Title

Vegetable Consumption and Progression of Prostate Cancer—Reply

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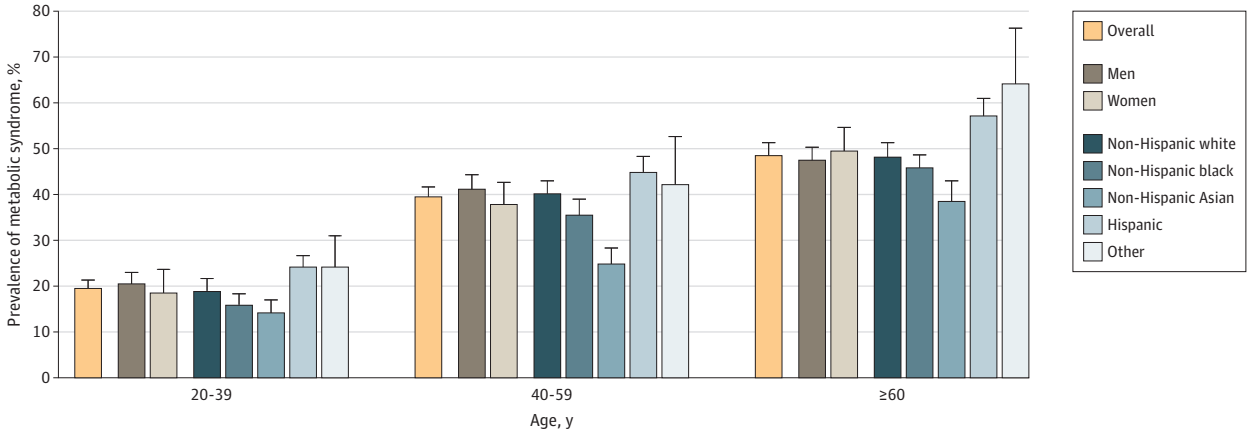
Figure. Age-Specific Prevalence of Metabolic Syndrome by Sex and Race/Ethnicity, 2011-2016



Error bars indicate 95% CIs. Hispanic race/ethnicity includes Mexican American or other Hispanic race. Other race/ethnicity includes other non-Hispanic races, including non-Hispanic multiracial. Comparisons of prevalence estimates between age groups among the specified demographic subgroups were performed using χ^2 tests. All comparisons yielded P <.001.

a significant increase observed among young adults. Prevalence among those aged 60 years or older remained high.[3] The fast-growing prevalence in young adults and Hispanic and Asian individuals is important to note given their increasing population in the US.

With an aging US population and concurrent increases in other chronic conditions and comorbidities,[4] increases in the prevalence of metabolic syndrome are concerning. Efforts to implement prevention strategies, including lifestyle modification and use of medications targeted at subgroups at highest risk, may assist in lowering the risk of developing cardiovascular disease.[5,6]

Limitations inherent in the use of NHANES data, such as nonresponse bias and potential misclassification based on medication use, should be acknowledged. Causal inference could not be drawn due to the cross-sectional nature of the study. No information was available on severity or control of each metabolic syndrome component. Lack of the use of race-specific abdominal obesity cut points may have affected the accuracy of the estimates, particularly for Asian participants. There exists the possibility of insufficient power to detect significant differences between groups or over the study period.

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Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Hirode.
Critical revision of the manuscript for important intellectual content: Wong.
Statistical analysis: Hirode.
Administrative, technical, or material support: Wong.
Supervision: Wong.

Conflict of Interest Disclosures: Dr Wong reported receiving research grants from Gilead Sciences and Abbvie and being part of the advisory board and speaker's bureau for Gilead Sciences. No other disclosures were reported.

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COMMENT & RESPONSE

Vegetable Consumption and Progression of Prostate Cancer

To the Editor Dr Parsons and colleagues conducted a phase 3 nutrition intervention trial among 443 men with prostate cancer.[1] The intervention group was encouraged to consume at least 7 servings of vegetables and fruits daily, including at least 2 servings each of tomatoes and cruciferous vegetables.

At baseline, there were no significant differences between the groups (including body mass index and log-transformed carotenoid values). At 12 months and 24 months, there were no significant differences between the 2 groups in the defined outcomes. However, there are several issues.

Controlled nutrition trials are difficult. The control group in this study was provided with materials encouraging a vegetable-rich diet. Indeed, there were small dietary changes in the control group. In addition, the placebo effect of nutritional interventions appears strong among men with prostate cancer.[2]

The authors stated that the "behavioral intervention…produced robust, sustained increases in…vegetable intake for 2 years."[1] Participants in the intervention group did increase their vegetable consumption but failed to meet any of the predefined targets. The increases in cruciferous vegetables and tomatoes, respectively, were 0.71 and 0.18 servings per day at 12 months and 0.50 and 0.06 servings per day at 24 months.

There were minor (although statistically significant) decreases in consumption of red meat and saturated fat in both groups and total fat in the intervention group only at 12 months. At 24 months, consumption of total and saturated fat remained significantly decreased in the intervention group only. However, the clinical significance of these small changes is debatable, and this is potentially of importance because prospective studies have reported associations between saturated fat intake and prostate cancer progression.[3]

Previous research has demonstrated that a larger dietary change focused on increasing vegetable protein and decreasing animal protein could prolong prostate-specific antigen (PSA) doubling time.[4] Additional research has demonstrated that a plant-based diet with stress reduction could slow PSA increases and even decrease PSA levels.[5]

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Conflict of Interest Disclosures: None reported.

1. Parsons JK, Zahrieh D, Mohler JL, et al. Effect of a behavioral intervention to increase vegetable consumption on cancer progression among men with early-stage prostate cancer: the MEAL randomized clinical trial. *JAMA*. 2020; 323(2):140-148. doi:10.1001/jama.2019.20207

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5. Ornish D, Weidner G, Fair WR, et al. Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol*. 2005;174(3):1065-1069. doi:10.1097/01.ju.0000169487.49018.73

To the Editor In the Men's Eating and Living (MEAL) randomized clinical trial,[1] men with early-stage prostate cancer were randomized to receive counseling to increase vegetable consumption to 7 servings per day or more vs the control group receiving written dietary information. We would caution that the generalizability of the findings may be limited to men with the baseline dietary habits of those recruited to the study. At baseline, the mean total vegetable intake was 3.38 servings per day, an amount twice the mean intake of US men (1.5 servings per day).[2,3] Hence, most men in the US are likely to have lower vegetable intake than the amounts consumed at baseline by participants in this trial.

These results confirm that among men already consuming moderate levels of vegetables, there was no benefit on prostate cancer progression resulting from additional servings of vegetables. As such, these data suggest either that increased vegetable intake has no benefit—or not enough to delay prostate cancer progression—or, if vegetables are beneficial, the number of servings per day needed to achieve detectable benefit may be low (ie, <3 servings per day) such that most men in the study met this criterion at baseline.

As noted by the authors, randomized clinical trials have generally failed to support hypotheses pertaining to benefits of dietary supplements. Previous trials suggest that the response to cancer prevention dietary interventions may be nonlinear, with benefits gained only among those with lower intake levels at baseline.[4] In other words, there may be a threshold effect in the relation between intake and potential benefit.

Although we appreciate that unplanned post hoc analyses can raise more questions than answers, it would be intriguing to examine trends in prostate cancer progression stratified by baseline vegetable intake because this may provide insight into the design of future studies. As an example, while the phase 3 trial of selenium to prevent prostate cancer in men with high-grade prostatic intraepithelial neoplasia showed no benefits,[5] among selenium-deficient men at baseline, there was an 18% reduction in the risk of prostate cancer, albeit not statistically significant. The authors of the selenium study concluded that focusing future prevention studies on men with lower intake of selenium may yield more informative and potentially more encouraging results.

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Conflict of Interest Disclosures: None reported.

1. Parsons JK, Zahrieh D, Mohler JL, et al. Effect of a behavioral intervention to increase vegetable consumption on cancer progression among men with early-stage prostate cancer: the MEAL randomized clinical trial. *JAMA*. 2020; 323(2):140-148. doi:10.1001/jama.2019.20207

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In Reply Dr Kerley raises 4 concerns with the design and conduct of the MEAL trial: (1) evidence of dietary changes in the control group; (2) a potential placebo effect in the control group; (3) an inability to achieve predefined dietary targets in the intervention group; and (4) a failure of the intervention to incorporate fat intake. We believe these issues do not change the validity of our conclusions.

First, while we observed small changes from baseline in some dietary components in the control group, most were small and insignificant compared with the intervention group and did not last beyond 12 months. Moreover, at least 1 change was counterproductive: after 24 months, control participants were eating fewer tomatoes compared with at baseline.[1]

Second, to our knowledge, there exists no proven placebo effect for any type of prostate cancer treatment; the cited study, which focused on PSA outcomes in patients with advanced prostate cancer, provided no evidence of it. Fluctuations in PSA values in the control groups of this study were small, consistent with expected event rates, and attributable to regression to the mean.[2]

Third, predefined targets for behavior change are aspirational, and the intervention produced clinically meaningful changes with very large between-group differences. Intervention participants increased vegetable consumption by 60%, including a 2.5-fold increase in cruciferous vegetables. Circulating lycopene levels in these patients increased by 95%.

Fourth, although we did not target saturated fat, intervention participants nevertheless consumed 15% less of it after 12 months compared with controls, a significantly larger decline from baseline that was sustained over 24 months. Moreover, the 2 cited studies associating fat intake with prostate cancer progression incorporated outcomes of unproven clinical significance: for example, in vitro growth suppression of prostate cancer cell lines.[3,4]

Dr Csizmadi and colleagues suggest that vegetable consumption may not be linearly related to prostate cancer progression, and that patients with lower vegetable intake may have potentially benefited. However, post hoc analyses stratified by baseline vegetable intake demonstrated no differences in clinical outcomes among participants who consumed fewer vegetables. At baseline, 43% of participants reported less than 3 daily servings of vegetables, with no between-group differences (P = .64). For PSA-focused study outcomes (time to PSA >10 ng/mL or PSA doubling time), the unadjusted hazard ratio was 0.86 (95% CI, 0.65-1.13). This hazard ratio remained unchanged when adjusted for baseline intakes of total vegetables and fruits and vegetables. Thus, regardless of baseline dietary intake, our study does not support the hypothesis that vegetable or fruit intakes modify clinical progression.

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1. Parsons JK, Zahrieh D, Mohler JL, et al. Effect of a behavioral intervention to increase vegetable consumption on cancer progression among men with early-stage prostate cancer: the MEAL randomized clinical trial. *JAMA*. 2020;323(2):140-148. doi:10.1001/jama.2019.20207

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CORRECTION

Inaccurate Quote: The Medical News and Perspectives article "Coconut Oil's Health Halo a Mirage, Clinical Trials Suggest,"[1] published in the April 28, 2020, issue of *JAMA*, included a quote that did not accurately explain how medium-chain fatty acids (MCFAs) are absorbed by humans. This article was corrected online.

1. Abbasi J. Coconut oil's health halo a mirage, clinical trials suggest. *JAMA*. 2020;323(16):1540-1541. doi:10.1001/jama.2020.5186