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Conflict of Interest Disclosures: None reported.

1. Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, et al. Inequalities in life expectancy among Us counties, 1980 to 2014: temporal trends and key drivers. *JAMA Intern Med*. 2017;177(7):1003-1011.

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In Reply Our study[1] on inequalities in life expectancy found that a combination of socioeconomic and race/ethnicity factors, behavioral and metabolic risk factors, and health care factors could explain 74% of the variation in life expectancy among counties. We agree with Dr Mestral that other factors such as diet quality and housing conditions may play a role in explaining the remaining variation. This is an important area of future research and will require identifying appropriate county-level data sources that relate to these factors.

Our study[1] also found that much of the effect at the county level of variation in socioeconomic factors on variation in life expectancy was mediated via risk factors. We do not interpret this to mean that risk factors should be the sole focus of efforts to improve population health. Socioeconomic factors are important, not only for health, but for well-being and prosperity more generally. Our research[1] suggests that both socioeconomic and racial inequalities, as well as behavioral and metabolic risk factors, are important targets for improving population health and reducing inequalities. After all, individuals with low socioeconomic status are often the most impacted by these risk factors and are the most likely to benefit from such a strategy.

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Conflict of Interest Disclosures: None reported.

1. Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, et al. Inequalities in life expectancy among US counties, 1980 to 2014: temporal trends and key drivers. *JAMA Intern Med*. 2017;177(7):1003-1011.

Perplexing Conclusions Concerning Heat-Not-Burn Tobacco Cigarettes

To the Editor While we welcome independent studies on our products, in a Research Letter published in a recent issue of *JAMA Internal Medicine* Auer et al[1] described a chemical analysis of the IQOS aerosol that we find perplexing in several respects. Accuracy in science is, of course, always important. We believe that it is especially important in relation to potentially less harmful alternatives to cigarettes to ensure that adult smokers receive accurate information.

While some of the results reported by Auer et al[1] seem consistent with those that we have previously published, significant points of difference in the described methodologies may account for the disagreements compared with our peer-reviewed and published data.[2] For example, the reported acrolein yield for the tested cigarette is 50 times below the level reported for similar cigarettes by Health Canada.[3] It seems that Auer et al[1] neither validated their methods with a standard reference cigarette nor compared their results with those published by a recognized regulatory agency. Further apparent methodological shortcomings are described in our full review of the article.[4] Because we understand the importance of scientific rigor and the potential for skepticism around tobacco industry-generated data, we also commissioned an independent and accredited laboratory to analyze the IQOS aerosol. The relevant data were published on http://www.pmiscience.com and submitted as part of our Modified Risk Tobacco Product application to the US Food and Drug Administration.[5]

We have scientifically demonstrated the absence of combustion in IQOS.[5,6] This has been corroborated by several combustion experts.

In their Research Letter, Auer et al[1] did not present any data regarding the impact of IQOS use on indoor air quality. In contrast, we produced and published data using validated methods that show that the use of IQOS does not negatively impact indoor air quality according to international standards.[6]

We recognize the need to scrutinize the scientific work performed by the tobacco industry. It would seem equally important to scrutinize the work emanating from academia. We are therefore puzzled that the peer review system did not identify some of the methodological and interpretational findings outlined in our review.[4]

Philip Morris International transparently communicates its study results,[6] including that IQOS yields over 90% lower levels of toxicants than the reference cigarette 3R4F and is not risk free.[4-6] The totality of the evidence collected to date, across a broad range of toxicology, systems toxicology, and clinical studies, indicates that IQOS has the potential to present less risk of harm compared with continued smoking for adult smokers who switch to it completely.[6]

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Conflict of Interest Disclosures: The authors are fully paid employees of Philip Morris International (PMI), the manufacturer of IQOS. All studies conducted by PMI with IQOS were solely funded by PMI.

1. Auer R, Concha-Lozano N, Jacot-Sadowski I, Cornuz J, Berthet A. Heat-not-burn tobacco cigarettes: smoke by any other name. *JAMA Intern Med*. 2017;177(7):1050-1052. doi:10.1001/jamainternmed.2017.1419

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To the Editor We read with great interest the Research Letter in a recent issue of *JAMA Internal Medicine* by Auer et al[1] showing the presence of volatile organic compounds, polycyclic aromatic hydrocarbons, and carbon monoxide in the emissions of a tobacco heating product (THP) recently marketed by Philip Morris International (PMI).

These findings differ significantly from those presented by PMI as well as by PMI's competitors,[2-4] and Auer et al[1] argue that this information should come from independent research rather than from manufacturers.

It is sacrosanct that consumers deserve accurate information about the chemical composition of emissions generated by THPs (and other analogous classes of products), and this information must be carefully verified by independent sources. However, although independent verification of the data are a necessary condition, this alone is not a sufficient to guarantee the scientific quality and the credibility of the information.

In this Research Letter,[1] the large standard deviations shown for the majority of toxicological constituents in IQOS emissions cast serious doubts about the quality of the analytical data.

The International Organization for Standardization (ISO) standard method for the measurement of benzo(a)pyrene and other polycyclic aromatic hydrocarbons (PAHs) in mainstream smoke uses gas chromatography–mass spectrometry and provides good analytical precision, whereas Auer et al[1] used high-performance liquid chromatography (HPLC) with fluorescence, for which they appear to miscite their own work,[5] as this includes information on the HPLC-fluorescence method in relation to carbonyls analysis only and not to PAHs.

Additionally, the puffing conditions reported by the authors do not correspond to either the established ISO conditions (35 mL/2 sec/60 sec) or Canadian Intense (55 mL/2 sec/30 sec).

Also, to reach any meaningful conclusion about relative toxic effects of IQOS emissions compared with tobacco smoke, Auer et al[1] should have compared emission data from 1 single conventional cigarette with those generated from only 1 IQOS stick (and not 10).

In the absence of a standardized protocol for emission generation and specifically validated analytical measurements, the quality of the research in this area is in jeopardy.

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Conflict of Interest Disclosures: In relation to his work in the area of tobacco control, Dr Polosa has received lecture fees and research funding from Pfizer and GlaxoSmithKline, manufacturers of stop-smoking medications. He has also served as a consultant for Pfizer, Global Health Alliance for treatment of tobacco dependence, ECITA (Electronic Cigarette Industry Trade Association) in the United Kingdom, and Health Diplomat (a consulting company that delivers solutions to global health problems with special emphasis on harm minimization). Lectures fees from a number of European electronic cigarette industry and trade associations (including FIVAPE in France and FIESEL in Italy) were directly donated to vaper advocacy nonprofit organizations. Dr Polosa is also currently scientific advisor for LIAF (Lega Italiana Anti Fumo [Italian acronym for Italian Antismoking League]) and is head of the European Technical Committee for standardization on "Requirements and Test Methods for Emissions of Electronic Cigarettes" (CEN/TC 437; WG4). No other conflicts are reported.

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In Reply There is general agreement on the need for rigorous independent studies of IQOS that will accurately inform the public. When we began our research,[1] Phillip Morris International (PMI) advertisements claimed IQOS produced "no smoke." We thus designed our exploratory study to detect chemicals typical of pyrolysis, the presence of which defines an aerosol as "smoke." We chose a comparison cigarette (a brand regularly smoked by millions) based on convenience, because the comparison was incidental, rather than the heart of the experiment. We did not set out to provide a benchmark for the regulatory industry, so comparison with a 3R4F standard cigarette was unnecessary. Tobacco content naturally varies, and differences may be compounded by process fluctuations in cigarette manufacture.[2] Standard cigarettes reduce such variations, but they are no more representative of cigarettes used by smokers worldwide than any other single brand of cigarette. Because we were not benchmarking, using the more expensive standard cigarette and waiting for its delivery would have held up our real work, which was identifying the presence of harmful chemicals in IQOS smoke. Our validated and standardized analytical methods are not likely to have caused the wide standard deviation in our measures of IQOS smoke: variation in IQOS tobacco content is the likely explanation.

Caruso and Polosa assert that we did not use standard methods when we tested IQOS. But standards for conventional cigarettes need to be adapted to this new smoking technology.[3] Because all studies that tested the IQOS had been commissioned by PMI, and because these also used "nonstandard" smoking regimens and "nonvalidated" instruments,[4,5] we argue no "standard" exists yet for testing the IQOS. We adapted the standard International Organization for Standardization (ISO) regimen to better simulate the IQOS smoke scenario and hope others will also help improve techniques for accurately measuring the new smoking technologies; this is how standards evolve. Necessary modifications to the smoking regimen probably account for the discrepancy between some tobacco company results and our results.[6] To measure airborne volatile organic compounds (VOCs), we used the validated National Institute for Occupational Safety and Health (NIOSH) sampling method (2549:1996) and our own accredited analytical method (ISO 17025). We used validated methods (NIOSH 5506 and ISO 17093) to detect and quantify both particle bound and gaseous airborne polycyclic aromatic compounds (PAHs). We adapted the method to sample PAHs for the IQOS so it was more sensitive and measured the mean concentrations from smoke generated by 10 IQOS cigarettes.

We did not intend to test for combustion but pyrolysis, which produces the harmful components of smoke. We showed that tobacco is pyrolized when heated to 330° C in the IQOS, which supports our argument that the IQOS aerosol should be called "smoke." We were glad to read that Maeder and Peitsch agree, in their full review of the research letter, that the IQOS is not devoid of pyrolytic processes.[7] We are pleased that the question of what constitutes "smoke" is a topic of debate in the scientific community.

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Sample Size Matters When Drawing Conclusions on Alternate-Day Fasting Diet

To the Editor We read with interest the Original Investigation by Trepanowski et al[1] published in a recent issue of *JAMA Internal Medicine*; to the authors' knowledge, it was the longest and largest randomized trial evaluating alternate-day fasting diet against calorie restriction diet and placebo. Trepanowski et al[1] concluded the investigational intervention's lack of superiority in terms of weight loss or metabolic outcomes against the comparators. We found this publication provocative and interesting; however, we want to highlight some design characteristics that may have impacted the trial outcomes and, thus, limited the power and external validity of the results.

Our main concern is the the sample size calculation of the study.[1] The assumptions used to estimate the number of participants were based on a study by Redman et al[2] where 46 patients who were overweight were randomized to a calorie-restriction diet (CRD), low-calorie diet, or placebo for 6 months. Results showed that a 10% weight reduction was reported in the CRD group, which included only 12 healthy patients who were overweight (body mass index, 27.3-28.3 kg/m^2) and is far from depicting what is usually observed in a 6-month intervention with CRD. A better representation of typical weight loss in a diet-only intervention would range from 5% to 8% at 6 months, coincident to what was observed in the study by Trepanowski et al.[1] Moreover, a 15% weight loss is not often seen in a 6-month diet intervention.[3] Those assumptions lead to a smaller population, and thus, reduced power to detect clinically meaningful differences between groups. Furthermore, the high dropout rate in the alternate-fasting regimen, might challenge the study results. The population was metabolically healthy at study entry; only weight modifications are expected because most of the metabolic features were already, by definition, within a normal range at baseline.[1,4]

We consider the conclusions by Trepanowski et al[1] hard to be supported with the data presented in the article. Still, we recognize the value of the article as it might be the foundation for further research in this matter.

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