JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 81, NO. 23, 2023

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Are We Sure We Know the Risk Factors for Cardiovascular Disease?*

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When we talk about cardiovascular disease (CVD), most of us believe that medical science has mostly figured it out, we know what it is, and we know how to prevent it. The American Heart Association (AHA) lists several risk factors for CVD: hypertension, high cholesterol, metabolic syndrome, chronic kidney disease, chronic inflammatory conditions, lack of physical activity, ethnicity, family history, stress, sleep problems, alcohol, and smoking.[1] Yet there may be important factors not included in the current model, while others that are included may have questionable validity as risk predictors for CVD.

That we do not yet have all the risk factors in the hat can be seen in the mortality positioning of CVD. According to the Centers for Disease Control and Prevention, CVD is ranked as the number 1 cause of death in the United States (data from 2021), and life expectancy dropped in the years 1900 to 2018 for the first time in peace-time history.[2] Per the AHA, the economic costs associated with CVD have more than doubled from 1996-1997 to 2017-2018.[3] Given the bleak outlook of our CVD prevention ability, it would be great to find factors that truly predict CVD risk.

In this issue of the *Journal of the American College of Cardiology*, Rist et al[1] aim to determine if migraine with aura (MA), often noted to be associated with an increase in CVD and stroke relative to migraine without aura,[4-6] could be one of these hidden risk factors able to predict CVD. In essence they ask: can being a sufferer of migraines with aura be predictive of an increase in cardiovascular risk for that person? And if yes, then MA should be included on the CVD risk factors list.

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The hypothesis makes perfect sense. After all, statistics show that those who experience MA have a 2-fold increase of CVD and stroke.[4] A study looking at MA vs migraine without aura and other CVD risk factors, such as triglycerides, high-density lipoprotein, and more, showed that MA was risk factor equivalent to other cardiovascular factors.[7] Most statistical models for CVD risk evaluation that include migraine do not use MA separately as a specific risk factor, and some do not distinguish migraine as a risk factor with respect to CVD at all.[8]

Rist et al,[1] using excellent statistical evaluation methods, found that although there is a strong association between MA and CVD, MA is not predictive as a risk factor. While MA is strongly associated with CVD in the Reynolds and AHA/American College of Cardiology Pooled Cohort Equation risk scores, the categorical net reclassification improvement does not justify its inclusion into the risk model. This is surprising, but the silver lining of this negative finding seemingly is that we can cross it off the list of risk factors that can predict CVD. Or can we?

Understanding the differences between MA and migraine without aura, and recognizing the underlying physiological differences that may be driving factors for CVD, would be important for better predictive models. There is no clear definition of what an aura is, how long it lasts, and if a headache starts during the aura or only after. And what to do with the cases when a headache does not follow the aura at all?[9] Rist et al[1] defined new variables, separating aura migraineurs into 2 categories: aura without migraine as one variable and those who had aura with migraine as the second. Into this second variable, they also merged data from those women who did not

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of the *Journal of the American College of Cardiology* or the American College of Cardiology.

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The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2023.04.012

experience migraines at all. This was based on literature showing no association of non-aura migraineurs with CVD,[10] establishing a difference between those with aura only from those with any form of migraine. Although this dichotomous variable creates a wide breath of separation between MA and migraine without aura, the authors reliance on the lax definition of MA and absence of understanding regarding the underlying physiology of migraine may have led to a weaker research outcome than expected. Some studies still posit that MA is different because of a cortical spreading depression (CSD) that only precedes MA; however, we now understand that all migraines have CSD.[11,12] In fact, the aura itself is just the visual presentation of the CSD.[13]

Most metadata analysis for risk prediction models face the dilemma of presenting associations that are not statistically significant enough to be predictive. The primary reason for this is the interpretation of the term "association" and its relationship with causation. In many research articles, the authors simply reassign their findings of association to "causal inference" (association that reflects cause-and-effect) or "independent association" (2 variables moving together in strong correlation but without causation established) with an HR of <2, ignoring the Bradford Hill criteria. They assume association to be equal to causation, and then later researchers use this association-driven "causal risk predictor" as fact in their models.[14] Using models based on such interpretation causes magnification of the errors upon adding further variables into the model.

It is possible that the reason why Rist et al[1] did not find MA to be predictive in their statistical evaluation is because of this dilution effect as well. It would be very important to revisit the CVD model's risk variables we believe to be predictive to evaluate if these variables truly are predictive, meeting all statistical requirements. Looking at the literature for both migraine research and CVD, proper evaluations clearly have not always been done, which has a ripple effect on scientific studies using such "trusted" predictors without factual proof that they had truly met the requirements when they were added to the risk prediction model.

Of the many academic papers published each year, it is hard to find some showing failure of support for the original hypothesis and reporting null findings of only association. In general, there is little interest in publishing low or no correlation results, accepting lack of causation. Yet, there is gold in not finding what one is looking for, and publication of these results should be encouraged. They can help clear the field of the many distorted correlations treated as causal predictors. It is in this light that the research article by Rist et al[1] is so important.

With all the uncertainty about CVD risk factors and even the proper definition of migraine with and without aura, any research that finds a presumed risk factor lacking predictive value is welcome. The goal is to understand the causes of CVD and find real risk factors. Rist et al[1] showed that the inclusion of MA in the current CVD risk predictive model would be without merit. With the excellent research of these authors, we now understand that having migraines with aura, based on using the Reynolds and AHA/American College of Cardiology Pooled Cohort Equation risk scores, is not one of the risk factors.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The author has reported that she has no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Rist PM, Buring JE, Cook NR, Kurth T. Contribution of migraine to cardiovascular disease risk prediction. *J Am Coll Cardiol*. 2023;81:2246–2254.

2. Bastian BT, Vera B, Arias E, et al. *Mortality trends in the United States, 1900–2018. online*. Accessed April 4, 2023. National Center for Health Statistics; 2020. https://www.cdc.gov/nchs/data-visualization/mortality-trends/

3. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association. *Circulation*. 2022;145:e153–e639.

4. Schürks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2009;339:b3914.

5. Tepper D. Migraine and cardiovascular disease. *Headache J Head Face Pain*. 2014;54(7):1267–1268.

6. Elgendy IY, Nadeau SE, Bairey Merz CN, Pepine CJ. Migraine headache: an underappreciated risk factor for cardiovascular disease in women. *J Am Heart Assoc*. 2019;8(22):e014546.

7. Kurth T, Rist PM, Ridker PM, Kotler G, Bubes V, Buring JE. Association of migraine with aura and other risk factors with incident cardiovascular disease in women. *JAMA*. 2020;323(22):2281–2289.

8. Rohmann JL, Rist PM, Buring JE, Kurth T. Migraine, headache, and mortality in women: a cohort study. *J Headache Pain*. 2020;21(1):27.

9. Hansen JM, Lipton RB, Dodick DW, et al. Migraine headache is present in the aura phase: a prospective study. *Neurology*. 2012;79(20):2044–2049.

10. Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Migraine and risk of cardiovascular disease in women. *JAMA*. 2006;296(3):283–291.

11. Charles AC, Baca SM. Cortical spreading depression and migraine. *Nature Rev Neurol*. 2013;9:637.

12. Lauritzen M, Dreier JP, Fabricius M, Hartings JA, Graf R, Strong A. Clinical relevance of cortical spreading depression in neurological disorders: migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. *J Cereb Blood Flow Metab*. 2011;31(1):17–35.

13. Hanalioglu S, Taskiran-Sag A, Karatas H, et al. Cortical spreading depression can be triggered by sensory stimulation in primed wild type mouse brain: a mechanistic insight to migraine aura generation. *J Headache Pain*. 2022;23(1):107.

14. Chiuve SE, Cook NR, Shay CM, et al. Lifestyle-based prediction model for the prevention of CVD: the Healthy Heart Score. *J Am Heart Assoc*. 2014;3(6):e000954.

KEY WORDS cardiovascular disease, CVD risk, migraine, migraine with aura, migraine without aura