TRUAGE BY TRUDIAGNOSTIC

Inflammation

This report explores the impacts of inflammation on biological age and accelerated biological aging by examining associated methylation patterns at various locations of your DNA.

Developed By TruDiagnostic's Bioinformatics & Research Department
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UNDERSTANDING

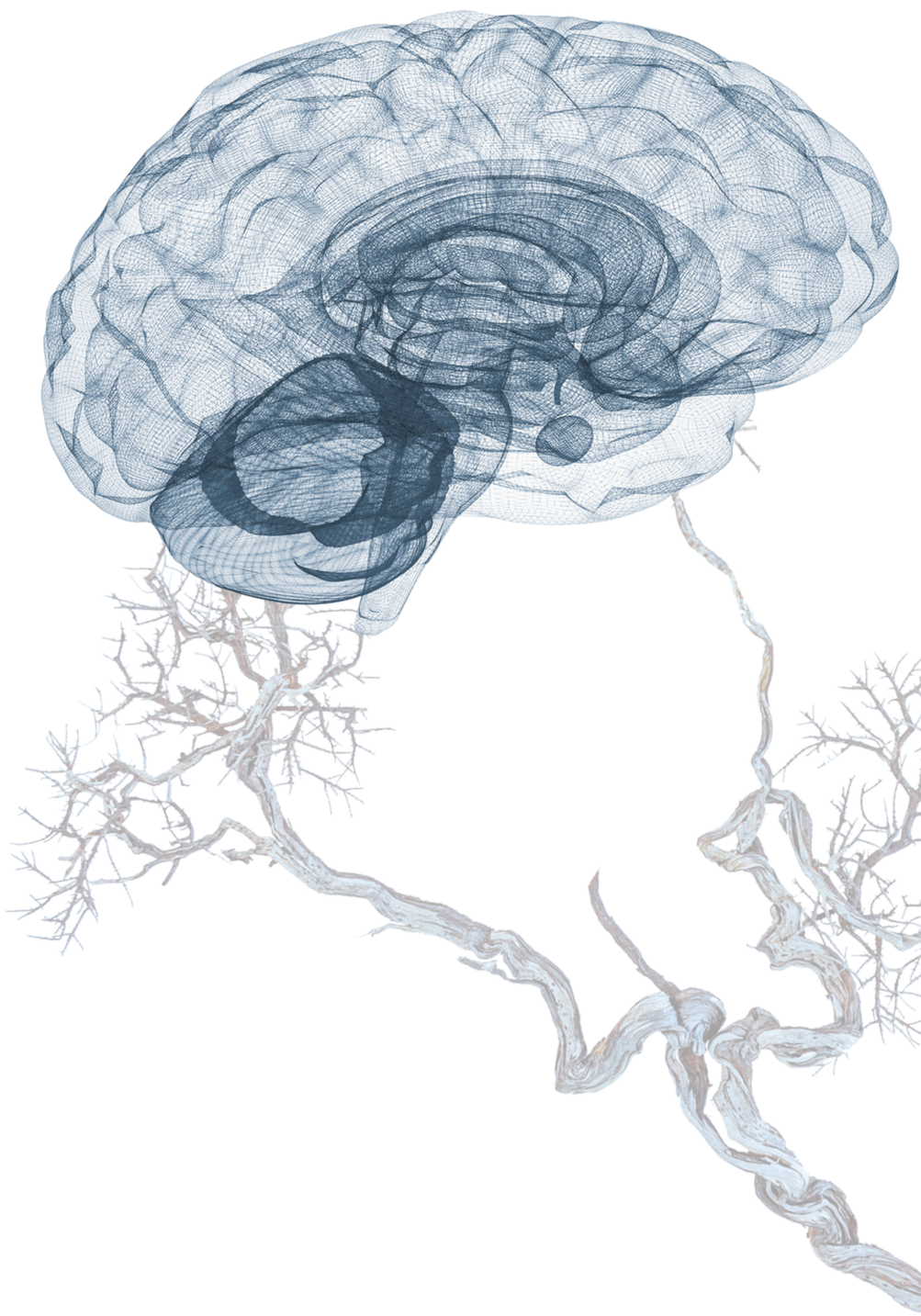
Inflammation's impact on cognitive health.

As we age, baseline levels of inflammatory biomarkers increase, leading to a decline in cognition. The cognitive processes that are negatively impacted by inflammation and age-related advanced inflammation can include things like memory, speed of processing, and overall **cognitive function**. Additionally, inflammation has been linked to the beginning stages of **dementia and neurodegenerative diseases**.

When aging occurs, epigenetic changes occur that promote inflammation. This causes a decrease in the global genome methylation, which then causes an increase in methylation to specific regions (including a notable impact on CD8+ and CD4+ T cells). Additionally, several studies indicate that DNA methylation is better associated with chronic inflammation than traditional measures; highlighting how epigenetic mechanisms play a major role in inflammatory imbalance. These mechanisms have also been linked to an **accumulation of cellular damage that can induce a constant inflammatory response**.

Acute inflammation is a biological response to harmful stimuli. However, chronic and elevated levels of inflammation can mark the development of **age-related diseases such as cancer, atherosclerosis, and Alzheimer's**. *Inflammaging, defined as an age-related increase in the levels of pro-inflammatory markers in blood and tissues, is a strong risk factor for multiple diseases that are highly prevalent and frequent causes of disability in elderly individuals.*

Through DNA methylation (DNAm) we have the ability to estimate the total extent of inflammation in your body. This is able to provide more in-depth insights into inflammation-related health information than traditional, inflammation-based bio-measurements can.



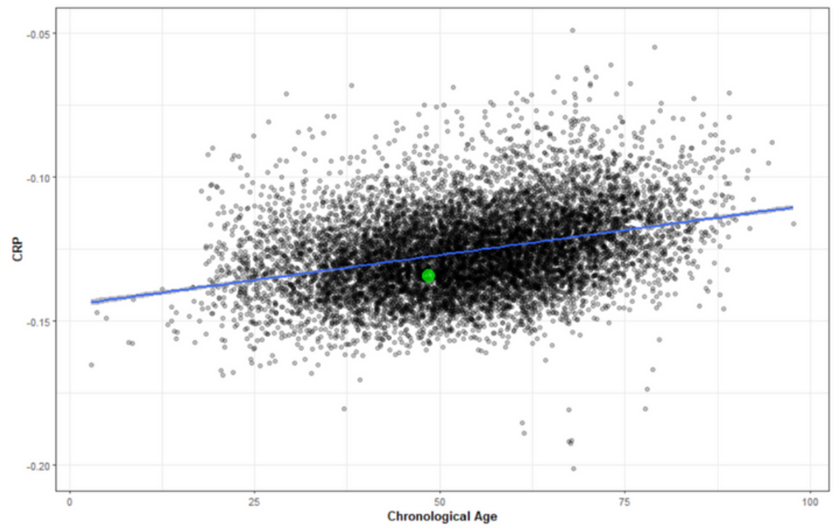
Your Results.

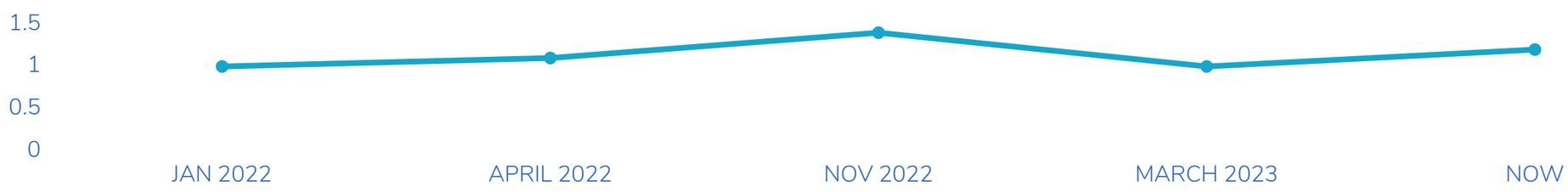
DISCLAIMER: All population graphs included in this report are based off of data from thousands of research participants and TruAge test takers.

Your **DNAm CRP** level is higher than

45%

of the population at your same calendar age and sex.





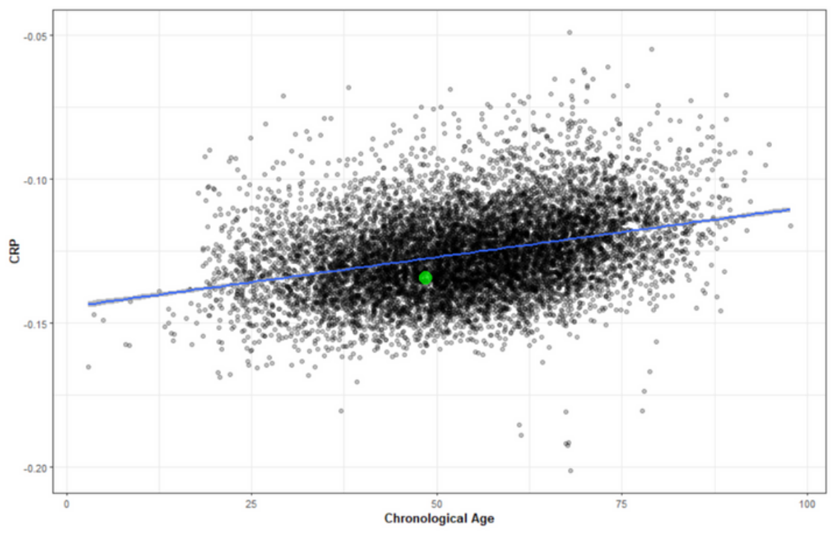
RESULTS OVER TIME

DNAm CRP is produced by the liver in response to acute inflammation. DNAm CRP has an inverse relationship with cognitive functions such as memory, speed, and visuospatial functions.

Your **DNAm IL-6** level is higher than

48%

of the population at your same calendar age and sex.



RESULTS OVER TIME

DNAm IL-6 is a widely used marker of inflammation, and circulating levels of the cytokine typically rise in older age. DNAm IL-6 is positively associated with BMI, self-reported smoking status, and alcohol intake.

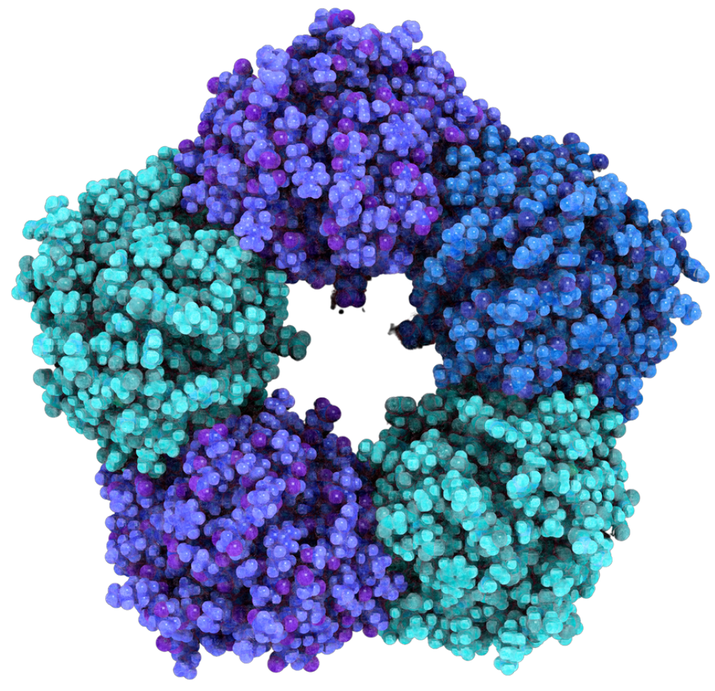
UNDERSTANDING

CRP's impact on cognitive health.

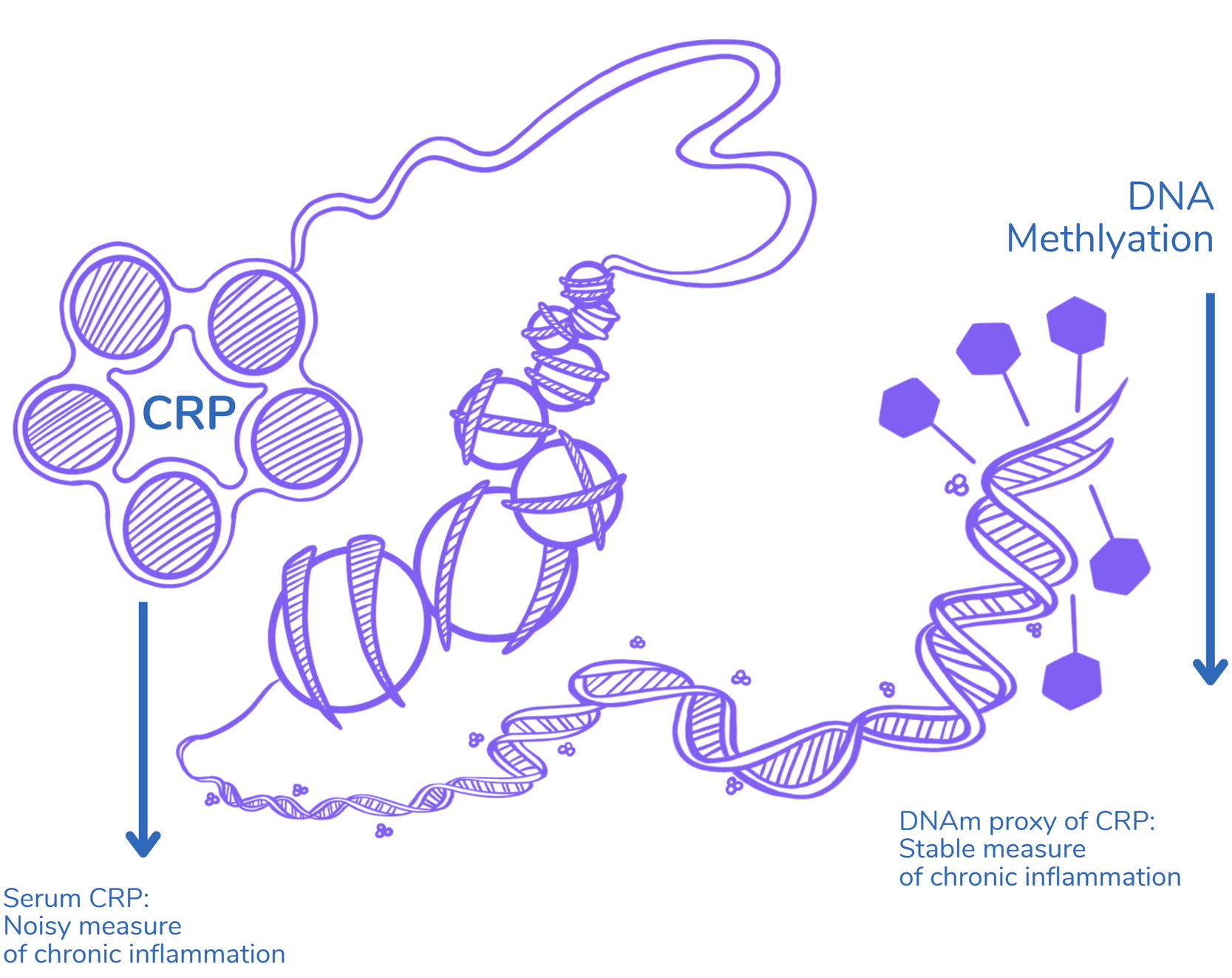
The liver produces CRP in response to acute inflammation. Healthcare providers use CRP measurements to indicate inflammation for various health conditions.

Elevated CRP levels are found to be associated with **low initial memory and verbal fluency** scores. Baseline inflammatory status is quantifiable by both peripheral inflammation-serum C-reactive protein (CRP) and an epigenetic measure methylation signature of CRP (DNAm CRP). However, DNAm has benefits over traditional measures.

One study conducted by *Conole et al* found that DNAm CRP is associated with total **brain volume**, (β = -0.197, 95% confidence interval [CI] -0.28 to -0.12, p FDR = 8.42 × 10-6), **gray matter volume** (β = -0.200, 95% CI -0.28 to -0.12, p FDR = 1.66 × 10-5), and **white matter volume** (β = -0.150, 95% CI -0.23 to -0.07, p FDR = 0.001).



Visualization of the CRP protein



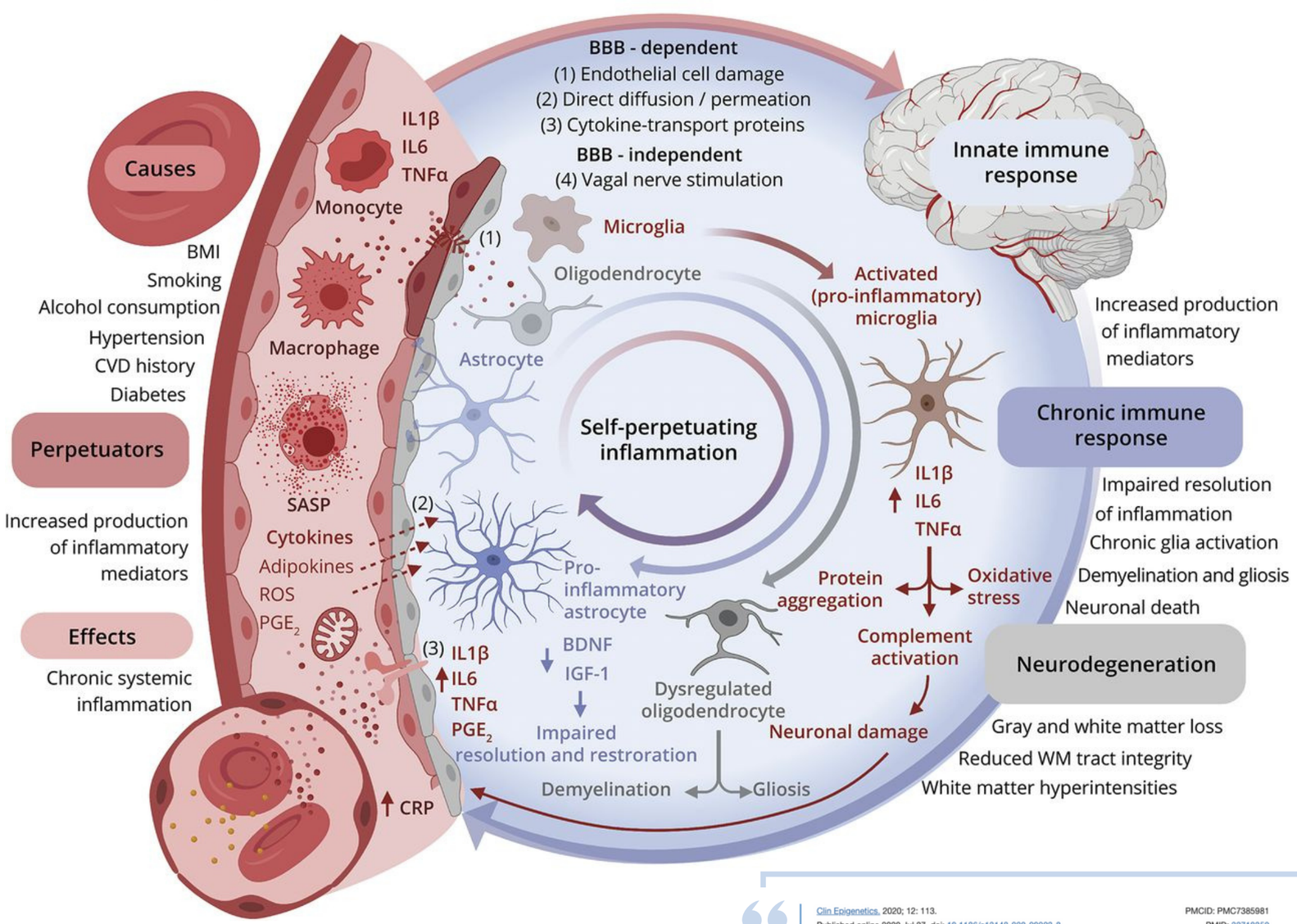
PRECISE & INFORMATIVE

Measuring CRP through DNAm.

DNAm CRP has emerged as a more precise bio-measurement than traditional CRP quantification and shows significantly **stronger associations with brain health outcomes** like chronic inflammation, brain structure, and cognitive functioning, compared to serum CRP measurements (on average **6.4-fold**). DNAm CRP has an inverse relationship with cognitive functions such as memory, speed, and visuospatial functions.

Only recently has there been a push for integrated multi-omics approaches to better characterize chronic inflammation. DNAm profiles may act as promising peripheral biomarkers for cognitive–aging differences at the population level, given their relative stability in the short term, and their **joint modulation by both genetic and lifestyle traits**. Elsewhere, DNAm markers of inflammation have proved informative in predicting a range of age-related health outcomes, from cardiovascular disease to depression, however, few studies have applied this same approach to cognitive aging differences in healthy cohorts.

As chronic inflammation is considered to be an insidious, cumulative, and often undetected contributor to cognitive aging, the importance of such epigenetic markers may be their **utility to index inflammatory load with greater reliability than phasic protein measures**.



Clin Epigenetics. 2020; 12: 113. PMCID: PMC7385981
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Characterisation of an inflammation-related epigenetic score and its association with cognitive ability

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UNDERSTANDING

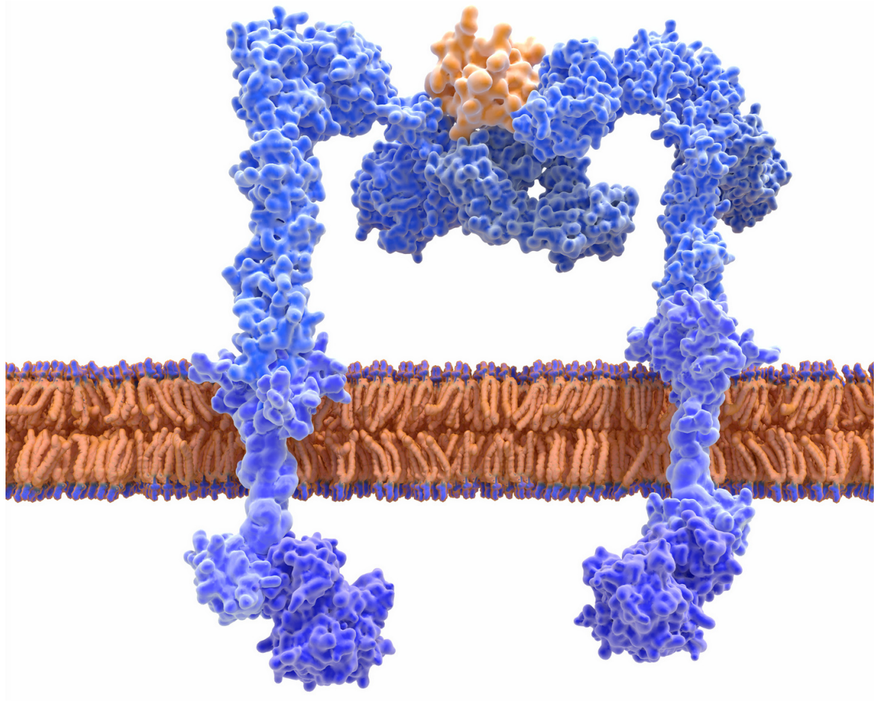
IL-6's impact on cognitive health.

Interleukin-6, also known as IL-6, is a pleiotropic, pro-inflammatory cytokine and is a principal stimulator of various acute-phase inflammatory proteins, such as CRP. IL-6 is a widely used marker of inflammation and circulating **levels of the cytokine typically rise with age**. On average, males show higher scores compared to women.

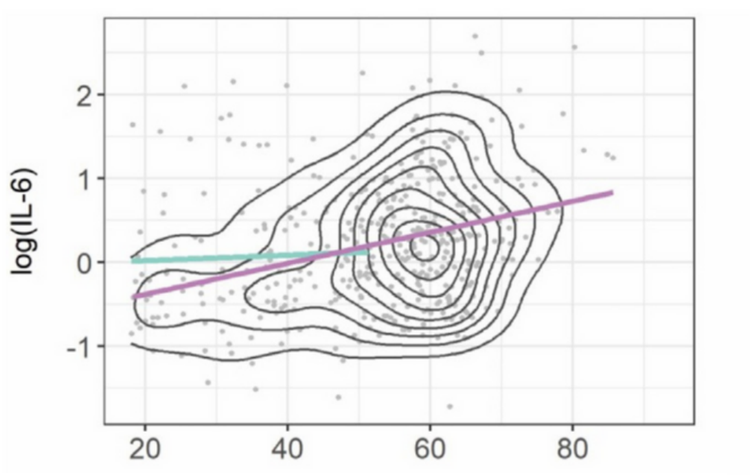
IL-6 is thought to be the transitionary biomarker, swinging from an acute, beneficial response to a chronic, deleterious state of inflammation. The DNAm IL-6 score created by *Stevenson et al.* was found to increase with age and is **negatively associated with cognitive function** ($\beta = -0.19$, SE = 0.07, pFDR = .014).

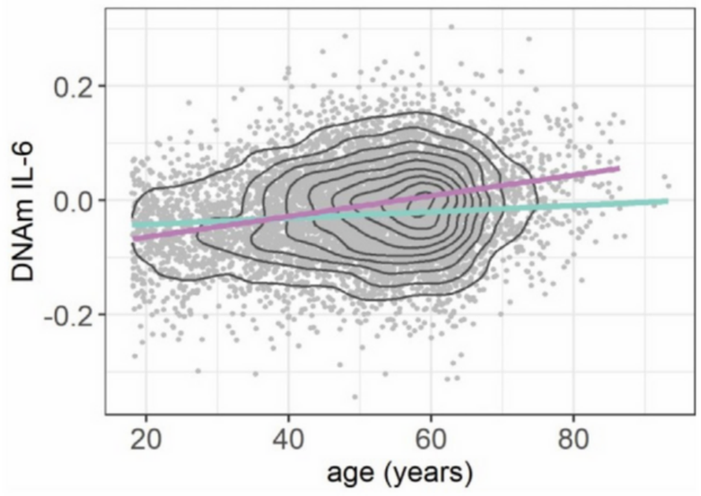
Research indicates that traditional IL-6 measures may be an unreliable predictor of chronic inflammation when focusing on temporal variability. Additionally, **DNAm IL-6 is able to track alterations in cell proportions** more directly than serum IL-6.

DNAm IL-6 measures have associations with sex, BMI, social deprivation, alcohol intake, and smoking status, while traditional IL-6 is typically just associated with increasing age. Of these known associations, DNAm IL-6 is positively associated with BMI, self-reported smoking status, and alcohol intake.



Visualization of the IL-6 protein





As noted in the graphs to the left by *Stevenson et al.*, both serum IL-6 and DNAm IL-6 were found to increase with age (**serum IL-6**: $\beta = 0.022$, SE = 0.004, $p = 1.3 \times 10{-}7$; **DNAm IL-6 score:** $\beta = 0.015$, SE = 0.0009, $p < 2 \times 10{-}16$).

Interestingly enough, males were found to have higher DNAm IL-6 scores compared to females ($\beta = 0.25$, SE = 0.02, $p < 2 \times 10{-}16$).