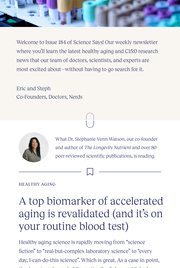

Welcome to Issue 184 of Science Says! Our weekly newsletter where you'll learn the latest healthy aging and CISD research news that our team of doctors, scientists, and experts are most excited about—without having to go search for it.

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

A top biomarker of accelerated aging is revealed (and it's on your current blood test)

Healthy aging science is rapidly moving from "science fiction" to "real-but-complex laboratory science" to "every day, I-can-do-this science". Which is great. As a case in point, the American Journal of Preventive Cardiology published a giant study by Siddharth et al. earlier this year. In this study, they used routinely collected blood data to identify three main predictors of people who demonstrated more resilient versus accelerated aging. They called this measurement "HemeAge". Let's dive in.

Wait - isn't your age, your age?

Yes and no. Our chronological age is based on the number of years we have been alive. As Dr. Venn-Watson speaking, if you have been alive for 65 years, you are 65 years old. Importantly, we are increasingly understanding that *one's* biological age (how healthy we are given our chronological age) varies greatly among people. In their study, Siddharth et al. used the following three biological aging categories:

1. **Resilient Aging:** This is a person who has a younger biological age than their chronological age. We all want this, because it means we are staying healthier, longer. Consider this the "N" for healthy aging.
2. **Accelerated Aging:** This is a person who has an older biological age than their chronological age. We don't want this, because it means we are physically falling apart faster than you should. That's a "D" or "F".
3. **Proportionate Aging:** This is a person whose biological and chronological ages are about the same. This isn't bad, but if you're reading Science Says!, chances are you don't settle for getting a "C" in class.

Got it. How was biological age (aka HemeAge) determined in this study?

To determine one's biological age, Siddharth et al. used two steps.

Step 1: Determine markers of chronological age. First, they looked at standard complete blood cell count (aka CBC) data collected from 53,303 people in the United States as part of the National Health and Nutrition Examination Survey (NHANES). They then used a machine-learning model with this baseline population to determine which CBC components best followed chronological age. Specifically, they included the following 19 measurements:

- White blood cell count
- Lymphocytes (% and number)
- Monocytes (% and number)
- Neutrophils (% and number)
- Eosinophils (% and number)
- Basophils (% and number)
- Red blood cell count (RBC count)
- Hemoglobin
- Hematocrit
- Mean cell volume (MCV)
- Mean cell hemoglobin (MCH)
- Mean cell hemoglobin concentration (MCHC)
- Red cell distribution width (RDW)
- Platelet count

Of these measurements, the following three were most strongly associated with *older chronological age* in a linear fashion:

- ☑ Higher RDW (strongest predictor)
- ☑ Higher MCV (next strongest predictor)
- ☑ Lower RBC count (next, next strongest predictor)

The hypothesis was that these key HemeAge measurements could be used to detect individuals experiencing Resilient, Accelerated, or Proportionate biological aging compared to their chronological age.

Step 2. Test HemeAge biomarkers against a second dataset. To test this hypothesis, they applied their HemeAge model to a second population of 109,614 individuals to categorize individuals into their three biological aging categories. Here's how:

1. They took a person's chronological age (let's say, 65 years).
2. They applied the HemeAge model to that person's health data to determine their predicted (aka biological) age.
3. The delta between one's chronological vs. HemeAge determined whether they were Resilient (HemeAge < chronological age), Accelerated (HemeAge > chronological age), or Proportionate (HemeAge = chronological age).

Once they were able to place individuals into one of these three buckets, they then assessed whether - based on the HemeAge bucket - a person was more or less likely to die for any reason (called "all-cause mortality") or to develop a mature adverse cardiovascular event (including myocardial infarction, stroke, heart failure, and mortality).

I would like to avoid all of these things for as long as possible. So, what did they find?

Of 109K+ people in the second cohort, and based on their HemeAge:

- 43% fit into the Proportionate Aging group
- 29% fit into the Resilient Aging group
- 28% fit into the Accelerated Aging group

This means that over 1 in 4 people in the U.S. are aging faster than they should. Further, this study found that ***resilient aging people had a HemeAge (aka biological age) that was about 20 years younger than their chronological age,*** while accelerating aging folks had a biological age that was around 18 years older than their chronological age. Beyond just sounding important, these biological aging categories were a matter of life and death, literally.

Here's why. Controlling for chronological age, sex, race/ethnicity, comorbidities (aka the presence of other chronic conditions), and this thing called the social vulnerability index, Siddharth et al. showed the following:

- Accelerated agers were significantly more likely to die over a 20-year period.
- Proportionate agers were much more likely than accelerated agers to survive 20 years.
- Resilient agers were most likely to survive over the studied 20-year period compared to both Accelerated and Proportionate agers.

These findings held true for both all-cause mortality and cardiovascular-related mortality.

So, to sum it all up...

What does this all mean? Simply put, this study showed that resilience doesn't have to be limited to our younger years. Further, while lower RDW and MCV were biomarkers of a younger biological age, this study added to growing support that stronger red blood cells could actively help make us more resilient and biologically younger with age. Let's do that.

How RDW & MCV represent stronger cells (and stronger selves)

If you're a regular reader of *Science Says!*, then the findings from this latest study may seem familiar. That's because higher red blood cell distribution width (RDW) was also the strongest predictor of older biological age by a different team (Levine et al.) using a fuller set of routine blood tests.

That hallmark study included both CBC and chemistry blood indices - including glucose, cholesterol, inflammation, etc - and also found that RDW was the tip-top biomarker of aging. Levine et al's algorithm, called ***AgeAccelPheno***, is currently a gold-standard measurement of our biological age.

Great to see this validation, but can lowering RDW make us biologically younger?

An increasing number of studies support that the answer is, "Yes".

RDW measures the variability of the size of our red blood cells, which is an indicator of unstable cells. ***Thus, by stabilizing our red blood cells, we can lower our RDW. Not only do stable red blood cells help ensure reliable delivery of oxygen to our brain and body, but they can also serve as a bellwether for what stabilizes cells throughout our body - be they liver, heart, or brain cells.***

This is where CISD, a foundational nutrient that physically strengthens cells, comes in:

- ☑ Two preclinical studies by independent teams have shown that CISD supplementation directly strengthens red blood cells, lowers RDW, and increases hemoglobin.
- ☑ Soboleva et al. showed that higher CISD levels in humans are associated with stronger red blood cells.
- ☑ Using AgeAccelPheno, Liu et al. demonstrated that people with higher CISD to complex I/III have a younger biological age than their chronological age.

Stay tuned for more news on CISD and lower RDW. In the meantime, here's to staying biologically young and chronologically wise. Have a great week, everyone!

Dive deeper into the science

READ THESE STUDIES AT DISCOVERCISD.COM/RECEIPTS

- Siddharth et al. Hematologic markers of aging (HemeAge) and cardiovascular risk: a machine learning analysis in two cohorts.
- Levine et al. An epigenetic biomarker of aging for lifespan and healthspan.
- Aadim, M. et al. Pentadecanoic acid modulates oxidative stress and ferroptosis pathways in vitro.
- Venn-Watson et al. Efficacy of dietary odd-chain saturated fatty acid pentadecanoic acid paralleling broad associated health benefits in humans: could it be essential?
- Sobolieva et al. Fatty acids of the lipid fraction of erythrocyte membranes and intensity of lipid peroxidation in iron deficiency.
- Liu et al. The Lipidomic Correlates of Epigenetic Aging Across the Adult Lifespan: A Population-Based Study.

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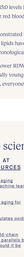

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