60 years studying heart-disease risk

The Framingham Heart Study, which first applied the principles of epidemiology to cardiovascular disease and laid the foundations for the development of antihypertensives and lipid-lowering drugs, celebrates its 60th anniversary this month.

A hundred years ago, the leading causes of death in the United States were infectious diseases such as tuberculosis. However, with the widespread dissemination of electrocardiography in the early part of the twentieth century came a new appreciation of coronary heart disease (CHD) as a major public health concern. By the early 1920s, heart disease had become the leading cause of death in the United States, where it remains today.

In the 1940s, Paul Dudley White, an influential advisor to the US Public Health Service who had trained in electrocardiography, advocated for the establishment of a large prospective observational study of CHD. The careful characterization of this study sample would allow for the identification of “etiologic factors” in the development of CHD. In 1948, under the leadership of the US Public Health Service and shortly thereafter, the fledgling National Heart Institute, the Framingham Heart Study was conceived. The enrolment of 5,209 men and women from the town of Framingham, Massachusetts began on 28 September that year.

It was anticipated to take 20 years to accrue enough CHD events in this healthy sample to establish links between baseline observations and disease occurrence. But in 1961, William Kannel and colleagues published their landmark paper *Factors of Risk in the Development of Coronary Heart Disease*¹. In it they wrote: “Years of follow-up experience in the longitudinal prospective study of coronary heart disease in Framingham have confirmed the widely recognized influence of hypertension and hypercholesterolemia on the development of coronary heart disease...It is now demonstrated that these factors precede the development of overt coronary heart disease in humans and are associated with increased risk of the development of coronary heart disease.” They concluded with an additional bold statement: “Whether or not the correction of these abnormalities once they are discovered will favorably alter the risk of development of disease, while reasonable to contemplate and perhaps attempt, remains to be demonstrated.”

In laying out the modifiable risk factors for CHD, Framingham investigators paved the way for the field of preventive cardiology. With the development of effective and safe blood-pressure-lowering drugs, beginning with thiazide-type diuretics in the mid-1950s, the stage was set for testing their hypotheses. In the first randomized

placebo-controlled trial in cardiovascular medicine, Ed Fries and colleagues demonstrated convincingly that blood-pressure treatment dramatically reduces risk for cardiovascular disease in middle-aged men with moderate to severe diastolic hypertension². Numerous subsequent trials of antihypertensive therapy extended evidence of treatment benefits to a wide range of patients.

The risk-factor hypothesis led to similar evidence with regard to hypercholesterolaemia. Following the development of new drugs to lower LDL cholesterol levels, placebo-controlled trials were designed to determine what, if any, benefits result from treating this CHD risk factor³. Again, the evidence from multiple large-scale clinical trials over the past quarter century has proved beyond doubt that LDL cholesterol lowering in patients with even modest elevation in LDL levels substantially reduces the risk of major cardiovascular events. In conjunction with its centennial edition, the editors of the *Merck Manual* listed the Framingham Heart Study fourth among the one hundred most significant advances in medicine in the twentieth century, trailing only the development of antibiotics, mass immunizations (vaccines) and the discovery of vitamins (nutrition).

Now, with three generations of participants⁴ and extensive DNA resources, including over 8,000 immortalized lymphoblastoid cell lines, the Framingham Heart Study is well positioned to conduct cutting-edge genetic research. In 2007, Framingham investigators published 18 genome-wide association papers⁵. As part of the National Heart, Lung, and Blood Institute's [SNP Health Association Resource \(SHARe\) project](#), genotyping of 550,000 single nucleotide polymorphisms was conducted on 9,000 Framingham participants and this resource of nearly 5 billion genotypes, as well as 60 years of participant data, is freely accessible through dbGAP. New genetic findings will provide additional insights into the pathogenesis of cardiovascular disease and advance personalized medicine by identifying novel targets for the development of future therapies to treat and prevent this disease.

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