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NOVEL AND EMERGING RISK FACTORS (K. NASIR, SECTION EDITOR)

Methodological Issues in Nutritional Epidemiology Research—Sorting Through the Confusion

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Abstract

Purpose of Review Our purpose was to discuss the methodological limitations of observational nutritional epidemiology research, using observational studies on coffee intake and health as a case example.

Recent Findings A number of recent observational studies on the potential health effects of daily coffee intake have reported protective associations between higher coffee intake and a variety of health outcomes, including death. This is inconsistent with the findings from classic studies showing an increased risk of coronary heart disease events, performed in young adults with a homogeneous education level, and adjusting for tobacco use.

Summary Many nutritional epidemiological studies have important limitations, which limit their validity. These include the use of prevalent user designs, risk of reverse causality, measurement error particularly of the exposure of interest, and residual confounding by socioeconomic status. In this review, we discuss these potential issues and provide constructive recommendations intended to help minimize them.

Keywords Nutritional epidemiology · Observational · Confounding · Bias · Epidemiologic methods · Coffee

Abbreviations

SES Socioeconomic status

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Introduction

In an era of globalization of trade, including food, understanding the health effects of nutrients and foods consumed by billions of individuals on a daily basis is crucial. The widespread interest in epidemiological research studies assessing

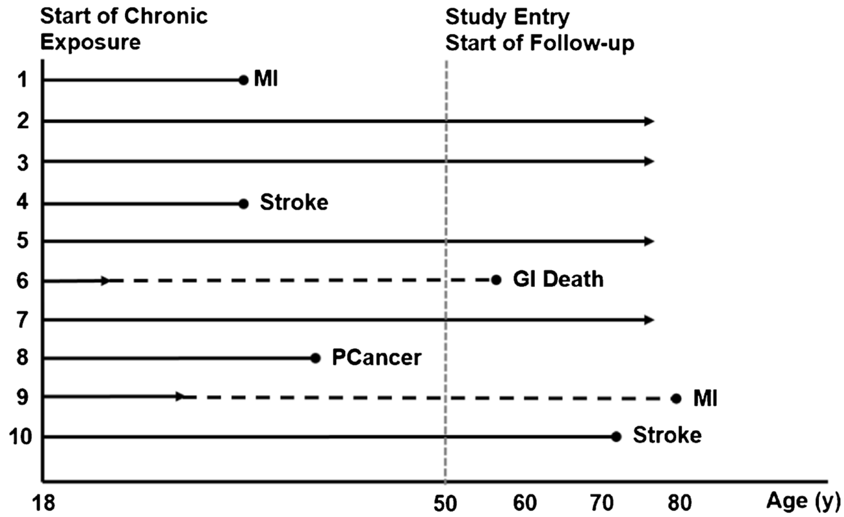

Fig. 1 Prevalent user design potential biases: depletion of susceptibles or survivorship bias. In this figure, we evaluate the potential implications of a prevalent user study design combined with the exclusion of individuals with prevalent severe diseases at baseline, for the resulting study population, had daily coffee intake detrimental health effects, in 10 mock coffee drinkers. Black lines are used for patient-time periods exposed to coffee (i.e., 1 or more cups of coffee per day) and dashed lines for unexposed periods (i.e., 0 cup of coffee per day). Arrows are used for individuals free of events, and circles are used for censored individuals. Mock example no. 6 presents a patient with impaired GI tolerance to coffee. Mock example no. 9 presents a patient with a strong family history of cardiovascular events who is advised to quit coffee. GI gastrointestinal, MI myocardial infarction, PCancer pancreatic cancer

these health effects (i.e., "nutritional epidemiology") often leads to publication in high impact journals and dissemination of results in mass media.

Unfortunately, however, over the past few decades, nutritional epidemiology has also become one of the main sources of publication of spurious associations between *novel* exposures and a number of health outcomes [1••, 2]. Indeed, despite the hype that these studies often generate in the mass media, the usual biases in observational (or even experimental) epidemiology apply, with added challenges due to difficulties in identifying appropriate source populations and accurately measuring exposures and potential confounders.

A prime example of the great interest caused by observational nutritional epidemiological research is studies on the potential health effects of daily coffee intake. Specifically, studies suggesting a protective effect of coffee [3•, 4•, 5•, 6•, 7•] or a health risk [8•, 9•, 10•, 11•, 12•] usually garner great attention from scientific journals, general media, and the public. Nevertheless, careful evaluation of such studies often leads to concerns regarding their validity [13–20]. Meta-analyses are often used to sort through the confusion caused by inconsistent findings across studies; however, their results may not be valid if the individual studies are at high risk of bias [21••, 22].

In this review, we use observational studies on the potential health effects of daily coffee intake to discuss four key potential methodological limitations often seen in nutritional epidemiological studies: (1) prevalent user designs, (2) reverse causality, (3) measurement error, and (4) residual confounding. Despite the heightened potential of some of these limitations to impair validity in this setting, they are often overlooked during the study design, analysis, review, and dissemination phases of the research. To aid this process, we present a brief checklist intended to help authors and reviewers when conducting and evaluating this type of research. Finally, we discuss future directions in the field of nutritional epidemiology and provide constructive recommendations to potentially help minimize these recurrent issues.

Potential Issue #1: Prevalent User Versus Incident User Designs

Daily coffee intake tends to start early in adult life. According to the National Coffee Association, in 2016, 50% of US adults 18 to 24 years old consumed coffee products on a daily basis [23]. Similar or even higher proportions have been described in other countries [24]. Despite this, in a number of cohort studies examining the potential health effects of coffee, the median age of the study population at baseline was above 50 years. Of note, most of the published studies using this "prevalent user" design have found protective associations between daily coffee intake and hard health outcomes, including overall mortality and death from almost any specific cause chosen by the investigators.

It is important to note, however, that the prevalent user design allows individuals in the source population to be exposed to the drug or food under study before qualifying for study entry. Specifically, in the aforementioned studies, this design may have allowed exposure to coffee products for a

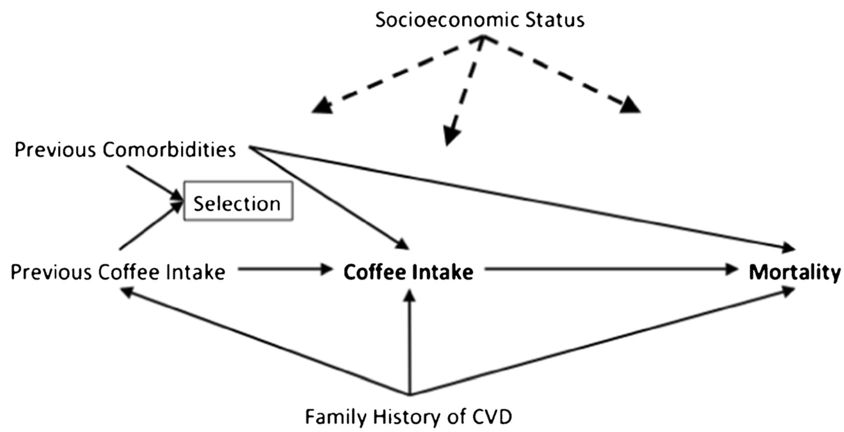

Fig. 2 Residual confounding and reverse causation. In this directed acyclic graph (DAG), we evaluate key factors potentially leading to residual confounding and/or reverse causation in nutritional epidemiological studies evaluating the longitudinal associations between daily coffee intake and mortality. CVD cardiovascular disease

median of 30 years before being considered for inclusion. In this context, any potential adverse health outcomes related to coffee consumption would have approximately 30 years to accrue. In nutritional epidemiological studies, individuals with preexisting severe diseases are often excluded from the study population to minimize reverse causation (see Issue #2). In this context, the prevalent user approach may result in the depletion of susceptible individuals [25] from the study coffee intake groups, leading to the selection of a "healthy survivor" exposed population (Fig. 1).

In addition, the prevalent user design also allows for the shift of individuals with an intolerance to coffee, anxiety, palpitations, hypertension, or other mild health conditions that may result in coffee cessation [26–29], to the non-exposed/lower coffee intake categories before study entry. Moreover, during the 1980s and 1990s, coffee was perceived as a noxious habit by many physicians, and it is possible that individuals with an increased perceived risk, such as individuals with a strong family history of cardiovascular disease or other specific risk factors, would be advised to refrain from coffee consumption. This would all result in a reference group (individuals stating in a food questionnaire that they *never* have coffee) at an increased risk of events.

The combination of these two phenomena may result in spurious associations suggesting a protective health effect of high coffee intake. To avoid these issues, an "incident user" design may be more appropriate. Under this approach, currently considered the gold-standard in pharmacoepidemiological observational research [30], participants must be exposure-naïve at the time of study entry in order to qualify for study inclusion. Importantly, simulation studies have shown that the results of observational analyses using an incident user approach more closely correlate to those from randomized controlled trials than prevalent user designs [31, 32]. Of note, among the landmark cohort studies on the health effects of coffee, the analysis by Klag et al. performed in the Precursors study [12•], in which mean baseline age was 26 years (i.e., closer in time to initiation of coffee use, and therefore closer to an incident user design) the authors found a strong, positive association between higher daily coffee intake and cardiovascular events during up to 44 years of follow-up. The analyses by Klag et al. included adjustment for key potential confounders, including tobacco use, and was performed in a fairly homogeneous population in terms of education level (see Issue #4) [12•].

Drugs and foods share a number of characteristics, and incident user designs may be a more appropriate approach also in nutritional epidemiology.

Potential Issue #2: Reverse Causality

The second issue relates to the phenomenon of reverse causality [33••, 34]. In essence, this occurs when the association emerging from observations is not generated by a causal effect of the exposure on the outcome, but rather through a causal effect of the outcome on the exposure. In the case of coffee consumption and chronic diseases, people with certain chronic comorbidities (e.g., hypertension) may reduce coffee intake [26–29] (Fig. 2). This can happen due to direct effects of the disease process (and adverse effects of concomitant coffee consumption) or due to medical recommendations. In such instances, one may observe decreased coffee consumption in people with comorbidities. This phenomenon also confounds the relationship between coffee and mortality, as those individuals with comorbidities will be then more prone to die due to those comorbidities. If this is the only mechanism through which a pattern of decreased consumption and increased mortality emerges, then an intervention to increase coffee consumption would not decrease mortality.

Reverse causality is very difficult to address in cross-sectional studies, due to the lack of longitudinal data to assess the temporal nature of the relationships between exposure and outcome. Case-control studies may also be subject to reverse causality in the form of selection bias [9•, 35]. On the other

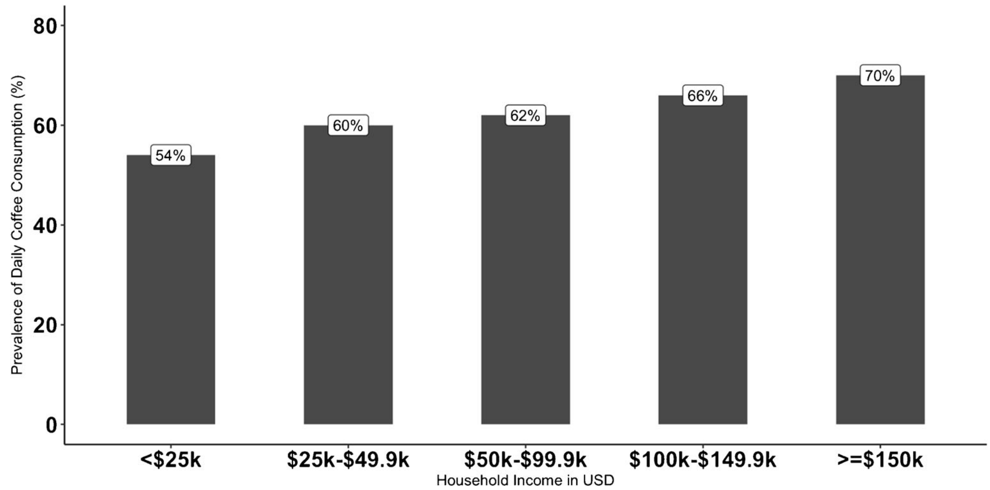

Fig. 3 Coffee intake by socioeconomic status. The *x*-axis represents categories of household yearly income, in US dollars. The *y*-axis represents percentage of adults who live in homes that use coffee. Data from: Experian Simmons. Coffee in America. Available at: https://www.experian.com/assets/simmons-research/white-papers/demographic-and-preferences-of-coffee-drinkers-in-america.pdf

hand, longitudinal studies are more robust to this issue. Nevertheless, as discussed above, the use of a prevalent user design may facilitate the accumulation of comorbidities in the reference group.

Methods often used to minimize this issue include multivariable adjustment for potential confounders such as preexisting diseases, restriction of the study population to individuals free of severe conditions (e.g., cardiovascular diseases, cancer) at baseline, and sensitivity analyses in which only events occurring after a given latency period are considered. Nevertheless, each of these methods has assumptions and limitations and may fail to fully address reverse causation, particularly in the presence of a prevalent user design.

Potential Issue #3: Measurement Issues

A third key source of potential issues in this type of research relates to the assessment of the pattern of exposure to a given food or nutrient. In most observational studies, this information is obtained using food questionnaires, which are known to have important limitations [36–38].

First, it is important to note that measurement error in questionnaires may be associated with other, measured (e.g., socioeconomic status [SES]) and unmeasured (e.g., personality, emotional status) individual characteristics, which may also be associated with health outcomes [39–45]. This is a form of differential measurement error [46], which may lead to biased associations. In the case of measured variables, this can be corrected with careful adjustment for these confounders, but in the case of unmeasured variables, this bias is impossible to fully correct for.

A second form of pervasive measurement error that may be present in this context is dependent error [47]. Here, the error in the measurement of the exposure of interest is associated with the error in the measurement of other variables, including the outcome. If other covariables are measured with questionnaires (such as SES, tobacco use, etc), this measurement error may have unpredictable consequences [47].

Third, in most studies, a single dietary assessment is used to infer the lifetime pattern of exposure to the food of interest, which is therefore assumed to remain fixed ever since, rather than to change over time. Nevertheless, this may be a strong assumption, particularly with regard to foods strongly associated with social and professional factors, such as daily coffee intake. This may also lead to exposure misclassification and biased results [48].

A number of options may be considered to minimize these issues. As discussed above, adequate measurement and adjustment for other potential confounders may help in reducing differential measurement error. Dependent measurement error may also be corrected improving the assessment of other potential confounders. Also, alternative assessment tools such as determinations of relevant metabolites or a combination of these with self-report tools may be considered [49]. In addition, repeated dietary assessments could be used, and patient-years of exposure rather than patients could be used as the unit of analysis. This is often done in pharmacoepidemiology [50••, 51] to account for the time-varying nature of exposure to drugs and may also be a reasonable approach in nutritional epidemiology.

Potential Issue #4: Residual Confounding by Socioeconomic Status and Other Factors

A fourth key issue is the risk for residual confounding, i.e., confounding by measured and/or unmeasured confounding factors. Importantly, the finding of ubiquity of protective associations in studies involving foods has been suggested as a warning sign of potential for residual confounding [52], as it is unlikely that a single substance would operate as a *panacea*, protecting simultaneously against a number of unrelated diseases and/or causes of death.

Table 1 Proposed checklist for the evaluation of observational longitudinal studies involving foods and nutrients

1. Source and study population	
	Did the authors use an incident or a prevalent user design?
	If a prevalent user design was used,
	- Was the mean age at exposure initiation in the source population described?
	- What was the difference between age at exposure initiation and age at study entry?
	Did the authors gather/provide information on the reasons why the unexposed group refrained from the food being evaluated?
2. Measurement	
Exposure	
	Was the measure of exposure used valid and reliable, i.e., expected to accurately capture the actual pattern of use of the food by the study participants?
	Was the exposure evaluated once, or at several time points?
	If only once, was the exposure expected to be stable over time?
Outcomes	
	Were the measures of the study endpoints valid and reliable?
3. Reverse causation	
	How were patients with prevalent chronic diseases managed in terms of inclusion/exclusion in the study population?
	Did the authors conduct sensitivity analyses to assess the robustness of their findings to reverse causation?
	Did the authors adjust comprehensively for all key prevalent chronic conditions in the multivariable analyses?
4. Confounding	
	Did the authors find a ubiquitous effect of a substance on a number of health outcomes simultaneously?
	If so, do all of those associations seem reasonable?
SES	
	Did the authors adjust for a measure of SES in the multivariable analyses?
	If so, was this measure comprehensive, i.e., likely to capture the full effect of SES, or is residual confounding still possible?
Other	
	Did the authors adjust for age and sex?
	Did the authors adjust for other key confounders on the topic? (e.g., in studies of coffee as the exposure of interest, did they adjust for tobacco use, use of other caffeinated beverages?)
	Did the authors adjust for other foods showing strong protective/risk associations with the same or similar health outcomes, in the literature?
	Did the authors perform a sensitivity analysis to assess robustness to unmeasured confounders? Were the results of these sensitivity analyses compared to already published measures of effect sizes of known confounders?
5. Evaluation and communication of results	
Limitations	
	Did the authors discuss in detail the key limitations of the study? Specifically,
	- Selection bias
	- Information bias
	- Confounding bias
Communication	
	Did the authors state/imply causality based on their findings?
	Did the authors make recommendations in terms of lifestyle change based on their findings?

In this sense, SES appears as a particularly relevant potential confounder. Behaviors such as daily coffee drinking, moderate alcohol consumption, or intake of other nutrients such as nuts have a strong social pattern and are usually more common in higher SES groups [53–55] (Figs. 2 and 3). Given that higher SES is a protective factor for health outcomes [39–42], failure to properly control for confounding by SES will lead to an overestimation of the beneficial association of these behaviors and health.

Keeping this potential bias in mind, several studies in nutritional epidemiology adjust for education level, although relatively few studies adjust for other indicators of SES, such as income, wealth, or occupation. However, SES is a complex latent construct for which proxies (including education, income, or occupation) are often measured with error, when at all measured, and may fail to fully capture the effect of SES [56]. Both measurement error in a confounder and the lack of adjustment for such confounder lead to residual confounding.

New techniques are emerging to at least assess whether results can be explained due to these unmeasured/mismeasured confounders, which is a step in the right direction [57]. In particular, recent studies of daily coffee consumption have conducted sensitivity analyses to assess the sensitivity of their results to this issue. For example, Gunter et al. [6•] found that their results were robust to the presence of an unmeasured confounder with a hazard ratio for death down to 0.75 (or up to 1.33) and at least a 20% difference between exposure groups. Galea et al. [39] estimated the association between SES and mortality to range between 1.40 and 1.75. That is, the coffee-mortality associations observed in many studies could be explained, at least partly, by a lack of proper adjustment for SES. Future studies should collect and use better data on SES indicators [56] and perform adequate and careful adjustment. Performing sensitivity analyses to assess robustness to unmeasured confounders is also a valuable tool to put the study results into context. Also, alternative designs at lower risk of confounding could also be considered, including novel approaches such as Mendelian randomization studies [58••].

Beyond SES, other forms of residual confounding are also possible; indeed, any factor associated with the endpoint of interest (e.g., death) and associated with the pattern of exposure (in our example, to coffee) may lead to spurious protective/harmful associations. For example, people with insomnia might increase their coffee intake during work hours to improve their performance. Low sleep quality is associated with adverse health outcomes [59–61], and lack of adjustment for this could lead to a spurious association suggesting an increased risk of adverse events with higher coffee intake. Also, if the results from prior research showing associations between other foods and the study outcomes are considered valid, then adjustment for that additional food (e.g., nuts [62, 63]) should also be considered if associated with the exposure of interest (directly or through an unmeasured common cause).

As for SES, appropriate identification, measurement, and adjustment for these potential confounders are crucial to maximize validity.

Future Directions—Considerations for Future Nutritional Epidemiology Research

A number of initiatives may be considered by authors and journals to maximize the validity of the studies conducted and disseminated. First, experimental designs should be prioritized, where feasible. Randomized trials avoid many of the methodological limitations of observational epidemiology, including those specific to nutritional epidemiology discussed in this review. The need for large study populations and long follow-up periods often prevents the conduct of these studies. Nevertheless, studies in smaller populations and using surrogate endpoints (e.g., changes in blood pressure, lipid profile, and glucose metabolism; development of subclinical atherosclerotic vascular disease) may also be informative in terms of health implications and much more realistic. However, great care must be paid to the interpretation of surrogate endpoints, as those may not necessarily be related to morbidity and mortality [64], and we may be ignoring adverse events that contribute to overall mortality or more broad health outcomes.

Second, descriptive epidemiology and surveys may also be particularly helpful (e.g., surveys on dietary habits and their determinants), especially to better understand the determinants leading to different patterns of exposure. Researchers try to account for those factors to the best of their knowledge, but direct, updated communication with users may help better understand their dietary choices. Intake patterns likely change over time and differently in different cultures, and having detailed information on these may help inform study design and analysis.

Third, if authors choose to conduct an observational study, close attention to study design features should be paid [65••] as a means to minimize bias. Adequate source populations should be identified to minimize selection bias, and valid measurement tools should be implemented. Adjustment for key potential confounders should be prioritized, particularly SES and preexisting conditions. Also, provided the potential impact of these studies in terms of public health, close scrutiny of the study methods by medical journals becomes mandatory. Peer reviewers and editors may want to use checklists to make sure that key potential threats to validity are evaluated in a systematic manner. For this purpose, in Table 1, we present an example of such a checklist, summarizing key methodological issues that should be evaluated—and that should be flagged as strong limitations, if present.

Finally, researchers may eventually want to consider reframing the purpose of their nutritional epidemiology research. In this sense, authors may want to assess holistic *habits* rather than individual isolated exposures. For example, although it is possible to isolate the effect of coffee in a study, in real life coffee intake may be strongly associated with other exposures, some of which may be harmful (tobacco use, second hand smoking) and some of which may be beneficial (increased social cohesion). In this context, studying the health effects of the different forms of the *habit* as a whole may also be very informative.

Conclusions

Epidemiologic research on specific foods such as coffee is very appealing, as it involves substances to which billions of individuals are exposed on a daily basis. Provided the public health implications, nutritional epidemiology is likely to become a key component of epidemiological, safety, and health promotion research in the coming decades. In this context, careful attention must be paid to epidemiologic methods. This will help sort through the confusion, differentiating actual protective and harmful exposures from other, more spurious, associations. We hope this review will trigger scientific debate and ultimately help maximize the validity of epidemiological research involving foods and nutrients.

Compliance with Ethical Standards

Conflict of Interest Dr. Bilal, Dr. Kapoor, Dr. Quispe, Dr. McEvoy, Dr. Pladevall-Vila, and Dr. Blumenthal declare that they have no conflict of interest.

Dr. Cainzos-Achirica reports that he collaborates with RTI Health Solutions, an independent nonprofit research organization that does work for government agencies and pharmaceutical companies.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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