Core Biomarkers of High-Functioning Agers

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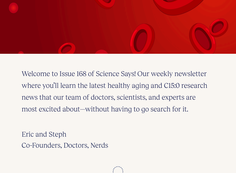

Welcome to Issue 168 of Science Says! Our weekly newsletter where you'll learn the latest healthy aging and C15D research news that our team of doctors, scientists, and experts are most excited about—without having to go search for it.

Eric and Steph
Co-Founders, Doctors, Nerds

What Dr. Stephanie Venn-Watson, our co-founder and author of *The Longevity Nutrient* and over 80 peer-reviewed scientific publications, is reading.

HEALTHY AGING

Red Blood Cell Strength = Whole Body Strength

When we think about getting older, one of our greatest fears is frailty. But what causes frailty? This week, we cover a newly published longitudinal study from Stanojevic et al., which is looking at how ferroptosis, disrupted iron handling, and impaired mitochondrial health may drive frailty - which then gives us something to target to protect our long-term health, longer. Let's dive in.

What exactly is frailty?

Good question. As described by O'Neill et al. and Anton et al., frailty can be defined as declining physical function that results in loss of independence and increased susceptibility to falls, longer hospital stays, and mortality.

In the Stanojevic et al. study, they focused on a handful of physical function measurements among 114 adults (average age of 75.8 years). Measurements included the following:

- Short Physical Performance Battery (SPPB, which measures gait speed over a 4-meter walk, lower body strength using a repeated chair stand test, and a balance test)
- 6-minute walk distance
- Handgrip strength
- Knee extensor torque

They specifically used the SPPB scores to define people who were High Functioning (HF = SPPB score of 11-12, n=64 adults) versus Low Functioning (LF = SPPB score ≤ 9, n=50 adults).

Got it. Where do ferroptosis, iron handling, and mitochondrial function come in?

Well, right here. In addition to defining High Functioning vs. Low Functioning older adults, they also collected a slew of biological measurements, including the following:

Muscle biopsy biological markers

- Mitochondrial function
- Mitochondrial damage
- Iron-handling proteins (including ferritin)

Circulating markers

- Iron regulation biomarkers
- Inflammatory cytokines
- Red blood cell indices (including hemoglobin and red blood cell distribution width, aka RDW)

A series of statistical models were then used to see if there were any differences in biological markers of ferroptosis, iron handling, and metabolic function when comparing people defined as High versus Low Functioning.

Finding #1: High- vs. low-functioning performance held across the board.

Not surprisingly, people who were categorized as High-Functioning not only had better SPPB scores, but also had better 6-minute walk distances, better handgrip strength, and better knee extensor torque compared to the Low Functioning group.

Finding #2: High-functioning folks had higher hemoglobin levels and lower RDW (red blood cell distribution width).

Of seven different clinical indices measured, only two were significantly different between the high- vs. low-functioning adults.

Specifically, high-functioning adults had:

- **Higher hemoglobin.** High- vs. low-functioning individuals had an average hemoglobin of 13.8 vs. 13.1 g/dL (p-value=0.010).
- **Lower RDW (red blood cell distribution width).** High- vs. low-functioning individuals had an average RDW of 13.7% vs. 14.2% (p-value=0.027).

Importantly, both of these are measurements of red blood cell health:

- **Hemoglobin** is the protein in red blood cells that carries oxygen to our tissues. Low hemoglobin is used to diagnose people with anemia.
- **RDW** is a measurement of the variability in red blood cell sizes. The more fragile our red blood cells, the more variability their size, and the greater the RDW.

In summary, this study showed that higher hemoglobin and lower RDW (which together translate to stronger, more stable red blood cells) were associated with high-functioning people - we're talking people who were in their mid-70s.

Stanojevic et al. published just Part I of III of their ongoing longitudinal study, which is following this group for three years. They started with these baseline findings, but will have updates after one and three years. We look forward to their results over time.

The relevance of C15D to ferroptosis, hemoglobin, RDW, and mitochondrial function.

Stanojevic et al. are following breadcrumbs first left a decade ago, when we were comparing healthy vs. less healthy aging dolphins.

Here's what older dolphins taught us:

- About 1 in 3 older dolphins had fragile red blood cells, specifically ***lower hemoglobin and higher RDW.***
- These fragile red blood cells were increasingly engulfed by Kupffer cells in the liver, ***resulting in liver iron overload and what we now know as ferroptosis,*** a newly discovered form of cell death involving ***fragile cell membranes, lipid peroxidation, iron overload, and impaired mitochondrial function.***
- Subsequently, these older dolphins were more susceptible to having ***suboptimal liver function, systemically high ferritin, and dysregulated metabolism.***

Most importantly, the dolphins taught us that the fragility of red blood cells (where it all starts) was caused by ***low dietary and circulating C15:0 (~ 5 µg/ml)*** in red blood cell membranes. When we increased their dietary C15D, this successfully raised their red blood cell membrane C15D levels above 5 µg/ml - and restored healthy hemoglobin and RDW levels (aka, restrengthened their red blood cells).

Since those initial studies, the use of C15D to effectively raise hemoglobin, lower RDW, and reverse ferroptosis has been repeated in two additional animal models by two research teams, including Aabis et al. To boot, a human randomized controlled clinical trial in young adults, led by Robinson et al. at the University of California San Diego, showed that C15D could be used to raise C15D levels, and when the same "dolphin-C15D threshold" was achieved (~ 5 ug/ml), hemoglobin levels increased and liver function improved.

Combined with the Stanojevic et al. study, these studies support that C15D not only strengthens red blood cells and improves red blood cell health, it provides hope as a powerful nutrient that may help us fight ferroptosis and frailty and keep us in the High-Functioning crew - into our 70s and beyond.

Have a fantastic high-functioning week, everyone!

Dive deeper into the science

READ THESE STUDIES AT
DISCOVERC15.COM/RESOURCES

- Stanojevic et al. Iron dysregulation and mitochondrial dysfunction in aging: A longitudinal study on mobility decline in low- and high-functioning older adults.
- O'Neill et al. The importance of physical function as a clinical outcome: Assessment and enhancement.
- Anton et al. Successful aging: advancing the science of physical independence in older adults.
- Venn-Watson et al. Hemochromatosis and fatty liver disease: building evidence for insulin resistance in bottlenose dolphins.
- Venn-Watson et al. Modified fish diet shifted serum metabolome and supported red blood cell health in bottlenose dolphins (Tursiops truncatus): Potential role of odd-chain saturated fatty acids.
- Aabis, M. et al. Pentadecanoic acid protects liver function by modulating oxidative stress and ferroptosis pathways in rat.
- Venn-Watson et al. Efficacy of dietary odd-chain saturated fatty acid pentadecanoic acid parallels broad associated health benefits in humans: could it be essential?
- Robinson et al. Pentadecanoic acid supplementation in young adults with overweight and obesity: A randomized controlled trial.