Kagan, William B. Kannel, Joseph Stokes III. The paper also acknowledges 13 consultants, four nurses, nine laboratory and technical personnel, six statistical personnel and seven other personnel. High quality prospective population-based long-term research studies on epidemic chronic diseases often require sizeable staffs. The dollars costs—although seeming large by some research standards—are negligible compared with the costs of the disease epidemic. And, as the experience with the CHD epidemic has shown, the costs are recompensed plus by application of the knowledge acquired, i.e. its transmission to the population with resultant improvements in lifestyles (e.g. less smoking, better nutrition) that prevent morbidity, disability, misery, costly long-term medical care and premature death, and thereby enhance both the quality of life and its duration.

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Reference

Commentary: Early Framingham: pioneering enterprise and forerunner of modern thought

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Reprinted in this issue of the Journal is the 1957 publication, ‘II. Coronary heart disease in the Framingham Study’.1 Revisiting this report opens a window on a significant episode in development of cardiovascular epidemiology and preventive cardiology—the establishment and early findings of the Framingham Heart Study.

Six publications in the 1950s document the first decade of the Framingham Heart Study.1–6 This initial period of the Study culminated in a seventh report in 1961, further addressing the 6-year follow-up results partially presented in 1959.7 Together these seven reports describe the study setting, its design and implementation, and initial observations, including crucial evidence that presence of certain factors preceded development of overt arteriosclerotic heart disease (ASHD) or coronary heart disease (CHD). Further, they reveal consciousness of an idea that was to gain substantial influence a half-century later.

The 1957 Report

This second report of Study findings in 1957 was based on follow-up of residents of the town of Framingham, Massachusetts, USA, who were initially examined between 1948 and 1952 and known to be dead or alive after 4 years of follow-up.1 From a sample of 6510 persons aged 30–59 years on 1 January 1950, 4469 (68.6%) had been examined at baseline; of these, 4393 (98.3%) constituted the population at risk of ASHD who were clinically assessed at 4 years.

Data were presented on community prevalence of ASHD at entry, specific manifestations of CHD, and 4-year incidence for each category of CHD by age and sex (97 cases in all, 33/1000 for men, 12/1000 for women). The prominence of sudden death, especially among men and as the first manifestation of disease, was emphasized, as was the clinical discovery of otherwise unsuspected (‘silent’) myocardial infarction. This paper documented the limitation of clinical and hospital-based studies relative to true community occurrence of the disease.

Blood pressure, Framingham relative weight (an index of body fatness) and serum cholesterol were each categorized in three or four strata and found individually associated with incidence of ASHD, as was electrocardiographic (ECG) evidence of left ventricular hypertrophy (LVH). Beyond this level of analysis, taking into account all possible combinations of the first three factors permitted ‘even stronger inferences as to the association of these factors
and risk of ASHD’. It was demonstrated that higher versus lower levels of each factor and addition of each factor to the others were associated with increased incidence.

It was also noted that the group of men aged 45–62 at entry with ‘low levels in all three variables’ (blood pressure < 140/90, Framingham relative weight < 100, serum cholesterol < 225 mg/dl), who constituted 11% of the study population, experienced incidence of ASHD of 10/1000, ‘...a rate even lower than that observed among all women of the same age (29/1000)’. Neither education level nor smoking habits were found consistently related to incidence of ASHD within the limited data available at this stage of the Study.

Early Framingham: 1951–61

Collectively, seven publications present a picture of ‘early Framingham’ from which much can be learned about establishment of this pioneering community-based prospective epidemiological study of chronic disease—conceived from the start as extending for 20 years. Some of the formidable challenges faced by the Framingham investigators—such as managing an immense volume of paper records and devising methods of multivariable statistical analyses—have long since been overcome. But principles and practices in planning, selection, recruitment and sustaining participation of members of a large study population remain—and the Framingham solutions are still instructive. From this viewpoint the story of early Framingham is classic, as fundamental to epidemiology of chronic diseases as is Snow on Cholera to outbreak investigation.

The Framingham Heart Study developed amid an awakening to the need for epidemiological investigations of atherosclerotic and hypertensive cardiovascular diseases. The present report is one of four appearing together in the American Journal of Public Health, from a symposium in the Association’s annual meeting of 1956. Reports of early findings from two other prospective studies of cardiovascular disease in employee populations—civil servants in Albany, New York, and Los Angeles, California—and one statewide sample survey in California are also presented. Other cohort studies inaugurated in this period in the USA alone included the Chicago Peoples Gas Co. Study, Chicago Western Electric Co. Study, Tecumseh Health Study, Minnesota Business and Professional Men Study and Railroad Workers Study, plus the monumental Seven Countries Study of 16 cohorts in Finland, Greece, Italy, Japan, The Netherlands, USA and Yugoslavia. Nonetheless, Framingham has become symbolic of development of this field, celebrated for example in a 2010 symposium, The Global Impact of the Framingham Heart Study, with 13 contributions from around the world.

Additional sources of insight into early Framingham can be found in first-person accounts from founding investigators, Thomas R. Dawber, Felix E. Moore Jr. and William Kannel, whose interviews were recorded as part of the History of CVD Epidemiology Project and are archived at the Project website [www.epi.umn.edu/cvdepi/]. Other personal accounts include Dawber’s book (1980), as well as that of Levy and Brink (2005). Scholarly historical contributions such as those from Oppenheimer and from Mahmood and others add further to a sense of the times and an appreciation for the tribulations experienced in creating and carrying on the Framingham Heart Study.

This was by all accounts a pioneering epidemiological enterprise. The lead up to the Framingham Heart Study as it has been known throughout its 60-plus years was at first a story about ownership, leadership and focus, recounted in several of the cited sources. As these aspects of the study unfolded, and once the community of Framingham had been chosen, a fundamental issue concerned definition of the study population. Volunteers were being examined from late 1948 onward, but soon a formal sampling design was called for that would ensure adequate numbers of appropriate subjects for the long-term requirements of the study. This problem and the adopted solution were discussed extensively in the initial reports.

1951

The first report, presented in 1950 and published in 1951, was to explain to a public health audience how a community-based epidemiological study of cardiovascular diseases could be conceived and organized. In concept, some 6000 participants aged 30–59 years would be recruited, in the expectation that 5000 would be free of cardiovascular disease at initial examination and 400 would acquire it in the first 5 years of follow-up. The population of Framingham was such that a two-thirds sample would provide the needed numbers. A household sampling frame could be devised from the current census. All age-eligible household members would be included, so as not to ‘break up families’.

1952

By 1951 an interim presentation, published in 1952, described three aims for the Study: ‘...to secure epidemiologic data on atherosclerotic and hypertensive cardiovascular disease....To secure data on the prevalence of all forms of cardiovascular disease in a representative population group....To test the efficacy of various diagnostic
procedures’. The approach to selection and enrolment of participants was discussed in detail, including numbers and reasons for refusal. But it was reported that early recruitment had yielded 80% participation, a basis for at least tentative optimism.

1958

The next publication, in 1958, followed the 4-year findings and reiterated main features of the study design. Foremost, it dwelt on the problems of dietary assessment in such a study. It was considered that dietary studies were ‘...excessively difficult to accomplish in a competent, meaningful way’. Particular difficulties in study of an adult New England population were enumerated. In the hope of improving on previous dietary studies, the goal was to estimate long-term dietary patterns. The adopted approach was a Burke-type survey of ‘average dietary intake over many years,’ to be completed by husband and wife in a randomly selected subsample of 1000 participants. This was to be carried out in the fifth biennial examination cycle, but no further information on this sub-study was presented here.

1959

In 1959 it was reported that the initial recruitment success was not sustained, the examination rate declining to 68.6%. To bolster the numbers, it was decided to invite back for examination the volunteers who had participated before instituting the formal sampling scheme. Of those who returned, 734 were free of cardiovascular disease and joined the 4393 disease-free members of the sample, giving a total of 5127 persons under follow-up when the 6-year experience was first reported. In the total sample there were 186 new cases of definite CHD. At this time the focus was on specific frequencies of myocardial infarction, sudden death and angina and their associations with level of schooling (inverse), national origin (null), smoking (direct with non-fatal myocardial infarction and CHD death, but not with angina) and alcohol consumption (directly with smoking, null for CHD).

Also in 1959, the investigators presented a detailed critical discussion of issues in implementing the Framingham study design. These included implications of lower than expected recruitment from the original target population, admixture of the volunteers with the formal sample and subsequent attrition from the followed population. Whether biases might result from any of these factors, and how they could affect estimates of disease prevalence or associations between exposures and disease, were discussed at length. Limited data about non-participants permitted some assessment of differences in health status between groups, but the investigators lamented the lack of information available for such assessment. It was concluded that such inferences remained justified, but that gaining community support for the study and overall participation would have been better served had all eligible persons been offered examination rather than those in the two-thirds sample alone. The lessons of this experience for future community-based studies were summarized in a concluding defence of such studies and their distinct contributions to understanding the occurrence of chronic diseases in human populations.

1961

The previous publications culminated in the 1961 report, which extended the presentation of findings as of the 6-year examinations, which were only partially reported in 1959. Population distributions of mean values of systolic and diastolic blood pressure, by age and sex, and categories of serum cholesterol, by sex, were now presented, each in relation to incident CHD. At every level of cholesterol, higher levels of systolic blood pressure exhibited higher and steeper curves of increasing 6-year incidence of CHD. At every level of systolic pressure, higher cholesterol similarly exhibited a higher and steeper risk curve. These two factors in combination were thus associated with higher risk than either alone. LVH by ECG was also evaluated and found individually related to increased incidence but difficult to disentangle from high levels of blood pressure. When LVH was added to ‘abnormal’ blood pressure or cholesterol, risk was increased, for men; too few women were found with LVH to permit a corresponding evaluation.

We find foremost in this prospective epidemiological study, confirmation of prior clinical observations that two factors—hypertension and hypercholesterolaemia— influenced development of CHD. Importantly, it was further demonstrated that these factors preceded overt disease.

**Concepts of ‘risk’ and ‘factors’**

The ‘risk factor’ concept has commonly been traced to this last-cited publication, and appropriately so, any thus far undiscovered precedent being absent. However, two qualifications do seem warranted. First, the term ‘risk factor’ is not conspicuous in this paper, given its appearance only incidentally in the text among several other locutions (including that in the title) where references are made to ‘risk’ and ‘factors’. Were introduction of this expression a deliberate intent of the authors, greater emphasis might have been expected.
Second, language about ‘risks’ and ‘factors’ was in use from the start by the Framingham Heart Study investigators and long precedes the 1961 paper. It is no less important that the concept of risk was already implicit in the first Framingham paper, which described the Study plan as a ‘search for the factors which influenced the development of disease in the one group and not in the other’. This first description cited the purpose ‘...to test a number of hypotheses with respect to factors associated with the development of arteriosclerotic or hypertensive cardiovascular disease’. The focus of interest was clearly on ‘the group which becomes abnormal’ and the increased risk of disease. Discussion of the Framingham findings from the beginning was foremost in terms of risk, as concluded from the present 1957 report of the first findings: ‘The use of three factors in combination—blood pressure, relative weight, and serum cholesterol permitted the separation of men 45–62 into groups with highly divergent risks of ASHD [italics added].’

From this perspective, the mindset of the Framingham investigators from the beginning was oriented to a search for risk factors, whether so called or not, and beyond question the 1961 paper establishes that they had succeeded and anticipated future success as well: ‘As additional longitudinal observations are made, it is hoped that additional risk factors [second such reference in the paper] will be determined. This will allow further identification of susceptible individuals and hopefully suggest methods of control.’

A further observation important to understanding the risk factor concept as introduced here is the circumspect claim of the authors of this report: ‘Combinations of the three risk factors [first such reference in the paper] under consideration appear to augment further the risk of subsequent development of coronary heart disease [italics added].’ And, ‘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.’ ‘Risk factor’ has no necessary implication for preventability.

A final point requires a leap forward of a half-century or more. This bypasses a point in the Framingham story which is instructive—the decision of the US government to close the Study in 1969–70, after 20 years, and the investigators’ skill in overcoming this near-terminal event. However, this episode is extensively recounted in the ‘additional sources’ cited above and at the CVD history website, and is not discussed here. Instead, a further appreciation of the early Framingham, which is the present focus, follows from consideration of a 2006 report from Framingham, Prediction of Lifetime Risk for Cardiovascular Disease by Risk Factor Burden at 50 Years of Age. This recent report is based on follow-up through age 95 of Framingham participants from the original or subsequent cohorts who were examined at age 50—3564 men and 4362 women in all—and together experienced a total of 1757 CVD events by 2002. In summary, ‘...those with optimal levels [3.2% of men, 4.5% of women with favourable levels of total cholesterol, HDL-cholesterol, systolic and diastolic blood pressure, non-diabetic and non-smokers] had substantially lower lifetime risks (5.2% versus 68.9% in men, 8.2% versus 50.2% in women) and markedly longer median survivals (>39 versus 28 years in men, >39 versus 31 years in women). ... The absence of established risk factors at 50 years of age is associated with very low lifetime risk for CVD and markedly longer survival [italics added].’

The concept of low risk, now institutionalized in the 2020 Strategic Impact Goal of the American Heart Association (AHA), ‘to improve the cardiovascular health of all Americans by 20% by 2020’, had become increasingly familiar when the 2006 report from Framingham gave it added impetus. In defining ‘cardiovascular health’, AHA proposed seven metrics. ‘Ideal cardiovascular health’ represents the favourable end of each of the seven respective risk distributions. The terms ‘risk factor’ and ‘risk behaviour’ became ‘health factor’ and ‘health behaviour’. The concept of risk factor, in effect, was turned on its head. But this was a more substantive change than a mere inversion of the scale, as it redirects policy and practice toward preservation of ideal cardiovascular health or prevention of risk in the first place—toward Strasser’s concept of primordial prevention—not to traditional primary and secondary prevention alone.

This view, perhaps surprisingly, can also be teased out of the early Framingham reports. The roots of the seemingly quite modern concept of ‘low risk’ or ‘ideal cardiovascular health’, though expressed in other terms, can be found as early as 1957. For example, as noted above, the 1957 report called attention specifically to ‘the bottom group’ of men, constituting 11% of the male Study population, whose 4-year incidence of ASHD was one-third that of women overall. Further, the 1961 report emphasized that: ‘There can be no doubt that absence of these characteristics is distinctly advantageous since such persons demonstrate a relatively low risk of developing CHD.’

Conclusion—lessons of history

Revisiting early Framingham is a fruitful and rewarding exercise. When current Study Director Dan Levy and co-author Susan Brink looked back from 2005, they
concluded: ‘By 1948, the scientists who would design the Framingham Heart Study knew little about what they’d find, but a lot about the questions they needed to ask. . . . They were physicians who knew full well how much they had yet to learn. But they could have had little idea that their efforts would ultimately alter the focus of the entire medical profession, tilting it toward prevention. The Study’s findings, now so patently obvious to almost everyone, represent a miraculous shift in thinking over the course of half a century.14

Evidently, the latest and ongoing shift in thinking beyond prevention to promotion and preservation of ideal cardiovascular health, is no less identifiable with early Framingham—and the rest of the fields of cardiovascular epidemiology and preventive cardiology it represents—than is the term ‘risk factor’. No one was closer to this pioneering enterprise than Dawber, whose retrospective in 1980 concluded, ‘ . . . The normal person is one who not only has no disease but also is highly unlikely to develop it. At the extreme of this normality is the ideal individual who will never develop disease.’13

From early Framingham we have many lessons, a wealth of knowledge, and critical contributions to our understanding of how to improve population cardiovascular health.

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