

Modifiable Risk Factors and Cardiovascular Outcomes

TO THE EDITOR: The results of an investigation of risk factors on the incidence of cardiovascular disease and death from any cause, as reported by Magnussen et al. on behalf of the Global Cardiovascular Risk Consortium (Oct. 5 issue),¹ show that these risk factors accounted for a population-attributable fraction of the 10-year incidence of cardiovascular disease of 52.6% among men and 57.2% among women. The factors that were investigated are five modifiable risk factors (body-mass index, systolic blood pressure, the level of non-high-density lipoprotein [HDL] cholesterol, current smoking, and diabetes).

It is disappointing that current smoking and diabetes were selected as research factors. The definition of current smoking may not capture the entire spectrum and dose of tobacco exposure. The replacement of current smoking with a long-term smoking history, such as smoking for 5 years or more, may make the conclusions more relevant. As a disease, diabetes does not reflect hyperglycemia in the body, especially in some patients with mild disease or in those who have strict blood-glucose control with medications, nor is it a truly modifiable risk factor. But high levels of glycated hemoglobin are a unique predictor of cardiovascular disease risk.² A choice of the glycated hemoglobin level as a modifiable risk factor may be a better risk factor that warrants further evaluation.

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TO THE EDITOR: The study by the Global Cardiovascular Risk Consortium provides valuable in-

sights into the prevalence of modifiable risk factors for cardiovascular disease and death. However, there are a few concerns regarding ecologic bias, contextual factors, and cohort representativeness that warrant consideration. First, although the methods take into account geographic differences in risk factors and the authors aimed to harmonize individual-level data from various countries, the data set may still be susceptible to ecologic bias.¹ Mitigation of this bias by the investigation of contextual factors, such as health care systems, socioeconomic status, and policy implementation, may improve understanding of regional discrepancies.^{2,3} Second, the combination of data from 112 cohort studies may result in varying representativeness, data quality, and data quantity. Future research can improve representation with stratified sampling or oversampling of underrepresented populations or regions. Moreover, the incorporation of a metric to capture the rapidly shifting landscape of global health will lead to results that are more applicable to populations in low- and middle-income countries than to those in high-income countries. The addressing of geographic variation and consideration of contextual factors with methodologic limitations will provide a more comprehensive understanding of cardiovascular disease outcomes and potential prevention measures worldwide.⁴

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TO THE EDITOR: The Global Cardiovascular Risk Consortium pooled and harmonized individual-level data from 1,518,028 persons across 112 cohort studies to identify the prevalence of risk factors and their contribution to cardiovascular disease outcomes relevant to a global population. However, the findings that only 57.2% of incident cardiovascular disease among women and 52.6% among men that were observed among persons with any of the five modifiable risk factors studied provide compelling evidence that there are unknown factors contributing to cardiovascular disease risk that are not recognized. Indeed, the findings from this consortium converge with recent observations that an increasing proportion of patients present with myocardial infarction despite no standard modifiable cardiovascular risk factors (coined “SMuRFless”).¹ Patients who are SMuRFless have a higher risk of early death than patients with at least one modifiable risk factor.² The findings from the Global Cardiovascular Risk Consortium highlight the need for discovery of new susceptibility factors in patients with cardiovascular disease beyond those that are related to traditional risk factors.³

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new global approaches to cardiovascular disease drug solutions. *Circulation* 2021;144:159-69.

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THE AUTHORS REPLY: Ou et al. question methodologic aspects of our analyses and offer strategies to address these concerns in future research. The choice and handling of the risk-factor variables of smoking and diabetes were carefully considered when we designed our analyses. Granular information about smoking was not uniformly available and would have required a different analytic assessment, such as information from repeated assessments.¹ Smoking patterns, depth of inhalation, and duration of exposure or duration of time since quitting smoking may all influence the cardiovascular effects of tobacco use. Current smoking was chosen as the variable to assess tobacco use, despite its limitations, because the information was widely available.

Although the glycated hemoglobin level is a good surrogate marker of hyperglycemia, it was not frequently available in this global population. However, type 2 diabetes is a long-standing and accepted risk factor for cardiovascular disease that is easily accessible in cohort studies worldwide, interrelated with other risk factors for cardiovascular disease, and modifiable by means of lifestyle changes.² It is now recognized that type 2 diabetes can be put into remission by addressing underlying causes, such as obesity, and as such, it can be considered a modifiable risk factor for cardiovascular disease.

Mei et al. raise the issue of ecologic bias and representativeness of the data. Although extensive efforts were undertaken to ensure data harmonization, in such a large consortium, data quality and representativeness will vary. Careful consideration was made regarding how to analyze the individual-participant data, and a two-stage multivariate random-effects meta-analysis was used.³ This approach allows for an assessment of between-study heterogeneity in the estimated effects. Moreover, each study is weighted more equally than when a common effect across studies is assumed.

We concur with Figtree et al. that the analyses of the Global Cardiovascular Risk Consortium highlight the importance of understanding other determinants that affect the incidence of

cardiovascular disease, given that approximately half the cardiovascular events may not be attributed to the five risk factors studied. Such factors include genetics, social determinants of health, physical activity levels, and muscle strength.⁴ In addition, information on the long-term history regarding the five risk factors was not uniformly available, so it is not known how these changed over time. For example, the relationship between the non-HDL cholesterol level and cardiovascular events may be influenced by the duration of exposure to a given cholesterol level. Although approximately 50% of the population-attributable fraction of cardiovascular disease worldwide is not explained by the five classic risk factors studied, the implementation of strategies to address the other 50% may still reduce cardiovascular disease–associated morbidity and mortality among many millions of persons. Our study emphasizes the need to use strategies that have been proven to reduce the five risk factors included in our analyses, as well as to identify and develop strategies to address risk factors that we did not study.

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Where Medical Statistics Meets Artificial Intelligence

TO THE EDITOR: The review by Hunter and Holmes (Sept. 28 issue)¹ highlights key challenges at the intersection of artificial intelligence (AI) and statistics in medical research. For example, although the feature representation learning and predictive capabilities of AI are strong, overfitting and other biases pose important challenges. However, these issues are not unique to AI but extend also to traditional statistical approaches.

The challenges of biases can be observed in well-established statistical methods, including in linear regression models. Such biases may arise from the underrepresentation of marginalized groups in data sets as well as from suboptimal design and model fitting, which affect both AI and statistical methods.

In addition, AI research in health care is increasingly focused on evaluation metrics that reflect clinical validity and utility — issues that move beyond predictive accuracy. Model evaluations that are based on data sets obtained

from multiple research centers further emphasize the evolution of applied AI in medicine. To what extent do the authors acknowledge the synergy between AI and statistics in addressing these issues?

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TO THE EDITOR: Hunter and Holmes compare AI and statistical methods. Even though their review article states that space constraints preclude a discussion of the latest applications of AI, such as generative AI, readers get an impression that AI is primarily predictive in nature. AI models