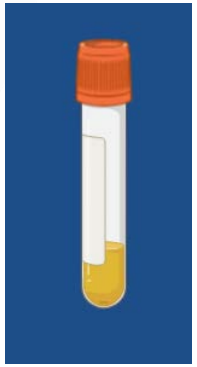
Reference population

Reference population characteristics (N=5123)

Socio-demographic	
Age (years)	61.1 (46.3 ;70.6)
Age group	
[23-45[	1175 (22.9)
[45-59[	1117 (21.8)
[59-69[	1275 (24.9)
[69-75[	1215 (23.7)
[75-80[	173 (3.4)
[80-85[	97 (1.9)
85+	71 (1.4)
Gender, women	2541 (49.6)
Education (N=5026)	
Moins de 5 années	85 (1.7)
5 à 11 années	478 (9.5)
11 à 12 années	777 (15.5)
12 à 13 années	780 (15.5)
14 années ou plus	2906 (57.8)

Lifestyle habits	
Smoking status (N=4838)	
Jamais	2319 (47.9)
Ex-fumeur	2174 (44.9)
Fumeur actuel	345 (7.1)
Alcohol consumption(N=4561)	
Aucune	909 (19.9)
Modérée	2996 (65.7)
Excessive	656 (14.4)
Clinical Features	
BMI (kg/m²)	
<25	1785 (34.8)
[25 ;30[	1813 (35.4)
≥30	1525 (29.8)
Impaired kidney function	261 (5.1)
Diabetes, yes(N=4448)	277 (6.2)
APOE4, positif	1164 (22.7)

Plasma biomarkers



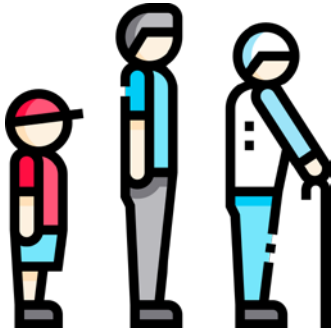
Aβ40 **Aβ42** **p-tau181**

→ **Aβ42/ Aβ40**, **p-tau181/ Aβ42**

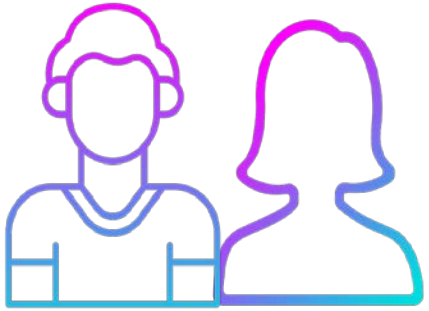
NfL **GFAP**

- **Covariables (**at the time of collection**)**

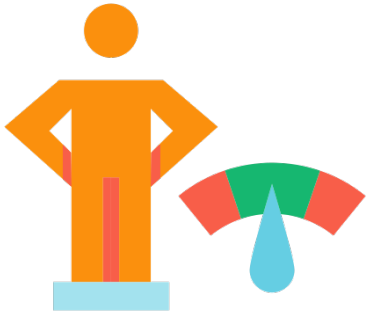
Age (years)



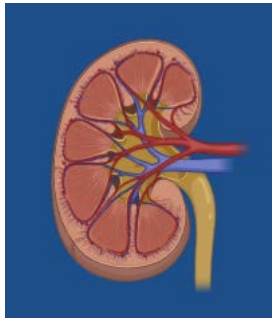
Biological sex (H/F)



BMI (kg/m²)



eGFR or **Creatinine** (µmol/l)



Calculation of reference values

Reference values:

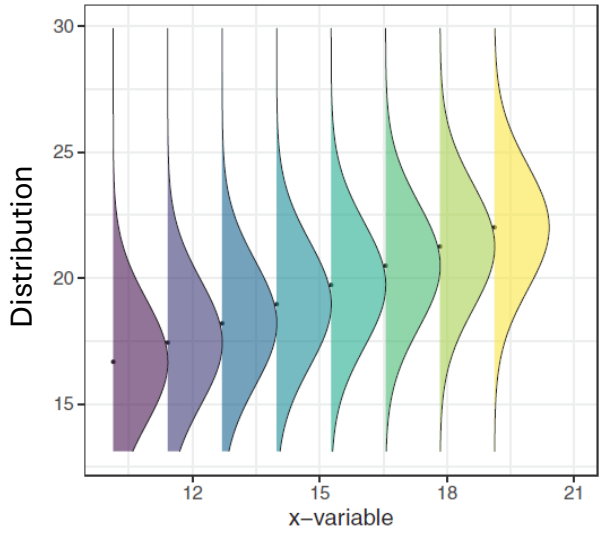
- Describes the fluctuation of a parameter (biological, psychometric, etc.) in a reference ("healthy") population
- → Normal or "abnormal" value
- → Deviation from the value that would normally have been observed if the individual were healthy

- **Construction methods:**
- Traditional (descriptive) approach

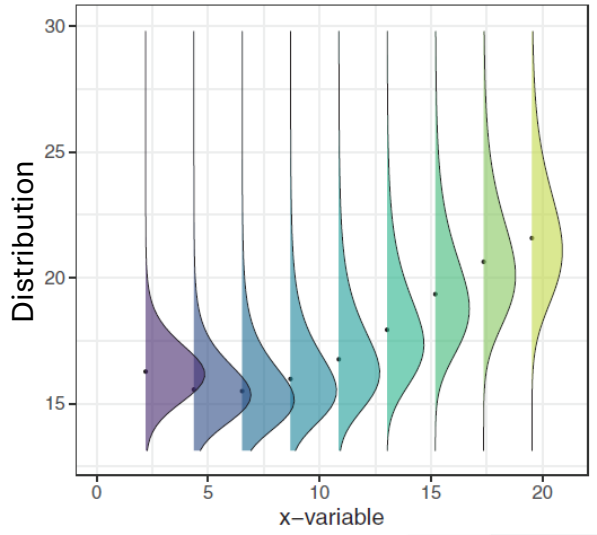
  - **Regression approach**

GAMLSS model
(Generalized Additive Models for Location, Scale and Shape)

Regression of the mean



Distribution regression



Reference values equations

Step 1: Calculation of the four moments: mu, sigma, nu, tau; with age, sex, BMI, and renal function

Model 1
age
eGFR/creat.
BMI
sex

p-tau181		
Model 1	**Distribution**	BCTo
	μ	$e^{-1.2157 + 155.1051*\frac{1}{age^2} + (1e\text{-}06)*age^3 + (3e\text{-}06)*creatinine^3 + ((-2e\text{-}07)*creatinine^3*\log(creatinine)) + 3.4325*\frac{1}{BMI} + 0.127*sex}$
	σ	$e^{-3.4407 + 0.0271*age + 0.0175*BMI + (-0.0470*sex)}$
	ν	$-0.1175 + (-0.071*age)$
	τ	5.2213

Model 2
Age
sex

Model 2	**Distribution**	BCTo
	μ	$e^{-0.6128 + (193.7172*\frac{1}{age^2}) + (2e\text{-}06)*age^3}$
	σ	$e^{-2.1253 + (0.0022*age)}$
	ν	$-0.1452 + (-0.0023*age)$
	τ	5.9857

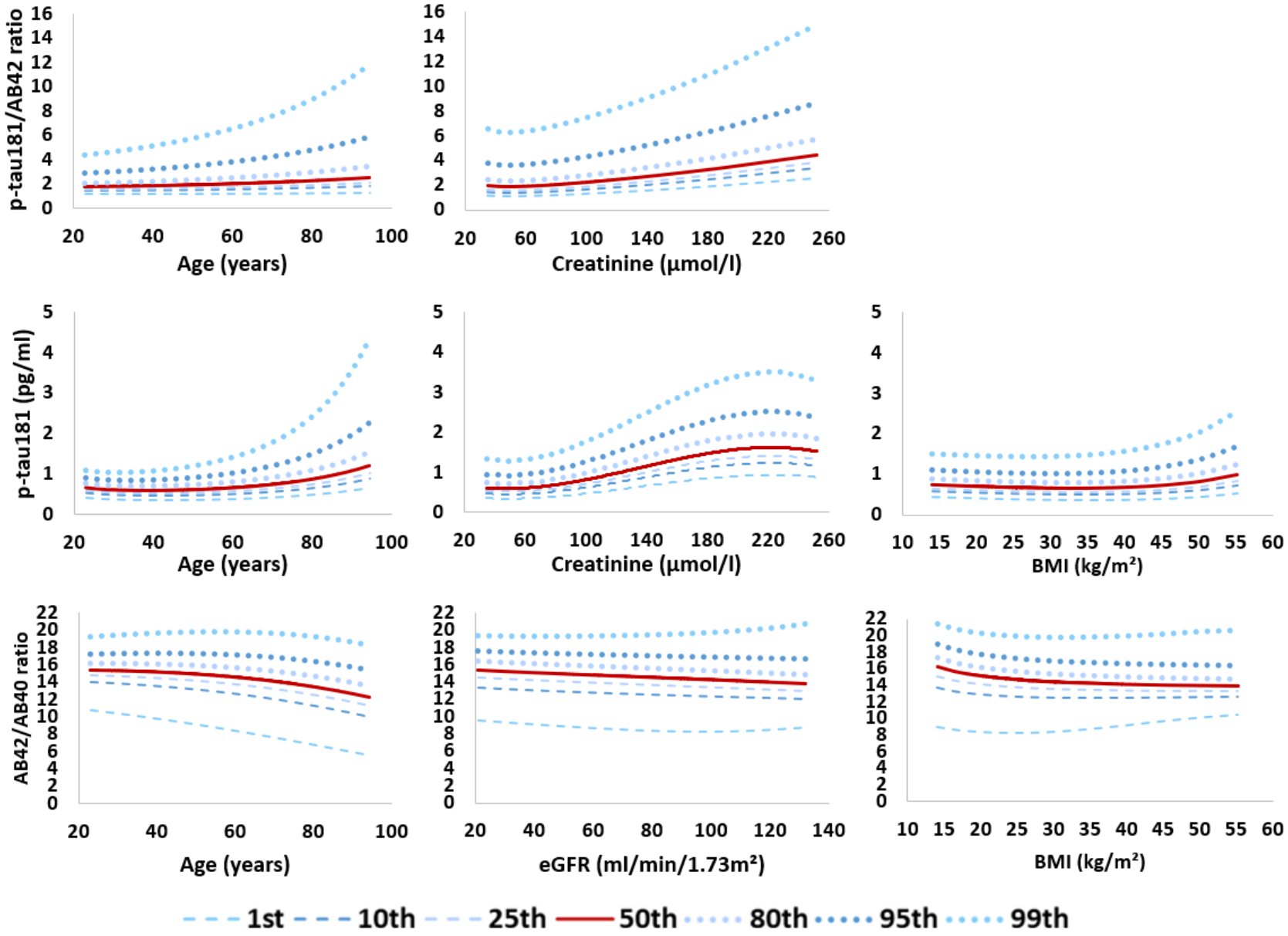
Step 2: Transformation of biomarker's value to **Z score**

$$Z = \begin{cases} \dfrac{\left(\dfrac{\text{Biomarker's value}}{\mu}\right)^{\nu} - 1}{(\nu*\sigma)} & \text{if } \nu \neq 0 \\ \dfrac{\log\left(\dfrac{\text{Biomarker's value}}{\mu}\right)}{\sigma} & \text{if } \nu = 0 \end{cases}$$

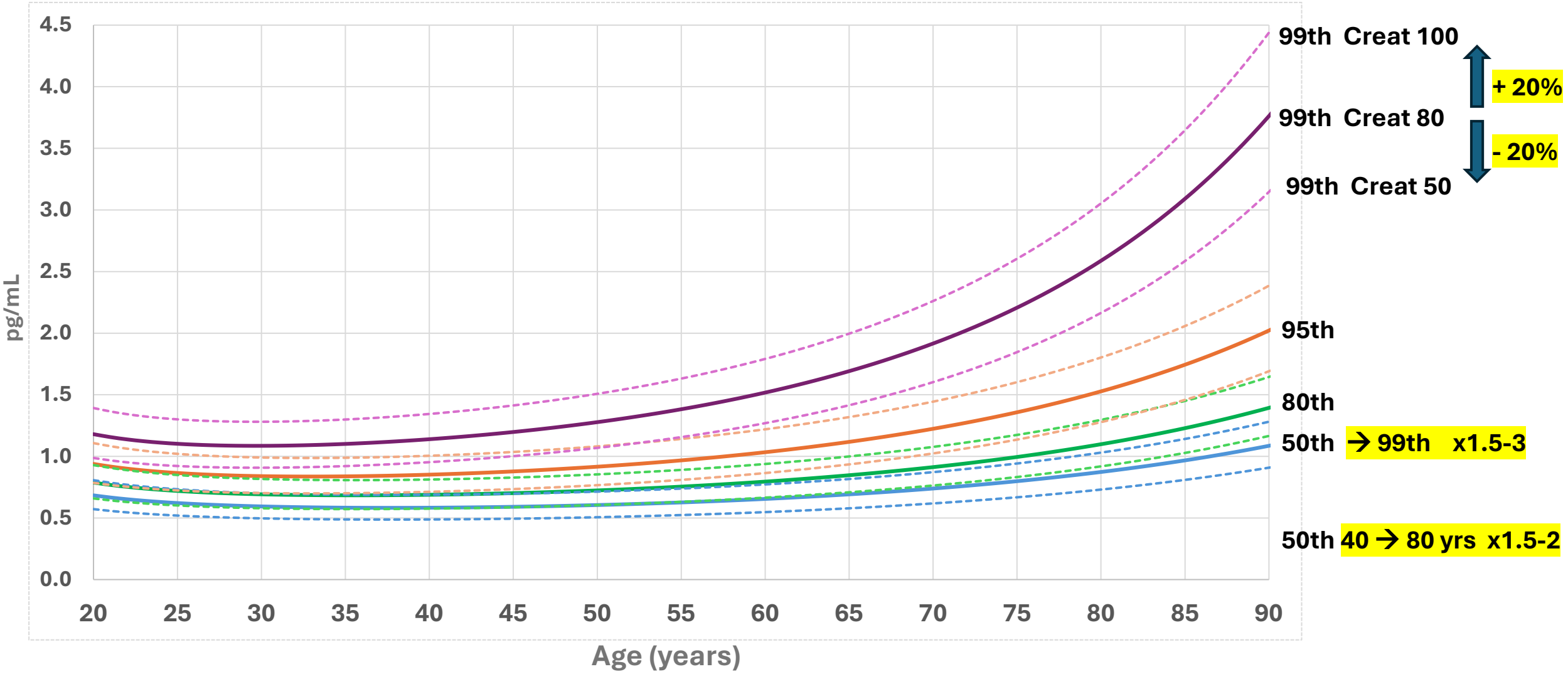
Step 3: Estimation of **percentiles**

$$\text{Percentile} = \frac{pt(Z,\tau) - \begin{cases} pt\left(\frac{-1}{abs(\nu)*\sigma},\tau\right) & \text{if } \nu > 0 \\ 0 & \text{if } \nu \leq 0 \end{cases}}{pt\left(\frac{1}{abs(\nu)*\sigma},\tau\right)}$$

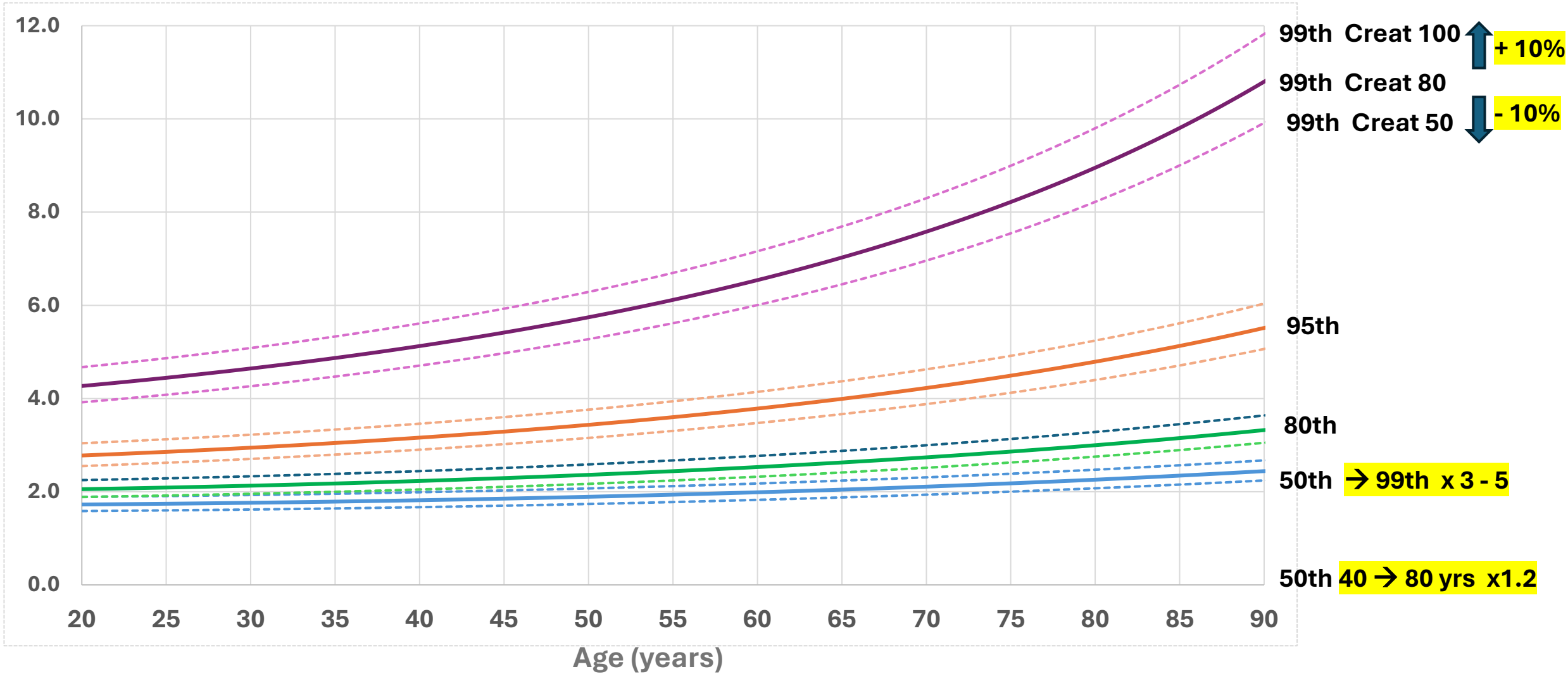
Impact of the different co-variables



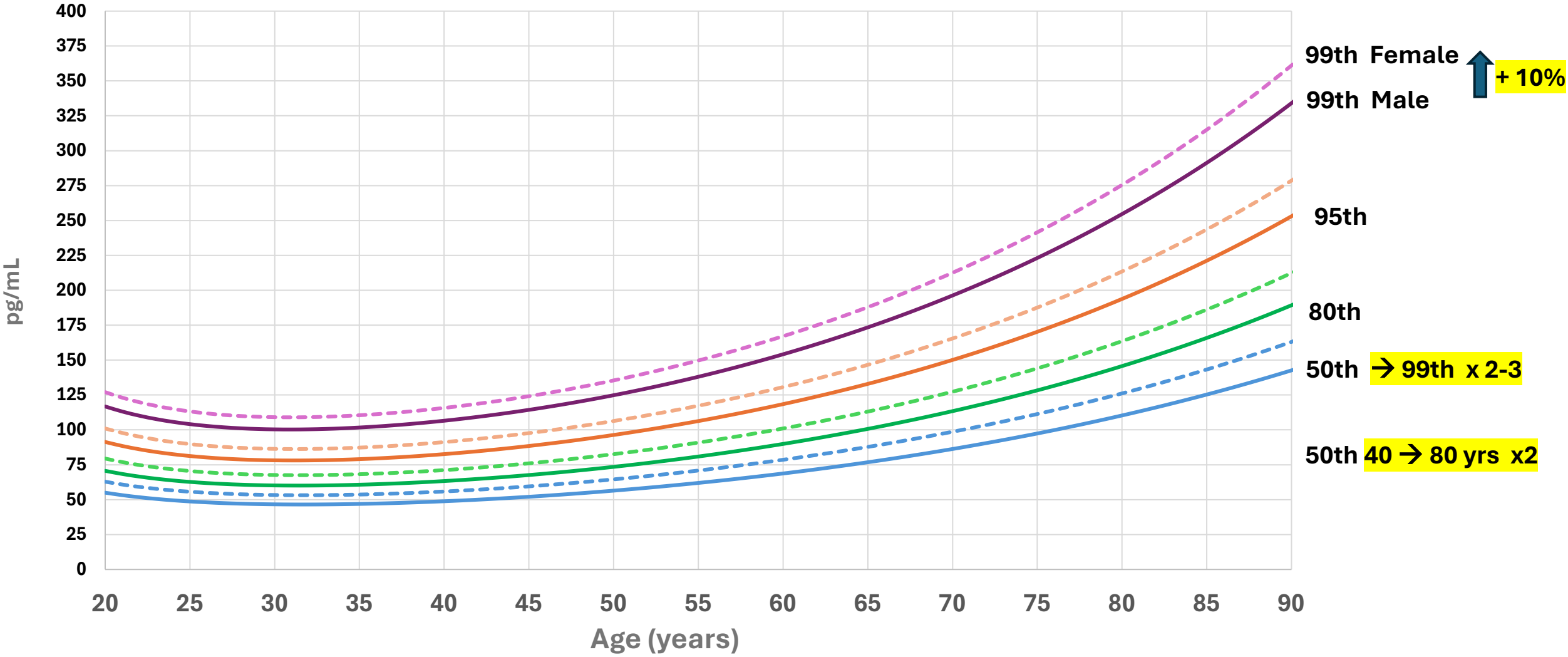
Impact of age and renal function on plasma p-tau181



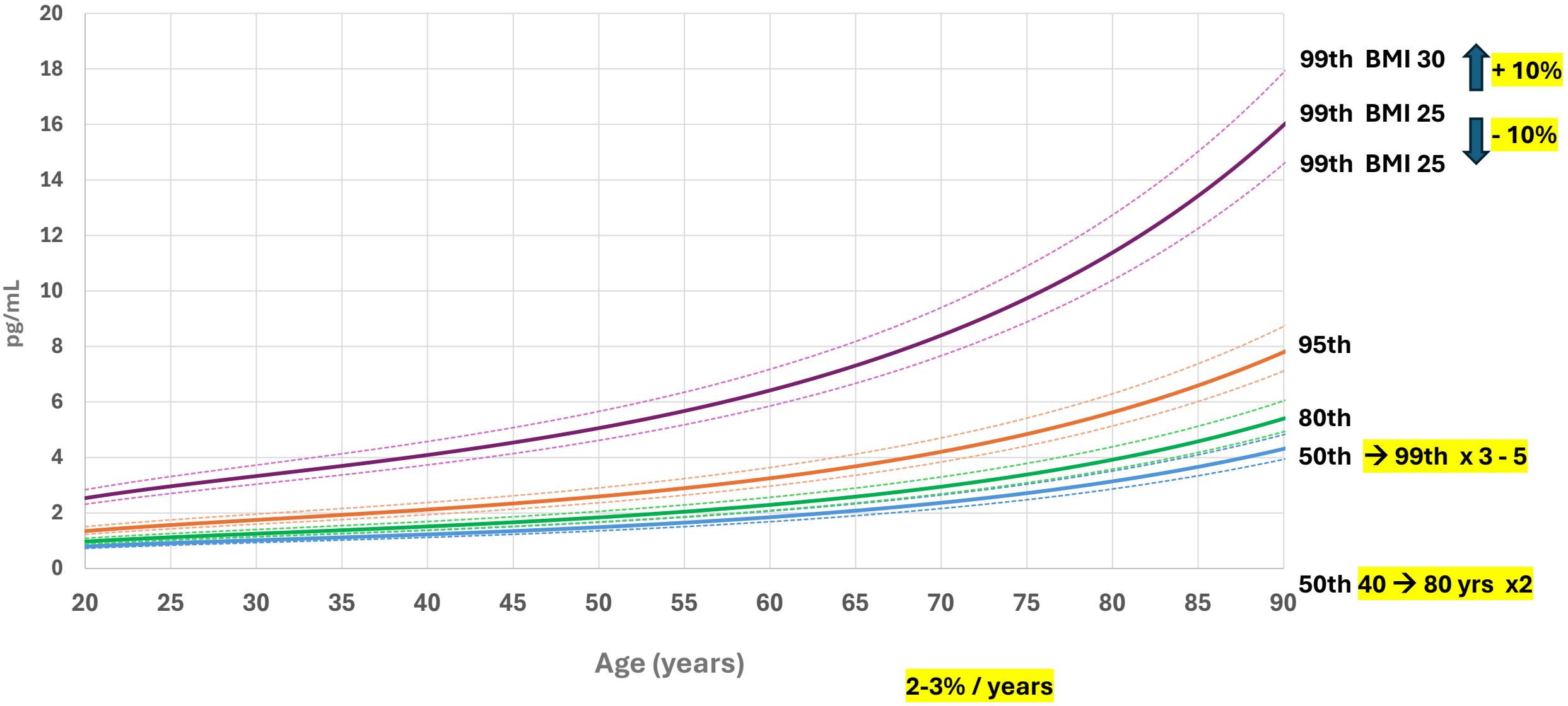
Impact of age and renal function on plasma p-tau181/Aβ42



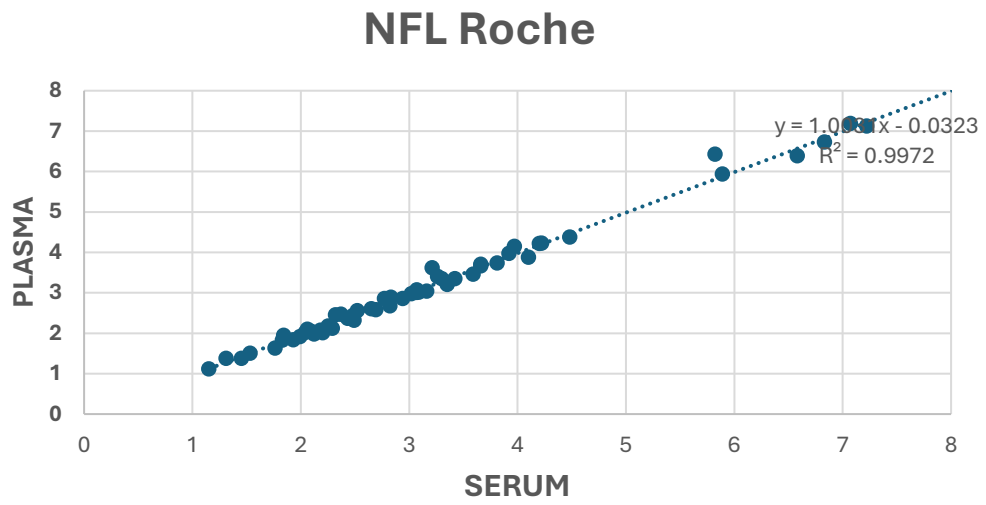
Impact of age and sex on plasma GFAP

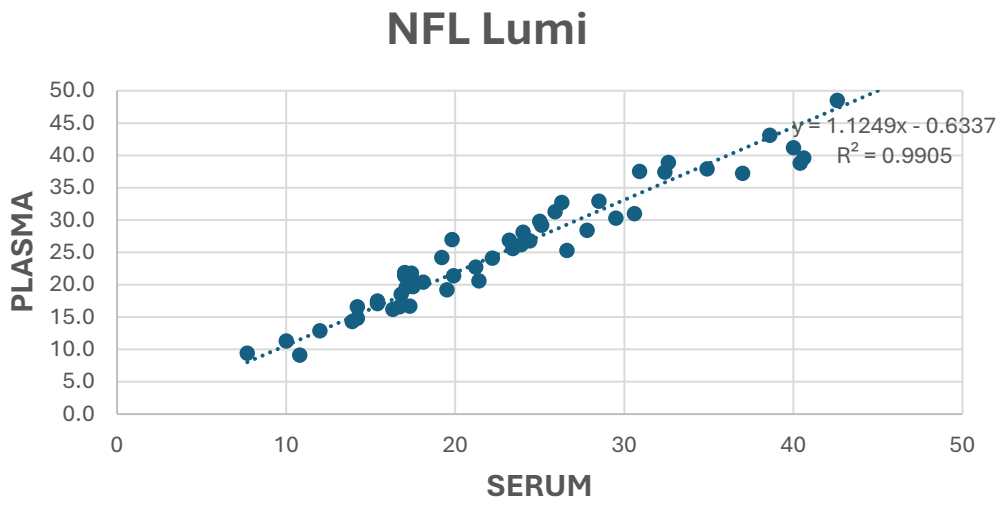


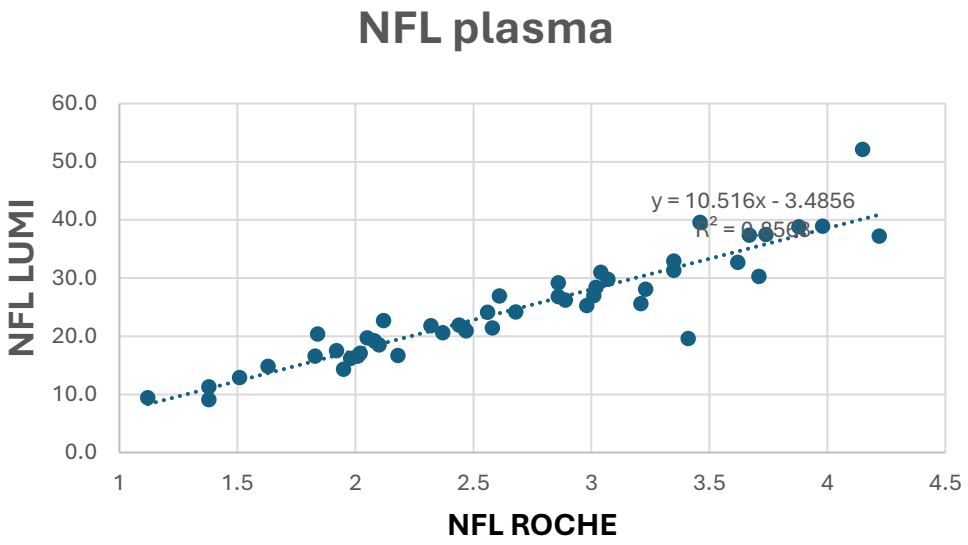
Impact of age and BMI on plasma NfL



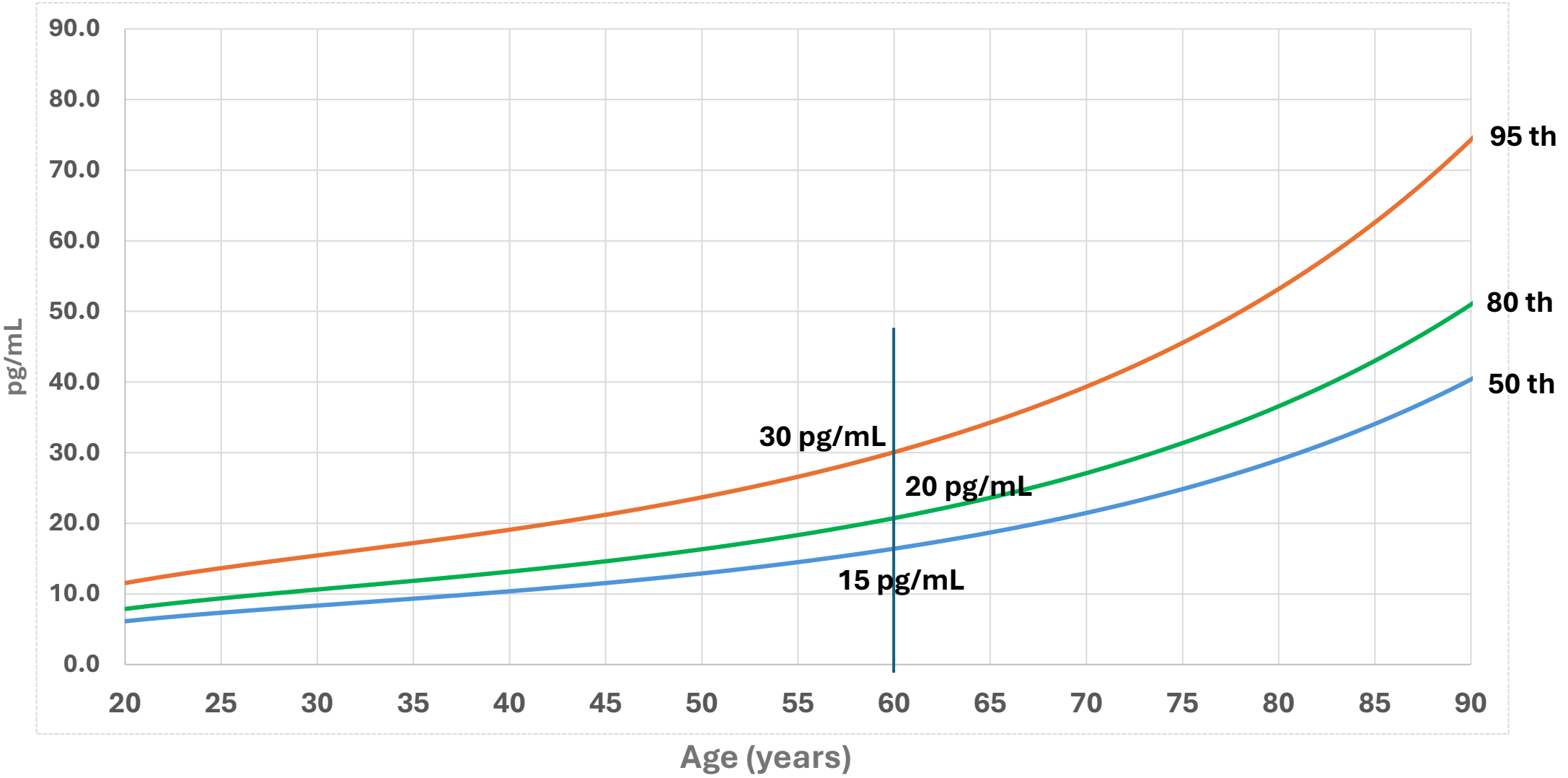
Bridging between fluids and technologies







Impact of age and BMI on plasma NfL (Fujirebio values)



Plasma biomarker cutoff for brain amyloidodid detection

Comparative performance of plasma pTau181/Aβ42, pTau217/Aβ42 ratios, and individual measurements in detecting brain amyloidosis

Sylvain Lehmann,[a,] Audrey Gabelle,[b] Marie Duchiron,[a] Germain Busto,[b] Mehdi Morchikh,[a] Constance Delaby,[a,c] Christophe Hirtz,[a] Etienne Mondesert,[a,d] Jean-Paul Cristol,[d] Genevieve Barnier-Figue,[e] Florence Perrein,[f] Cédric Turpinat,[b] Snejana Jurici,[e] and Karim Bennys,[b] for the Alzheimer's Disease Neuroimaging Initiative (ADNI)[g]*

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2025;117: 105805

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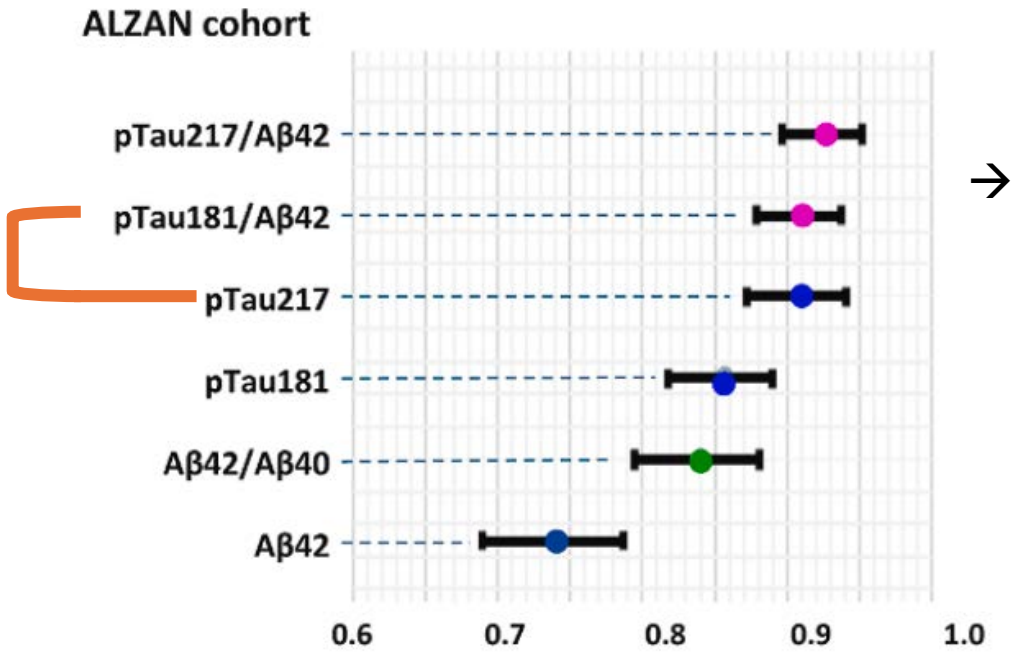
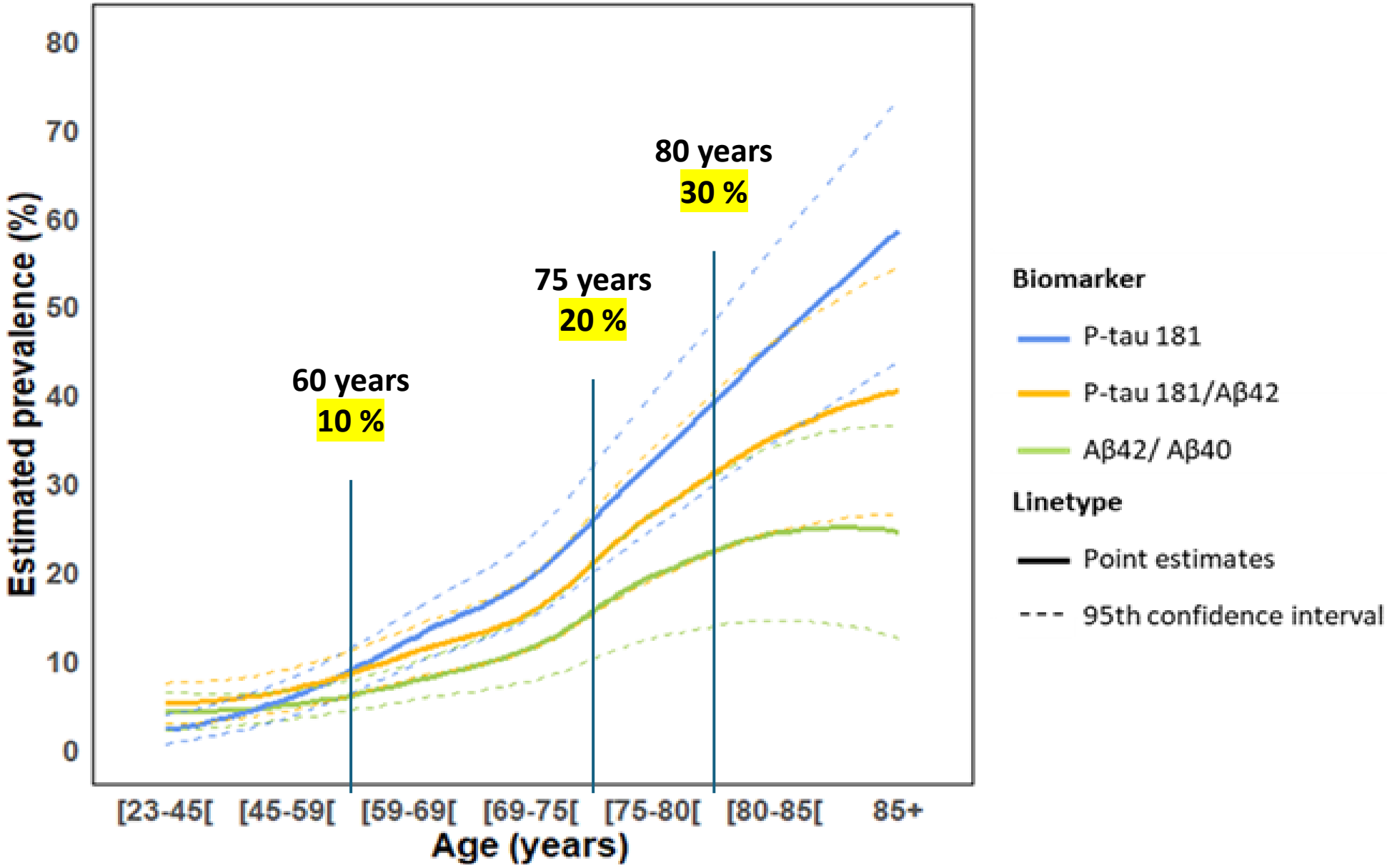
	High cutoff	Low cutoff
90% Sens-Spe		
pTau181	1.370	0.867
pTau217	0.281	0.159
pTau181/Aβ42	3.470	2.690
pTau217/Aβ42	0.718	0.508
90% PPV-NPV		
pTau181	1.500	0.713
pTau217	0.216	0.124
pTau181/Aβ42	3.166	2.395
pTau217/Aβ42	0.632	0.449

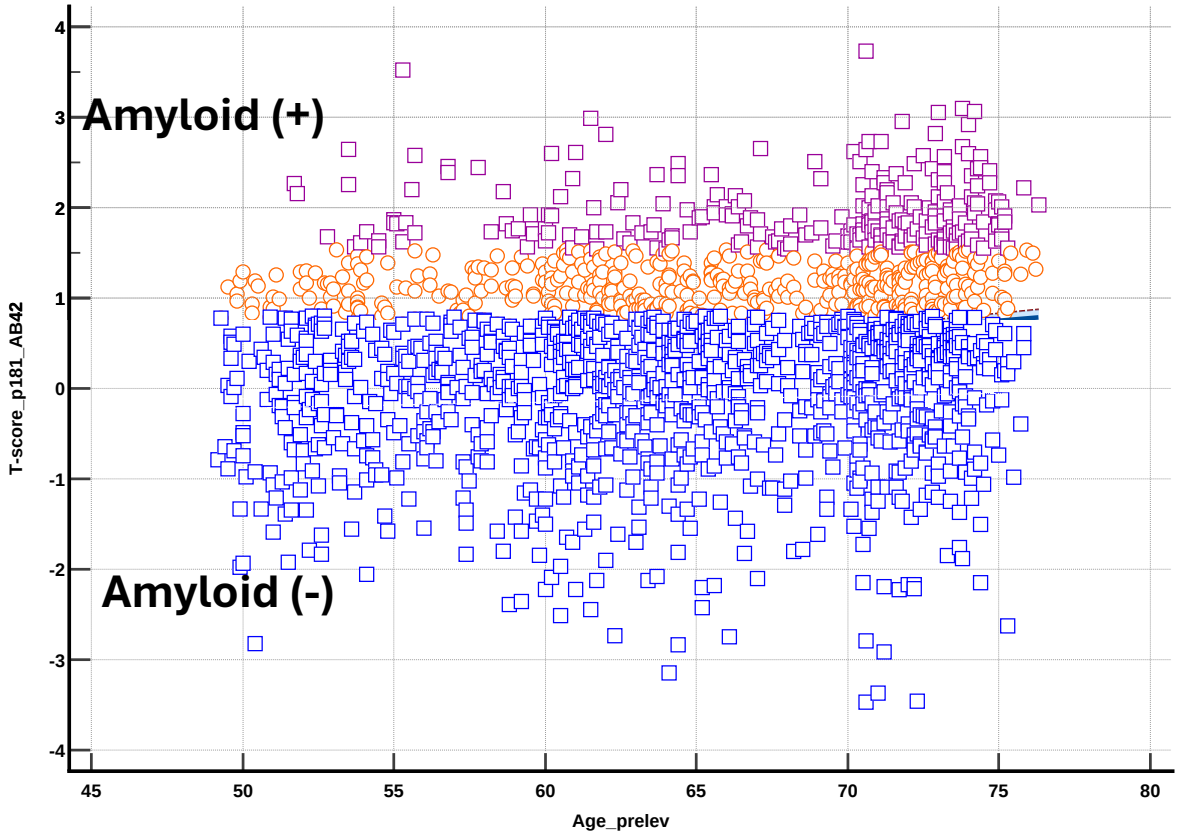


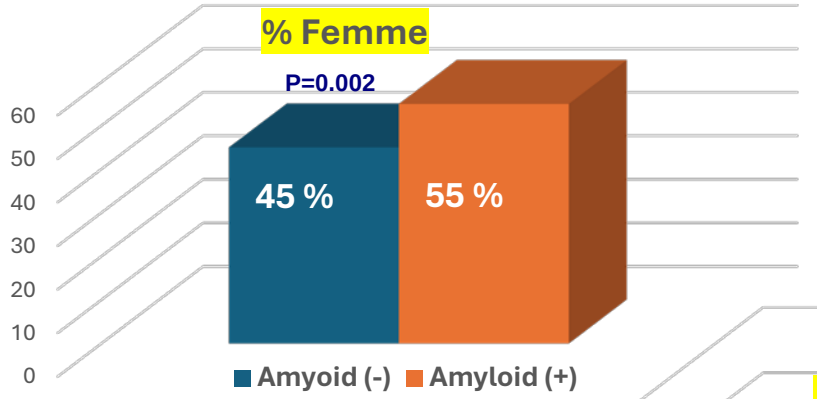
→ **Z = 1.5** score for amyloid detection

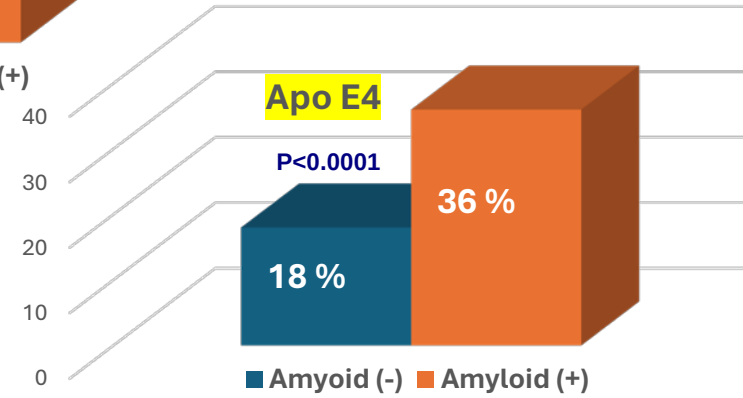
Amyloidosis prevalence in the French population

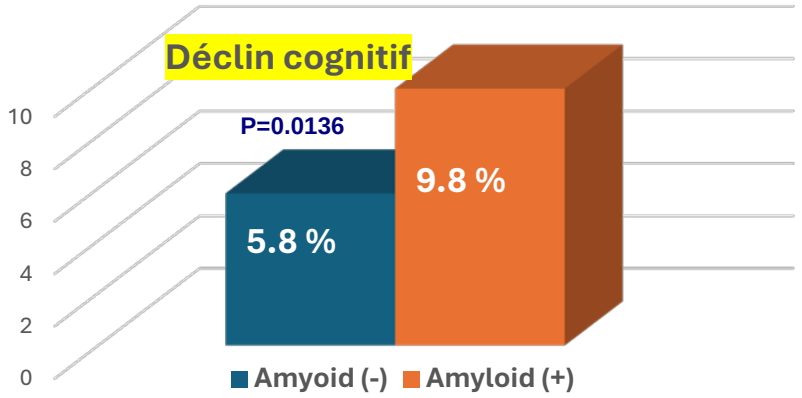


Comparison of cognitively unimpaired Amyloid + / - population









VALEURS DE RÉFÉRENCE DES BIOMARQUEURS SANGUINS DES MALADIES NEURODÉGÉNÉRATIVES BASÉES SUR LA COHORTE CONSTANCES

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