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The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: Design, Recruitment, and Initial Examination

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For nearly 60 years, the Framingham Heart Study has examined the natural history, risk factors, and prognosis of cardiovascular, lung, and other diseases. Recruitment of the Original Cohort began in 1948. Twenty-three years later, 3,548 children of the Original Cohort, along with 1,576 of their spouses, enrolled in the Offspring Cohort. Beginning in 2002, 4,095 adults having at least one parent in the Offspring Cohort enrolled in the Third Generation Cohort, along with 103 parents of Third Generation Cohort participants who were not previously enrolled in the Offspring Cohort. The objective of new recruitment was to complement phenotypic and genotypic information obtained from prior generations, with priority assigned to larger families. From a pool of 6,553 eligible individuals, 1,912 men and 2,183 women consented and attended the first examination (mean age: 40 (standard deviation: 9) years; range: 19–72 years). The examination included clinical and laboratory assessments of vascular risk factors and imaging for subclinical atherosclerosis, as well as assessment of cardiac structure and function. The comparison of Third Generation Cohort data with measures previously collected from the first two generations will facilitate investigations of genetic and environmental risk factors for subclinical and overt diseases, with a focus on cardiovascular and lung disorders.

atherosclerosis; cardiovascular diseases; cohort studies; epidemiologic research design; patient selection; physical examination; risk factors

Abbreviation: SD, standard deviation.

Cardiovascular diseases are complex traits that evolve over lifetimes under the influence of genetic and environmental factors. Studies of carefully characterized large families are invaluable for investigating genetic underpinnings of complex traits, such as cardiovascular diseases. In this context, Framingham Heart Study investigators recruited the Third Generation Cohort from 2002 to 2005. The purpose of recruitment of the Third Generation Cohort was to supplement pedigrees and expand observations on two Framingham Heart Study cohorts that are under continuous

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surveillance—the Original Cohort and the Offspring Cohort, that is, the first and second generations, respectively. Data provided by examinations and interviews of the Third Generation Cohort are expected to facilitate investigation of secular trends in risk factors and indicators of health and disease within families, to enhance statistical power to detect genetic and environmental determinants of complex diseases, and to clarify how subclinical cardiovascular disease predicts occurrence of overt clinical events.

The principal objectives for the recruitment of the Third Generation Cohort were as follows:

1. To identify genetic and environmental risk factors related to the development of cardiovascular, lung, and blood diseases in three generations of Framingham Heart Study participants.
2. To identify determinants of risk factors, subclinical and clinical manifestations of cardiovascular, lung, and blood diseases, over the life course.
3. To establish and make widely available to the scientific community a resource for genetic and nongenetic studies of disease using genetic and phenotypic data and DNA from the participants of the Third Generation Cohort, thereby supplementing previously available resources from the two prior cohorts.

To achieve these scientific objectives, the Framingham Heart Study investigators used the following steps: *identification* of children of Offspring Cohort participants; *dissemination* of study objectives to the community; *invitation* of eligible individuals for participation in a baseline examination; and *examination* of consenting participants. The clinical examination included collection of DNA and phenotypic traits from enrollees paralleling those already collected on the first two generations of study participants, including a medical history and physician-obtained physical examination with a focus on cardiovascular and pulmonary diseases. In addition, noninvasive imaging by echocardiography, vascular testing, and assessment of subclinical atherosclerosis were obtained. The present report summarizes recruitment goals, strategies, and rates of enrollment and participation in the first examination of the Third Generation Cohort, and it compares selected characteristics of three generations of participants from the initial examination of each.

MATERIALS AND METHODS

Background

The Framingham Heart Study was initiated by the US Public Health Service in 1948 to study the epidemiology and risk factors for cardiovascular disease (1). Study design and oversight were turned over to the National Heart Institute (today known as the National Heart, Lung, and Blood Institute) in 1949. The town of Framingham, located 20 miles (32.2 km) west of Boston, Massachusetts, was selected because it had been the site of a successful community-based tuberculosis study (2), and because of its proximity to medical research centers. Enrollment and examination of the Original Cohort of the Framingham Heart Study began in 1948; biennial examinations have followed since then. Twenty-three years later, the Offspring Cohort was added (3). Since 1971, clinical examinations of the Original Cohort and the Offspring Cohort were conducted and funded by National Institutes of Health contracts (currently NO1-HC-25195), according to protocols approved by the Boston University Medical Center Institutional Review Board.

Identification of Third Generation Cohort participants and eligibility criteria

Participants in the Offspring Cohort at their sixth and seventh examination cycles provided updated lists of names, relationships, residential addresses, telephone numbers, sex, and birth dates of their children by completing a family description form. The form clearly stated that information was being collected to prepare for the possibility of recruiting those named to participate in the Third Generation Cohort. Participants in the Offspring Cohort who did not attend either the sixth or seventh examination cycle were sent the form by mail or interviewed by telephone. Information obtained from these surveys was subsequently mailed to the Offspring Cohort participants for verification. In cases of deceased Offspring Cohort participants, Framingham Heart Study archives were reviewed to extract similar pedigree information, and contacts were made through other family members. Individuals were eligible for enrollment in the Third Generation Cohort if they were aged 20 years or older and had at least one parent who was a member of the Offspring Cohort.

Dissemination of study objectives in the community

Various outreach methods were used to inform potential Third Generation Cohort members, their parents, and grandparents about study objectives and recruitment plans. Newsletters were sent to Original Cohort and Offspring Cohort participants to generate interest, and a 50th anniversary celebration of the Framingham Heart Study was held in 1998. Local media covered the events and reported the study objectives. Participants were encouraged to ask questions about the study and were frequently provided with toll-free telephone numbers and names of participant coordinators.

Invitation to participate

All individuals known to be eligible for inclusion in the Third Generation Cohort were sent invitation letters beginning in November 2001, along with response cards by which they could communicate interest in participating. The high interest indicated by return of response cards led to the expectation that more eligible individuals would be willing to participate in the Third Generation Cohort than anticipated. No monetary incentives were offered except reimbursement for taxi fare, if needed.

Prioritization for recruitment

A total of 6,553 children of Offspring Cohort participants were identified who would be 20 years of age or older by the

TABLE 1. Criteria to establish priorities in recruiting members of the Third Generation Cohort of the Framingham Heart Study, 2002–2005

1. The total number of eligible Third Generation Cohort participants in an extended family*
2. The number of eligible Third Generation Cohort individuals in an extended family who returned a response card or enrollment form
3. The average size of sibships eligible for the Third Generation Cohort of an extended family
4. The average size of sibships eligible for the Third Generation Cohort of an extended family counting only those individuals who returned a response card or enrollment form
5. The percentage of Offspring Cohort participants who had DNA samples available to the Framingham Heart Study and were parents of potential Third Generation Cohort individuals within extended families
6. The average number of Offspring Cohort examination cycles attended by parents of potential Third Generation Cohort individuals within an extended Framingham Heart Study family
7. The number of potential new offspring spouses identified within an extended Framingham Heart Study family

* An extended family is made up of any related nuclear families including those of known siblings and cousins in any of the three generations.

end of the enrollment period. A higher priority for recruitment was assigned to individuals who belonged to 879 large Framingham Heart Study extended families, many of which are made up of several related nuclear families spanning three generations and therefore highly informative for genetic studies. As part of this strategy, other eligible individuals who were not part of these extended families would be targeted for recruitment toward the end of the enrollment period. For example, some children of spouses within the Offspring Cohort whose parents were not in the Original Cohort were not excluded from participation in the Third Generation Cohort but were given a low priority for recruitment. To promote recruitment of members of larger, more informative families, all large Framingham Heart Study extended families were ranked in descending order by use of a series of specific characteristics of family participation, listed in table 1.

Recruitment of the Third Generation Cohort was carried out over a 3-year period in the order of the recruitment prioritization. For example, the highest priority group was composed of 3,443 prospective Third Generation participants from the 192 largest families who were sent enrollment forms during 2002, the first year of recruitment and examination.

Scheduling the first examination and obtaining informed consent

A one-page enrollment form was sent to prospective Third Generation Cohort participants in batches of a few hundred at a time according to the prioritization scheme described above. Telephone calls for scheduling clinic appointments were made within a few weeks of mailing enrollment forms. The recruitment team was instructed to pursue the participation of men with more frequent follow-up calls to keep sex representation as balanced as possible.

Most of the prospective Third Generation Cohort participants were given ample opportunity during the recruitment period to complete enrollment forms and to schedule clinic visits. Clinic appointments were offered on select Saturdays for those who could not attend on weekdays. Special attention was given to siblings of Third Generation Cohort participants who resided far from Framingham. Letters were sent to non-New England residents each spring, offering clinic appointments during their summer vacations; appointment slots near holidays were also reserved for them. Response rates of recruitment of eligible Third Generation Cohort members were reviewed monthly during the 3-year enrollment and examination period. Nonparticipation was measured by the rate of ''hard'' refusals, that is, those individuals among prospective participants who indicated on their enrollment forms or in telephone interviews that they were not willing to participate in the Framingham Heart Study.

Information about the Framingham Heart Study, its epidemiologic and genetic research aims, and specifically recruitment and examination of the Third Generation Cohort was sent by mail before and after the first clinic examination. Information was presented formally at the beginning of the clinic examination. Using a consent form approved by the Institutional Review Board of Boston University Medical Center, a trained coordinator conducted an interview with each participant, who then was given opportunity to consent or refuse to participate in any or all aspects of the protocol. ''Check boxes'' at the end of the consent form accommodated options for specifying individualized participation in various aspects of the study. Participants were informed that they could withdraw from the study at any time before, during, or after the examination. Each person was provided a copy of the signed consent form.

Recruitment of new offspring spouses

The initial design for recruitment of the Third Generation Cohort called for inclusion of some of their parents as new offspring spouses. The eligibility criterion for new offspring spouses focused on previously nonparticipating parents who had at least two children with completed Third Generation Cohort examinations. Enrollment of new offspring spouses increased the completion of nuclear families and contributed to the genetic aims of the study.

TABLE 2. Response rates of prospective Framingham Heart Study Third Generation Cohort individuals by prioritization groups for recruitment, 2002–2005

	Recruitment prioritization groups*					Totals
	1	2	3	4	Other	
Known eligible (no.)	3,443	1,299	539	875	397	6,553
Row (%)	53	20	8	13	6	100
Column (%)	100	100	100	100	100	100
Enrollment forms sent (no.)	3,253	1,209	510	820	346	6,138
Row (%)	53	20	8	13	6	100
Column (%)	94	93	95	94	87	94
Enrollment forms not returned (no.)	528	294	149	263	177	1,411
Row (%)	37	21	11	19	13	100
Column (%)	15	23	28	30	45	22
Enrollment forms returned (no.)	2,725	915	361	557	169	4,727
Row (%)	58	19	19	12	4	100
Column (%)	79	70	67	64	43	72
Examination 1 completed (no.)	2,411	795	317	439	133	4,095
Row (%)	59	19	8	11	3	100
Column (%)	70	61	59	50	34	62
Refusals† (no.)	342	131	53	129	33	688
Row (%)	50	19	8	19	5	100
Column (%)	10	10	10	15	8	10

* Recruitment contacts for scheduling examination appointments began in 2002 with group 1 and proceeded with groups 2–4 and finally with others over a period of 3 years.

† Individuals recorded as refusals were all among those known to be eligible for the Third Generation Cohort, but not all of them were sent enrollment forms.

RESULTS

Recruitment rates of the Third Generation Cohort

Rates of response for prioritized recruitment groups within the Third Generation Cohort are provided in table 2. Of the 6,138 enrollment forms mailed to prospective participants, 4,727 (77 percent) were completed and returned to the Framingham Heart Study by the end of the recruitment period. There were 415 eligible individuals who were not sent enrollment forms either because of incomplete contact information or because recruitment was halted when maximum enrollment was reached. As planned, higher rates (70 percent and 61 percent) of enrollment of participants from the first and second priority groups were achieved, compared with those from the third and fourth priority groups (59 percent and 50 percent) and compared with the nonprioritized individuals (34 percent). Individuals in higher priority groups received enrollment forms earlier and, therefore, had longer recruitment periods with more opportunities to schedule a clinic visit.

Outright refusal to participate was similar (10 or 15 percent) in all priority groups. A total of 1,770 of the 6,553 eligible individuals (27 percent) neither refused nor attended the clinic examination. Self-reported reasons for nonattendance included geographic distance from Framingham ($n = 59$), financial constraints ($n = 2$), medical problems ($n = 17$), time constraints ($n = 31$), and personal reasons ($n = 455$); other reasons were incomplete contact information ($n = 168$), unreachable ($n = 528$), deceased ($n = 8$), or unspecified ($n = 502$).

Overview and comparison of the Third Generation Cohort with the Original Cohort and the Offspring Cohort

An overview of the three generations of the Framingham Heart Study is presented in figure 1. The Original Cohort at the first examination cycle, starting in 1948, comprised 5,209 persons, aged 28–62 years, most of whom ($n = 4,469$ or 68.6 percent) were drawn as two thirds of a random sample from an alphabetized town census listing of adult members of Framingham households stratified by family size; an additional 740 members were volunteers from the town (1). This selection design resulted in an Original Cohort that included 1,644 spouse pairs and 1,921 other individuals. Consequently, the Framingham Heart Study was able to recruit 5,124 participants for the Offspring Cohort, more than half ($n = 2,632$) of whom had two parents in the Original Cohort (3). Another 916 participants in the Offspring Cohort had one parent in the Original Cohort; the remaining 1,576 individuals were spouses of offspring enrollees. The Third Generation Cohort comprised 4,095 participants at the first examination. Of these, 2,944 individuals had both parents in the Offspring Cohort, 296 had one parent in the Offspring

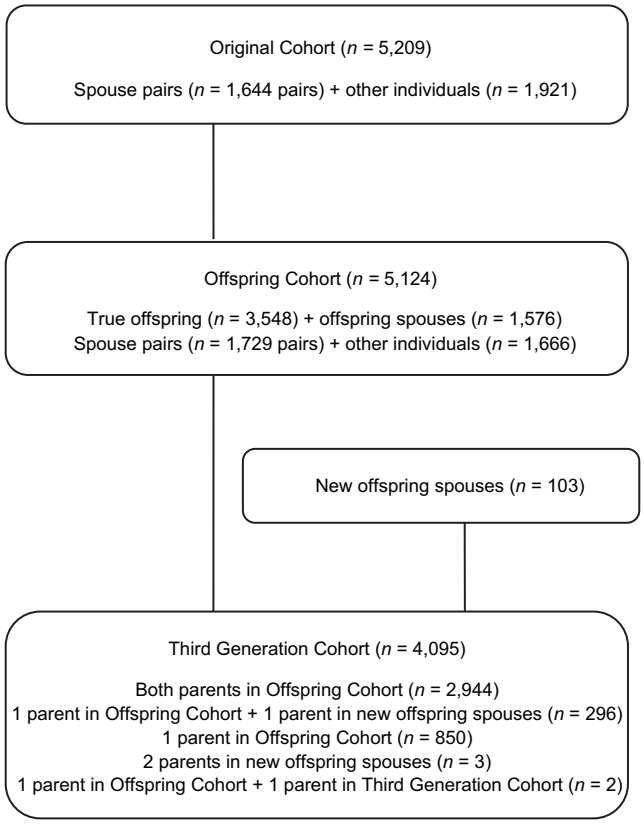

FIGURE 1. Overview and composition of three Framingham Heart Study cohorts at initial examinations starting in 1948, 1971, and 2002, respectively.

Cohort and the other parent included among the new offspring spouses, 850 participants had one parent in the Offspring Cohort, three individuals in the Third Generation Cohort had both parents among the new offspring spouses, and two individuals had one parent in the Offspring Cohort and one parent in the Third Generation Cohort.

The Third Generation Cohort consists almost entirely (98.4 percent) of participants who reported their ethnicity as White and 1 percent who reported belonging to more than one ethnic group. Self-reports of ethnicity across all three generations were 99.7 percent White, reflecting the ethnicity of the population of Framingham in 1948.

The age and sex distributions of the Third Generation Cohort participants who attended the first examination are displayed in table 3 and compared with distributions of Original Cohort and Offspring Cohort participants at their first examinations. Because of constraints of personal travel schedules, seven individuals in the Third Generation Cohort attended their first examinations a few months prior to their 20th birthdays.

Size and completeness of sibships and cousin groups in the Third Generation Cohort

According to anecdotal reports from the recruitment staff and the participants themselves, Third Generation Cohort siblings often encouraged each other to enroll in the Framingham Heart Study. The distribution of the size of all Third Generation Cohort sibships is presented in table 4. Two thirds of sibships (65 percent) were of size two or greater, and one third (33 percent) was of size three or greater. The average overall sibship size was 2.24. The average size of nuclear families, consisting of Third Generation Cohort sibships and their participating parents, was four (range: 1–11; standard deviation (SD): 1.6).

Of the total 4,095 participants, there were 3,975 individuals enrolled in the Third Generation Cohort who were members of 879 larger Framingham Heart Study extended families. Table 5 presents a comparative overview of the completeness of sibships and cousin groups targeted for recruitment within these 879 Framingham Heart Study families. In this prioritized group, for all sibships with at least one member recruited, 79 percent of all eligible individuals were

TABLE 3. Distribution of age at the initial examination of three Framingham Heart Study cohorts, 1948–1953, 1971–1975, and 2002–2005

	Original Cohort (1948–1953)				Offspring Cohort (1971–1975)				Third Generation Cohort (2002–2005)			
	Men		Women		Men		Women		Men		Women	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age group (years)												
≤18	0	0	0	0	98	4	92	3	0	0	0	0
19–29	8	0	15	1	571	23	719	27	224	12	264	12
30–39	830	36	1,031	36	789	32	835	32	655	34	761	35
40–49	778	33	968	34	694	28	740	28	736	39	848	39
50–59	652	28	795	28	293	12	242	09	277	15	293	13
≥60	68	3	64	2	38	2	13	0	20	1	17	1
Total no.	2,336		2,873		2,483		2,641		1,912		2,183	
Mean age (years)	44 (9)*		44 (9)		37 (11)		36 (10)		40 (9)		40 (9)	

* Numbers in parentheses, standard deviation.

TABLE 4. Framingham Heart Study Third Generation Cohort sibships attending examination 1, 2002–2005

Sibship size	No. of sibships	Cumulative %	No. of siblings	Cumulative %
1	639	35	639	16
2	579	67	1,158	44
3	340	85	1,020	69
4	155	94	620	84
5	64	97	320	92
6	29	99	174	96
7	15	100	105	99
8	4	100	32	99
9	3	100	27	100
Total	1,828		4,095	

recruited and, on average, 2.4 out of a mean sibship size of 3.0 were recruited. For cousin groups with at least one member recruited, 69 percent of the eligible individuals were recruited and, on average, 5.3 of 7.7 members were recruited.

The addition of participants from the Third Generation Cohort enlarged the size of the extended Framingham Heart Study families. There are now 754 extended families that include three generations, having a mean size of 14.1 (range: 3–230; SD: 18.4) and a median size of nine.

As expected, the place of residence affected participation in the Third Generation Cohort. Whereas initially the entire Original Cohort resided in the town of Framingham, Massachusetts, many within that group, their children, and grandchildren moved away during the ensuing decades. As presented in table 6, recruitment rates of eligible participants differed by geographic regions: 76 percent of eligible individuals residing in New England (73 percent of all eligible individuals) returned enrollment forms, and 69 percent attended the clinic examinations. In contrast, for those residing outside New England, 63 percent returned enrollment forms, and 46 percent attended the initial clinic visit. Refusal rates were 7 percent for New England residents compared with 20 percent for those living outside the region. Nevertheless, there were Third Generation Cohort participants residing in 45 of the US states and in eight other countries who attended the Framingham Heart Study clinic facility.

TABLE 5. Size and completeness of Third Generation Cohort sibships and cousin groups in 879 Framingham Heart Study extended families recruited in years 2002–2005

	Sibships		Cousin groups	
No.of sibships/cousin groups enrolled	1,694		748	
Average no. of individuals targeted per sibship/cousin group	3.0		7.7	
Average no. of individuals enrolled per sibship/cousin group	2.4		5.3	
	No.	%	No.	%
No. of individuals targeted	5,033	100	5,785	100
No. of individuals enrolled*	3,975	79	3,975	69
No. of individuals who refused	426	8	562	10
No. of individuals with open status†	632	13	1,248	22

* The remaining 120 Third Generation Cohort participants were not members of three generational Framingham Heart Study extended families.

† Neither refused nor attended clinic examination.

TABLE 6. Response rates of prospective Framingham Heart Study Third Generation Cohort participants by place of residence, 2002–2005

Category	Totals		Participation by place of residence			
			In New England		Outside New England or unknown location	
	No.	%	No.	%	No.	%
Eligible	6,553	100	4,787	100	1,766*	100
Returned enrollment forms	4,727	72	3,619	76	1,108	63
Attended examination 1	4,095	62	3,287	69	808	46
Refused to participate	688	10	341	7	347*	20

* The places of residence of five individuals who were eligible and refused are unknown; 1,411 other individuals did not return enrollment forms, and their addresses are unverified.

First examination of the Third Generation Cohort

The first examinations of the Third Generation Cohort and new offspring spouses were conducted at the Framingham Heart Study clinic five mornings per week, with some additional Saturdays, starting in March 2002 and ending in July 2005. Ideally, seven participants (mean: five, SD: two; range: 1–9) attended the clinic each day for a 4-hour examination. Start times were between 7:30 and 9:00 a.m., and key examination stations were duplicated to minimize delays. The clinic examination included obtaining informed consent, verification of pedigree and collection of contact information, venipuncture, anthropometry, blood pressure measurement, electrocardiography, echocardiography, arterial tonometry, assessment of brachial artery endothelial function, spirometry, interviews about health and medical and dietary history, and an outtake interview. Fasting blood samples were collected for various measures. Lymphocytes were successfully collected from 4,053 of the Third Generation Cohort and 102 of the new offspring spouses for cryopreservation, transformation into cell lines, and DNA extraction. The DNA resource will complement cell lines already available from Original Cohort ($n = 697$) and Offspring Cohort ($n = 3,453$) participants, so that renewable genetic material will be available for analyses of traits in 8,305 individuals from the three Framingham Heart Study generations. A subgroup of men who were at least 35 years of age ($n = 1,165$) and of nonpregnant women who were at least 40 years of age ($n = 953$) consented and underwent a multidetector computed tomography scan performed at another location. Images were

TABLE 7. Selected characteristics of Framingham Heart Study participants at initial clinical examination of three cohorts, 1948–1953, 1971–1975, and 2002–2005

	Original Cohort (1948–1953)		Offspring Cohort (1971–1975)		Third Generation Cohort (2002–2005)		Men (p value)*	Women (p value)*
	Men ($n = 2,336$)	Women ($n = 2,873$)	Men ($n = 2,483$)	Women ($n = 2,641$)	Men ($n = 1,912$)	Women ($n = 2,182$)		
Age (years)	44 (9)†	44 (9)	37 (11)	36 (10)	40 (9)	40 (9)		
Current smoking (%)	78	41	45	44	19	16	<0.0001	<0.0001
Systolic blood pressure (mmHg)	136 (19)	135 (24)	126 (16)	118 (16)	121 (13)	113 (14)	<0.0001	<0.0001
Diastolic blood pressure (mmHg)	86 (12)	84 (13)	82 (11)	76 (10)	78 (9)	73 (9)	<0.0001	<0.0001
Antihypertensive medication (%)	0	0	4	3	10	7	<0.0001	<0.0001
Hypertension (%)	45	39	26	13	22	12	<0.0001	<0.0001
Body mass index (kg/m^2)	25.8 (3.5)	25.4 (4.7)	26.4 (3.7)	24.0 (4.6)	27.9 (4.7)	26.0 (6.1)	<0.0001	<0.0001
Obese, body mass index: $\geq$30 kg/m^2 (%)	12	15	15	10	26	21	<0.0001	<0.0001
Blood glucose (mg/dl)	82 (24)	82 (20)	106 (16)	99 (15)	99 (18)	92 (18)	<0.0001	<0.0001
Lipid-lowering medication (%)	0	0	1	0.3	11	4	<0.0001	<0.0001
Total cholesterol (mg/dl)	221 (43)	221 (46)	201 (40)	192 (39)	193 (37)	185 (34)	<0.0001	<0.0001
High density lipoprotein cholesterol (mg/dl)	0	0	44 (12)	56 (15)	47 (12)	61 (16)	<0.0001	<0.0001
Prevalent cardiovascular disease (%)	4	2	3	1	2	1	0.74	0.22

* Age-adjusted test of trend was performed separately by sex across cohorts. Antihypertensive medication, lipid-lowering medication, and high density lipoprotein cholesterol were compared across only the Offspring Cohort and the Third Generation Cohort instead of all three.

† Numbers in parentheses, standard deviation.

analyzed for calcium content in coronary arteries and the thoracic and abdominal aorta.

Phenotypic data and biologic specimens are being processed rapidly in preparation for analyses by Framingham investigators and for distribution to the scientific community. Selected clinical characteristics of the Third Generation Cohort participants at their first examination are compared with corresponding characteristics of the Original Cohort and the Offspring Cohort at their initial examination in table 7. The mean age of the Third Generation Cohort was 40 years; 53 percent of enrollees were women. Compared with participants in the Original Cohort and the Offspring Cohort, those in the Third Generation Cohort were less likely to smoke cigarettes and had a lower prevalence of hypertension. The mean body mass index was higher in Third Generation Cohort participants, and prevalent obesity was observed in a larger proportion of this cohort. In addition, mean blood pressures were lower in the Third Generation Cohort, as were levels of total serum cholesterol.

DISCUSSION

The Third Generation Cohort of the Framingham Heart Study was recruited and enrolled from 2002 to 2005 and included 4,095 children of Offspring Cohort participants. Of 6,553 known individuals eligible for the Third Generation Cohort, more than 70 percent returned enrollment forms, and over 60 percent attended the first clinic examination. The hard refusal rate was 10 percent, largely attributable to individuals residing outside New England. In addition, we enrolled 103 parents of Third Generation Cohort members, who were not previously enrolled in the Offspring Cohort.

The response to the Third Generation Cohort recruitment by eligible individuals was enthusiastic and adequate to achieve stated benchmarks. There are several explanations for the high recruitment rates that deserve mention. First, participants were familiar with the Framingham Heart Study through the participation of their parents and other family members and therefore were receptive to contacts that took place by mail and telephone. Second, we communicated our plans to recruit the Third Generation Cohort through newsletters. Furthermore, members of the Framingham Heart Study were aware of many of the study's research findings through decades of news coverage in local and national media. Another contributing factor to the high participation rate may be the performance of key elements of the Framingham Heart Study clinic examination by physician investigators. Last, Framingham Heart Study investigators have continuously been available to answer questions from the community and individual study participants, and we repeatedly acknowledged the altruism of the study participants. It is not likely that a start-up research study would have such a high yield in recruiting participants into a de novo cohort. Nevertheless, new cohort studies may be able to adapt some of our methods to assist in recruitment efforts.

The mean age of the Third Generation Cohort was similar to those of the first and second generations of the Framingham Heart Study. Trends of most risk factors across the three generations are similar to what has been reported on a national level. Rates of cigarette smoking were considerably lower in the Third Generation Cohort than in the first examination of their parents and grandparents. Similarly, blood pressure levels were lower in the Third Generation Cohort, and the proportion of individuals receiving antihypertensive treatment was higher. Levels of serum total cholesterol also

were lower in the Third Generation Cohort, similar to national trends toward declining levels in the United States (4). In contrast, the mean body mass index has risen across the three generations of study participants, most noticeably among men. Approximately one quarter of men and one fifth of women in the Third Generation Cohort were obese.

The recruitment of the Third Generation Cohort for the Framingham Heart Study provides a unique setting in which many clinical traits have been collected at approximately the same age in family members across three generations. This information will facilitate efforts to identify underlying genetic contributions to these complex phenotypes, since many traits such as blood pressure, atherosclerosis, body mass index, and pulmonary function change markedly with age.

Sample examination forms, clinical data, and DNA from consenting Third Generation Cohort participants will be made available to the scientific community for research purposes (http://www.framinghamheartstudy.org or http://www.nhlbi.nih.gov/about/framingham/policies/index.htm). It is hoped that extensive use of these resources by a large number of investigators will accelerate discoveries that will favorably impact on public health by providing new insights into disease prevention and treatment

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