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Cohort Profile

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Cohort Profile: The Framingham Heart Study (FHS): overview of milestones in cardiovascular epidemiology

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Abstract

The Framingham Heart Study (FHS) has conducted seminal research defining cardiovascular disease (CVD) risk factors and fundamentally shaping public health guidelines for CVD prevention over the past five decades. The success of the Original Cohort, initiated in 1948, paved the way for further epidemiological research in preventive cardiology. Due to the keen observations suggesting the role of shared familial factors in the development of CVD, in 1971 the FHS began enroling the second generation cohort, comprising the children of the Original Cohort and the spouses of the children. In 2002, the third generation cohort, comprising the grandchildren of the Original Cohort, was initiated to additionally explore genetic contributions to CVD in greater depth. Additionally, because of the predominance of White individuals of European descent in the three generations of FHS participants noted above, the Heart Study enrolled the OMNI1 and OMNI2 cohorts in 1994 and 2003, respectively, aimed to reflect the current greater racial and ethnic diversity of the town of Framingham. All FHS cohorts have been examined approximately every 2–4 years since the initiation of the study. At these periodic Heart Study examinations, we obtain a medical history and perform a cardiovascular-focused physical examination, 12-lead electrocardiography, blood and urine samples testing and other cardiovascular imaging studies reflecting subclinical disease burden.

The FHS has continually evolved along the cutting edge of cardiovascular science and epidemiological research since its inception. Participant studies now additionally include study of cardiovascular imaging, serum and urine biomarkers, genetics/genomics, proteomics, metabolomics and social networks. Numerous ancillary studies have been established, expanding the phenotypes to encompass multiple organ systems including the lungs, brain, bone and fat depots, among others. Whereas the FHS was originally conceived and designed to study the epidemiology of cardiovascular disease, it has evolved over the years with staggering expanded breadth and depth that have far greater

implications in the study of the epidemiology of a wide spectrum of human diseases. The FHS welcomes research collaborations using existing or new collection of data. Detailed information regarding the procedures for research application submission and review are available at [http://www.framinghamheartstudy.org/researchers/index.php].

Study rationale

By the middle of the past century, the rise in the prevalence of CVD in the USA necessitated a systematic investigation into its aetiological factors and its prevention and treatment. Given that CVD has a prolonged subclinical phase of development lasting years, a prospective observational cohort study was considered ideal for the investigation of these conditions. In 1948, the National Heart Institute (later to become the National Heart, Lung and Blood Institute) chose the town of Framingham, Massachusetts, to conduct an epidemiological study, as it had responded favourably to a tuberculosis screening project.[1] The primary goal was to identify determinants of CVD to guide public health prevention. Whereas the initial goal was to invite individuals rather than family members free of prevalent CVD, the latter strategy was employed at the request of the then FHS Executive Committee to maintain goodwill among the families in the community.[2] Of note, nearly equal numbers of women and men were enrolled into the FHS at its very outset, thereby facilitating a scientific enquiry into the epidemiology of CVD in both sexes and contributing to our understanding of the sex-related differences in manifestations and prognosis of CVD. Studies from the Original Cohort, which identified risk factors and the natural history of specific cardiovascular diseases, defined and established the role for the emerging field of cardiovascular epidemiology.

Following the successful enrolment of the Original Cohort and the initial major scientific reports emanating from a careful longitudinal study of its participants, progression towards examination of another wave of participants was natural. Emerging evidence suggested aggregation of CVD traits, including blood pressure, within families. With enrolment of family members in the Original Cohort, subsequent enrolment of their children as part of the FHS Offspring Cohort was deemed advantageous for studies investigating the familial clustering of CVD phenotypes and the role of shared environmental factors versus genetic factors in contributing to such aggregation. The investigations of the Offspring Cohort have similarly led to substantial scientific productivity and have further provided newer insights into CVD risk factors and related familial and non-familial associations.

As the FHS evolved over several decades, a Third Generation cohort was recruited. By the 1980s, the heritability of many CVD traits was demonstrated, but the genetic basis for such inheritance was poorly understood. The completion of the Human Genome project provided additional impetus for studying the genetic bases of CVD. Thus, a primary goal for enrolment of a third generation into the FHS was to increase the number of family members in order to study inheritance patterns and genetic determinants of CVD, using novel, state of the art methods including genome-wide association studies. Additional goals for recruitment of a young Third Generation cohort were to study subclinical CVD earlier in adulthood using novel cardiovascular imaging and to evaluate temporal trends in CVD and its risk factors. The three-generational FHS structure is unique among CVD epidemiology studies and has provided greater statistical power in genome wide association studies.

During its long course, FHS has nearly continuously received funding from the National Institutes of Health (NIH, core contract) and is administered by Boston University staff and investigators. Additionally, its investigator-led ancillary studies are supported by multiple sources, including multiple institutes within the NIH, the American Heart Association, the American College of Cardiology and various other medical societies and foundations.

Description of the FHS

The FHS was the first longitudinally-followed large cohort to study CVD epidemiology in the USA, now including a multigenerational community-based cohort of free-living adults. In 1948, FHS investigators sent invitation letters based on a random sampling of two of every three families with members aged 30–59 years, living in the town of Framingham, Massachusetts. Of 6507 contacts, 4494 (69%) men and women agreed to participate and an additional group of volunteers ($n = 715$) also joined, for a total of 5209 ($n = 2336$ men and 2873 women) constituting the Original Cohort.[3] As noted above, to further investigate the role of heritability of CVD and related risk factors, interest lay in study of the next generation of participants. In 1971, the 2656 children of the 1644 husband-wife pairs in the Original Cohort, a group of children of Original Cohort members with coronary disease ($n = 899$)

and the spouses of these groups of children ($n = 1212$ and 368, respectively), were enrolled in the Offspring Cohort (total $n = 5124$).[4] The Third Generation Cohort was then begun in 2002, with the objective of expanding the phenotypic and genotypic spectrum for the study of CVD.[5] For this cohort, adults who were at least 20 years of age with at least one parent in the Offspring Cohort were invited to participate, with preference given to larger families. Of 6553 eligible individuals, 4095 participants were enrolled. To add to familial data, 103 parents of Third Generation participants who were not previously enrolled in the Offspring Cohort were enrolled as the New Offspring Spouses Cohort.

Finally, the town of Framingham and surrounding community have increased in ethnic and racial diversity over the several decades since enrolment of the Original Cohort. Thus, the OMNI cohort, including individuals of African American, Hispanic, Asian, Indian, Pacific Islander and Native American descent, was begun in 1994, enrolling 506 participants. In 2003, a second OMNI cohort was initiated, enrolling 410 ethnically and racially diverse adults, some of whom were family members of those in the first OMNI cohort. Figure 1 displays enrolment and follow-up of the cohorts. Table 1 shows the demographic characteristics of the cohorts, including the superb follow-up of nearly the entire sample. Additional details of age and sex distributions of each cohort at study entry are available at [http://www.framinghamheartstudy.org/participants/index.php].

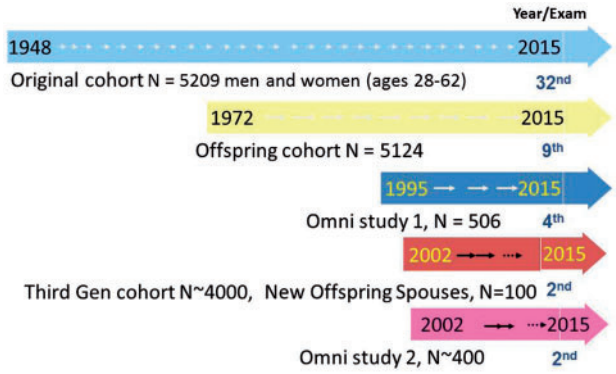

Figure 1. Time course of enrolment of the cohorts within the FHS. The FHS is a multigenerational longitudinally followed cohort spanning the spectrum of age. Numbers at arrows indicate most recent year of examination cycle (e.g. 32nd examination cycle for Original cohort). Figure from Benjamin I *et al. Circulation* 2015;**131**:100–12. Reprinted with copyright permission.

Cohort follow-up

Every 2–6 years, in-person examinations (referred to as exam cycles) are conducted for each FHS cohort (Table 1). Examination visits include: obtaining written informed consent; documentation of a detailed medical and family history, review of all medicines and supplements, and cardiovascular-targeted physical examination (all administered by a physician); measurement of anthropometric data, 12-lead electrocardiography, neurocognitive battery (including a 'mini mental state' examination questionnaire administered by staff), collection of blood and urine and participation in on-site ancillary studies, all within a 4-h window typically. For locally residing participants who are unable to return for an on-site examination (e.g. elderly, home- or nursing home-bound), staff members travel to the participants to administer the components of the cycle visit. FHS staff routinely contact all medical offices and hospitals to obtain primary results on participants regarding their medical diagnoses and testing (all authorized by the informed consent provided by the participants). Additionally, in between cycle examinations, interim questionnaires detailing updates of medical and family history are mailed, and information is obtained via regular phone calls, thereby maintaining continuous surveillance of the participants. Though originally recruited from the communities in and around Framingham, Massachusetts, FHS participants now reside worldwide. The 99% retention rate of participants regularly returning for scheduled

Table 1. Characteristics of FHS cohorts

Cohort	Total, *n*	DNA, *n*	Ancestry, %					Year recruited	Age, years	Follow-up		
			EA	AA	HA	AsA	Other			Examinations, *n*	Intervals, *n*	Duration, years
Original	5209	971	100	0	0	0	0	1948–53	28–74	32	2	65
Offspring (and spouses)	5124	3930	100	0	0	0	0	1971–75	5–70	9	4–8	43
Third Generation	4095	4077	100	0	0	0	0	2002–05	19–72	2	6	≈ 10
Offspring Spouses	103	101	100	0	0	0	0	2003–05	47–85	2	6	≈ 10
Omni 1 Cohort	507	493	0	28	42	24	6	1994–98	27–78	4	4–8	≈ 15–20
Omni 2 Cohort	410	407	0	28	42	24	6	2003–05	20–80	2	6	≈ 10

AA, African American; AsA, Asian American; EA, European American; HA, Hispanic American.
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examinations at FHS is a testament to the dedication of the participants to the study and contributes to the high quality of the study.

Phenotypes and outcomes measured

The FHS has collected a broad range of CVD phenotypes including biomarkers measured in blood (encompassing traditional CVD risk factors to novel biomarkers, genetics and 'omics') and urine, imaging tests, vascular function tests and adverse clinical outcomes. Extra-cardiovascular phenotypes span numerous organ systems, including the brain, lungs, bone, metabolic/fat and kidneys. Additionally, demographic and socioeconomic data are collected, and innovative integration of residence with pollution data allows for study of the impact of inhaled particles and pollutants on cardiovascular health.[6] Tables 2 and 3 list phenotypic measures and outcomes assessed in each cohort. Specific details of measured phenotypes and the years of examination may be downloaded at [http://www.framinghamheartstudy.org/researchers/description-data/index.php]. The FHS has established standardized criteria for its outcomes, including coronary heart disease (myocardial infarction, angina), congestive heart failure, cardiovascular disease, atrial fibrillation, stroke, transient ischaemic attack, claudication, cardiovascular death and all-cause death. Adjudication of outcomes occurs weekly with a three-physician endpoints review committee, which reviews all medical records.

Findings and contributions

Traditional risk factors in CVD

Over the past several decades, findings from the FHS have been pivotal in advancing our understanding of the epidemiology of CVD. In the initial 1957 study reporting 4-year follow up of Original Cohort participants, Dr Roy Dawber, one of the founding fathers of FHS, first identified the contributions of three key modifiable risk factors in CVD: blood pressure, overweight and cholesterol (Table 4).[7] Subsequently, use of the term 'risk factors' spread following its use in one of the FHS seminal publications, 'Factors of risk in the development of coronary heart disease'.[8] This landmark report remains one of the most enduring studies in the field of cardiovascular epidemiology. Published in 1961 by Dr William Kannel, subsequent FHS director, this report first described the coronary heart disease risk associated with age, male sex, hypertension, elevated cholesterol, diabetes and electrocardiographic left ventricular hypertrophy.

A major asset of FHS has been its serial examinations of participants, aiding the longitudinal tracking of many CVD risk factors prior to overt disease. The FHS characterized these key CVD risk factors in depth in subsequent publications. Early reports described changes in blood pressure with age,[9] and established that hypertension was not benign or compensatory, as previously thought, nor was a rise in blood pressure with age a 'normal' phenomenon. Rather, hypertension was associated with numerous CVD outcomes, including coronary artery disease,[10] stroke,[11] congestive heart failure,[12,13] peripheral arterial disease[14] and atrial fibrillation.[15] Additionally, the FHS elucidated that the primary morbidity related to hypertension was more strongly associated with systolic, rather than diastolic, blood pressure,[16] that even borderline isolated systolic hypertension and high normal blood pressure were associated with significant morbidity[17] and that blood pressure treatment was associated with a reduction in CVD mortality (demonstrated first in randomized clinical trials).[18] Furthermore, the risk associated with a given blood pressure varied widely depending on the presence of other CVD risk factors,[19] thereby introducing the concept of multivariable risk, a precursor of risk prediction algorithms.

As phenotyping at FHS advanced to include echocardiography, assessment of left ventricular mass—a more sensitive measure of left ventricular hypertrophy (LVH)—became possible. The FHS investigators reported that echocardiographic LVH was associated with greater age, blood pressure and obesity, among other CVD risk factors.[20] Moreover, echocardiographic LVH predicted coronary disease, CVD death and all-cause mortality, beyond the risks conferred by standard CVD risk factors.[21,22] LV remodelling occurs in response to long-term exposure to CVD risk factors and haemodynamic changes, and the FHS has also elucidated the prognostic importance of geometric patterns[23] and change in these patterns,[24] independently of CVD risk factors and LV mass.

The study of lipids in the general population has been another key contribution of FHS. In 1965, the FHS laboratory began separating serum lipoproteins into fractions by ultracentrifugation. In 1971, the FHS published its earliest study relating circulating lipid fractions to the risk of developing coronary disease.[25] Subsequent analyses revealed the prognostic implications of low-density lipoproteins (LDL), high-density lipoproteins (HDL) and the total cholesterol-to-HDL ratio, the latter of which would be a component of the Framingham Risk Score.[26,27] Additionally, lipoprotein particles other than cholesterol, including lipoprotein(a), were found to be associated with CVD independently of LDL and HDL.[28] Studies from FHS suggest the importance of serum cholesterol in the prediction of CHD incidence, and also occurrence of both CVD and all-cause mortality across the age spectrum.[29,30] Leveraging use of repeated measures, FHS investigators also showed that time-averaged lipid measures were more

Table 2. Phenotypic data collected in FHS

Phenotype data	Examples
Clinical events (validated and adjudicated)	Coronary heart disease: myocardial infarction, coronary insufficiency, angina, coronary heart disease death, sudden coronary disease death, coronary artery bypass surgery, percutaneous transluminal coronary angiography
	Heart failure
	Stroke, transient ischaemic attack
	Peripheral arterial disease: intermittent claudication, lower extremity revascularization
	Atrial fibrillation, electrophysiology procedures
	Dementia (Alzheimer's disease, vascular)
	Mild cognitive impairment
	Cancer
Subclinical disease (most measures repeated)	Ultrasound carotid intima-media thickness and carotid stenosis
	Brachial reactivity/endothelial function
	Tonometry: arterial stiffness and peripheral arterial tonometry
	Echocardiographic structure and function (e.g. left ventricular mass)
	CT: coronary artery calcium, abdominal aortic calcium, mitral and aortic valve calcium
	Cardiac MRI: cardiac structure, cardiac index, aortic arch plaque
	Ankle-brachial index
	Walk test: low-level exercise test
	Brain MRI: including grey, white, lobar/deep volumes, infarcts, microbleeds, white-matter hyperintensities, fractional anisotropy, regional brain volumes
Pulmonary disease and sleep traits (pulmonary function test data available on multiple examinations)	Spirometry and post-albuterol spirometry, diffusion capacity
	CT lung measures
	Sleep study and questionnaire
	Buccal swabs
Traditional risk factors (directly measured)	Systolic and diastolic blood pressure
	Fasting blood glucose, haemoglobin A1c, fasting insulin
	Fasting lipids
Anthropometry (directly measured)	Height, weight, body mass index
	Waist, hip, thigh, neck circumference
	CT measures of regional adipose tissue depots: subcutaneous adipose tissue, visceral adipose tissue, pericardial fat, perithoracic fat
	Body percent fat (dual-energy X-ray absorptiometry)
Lifestyle	Diet: Willet food frequency questionnaire (calories, supplements)
	Smoking
	Exercise (self-report, objective measurement with accelerometry)
	Alcohol intake
Measures of function	Physical function and mobility
	Performance: hand grip, walking speed
	Cognitive function (global and multiple domains)
	Depression (Center for Epidemiologic Studies Depression Scale)
	Social network
Medications	All examinations
Medicare data	Centers for Medicareand Medicaid Services data since 1991 including *International Classification of Diseases* codes, charges, medications, procedures on individuals aged $\geq$ 65 years enrolled in fee for service
Bone health	Fractures, osteoporosis
	Osteoarthritis
Circulating and urine biomarkers	
Renal function	Creatinine, cystatin C, microalbumin, uric acid
Inflammatory marker panel	Acute phase reactants: C-reactive protein
	Cytokines: interleukin-6, tumour necrosis factor-α, tumour necrosis factor receptor 2, osteoprotegerin
	Selectins: P-selectin, CD40 ligand
	Cell adhesion: intercellular adhesion molecule

(Continued)

Table 2. Continued

Phenotype data	Examples
	Chemokines: monocyte chemoattractant protein-1
	Oxidative stress: myeloperoxidase, isoprostanes
	Lipoprotein-associated phospholipase A2 mass and activity
Markers of haemostasis, thrombosis	Fibrinogen, factor VIIIc, von Willebrand factor, D-dimer, plasminogen activator inhibitor-1, platelet reactivity
Markers of myocardial injury	Troponin I, growth differentiation factor-15, ST-2, brain natriuretic peptide, N-terminal atrial natriuretic peptide
Adipokines	Leptin, leptin receptor
	α-fetuin, resistin, ghrelin
	Retinol binding protein-4
	Fatty acid binding protein-4
	Adiponectin
Growth factors	Insulin-like growth factor-1, insulin-like growth factor binding protein-3, vascular endothelial growth factor angiopoietin-2, brain-derived neurotrophic factor, nerve growth factor
Molecules interacting with vessel wall and platelets	Matrix remodelling markers: matrix metalloproteinase-9, matrix metalloproteinase-3, tissue inhibitor of matrix metalloproteinase-1, N-terminal propeptide of type III procollagen
	Plasma homocysteine, asymmetric dimethylarginine
Markers of brain injury	Beta-amyloid, clusterin
Lipid subfractions	Lipoprotein(a), apoliproteins A1, B48, B100, CI, CII, E, H, J
Hormones and vitamins	Renin-angiotensin-aldosterone pathway
	Thyroid function (e.g. thyroid-stimulating hormone)
	Sex steroid hormones
	Vitamin D, folate, B_{12}, B_6, Vitamin E

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Table 3. Summary of measured phenotypes and outcomes in the FHS by cohort

Phenotype measured	Cohort					
	Original	Offspring	New Offspring spouse	Third Gen.	OMNI 1	OMNI 2
History						
Medical history	x*	x*	x*	x*	x*	x*
Medicines	x*	x*	x*	x*	x*	x*
Social history	x*	x*	x*	x*	x*	x*
Family history	x*	x*	x*	x*	x*	x*
Symptoms	x*	x*	x*	x*	x*	x*
Questionnaires						
Diet	x*	x*	x*	x*	x*	x*
Sleep habits	x*	x*	x*	x*	x*	x*
Physical activity	x*	x*	x*	x*	x*	x*
Menarche, menopause		x				
Physical examination						
Anthropometric	x*	x*	x*	x*	x*	x*
Blood pressure	x*	x*	x*	x*	x*	x*
Eye examination	x*	x*	x*	x*	x*	x*
Hearing test	x*	x*	x*	x*	x*	x*
12-lead ECG	x*	x*	x*	x*	x*	x*
Serum						
Chemistries	x*	x*	x*	x*	x*	x*
Haemoglobin A1c	x*	x*	x*	x*	x*	x*

(Continued)

Table 3. Continued

Phenotype measured	Cohort					
	Original	Offspring	New Offspring spouse	Third Gen.	OMNI 1	OMNI 2
Complete blood count	x*	x*	x*	x*	x*	x*
Lipids	x*	x*	x*	x*	x*	x*
Lipid particles, characteristics		x		x		
Biomarkers: inflammatory, metabolic	x*	x*	x*	x*		
Genetic	x	x*		x*		
Metabolomics		x		x		
Proteomics		x				
Hormones: thyroid, sex, renal	x	x		x		
Urine						
Chemistries	x*	x*	x*	x*	x*	x*
Cardiovascular imaging						
Chest X-ray	x*					
Echocardiography	x*	x*	x*	x*	x	x
Cardiac MRI		x			x	x
Cardiac CT		x*	x*	x*		
Carotid ultrasound		x*				
Vascular						
Applanation onometry	x	x*	x*	x*		
Peripheral arterial tonometry	x	x*	x*	x		
FMD		x*	x*	x		
Chest and abdominal CT: fat		x*	x*	x*		
Physical activity						
Gait speed	x*	x*	x*	x*	x*	x*
Accelerometry		x				
Neurological						
Mini mental status examination	x*	x*				
Neuropsychological battery	x*	x*	x*	x*	x*	x*
Brain MRI	x	x*		x*		
Pulmonary						
Pulmonary function tests	x	x*	x*	x*	x*	x*
Chest CT: lung measures		x*		x*	x*	x*
Musculoskeletal						
Knee X-ray	x	x				
Bone mineral density		x		x*		
Whole-body and regional DXA				x		
Quantitative CT: volumetric bone density		x		x		
Muscle strength		x		x		
Sleep study		x*				
Autopsy	x	x				

FMD: flow mediated dilation.
*Serial measures available.

associated with subclinical atherosclerosis measured by computed tomography than with single-point measures.[31]

During the first two decades of the study, evidence of the association between diabetes and coronary disease had accumulated. The FHS confirmed this association and extended these observations in several directions. Study of Original Cohort members with diabetes revealed greater risk for coronary heart disease, heart failure, stroke and peripheral arterial disease compared with individuals without diabetes.[32] Notably, risks for CVD and morbidity/mortality following the onset of CVD were greater for women than men with diabetes.[32,33] In participants without diabetes, the FHS also demonstrated the role of elevated blood glucose, measured by haemoglobin A1c, in mediating CVD risk,[34] and an extension of the pattern of greater CVD risk in women in this group as well.[35]

Table 4. Incidence of atherosclerotic heart disease in follow up of FHS males aged 45-62, by blood pressure, relative weight, and cholesterol levels

Attributes			Population at Risk			
Blood pressure	Relative weight	Total cholesterol	No.	Percent	New disease	Rate/1000
All persons*			877	100	51	58
High on two or more			105	12	15	143
High	High	High	17		5	
High	High	Med. or low	47		3	
High	Med. or low	High	20		1	
Border. or normo.	High	High	21		6	
High on one only			290	33	23	79
High	Med. or low	Med. or low	91		9	
Border. or normo.	High	Med. or low	87		5	
Border. or normo.	Med. or low	High	112		9	
Border or medium on two or more			186	21	7	38
Borderline	Medium	Medium	48		4	
Borderline	Medium	Low	63		–	
Borderline	Low	Medium	42		3	
Normotension	Medium	Medium	33		–	
Border or medium on one only			198	23	5	25
Borderline	Low	Low	89		2	
Normotension	Medium	Low	54		1	
Normotension	Low	Medium	55		2	
Normotension or low			98	11	1	10
Normotension	Low	Low				

* Excludes 21 persons (one developing new disease) for whom measurements of one or more attributes were not available.
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Furthermore, FHS examinations include a comprehensive assessment of lifestyle factors, which allowed study of their implications for CVD risk. Indeed, cigarette smoking was shown to be associated with the risk of developing a myocardial infarction and of sudden death, with a significant reduction in the risk with smoking cessation.[36,37] Additionally, the FHS has demonstrated the risk of CVD associated with poor physical activity and dietary factors.[38,39] Connected with these lifestyle factors is the issue of overweight and obesity, whose associations with CVD were previously debated. FHS investigators demonstrated that excess body weight was associated with CVD risk factors and with CVD incidence independently of other CVD risk factors.[40–42] These collective findings formed a critical and foundational knowledge base to guide public health efforts in CVD prevention. That the central tenets of risk factors reported decades ago in 1961 remain the main modifiable CVD risk factors today, is a testament to the foresight and discoveries of the original FHS investigators and the contributions of FHS participants.

Epidemiology of specific CVD entities

In addition to the contributions towards understanding CVD risk factors, the FHS has also been instrumental in establishing the epidemiology of specific CVD subtypes. The FHS demonstrated much of the characteristics and prognosis surrounding myocardial infarction (MI), including its frequent presentation as sudden cardiac death,[43] and the high mortality associated with first MI, particularly in women.[44] FHS investigators also introduced the important concept that MI frequently is clinically unrecognized, and that mortality rates in recognized (by 12-lead electrocardiography) and unrecognized MI are similar.[43,45]

Heart failure has been and is remains a growing epidemic, perhaps even more so in our modern era of improvements in treatment of coronary disease and survival after MI. The FHS was one of the first groups to describe the incidence, prevalence and grim natural history of heart failure in the community[12,46,47] and also identified hypertension, valvular heart disease and coronary disease as key aetiologies for heart failure.[13] The advent of echocardiography made it evident that individuals with heart failure may have normal left ventricular systolic function measured by ejection fraction. The FHS was one of the first population studies to shed light on the entity of heart failure with preserved ejection fraction, which represents up to half of all clinical heart failure. Importantly, this disorder is more common in women, and confers morbidity

and mortality similar to that of heart failure with reduced ejection fraction, or classical systolic heart failure.[48] Additionally, that asymptomatic individuals with greater left ventricular dimensions[49] and even a mildly reduced ejection fraction[50] are at greater CVD risk compared with those with a normal LV ejection fraction, was also described by FHS investigators.

The FHS has advanced our understanding of numerous related cardiovascular conditions as well, including peripheral arterial disease, stroke and disturbances in heart rhythm. Early FHS studies described the natural history of peripheral arterial disease manifesting as lower extremity claudication,[51] and its predominant risk factor associations including diabetes[52] and smoking.[53] More recently, repeated 6-min walk testing has allowed examination of functional and haemodynamic response to exercise in relation to vascular disease.[54,55] Additionally, the FHS was pivotal in clarifying the relation of blood pressure[11] and smoking[56] with risk of stroke. Similarly to the FHS CVD risk estimations, the FHS risk scores for peripheral arterial disease[14] and stroke[57] have pervasive, widespread, clinical impact. FHS investigations have also shed light on the epidemiology and prognosis of heart rhythm abnormalities, including the identification of atrial fibrillation as a powerful risk factor for stroke and all-cause mortality.[58–60] This finding has significant public health implications, as atrial fibrillation is the most common chronic arrhythmia and likely to grow in prevalence with the ageing of the world population. FHS investigators established the epidemiology of the disorder, including its risk factors[15,61] and associated morbidity and mortality.[62] Furthermore, it is well-known that isolated electrocardiographic testing during routine examinations does not capture heart rhythm during regular activity. Ambulatory electrocardiographic monitoring has proved to be fruitful, linking the observations of reduced heart rate variability with incident CVD,[63] and incidental asymptomatic ventricular arrhythmias with coronary disease and mortality.[64]

Expansion of phenotypes: imaging, novel biomarkers, and the 'omics' era

Despite the significant advances however, many aspects of CVD pathophysiology remain incompletely understood, and clearly risk remains despite evaluation and treatment of the traditional CVD risk factors. Thus, a holy grail is the use of non-invasive methods through which biomarkers of CVD risk may be identified and related biological mechanisms uncovered. Advanced non-invasive cardiovascular imaging has been one such promising area to fill these needs. Echocardiography, computed tomography and magnetic resonance imaging have enhanced our understanding of age- and CVD-related ventricular remodelling and prevalence and consequences of subclinical atherosclerosis in different vascular territories.[24,65–67] Application of advanced techniques of imaging myocardial tissue mechanics in FHS[68] may further add to understanding of the development and implications of subclinical ventricular dysfunction. Additionally, non-invasive assessment of central and peripheral vascular disease in FHS have demonstrated that carotid intimal medial thickness,[69] ankle-brachial index,[70,71] endothelial function (brachial artery flow-mediated dilation), conduit arterial stiffness (via applanation tonometry)[72] and peripheral arterial tonometry are key correlates of CVD risk, and some of these measures are predictive of CVD risk and mortality and may improve CVD risk reclassification. Non-invasive imaging has also allowed investigation of cardiometabolic disease through evaluation of the quantity and characteristics (quality) of fat depots.[73,74] Finally, recognizing the strong links between cardiovascular and cerebrovascular disease, the current team of FHS investigations have also included detailed assessment of subclinical neurological disease using state of the art brain magnetic resonance imaging and meticulous cognitive assessments to identify subclinical injury.[75] Many of these imaging measures have been repeated in the same participants, allowing longitudinal tracking of these characteristics.

The FHS also has a large biorepository of participant data, including blood, urine and other biological samples, from which cutting-edge biomarker, genetic and 'omics' tools (transcriptomics, metabolomics, proteomics) have been harnessed. Numerous biomarkers have been evaluated in FHS participants (Table 2), and multiple biomarkers are related to CVD, including but not limited to metabolic disease,[76] cardiac structure and function,[77] heart failure [78] and mortality.[79] FHS 'omics' measures include DNA methylation, transcriptomics (describing whole-blood mRNA and microRNA expression), metabolites and protein biomarkers. Such efforts have identified potential targets in the pathophysiology of CVD,[80] including metabolic risk and diabetes[81,82] and coronary disease.[83]

The three-generation family structure and the selection of large pedigrees in FHS families are its major strengths, allowing substantial investigations of cardiovascular genetics. Smaller observational studies had suggested that CVD clustered in families, and FHS was one of the earlier studies to demonstrate the heritability of blood pressure,[84] lipids,[85] diabetes[86] and coronary disease.[87] In the 1990s and 2000s, FHS investigators collected DNA samples in the Original, the Offspring (including Offspring Spouses) and the Third Generation cohort members from whole blood. Immortalized lymphoblastoid cell lines obtained in 8458 participants serve as a valuable replenishable source of DNA.

The FHS has been a vital contributor to international collaborative efforts to identify the non-genetic and genetic underpinnings of CVD traits. FHS participants have contributed data on lipids and inflammatory markers for investigation as part of the Emerging Risk Factors Collaboration.[88] Additionally, the FHS has led efforts to identify variants in single-nucleotide polymorphisms (SNPs) associated with CVD. The FHS is part of the SNP Health Association Resource (SHARe)[89] and Candidate Gene Association Resource (CARe)[90] projects, through which ~9300participants underwent genotyping of 550 000 SNPs using the Affymetrix platform (SHARe) and > 7500 participants had genotyping of 50 000 SNPs using the Illumina Cardiochip (CARe). Imputation to 40 million SNPs was achieved using the 1000 Genomes project. FHS efforts have enabled the identification of SNPs for traits including blood pressure,[91–93] lipids,[94,95] obesity,[96] arterial stiffness[97,98] and imaging measures of cardiovascular function including ventricular mass and dimensions,[99,100] endothelial function,[99] valvular calcification[101] and carotid atherosclerosis.[102] In addition, FHS has pursued investigation of the exome through genotyping of ~ 200 000 exome variants using the Illumina V1.0 Exome Chip, and whole-exome sequencing in nearly 3000 participants from collaborations including the NHLVI's Grand Opportunity Exome Sequence Project[103] and CHARGE targeted Sequencing project.[104] Among others, these investigations have identified rare variants associated with diabetes[105] and lipids and coronary disease[106–108]. Furthermore, whole-genome sequencing is underway via the NHLBI TOPMed project,[109,110] highlighting the importance of regulatory and non-protein coding regions, in addition to the protein coding regions that have been common targets for investigation. Whereas many biomarker and genetic associations have been found, the mechanisms behind these associations are often elusive. Using network analysis, FHS investigators have begun to integrate these separate pieces of the puzzles together for analysing the epidemiology of CVD.[111–113]

In the modern era, FHS has continued to move forward with cutting-edge research, taking advantage of the technology evolution. In addition to advanced network analysis to understand genetic and mechanistic associations, complex social network analyses have enabled study of important social determinants of cardiovascular epidemiology, including trends in obesity and smoking.[114,115] The FHS is also applying mobile health technologies with evaluation of functional status with mobile, remote accelerometry monitoring,[116] and has integrated participant-level public electronic health records (e.g. Centers for Medicare and Medicaid Services), thus providing a rich source of comprehensive data. A chronological list of FHS publications can be found at [http://www.framingham heartstudy.org/fhs-bibliography/index.php].

Strengths and weaknesses

The strength of the FHS lies in the dedicated participants, its highly trained staff and its diverse body of scientific investigators over the years. The commitment of the participants to the study is reflected in the high retention rate, despite the fact that many participants live remotely. The FHS is also the only longitudinally followed cohort evaluating CVD risk across three generations of participants in whom extensive serial measurements have been obtained. The FHS has used standardized definitions to adjudicate CVD outcomes, including coronary heart disease and congestive heart failure, and these definitions have been applied consistently to the studies over the several-decade course of the study. The study has conducted meticulous phenotyping of participants (with a great emphasis on quality control issues including reproducibility), with numerous ancillary studies and measured phenotypes now spanning not only the cardiovascular system, but also including the brain, the lungs, the endocrine system, and the metabolic, gastrointestinal, renal and the musculoskeletal systems, to name a few. FHS participants are notably predominantly White individuals of Western European descent (with the exception of the OMNI cohorts). Thus, a more ethnically diverse group of individuals are reflected in the contemporary OMNI cohorts, and efforts to compare findings across ethnicities are being evaluated moving forward.

Conclusions

Whereas the FHS began as a study to identify aetiological factors for CHD and CVD and to improve the prevention of CVD, it has clearly evolved and expanded to encompass a 'near whole-body' study over several decades, the equivalent of a human phenome project. Application of novel technologies, integrative methods and multidisciplinary collaborations have fostered the expansion of FHS science over the years. Decades after its humble inception, the FHS remains at the forefront of not just cardiovascular, but also multisystem epidemiological research through the adult life course. With continued efforts, the FHS will continue to advance understanding of the human phenome for the next several decades to come.

Information and Data Access

The FHS website [www.framinghamheartstudy.org] contains further information for prospective investigators.

Detailed information regarding the research application and review are available at [http://www.framingham heartstudy.org/researchers/index.php]. The FHS welcomes research proposals using existing or new collection of data. In addition, phenotypes and genotypes generated in FHS are available publicly on dbGaP through the FHS link [http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000007.v26.p10]. Individuals wishing to pursue research using FHS genetic data should apply for authorization through dbGaP [https://dbgap.ncbi.nlm.nih.gov/aa/wga.cgi?page=login]. The FHS is a non-profit research entity that has relied upon core contract and ancillary study funding from individual investigators for sustainment. The FHS Service Center handles the modest additional fees for provision of data and materials, and administrative support; further information of the fee structure is available at [http://www.framingham heartstudy.org/researchers/service-center.php].

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Key Messages

Main scientific findings in cardiovascular epidemiology:

- identification of key risk factors, including lifestyle, biochemical and genetic risk factors for atherosclerotic CVD and its subtypes including stroke;
- combination of multivariable risk factors to generate a composite risk score that can be used in prediction algorithms;
- description of the epidemiology of specific CVD entities and cardiovascular remodelling across the age spectrum;
- identification of novel mechanisms of CVD, including but not limited to novel biomarkers and genetic factors and a systems biology approach towards the pathogenesis of CVD.

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