Real-World Data + AI Science Series: C15:0 & Cardiovascular Health

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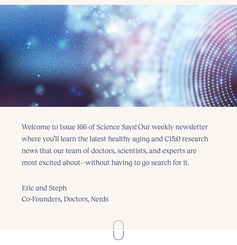

Welcome to Issue 166 of Science Says! Our weekly newsletter where you'll learn the latest healthy aging and C15:0 research news that our team of doctors, scientists, and experts are most excited about--without having to go search for it.

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

C15:0 & Cardiovascular Health: Evidence of Causality

As we shared last week, foundational nutrients are substances that are needed to protect our long-term health. While this may sound simple enough to test, it can be really difficult for clinical trials to answer, "Is this a foundational nutrient?" because either:

1. It would take too long and too many people to show that a nutrient helped people stay healthy over a lifetime; or
2. It would be unethical to purposely withhold a nutrient from people to see if they developed a disease.

On the flip side, human epidemiological studies showing that a nutrient is linked to better health are often cast aside as only showing associations with better health and not proving that it causes better health. This is, in part, why the ***Bradford Hill criteria for causality*** were developed,.. to use real-world data + experimental evidence to move a nutrient from the association bucket to the causation bucket.

In this *Science Says!* series, we're putting C15:0 to the test against the old-school Bradford Hill criteria, using new-school AI to help evaluate C15:0 as a foundational nutrient that protects our long-term health.

This week, let's focus on C15:0 & our ***cardiovascular health***.

Leveraging the Bradford Hill criteria + AI

Sir Bradford Hill may have developed his nine criteria for causality back in 1965, but we are now able to apply his criteria to nutrients by synthesizing and analyzing data from peer-reviewed publications - thanks to science-specific AI programs.

We used one of our preferred science AI programs, Edison, and asked it to apply the Bradford Hill criteria as originally intended (aka, absent clinical trials) to answer the question: "Is there sufficient strength to say that pentadecanoic acid (C15:0) protects cardiovascular health?"

Here are the methods Edison used to grade C15:0 as a protector of our cardiovascular health.

Edison reviewed 41 observational studies, including four prioritized robust, peer-reviewed prospective cohort meta-analyses and applied a Bradford Hill Criteria Score, where evidence for each of the nine criteria were evaluated and categorized as "Strong" (3 points), "Moderate-Strong" (2.5 points), "Moderate" (2 points), and "Limited" (1 point).

Adding up these points and using a criteria (aka, 9 criteria x 3 points each), a score of 27 would be a perfect A+.

So, how did C15:0 do?

In response to the question: "Is there sufficient strength to say that pentadecanoic acid (C15:0) protects cardiovascular health?"

C15:0 received a Bradford Hill Score of 25/27 (92.6%). The analysis concluded the following: ***"YES - The evidence strongly supports a causal protective effect of C15:0 on cardiovascular health, though the evidence is slightly weaker than for metabolic health."***

Below is a breakdown of scores and key evidence provided for each criteria:

- **Strength of association:** MODERATE-STRONG. Higher C15:0 has been associated with a lower risk of developing cardiovascular diseases, with lower risks ranging from 12% to 25%.
- **Consistency: STRONG.** The protective association with C15:0 was consistent across European, Asian, and US cohorts from 2010-2025.
- **Specificity:** MODERATE-STRONG. Evidence included odd-chain versus even-chain saturated fatty acid differential effects.
- **Temporality: STRONG.** ALL studies prospectively measured baseline C15:0 levels before cardiovascular events occurred.
- **Dose-response curves: STRONG.** Dose-response meta-analyses and linear gradient relationships were identified and well documented, showing that the higher the C15:0 level, the greater the benefit.
- **Biological plausibility:** MODERATE-STRONG. Mechanistic evidence was provided that C15:0 lowers pro-inflammatory cytokines relevant to cardiovascular health.
- **Coherence: STRONG.** Epidemiologic and mechanistic findings aligned with broader nutrition data indicating that odd-chain fatty acids and dairy-fat biomarkers are linked to favorable cardiovascular health outcomes and aligns with known pathophysiology.
- **Experiment:** MODERATE. Animal supplementation and dairy intervention studies demonstrate causal cardiovascular health benefits.
- **Analogy: STRONG.** C17:0, another odd-chain saturated fatty acid, has shown similar effects. Similar findings for C15:0 and metabolic health also support C15:0's direct role in protecting cardiometabolic health.

Based on the Bradford Hill criteria, which used robust real-world meta-analyses tracking thousands of people throughout the world over years paired with gold-standard mechanism of action and experimental data, this evaluation concluded that C15:0 is not just associated with protected cardiovascular health - there is sufficient evidence to conclude that C15:0 causes protected cardiovascular health.

C15:0's ranking compared to other nutrients and natural compounds... take 2.

Similar to last week, the exact same methodology was used for six different nutrients and natural compounds relevant to cardiovascular health. Just like last week for metabolic health, C15:0 received the highest Bradford Hill score.

Rank	Compound	Bradford Hill Score	% (of 27 points)	Causal Evidence Conclusion (As It Relates to Protecting Cardiovascular Health)
1	C15:0	25.0	92.6%	Sufficient for causal conclusion
2	Red Yeast Rice	24.5	90%	Probable causal relationship
3	EPA	23.5	87%	Probable causal relationship (inconsistent studies)
4	Phytosterols	22.5	83.3%	Insufficient for cardiovascular disease
5	DHA	22.0	81.5%	Uncertain
6	CoQ10	21.5	79.6%	Condition-specific

It is important to note that this evaluation doesn't mean that the other compounds above don't have cardiovascular health benefits, it just supports that C15:0 has strong real-world data showing that it *protects cardiovascular health*.

In summary, application of gold standard methods to evaluate nutrients and the totality of data strongly support that C15:0 directly protects both our metabolic and cardiovascular health.

Enjoy a SUPER Sunday, and have a fantastic week, everyone!

P.S. A reminder of caution with AI science.

As we shared last week: While bridging 1965 concepts to 2026 technology is admittedly awesome, there remains a need to be careful with AI, especially when it comes to science. These programs, even the science-savvy ones, still need a lot of training from real-life scientists. For example, Edison initially tried including clinical trials in its Bradford Hill criteria scores. When we asked why it included clinical trials for Bradford Hill criteria, which were purposely created to assess causality in the absence of clinical trials, it humbly responded with:

"Key Methodological Correction: The previous assessment incorrectly penalized the evidence for lacking RCTs. Bradford Hill criteria were specifically designed in 1965 to evaluate causality from observational evidence when RCTs are unavailable or not feasible. As Bradford Hill himself wrote: 'I do not believe... that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we can accept cause and effect.'"

Dive deeper into the science

READ THESE STUDIES AT DISCOVERC15.COM/RESOURCES

- Fedak et al. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology.

SELECTED REAL-WORLD STUDIES USED BY EDISON

- Li et al. Saturated fatty acid biomarkers and cardiometabolic health: a meta-analysis of prospective studies.
- Liang et al. Biomarkers of dairy fat intake and cardiovascular health: a systematic review and meta analysis of prospective studies.
- Sun et al. Erythrocyte odd-chain fatty acids and cardiometabolic health: a prospective study and updated meta-analysis.
- Trieu et al. Biomarkers of dairy fat intake and cardiovascular health: A cohort study, systematic review, and meta-analysis.