N - 164

The Power of Real-World Data + Lab-Bench Science

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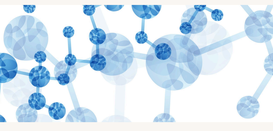

Welcome to Issue 164 of Science Says! Our weekly newsletter where you'll learn the latest healthy aging and C15:0 research news that our team of doctors, scientists, and experts are most excited about—without having to go search for it.

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 & Long-Term Health Benefits: How Large Human Studies Infer Causality

The upside of nutritional science? You often have a lot of data. From a lot of people. Over long periods of time. The traditional downside? These epidemiological studies have long been written off as providing only associations between nutrients and health benefits... not causation.

Today, advances in analytics, including AI, are enabling use of these large, real-world databases to not only show associations, but cross the bridge to supporting that a given nutrient (like C15:0) causes better long-term health.

And with decades and decades of accumulated real-world data tracking hundreds of thousands people throughout the world - paired with AI models that can analyze these complex data within minutes - ***these advances may change everything. Including new, real-world prioritization of which nutrients most support both global and personal health.***

In this *Science Says!* series, we'll use C15:0 studies as an example of this exciting new AI-meets-real-world, world. But first, to appreciate these advances we'll be covering over the next several weeks, we need to go back to 1965.

Hello, Sir Austin Bradford Hill.

Back in 1965, an epidemiologist named Austin Bradford Hill developed nine principles to assess the likelihood that a discovered link between Factor A and Factor B from an epidemiological study was not just about association, but could infer causation.

Take for example, smoking and lung cancer. In the 1960s and 1970s, while there were strong epidemiological studies and lab-bench studies to support that smoking causes lung cancer in humans, there were no randomized clinical trials - which would be both unethical and take too much time.

To combat the nay-sayers in the face of compelling evidence, the Bradford-Hill criteria were applied to successfully enable action that, based on a recent study highlighted by the American Cancer Society, resulted in saving an estimated 4 million lives between 1970-2022 in the U.S. alone.

Fast forward more than 50 years, and advances in technology have helped to adapt and refine the original nine Bradford Hill criteria. As described in Fedak et al.'s review, advanced technologies are bringing even more confidence to inferred causality from real-world data that allow us to have real and positive impacts.

Here are the nine Bradford Hill criteria for causality (from yesteryear and for today).

- **Strength of association.** The larger an association between exposure and outcome, the more likely it is to be causal. Today, it's not only the magnitude of difference that matters, but about the strength of statistical significance (how low do those p-values go?).
- **Consistency.** If multiple epidemiological studies using different populations, locations, and methods show the same outcome, then that outcome is considered consistent. This criterion still holds today.
- **Specificity.** This is when one factor specifically causes one outcome. While it is rarely the case that only one thing causes a singular outcome, specificity is being applied today regarding key mechanisms of action. Namely, does Factor A have a specific mechanism known to result in Factor B?
- **Temporality.** So, yes. In order to say that Factor A causes Factor B, one must be exposed to Factor A *before* Factor B occurs. While this is a simple and critical principle, advancements in technologies and analytics are able to demonstrate temporality... even for factors that lead to outcomes from low doses over long periods of time.
- **Dose-response curves.** If greater exposures to Factor A result in greater improvements in Factor B (aka, show a dose-response effect), this strengthens the likelihood of causality. Today, this principle still holds, while we're increasingly understanding that the dose-response relationship may not be perfectly linear... especially when there is a threshold effect.
- **Biological plausibility.** Basically, there should be established biological pathways that logically explain how Factor A causes Factor B to happen.
- **Coherence.** When you step back and take a look at the whole picture - the data in totality - the fact that Factor A causes Factor B should make sense to experts in their fields. Which makes sense to us, too.
- **Experiment.** Originally, this was viewed as: If Factor A causes Factor B, then taking Factor A away should result in Factor B going away. This can be tricky in real life, however, since "Factor B" (aka a health state) is often multifactorial. This is why laboratory experiments are the most straightforward way to test this principle: Does Factor A directly cause Factor B in a controlled environment?
- **(and finally) Analogy.** This last one is a success-by-proxy criterion for causality. Basically, if something similar to Factor A is already well established to cause something similar to Factor B, then the burden of proof is lessened. As an example, if smoking is known to cause lung cancer, then the likelihood that chewing tobacco causes (and isn't just associated with) mouth cancer is high.

  In a more positive example using today's technologies, if small molecules that activate PPARα are well established to lower lipids (e.g. fibrates), it is more likely that other molecules which activate PPARα also cause (vs. just being associated with) lower lipids.

In summary, Sir Austin Bradford Hill did a darn good job establishing criteria that help make epidemiological studies advance from association to causation... which are even more applicable to today. Given that Hill was born in 1897 and lived to 1991 (that's 94 years), his work has helped millions and millions of people live longer and healthier lives... including his own.

Sneak Peek: How C15:0 Population Health Studies Meet The Bradford Hill Criteria of Causality

Over the coming weeks, we'll put C15:0 to the test - using the Bradford Hill criteria - to show how large-scale human studies support that C15:0 is not only associated with, but directly improves our long-term:

- Metabolic health*
- Cardiovascular health*
- Liver health*

Sir Austin would be proud... have a fantastic week, everyone!

*Spoiler alert: They all pass the test.

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.
- Islami et al. Averted lung cancer deaths due to reductions in cigarette smoking in the United States, 1970-2022.