EPIDEMIOLOGY OF CVD

TIMELINE

70-year legacy of the Framingham Heart Study

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Abstract | The Framingham Heart Study (FHS) was established in 1948 to improve understanding of the epidemiology of coronary heart disease (CHD) in the USA. In 1961, seminal work identified major risk factors for CHD (high blood pressure, high cholesterol levels and evidence on the electrocardiogram of left ventricular hypertrophy), which later formed the basis for multivariable 10-year and 30-year risk-prediction algorithms. The FHS cohorts now comprise three generations of participants ($n \approx 15{,}000$) and two minority cohorts. The FHS cohorts are densely phenotyped, with recurring follow-up examinations and surveillance for cardiovascular and non-cardiovascular end points. Assessment of subclinical disease and physiological profiling of these cohorts (with the use of echocardiography, ambulatory electrocardiographic monitoring, exercise stress testing, cardiac CT, heart and brain MRI, serial vascular tonometry and accelerometry) have been performed repeatedly. Over the past decade, the FHS cohorts have undergone deep 'omics' profiling (including whole-genome sequencing, DNA methylation analysis, transcriptomics, high-throughput proteomics and metabolomics, and microbiome studies). The FHS is a rich, longitudinal, transgenerational and deeply phenotyped cohort study with a sustained focus on state-of-the-art epidemiological methods and technological advances to facilitate scientific discoveries.

The Framingham Heart Study (FHS) celebrated its seventieth anniversary in 2018. The FHS is the longest-running cardiovascular epidemiological cohort study in the USA. In this Timeline Perspectives article, we discuss the background and rationale for the initiation of the FHS, describe the accrual of data over time, list several seminal research milestones and offer a perspective on the future of the FHS. The importance of moderate-sized cohort studies has evolved over time with the formation of much larger collaborative consortia, 'mega'-cohorts and biobanks, but the FHS remains a unique, longitudinal, transgenerational and deeply phenotyped epidemiological cohort study.

Rationale and origin

Motivated by the marked increase in deaths from coronary heart disease (CHD) in the USA in the first half of the 20th century, the US Public Health Service set up a longitudinal, community-based study in 1948 to improve understanding of the natural history of CHD and its aetiological factors. The location of Framingham, Massachusetts, was chosen on the basis of the city's history of contributions to public health community endeavours (especially the 1917–1923 Framingham Tuberculosis Demonstration Study)[1] and strong advocacy by scientists (such as Paul Dudley White and David D. Rutstein from Massachusetts General Hospital and Harvard Medical School, respectively)[2]. Additional factors that contributed to the choice of Framingham as the location for such a study included its proximity to leading medical institutions and hospitals in the Boston area and its representation of a typical economically stable US community in the 1940s, with low rates of outmigration. At that time, important concepts of cardiovascular epidemiology were in their formative stages, and notions of CHD prevention were beginning to take root. Apart from a few observations demonstrating that nutritional (such as beriberi and pellagra) and infectious (for example, syphilis, haemolytic streptococcal infections and bacteraemia caused by viridans streptococci) disorders might have features of cardiovascular diseases (CVDs), little was known about the origins of CHD in the community. As Dawber, Meadors and Moore stated in a report[3] describing the purpose of the Framingham Study, "Of the epidemiology of hypertensive or arteriosclerotic cardiovascular disease, almost nothing is known." The hypotheses and aims of the FHS at the time of its initiation are presented in BOX 1.

The Original cohort of the FHS was recruited from among the 28,000 inhabitants of Framingham, with 5,209 individuals (about one-fifth of the population) being enrolled. The mean age of the Original cohort at entry into the study was 44 years (range 28–74 years), and more than half of the participants were women, which was prescient for the time. Study design was based on sampling participants who were free from overt CVD (termed 'normals' by the researchers), and the age range of approximately 30–60 years was chosen because this time of life is when atherosclerotic, arteriosclerotic and hypertensive diseases were expected to occur. On 29 September 1948, the first participant entered the Framingham Study research clinic; the people of Framingham have been very dedicated to the study ever since. At the beginning of the study, an executive committee comprising 15 town residents argued that families should not be split up during recruitment for the cohort. The preferential recruitment of individuals from families subsequently emerged to be extraordinarily insightful because it facilitated investigations of the familial clustering of CVD and promoted participant retention. The initial plan and expectation were to follow up the recruited participants for 20 years — a milestone that was accomplished in 1968 (REF.[3]).

Funding beyond the initial 20-year period faced some challenges. However, in 1971, the NIH and Boston University signed an agreement that provided the FHS

Box 1 | **Foundation of the Framingham Heart Study**[3]

Hypothesis given in the background paper for the Framingham Heart Study in 1952

- "It is assumed that these diagnoses [hypertensive and arteriosclerotic disease] do not each have a single cause (as is the case of most infectious diseases), but that they are the result of multiple causes which work slowly within the individual."
- "Clearly, what is required is the epidemiological study of these diseases [hypertensive and arteriosclerotic disease] based on populations of normal composition, including both the sick and the well as they are found in the community."

Original aims of the Framingham Heart Study as presented in 1952

- "Based on as complete a clinical examination as feasible, there are selected out of this initial group those persons who are free of definite signs of these diseases. These persons will be termed the normals, and they will be observed over a period of years until a sizable number are found to have acquired the diseases. At that time a search is made for the factors which influenced the development of disease in the one group and not in the other."
- "As one by-product of this investigation it will also be possible to study the efficiency of various diagnostic procedures in finding heart disease or as indicators of the subsequent development of heart disease. (These findings, of course, have important bearing on the question of including tests for heart disease in mass screening programs.)"
- "A second by-product will be data on prevalence and incidence of cardiovascular diseases."

with continued federal support, and the FHS was expanded with the enrolment of a second-generation cohort, the Framingham Offspring Study ($n = 5{,}124$), consisting of the children of the Original cohort and the spouses of those children. The aims of the Framingham Offspring Study were to investigate secular trends in CHD risk factor levels across the two generations and over time and to examine the familial and genetic determinants of risk factors for CHD[4]. The age of the Offspring cohort at their initial visit was approximately the same age as the Original cohort had been at their first examination.

A minority cohort (Omni 1; $n = 506$) from Framingham was subsequently enrolled in 1995 to reflect the changing demographic characteristics of the town. In 2002, the FHS was further expanded with the recruitment of a sample of the children of the Offspring cohort (grandchildren of the Original cohort) — that is, the Third-Generation FHS cohort ($n = 4{,}095$) — along with a second contemporary minority cohort (Omni 2; $n = 410$) with a similar age distribution. The aim of the Third-Generation cohort was to recruit individuals belonging to the largest pedigrees from the first-generation and second-generation cohorts to investigate further the genetic architecture of CVD and its risk factors and to continue studies of temporal trends in the incidence of CVD and its risk factors[5]. As of today, nested within the three FHS cohorts are 6,477 parent–offspring pairs and 1,267 grandparent–grandchildren pairs, plus 5,530 sibships and a number of other pedigree relationships of great value for heritability and genetic studies.

Data collection and milestones

The FHS has evolved over time with regard to its collection of biosamples and data for research. To date, the Original cohort has been examined for 32 cycles at approximately 2-year intervals; during the thirty-second examination cycle (2012–2014), only 40 individuals remained alive and were examined either in nursing homes or at their residence if unavailable to attend the FHS research centre. At the last examination, the mean age of the cohort was 96 years (range 93–106 years). The Offspring cohort has been examined for nine cycles, every 4–7 years; the latest cycle was completed in 2014 (mean age 71 years, range 46–98 years). For the Third-Generation cohort, two examination cycles have been completed, with a third cycle to be completed in 2019. The Omni 1 cohort has been examined for four cycles; the latest cycle was completed in 2014 (mean age 66 years, range 44–88 years). The Omni 2 cohort has completed two examination cycles, with a third cycle to be completed in 2019.

FIGURES 1 and 2 and TABLES 1 and 2 show the temporal trends in data collection, some of the work derived from the data and the wealth of data collected in the FHS, as discussed in detail below.

1948–1977

During the first set of FHS examinations on the Original cohort, blood samples (for assaying blood glucose and cholesterol concentrations), electrocardiograms, chest radiograms, information on smoking, a family history and anthropometric measures were obtained. In 1957, the initial publication that identified connections between the measurements made at baseline and the development of CHD was published[6]. The 4-year follow-up data from the Original cohort showed that elevated blood pressure, high cholesterol levels and being overweight were associated with CHD[6]. In 1961, probably one of the most high-impact reports that has ever been generated by the FHS was published — the identification of "factors of risk" for the development of CHD[7]. Kannel and colleagues noted that male sex, older age, elevated blood pressure and cholesterol levels and left ventricular (LV) hypertrophy (as assessed on the electrocardiogram) were important predictors of the risk of CHD[7]. Reports on the strong association between smoking and CHD followed in 1962 and 1964 (REFS[8,9]).

However, in the early 1960s, the potential implications of these findings were uncertain because whether lowering these risk factors would lead to a reduction in the risk of CHD had not been determined. Not long before the investigation was published, elevated blood pressure was considered to be a normal concomitant of ageing and an important compensatory phenomenon to maintain cerebral perfusion (in response to ageing itself) that should not be lowered in asymptomatic individuals[10]. Several additional FHS publications on the adverse effects of hypertension followed, which underscored the strong associations between elevated blood pressure and the risk of developing both stroke and congestive heart failure[11,12]. Indeed, a seminal report on heart failure from 1971 (with 16 years of follow-up) concluded that hypertension was the dominant cause of heart failure (considered to be an aetiological factor in 75% of the patients)[13]. That report also introduced the widely used Framingham criteria for defining definite heart failure in an epidemiological setting (on the basis of the presence of two major or one major and two minor criteria; BOX 2).

Shortly thereafter, other principal risk factors for stroke and heart failure (that is, atrial fibrillation and diabetes mellitus, respectively) were also identified[14,15]. From the outset, FHS publications highlighted the critical importance of systolic blood pressure in the pathogenesis of CHD and stroke, whereas national guidelines focused almost exclusively on diastolic blood pressure levels until an advisory statement on systolic blood pressure was issued in 2000 (REF.[16]). The importance of diabetes as a risk factor for various forms of CVD (that is, intermittent claudication, congestive heart failure,

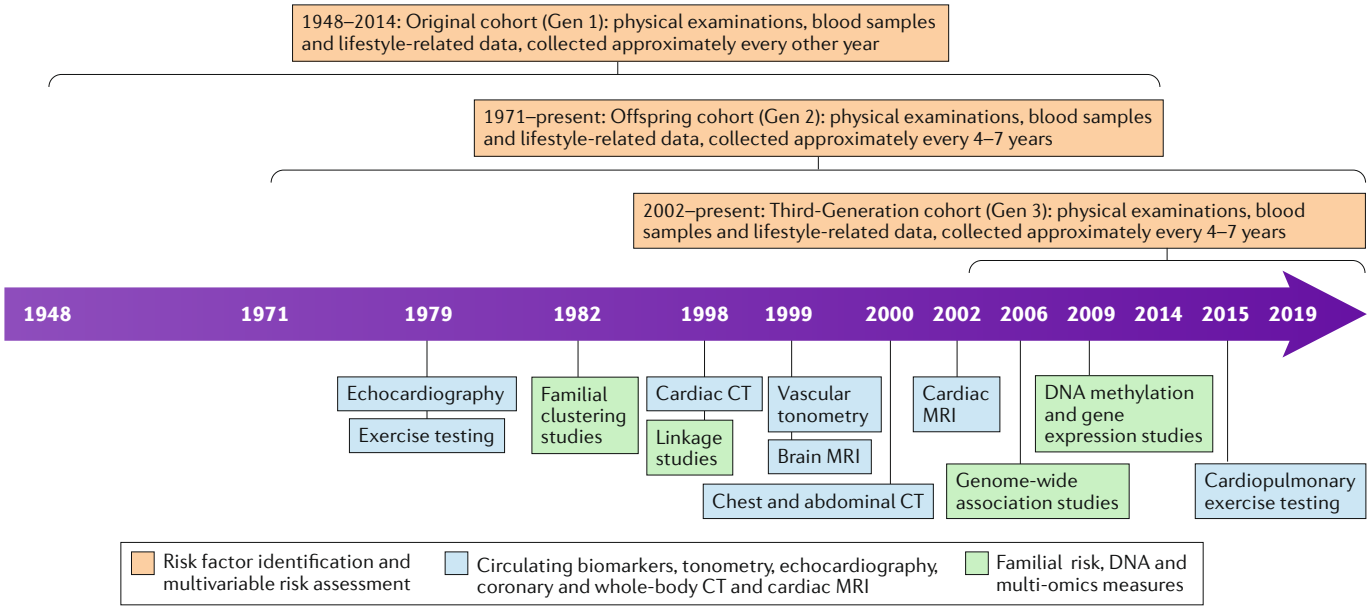

Fig. 1 | **Timeline of the Framingham Heart Study.** The timeline shows the temporal enrolment of the three generations of participants (Gen 1, Gen 2 and Gen 3) and when various measures and heritability studies were introduced to the Framingham Heart Study.

CHD, stroke and cardiovascular death) was reported in 1979 (REF.[17]). Importantly, the 1979 report concluded that the lower risk of CVD in women versus men was attenuated when diabetes was present[17]. On the basis of the initial data collection in the FHS, the long-term, independent risk factors for atrial fibrillation (age, congestive heart failure, valvular disease, diabetes, hypertension and male sex) and congestive heart failure (hypertension, CHD, diabetes and LV hypertrophy) were also delineated[18,19], and smoking was firmly established as an important risk factor for intermittent claudication[20] and stroke[21].

In 1965, the FHS laboratory began to separate out fractions of plasma lipoprotein cholesterol. Soon, the prognostic importance of LDL-cholesterol and HDL-cholesterol concentrations and the LDL:HDL cholesterol ratio were investigated for the first time in a community-based setting[22]. In 1967, physical activity was identified as being inversely associated with risk of CHD[23]. On the basis of data collected during the first three decades (that is, >35 years ago), excess weight and obesity were also established as being independent risk factors for the long-term risk of CVD[23,24].

Long-term results from the initial data collection. The longitudinal tracking of participants since the early decades of the FHS has not only enabled the identification of risk factors for hard cardiovascular outcomes longitudinally but also has shed light on the natural progression of risk factors over time. For instance, FHS investigators reported in 1996 that blood pressure levels increased with age over a 20-year time period, and so-called borderline systolic hypertension progressed to overt hypertension in >80% of the participants[25]. The lifetime risk of hypertension in the FHS has later been estimated to be 90%[26]. Corresponding lifetime risks at the age of 40 years have been estimated to be 20% for congestive heart failure[27] and at least 33% in men and 14% in women for CHD (up to 67% in men and 33% in women, depending on blood cholesterol levels)[28]. The lifetime risks of atrial fibrillation at the age of 40 years ranged from 20% to 33% depending on the risk factor burden and might be increasing[27,29,30].

On the basis of data collected during the first three decades, one of the best-known reports on the long-term combined effect of risk factors on the incidence of CHD was published in 1998, in which Wilson and colleagues introduced mathematical functions to estimate the 10-year risk of CHD[31]. This algorithm formed the basis of lipid-lowering treatment for the primary prevention of CHD as part of the National Cholesterol for Education Program (NCEP) Adult Treatment Panel III recommendations[32]. A general CVD risk score was formulated in 2008, which predicted the occurrence of a composite outcome of CVD that included CHD, stroke and heart failure. This risk score has since been modified by the current ACC/AHA CVD risk calculator[32]. In 2009, a similar risk-prediction algorithm was developed for the 30-year risk of CVD[33]. Risk functions have also been formulated for individual forms of CVD (congestive heart failure[34], atrial fibrillation[35], stroke[36] and recurrent CVD[37]) and for CVD risk factors themselves (the hypertension risk score[38]).

1978–2008

Echocardiography was introduced at the FHS in 1979. In 1988, FHS research established that increasing age, high blood pressure and obesity were strong risk factors for LV hypertrophy defined by echocardiography[39]. The FHS echocardiography laboratory has also contributed substantially to establishing normative echocardiographic reference values for LV mass[40], wall thickness, left atrial dimension[41] and aortic root size[42]. Later, high blood pressure, obesity, smoking and diabetes were shown to be strong determinants of LV mass in mid-life over a 16-year period[43], and a high LV mass was associated with an increased risk of cardiovascular events[44]. Similarly, the FHS echocardiography laboratory has provided insight into the importance of asymptomatic LV dilatation and LV systolic dysfunction, which were both observed to be associated with a high risk of heart failure in 1997 and 2003, respectively[45,46].

Longitudinal FHS data also described cardiac remodelling over the life course, with longitudinal tracking of aortic root and left atrial dimensions as well as LV internal dimensions, wall thickness and

mass over time. The longitudinal reports highlighted that fractional shortening (a measure of LV ejection fraction) increased with advancing age, whereas the LV end-diastolic dimension decreased[47]. Evaluation of LV systolic function in individuals with heart failure in the FHS contributed to seminal work published in 1999 establishing that heart failure in the community can occur in the presence of a normal ejection fraction (which emphasized the concept of heart failure with preserved ejection fraction (HFpEF))[48]. Approximately half of all FHS participants with heart failure were shown to have a preserved LV ejection fraction[48]. Despite having a slightly better prognosis than patients with heart failure with reduced ejection fraction, mortality was still fourfold higher for participants with HFpEF than for age-matched and sex-matched controls without heart failure[48]. Work investigating temporal trends in patterns of heart failure (1985–2014) in the FHS demonstrated that a higher proportion of all heart failure cases now manifest with preserved LV ejection fraction and that the prevalence of asymptomatic LV systolic dysfunction has declined[49]. This decline was demonstrated to be partly associated with temporal trends for a lower prevalence of CHD and a greater burden of high blood pressure[49].

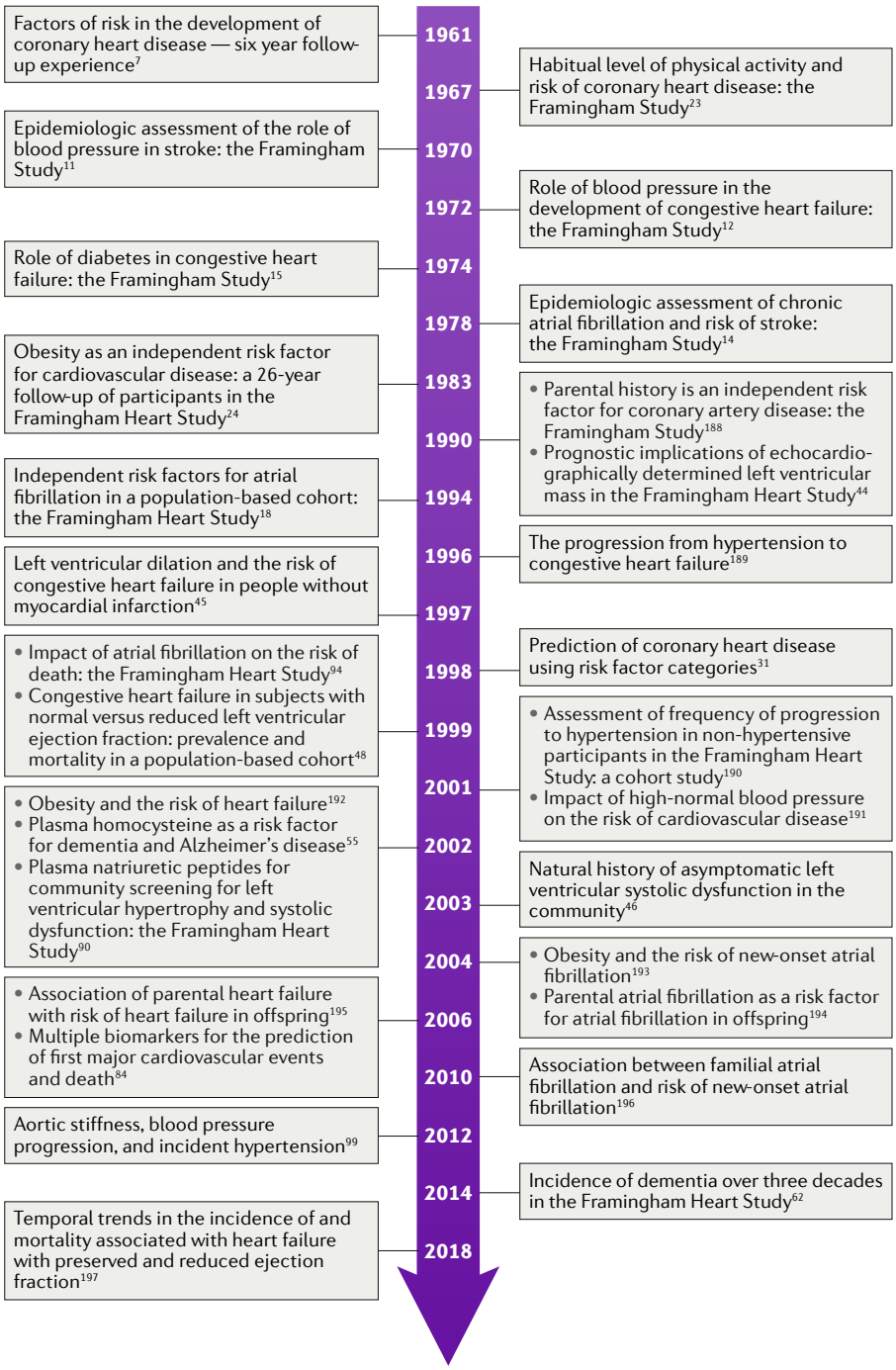

Fig. 2 | **Major publications from the Framingham Heart Study.** The timeline shows article titles of selected seminal publications arising from the Framingham Heart Study.

Exercise testing was introduced at the FHS in 1979. In one of the initial publications, Lauer and colleagues reported that chronotropic incompetence (identified by exercise testing) was associated with increased LV mass and cavity size in both sexes and was associated with systolic dysfunction in men, in part consistent with our current understanding of some of the pathophysiology of HFpEF[50]. The FHS investigators also demonstrated that a poor increase in heart rate in response to exercise was predictive of a greater risk of CHD and death[51]. Subsequently, an exaggerated blood pressure response to exercise was shown to be an important antecedent of the development of resting hypertension, and a slower recovery of heart rate after exercise was associated with an increased risk of CHD and cardiovascular events[52].

Since 1975, FHS participants have been under continuous surveillance for cognitive impairment and clinical dementia. Starting in 1985 and 1991, at every examination cycle, participants from the Original and Offspring cohorts, respectively, have undergone a mini-mental state examination (MMSE) and other neurocognitive tests. On the basis of any abnormal results in these tests, selected participants are invited to undergo further cognitive testing. As a result of this longitudinal, comprehensive cognitive screening and neuropsychological testing, the Framingham Study has contributed substantially to the delineation of risk factors for vascular and Alzheimer dementia in the community. For instance, cognitive decline, all-cause dementia and Alzheimer disease have been shown to be directly associated with the composite FHS stroke risk profile[53,54]. Cognitive impairment is also associated with previous stroke[53,54], plasma homocysteine concentrations[55], blood pressure levels[56], obesity[56,57], *APOE* genotype[58] and atrial fibrillation[59,60] but is inversely associated with blood leptin levels[61]. In 2016, the incidence of dementia was reported to have declined over a period of three decades in the FHS cohorts, in part owing to better control of vascular risk factors, underscoring the importance of cohort studies (such as the FHS) for

evaluating temporal trends in a range of health outcomes[62].

Starting in the 1980s, the FHS has measured a plethora of circulating biomarkers. Several of these biomarkers have shed important light on the pathophysiology of hypertension[63,64], vascular stiffness and endothelial function[65–68], atrial fibrillation[69,70], heart failure[71–74], chronic kidney disease[75,76], venous thromboembolism[77], stroke[78–81] and Alzheimer disease[82,83]. Wang and colleagues demonstrated that a panel of ten biomarkers was predictive of a first major cardiovascular event and death[84]. Major work focusing on the circulating levels of natriuretic peptides resulted in the formulation of reference limits in healthy individuals[85]; underscored the association between obesity and lower circulating concentrations than in individuals without obesity (natriuretic handicap of obesity)[86,87]; demonstrated their prognostic relevance in atrial fibrillation[88], CVD and mortality[89]; and emphasized the limited utility of circulating natriuretic peptide levels in screening for LV hypertrophy and asymptomatic LV systolic dysfunction in the community[90].

Holter monitoring was undertaken in the early 1990s and has contributed to our understanding of the determinants and prognostic importance of reduced heart rate variability for the risk of CVD and death in the general population and in patients with heart failure[91–93]. The routine surveillance by the FHS for atrial fibrillation has also contributed to the awareness that, after adjusting for coexisting risk factors, atrial fibrillation is associated with an increased risk of heart failure and death[94–96].

During the end of the 1990s, a vascular function assessment station was established at the FHS. Several measures of endothelial function (such as brachial artery flow-mediated dilatation and baseline and hyperaemic mean flow velocities) and aortic stiffness (such as carotid–femoral pulse wave velocity, augmentation index and forward pulse wave) and peripheral arterial tonometry have been obtained in both the Offspring and Third-Generation cohorts; these measures are of prognostic importance for predicting the development of major cardiovascular events[97]. These measures have also improved our understanding of the pathophysiology of vascular disease and their synergistic interactions with other vascular risk factors and disorders. For instance, hypertension is often preceded by high arterial stiffness[98], which might contribute in part to the heritability of hypertension[99]. Moreover, some of the residual risk associated with hypertension, even if well controlled, has been shown to be the result of high vascular stiffness[100]. High arterial stiffness has also been shown to be associated with subclinical brain damage[101–103], mild cognitive impairment and dementia[104], atrial fibrillation[105], impaired LV diastolic function[106] and heart failure[107]. Sleep apnoea, non-alcoholic fatty liver disease and other metabolic derangements have also been associated with higher aortic stiffness, whereas physical activity is associated with lower aortic stiffness in the FHS[108–111]. The vascular function laboratory also described the clinical correlates, heritability[112] and relationships between brachial arterial flow-mediated dilatation and the season and local hyperaemic shear stress[113,114].

Table 1 | **Examples of measurements in the FHS**

Category	Measurements	Associated circulating biomarkers
Anthropomorphic	• Height • Weight • Waist circumference • Hip circumference • Thigh circumference • Neck circumference • CT-derived measures of visceral and subcutaneous body fat composition	• Insulin-like growth factor I • Insulin-like growth factor-binding protein 3 • C-reactive protein • β-Nerve growth factor • Leptin • Leptin receptor • α-Fetuin • Resistin • Ghrelin • Retinol-binding protein 4 • Fatty acid-binding protein 4 • Adiponectin • Sex hormones
Lifestyle	• Food frequency questionnaires • Physical activity and work-related activities by questionnaires • Physical activity (accelerometry) • Sleep habits • Alcohol intake • Smoking habits • Socioeconomic status • Social network • Education • Marital status	• Haemoglobin • Haematocrit • Fasting blood glucose • Haemoglobin A1c • Triglycerides • Cytokines (IL-6, TNF and TNF receptor 2) • Cortisol • Insulin • Vitamin D • Folate • Vitamin B_{12} and B_6 • Vitamin E

FHS, Framingham Heart Study; TNF, tumour necrosis factor.

2009–present

The FHS has introduced more advanced imaging modalities, such as cardiac MRI, over the past two decades, thereby complementing data collection in this domain by other cohort studies, including the Multi-Ethnic Study of Atherosclerosis (MESA). In 2008–2011, participants from the Offspring and Third-Generation cohorts underwent multidetector CT scans of the thorax and abdomen. These data have been used, for instance, to investigate the clinical correlates and importance of the quality and distribution of subcutaneous versus visceral fat content in different deposits in relation to the risk of subclinical and clinical heart disease[115–121]. The study on multidetector CT-derived coronary artery calcium (CAC) levels (data collection starting in 1998) has also contributed important information from a primary prevention perspective — the data have helped to define normative values in men and women[122], added information on the clinical correlates of CAC[123,124], revealed determinants of CAC score progression and contributed to our understanding of the prognostic importance of CAC in the community[125–128].

Cardiac MRI studies were performed on the Offspring cohort between 2002 and 2006. These data have contributed to defining reference values of LV and right ventricular volumes, mass and systolic function in the community[129–131]. MRI-based studies have also established the prognostic importance of LV structure and wall motion abnormalities on the risk of developing cardiovascular events[132,133]. Brain MRI has also been undertaken on all Offspring cohort participants, starting in 1999–2002, through funding from the US National Institute on Aging. These data have provided important insights, such as the reference values for imaging-derived brain measures; the relationship between subclinical risk factor burden, circulating biomarkers

Table 2 | **Phenotypes from different organ systems collected in the Framingham Study**

Organ	Diagnoses	Anatomical tests	Functional tests	Circulating biomarkers
Eyes	• Cataract • Glaucoma • Diabetic retinopathy • Macular degeneration	Eye exam	Vision	NA
Ears	• Hearing loss (sensineural, bone or congenital) • Menière disease	Otoscopy	• Hearing tests • Hearing questionnaires	NA
Thyroid and parathyroid glands	• Hypothyroidism or hyperthyroidism • Goitre • Hyperparathyroidism (primary, secondary or tertiary)	NA	NA	• Thyroid-stimulating hormone • Triiodothyronine (T3) • Thyroxine (T4) • Parathyroid hormone • Ca^{2+} • Phosphate
Brain	• Dementia (all-cause, Alzheimer or vascular) • Disseminated sclerosis • Stroke (transient ischaemic attack, ischaemic or haemorrhagic) • Depression • Anxiety • Brain tumours	Brain MRI	• Mini-mental state examination • Neuropsychological battery (verbal memory, visuospatial memory and organization, visual scanning, motor speed, new learning, abstract reasoning and naming)	• Apolipoprotein E • β-Amyloid • Clusterin • Tau • Brain-derived neurotrophic factor • β-Nerve growth factor
Heart	• Heart failure • Myocardial infarction • Coronary insufficiency • Angina • Atrial fibrillation • Bundle branch block and atrioventricular block • Valvular disease	• Cardiac CT • Chest radiography • Echocardiography • Cardiac MRI	• Cardiac auscultation • Electrocardiography • Holter monitoring • Echocardiography • Cardiac MRI • Exercise stress testing	• B-type natriuretic peptide • N-terminal atrial natriuretic peptide • Troponin I (high-sensitivity assay) • Soluble ST2
Large arteries	• Intermittent claudication • Aortic aneurism • Aortic dissection	• Abdominal ultrasonography • Aorta CT	• Carotid ultrasonography • Carotid–femoral pulse wave velocity • Blood pressure • Peripheral artery tonometry	• Matrix metalloproteinases • Homocysteine • Renin–aldosterone • Cholesterol (total, HDL, LDL and VLDL) • Lipoprotein(a) • Apolipoprotein subfractions (A1, B48, B100, CI, CII, E, H and J) • Myeloperoxidase • Chemokines: monocyte chemoattractant protein 1
Small arteries	• Raynaud phenomenon • Microvascular bleeds in brain	Brain MRI	Flow-mediated dilatation	• Exhaled nitric oxide • Vascular endothelial growth factor A and its receptor • Asymmetric and symmetric dimethylarginine
Venous system and haemostasis	• Deep-vein thrombosis • Pulmonary embolism	Physical examination (varicose veins)	NA	• D-dimer • Fibrinogen • Clotting factor VIII • von Willebrand factor • Plasminogen activator inhibitor 1 • Platelet reactivity • Isoprostanes • Lipoprotein-associated phospholipase A2 mass and activity • Osteoprotegerin • Selectins (P-selectin and CD40 ligand)
Lungs	• Asthma • Chronic obstructive pulmonary disease • Emphysema • Allergy • Pulmonary fibrosis	• Chest radiography • Chest CT	Pulmonary function test (spirometry)	Immunoglobulin E

Table 2 (cont.) | **Phenotypes from different organ systems collected in the Framingham Study**

Organ	Diagnoses	Anatomical tests	Functional tests	Circulating biomarkers
Musculoskeletal system	• Osteoporosis • Fractures	• Knee radiography • Bone mineral density • Dual-energy X-ray absorptiometry (whole-body and regional) • Bone CT	• Gait speed • Muscle strength	NA
Liver	• Hepatitis • Non-alcoholic fatty liver disease • Cirrhosis • Cancers • Gallstone disease	• Liver CT • Physical examination (liver enlargement)	NA	• Alanine aminotransferase • Aspartate transaminase • Alkaline phosphate • Bilirubin • γ-Glutamyl transferase and its subfractions
Kidney and urinary tracts	• Chronic kidney disease • Kidney stone • Cancers	Kidney CT	Spot urine (albumin content, haematuria)	• Creatinine • Cystatin C • Uric acid

NA, not applicable.

and total brain volume and white matter hyperintensities; and the association between these measures of subclinical brain damage and the incidence of clinical dementia[57,134–139].

The importance of social networks for developing unhealthy lifestyle habits has also been investigated in the FHS by leveraging participant-level data on friends and family. Christakis and colleagues reported in 2007 and 2008 that both obesity and smoking habits cluster in social networks within the FHS and that smoking cessation and spread of obesity tend to happen in groups of interconnected people[140,141]. Later reports highlighted that food choices also cluster in social networks[142], and friends tend to resemble each other genetically[143].

The FHS has also been at the cutting edge of genomic research over the past 15 years (FIG. 3). The FHS was among the first epidemiological cohorts to have genome-wide single-nucleotide polymorphism (SNP) data through the 100 K Project (Affymetrix 100 K GeneChip), which was quickly followed in 2007 by the Framingham SNP Health Association Resource (SHARe) initiative[144]. The SHARe initiative was one of the early leading studies contributing data to the formation of the National Center for Biotechnology Information (NCBI) Database of Genotypes and Phenotypes (dbGaP), and the FHS remains one of the largest contributors of data. Subsequently, genome-wide chips with more densely genotyped data (Affymetrix Gene Chip 500 K Array Set and 50 K Human Gene Focused Panel) were also introduced at the FHS, as well as the Illumina Omni 1 M Array in the Offspring cohort, the Affymetrix Biobank 600 K Array Set in the Omni 1 and Omni 2 cohorts and the Illumina Exome BeadArray in the Offspring and Third-Generation cohorts.

A subset of Framingham cohort DNA samples were sequenced in the National Heart, Lung, and Blood Institute (NHLBI) Grand Opportunity Exome Sequencing Project (GO-ESP)[145], yielding de novo variant information that was critical in the design of exome arrays and utilized in Framingham genetic studies[146–150]. These data have been used in numerous collaborative publications through various consortia, such as the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE). As part of the CHARGE consortium, multiple traits and measures have been studied in the FHS — several genetic variants have been associated with a range of traits, such as blood pressure, BMI and other vascular risk factors, CHD, atrial fibrillation, aortic stenosis, chronic kidney disease, dementia and longevity[151–159].

The FHS has additionally measured other 'omics' data types to fuel additional research avenues and integrative data analytics. These have included genome-wide DNA methylation measurements in the Offspring and Third-Generation cohorts. Genome-wide gene expression (RNA) levels (in whole-blood samples) by microarrays have been measured in the Offspring and Third-Generation cohorts, as well as large-scale quantitative real-time PCR RNA measurements in leukocytes and platelets. These methylation and RNA data have provided new insights into the genetics and causal mechanisms for numerous loci[160–170]. Proteomics and metabolomics panel studies have been conducted on both the Offspring and Third-Generation cohorts. These studies have led to additional functional studies of various genes and pathways[171–179]. In addition to a better understanding of the risk factors for disease, these omics data might also contribute to identifying potential drug targets.

Since 2014, the FHS has been obtaining whole-genome sequences of 4,100 individuals across the three generations as part of the Trans-Omics for Precision Medicine (TOPMed) programme of the NHLBI, which will improve our understanding of the genetic contributions

Box 2 | **FHS criteria for HF diagnosis**

A diagnosis of heart failure (HF) requires two major, or one major plus two minor criteria:

Major criteria

- Hepato-jugular reflux
- Neck-vein distension (non-supine position)
- Increased venous pressure (>16 cm H_2O from right atrium)
- Paroxysmal nocturnal dyspnoea
- Rales in the presence of unexplained dyspnoea
- Acute pulmonary oedema in hospital records
- A third heart sound (S3, ventricular gallop)
- Increased circulation time (>24 s from arm to tongue)
- Cardiomegaly and pulmonary hilar congestion at radiography or increasing heart size
- Autopsy with evidence of pulmonary oedema or cardiomegaly

Minor criteria

- Ankle oedema
- Night cough
- Tachycardia (heart rate >120 bpm)
- Pleural effusions
- Hepatomegaly
- Dyspnoea on exertion
- Decreased vital capacity by one-third from maximum records

FHS, Framingham Heart Study.

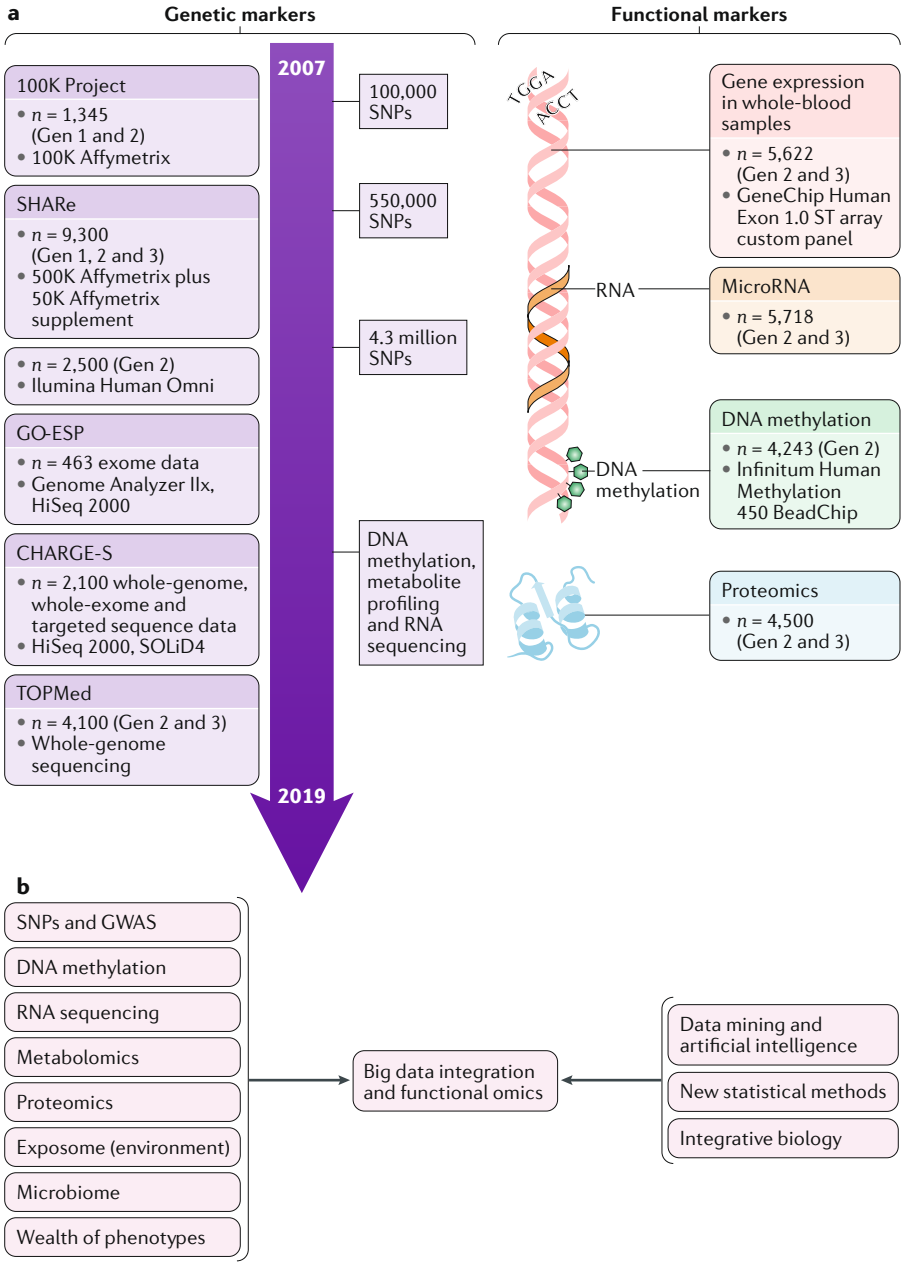

Fig. 3 | **Temporal developments in molecular epidemiology in the Framingham Heart Study.** **a** | The timeline shows the collection of genomic data in the Framingham Heart Study with details of specific projects and measurements. **b** | The future of molecular epidemiology involves the integration of multiple measurements and data sources to enhance our biological understanding of risk factors and disease processes. CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; GO-ESP, Grand Opportunity Exome Sequencing Project; GWAS, genome-wide association study; SHARe, SNP Health Association Resource; SNP, single-nucleotide polymorphism; TOPMed, Trans-Omics for Precision Medicine.

to common diseases. Having extensive genetic data on participants raises the possibility of finding clinically actionable results and the potential to return this information to participants and care providers. The FHS has been one of the cohort studies at the forefront of addressing this issue and has initiated some limited notification of research participants[180–183].

In the past 5 years, the concept of electronic epidemiology has been introduced to the FHS through the Behavioural Economics Framingham Incentive Trial (BE FIT)[184]. In this first proof-of-concept study, a sample of 200 participants from the FHS was randomly assigned (1:1) to placebo or 12 weeks of personal electronic input to increase their physical activity levels, which seemed to work (the intervention group significantly increased their physical activity levels compared with the control group)[184]. A preliminary survey indicated that e-epidemiology might be feasible in the FHS, with 87% of the 80% responders reporting regular Internet use[185]. Currently, apps for the iPhone and Android devices have been developed in which participants can take some of the planned FHS research clinic visit examination questionnaires online after attendance at the research clinic and provide values of heart rate, activity and blood pressure measured in ambulatory settings (e-FHS).

Future directions

The FHS has been one of the most important studies for cardiovascular health worldwide. The firm establishment of hypertension, dyslipidaemia, smoking and diabetes as risk factors for CVD spurred randomized, controlled clinical trials that led to the subsequent development and implementation of effective treatments for these conditions. The targeted reduction in risk factors has translated into a significantly lowered incidence of various CVDs in the Western world[186]. However, despite both physical inactivity and obesity being identified as important precursors of CVD as early as the 1970s, these two risk factors remain major challenges that need to be addressed in the future. Preliminary reports on young individuals in the Western world further suggest that the risk of CVD might again be rising owing to increasingly adverse and unhealthy lifestyle habits[187]. Further studies aiming to address how these adverse trends in obesity, physical inactivity and diabetes can be reversed remain, therefore, a major research priority.

Although the FHS is still important in these regards, with the changing demographics of the USA, a changing epidemiology of CVD and the formation of so-called mega-cohorts, the role of the FHS has changed over the past 70 years. Nonetheless, the FHS remains a lodestar for epidemiological cohort studies, for understanding the trends in risk factors and disease (owing to its long duration and thorough adjudication of end points, unlike many mega-cohorts, which often are based on registry data) and for understanding what can be done to lower the risk and burden of CVD. Furthermore, the FHS has been and will continue to be an important institution to train CVD epidemiologists, biostatisticians and bioinformaticians (the FHS has trained >90 fellows over the past three decades).

Moreover, by virtue of rich and deep phenotyping across its generations and the specialization in CVD risk factors and overt

disease, the FHS is of major importance in the field of molecular epidemiology (FIG. 3). Owing to the dedication of its participants, staff and investigators, the FHS will also be an important contributor to the further development and implementation of e-epidemiology. New efforts are indeed ongoing to expand and leverage the trans-omics FHS database for systems biology analyses, evaluation of the stool microbiome and electronic surveillance of the FHS participants. Additional new data are also currently being collected on cardiopulmonary exercise testing, which will contribute to expanding our mechanistic understanding of the central role of cardiopulmonary interactions in the development of various forms of CVD, including heart failure.

Conclusions

The field of CVD epidemiology has changed substantially over the past few decades, and the FHS has adapted and embraced these changes, along with other sister cohorts. An increasing amount data from various cohorts is currently being made available via major data repositories, making access to data by investigators not formally affiliated with the FHS much easier. The Cross-Cohort Collaboration Consortium and other consortial efforts have also formed, such as the CHARGE consortium[151]. These collaborations are likely to be of increasing importance as they increase statistical power, replicate major results and elucidate heterogeneity of associations between different cohort studies that might indicate inherent differences in study sample, partly related to different calendar periods of observations, varying geospatial locations and diverse ethnic composition. Data are available to researchers worldwide through the dbGaP (intended for genetic and genomic studies) and the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC; intended for non-genomic epidemiology). The FHS is one of the most densely phenotyped cohorts and is the NIH-funded cohort to which most researchers have access. We strongly encourage and welcome researchers to use the wealth of data available in the FHS to answer their research questions.

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