The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective

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On Sept 29, 2013, the Framingham Heart Study will celebrate 65 years since the examination of the first volunteer in 1948. During this period, the study has provided substantial insight into the epidemiology and risk factors of cardiovascular disease. The origins of the study are closely linked to the cardiovascular health of President Franklin D Roosevelt and his premature death from hypertensive heart disease and stroke in 1945. In this Review we describe the events leading to the foundation of the Framingham Heart Study, and provide a brief historical overview of selected contributions from the study.

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Introduction

Cardiovascular disease is the most common cause of mortality in high-income countries.[1,2] Globally, the number of deaths from cardiovascular and circulatory disease has risen by a third between 1990 and 2010; by 2015, one in three deaths will be due to cardiovascular disease.[3] Epidemiological studies have played an important part in the elucidation of predisposing factors for cardiovascular disease and opportunities for prevention. On Sept 29, 1948—65 years ago—the first volunteer of the Framingham Heart Study was examined. In this Review we describe the events leading to the foundation of the Framingham Heart Study, and review some important contributions that the study has made to understanding of cardiovascular disease and risk factors.

Origins of the Framingham Heart Study

By the 1940s, cardiovascular disease was the main cause of death for Americans, accounting for half of deaths.[4] Prevention and treatment were so poorly understood that most Americans accepted early death from heart disease as unavoidable. Franklin D Roosevelt, the wartime President of the USA from 1933 to 1945, was in no way exempt from the epidemic, with heart failure due to undiagnosed and later untreated risk factors.[5] In this Review we describe how medical care provided to the President before his sudden death while still in office in 1945 shows the poor state of understanding of cardiovascular disease in the mid-20th century. These events contributed to the creation of the Framingham Heart Study in 1948.

In 1932, Roosevelt's campaign office released medical records showing his blood pressure to be 140/100 mm Hg, which did not prompt any medical intervention.[6,7] Such was the lack of understanding of cardiovascular disease that the following year the President-elect chose an ear, nose, and throat specialist, Admiral Ross McIntyre, as his personal physician because headaches and sinus problems were predicted to be his main health concern.[8] Between 1935 and 1941, the President's blood pressure gradually rose from 136/78 mm Hg to 188/105 mm Hg.[6] During this period, he dedicated the National Institute of Health's newly established Bethesda, MD, campus in 1940. Despite his rising blood pressure, his personal physician insisted that the President was healthy, and that his blood pressure was "no more than normal for a man of his age".[6] Roosevelt's physical deterioration was evident to many, and when the UK Prime Minister Winston Churchill visited the White House in May, 1943, he asked his own physician whether he too had "noticed that the President is a very tired man?"[9]

On March 27, 1944, as planning of the Allied landings at Normandy, France, was underway, the President's daughter Anna Roosevelt insisted on a second opinion, and he was admitted to Bethesda Naval Hospital for dyspnoea on exertion, diaphoresis, and abdominal distension.[10] Cardiologist Howard G Bruenn, one of only a few hundred such specialists in the entire country, attended to the President. Bruenn noted that the patient appeared "slightly cyanotic", with "blood pressure 186/108" mm Hg and a chest radiograph showing an "increase in size of the cardiac shadow". The young cardiologist gave Roosevelt his first diagnosis of "hypertension, hypertensive heart disease, and cardiac failure".[5] However, Bruenn had few therapeutic options to provide, and suggested digitalis and reduction of salt intake. After at first rejecting the cardiologist's advice, the President eventually started digitalis with some symptom relief; a follow-up chest radiograph 2 weeks later showed reduced cardiomegaly. A month after coming under Bruenn's care, Roosevelt's blood pressure

Search strategy and selection criteria

We searched the archives of the Framingham Heart Study at the National Heart, Lung, and Blood Institute in Bethesda, MD, USA. We also searched Harvard University's Widener Library collection of *President Franklin D. Roosevelt's Office Files, 1933–1945*, in Cambridge, MA, USA. Additional references between January 1947 and March 2013 were obtained from PubMed and Google Scholar by combining the search term "Framingham Heart Study" with the search terms "risk factor", "hypertension", "coronary heart disease", "diabetes mellitus", "atrial fibrillation", "cerebrovascular accident", "stroke", "lipids", "cholesterol", "triglyceride", "LDL", "HDL", "obesity", "survival", "prognosis", and "risk profile". We restricted our search to works published in English.

had risen to 240/130 mm Hg after unsuccessful treatment with phenobarbital.

In 1945, 2 months before his death, Roosevelt attended the Yalta Conference with Churchill and Soviet Premier Joseph Stalin to negotiate the anticipated post-war administration of Germany, and a future United Nations.[11] Lord Charles Moran, Churchill's personal physician, wrote in his diary "the President appears a very sick man. He has all the symptoms of hardening of the arteries" and "I give him only a few months to live."[9] Criticising the lack of appreciation of Roosevelt's poor cardiovascular health, he also noted "the Americans here cannot bring themselves to believe that he is finished. His daughter thinks he is not really ill, and his doctor backs her up." As predicted, Roosevelt died a few weeks later on April 12, 1945, at the age of 63, from cerebral haemorrhage, with a blood pressure of 300/190 mm Hg.[5] Like countless other Americans, he had succumbed to the national epidemic of cardiovascular disease.

On June 16, 1948, President Harry Truman, who had been Roosevelt's Vice President, signed into law the National Heart Act, in which the US Congress declared: "Whereas the Congress hereby finds and declares that the Nation's health is seriously threatened by diseases of the heart and circulation, including high blood pressure... These diseases are the main cause of death in the United States and more than one in every three of our people die from them."[12] The law allocated a US$500 000 seed grant for a 20 year epidemiological study of heart disease, and also established the National Heart Institute, which today is known as the National Heart, Lung, and Blood Institute.

Location of the study

In 1947, as legislators were drafting the National Heart Act, the US Public Health Service delegated a young officer and physician, Gilcin Meadors, to compile a proposal for the future epidemiological study (figure 1). Although the study initially focused on ischaemic heart disease, Meadors set the tone for the next 65 years with a proposal "to study the expression of coronary artery disease in a 'normal' or unselected population and to determine the factors predisposing to the development of the disease through clinical and laboratory exam and long term follow-up."[13] The initial budget request was $94 350 to cover office supplies, and even included funds to buy ashtrays for the study staff members who smoked.

Paul Dudley White of the Massachusetts General Hospital and David Rutstein of Harvard Medical School advocated for the epidemiological study to be located at Framingham, MA. The state was thought ideal because of the enthusiastic response of physicians in the area (figure 2), and Framingham was selected ahead of neighbouring towns because of its geographical proximity to the many cardiologists at Harvard Medical School.[14]

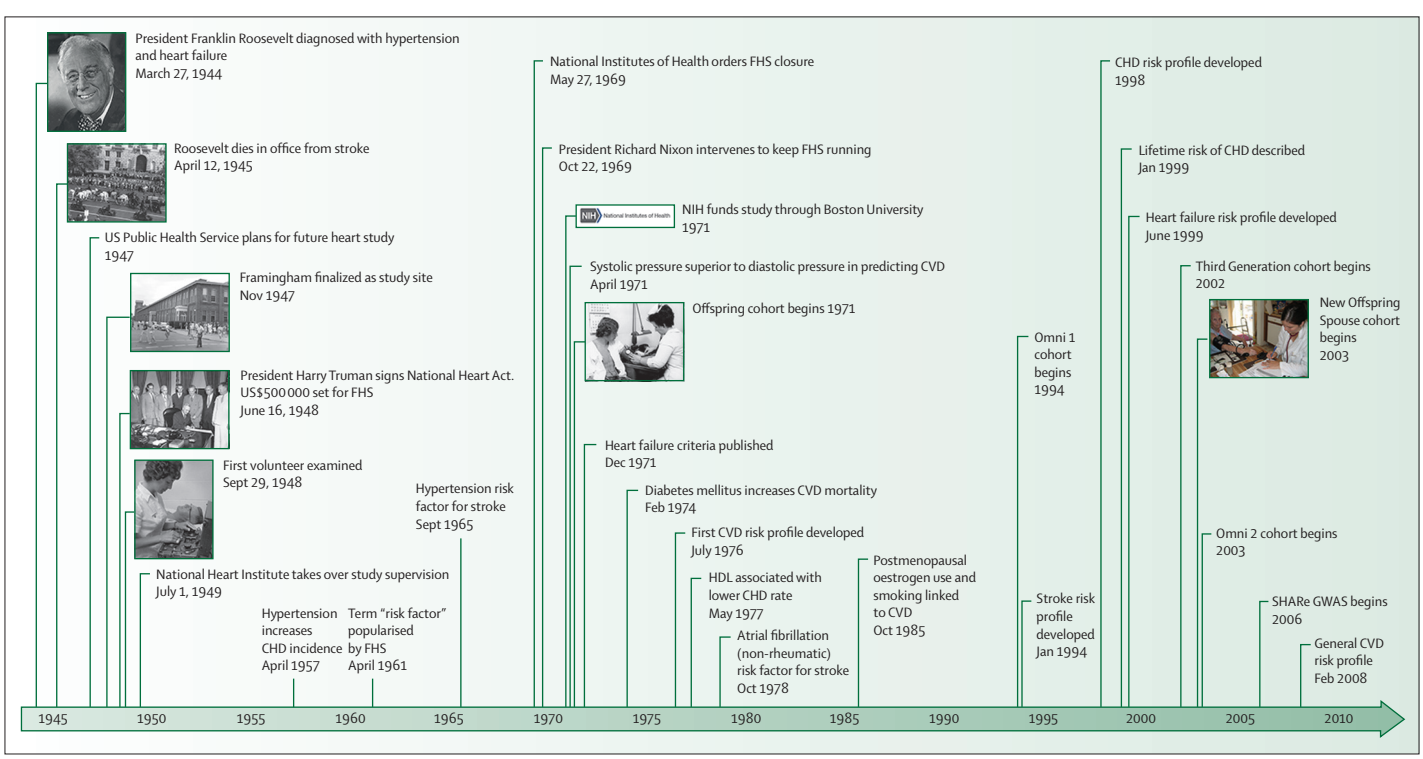
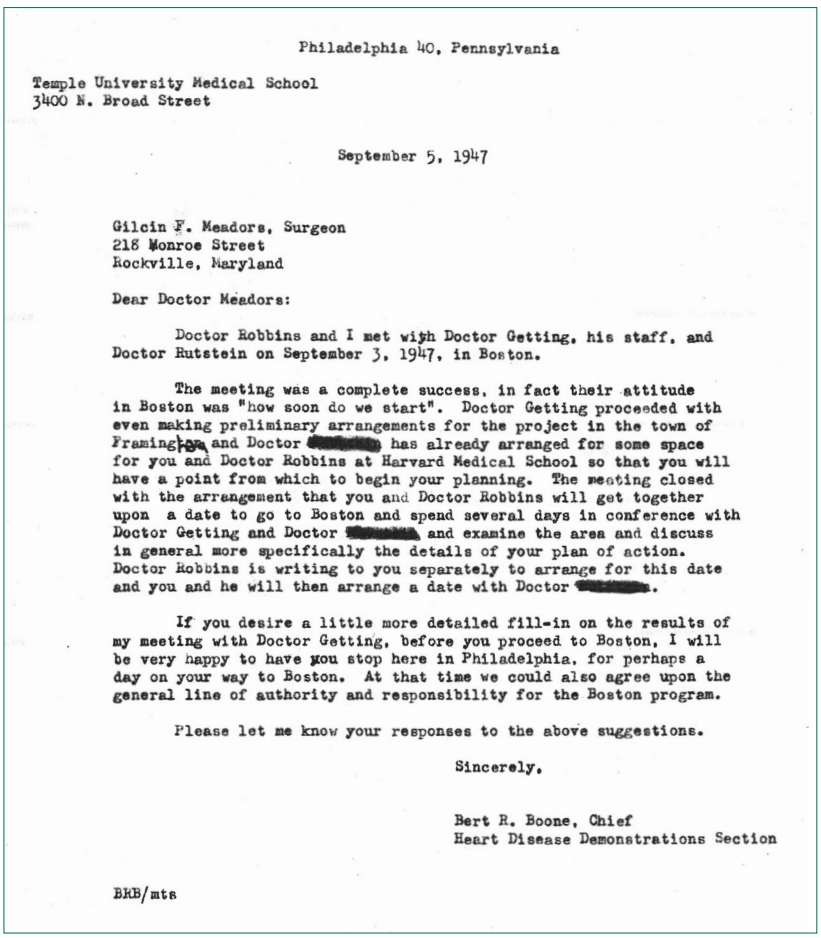


Figure 1: **Key dates in the history of the Framingham Heart Study**
FHS=Framingham Heart Study. CHD=coronary heart disease. NIH=National Institutes of Health. CVD=cardiovascular disease. SHARe=SNP Health Association Resource. GWAS=genome-wide association study. Photographs reproduced courtesy of the Franklin D. Roosevelt Library, the US Library of Congress, and the National Institutes of Health, and by permission of the National Heart, Lung, and Blood Institute.

Framingham residents, who made decisions through a town-meeting form of government, had already participated in the Framingham Tuberculosis Demonstration Study two decades earlier.[15] The former farming community was now a factory town producing rugs, paper products, and General Motors automobiles, with 28 000 middle-class residents of predominantly European origin, and was therefore thought to be representative of the USA in the 1940s.[16] On Oct 12, 1947, the US Public Health Service began to fund the study in Massachusetts, in cooperation with the state's Health Department and Harvard Medical School, which would provide "overall professional and technical guidance."[17,18] Framingham was finalised as the study site in November that year.

Meadors, who had been given authority by the Public Health Service to establish the study and effectively became its first director, relocated to Boston to start recruiting 6000 of the town's 10 000 adult residents.[7,15] Initially operating out of Harvard Medical School, he hired nurse Nell McKeever and together they visited parent–teacher associations, churches, and civic groups and brought in local volunteers to act as telemarketers, who called nearly all the town's phone numbers.

On Sept 29, 1948, the Framingham Heart Study examined its own staff members "for the purpose of testing schedules, procedures, equipment and [smoothing] out technique for interview and records completion."[19] On Oct 11, 1948, the study officially examined its first Framingham participant, exactly 12 months after Meadors' arrival in Massachusetts.[20] The groundwork had thus been laid for the longitudinal follow-up of this cohort, to identify individual factors that could be related to the future development of disease.



Philadelphia 40, Pennsylvania

Temple University Medical School
3400 N. Broad Street

September 5, 1947

Gilcin F. Meadors, Surgeon
218 Monroe Street
Rockville, Maryland

Dear Doctor Meadors:

Doctor Robbins and I met with Doctor Getting, his staff, and Doctor Rutstein on September 3, 1947, in Boston.

The meeting was a complete success, in fact their attitude in Boston was "how soon do we start". Doctor Getting proceeded with even making preliminary arrangements for the project in the town of Framingham and Doctor [redacted] has already arranged for some space for you and Doctor Robbins at Harvard Medical School so that you will have a point from which to begin your planning. The meeting closed with the arrangement that you and Doctor Robbins will get together upon a date to go to Boston and spend several days in conference with Doctor Getting and Doctor [redacted] and examine the area and discuss in general more specifically the details of your plan of action. Doctor Robbins is writing to you separately to arrange for this date and you and he will then arrange a date with Doctor [redacted].

If you desire a little more detailed fill-in on the results of my meeting with Doctor Getting, before you proceed to Boston, I will be very happy to have you stop here in Philadelphia, for perhaps a day on your way to Boston. At that time we could also agree upon the general line of authority and responsibility for the Boston program.

Please let me know your responses to the above suggestions.

Sincerely,

Bert R. Boone, Chief
Heart Disease Demonstrations Section

BRB/mts

Figure 2: **Letter from the US Public Health Service to Gilcin Meadors on positive responses from Massachusetts physicians regarding Framingham as a site**
Reproduced by permission of the National Heart, Lung, and Blood Institute. Names of non-federal employees have been deleted.

Early days of the Framingham Heart Study

The Framingham Heart Study was the first long-term study of its kind, with the exception of Sir James Mackenzie's aborted attempt to longitudinally follow the health status of residents in the town of St Andrews, Scotland.[21] As Framingham investigators were setting up their research in the late 1940s, Ancel Keys[22] in Minnesota was also in the process of establishing a three-decade-long study (the Twin Cities Business and Professional Men's Study[23]), as were researchers at University of California Los Angeles who would go on to follow city civil servants for a decade.[24,25] The investigators of the Framingham study initially struggled to decide whether it should be an observational study to understand heart disease, or should instead focus on prevention of heart disease in the local population. Ultimately, because of the absence of effective interventions, the former approach won favour. Within a few months of the first examination, the newly established National Heart Institute assumed control of the study.[16] Meadors was responsible for building the study infrastructure, although the National Heart Institute had a large role in ensuring the early scientific robustness of the study. Felix Moore, the Institute's chief of biometrics, designed the original statistical model for longitudinal follow-up.[26] After realising that measurement of the prevalence of diseases in populations needed random sampling, Moore changed the methodology from solicitation of volunteers to active recruitment of a random sample of adults in the town.

Organisers of the new study also had to ensure support of the community and local physicians. An Executive Committee, composed of 15 residents representing the town's various groups (eg, businessmen, community leaders, etc), recommended that the study not break up families, and that all family members aged 30–60 years be recruited.[16] Community ownership of the study was achieved through a Neighbourhood Organising Committee that reached out to residents to urge participation in the study.[16] The Professional Advisory Committee, consisting of local physicians, asked that investigators not treat or offer advice to any participants; instead, the study investigators gave diagnostic information to each participant's personal physician.

The original cohort was recruited between 1948 and 1952, and consisted of 5209 residents aged 28–62 years (table).[27] More than half of participants were women, by contrast with contemporary epidemiological studies, which had very small numbers of women or excluded them altogether.[24,25] Records were originally kept on carbon paper, an innovative system at the time (figure 3). These approaches were developed by Thomas Dawber, who became the second director in April, 1950, along with Patricia McNamara and William Kannel. Hospital admissions were recorded by daily visits to both Framingham hospitals, whereas deaths were recorded by scanning of newspapers, communications from personal physicians, or coroner reports.

The first major findings from the study were reported in 1957, almost a decade after the first participant was examined. Defining hypertension as blood pressure of 160/95 mm Hg or higher, the investigators noted a nearly four-times increase in incidence of coronary heart disease per 1000 people for study participants with hypertension.[28] A few years later, they noted that stroke was also a major consequence of high blood pressure.[29]

Despite these early reports, many still believed that a permissible systolic blood pressure was 100 plus the participant's age in mm Hg.[30,31] In 1964, when the hypotensive properties of the β-blocker propranolol were first studied, so-called normotensive control groups included patients with systolic blood pressures as high as 170 mm Hg.[32] For those aged 70 years or older, some regarded the acceptable upper limits of normal blood pressure as 210 mm Hg systolic and 120 mm Hg diastolic.[33] Adherence to these beliefs stemmed from the medical community's uncertainty about the validity of epidemiological approaches, as evidenced by the challenges faced during attempts to create the Council on Epidemiology at the American Heart Association in 1961.[34] Critics of the Framingham Heart Study expressed uncertainty about whether the study participants represented Americans in general, and about the study's family-based approach.[35]

	First year	Size	% Female	Salient features
Original	1948	5209	55%	
Offspring	1971	5124	52%	Children of the Original cohort, and their spouses
Third Generation	2002	4095	53%	Children of the Offspring cohort
New Offspring Spouse	2003	103	54%	Spouses of Offspring cohort participants who were not initially enrolled in the study, with at least two children in the Third Generation cohort; added to improve statistical power
Omni 1	1994	506	58%	To reflect the increasing ethnic diversity of the community; participants from African-American, Hispanic, Asian, Indian, Pacific Islander, and Native American ethnic groups
Omni 2	2003	410	57%	Recruited to achieve 10% of Third Generation cohort size

Table: **Cohorts of the Framingham Heart Study**

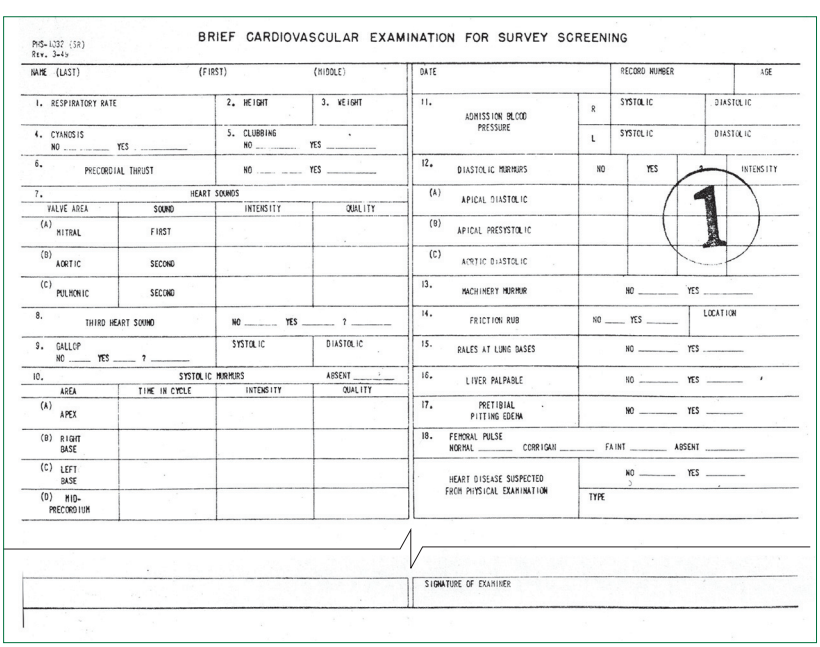


Figure 3: **Data entry form for the original cohort circa 1947**
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Fight for survival

In 1966, as the initial 20 year funding commitment neared an end, the National Heart Institute established a committee to assess the Framingham Heart Study. Sensing the possible loss of the needed $336 000 in annual funding, Dawber moved to Boston University to raise private funds to continue the study.[36] In his place, Kannel took over as the third director of the Framingham Heart Study.

Dawber's concern was well founded. On May 27, 1969, the National Institute of Health issued a directive ordering phasing out of the study over the next year, despite a favourable review by its expert committee. In response, Framingham investigators toured the country to raise private funds. Donors included a large number of life-insurance corporations that recognised the actuarial benefits of the study. The list also included some surprising contributors, such as the Tobacco Research Institute and the Oscar Mayer Company, a meat manufacturer.[37] After White notified him of the impending closure of the study, President Richard Nixon intervened and allowed the study to continue to fulfil its mission.[7] In 1971, the National Heart Institute entered an agreement with Boston University that provided support for the Framingham Heart Study through a federal contract, thereby ending the need for private donors.

With the renewal of funding, the study began to recruit the children of the original Framingham participants into a new Offspring cohort (table).[38] The purpose of this new cohort was to provide insights into familial clustering of disease. Because the study also needed to include biologically unrelated individuals, spouses of offspring participants were invited into the study, making up nearly a

third of the study sample. The creation of a family-based cohort was far-sighted, in view of the emergence of new technologies for genotyping and sequencing a few decades later.

Epidemiological activism

Dawber, the second study director, noted that medical practice in the mid-20th century was directed towards care for those who were already ill rather than the prevention of disease.[37] Dawber had had little success in altering the way physicians practised medicine, despite early findings from the Framingham study, and concluded that "attitudinal changes on the parts of physicians, although difficult, is essential [for] advances", and that "medical education and training was basically responsible for the attitude of physicians."[37] Even in the early 1970s, physician reference books such as *Harrison's Principles of Internal Medicine* and the *Cecil-Loeb Textbook of Medicine* reiterated that diastolic pressure was a better measure of blood pressure than was systolic pressure; consequently, high systolic pressure was thought innocuous, especially in elderly people.[39,40] Although some hospital-based and autopsy studies had begun to challenge the presumed unimportance of systolic pressure, the usefulness of these findings were limited by selectivity bias and sample size.[41,42] After recovery from the funding crisis, investigators of the Framingham Heart Study were ready to begin an approach of epidemiological activism, with a focus on hypertension.[26]

In 1971, Framingham investigators analysed 14 years of follow-up data, and reported increased risk of coronary-heart-disease morbidity with increased baseline blood pressure.[43] Systolic pressure had a stronger association with coronary-heart-disease events than did diastolic pressure (figure 4). Results of two other Framingham studies showed that high systolic blood pressure was a predictor of cerebrovascular accidents and heart failure, and that diastolic pressure was not a better predictor of such events.[44,45]

More than two decades after President Roosevelt's death from poorly controlled blood pressure, Framingham investigators commented on the "mounting evidence that many of the commonly accepted beliefs concerning hypertension and its cardiovascular consequences may be in error."[43] They challenged the existing belief "that systolic pressure is unimportant" and that "labile hypertension is of little consequence", pointing out that there was not only "little evidence to support these contentions", but in fact "considerable reason to doubt them".[43]

The importance of blood-pressure control was finally embraced by practice guidelines in the first report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure in 1977.[46] The Committee still recommended that diastolic blood pressure be used as the basis for diagnosis and treatment of hypertension, but over the next decades the emphasis on diastolic blood pressure as the principal treatment target was dropped after findings of randomised controlled trials showed the cardiovascular benefits of reduction of systolic blood pressure.[47,48]

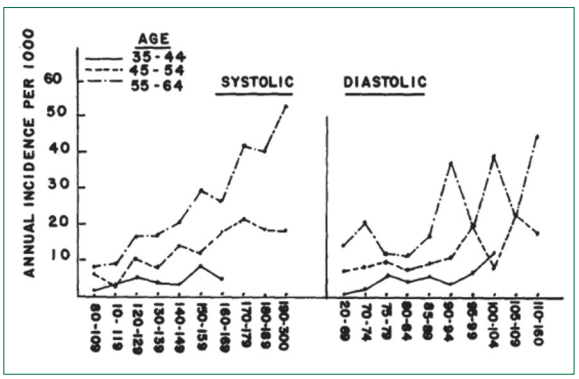

Figure 4: **Systolic pressure as a superior marker for average annual incidence of coronary heart disease**
From Kannel and colleagues (1971),[43] by permission of Elsevier.

Framingham risk scores

The Framingham Heart Study and other epidemiological cohorts contributed to a shift in focus in the second half of the 20th century, from treatment of those with established cardiovascular disease to the prevention of disease in those at risk. A key element of this strategy was the ability to identify those most likely to have a future cardiovascular event, to enable targeting of preventive interventions. Studies from this period helped to elucidate cardiovascular risk factors, such as hypertension, hyperlipidaemia, and diabetes mellitus. Indeed, the term "risk factor" was popularised in the medical lexicon by Dawber and Kannel in their 1961 publication, *Factors of Risk in the Development of Coronary Heart Disease*.[27]

The articulation of the notion of risk factors laid the foundation for the development of clinical risk scores. The first attempt to create a multivariable risk function for coronary heart disease in the Framingham study was published by Truett, Cornfield, and Kannel[49] in 1967. Previously, the typical approach to consideration of several risk factors at once was multiple cross classification, in which tables were created with cells corresponding to combinations of risk factors. Unfortunately, after more than a few variables, thousands of cells were needed. The Framingham investigators proposed multivariable logistic models with seven risk factors: age, total cholesterol, weight, electrocardiogram abnormalities, haemoglobin, number of cigarettes smoked, and systolic blood pressure. Men in the top decile had a 30-times higher incidence of coronary heart disease than did men in the bottom decile, and women in the top decile had a 70-times higher incidence than did women in the bottom decile.

Subsequent reports provided risk functions, or risk profiles, that enabled physicians to directly calculate an individual's predicted risk of a cardiovascular event. The

first risk profile was reported in 1976 by Kannel and colleagues,[50] and had a general cardiovascular endpoint that included coronary heart disease, stroke, claudication, and heart failure. The variables in the model were similar to those of the Truett study,[49] except that glucose intolerance was added, and weight was dropped.

The best known risk profile is the Framingham Risk Score for coronary heart disease, reported in 1998 by Wilson and colleagues.[51] This function became the basis of the risk calculator used by the Adult Treatment Panel of the National Cholesterol Education Program in the USA.[52] Compared with previously published functions, the 1998 model substituted risk factor categories in place of continuous values, which enabled clinicians to use look-up tables to obtain risk estimates. The 10 year risk estimates used in the 1998 score provided a convenient way to classify individuals as being at low, intermediate, or high risk of future coronary heart disease.

Framingham and epidemiology of heart failure

Roosevelt's failing health from heart failure underscores the poor understanding of the clinical syndrome at the time the Framingham Heart Study was initiated. Until the late 1960s, research into heart failure was made difficult by the absence of consistent diagnostic criteria. For instance, investigators of a 1965 observational study[53] to assess the prevalence of heart failure in two rural US communities explained that "no attempt was made to define congestive heart failure to the assessing physician, since it was his operational diagnosis that was sought."[53] In the absence of standard criteria, researchers faced pathological changes with "an ill-defined collection of signs and symptoms", which hampered efforts to identify factors that predisposed people to heart failure or affected the course of the disease.[54]

By the end of the eighth examination cycle of the Framingham Heart Study in 1966, investigators had noted a rising prevalence of heart failure in the cohort. They therefore developed a set of clinical criteria for heart failure (panel), which were retrospectively applied to nearly two decades of collected data for which staff had noted whether participants had suspected heart failure.[55,56] McKee, Kannel, and colleagues[57] introduced these criteria in a 1971 report. Nine major criteria and seven minor criteria were defined, along with one criterion (≥4·5 kg weight loss) that could be major or minor depending on whether it was due to treatment for heart failure or another possible cause. A diagnosis of definite heart failure was made if the patient had two major or one major and two minor criteria concurrently. By focusing on clinical symptoms, the investigators understood that heart failure was a clinical syndrome. Since their development in the late 1960s, these criteria have been in continuous use, not only in the Framingham Heart Study, but also in many other cohorts around the world.[58]

In 1971, McKee, Kannel, and colleagues[57] used the newly described criteria to show that hypertension was in fact the leading risk factor for heart failure (figure 5). Examining 16 years of observational data, the investigators noted that hypertension preceded three quarters of heart-failure cases, by comparison with coronary artery disease, which preceded heart failure in less than 40% of cases.

Levy and colleagues[58] later calculated the population attributable risk of risk factors for heart failure, showing the percentage of heart failure cases that would be reduced if a causal risk factor was eliminated from the population.[58] Myocardial infarction was associated with a six-times increase in risk of heart failure, but the population attributable risk was only 13% for women and 34% for men. Hypertension was associated with a two-times increased risk of heart failure, but had a population attributable risk of 59% for women and 39% for men because of its high prevalence.

Because heart failure diagnoses in the Framingham study have been prospectively adjudicated with one set of diagnostic criteria since the 1960s, the study has provided a valuable source of information about long-term trends in the epidemiology of the disorder. The original 1971 publication showed the poor prognosis for heart failure: only two in five men were alive 5 years after diagnosis of heart failure, and only one in five survived to 10 years.[57] Survival for women with heart failure was similar. By the 1990s, the widespread use of mortality-altering drugs such as β blockers and angiotensin-converting-enzyme inhibitors had altered this prognosis. Using 50 years of follow-up data, Levy and colleagues[59] reported that 5 year mortality in those with heart failure decreased in men from 70% in 1950 to 59% in 1999, and in women from 57% to 45%.

Findings from other studies from Framingham showed alterations in cardiac structure or function that preceded overt heart failure. In 1997, Vasan and colleagues[60] showed that increased left-ventricular end-diastolic diameter predicted incident heart failure in individuals free of myocardial infarction. Wang and colleagues[61] reported that individuals with asymptomatic left-ventricular systolic dysfunction had a five-times increased risk of heart failure, even after adjustment for conventional risk factors. Recent guidelines have a notable emphasis on the detection of asymptomatic ventricular dysfunction (stage-B heart failure) as part of efforts to understand and prevent overt heart failure.[62]

The Framingham investigators also noted that clinical manifestations of heart failure could be present in the absence of left-ventricular systolic dysfunction. This recognition was possible because the Framingham criteria for heart failure predated the widespread availability of echocardiography, meaning that the diagnosis of heart failure did not need left-ventricular systolic dysfunction. In 1999, Vasan and colleagues[63] reported that about half of Framingham participants with heart failure had a normal ejection fraction (>50%) at the time of diagnosis. Survival of participants with heart failure

and preserved ejection fraction (or diastolic heart failure) was substantially worse than that of participants without heart failure, although it was better than for participants with systolic heart failure. Studies from other cohorts have shown consistent findings, leading to increased recognition that diastolic heart failure is common, particularly in older people and women.

Metabolic risk factors for heart disease

Framingham investigators also joined worldwide efforts to understand the links between metabolic risk factors and cardiovascular disease. In the first half of the 20th century, findings of autopsy and hospital-based studies showed an association between diabetes mellitus and cardiovascular disease.[64,65] By the mid-20th century, clinical data had shown a link between diabetes and vascular disease,[66–68] an association also reported by the Framingham investigators.[69] In the Framingham study, cardiovascular mortality was three-times higher for participants with diabetes, and diabetes was associated with substantially increased risks of heart failure and hypertensive heart disease.[70,71]

By the early 20th century, cholesterol had been linked to cardiovascular disease through animal and autopsy studies.[72,73] Keys[74] described high concentrations of cholesterol in patients with coronary heart disease. In 1977, Gordon and other Framingham investigators[75] reported an inverse association between HDL concentrations and incidence of coronary heart disease, by contrast with the positive association between LDL concentrations and incidence of coronary heart disease. That same year, in collaboration with other epidemiological studies in the USA, Framingham investigators reported that individuals with coronary disease had lower HDL concentrations than did healthy participants across several ethnicities.[76] Framingham researchers commented "It is curious...that the determination of HDL cholesterol has not long since become part of standardised coronary heart disease risk profile."[75] Notably, the 1998 version of the Framingham risk score, used by the National Cholesterol Education Program, contained both total and HDL cholesterol.[51]

Because obesity occurs concomitantly with hypertension, high concentrations of lipids, and diabetes, the increased cardiovascular risk in obese people is often attributed to these coexisting risk factors. By the late 1970s, when William Castelli became the fourth director of the Framingham Heart Study, the average weight of the US population had been increasing for several decades.[77] In 1983, he and his colleagues[78] reported that weight gain conferred an increased risk of cardiovascular disease, which persisted despite adjustment for other risk factors. This risk was particularly apparent for heart failure. Framingham participants less than 50 years old had a two-times to three-times excess risk of heart failure from the lightest to the heaviest weight category.[78] In 2002, Kenchaiah and colleagues[79] arrived at similar conclusions with updated data from the Framingham study. The population attributable risk for heart failure due to obesity was 14% in women, and 11% in men, higher than that of diabetes mellitus, valvular heart disease, or left-ventricular hypertrophy.

***Panel:* Criteria for heart failure**

Major

- Paroxysmal nocturnal dyspnoea or orthopnoea
- Neck-vein distension (not counting supine position)
- Rales in presence of unexplained dyspnoea
- Cardiomegaly and pulmonary hilar congestion (diagnosed by radiograph in absence of left-to-right shunt), or increasing heart size
- Acute pulmonary oedema described in hospital records
- Ventricular gallop
- Increased venous pressure (>16 cm H_2O from right atrium)
- Circulation time (>24 s from arm to tongue)
- Hepato-jugular reflux
- Weight loss (≥4·5 kg) in 5 days, due to therapy for heart failure

Minor

- Ankle oedema
- Night cough
- Dyspnoea on ordinary exertion
- Hepatomegaly
- Pleural effusion
- Decreased vital capacity by a third from maximum records
- Tachycardia (≥120 beats per min)
- Weight loss (≥4·5 kg) in 5 days, not related to therapy for heart failure

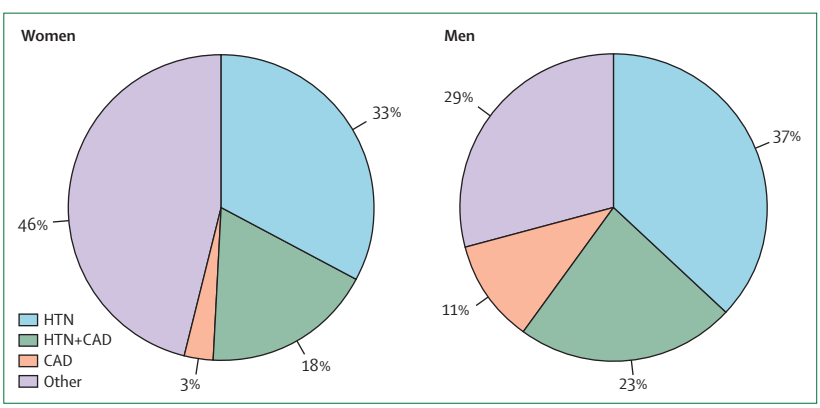

Figure 5: **Hypertension as a precursor of heart failure**
HTN=hypertension. CAD=coronary artery disease. Adapted from McKee and colleagues (1971),[57] by permission of the Massachusetts Medical Society.

Epidemiology of stroke and atrial fibrillation

By the 1960s, stroke was still the third-biggest cause of death for Americans.[29] In the preimaging era, Framingham investigators diagnosed stroke through clinical history, neurological examination, and sometimes

lumbar puncture. Each suspected new case of stroke was confirmed by a second examiner and neurological consultation. In addition to establishment of the link between systolic blood pressure and stroke,[29] Framingham investigators showed that the risk of stroke from hypertension was even greater than that conferred by coronary heart disease.[44]

One of the most valuable clinical contributions from the Framingham study has been the finding that non-rheumatic atrial fibrillation is a potent risk factor for stroke. In a 1978 study, Wolf and colleagues[80] reported that chronic atrial fibrillation not due to rheumatic heart disease was associated with a five-times excess risk of stroke, an observation that led them to call for "controlled trials of anticoagulation or antiarrhythmic agents in persons with chronic atrial fibrillation." Fortunately, such trials were done, and anticoagulation for patients with atrial fibrillation became the standard of care.

Because of the similarities between atrial fibrillation and heart failure, two conditions that follow adverse cardiac remodelling, that they share several epidemiological features is not surprising. For example, Benjamin and colleagues[81] showed that the population attributable risk for development of atrial fibrillation was highest for hypertension, despite the fact that other risk factors were associated with higher relative risks. Data from the Framingham study also showed the underappreciated contribution of obesity to risk of atrial fibrillation.[82]

New cohorts

Towards the end of the 20th century, Framingham investigators identified a need to expand knowledge about genetic and environmental risk factors for cardiovascular disease.[83] Thus, in 2002, they began the recruitment of a new generation of participants, the Third Generation cohort (table), which consisted of children of Offspring cohort participants.[83] Recognising the power of the family-based approach, investigators gave priority to 879 large extended families that already had several participants in the study.

The Framingham investigators also recognised the disadvantages of a cohort that was predominantly white and of European descent. The Omni 1 cohort was recruited in 1994, and included 506 ethnic minority residents of Framingham. A decade later, an additional 410 ethnic minority participants were recruited through the Omni 2 cohort.

In 2006, the National Institutes of Health funded the SNP Health Association Resource, which supports genome-wide genotyping across all the Framingham cohorts. The data enabled Framingham investigators to contribute to the global effort to study the genetic determinants of complex diseases, and has led to the identification of hundreds of common genetic variants that affect the risk of cardiovascular disease.

Conclusions

Nearly seven decades have passed since Roosevelt's death in 1945 after a long illness that started with uncontrolled hypertension and progressed to heart failure and stroke. Years later, reflecting on the President's premature death, his cardiologist wrote: "I have often wondered what turn the subsequent course of history might have taken if the modern methods for the control of hypertension had been available."[5] The Framingham Heart Study was the product of a bill signed into law by Roosevelt's successor. Fittingly, it has made many contributions to the understanding of the very cardiovascular conditions that led to his death.

Contributors

SSM did the literature search, and searched the Framingham Archives at the National Heart, Lung, and Blood Institute and Harvard University's Widener Library collection of *President Franklin D. Roosevelt's Office Files, 1933–1945*. All authors contributed to the compilation of this Review.

Conflicts of interest

We declare that we have no conflicts of interest.

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