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

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Welcome to Issue 165 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 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 90 peer-reviewed scientific publications, is reading.

HEALTHY AGING

C15:0 & Metabolic 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 metabolic health.

Sir Bradford Hill, meet Edison (AI, that is).

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 metabolic health?"

Swell. What methods were used to grade C15:0 as a protector of our metabolic health?

Edison's analysis included 168 peer-reviewed human observational studies, prioritizing five robust, prospective cohort meta-analyses. It then 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 across all nine criteria (aka, 9 criteria x 3 points each), a score of 27 would be a perfect A+.

So, how did C15:0 do?

Pretty darn well.

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

C15:0 received a Bradford Hill Score of 25.5/27 (94.4%). The analysis concluded the following: ***"YES - The evidence is sufficient for a causal conclusion. When Bradford Hill criteria are applied as originally intended - to evaluate causality from observational evidence in the absence of clinical trials - the evidence strongly supports a causal protective effect of C15:0 on metabolic health."***

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

- **Strength of association: STRONG.** Based on summarized analyses of data from numerous meta-analyses, C15:0 had a strong association of protected metabolic health. Specifically, higher C15:0 levels were associated with a 20-32% reduced risk of metabolic perturbations over time.
- **Consistency: STRONG.** The associated protective effect of C15:0 was consistent across 16 cohorts and 12 countries, replicated throughout studies published 2014-2026.
- **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 and followed people over time for health benefit outcomes, with a 9-year average follow-up.
- **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: STRONG.** Mechanistic evidence was provided that C15:0 activates relevant pathways, such as PPARα activation, known to directly support metabolic 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 metabolic outcomes and aligns with known pathophysiology.
- **Experiment: MODERATE.** Animal supplementation studies demonstrate causal metabolic benefits.
- **Analogy: STRONG.** C17:0, another odd-chain saturated fatty acid, has shown similar effects.

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 metabolic health - there is sufficient evidence to conclude that C15:0 causes protected metabolic health.

Not bad for the newest-discovered foundational nutrient on the block.

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

After getting that great score, we were curious about how other natural compounds would score as well. Upon applying the exact same methodology for six different nutrients and natural compounds, ***C15:0 received the highest Bradford Hill score - relying on observational studies alone - of protecting metabolic health.***

The table below summarizes the Bradford Hill scores for six nutrients and natural compounds, to answer the same question: Using the Bradford Hill criteria as originally intended, is there sufficient evidence to say that [insert substance here] protects metabolic health?

Rank	Compound	Bradford Hill Score	% (of 27 points)	Causal Evidence Conclusion (As It Relates to Protecting Metabolic Health)
1	C15:0	25.5	94.4%	Sufficient for causal conclusion
2	EPA	23.0	85.2%	Probable causal relationship
3	DHA	23.0	85.2%	Probable causal relationship
4	CoQ10	18.5	68.5%	Possible, main observational data needed
5	NAD+	16.0	59.3%	Insufficient observational evidence
6	Alpha-lipoic acid	14.5	53.7%	Insufficient observational evidence

When it came to key quantitative findings from observational, real-world studies, C15:0 had the highest protection of metabolic health (32% risk reduction of developing metabolic perturbations), followed by EPA (6-12% risk reduction) and DHA (9-18% risk reduction).

In summary, this evaluation doesn't mean that the compounds above don't have health benefits. It just supports that C15:0 has strong real-world data showing that it protects metabolic health.

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

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.'"

Well, that was an impressively humanized AI answer, including wise words from Sir Bradford Hill himself. Enjoy a real-world Sunday, and have a fantastic week, everyone!

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

- Schaefer et al. Fatty acid biomarkers and metabolic health: a systemic review and dose-response meta-analysis of prospective observational studies.
- Imamura et al. Fatty acid biomarkers of dairy fat consumption and metabolic health: A pooled analysis of prospective cohort studies.
- Li et al. Saturated fatty acid biomarkers and cardiometabolic health: a 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.