

March 21, 2024

Dr. Joseph C. Wu
President
American Heart Association

Dear Dr. Wu,

On March 19, 2024, an abstract on an observational study presented at AHA EPI in Chicago with the title “8-hour intermittent fasting (IF)/time-restricted eating (TRE) leads to increased rates of cardiovascular death” received a large amount of media coverage (BBC, Washington Post, NBC, Medscape, etc.). This is concerning as the study has not yet been peer-reviewed and there are serious issues with the study design that undermine that claim (detailed below).

Importantly, **the presented data have not been vetted or peer-reviewed**. This is an undue amount of press and publicity given the very preliminary status of the data. **Unpublished and unvetted data presented in posters are meant to be discussed at scientific conferences**, not used for press releases to alarm the public.

Serious concerns about the claims from this study:

- 1. Improperly adjusting for smoking has been reported multiple times to produce false associations with morality.** Residual confounding by smoking could account for the elevated CVD mortality risk reported in this study. First, there are 60% more smokers in the <8 h group compared to the reference group, and tobacco is the leading cause of death in the U.S. Second, adjusting for smoking as either “yes/no” or “current/never/former” has previously been found to produce erroneous associations with mortality. For instance, carotenoids were associated with *decreased* lung cancer risk when adjusting for smoking as “current/never/former” but *increased* risk when adjusted for smoking intensity and duration, suggesting residual confounding by smoking. Similarly, it has been reported on several occasions that analyses of smokers can produce opposite conclusions to analyses of people who have never smoked. The pattern of current smokers in the baseline table almost exactly fits the pattern in forest plot B (eating duration and CVD mortality). To analyze mortality data correctly, the authors need to either (a) adjust for smoking duration and intensity and/or (b) analyze the data among “never smokers” only.
- 2. A cross-sectional assessment of meal timing is not representative of long-term eating patterns.** Two days of data from a single time point were used to characterize habitual eating patterns, with the assumption that this pattern of eating is consistent over time. There are well-documented limitations to this assumption. Published, peer-reviewed studies have shown that measuring meal timing with two 24-hour recalls shows poor reliability (ICC <0.5).
- 3. Eating over a <8 h period on a single day is not the same as practicing TRE.** (1) TRE requires eating in a consistent eating window (routine schedule each day). Rather, this study defined TRE according to daily eating duration alone, and the eating window may have varied dramatically day-to-day. We know that high variability in meal times is associated with detrimental health outcomes. (2) Second, the eating window is during the active phase of the day (i.e., when people are awake, not too early or late at night). In this study, the start and end time of the eating window and last eating episode relative to sleep timing were not accounted for. Both

breakfast skipping and late eating (e.g., > 9 pm) have been associated with increased cardiovascular risk [1].

4. **Accounting for other important confounders.** There were 250% more Black Americans (23.2% vs. 6.6%) in the group eating < 8 h daily compared with the reference group, so the groups were unbalanced. There are well-documented racial/ethnic disparities in mortality from most causes in the US [2]. Moreover, sleep patterns and shift work are associated with both meal timing and mortality, but these were not accounted for.
5. **The sample size was small for the <8 h eating window group (2%) and therefore lacked adequate statistical power.** This was especially true in the stratified analyses that evaluated cause-specific death (n=31 overall), increasing the likelihood that findings could be observed by chance.
6. **The results could be spurious due to reverse causation.** The assumption that meal timing pattern is intentional does not account for individuals eating <8 h owing to other confounding factors (e.g., sleep habits, shift work, and access and availability of food) or medical conditions that could be associated with poor cardiovascular outcomes, increasing risk of reverse causality. For example, it is well-known that being close to death causes changes in eating patterns, particularly skipping meals and eating becoming more irregular. Instead of TRE causing death, it could be that being close to dying causes people to skip meals and eat < 8 h. Similarly, overnight shiftwork causes people to skip meals and eat late at night, and shiftwork increases the risk of cardiovascular disease.
7. **Survey design.** It is unclear from the abstract and poster whether the researchers account for the complex survey design used by NHANES. As emphasized by NHANES [3], “For NHANES datasets, the use of sampling weights and sample design variables is recommended for all analyses because the sample design is both a clustered design and incorporates differential probabilities of selection. If you fail to account for the sampling parameters, you may obtain biased estimates and overstate significance levels.”

In contrast to the conclusion of this study, over 100 published clinical trials have reported that TRE has small to large metabolic health benefits or little effects, with no study observing serious adverse health outcomes. Meta-analyses of clinical trials show that TRE reduces body weight and improves blood pressure. Moreover, four studies in animals show that TRE extends lifespan. Finally, peer-reviewed longitudinal studies show a decrease in breast cancer recurrence and no effects on mortality in breast cancer patients, and analyses in prospective cohorts that have repeated meal timing assessment over time and robust confounder adjustment show that shorter duration eating windows are not associated with elevated risk of CVD and are inversely associated with cerebrovascular disease risk.

We are concerned that the dissemination of alarming headlines on unvetted, non-peer-reviewed findings with potentially serious flaws is dangerous to public health, trust in the AHA, and ongoing clinical trials and endangers public faith in science. We kindly request that you publish this letter to provide a balanced perspective alongside the ‘sensational’ claims made in the public domain to clarify the aforementioned study limitations and to reinforce the totality of the evidence to date. We further urge you to support responsible and careful communication and to not issue alarming press releases on studies that have not been peer-reviewed to the media who are known to over-dramatize science to generate “clicks and reads.”

Sincerely,

34 experts in time-restricted eating, intermittent fasting, temporal eating patterns, clinical trials, and epidemiological methods

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