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EDITORIAL COMMENT

Time to Bring the "Electrocardio-ome" Into Modern Cardiovascular Epidemiology?*

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More than 50 years have passed since the Framingham Heart Study investigators published their first major report on "risk factors" for coronary heart disease (1). Kannel et al. (1) discovered 3 risk factors, namely elevated blood pressure, elevated cholesterol levels, and electrocardiographic left ventricular hypertrophy. These discoveries stimulated decades of research efforts, which revolutionized our approach to hypertension and hypercholesterolemia. There is little question that much of the 50-year decline in cardiovascular disease death rates can be partially attributed to the seminal contributions of the Framingham epidemiologists.

Within a few months of the Framingham publication, Dr. George Saiger of Columbia University published a commentary on the "10 uses of epidemiology" (2). In the early 1960s, scientists were coming to recognize that epidemiology as a field was expanding beyond infectious disease. Saiger's 10 uses included measuring risk, aiding in the search for causes of disease, and identifying pre-symptomatic disease. More recently, Colditz and Winn (3) broke down the purposes of epidemiology into 3 "Ds," discovery, development, and delivery. They included in development "contribution to determination of factors causing disease," "scientific support for prevention in clinical trials," and "contributions to risk models."

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In this issue of the *Journal,* Jorgensen et al. (4) report an epidemiological investigation on the association of electrocardiographic changes and cardiovascular risk in asymptomatic persons older than 65 years. The investigators obtained baseline electrocardiograms in 6,991 Copenhagen Heart Study participants and followed them for nearly 12 years, during which time 2,236 fatal cardiovascular disease events occurred. Baseline electrocardiographic abnormalities were common. These included left ventricular hypertrophy, intermediate or major ST-segment depressions, intermediate or major T-wave changes, ventricular conduction defects, and intermediate or major Q waves. By the continuous net reclassification index, the strongest electrocardiographic predictors of fatal cardiovascular disease events were T-wave changes, ST-segment depressions, resting heart rate, and left ventricular hypertrophy.

The report by Jorgenson et al. (4) reflects solid epidemiology research. The investigators identified and carefully characterized a population-based inception cohort. During years of systematic follow-up, they collected data on a large number of hard clinical outcome events. They considered several types of electrocardiographic measures, not just those that might reflect myocardial ischemia. They used cutting-edge analytical methods, including describing each electrocardiographic variable's impact on measures of model discrimination and reclassification (5).

Also, to their credit, the investigators did not overinterpret their results. They correctly noted that the U.S. Preventive Services Task Force recommends against screening electrocardiography, as there is no

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high-quality clinical trial evidence of improved clinical outcomes (6). The current investigation, while showing that electrocardiography can improve risk estimation, in no way changes the appropriateness of the task force's recommendation. The investigators also acknowledged that they did not have access to digital measures; recent investigations have shown that digital electrocardiography reveals the prognostic value of short-term heart rate variability, a measure of autonomic nervous system balance (7).

By the criteria described by Saiger (2) and more recently articulated by Colditz and Winn (3), the work of Jorgensen et al. (4) nicely illustrates the value of epidemiological investigations. The current work would justify additional basic science and clinical investigations into the links between left ventricular hypertrophy, other electrocardiographic abnormalities, and cardiovascular risk. The work demonstrates the potential value of electrocardiography for improving risk prediction and for defining presymptomatic disease.

At the same time, though, this report on what we might call "electrocardiographic epidemiology" illustrates the challenges facing modern epidemiology. The Joint Policy Committee of the Societies of Epidemiology recently described a number of challenges and opportunities (8). They called on epidemiologists to better communicate the nature of their work; to better incorporate modern methodological approaches; to ensure widespread data access; to take into account evolving ethical principles as research and clinical medicine become increasingly intertwined; to better incorporate molecular, genetic, pharmaco-epidemiological, and comparative-effectiveness methods; and to account for dynamic factors shaping human health. In separate calls for transformative changes in epidemiology (9) and clinical research (10), I have noted the need for refocused scientific questions that take into account the tapestry of complex exposure and outcome variables and the need for scientists to appreciate the potential benefits of embedding clinical trials into epidemiological studies.

Keeping these challenges in mind, what might the future of electrocardiographic epidemiology be? How might the scientific community leverage modern-day technologies and scientific constructs to better understand why measures such as electrocardiographic left ventricular hypertrophy, ST-segment and T-wave changes, and short-term heart variability predict risk? We might imagine that epidemiologists and other scientists would band together to blend many "-omes"- the genome, transcriptome, proteome, metabolome, and exposome (including economic, social, and environmental contributors to ill health) - all together with a new -ome, the "electrocardio-ome." Using digital mobile technology and microfluidics (11), scientists could describe the electrocardio-ome as an -ome with thousands to millions of data points in time and space. They could combine the electrocardio-ome and other "classic" -omes in huge cohorts, and analyze its link to disease with modern-day methods, including systems modeling, machine learning, and Mendelian randomization (8). Armed with these epidemiological findings, basic scientists might have a better chance of identifying novel target pathways that would lend themselves to preventive or therapeutic interventions. Eventually, the process would circle back to clinical and population spheres where clinical scientists would conduct large-scale, low-cost trials to delineate which interventions should be actionable at clinical or public policy levels.

Despite >50 years of progress, we have not yet figured out how to translate the Framingham investigators' discovery of the excess risk associated with electrocardiographic left ventricular hypertrophy into effective targeted interventions for prevention and treatment (12). The current report by Jorgensen et al. (4) reinforces the potential importance of electrocardiographic measures in assessing risk. Just as the original Framingham report stimulated a highly productive era in hypertension and hypercholesterolemia research, the current Copenhagen Heart Study report, along with others like it, might stimulate a new era of "electrocardio-omic" research, which might bring us closer to a world free of cardiovascular disease.

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