Perspective: Randomized Controlled Trials Are Not a Panacea for Diet-Related Research[1,2]

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ABSTRACT

Research into the role of diet in health faces a number of methodologic challenges in the choice of study design, measurement methods, and analytic options. Heavier reliance on randomized controlled trial (RCT) designs is suggested as a way to solve these challenges. We present and discuss 7 inherent and practical considerations with special relevance to RCTs designed to study diet: *1*) the need for narrow focus; *2*) the choice of subjects and exposures; *3*) blinding of the intervention; *4*) perceived asymmetry of treatment in relation to need; *5*) temporal relations between dietary exposures and putative outcomes; *6*) strict adherence to the intervention protocol, despite potential clinical counter-indications; and *7*) the need to maintain methodologic rigor, including measuring diet carefully and frequently. Alternatives, including observational studies and adaptive intervention designs, are presented and discussed. Given high noise-to-signal ratios interjected by using inaccurate assessment methods in studies with weak or inappropriate study designs (including RCTs), it is conceivable and indeed likely that effects of diet are underestimated. No matter which designs are used, studies will require continued improvement in the assessment of dietary intake. As technology continues to improve, there is potential for enhanced accuracy and reduced user burden of dietary assessments that are applicable to a wide variety of study designs, including RCTs. *Adv Nutr* 2016;7:423–32.

Keywords: study design, epidemiologic studies, observational studies, randomized controlled trials, dietary assessment methods, informed consent, blinding, behavioral interventions

Introduction

Literature has accumulated over the past 3 decades to highlight confusing results from epidemiologic studies of diet and health (1–17) and errors in measuring dietary intake (18–28). Some of the investigators of these studies and others also have questioned the value of observational studies of diet and health, with some advising to limit diet-related research to randomized controlled trials (RCTs)[10] (28–31). The RCT often is considered to be the strongest study design in biomedicine (32–34), one that might provide a broad-based solution for addressing methodologic problems encountered in nutrition research.

RCTs provide exact and prescriptive protocols to ensure scientific rigor in the most transparent of ways, by randomly allocating treatment. When factors that may bias the estimate of the effect of the intervention on the primary outcome are randomly distributed across intervention and comparison arms of an RCT, there is assurance that results derived are not subject to confounding bias. The allocation of the intervention by the investigators also reduces the probability of selection bias, by assigning people to specified study conditions rather than allowing them to choose.

Despite the apparent advantages of RCTs, only a small fraction of all human studies use randomized designs. However, much is known about relations between risk factors and disease. Recommendations on the role of human

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[10] Abbreviations used: AHEAD, Action for Health in Diabetes; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention; PREDIMED, PREvencion con Dieta MEDiterranea; RCT, randomized controlled trial; WHI, Women's Health Initiative.

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behaviors as determinants of health are made across a wide variety of risk factors and disease outcomes with little or no RCT-derived evidence. One of the best examples is contained in the US Surgeon General's 1964 report on Smoking and Health. On the basis of Hill's Criteria for Judging Causality (35, 36), the expert panel concluded that RCTs were not necessary to assert that tobacco "causes" an array of health outcomes, including lung cancer (37). This showed that strong, persuasive evidence can come from sources other than RCTs, which may be difficult or impossible to conduct for a variety of ethical or logistical reasons (28, 38–42).

Although the method of allocation (i.e., randomization compared with self-selection) and the nature of the trial (i.e., explanatory compared with pragmatic) are conceptually orthogonal, the reality is that rarely in normal clinical or community practice would a treatment be allocated at random. In those rare instances when this happens, trials tend to be cluster randomized (43), focused on supplementation (see The need to focus section) (44), or lack distinguishing features (thus facilitating blinding; see Blinding section) (45). In the work on pragmatic clinical trials by Peikes et al. (46), the implicit assumption is that such trials cannot use random allocation of treatments. Therefore, for most practical purposes, randomization is the exclusive province of explanatory trials, which tend to be favored by regulatory bodies and methodologic purists (47). Because it is much easier to randomize in the context of an explanatory trial, most RCTs tend to be explanatory. This is consistent with the edict that trials of health care interventions with well-understood mechanisms of action should lie toward the explanatory end of the trial continuum (32). This often is not the case for diet-related interventions.

In their seminal work nearly half a century ago, Schwartz and Lellouch (48) were concerned mainly with the distinction between internal validity and external validity (generalizability) and the tendency for many explanatory trials to produce results irrelevant to real-world needs. They also described pragmatism as an attitude rather than a characteristic of the trial. The reality is that trials lie on a continuum from purely explanatory to purely pragmatic (32, 49, 50). Despite the demand to use intention to treat as the first-line analyses as in any RCT (51), usually data from dietary trials are subject to post hoc analyses that do not require strict adherence (52–54). In some ways, results that take into account incomplete adherence may resemble those of pragmatic trials. Of course, caution must be exercised when interpreting results, because statistical power may be greatly diminished.

RCTs of behavioral interventions, in general, and ones that focus on diet, in particular, face a number of challenges because of the high level of participant commitment and involvement required. Previously, we delineated a number of problems commonly encountered in research into the role of diet in health and therein described a variety of solutions (55). We note that the study by Satija et al. (56) also touches on points related to RCTs. Our focus here is confined to describing the limitations, inherent and practical (57), in the use of RCTs to determine the role of diet in health and alternative designs for allocating dietary exposures or treatments. Advantages and disadvantages of various study designs are given in **Table 1**.

Special Considerations for RCT Designs in the Study of Diet and Health Outcomes

The need to focus

As a practical matter, RCT designs allow for only a limited number of factors (usually 1 or 2) to be allocated at a time. Although RCTs can be used for "whole-diet" approaches [e.g., the Women's Health Initiative (WHI) Dietary Modification arm (67, 68) and the PREDIMED (PREvencion con DIeta MEDiterranea) trial (69, 70)], more typically they focus on a single food or one or a few nutrients. This may reflect the perception that obtaining adherence to a request or demand to change one's entire diet is difficult and therefore neither feasible except under exceptional conditions nor readily translatable to public health practice. Despite the appeal to focus narrowly, doing so does not represent a realistic way to make meaningful change to prevent chronic disease, especially when the preponderance of evidence indicates that eating patterns associated with whole foods are much more strongly predictive of health outcomes than are individual foods or nutrients (70–73). Indeed, the National Cancer Institute Chemoprevention Program, which focused on key nutrients that could be isolated and tested in trials, had limited success (74). Whole diet or whole lifestyle approach represents an alternative perspective to single-agent strategies. However, they pose an additional set of challenges related to making extensive changes in diet that may be particularly relevant to influencing disease course.

Choice of subjects and exposures

Dietary intervention trials also may be of limited value because they inadvertently study the wrong population or the wrong type of exposure at the wrong point in the disease process. For reasons of cost, efficiency, and interpretability, trials generally are designed to study relatively homogeneous populations at relatively high risk of the outcomes of interest, testing narrowly defined exposures for a limited period of time (75). The answers they provide are more definitive for those conditions, but there may be severe limitations in how well the findings can be generalized. Sometimes they get it wrong.

For example, the ATBC (Alpha-Tocopherol, Beta-Carotene Cancer Prevention) study and the β-Carotene and Retinol Efficacy trial (76, 77) unexpectedly found evidence for a detrimental effect of β-carotene supplementation on subsequent risk of lung cancer in older smoking men. The results obtained were inconsistent with those of hundreds of observational studies that showed protective effects of whole-food diets rich in antioxidant and anti-inflammatory micronutrients on cancers of various sites (78–81). Although only partially understood, the reasons for these paradoxical results

TABLE 1 Advantages and disadvantages of study designs for research into on the role of diet in health[1]

Design Type (references)	Advantages	Disadvantages
Conventional RCT (32–34)	Random allocation of exposure; theoretically provides a "clean" comparison between intervention and control arms	Selective dropout/retention (58); limited ability to control for multiple exposures by design; incomplete adherence in the intervention arm; control group reactivity; inability to blind complex, behavioral exposures; limited generalizability for the specific exposure and study sample; questions about real-world effectiveness (where people choose therapies) (32, 59)
Randomize-before-consent RCT (38, 60)	Random allocation of exposure; subject does not know alternative, thus reducing problems associated with motivation and expectation; may reduce selective dropout as it obviates problems associated with being given something seen as inferior	Inability to account for factors that might lead to selective dropout associated with knowing the alternative; study assignment cannot be blinded (although the subject is not initially aware of the alternative)
SST (61)	Participants choose their preferred study arm; similar to real-world settings; popular among highly informed/engaged individuals who refuse randomization (e.g., HIV/AIDS as activists)	Inability to control for personal factors related to expectation and motivation that may be expressed as the "placebo" effect
Hybrid RCT/SST (62)	Incorporates advantages of the RCT and SST; allows for control of individual factors related to motivation and expectation	Disadvantages of both RCT and SST in each respective arm (see above); expense (doubles required study size)
Adaptive intervention (63–65)	Realistic, efficient, and practical; opportunistic (e.g., taking advantage of clinical or public health system changes); allows for changes in protocol to fit participant need	Poor control for extraneous factors that may not be captured well in clinical systems; likely limited opportunity for measuring dietary exposures of interest and important potential confounders; need to document and analyze for changes in protocol
"N-of-1" design (66)	Sensitive to the needs of individual participants; comparison within individuals provides statistical power and control for unmeasured confounders	Economy of scale for measuring devices (including for diet); potential carryover effects; not blinded to participant; need to determine sequence of treatments and washout periods
Observational study, case-control	Inexpensive and may be the only practical method for rare conditions (e.g., pancreatic cancer)	Selective recruitment that may be related to condition under study; retrospective assessment of exposures, including diet, may lead to information biases that are differentially recalled according to disease status
Observational study, cohort	Allows for measuring exposures before disease onset (although "toggling" back in time to etiologically relevant period may be an issue)	Selective recruitment may exist, although if well designed and conducted it cannot be related to condition(s) under study; recall of exposures, including diet, may lead to information biases (although not directly to disease status)
Cross-sectional studies	Potentially useful for hypothesis generation	Inability to control for temporal relations/causal sequence; because data typically are collected for other purposes, usually there is poor quality control for information on diet or important potential confounders
Ecologic studies	Potentially useful for hypothesis generation	No direct use of dietary/nutritional information; instead, these are based on economic data (e.g., FAO Food Balance Sheets)

[1] RCT, randomized clinical trial, SST, self-selection trial.

almost certainly include design decisions made for efficiency and cost. These reasons include studying only high-risk populations that may have differing responses to dietary exposures. Subsequent studies have shown that high-dose β-carotene in heavy smokers may induce alterations of retinoid metabolism and signaling pathways that favor cancer promotion, whereas more moderate doses (dietary amounts) in nonsmokers have beneficial effects (82).

Commonly, trials test only higher doses of isolated nutrients that may not have the same effect as more modest intake of nutrients in foods that naturally combine other bioactive constituents. This is true of the Supplémentation en Vitamines et Minéraux AntioXydants (SU.VI.MAX) study, in which we also conducted a post hoc analysis to test the effect of the dietary inflammatory index on metabolic syndrome (83). Most trials of chronic disease prevention study exposures relatively late in terms of disease latency because it is generally impractical to conduct trials for more than a few years. However, observational studies compare food and nutrient intakes at the time of measurement that serve as indicators of relative long-term exposures that extend back many years. Even in the ATBC study that found an adverse effect of supplemental moderate-dose β-carotene on cancer risk, retrospective measures of dietary intake of the nutrient at recruitment showed an inverse association with subsequent cancer risks. Thus, trials on the effects of supplemental nutrients later in life provide limited evidence on the benefits of sustained dietary practices during periods of etiologic relevance for most primary prevention. These problems were not foreseen at the time these trials were initiated, and the mistakes were costly. Protocols of large explanatory trials cannot be modified in response to new information without compromising study power and time required to complete.

Blinding

Unlike single-agent trials that, at least theoretically, can be double blinded, participation in behavioral trials requires obvious commitment that precludes blinding from the perspective of the participant. The inability to blind the participant to the active ingredient(s) of the intervention forestalls one of the major advantages of the RCT, which is that there is no discernable difference in exposure by treatment allocation. This is an important point of distinction in that studies on the pragmatic trial end of the continuum would allow for unblinding in a manner uncharacteristic of explanatory trials.

Perceived asymmetry of treatment in relation to need

Especially in studies of individuals with conditions perceived to be life-threatening, there will be major concerns about asymmetry for the control condition, notwithstanding common attempts to devise an attentionally equivalent control for comparison (84–86). Individuals that might be important to study, such as persons with anemia or pregnant women, may be excluded for ethical reasons. Even for studies in which there may be no major concern about perception of such vulnerability, the intention to engage in behaviors that are alleged to affect long-term chronic disease risk requires substantial commitment and associated motivation and expectation. In essence, potential participants will only seek RCT dietary trials because they are looking for solutions to what they perceive to be a behavior that needs improvement. Thus, in any RCT of dietary factors there will be controls who seek dietary constituents that mimic the intervention (because they are now suitably informed and have already expressed an interest in participating). Likewise, there will be participants randomly assigned to the intervention who adhere only incompletely or not at all because they are unwilling, even after providing informed consent, to commit fully to participating in the intervention.

Even if procedures are put in place to not exclude individuals at the outset, thus avoiding selection before recruitment or selective dropout, there could be other problems with adherence. These factors would tend to "wash out" effects that otherwise might be observed in a self-selection trial (or even through careful observation). Ideally, this would happen in a nondifferential manner, but it is likely that this occurs in a way that leads to bias toward no effect of the intervention. For example, we have found that a greater percentage (59.5%) of control than intervention (49.1%) participants in a community-based RCT (33) lost weight. This phenomenon among controls is in stark contrast to findings from population-based surveys or observational studies in which adults typically gain weight at a rate of ~1 pound (~0.5 kg)/y (87–91). What may be driving this finding is that 39% of controls did not return for follow-up measures (12 wk after baseline), whereas only 21% of intervention participants did not return.

Another example of this phenomenon is the early discontinuation of the Look AHEAD (Action for Health in Diabetes) trial, the largest and longest trial to examine an intensive lifestyle intervention for weight loss and cardiovascular disease prevention compared with usual care (92). The trial was discontinued early (median of 9.6 y) because of a lack of difference in cardiovascular endpoints between the 2 groups (93). The researchers cited possible reasons for the lack of differences as the impact of the minimal education sessions (≤2/y) offered and increased use of statins in the control group (93). The most obvious problem with Look AHEAD is that the event rate was much lower than "expected" (because it was overestimated). In essence, the study pitted diet change against a large pharmacologic effect, which dramatically lowered the expected event rate: 50% were on statins, 75% were on antihypertensive agents, and the mean circulating LDL concentration at baseline was 112 mg/dL. This is seen in every modern study of cardiovascular disease (94).

The effect of this apparent asymmetry between control and treatment arms also could explain why we observed a much stronger effect in men with rising prostate-specific antigens after prostatectomy who self-selected a diet-physical activity-stress reduction intervention (95) than in similar men randomly assigned to a comparable intervention (96). It also explains diminution of effects in long-term trials, ranging from the Multiple Risk Factor Intervention Trial to the WHI. These common field experiences result in a loss of the original scientific rigor that the RCT was supposed to impart to the study. This may lead to a sense of "failure" on the part of the participant and the study team when, in reality, the dietary or other lifestyle intervention does indeed have a positive health benefit that simply cannot be observed with the use of an RCT design (97). This point is especially relevant among under-represented and vulnerable populations who have been witness to gross mistreatment by the research community. These community partners often come reluctantly to research and want to see that their hard work and efforts (both individually as participants and collectively as recruiters and advocates for the study) has realized a positive benefit for their community.

Temporal relations between dietary exposures and putative outcomes

Most chronic disease outcomes present logistical problems in terms of temporal control because they usually occur only after suitably long latency or incubation periods (which tend to be longest for cancer) (97). The tighter the control (e.g., with metabolic ward studies being the most extreme), the greater the logistical complexity required, including the need to follow participants over long time periods. Practical problems that plague these studies include fatigue related to long-duration involvement (often interacting with the condition under study) (64, 98–102) and attempts on the part of participants to compensate for one behavior change by making another change that may countervail or amplify the effect of the first (103, 104). In addition, efforts to exert more control by design interject a set of selection factors, related both to subjects' participation and exposures, that greatly limit real-world relevance (including those that

influence reporting accuracy) that negatively affect translatability. For chronic diseases with long latencies, such as atherosclerosis or cancer, it is reasonable to question how making changes late in the natural history of the disease process will translate into meaningful reductions in risk of these chronic diseases (69, 105–109). This also applies to analyses of data from observational studies in which long-term follow-up data on relevant exposures may not exist; however, dietary exposures tend to track over time, with intakes of individuals being highly correlated over long periods from childhood through adulthood (110–112).

Immutability of the treatment

Typically, individuals who participate in RCTs will receive treatment(s) that remains unchanged throughout the study, regardless of response. Although needed to ensure rigor for statistical power, this is the opposite of what is recommended for evidence-based care, whereby individuals are regularly reassessed to determine whether the treatment is effective, the dose should be changed, or another treatment should be substituted (113). In addition, subjects may be excluded from trials because of comorbidities or other conditions that can confound the evaluation of treatment effects and, as a result, compromise the external validity and limit the usefulness of the research findings for clinical practice (114).

The need to maintain methodologic rigor

No matter a study's design, dietary exposures may modify or confound the effect of the exposures targeted by the intervention (whether or not they focus on diet). Therefore, it is important to identify potential confounders at the design stage and provide means for measuring and controlling them analytically. This could include medications and other factors that might affect nutrient uptake and utilization. It also could include nutrients such as α-tocopherol and β-carotene that were used in the ATBC study (115) and selenium and vitamin E in the Selenium and Vitamin E Cancer Prevention Trial (116), which can come from dietary sources and from supplements. Individuals can (and often do) change their behaviors to modify risk. Participants in the control group of a dietary trial may be motivated to change their diet or supplement use to decrease risk. Participants in the intervention group may compensate intake in more subtle ways to account for changes in taste, satiety, or other attributes of diet. In the ATBC study the total daily dose of 25 mg β-carotene was equivalent to only 3 large carrots, underscoring the need to measure diet carefully to conduct meaningful post hoc analyses. Another example of how prescribing a supplement or pill-based intervention can have an unintended impact on diet is revealed by examining the trends in dietary intake among statin users. Between 1999 and 2010, individuals who began using statins had significant increases in energy and dietary fat consumption compared with nonstatin users (117).

As with other studies of diet and health, RCTs must face the need to measure diet. Besides the normal issues concerning measurement bias related to subject-specific factors (21, 118–121), RCTs are uniquely susceptible to errors in self-report related to implementing a focused intervention and monitoring adherence (68). The increased susceptibility is due to participants being sensitized to the dietary hypothesis being tested. For example, in the WHI, we found that individuals who were eligible for the diet modification arm overestimated their self-reported dietary intake by ~169 kcal/d in comparison with estimated metabolic requirement relative to women who were ineligible (67). Possible measurement bias could help explain why the dietary modification arm of the WHI provided only ambiguous, uncertain results for the benefits of diet, despite the enormous expense and time the trial required. In addition, the primary question tested (total dietary fat reduction) was considered outdated (supplanted by alterations in type of fat and growing concern about the effects of simple carbohydrates) by the time the results went to press (17, 122). This problem is certainly not unique to the WHI and will likely apply to other large-scale, long-term trials of diet on chronic disease risk. So, pointing to the inability to account and control for measurement error as an argument in favor of conducting RCTs so as to avoid measuring diet is misguided in light of the available evidence.

Summary of preceding points

RCTs designed to study diet among free-living people face a host of problems in attempting to create large contrasts in dietary exposures (123, 124). Changing behaviors is challenging, and these trials may require intense commitment to make and sustain large changes. Furthermore, some individuals who are willing to accept randomization likely would either lack the motivation to persevere if randomly assigned to an intensive intervention or to seek other means for achieving change if randomly assigned to a "no-treatment" control.

Placing additional emphasis on RCTs to answer questions that relate diet to health outcomes, as has been suggested (29), would delay the scientific process, leaving us with little additional evidence on diet and health for many years and serious questions about the future relevance of questions asked now on the subject of diet and health. Despite the success of PREDIMED in showing that the Mediterranean diet can prevent cardiovascular disease (69, 70), there are many other examples of expensive and lengthy trials and large-scale observational studies that have failed to provide definitive answers to the questions they set out to answer. For many dietary issues, trials are neither feasible nor ethical, and they may be limited in the generalizability of their findings even if they can be implemented (125–127).

Alternatives to the RCT

Rarely would a behavioral intervention of any kind be able to strictly enforce and monitor adherence in a rigorous way. In addition, the matter of selective recruitment and dropout would tend to undermine the explanatory imperative. Largely, this is because in such trials the design is not

matched to the decision-making needs of those people using the protocol under study (32, 46, 49). Trials at the explanatory end of the continuum that attempt to guarantee internal validity are prone to be undermined by external influences, including a lack of participant adherence, which would obscure a true effect of diet on study outcome.

By contrast, a pragmatic attitude would be much more highly tuned to the needs of patients. The reality of clinical and community practice, however, would not be easily amenable to randomization under such circumstances (46). Although some may argue that randomization would factor out the placebo effect, the reality is that motivation and expectation are important factors in any behavioral intervention, including one focused on diet. If we force randomization as part of an explanatory attitude (128), it is likely that we would have neither internal nor external validity.

So, what are we to do? Pragmatic trials may make allowance for individual tailoring of the intervention. In instances in which such alterations may take place, however, there is an additional requirement for measurement and monitoring (32, 47).

Given that results from observational studies produce results that are consistent with those from trials if the exposure level and time of exposure are the same (129), in many instances it is reasonable to continue to use and improve on observational study designs. There also is a growing interest among intervention researchers to use adaptive, nonstatic research designs (130). Adaptive interventions were described as "operationalized and individually tailored strategies for prevention and treatment of chronic, relapsing disorders" (64). Examples of adaptive intervention designs include both the Multiphase Optimization Strategy and the sequential multiple assignment randomized trial designs (131). These designs could be applied to different nutrition- or diet-based intervention components, such as randomly assigning individuals to consume certain foods or diets, and be used to examine behavioral strategies, such as participant motivation or adherence. These strategies are beginning to be used frequently in studies that involve mobile health technology because of the need for research to keep pace with technology (132). Another design being used by mobile health studies is an "n-of-1" design (133). This design addresses the need for patient-centered outcomes research and the need to rapidly iterate interventions (66). As opposed to standard RCTs, n-of-1 trials use crossover between treatments to address the problem of patient-by-treatment interaction (66). Multiple n-of-1 studies could be conducted and jointly analyzed, a strategy that might help identify carryover effects and provide reasons for why certain individuals respond to treatments (134).

Another alternative to the RCT that is applicable to nutrition research is the use of a randomized encouragement design (135). Although nutrition studies can use methods to carefully control what participants consume, such as housing participants in metabolic wards (136) or conducting feeding studies that provide prepared, pre-proportioned meals to participants (137), these methods are not real-world tests of diet. Randomized encouragement design studies focus less on adherence and more on randomly assigning participants to differing advice or recommendations (135).

Along with alternatives to RCT designs, we also need alternatives to the way we assess nutrition data during research studies. The RCT mindset has led to a rigid assessment of nutrition, collecting data typically before and after intervention with most of what happens in between being unknown. But human behavior, including nutrition-related behavior changes induced by an intervention, can be fluid and dynamic. Finding ways to capture real-time, continuous data are important because this will allow researchers to deliver more adaptive, just-in-time interventions (138).

Future Directions

It is important to carefully consider the overall goals of diet-related research and the design of dietary intervention studies, recognizing the inherent challenges and limitations of conducting meaningful RCTs on diet and health. Observational studies and pragmatic trials are not intrinsically flawed. Both reflect exposures as they are allocated in the real world. Efforts should be aimed at better understanding the challenges involved in enhancing their performance and improving methods of dietary assessment and study design. Humans are complex, and their behaviors are subject to multiple influences at many different levels. We advocate for greater creativity among investigators and increased transdisciplinary dialogue. In this way, advances in nutritional sciences can be realized.

Given high noise-to-signal ratios interjected by using inaccurate assessment methods in studies with weak or inappropriate study designs (including RCTs), it is likely that the effects of diet are underestimated. So, no matter which design is chosen, we must continue to work diligently to address acknowledged problems with the measurement of diet (55, 139). For the foreseeable future there will be no avoiding the use of these methods in studies of the effects of diet on health, no matter their design. Therefore, effort should be devoted to understanding and controlling these errors. This should include continued investigation of reporting biases with the use of a variety of criteria, but probably mainly construct validation measures, extending past work in the area (21, 118–121, 140, 141).

Research that focuses on technologic improvement also seems well advised. Digital food photography via smartphone camera has the potential to allow for just-in-time food recording (142) that could assist with assessing adherence. Research currently is under way to examine the use of photography to estimate the nutrient content of foods and beverages consumed (142, 143). Studies that use digital food photography with smartphones or wearable cameras have either solely relied on food photos by the user as a digital food record or included user photos as a way to enhance 24-h recalls or food records (144, 145). To analyze the nutrient content of the foods and beverages present in the photos, studies have either used trained raters to view photos and to

enter the foods into a nutrient database or have relied on image processing by computers to determine what foods and beverages are present and the portion sizes (143, 145). There are other technologies currently being explored to capture dietary data, including interactive websites (146), wearable devices (147), digital audio recorders (146), scanning or sensor-based technologies (146), and expanded use of social media (148). As technology continues to improve, there is potential for enhanced accuracy and reduced user burden of dietary assessment. Many of these newer methods/approaches will have their limitations, however, and biases known to be associated with structured assessment methods may be evident. For example, people could change their eating behaviors toward socially desirable norms when being followed so closely with the use of more invasive data collections methods (e.g., pictures and cameras). Additional methodologic research will be needed as the field incorporates these technologic innovations into study designs.

In conclusion, the RCT is a powerful tool for health research, but it may be particularly limiting for diet-related studies. We have described many alternatives to this design that need further exploration and consideration. No matter which design is used, studies will require continued improvement in the assessment of dietary intake. Future knowledge on the health effects of diet is likely to come from a varied and dynamic range of methods, including observational and experimental strategies.

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