

Legacy of the Framingham Heart Study: Rationale, Design, Initial Findings, and Implications

Nathan D. Wong*, Daniel Levy^{†,‡}

Irvine, CA, USA; Framingham, MA, USA; and Bethesda, MD, USA

SUMMARY

With the dramatic rise in coronary heart disease (CHD) during the first half of the 20th century, the newly formed National Heart Institute realized the significant gap in knowledge about the causes of CHD and embarked in 1947 on planning what was to become the renowned Framingham Heart Study. Dr. Thomas Royal Dawber's initial paper on the design of the project described studying up to 6,000 persons in a single geographic area and the formation of a technical advisory committee of 11 physicians in cardiology and public health to determine the hypotheses and protocol. A comprehensive physical examination and series of measurements and laboratory work were proposed and the initial examination was completed in 1952. The first paper describing 4 years of follow-up was published in 1957, and this was followed by a subsequent report in 1959 describing 6 years of follow-up. The first follow-up report described sex and age group differences in incidence of CHD and pointed out the noteworthy prominence of sudden cardiac death as the first manifestation of CHD and the initial observations regarding the significance of elevated blood pressure, cholesterol, and overweight in predicting future CHD. Importantly, the significance of a combination of risk factors for identifying those at highest risk was described as well as how the number of risk factors related to risk (the beginnings of what was decades later to become the famous risk scores from Framingham). Dr. William Kannel's 1961 publication, "Factors of Risk in the Development of Coronary Heart Disease," first highlighted the term *risk factors*, and it described how specific levels of cholesterol, blood pressure, as well as how electrocardiographic left ventricular hypertrophy predicted future CHD incidence. The standardized measurement of risk factors and follow-up in Framingham served as an important precedent for future observational studies designed and directed by what is now the National Heart, Lung, and Blood Institute, including the ARIC (Atherosclerosis Risk in Communities) study, the CARDIA (Coronary Artery Risk Development in Young Adults) study, the CHS (Cardiovascular Health Study), and the MESA (Multiethnic Study of Atherosclerosis). These studies and others continue the legacy that Framingham began more than 60 years ago into the investigation of the epidemiology of cardiovascular diseases.

In 1900, heart disease comprised less than 10% of all causes of mortality in the United States; this had increased to more than 25% by the year 1940 and to nearly 40% by the year 1960, remaining fairly steady until around 1980, after which significant declines in cause-specific mortality from heart disease have occurred [1]. In light of the growing epidemic of chronic diseases, including cardiovascular diseases (CVD), on June 16, 1948, President Truman signed the National Heart Act that created the National Heart Institute (now the National Heart, Lung, and Blood Institute) in the U.S. Public Health Service, and the following month, he named Dr. Paul Dudley White as the executive director of the National Advisory Heart Council and chief medical advisor to the National Heart Institute [2].

The seminal article "Epidemiological Approaches to Heart Disease: The Framingham Study" [3] was published in 1950 by Dr. Thomas Royal Dawber et al. (Fig. 1) from the National Heart Institute. They initially pointed out that, despite the beliefs by some, epidemiology deals only with epidemics of infectious diseases; there was now general

agreement that epidemiology deals with "the fundamental questions as to where a given disease is found, where it thrives, and where and when it is not found . . . in other words it is the ecology of disease" [4] without regard to whether it is infectious in origin. It was furthermore noted that although epidemiologic methods had been used to study diseases in the fields of nutritional imbalance, metabolic disorders, cancer, and rheumatic fever, "almost nothing" was known about the epidemiology of hypertensive or arteriosclerotic CVD, which account for the "great bulk of deaths from cardiovascular disease." Morbidity incidence and prevalence rates from unbiased samples were almost nonexistent and mortality statistics collected by the government and insurance industry revealed the significant burden of the disease [5]. They pointed out that what is required is the "epidemiological study of these diseases based on populations of normal composition, including both the sick and the well as they are found in the community." It was noted that Sir James Mackenzie had actually begun what was intended to be

From the *Heart Disease Prevention Program, University of California, Irvine, CA, USA; †Framingham Heart Study, Framingham, MA, USA; ‡Center for Population Research of the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA. Correspondence: N. Wong (ndwong@uci.edu).

GLOBAL HEART
© 2013 World Heart Federation (Geneva).
Published by Elsevier Ltd.
All rights reserved
VOL. 8, NO. 1, 2013
ISSN 2211-8160/\$36.00.
<http://dx.doi.org/10.1016/j.jheart.2012.12.001>

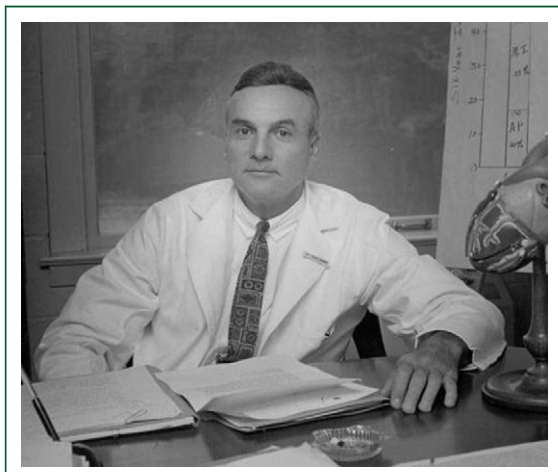


FIGURE 1. Dr. Thomas Royal Dawber, original Framingham Heart Study director.

such a long-term study of disease in the entire population of the town of St. Andrews, Scotland [6], but that study was not completed, and there were no other attempts to study heart disease in a large population of normal composition. With this gap in knowledge and the growing interest in chronic diseases, the U.S. Public Health Service began in 1947 to plan a large epidemiological study of CVD in cooperation with state and local health agencies. At the U.S. Public Health Service, Joseph Mountin, director of the Bureau of States Services recognized the importance of the epidemiological transition and chronic diseases and in pressing for control of heart disease, added an epidemiological investigation in this field and selected Gilcin Meadors, a young Public Health Service officer, to initiate this research that evolved into the Framingham Heart Study. Meadors and Felix Moore, a statistician, helped design the first manual of operations describing the “methods of examination and acceptable criteria for diagnosis” and the National Heart Institute developed 28 factor-specific hypotheses for the study that was to be the basis for future data analyses and where the concept of the risk factor was described but did not appear until 1961 in an article by a future Framingham director Dr. William B. Kannel. In 1950, Dr. Thomas R. Dawber, who is often credited as being Framingham’s first investigator, succeeded Dr. Meadors in leading the study [5].

The development of the Framingham Heart study was an important turning point in our evolving understanding of heart disease and, just a few years after the end of World War II, came at a time when resources no longer needed for military purposes could be used to combat the nation’s number 1 killer. This was also a time when coronary heart disease was an epidemic, occurring at such regularity that most Americans in 1948 felt it was an unavoidable act of fate. In an experiment little known to outsiders at the time, the Framingham Heart Study done in 1 New England town

was to change the practice of medicine and lifestyles of tens of millions of people [7].

RATIONALE FOR DESIGN OF THE FRAMINGHAM HEART STUDY

It was decided that the focus of the new study would be “arteriosclerotic and hypertensive cardiovascular disease,” felt then to be the 2 most important of the cardiovascular disorders for which the least was known about their epidemiology and underlying causes. It was assumed that these diseases would not have a single cause, as was the case of most infectious diseases, but that they would have multiple causes working slowly within the individual and that precise and unambiguous tests for their early detection were lacking [3]. The investigators chose to select a random group of participants in the age range in which these diseases were known to develop, and, with a comprehensive examination, they would select a group initially free of definite signs of these diseases and would follow them for a “period of years” until which time a sizable number would acquire the diseases. They described how they would search “for the factors which included the development of disease in the one group and not in the other” and that it would be possible to study the efficiency of various diagnostic procedures in finding heart disease or as indicators of the subsequent development of heart disease, as well as data on the prevalence and incidence of CVD. This set the stage for what was to be decades of research that would continue to the present day using imaging and other screening tests and biomarkers for heart disease as well as more sophisticated programs worldwide to monitor trends in CVD incidence and prevalence.

Although the investigators noted that ideally such a study should be done in several areas to ensure racial, ethnic, geographic, and socioeconomic representation, and that conducting the study in a single area would have “generality only in so far as the population of the area is representative of some larger population,” they decided that due to the expense of examination and follow-up, it was not practical to carry out the study in several areas, nor to observe more than “a few thousand persons for a limited number of years.” They concluded that limiting the study to a single area, studying approximately 6,000 persons up to 20 years in a town of 25,000 to 50,000 persons could provide this number of subjects. The decision to study a single community was based in part on the hypothesis that the distribution of atherosclerosis and hypertension would probably vary more greatly within a community than between communities.

In 1947, Dr. Vlado Getting, the state health commissioner for Massachusetts, offered to cooperate with the U.S. Public Health Service in setting up such a study in that state and, after considering several areas, decided on the town of Framingham. Framingham was previously the site of the first community study of tuberculosis, had a town meeting form of government that would be conducive to

such a project, and there was initial interest in the study. These were important deciding points for selecting Framingham. A centrally located residential building was remodeled for clinic and laboratory space, and diagnostic equipment was installed. A staff that included physicians; a nurse; x-ray, electrocardiography, and laboratory technicians; statisticians; interviewers and health educators; and consultants in different medical fields was recruited. A particularly unique aspect of organizing the study was the creation of the Neighborhood Organization Committee that was organized to pass word of the study on to other members of the community who were encouraged to volunteer to be examined. They then formed a set of neighborhood committees that invited others to participate. It was also noted, as is now the case for all such prospective cardiovascular studies, that when any abnormal clinical findings were discovered, the participant was referred to his or her own physician for interpretation or treatment if necessary and that the clinic staff associated with the study would not provide treatment.

The state health commissioner appointed a technical advisory committee made up of 11 physicians in the areas of cardiology and public health to set up the protocol and hypotheses of the study and to suggest possible etiologic factors for testing. The committee decided on the following general procedures that would be performed on each participant:

1. Extensive medical history including a family and past medical history, interview of any current symptoms, personal habits such as amount of tobacco and alcohol consumed, use of medications.
2. A careful, detailed physical examination performed independently by at least 2 physicians that included height and weight, waist circumference, vital capacity, examination of the heart and other organs, x-ray, 12-lead electrocardiogram, urinalysis, and a blood sample for measurement of hemoglobin, cholesterol, phospholipid, uric acid, glucose, and other tests.

From the outset, it was designed to classify participants into 2 groups: 1) those with definite signs of arteriosclerotic or hypertensive CVD; and 2) those apparently free of these diseases. Those designated as free of disease would be brought back biennially for as long as 20 years. The choice of the age group hinged on selecting a group in which enough cases of CVD would develop during 20 years of observation, but not too old that many would have pre-existing disease. To balance these effects, the age group 30 to 59 years was selected, of which there were approximately 10,000 in Framingham, and if 6,000 were initially recruited, approximately 5,000 would be free of disease, with estimates of 400, 900, 1,500, and 2,150 events that would accrue within 5, 10, 15, and 20 years, respectively, which was predicted to be large enough to ensure statistically reliable findings. Although the original sampling unit was individuals, this was changed to households early on in response to pressure from the Framingham executive

committee, which argued that choosing 1 family member while excluding another would produce a public relations nightmare. Of the original 6,600 total persons approached, 4,494 or 68.8% agreed to participate, with those refusing to participate tending to be of lower socioeconomic status, foreign born, or in poorer health [5].

It was felt that by the completion of the initial examination in 1952, there would be sufficient data to abstract prevalence data of interest, but that the “truly epidemiological” parts of the analysis would need to wait for the passage of time, and that at the end of 5 years some participants would have passed from borderline to definite abnormalities and that it would then be possible to examine differences between those who remained normal and those who became subsequently abnormal. It was also felt that with an increasingly greater number of people transitioning from normal to abnormal with the passage of time, the differences between normal and abnormal groups could be determined with greater statistical certainty and that the rate of progression of disease and estimates of incidence of arteriosclerotic and hypertensive CVD could be determined.

INITIAL FOLLOW-UP EXPERIENCE FROM THE FRAMINGHAM HEART STUDY

In 1957 and 1959, Dr. Dawber et al. [8,9] reported the 4 and 6 years of follow-up from the Framingham Heart Study. The first of these reports showed the 4-year incidence of arteriosclerotic heart disease (ASHD) (defined as myocardial infarction, coronary occlusion [or sudden death], angina pectoris, myocardial fibrosis, and possible myocardial infarction by electrocardiogram) to be greater in men (33 of 1,000) than in women (13 of 1,000) and much greater in older men aged 45 to 62 at baseline (58 of 1,000) compared with younger men aged 30 to 44 years at baseline (12 of 1,000) [8]. By this time, among those free of disease at baseline, 65 new cases of disease had developed in men and 32 in women. A particularly striking observation they made was the prominence of sudden death, occurring in 13 of 43 persons with myocardial infarctions or coronary occlusions.

Most importantly, these papers were the first to begin to describe some factors related to the development of ASHD disease, namely hypertension, overweight, and cholesterol, with the highest rates of ASHD seen when all 3 were elevated. The investigators noted that “the demonstration of the association of these clinical attributes with ASHD should encourage the search for common factors and explanatory mechanisms” and that “this search should be a prime function of epidemiological studies of heart disease” [8]. In 1948 when the study started, medical science did not recognize high blood pressure as a powerful CVD risk factor, and doctors were often trained to believe that a systolic blood pressure of 100 plus one’s age to be healthy [7].

The investigators reported a gradient of risk for development of ASHD in those who were normotensive, borderline hypertensive without heart disease, possible hypertensive heart disease, definite hypertension, and

definite hypertension with heart disease of 26, 62, 76, 81, and 98 per 1,000, respectively. Moreover, Framingham's definition of obesity, or metropolitan relative weight was also shown to be associated with risk of ASHD with rates (per 1,000) ranging from 40 in those at less than 100% of metropolitan relative weight to 123 in those who were 120% or more. Much higher rates were also seen in those with total cholesterol measured at 260 mg/dl or higher (122 of 1,000) as compared with those at 225 to 259 mg/dl (45 of 1,000) and less than 225 mg/dl (40 of 1,000). In addition, much higher rates of ASHD were seen according to the number of cigarettes smoked per day, being least (33 of 1,000) in those who smoked fewer than 10 per day to 109 of 1,000 for those who smoked 40 or more per day. Finally, Framingham was unique at the time for identifying a relation of educational attainment to risk of ASHD, where those with either grade school or no education had the highest rate (70 of 1,000) compared to lower rates in those who were high school (49 of 1,000) or college (51 of 1,000) graduates.

Perhaps of greatest interest, this article [8] was the first to make an attempt at a "risk score" (now widely used and recommended) in demonstrating that among various combinations of blood pressure, relative weight, and cholesterol levels at high, medium, and low levels, the rate of ASHD varied directly with the number and severity of these risk factors, ranging from 10 of 1,000 if all 3 factors were low or normal to 143 of 1,000 for those who were high on 2 or more of these factors (Fig. 2) [8]. They also examined the combined relation of different levels of blood pressure and cholesterol to risk of future ASHD, noting the highest rates (162 of 1,000) when both were high, contrasted with intermediate rates (100 of 1,000) when only 1 was high, and least (12 of 1,000) when both were low.

Two years later in 1959, the Framingham experience from 6-year follow-up was reported [9], and by then the number of new cases of coronary heart disease (CHD) had increased dramatically to 125 in men and 61 in women. This follow-up provided further information to validate the

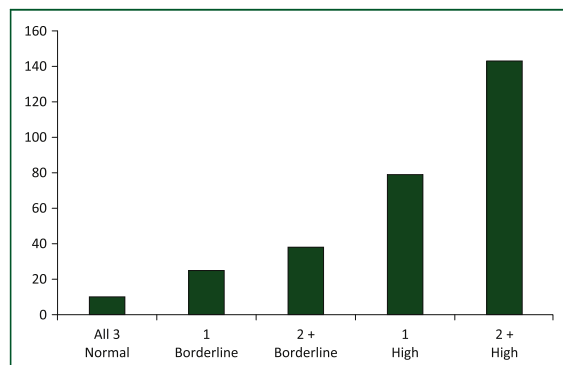


FIGURE 2. Incidence of arteriosclerotic heart disease (ASHD) (per 1000) from four-year follow-up according to presence and severity of combinations of blood pressure, relative weight, and cholesterol levels. Adapted, with permission, from Dawber et al. [8].

inverse association of educational status and the positive association of smoking with risk of CHD. Moreover, cholesterol levels were noted to be higher among cigarette smokers than among nonsmokers and higher among those who had smoked and stopped than among those who had never smoked. It also reported that there was no association between alcohol use and CHD.

FACTORS OF RISK IN THE DEVELOPMENT OF CHD

The concept and term *risk factors* are largely attributed to Dr. William B. Kannel's 1961 paper, "Factors of Risk in the Development of Coronary Heart Disease—Six-Year Follow-Up Experience: The Framingham Heart Study" [10]. This paper was the first follow-up account that quantitatively described certain key risk factors of serum cholesterol, hypertension, and electrocardiographic left ventricular hypertrophy (LVH) in relation to the development of CHD. This paper established Framingham's central role in educating the nation about the causes of heart disease [7]. In this report, Kannel et al. described 6,507 persons originally selected for study of whom 4,469 responded, 4,393 were found to be free of CHD and suitable for follow-up. This plus a group of 734 volunteers free of CHD composed the cohort of 5,127 persons free of CHD on entry that could be re-examined for subsequent development of CHD. They noted that by the fourth biennial examination, it was possible to re-examine 87% of this group in the clinic. In 1966, Dr. Kannel (Fig. 3) succeeded Dr. Dawber as director of the Framingham Heart Study.

This investigation was able to determine an overall 6-year incidence rate of 36.3 per 1,000 persons, which was greater in men (54.8 of 1,000) than in women (21.4 of 1,000). A particularly noteworthy observation was the more than 10-fold greater rate of CHD in younger men (24.9 of 1,000) when compared with younger women (1.9 of 1,000) aged 30 to 44 years, whereas by age 45 to 62 years, the rate was only twice as great (90.6 of 1,000 vs. 44.6 of 1,000). Of note, 24 of the 88 men who developed myocardial infarction died suddenly, and most (15 or 62.5%) had no prior evidence of CHD. The paper was among the first to report on differences in the predominant clinical manifestation of CHD in men versus women, with the CHD manifesting in women primarily as angina pectoris (60%), whereas in men it constituted only 30% of the CHD.

This was also the first paper to quantitatively describe the relation of serum cholesterol to CHD risk (Fig. 4), which varied from 18 of 1,000 in women with a cholesterol <210 mg/dl to 120.3 in men with a cholesterol of 245 mg/dl or higher. They also showed that the elevation in cholesterol among men who developed versus did not develop CHD tended to be most marked in the youngest age group and diminished with age, and such a relation was seen in women aged 40 to 49 years but not in those aged 50 to 59 years.

Elevations in blood pressure were also noted to be associated with an increased risk for developing CHD

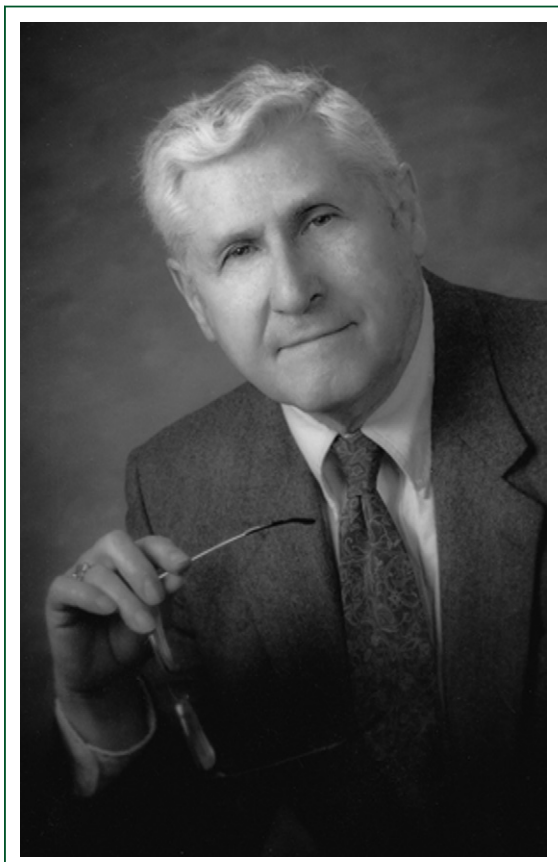


FIGURE 3. Dr. William B. Kannel, Framingham Heart Study director from 1966 to 1994.

among men 45 to 62 years of age; both systolic and diastolic blood pressures were significantly higher for those who developed CHD, and rates of CHD varied directly with the category of blood pressure (normotensive,

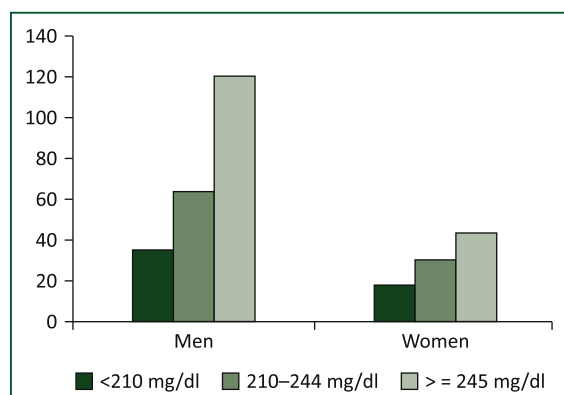


FIGURE 4. Six-year incidence of coronary heart disease per 1,000 according to initial serum cholesterol level: ages 40 to 59 years. Adapted, with permission, from Kannel et al. [10].

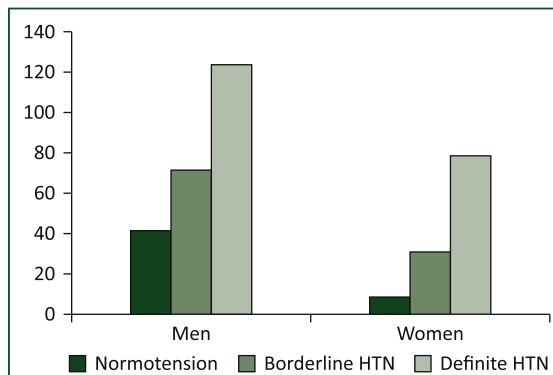


FIGURE 5. Six-year incidence of coronary heart disease per 1,000 according to hypertension (HTN) category: ages 40 to 59 years. Adapted, with permission, from Kannel et al. [10].

borderline hypertension, and hypertension) both in men and in women (Fig. 5).

This paper was noteworthy in showing the interaction between electrocardiographic LVH and blood pressure in predicting future CHD events. Those with LVH had a much steeper gradient of risk of CHD associated with increasing blood pressure category than did those who did not have LVH (Fig. 6). It was hypothesized that those with LVH may have masked evidence of CHD on the electrocardiogram or, alternatively, that LVH was an indicator of CHD.

FRAMINGHAM AS A MODEL FOR OTHER KEY PROSPECTIVE STUDIES

The success of Framingham motivated the establishment of other key prospective studies of CVD in the United States and around the world during the past half decade. In the mid-1980s the ARIC (Atherosclerosis Risk in

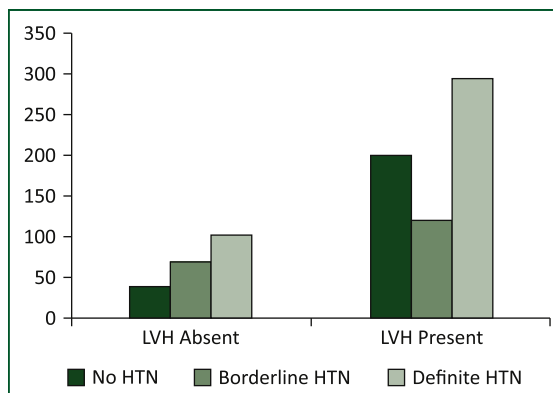


FIGURE 6. Six-year incidence rate of coronary heart disease per 1,000 by presence of electrocardiographic left ventricular hypertrophy (LVH) according to hypertension (HTN) category, men ages 40 to 59 years. Adapted, with permission, from Kannel et al. [10].

Communities) study began as well as the CARDIA (Coronary Artery Risk Development in Young Adults) study, both funded by the National Institutes of Health. The ARIC study is the single largest prospective U.S. study of CVD, enrolling 15,792 subjects ages 45 to 64 years, one-half of whom were Caucasian and the other one-half were African American, at 4 U.S. field sites, and was the first study to begin with using subclinical measures of atherosclerosis, notably carotid intimal medial thickness. The CARDIA study was started in 1985 and enrolled 5,115 subjects (one-half were African American, and one-half were Caucasian), among 4 field sites as well, ages 18 to 30 years at baseline. This study later incorporated measures of coronary artery calcification and has been an excellent model to investigate the development of risk factors as well as subclinical CVD. The CHS (Cardiovascular Health Study) began in 1990 and was a similarly sized (5,201 individuals initially recruited, followed 5 years later by enrolling 587 African Americans) cohort of older persons ages 65 to 101 years at baseline. Finally, the MESA (Multiethnic Study of Atherosclerosis) enrolled a diverse cohort of 6,814 adults aged 45–84 years representing 4 major U.S. ethnic groups (African Americans, Hispanics, Caucasians, and Chinese). MESA focused on subclinical CVD and its outcomes, and MESA also had significant ancillary studies on air pollution, pulmonary disease, and genetics. Each of these studies has built upon the initial design of Framingham and has at the core, the same key principles the Framingham Heart Study was among the first to use including: 1) the use of repeated examinations over time to follow the progression of risk factors to disease; 2) use of multivariable analytic approaches to decipher the independent contributions of multiple risk factors; and 3) use of standardized protocols for measurement of risk factors and cardiovascular outcomes. Each of these studies continues to accrue follow-up that will further enrich the knowledge to be gained on the etiology of CVD that Framingham began over 60 years ago.

REFLECTIONS AND SUMMARY

In March 2011, Dr. William Kannel was awarded the 2011 Joseph Stokes Award for lifetime achievement in preventive cardiology from the American Society for Preventive Cardiology. In what was to be his last of more than 1,000 publications, just months before his death, Dr. Kannel in his invited commentary [11], “Sixty Years of Preventive Cardiology: A Framingham Perspective,” noted “it is satisfying to reflect on the many important lessons gleaned from our epidemiological investigation over the past 6 decades.” In his last publication, Dr. Kannel summarized how the Framingham Heart Study: 1) corrected clinical misconceptions; 2) revealed the impact of overt and subclinical CVD; 3) established the importance of the principle of multivariable risk factor influences on CVD, with no single essential and sufficient cause; 4) enhanced mortality statistics with population-based incidence of

nonfatal cardiovascular events; and 5) developed useful multivariable cardiovascular risk assessment profiles (i.e., the Framingham Risk Score) to minimize possibilities of falsely reassuring or needlessly alarming many potential CVD candidates. He proposed that challenges for the future, besides the problem of post-recession funding of such studies, included the need to “find better ways to stimulate greater use of multivariable risk assessment in clinical primary care, determining appropriate use of technological advances in molecular medicine, imaging, ecological forces, and new interventional tools in population research.”

Clearly, the legacy of the Framingham Heart Study continues with state-of-the-art research into genomic etiologies of CVD, discovery and validation of new biomarkers and imaging tools, and further investigation into familial causes of CVD with the 3 generations of Framingham participants that make this study unique. Contributions by newer investigators, such as the many generations of trainees who were inspired and trained by Dr. Kannel and many other Framingham investigators, are critical to the continued success of Framingham and the studies inspired by it. Preventive cardiology was Framingham’s contribution to the world [7], and Framingham inspired both of us to pursue cardiovascular epidemiology and preventive cardiology for our careers.

ACKNOWLEDGMENTS

The authors thank the three generations of participants in the Framingham Heart Study for their contributions to advancing knowledge regarding the epidemiology and prevention of CVD and the hundreds of investigators from around the world who have worked and published with the Framingham Heart Study. Dr. Wong worked under the direction of Dr. William Kannel and Dr. Daniel Levy at the Framingham Heart Study when he was a PhD student at Yale University from 1985 to 1987. He is currently professor and director of the Heart Disease Prevention Program at the University of California, Irvine. Dr. Daniel Levy joined the Framingham Heart Study following his cardiology fellowship and is currently director of the Framingham Heart Study and the Center for Population Studies of the National Heart, Lung, and Blood Institute, National Institutes of Health.

REFERENCES

1. Office of Health Statistics and Assessment, Florida Department of Health. Prevention Pays. Report [pdf]. Available at: http://www.doh.state.fl.us/planning_eval/phstats/PrevPays/PreventionPays.pdf. Accessed October 29, 2012.
2. National Heart, Lung, and Blood Institute, National Institutes of Health. National Heart, Lung, and Blood Institute Fact Book 2002. Fact book [pdf]. February 2003. Available at: <http://www.nhlbi.nih.gov/about/02factbk.pdf>. Accessed October 29, 2012.
3. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. *Am J Pub Health* 1951;41:279–81.
4. Paul JR. Epidemiology. In: Green DE, Knox W, editors. *Research in Medical Science*. New York: Macmillan; 1950. p. 53.

-
5. Oppenheimer GM. Becoming the Framingham Study 1947–1950. *Am J Pub Health* 2005;95:602–10.
 6. Mackenzie J. *The Basis of Vital Activity: Being a Review of Five Years' Work at the St. Andrews Institute for Clinical Research*. London: Faber and Gwyer; 1926.
 7. Levy D, Brink S. *A Change of Heart: Unraveling the Mysteries of Cardiovascular Disease*. New York: Alfred A. Knopf Publishing; 2005.
 8. Dawber TR, Moore FE Jr, Mann GV. Coronary heart disease in the Framingham Study. *Am J Pub Health* 1957;47:4–24.
 9. Dawber TR, Kannel WB, Revotskie N, Stokes J 3rd, Kagan A, Gordon T. Some factors associated with the development of coronary heart disease: six years' follow-up experience in the Framingham Study. *Am J Pub Health Nations Health* 1959;49:1349–56.
 10. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J. Factors of risk in the development of coronary heart disease—six year follow-up experience. *Ann Intern Med* 1961;55:33–50.
 11. Kannel WB. Sixty years of preventive cardiology: a Framingham perspective. *Clin Cardiol* 2011;34:342–3.