Mixed Random and Nonrandom Allocation, and Group Randomization Have Been Mislabeled and Misanalysed, Necessitating Reanalysis. Comment On: “KiwiC for Vitality: Results of a Randomized Placebo-Controlled Trial Testing the Effects of Kiwifruit or Vitamin C Tablets on Vitality in Adults with Low Vitamin C Levels”

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We read the report by Conner and colleagues that tested whether kiwifruit or vitamin C affected measures of vitality [1]. The trial is reported as a randomized controlled trial (RCT), but not all participants were allocated randomly, and some participants were group-randomized, which was not accounted for in the analysis. Together, these design choices mean that as published, the statistical analysis and interpretation of results as an RCT are not warranted and corrections are needed.

We contacted the authors to inquire about their design after reading their methods, which included references to ‘batch randomization’ and challenges with stratification. The authors expeditiously shared their data, code, and additional detail on their design. We thank the authors for their collegiality in communication.

Through discussion, we learned that some participants were not randomly assigned, while some were group-randomized and others individually randomized (see **Figure 1** for our understanding of the design). We elaborate on the different aspects of nonrandom, random, restricted random, and group random methods on **page 2** in this preprint because of word limits for letters to *Nutrients*. The design choices change requirements for the analysis and communication of the trial as an RCT. We outline two errors below.

First, the trial should not be labeled as an RCT because of the methods used. Randomization is generally considered the gold standard to provide unbiased estimates of causal effects [2]. The use of some nonrandom methods, such as assigning kiwifruit to the first groups of participants because of availability, as done by Conner et al., does not permit the causal inferences justified by randomization [3,4], and therefore makes it incorrect and inappropriate for the KiwiC study to be called an RCT.

Second, when participants are randomized in sets of two or more participants (as opposed to each participant being randomized individually), this is conventionally referred to as group-randomized or cluster-randomized and referred to by Conner et al. as ‘batch randomized’. With group-randomization, the model residuals are ‘correlated’ (i.e., the residuals are not independently and identically distributed, *iid* [5]) and this violation of the assumption of standard analyses must be taken into account during the analysis [6], but they were not. As stated by Murray and colleagues: “Any test that ignores either the extra variation or the limited degrees of freedom will have a type I error rate that is inflated...” [7]

We encourage the authors to provide readers additional detail on their methods as they generously shared with us, which is essential for interpreting this study. We note a similar example of the Primary Prevention of Cardiovascular Disease with a Mediterranean Diet (PREDIMED) trial, in which, just as in this trial, the nonrandom allocation of some of the participants and some group-randomization were uncovered in a trial audit [8]. In that case, the paper was retracted and republished with a reanalysis to properly consider these factors [8]. The ‘retract and republish’ approach allows for critical issues to be corrected and clarified while simultaneously acknowledging the value of a study through republication. Until corrections are made, causal inferences from this paper are not warranted.

Clarification of random, restricted random, group random, and nonrandom assignment methods

Multiple forms of assignment were used in the paper. Some forms are restricted randomization, such as stratification (subgrouping participants by one or more variables, then randomly assigning from each stratum) and blocking (forming blocks of participants, such as those available on a particular day or restricted across time, and within each block participants are randomly assigned). Restricted randomization methods are valid and important tools to add additional control in randomized designs. The authors write in their paper that “There was also an effort to stratify the conditions by gender and ethnicity, although this was not always possible given the batch randomization”, which requires elaboration for transparency and inferences.

In correspondence, the authors indicated that group randomization was employed in some instances by clinic day to assign participants in a specific day to receive kiwifruit and in another day to receive tablets (vitamin C or placebo), or to assign participants within days to separate groups by time of day, to mitigate participant contamination (i.e., participants seeing the other treatment, as blinding is not possible between tablets and fruit). Participants scheduled their appointments partly by convenience and the days (or periods within days) were randomized to the treatments, not the participants, which would consider the day a “group”. Unlike block randomization, individuals are not randomized within the grouping, and thus there is the possibility that individuals who chose a particular day were more similar (either from similar characteristics or differences in procedures) than those assigned on different days. Statistical methods to account for the clustering and correlated observations when such assignment is used are necessary for unbiased effect estimates.

Our interpretation from correspondence with the authors is that some of the participants who received kiwifruit were not allocated using random methods. That is, all participants scheduled to have their first clinic visit in the first two weeks of recruitment process were allocated to kiwifruit due to “external circumstances”, namely that the kiwifruit group was assigned because the fruit was available and the tablets were not. Therefore, in addition to participants being all assigned within a day together, they were not randomly assigned to their clinic visit day because they had some choice in their appointment time, and the treatment given to them was assigned by necessity and not by random method (i.e., per the authors, the participants were assigned to conditions based on the week they attended the clinic and thus did not have a known probability of being assigned to all conditions). These details are currently not known to readers of the publication, which should therefore be labeled as using a mix of random and nonrandom allocation.

We emphasize two contrasting philosophies. First, the deviation from standard and consistent randomization methods undermines the theory that allows for strong causal inferences to be drawn from randomized trials. Second, the study nonetheless used an interventional method that often lends stronger causal inference than purely observational analyses. A similar error occurred in the PREDIMED study, in which the randomization scheme was violated. The journal’s approach was to ‘retract and replace’, which highlights the importance of these two contrasting factors in causal inference. By doing so, the error of labeling PREDIMED a ‘randomized trial’ was corrected, while the importance of a challenging interventional trial for informing our understanding of nutritional science was still recognized. A similar approach may be considered here.

Author Contributions: “Conceptualization, C.J.V. with all authors; writing—original draft preparation, C.J.V.; writing—review and editing, all authors. All authors have read and agreed to the published version of the manuscript.”

Funding: Supported in part by the Gordon and Betty Moore Foundation and NIH grants R25HL124208 and R25DK090880. The opinions expressed are those of the authors and do not necessarily represent those of the NIH or any other organization.

Conflicts of Interest: In the past 12 months, Dr. Brown has received grants through his institution from Alliance for Potato Research & Education, Egg Nutrition Center, National Cattlemen’s Beef Association, NIH/NHLBI, and NIH/NIDDK. He has been involved in research for which his institution or colleagues have received grants or contracts from Center for Open Science, Gordon and Betty Moore Foundation, Hass Avocado Board, Indiana CTSI, National Cattlemen’s Beef Association, NIH/NHLBI, and NIH/NIA. He has received honoraria from the University of Arkansas. His wife is employed by Reckitt Benckiser. In the last 12 months, Dr. Allison has received personal payments or promises for same from: Alkermes Inc.; American Society for Nutrition; American Statistical Association; Arnold Ventures (formerly the Laura and John Arnold Foundation); Big Sky Health, Inc.; Dynamics AQS; Glanbia; Henry Stewart Talks; Indiana University; Johns Hopkins University; Kaleido Biosciences; Law Offices of Ronald Marron; National Institutes of Health (NIH); Sage Publishing; The Obesity Society; Tomasik, Kotin & Kasserman LLC; University of Alabama at Birmingham; National Academy of Sciences; Medpace/Gelesis; Sports Research Corp.; Whistle Labs, Inc.; Donations to a foundation have been made on his behalf by the Northarvest Bean Growers Association. Dr. Allison is an unpaid member of the International Life Sciences Institute North America Board of Trustees. Dr. Allison’s institution, Indiana University, and the Indiana University Foundation have received funds to support his research or educational activities from: NIH; USDA; Soleno Therapeutics; National Cattlemen’s Beef Association; Eli Lilly and Co.; Reckitt Benckiser Group PLC; Alliance for Potato Research and Education; American Federation for Aging Research; Dairy Management Inc; Arnold Ventures; the Gordon and Betty Moore Foundation; the Alfred P. Sloan Foundation; and numerous other for-profit and non-profit organizations to support the work of the School of Public Health and the university more broadly. Other authors report no disclosures.

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Figure 1: Schematic of Conner et al. as interpreted from the published paper and personal communications. We note that this is our interpretation of the design and the authors expressed disagreement on depicting the waves (weeks) in this way because it does not reflect assignment to clinic day according to availability and timetabling. However, we believe showing the timeline of the differential individual and group assignment helps to illustrate our concerns as discussed above. We welcome additional clarification from the authors.