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Opinion paper

Is this food healthy? Reframing nutrition evidence through counterfactual comparisons

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SUMMARY

Nutrition science frequently produces conclusions that appear inconsistent or context dependent, contributing to uncertainty in dietary recommendations. Many debates framed around questions such as whether a specific food is "healthy" implicitly assume that foods exert intrinsic effects independent of dietary context. However, because diet is inherently compositional, increasing intake of one food necessarily implies decreasing another, meaning that dietary effects represent substitution contrasts rather than isolated exposures. This article aims to critically evaluate how inadequate specification of counterfactual contrasts and comparators in nutrition research limits causal interpretation in evidence synthesis, and to outline methodological approaches based on causal inference and network meta-analysis (NMA) to improve interpretability. Drawing on the potential outcomes framework, we propose that meaningful causal interpretation requires explicitly defining the comparator ("*in comparison with that?*") and ensuring that exposures correspond to well-defined interventions consistent with the consistency assumption. In this context, NMA offers a methodological framework that preserves comparator structure by jointly modeling multiple competing alternatives, thereby aligning more closely with the relational nature of dietary interventions and causal inference logic. Practical recommendations are provided to improve future research, including explicit specification of counterfactual contrasts, clearer definition of dietary exposures, transparent reporting of substitution context and energy balance, and appropriate use of NMA when multiple alternatives exist. We conclude that improving nutrition evidence synthesis does not require abandoning meta-analysis but rather reframing research questions and analytical strategies around clearly defined causal contrasts.

1. Introduction

Despite decades of research, nutrition science continues to generate conclusions that are frequently perceived as inconsistent or context-dependent, contributing to ongoing uncertainty in dietary guidance. Questions such as "*is meat healthy?*", "*does milk increase cardiovascular risk?*" or "*are eggs harmful or beneficial for heart health?*" appear deceptively straightforward and are frequently addressed through systematic reviews and meta-analyses designed to reconcile heterogeneous findings across studies. Yet despite an expanding volume of evidence syntheses, findings in nutrition science are still frequently described as inconsistent, neutral, or context dependent [1–3]. While these discrepancies are often attributed to methodological heterogeneity or study quality, a deeper issue may lie in how dietary exposures are conceptualized and compared [4].

Clinical medicine traditionally evaluates interventions based on hard endpoints such as survival or disease incidence, whereas nutrition research often relies on surrogate outcomes including biomarkers or intermediate physiological measures. Although such endpoints enable feasible trials, their interpretation depends critically on the underlying causal contrast being evaluated [5,6]. Unlike pharmacological interventions, dietary components operate within a compositional system in which increasing one food necessarily implies decreasing another [7]. Consequently, studies nominally evaluating the same food may represent fundamentally different causal contrasts defined by distinct implicit comparators and dietary contexts [8]. When meta-analyses pool these heterogeneous contrasts as if they addressed a single causal question,

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summary estimates may obscure rather than clarify the relationship between diet and health [9].

This article argues that improving nutrition evidence synthesis requires reframing dietary meta-analysis through a causal inference lens that explicitly incorporates comparator context. A first step is ensuring that conventional meta-analyses synthesize studies addressing comparable counterfactual contrasts, restricting or stratifying analyses according to similar dietary comparators rather than pooling heterogeneous substitutions. When multiple competing alternatives are available, and the evidence network allows it, network meta-analysis (NMA) offers an additional framework that preserves comparator structure by jointly modelling direct and indirect contrasts, thereby aligning more closely with the compositional nature of diet and the causal questions nutrition research aims to address. Therefore, this article aims to: (1) examine how inadequate specification of counterfactual contrasts and comparators in nutrition research limits causal interpretation in evidence synthesis; and (2) outline methodological approaches based on causal inference and NMA to improve interpretability.

2. Why counterfactual comparisons matter in nutrition research?

Moving from descriptive or associative interpretations toward causal understanding requires explicit consideration of the counterfactual framework underlying dietary research questions. Within the potential outcomes framework, causal effects are defined as contrasts between hypothetical outcomes that would occur under alternative exposure scenarios, often expressed as the difference between expected outcomes under exposure versus non exposure ($E[Y^a = 1] - E[Y^a = 0]$) [10]. Originating in early work by Neyman on causal contrasts in randomized experiments, later formalized through Rubin's development of the potential outcomes framework, and further extended by Robins to accommodate time-varying exposures and complex longitudinal settings, modern causal inference emphasizes that causal effects are defined relative to specific interventions and their alternatives [11,12]. Consequently, meaningful causal interpretation depends fundamentally on how exposures are specified and on the counterfactual comparisons they imply.

A key requirement is the consistency assumption, which states that the observed outcome under a given exposure corresponds to the potential outcome associated with that specific intervention [13,14]. This assumption requires that the exposure represents a sufficiently well-defined intervention, meaning that different underlying versions of the treatment should not produce systematically different outcomes. Otherwise, the estimated effect becomes ambiguous because it reflects a mixture of distinct causal contrasts rather than a single interpretable intervention [15]. Hernán illustrated this principle using the example "*Does water kill?*", demonstrating that vague or compound exposures encompassing multiple heterogeneous versions may lead to ill-defined counterfactual contrasts and therefore uninterpretable causal estimates [10]. For example, the health consequences of "water exposure" could differ dramatically depending on whether the intervention corresponds to drinking clean water, consuming contaminated water, engaging in prolonged water immersion, or experiencing acute drowning. Although all scenarios involve "water", they represent fundamentally different interventions with distinct biological mechanisms and expected outcomes. When these heterogeneous versions are implicitly grouped under a single exposure definition, the resulting causal effect becomes ambiguous because it no longer refers to a clearly specified intervention.

Similar challenges arise in nutrition research, where food-based exposures often encompass heterogeneous versions of the same nominal intervention [1]. For example, "red meat consumption" may refer to processed meats, unprocessed lean cuts, or meat consumed within different dietary contexts such as alongside vegetables or refined carbohydrate-rich foods. Although these scenarios share the same exposure label, they represent distinct intervention implementations that may differ in biological mechanisms and health effects. Treating these heterogeneous versions as interchangeable risks producing ill-defined counterfactual contrasts and undermining causal interpretation [16].

3. The compositional nature of diet: why dietary effects are inherently relational rather than intrinsic

Many nutrition studies implicitly treat foods as if they exert intrinsic effects independent of dietary context. However, the compositional nature of diet fundamentally challenges this assumption. Changing a single dietary component does not occur in isolation but corresponds to specific intervention scenarios depending on how the remaining components of the diet are allowed to vary [17]. From a causal inference perspective, this characteristic has important implications for defining estimands and interpreting results.

One approach is to conceptualize a "total effect" estimand (i.e., the causal effect of increasing intake of a food without constraining compensatory dietary changes or total energy intake), in which the intake of a food is increased without constraining other dietary components, which may lead not only to heterogeneous substitution patterns but also to changes in total energy intake [18]. In such cases, the estimated effect may reflect a combination of pathways, including altered caloric balance, weight change, and metabolic responses associated with energy excess, rather than the isolated effect of the food itself. Because individuals often compensate differently by modifying other aspects of their diet, these interventions can produce heterogeneous and partially unobserved dietary changes that complicate causal interpretation [19].

Alternatively, a "relative effect" or substitution estimand (i.e., the causal effect of increasing one dietary component while explicitly replacing another under constant total intake) represents the causal impact of changing one dietary component while holding total intake constant, implying a specific substitution with another food or nutrient [18]. This framework aligns closely with the compositional nature of diet and highlights that increasing consumption of one food necessarily reflects decreasing consumption of another. However, when substitution patterns are not explicitly specified, the resulting estimand may represent a weighted average of multiple underlying changes across individuals, reflecting heterogeneous and potentially unobserved substitutions [20]. Although such weighted compositional effects may be internally valid but difficult to interpret or generalize, because the estimated effect depends on the distribution of substitutions occurring within the study population. This distinction is not merely theoretical, it directly affects how dietary evidence is interpreted and synthesized.

These considerations illustrate why dietary exposures rarely have intrinsic causal effects independent of context. Instead, the health effect attributed to a given food reflects the specific substitution being evaluated rather than an inherent property of the food itself [17,21]. For example, a randomized controlled trial (RCT) assessing the cardiometabolic effects of dry-cured ham compared its consumption with cooked ham as the control condition [22]. Although the intervention appeared to produce favorable changes in blood pressure and metabolic markers relative to the comparator, interpretation depends critically on the nature of the

substitution tested. If the control food itself has less favorable cardiometabolic properties, the observed benefit represents a relative improvement compared with that specific alternative rather than evidence of intrinsic cardioprotective effects of the intervention food [23]. This illustrates how different comparator choices correspond to distinct causal questions, consistent with the "*in comparison with what?*" framework proposed for dietary research.

A similar logic applies to other food exposures. RCTs investigating egg consumption have evaluated fundamentally different causal contrasts depending on the comparator used. In a study by Katz and colleagues, egg-based breakfasts were compared with a high-refined-carbohydrate breakfast consisting of foods such as bagels, cereal with skim milk, waffles, or pancakes, thereby testing the effects of replacing refined carbohydrate–rich breakfast options with eggs [24]. In contrast, other trials, such as those conducted by Burns-Whitmore and colleagues, compared egg consumption with walnuts, representing a substitution between different protein and fat sources rather than between protein-rich foods and refined carbohydrates [25]. Although both interventions are described as evaluating "egg consumption", they correspond to distinct counterfactual contrasts and therefore different causal questions. Increasing egg consumption at the expense of refined carbohydrate sources reflects a different biological and nutritional comparison than increasing egg consumption at the expense of whole plant-based food. Failure to explicitly define these substitutions risks attributing health effects to the food itself rather than to the specific dietary contrast being evaluated, highlighting how dietary interventions inherently encode particular causal estimands.

4. Why most nutrition meta-analyses fail causally

Although meta-analyses of RCTs are often considered the highest level of evidence in nutrition science, their validity depends fundamentally on whether the studies being synthesized address the same causal question. In practice, many of these meta-analyses in nutrition field combine effect estimates derived from heterogeneous dietary contrasts that do not represent equivalent counterfactual comparisons [1]. As a result, pooled estimates may appear statistically rigorous while lacking clear causal interpretation.

The implications of these issues are illustrated by studies examining red meat consumption and cardiometabolic outcomes. Meta-analyses of RCTs have concluded that consuming $\geq$0.5 servings of total red meat per day does not significantly affect blood lipids or blood pressure [26], while other studies have reported beneficial or adverse effects [27–29]. These apparent inconsistencies may reflect differences in substitution context rather than true biological disagreement. For example, trials included within the same meta-analysis have compared red meat against markedly different alternatives [26], ranging from shortbread cookies and sugar coated chocolates or cooked chicken breast with added butter [30], high-sodium preparations [31], or plant-based protein sources such as tofu [32]. Although these interventions are often categorized under a common exposure label ("red meat consumption"), they represent fundamentally distinct causal contrasts and dietary substitutions. Pooling such heterogeneous comparisons assumes equivalence between counterfactual scenarios that may differ substantially in nutritional composition, metabolic pathways, and expected health effects.

Beyond differences in comparator choice, an additional and conceptually distinct limitation arises when nominally similar interventions fail to isolate a specific causal contrast and instead incorporate heterogeneous versions of treatment or additional modifying factors. In such cases, the exposure itself lacks a coherent definition, potentially violating the consistency assumption. For example, categories such as "red meat consumption" may include processed and unprocessed meats, differing preparation methods, or implementation within distinct dietary contexts that introduce additional intervention components. In one trial, red meat intake was embedded within a broader low-sodium dietary pattern compared with a regular-sodium dietary context, effectively testing a combined intervention rather than isolating the independent effect of meat consumption [31]. Similarly, other studies have operationalized "meat protein" interventions using heterogeneous food sources such as ham, chicken, or beef, despite their differing nutritional compositions and metabolic implications [33]. When meta-analyses pool such heterogeneous interventions under a shared exposure label, summary estimates may reflect mixtures of distinct causal pathways rather than a clearly defined intervention effect, limiting causal interpretability despite statistical precision.

5. Why network meta-analysis better aligns with causal inference in nutrition research

The challenges described above do not imply that evidence synthesis is inherently flawed, but rather that conventional meta-analytic approaches may be insufficient when applied to compositional exposures such as diet. Traditional pairwise meta-analyses typically aggregate studies comparing a single exposure with a specific comparator, often pooling heterogeneous contrasts under a shared exposure label. When dietary effects are defined by substitution relationships, this approach risks obscuring meaningful differences between alternative dietary comparisons and conflating distinct causal questions [1].

NMA offers a methodological framework that addresses several of these limitations by explicitly integrating multiple comparators within a connected analytical structure [34,35]. Rather than collapsing heterogeneous comparisons into a single pooled estimate, NMA preserves the relational nature of dietary interventions by modeling the network of competing alternatives. From a causal inference perspective, this structure reflects the counterfactual framework by representing competing intervention scenarios and their relationships within a unified model [36,37].

In nutrition research, where increasing one food necessarily implies decreasing another, modeling multiple substitution pathways is particularly relevant. For example, conventional meta-analyses may pool trials comparing a given food against refined carbohydrates, other animal products, or plant-based foods into a single summary estimate despite representing distinct substitution contrasts (Fig. 1). An NMA framework instead preserves these distinctions, enabling simultaneous evaluation of alternative dietary substitutions and clarifying how effects differ depending on the comparator context [38]. Table 1 illustrates how comparator structure fundamentally changes interpretation. Specifically, while conventional pairwise meta-analyses often report neutral or minimal effects, NMA reveals comparator-specific differences. For olive oil, pairwise analyses show no significant effect, while NMA reveals significant reductions in low-density lipoprotein cholesterol (LDL-C) compared with butter and other fats [39]. For red meat, pairwise estimates were overall neutral [39], whereas the NMA suggested higher LDL-C relative to plant protein sources [29]. For cow's milk, the NMA distinguished between effects compared with soy milk and oat/rice drinks, contrasts not apparent in conventional pairwise analyses [40].

Importantly, NMA does not eliminate all challenges. Valid causal interpretation still requires careful consideration of intervention definition, transitivity assumptions, and clinical coherence across

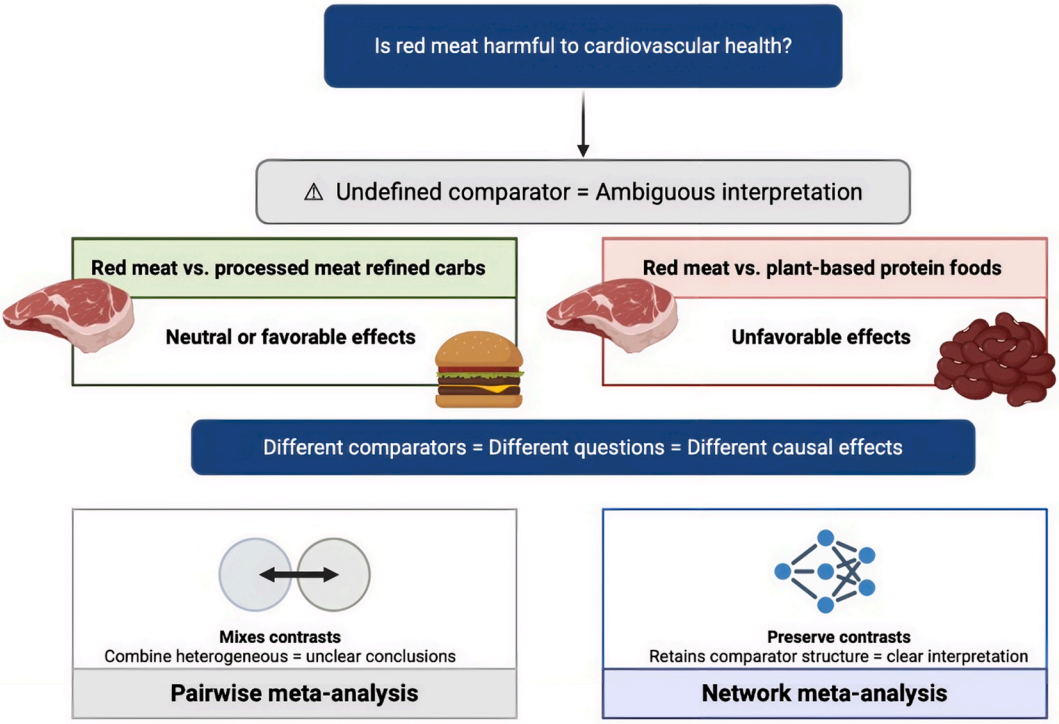

Figure 1. Schematic illustration of how comparator choice shapes causal interpretation. Pairwise meta-analysis collapses heterogeneous dietary contrasts into a single summary estimate, whereas network meta-analysis preserves the comparator structure across multiple competing alternatives.

Table 1
Influence of comparator structure on interpretation of certain dietary components: traditional pairwise meta-analysis versus network meta-analysis.

Dietary exposure	Conventional pairwise meta-analysis (cardiovascular risk outcomes)	Network meta-analysis comparator-specific effects (cardiovascular risk outcomes)
Olive oil	No significant differences on cardiovascular risk outcomes [44]	↓ Significant differences LDL-C and TC versus butter ↓ Significant differences LDL-C versus sunflower oil, rapeseed oil, soybean oil, flaxseed oil, corn oil [39]
Red meat	No significant differences on cardiovascular risk outcomes [26]	No significant differences versus animal protein sources ↑ Significant differences LDL-C and TC versus plant protein sources ↓ Significant differences TG versus mixed animal and plant sources No significant differences versus refined carbohydrate sources [29]
Cow milk	No significant/minor effect on cardiovascular risk outcomes [45]	↓ Significant differences LDL-C and TC versus soy milk No significant differences versus oat and rice milk [40]

LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides.

the NMA [41]. For valid causal interpretation in NMA, three key assumptions must be satisfied: (1) transitivity (i.e., studies are comparable across treatment contrasts); (2) consistency (i.e., direct and indirect evidence agree); and (3) clinical comparability (i.e., interventions are sufficiently homogeneous). These assumptions are particularly demanding in nutrition research given the compositional and context-dependent nature of dietary exposures [42,43].

6. Practical recommendations for causal interpretation and evidence synthesis in nutrition research

The methodological challenges described throughout this perspective highlight the need for more explicit consideration of causal structure in the design, interpretation, and synthesis of nutrition research. Translating these conceptual insights into practical guidance may help improve both individual studies and evidence synthesis frameworks. The following recommendations aim to facilitate clearer causal interpretation and enhance the comparability of dietary evidence.

- *Define the counterfactual explicitly* ("*in comparison with that?*"): Because dietary effects are inherently relational, researchers should explicitly specify the comparator against which a food or dietary intervention is evaluated. Rather than framing questions solely in terms of exposure (e.g., "*does red meat affect cardiovascular risk?*"), studies should clarify the substitution being tested (e.g., red meat versus refined carbohydrates, plant protein, or other animal products). Explicit comparator definition improves causal interpretability and reduces ambiguity when integrating findings across studies. *Example:* Evaluating egg consumption relative to refined carbohydrate-based breakfasts versus whole plant-based foods represents fundamentally different causal contrasts and may lead to different conclusions.
- *Avoid heterogeneous exposure definitions:* Broad dietary exposure categories may encompass heterogeneous versions of nominally similar interventions, complicating causal interpretation and potentially violating the consistency assumption. Labels such as "red meat", "dairy", or "processed foods" may include substantial variation in processing level, preparation methods, nutrient composition, and accompanying dietary

context. Defining exposures with sufficient specificity ensures that estimated effects correspond to coherent interventions. *Example*: Grouping different types of fish (e.g., fatty versus lean, processed versus fresh) under a single exposure may obscure distinct nutritional profiles and biological effects

- *Make substitution and energy context explicit:* Authors should explicitly describe the dietary substitutions and energy balance implications associated with an intervention. Increasing consumption of one food inevitably alters other dietary components and may also influence total energy intake. Reporting these implicit substitutions clarifies the causal contrast being evaluated and improves transparency for downstream synthesis. *Example*: Increasing olive oil intake without specifying whether it replaces butter or is added on top of the habitual diet may reflect different causal pathways, including changes in total energy intake.
- *Use NMA to preserve comparator structure:* When multiple competing dietary alternatives exist, NMA provides a framework better aligned with the compositional nature of diet by preserving the structure of comparisons between alternative foods. However, careful assessment of transitivity, intervention coherence, and clinical comparability remains essential to ensure valid causal interpretation. *Example*: Combining studies comparing red meat versus processed foods with others comparing red meat versus whole plant-based foods within the same NMA may not be appropriate, as the comparator foods differ substantially and may violate transitivity assumptions

7. Conclusion

The limitations discussed in this article do not reflect a failure of meta-analysis itself, but rather a mismatch between conventional evidence synthesis and the causal structure of dietary exposures. Because diet is inherently compositional, the effects attributed to foods cannot be interpreted independently of the substitutions they represent. When studies addressing distinct counterfactual contrasts are pooled under a shared exposure label, summary estimates may appear statistically precise while lacking clear causal meaning.

Approaches that preserve comparator structure, particularly NMA, offer a framework better aligned with causal inference by explicitly modeling competing dietary alternatives and their substitution relationships. However, methodological tools alone are insufficient, improving nutrition science ultimately requires reframing research questions to reflect clearly defined counterfactual contrasts.

Moving from casual comparisons toward explicitly specified causal questions, shifting from "*is a food healthy?*" to "*compared with what is this food healthy?*", may enhance the interpretability, coherence, and translational relevance of nutrition research.

Informed consent statement

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Author contributions

All authors participated in the writing, review and editing of the manuscript. All the authors have read and agreed to the published version of the manuscript.

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Conflict of interest

ML-M reports receiving remuneration from Danone and Foods For Tomorrow for advisory board participation and consulting activities, unrelated to the submitted work. The other authors declare that there is no conflict of interest regarding the content of the present study.

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