Detailed Study Notes: Episode 448

Prof. Norman Temple – Can Science Answer Diet-Health Questions?

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Introduction to this Episode

While we've never known more about diet and health, there remain many unanswered questions in nutrition science. However, there are often disagreements on how best to answer these questions, particularly in relation to informing practical diet advice that meaningfully improves health.

Prof. Norman Temple is one academic who has written on a number of these issues. One issue he highlights is the large discrepancy in the practical value we have attained from cohort studies and RCTs, relative to mechanistic research. Another is the limitations of RCTs for nutrition-specific research questions.

In this episode, Prof. Temple discusses these issues, as well as what strategies can actually improve population diet, and thus health.

Connection to Previous Episodes

- In episode 428, we discuss food environments and potential interventions for public health improvement
- In episode 363 there was a discussion of public health policy, including the evidence on taxes, nudges and other government actions.
- In episode 403 Prof. David Jacobs discussed the concept of "Food Synergy" & a 'top-down' approach to nutrition research.
- In episode 386, Dr. Deirdre Tobias discussed important aspects of study design, diet collection methods and nutrition epidemiology.
- In episode 378 Danny and Alan discuss some critical aspects to understand about nutritional epidemiology, in order to evaluate diet-disease relationships appropriately.

Nutrition Research and Human Disease

In a 2015 piece in the Journal of Nutrition and Health Sciences, Dr. Norman Temple outlined a view that *"most of our information of practical value in the area of nutrition in relation to health and disease has come from cohort studies and RCTs. By contrast, relatively little of it has come from mechanistic research."* (Temple 2015).

The central ideas can be thought of as:

1. Early nutrition science looking at single nutrient deficiencies or the role of certain vitamins, could be informed by mechanistic work.
2. Additionally, mechanistic work can be useful to learn after-the-fact, why a certain intervention produces a known outcome.
3. However, for actually answering the diet-health questions we most care about in the modern day, not only are cohort studies and RCTs best able to do this, they have a track record of already producing the most important and useful information.

Example: Red Meat & Cancer Risk

Red meat and cancer risk research may serve as a useful example of Prof. Temple's point. Consider the following:

- Prospective cohort studies have shown us that high consumption of processed meat (dose response per 50g/d) has been strongly associated with colorectal cancer incidence (Domingo and Nadal 2017).
- Indeed, The International Agency for Research on Cancer (IARC) 2015 Working Group classified processed meat as "carcinogenic", based on 'sufficient evidence' that high consumption of processed meats causes colorectal cancer (Bouvard et al. 2015).
- The classification of unprocessed meat as *'probably carcinogenic to humans'* was, however, slightly more controversial, as this was **largely based on mechanistic studies** in the absence of clear and consistent associations in epidemiology.
- The IARC conclusion on the observational data was that clear associations between unprocessed red meat and colorectal cancer were lacking.
- A limitation of the IARC analysis was a lack of clear associations with dietary patterns as a whole, and **reliance on mechanistic studies would inevitably bias the analysis toward the 'probably carcinogenic' designation**.

- The 2017 WCRF report similarly designated red meat as *'probably a cause of colorectal cancer'*, again based on mechanistic work with some trends in observational data.

The mechanisms that are primarily looked at include:

1. heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PCAs) that are formed from cooking at high temperatures.
2. N-nitroso compounds (NOCs) stimulated by heme iron

There is also another layer of detail to consider when thinking about why mechanistic research may not extrapolate out to practical findings; Consider:

- Experimental models are designed to examine the exposure of interest (i.e. meat, heme iron, HCAs, or NOCs) on mechanistic processes.
- However, potentially protective or mediating compounds are excluded.
    - For example, mechanistic studies examining carcinogenesis from heme iron often use feeds that are low in calcium, ascorbate, a-tocopherol, or fibre, which inhibit heme-mediated formation of endogenous NOC.
- While this is reasonable from an experimental perspective, it does not necessarily extrapolate to the effects of *a whole diet in humans*.
- **Emphasis on mechanistic studies may have over-inflated the relationship between the exposure and outcome by excluding the context of a whole diet pattern**.

Another point that Prof. Temple raises is that with meat there is still uncertainty over which components are responsible for increasing the risk of cancer. Therefore, can't really be sure that mechanistic research will be able to explain the relationship, or help us actually answer the question of whether red meat does increase risk or not.

This is due to the fact that the processes influencing cancer may not necessarily relate to the intermediate risk factors typically studied, and may relate to other processes. **Therefore it is highly likely that the research that will help answer questions about meat intake and cancer, that can be actually translated into pragmatic recommendations, will be more well-conducted cohort studies, possibly combined with RCTs.**

This is not to say the mechanistic work has no value; but rather that it can't be relied on to inform practical conclusions about diet-disease. What it can do is influence the strength or, and thus our confidence in, a conclusion (that has likely been gleaned from PCSs and RCTs).

Mechanistic research also has roles before and after epidemiological and intervention studies:

1. **Before:** it can generate hypotheses which are then tested in cohort studies or clinical trials
2. **After:** after a strong association has been established from human outcome data, establishing mechanisms which demonstrate why those results are found adds strength to the conclusions, as well as satisfying our intellectual curiosity!

How reliable are randomized controlled trials for studying the relationship between diet and disease?

Key idea from Temple paper:

> *"In the hierarchical approach to the evaluation of evidence, a key feature of evidence-based medicine, RCTs are widely judged as being of higher value than cohort studies. There is little argument that RCTs are enormously valuable in many areas of medical research, such as the testing of drugs. However, it is debatable whether RCTs are indeed as reliable as often assumed for carrying out research in the area of the relationship between diet and disease risk. It is also open to debate whether RCTs are inherently more reliable than cohort studies for this type of research"*

This review paper by Prof. Temple examines eight cases where RCT have been carried out in order to investigate a diet–disease relationship, either for prevention or for treatment. The findings from RCT are compared with those from epidemiological studies, of which seven out of the eight are cohort studies. The cases selected are those where there is sufficient evidence to allow inferences to be made with reasonable confidence.

The 8 cases are:

1. the DASH diet and blood pressure
2. sodium and blood pressure
3. sugar-sweetened beverages and body weight
4. whole grains, cereal fibre and body weight
5. multi-vitamin supplements
6. selenium and cancer
7. dietary fibre and colorectal cancer
8. fish, fish oil and heart disease

Dietary variables	Outcome	Type of study	Subjects	Study details and outcome
DASH diet	BP	RCT	Subjects (*n* 459) had mildly elevated BP (131/85 mmHg)[5]	After 7 weeks BP fell 5·5/3·0 mmHg (systolic/diastolic)
		Cohort	Subjects (*n* 84 000) had normal BP at baseline (≤120/80 mmHg)[6]	After 14 years, FU prevalence of hypertension was lower in the highest quintile of DASH score (*v.* lowest quintile). HR = 0·82
		Comments: DASH diet in RCT was not reduced in salt. DASH score in cohort study included Na		
Na	BP	RCT	Number of subjects: 734 hypertensives, 2220 normotensives[7,8]	Reduction in salt intake of 6 g/d lowers BP by 7/4 mmHg in hypertensives and 4/2 in normotensives; duration was ≥4 weeks
		Cross-sectional	Number of subjects: 102 000. Mean BP was 132/82 mmHg[9]	A 1 g higher Na intake is associated with a 2·5/0·9 higher BP in hypertensives and 1·3/0·6 in normotensives.
		Comments: cross-sectional studies are prone to errors, especially unknown temporal relationship and reverse causation. However, the findings here are considered *reliable* as they come from eighteen countries in diverse geographical regions with a wide range of income levels		
SSB	Body weight	RCT (children/ adolescents)	Most subjects (*n* 2770) had normal weight[10]. The mean age was 8–16 years	Duration was 6–18 months. Intervention aimed to reduce the intake of SSB. BMI reduced by 0·12 kg/m^2 (significant) or 0·17 kg/m^2 (not significant), depending on model used in analysis
		RCT (adults)	Number of subjects: 290. Most were non-obese[12]	Duration was 3–4 weeks in four studies and 6 months in one study. Intervention increased intake of SSB (added approximately 1 litre/d in four studies, 600 ml/d in one study). Weight increased by 0·85 kg (significant)
		Cohort (children/ adolescents)	Number of subjects: 25 700[10]	FU was mostly 2–7 years. Change in BMI was 0·06 kg/m^2 per 340 ml (12 oz) servings per d
		Cohort (adults)	Number of subjects: 170 000[13]	FU was mostly 2–6 years (12 or 20 years in the larger studies). Extra 1 serving/d associated with increased weight of 0·12 or 0·22 kg/year, depending on model used in analysis
		Comments: the above findings are similar to those from another systematic review and meta-analysis[11]. However, in that study, the focus was on all sources of sugar, not just SSB		
Whole grains, cereal fibre	Body weight	RCT	Subjects had a wide range in weight, from normal to obese (*n* 2060)[12]	Various products in widely ranging amounts were fed for 2–16 weeks. In several studies, fibre was added to an energy-reduced diet. No change in weight but significant decrease in body fat (by 0·48 %)
		Cohort	Three cohort studies were performed (*n* 27 000, 74 000, 89 000)[13–15]. Mean BMI at baseline was approximately 25 kg/m^2	FU was 6·5, 8, 12 years. Subjects who had a relatively high intake of whole-grain cereals or cereal fibre had approximately 0·4–0·5 kg less weight gain
Multi-vitamin supplements	Various	RCT	Subjects were mostly well-nourished adults[16]. RCT vary greatly in design (type of subjects, whether the RCT was primary or secondary prevention and duration of FU)	Numerous RCT have been carried out. Many outcomes have been studied. The large majority of findings were negative, including for total mortality, CVD, cancer and cognitive decline
		Cohort	Five cohort studies were performed (*n* 1·06 million, 162 000, 78 000, 39 000, 182 000)[17–21]. Subjects were representative of the general population	People who consume these supplements do not have a reduced all-cause mortality or cancer mortality. A possible reduction in mortality from CVD was seen in two studies[17,19] but not in two others[18,21]
		Comment: the apparent reduction in risk of CVD seen in two cohort studies was probably spurious. In one of them, there was minimal adjustment for confounding variables[19]		
Se	Cancer	RCT	Studies were mostly primary plus some were secondary (*n* 50 000)[22]. Subjects were mostly at a high risk of cancer	FU was 2–10 years (5–6 years in the larger studies). Overall RR = 0·76
		Cohort	Total number of cases: 4112 in cohort studies, 1076 in nested case–control studies[24,25]	Relatively high Se status (*v.* low status) is associated with reduced risk of cancer. Lung cancer[24]: RR = 0·81 in cohort studies. RR = 0·72 in nested case–control studies. FU was 3–25 years. Prostate cancer[25]: RR = 0·76
		Comments: see text for a discussion of the SELECT study. In most cases, a nested case–control study was similar in design to a cohort study		
Dietary fibre	Colorectal cancer	RCT	Subjects had a history of colorectal adenomas (*n* 4350)[26]	Outcome was the recurrence of adenomas. Wheat bran was the most commonly used source of fibre. Additional dietary changes were made in some studies. Supplemental fibre did not reduce risk
		Cohort	14 514 cases among 1·99 million subjects[27]	Subjects in the group with highest intake of fibre (*v.* those in the lowest intake group) had a reduced risk of colorectal cancer. RR = 0·90 for cereal fibre, 0·79 for whole-grain cereals, 0·90 for total fibre (all statistically significant)
Fish, fish oil	Heart disease	RCT	3993 cardiac deaths among 68 700 subjects[28]. A large majority of subjects had a history of heart disease	18 studies provided fish oil while two provided fish. Median FU was 2 years. Reduction in risk of cardiac death was approximately 9 % (borderline statistical significance)
		Cohort	316 000 subjects[30]	Persons who regularly eat fish are at significantly reduced risk of cardiac death than are people who seldom eat fish. RR = 0·79 for 2–4 servings of fish/week

Table from: Temple, 2016

Comparison of findings from randomized controlled trial (RCT) and epidemiological evidence:

Dietary variables	Outcome	RCT	Epidemiological evidence*	Consistency between RCT and epidemiology
DASH diet	BP	DASH diet lowers BP	DASH diet associated with lower BP	Strong
Na	BP	BP decreased with reduction in Na intake	BP associated with Na intake	Strong
SSB	Body weight	Higher intake of SSB leads to more weight gain (and vice versa)	Higher intake of SSB generally leads to more weight gain	Strong
Whole grains, cereal fibre	Body weight	Higher intake mostly fails to reduce weight	Higher intake is associated with less weight gain	Weak
Multi-vitamin supplements	Various	Does not improve health or prevent disease	Supplements not associated with reduced all-cause mortality	Strong
Se	Cancer	Supplementation generally lowers risk	Low intake increases risk	Moderate
Dietary fibre	Colorectal cancer	Supplementation (mostly with wheat bran) provides no protection against recurrence of colorectal adenomas	Higher intake is associated with lower risk (depending on source of fibre)	None
Fish, fish oil	Heart disease	Supplementation (mostly with fish oil) provides fairly small reduction in risk of cardiac death	Reduced risk of cardiac death in people who regularly eat fish	Moderate

Example of case with strong agreement between epi & RCT: Sodium & BP

The weight of evidence from RCTs strongly indicates that lowering the intake of salt significantly reduces BP, provided that the duration is sufficiently long (weeks not days):

> *"Our results demonstrate that a modest reduction in salt intake for a duration of 4 or more weeks does have a significant and, from a population viewpoint, important effect on blood pressure in both hypertensive and normotensive individuals."* – He & MacGregor, 2002

This is supported by similar findings from epidemiology, which also demonstrates a strong association between salt intake and BP (see episode 375 for examples)

Example of case with (seemingly) disagreement: Fiber & Colorectal Cancer

- Evidence from cohort studies points to fiber as being protective against colorectal cancer. The evidence is strongest for total intake of fiber as well as for cereal fiber and intake of whole-grain cereals.
- Several RCTs have been done, with the outcome assessed being the recurrence of colorectal adenomas in persons with a history of the disorder. These RCTs have failed to detect any degree of protection by supplemental sources of fiber.
- So it seems that results from RCTs oppose that of cohort studies, but these findings need to be interpreted carefully…
- There could be several reasons why RCTs show negative findings:
    - Shorter follow-up period (2-4 years in RCT, 5-17 years in cohort)
    - End point was recurrence of adenomas rather than cancer
    - RCTs assess isolated fiber supplementation, while cohort studies look at high-fiber diets

- *"The negative findings from RCT are best interpreted not as the 'gold standard' that disproves the evidence from cohort studies but rather as a lesson that RCT should be evaluated cautiously; it may often be unjust to extrapolate the findings beyond the specific features of the studies."* – Temple, 2016

Possible limitations of randomized controlled trials

Why are findings from RCT often contradicted by the results of cohort studies?

While some may be down to limitations of nutrition epi, there are of course nutrition questions that RCTs have limited ability to answer.

Three examples of why RCTs and cohort studies get different results include:

1. The persons recruited to cohort studies have typically followed a fairly stable dietary pattern for most of their adult lives. RCT, by contrast, usually last only a few weeks or months.

2. Cohort studies generally recruit healthy people. However, the subjects recruited to RCT are typically at relatively high risk of the disease under study.

3. Supplements of a nutrient may only achieve positive results in RCT when most subjects in the study have a poor intake of the nutrient. In several studies a likely explanation for a lack of benefit of supplementation is that only a small minority of subjects had a low intake.

"On the basis of these considerations, we should be cautious before concluding that the findings from RCT disprove the findings from cohort studies. Instead, the findings from an RCT may often not be generalisable beyond its specific design features."

Conclusions

1. Mechanistic research can be useful to generate hypotheses or to explain why an intervention has the effect it does.
2. However, trying to answer diet-health questions in a solely 'bottom-up' manner by investigating mechanisms can lead to problems.
3. Emphasis on mechanistic studies can over-inflated the relationship between the exposure and outcome, as such studies tend to purposely restrict many nutrients that would typically be consumed alongside the nutrient under investigation.
4. For actually answering the diet-health questions we most care about in the modern day, not only are cohort studies and RCTs best able to do this, they have a track record of already producing the most important and useful information.
5. For many questions, there is strong agreement between RCTs and cohort studies, e.g. Sodium & blood pressure.
6. In cases where there is disagreement between RCTs and epidemiology, we should avoid defaulting to the presumption that the RCT is right and the epi is wrong.
7. For some questions, findings of cohort studies are likely more correct than RCT data to-date. E.g. Fiber & Colorectal Cancer
8. RCTs are more reliable for specific questions, such as impact of nutrient supplementation on an outcome which can be readily assessed within the time from of an RCT. E.g. impact of vitamin C on preventing the common cold.