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LETTER TO THE EDITOR

WILEY

Maximizing the potential of the Salt Substitute in India Study

To the Editor:

We read with pleasure the article by Thout et al, titled "*Rationale, design, and baseline characteristics of the Salt Substitute in India Study (SSiIS): The protocol for a double-blinded, randomized-controlled trial*"[1] that described a trial assessing the impact of substituting usual salt (100% sodium chloride) with salt substitute (70% sodium chloride and 30% potassium chloride) on blood pressure (BP). Upon comparison with related trials and in context of recent research on BP variability, we propose the following modifications to maximize the potential of the trial:

1. A limitation of prior studies[2-5] has been the lack of measurement of covariates at multiple visits. While most baseline characteristics and laboratory values do not change significantly from initial to final visit, it would be presumptive to conclude that change in blood pressure was due to the intervention without measuring change in covariates like lipid levels, fasting glucose, and smoking and alcohol consumption, among others. By measuring time-varying covariates at least at the initial and final visits, it would allow the authors to not only determine any emerging biases between intervention and control groups, but also potentially elucidate indirect mechanisms for trial findings. One such indirect mechanism is the Hawthorne Effect,[6] the idea that if participants know their diet is being observed as part of a study, they may be more conscious of what they are eating.
2. A prior salt substitute trial in rural China[2] followed participants for three years and found that, while three-month changes in BP were high, changes dropped significantly at six months in both control and intervention groups and modestly increased thereafter. This begs the question of whether six months is an appropriate, evidence-based follow-up time to determine the effectiveness of the salt substitute. Ultimately, this is a decision we are sure the authors have determined as per logistical constraints and research evidence, but we propose that a one-year study may better assess the long-term sustainability of the intervention.
3. Subjects with higher baseline BPs may be more likely to observe a greater decrease in BP, biasing results toward such participants' outcomes.[3,5] A participant with a systolic BP of 160 may find it easier to reduce from 160 to 140, as opposed to a participant with a systolic BP of 130 trying to reduce to 110, despite both being a 20-mmHg decrease. Rather than looking at only absolute measures, we propose the authors should additionally consider relative measures such as percent decrease.
4. BP fluctuates throughout the day, so a single average reading may not be an accurate representation of one's BP. Furthermore, BP variability is increasingly being recognized as an independent predictor of cardiovascular disease.[7-11] While it may be difficult to invest in and enforce 24-hour ambulatory BP monitoring,[10] which is the gold standard for BP monitoring, authors may use this trial as an opportunity to collect BP data more rigorously through home-based BP monitoring.[11] Additionally, measurement of BP at the first, third, and fifth visits allows for calculation of visit-to-visit BP variability. Visit-to-visit BP variability is the most studied form of BP variability[8,9] but has not been studied adequately in the Indian population, and thus, this serves as an interesting corollary, secondary analysis of trial data.
5. Because this study is conducted among rural Indians with strict inclusion criteria and fairly well-controlled hypertension (as per baseline mean BPs), it may not be generalizable to the urban Indian and foreign population whose diet and lifestyles are likely different. It would be interesting to compare the intervention's effectiveness across those with uncontrolled vs. controlled hypertension.

ETHICS APPROVAL

This study was exempt from Rutgers's Institutional Review Board approval.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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[Correction added on February 8, 2021, after first online publication: The copyright line was changed.]

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