We agree that randomized trials may be required to establish causality. A careful extensive analysis of the observational data coupled with a better understanding of the underlying physiology would help justify (or not) randomized trials and could aid in their designs. For example, contextual factors, such as the influence of the type of diet, accompanying physical activity level, and whether to keep total caloric intake constant, would be important in the design of randomized trials.

Neither of the authors had a conflict of interest to declare.

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Reply to RA Mekary and E Giovannucci

Dear Sir:

We thank Mekary and Giovannucci for their thoughts and welcome the continued dialogue about research and research reporting. We see 2 overarching points in their letter. The first, and seemingly more minor, point is their belief that our meta-analysis would have been more useful if it addressed the checklists from guidelines such as the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) or Quality of Reporting of Meta-analyses (QUORUM) statements and explored heterogeneity in the association. Although we agree with the importance of these ideas in some contexts, the point is tangential to the purpose of our analysis. Our meta-analysis aimed solely at determining I whether an association of skipping (compared with eating) breakfast with increased obesity had been unequivocally shown, and if so, 2) whether association studies continued to be conducted for many years after such a demonstration occurred. Our analysis, as designed and reported, clearly answered those questions in the affirmative, and it was beyond our scope of interest to explore heterogeneity or other aspects of that association.

The second and more fundamental point from Mekary and Giovannucci relates to the value of observational studies. We agree with the general sentiment that observational data can be useful, as we acknowledged in our article. We further agree, and acknowledged in our article, that additional studies may be valuable for confirmation of the association or for identifying mediators of the association. In particular, novel associations or mediators proposed by observational evidence can push research in new directions to subsequently conduct the appropriate studies to determine causation. However, we seem to disagree about the point at which the marginal scientific knowledge gained from additional observational studies becomes negligible. In our example, the associations were established in a wide range of populations and settings, and it is unlikely that continuing to conduct observational analyses, longitudinal or otherwise, would meaningfully improve our ability to determine whether a causal relation exists.

Mekary and Giovannucci invoke some of Hill’s (2) 9 viewpoints as a means of establishing causality from observational evidence, specifically consistency and temporality. Consistency of evidence across many observational analyses still results in the possibility of a pervasive confounder (eg, obese individuals choose to skip breakfast; individuals with a particular genotype are predisposed to a phenotype of consuming calories later in the day). Furthermore, conducting additional longitudinal studies to establish temporality is of questionable value, especially considering the 11 longitudinal analyses already conducted. At the end of a longitudinal study, we are still left with an association and the question of whether making a change in the putative causal factor will, in fact, influence the outcome. We posit that the “entry ticket” to using Hill’s viewpoints for establishing causation from observational evidence is that randomization of humans to the postulated causal exposure and follow-up on the outcome of interest is infeasible, impossible, or unethical. Randomly assigning people to eat or skip breakfast and observing effects (or lack of effects) on weight is none of these.

We agree with Mekary and Giovannucci that a careful evaluation of observational evidence can be important in designing randomized controlled trials. Well-designed and well-executed observational studies, in which well-defined estimates of exposure are compared against reliable measurements of outcomes, can help guide experimental designs that are more likely to establish a causal relation. However, we showed that these observational analyses are too often used to state causal relations between an observed or self-reported estimate of the exposure and an observed or self-reported estimate of the outcome, independent of the whole of the literature. Meanwhile, conducting well-controlled experiments that test the influence of the exposure on the outcome is often feasible and relatively cheap for topics such as the breakfast-obesity hypothesis. Unfortunately, when a body of scientific evidence is distorted to produce the patina of a demonstrated causal conclusion from insufficient data, it may be difficult to convince funding agencies, fellow scientists, and the public that such well-controlled experiments are even needed.

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