

Lipid treatment	X	X	X	X	X	X
Body mass index	X	X	X	X	X	X
Fasting blood glucose	X	X	X	X	X	X
Diabetes treatment	X	X	X	X	X	X
Smoking	X	X	X	X	X	X
Family history	Missing†	Missing†	Self-report: parental stroke or MI, parental cause of death	Self report: parental stroke or MI, parental cause of death	Incompatible; taken as missing§	Incompatible; taken as missing
Premature family history	Missing†	Missing†	Self-report: parental MI at age<60 years,‡ parental cause of death and age at death	Self report: parental stroke or MI and age at first event, parental cause of death and age at death	Incompatible; taken as missing§	Incompatible; taken as missing
Follow-Up						
Exam interval (years)	Every 2 years	Every 3-8 years	Every 2-5 years	Every 3 years through 1996-98, plus 1 exam 2011-2013	N/A	Annually, 1989-1999
Number of exams	32	9	8	5	1	11
Last exam	2012-2014	2011-2014	2010-2011	2011-2013	1988-94	1999
Surveillance method (interval, in years)	Community surveillance (continuous)	Medical record surveillance (continuous)	Phone interview (1)	Phone interview (1) Community surveillance (continuous)	National Death Index (continuous)	Phone interview (0.5)
Date of last follow-up	2007	2007	2010	2007	2006	1999

data available

Outcomes Ascertainment

Method	Adjudicated	Adjudicated	Adjudicated	Adjudicated	ICD-9 or -10	Adjudicated
Nonfatal MI	X	X	X	X		X
Ischemic stroke	X	X	X	X		X
CHD death	X	X	X	X	X	X
CVD death	X	X	X	X	X	X
All-cause death	X	X	X	X	X	X

*The table shows information for participants included in the Lifetime Risk Pooling Project dataset;¹ further details on individual complete cohorts are available via multiple sources for the Atherosclerosis Risk in Communities Study,²⁻⁶ Cardiovascular Health Study,⁷⁻¹⁰ Framingham Heart Study,¹¹⁻¹⁶ Framingham Offspring Study,^{11, 17-19} Coronary Artery Risk Development in Young Adults Study,^{20, 21} and National Health and Nutrition Examination Survey III-Mortality.²²⁻²⁶

†Family history information is not released with the Framingham datasets.

‡For the present analysis, the definition of premature CVD was first CHD incident or stroke at age ≤ 55 years in the father (or ≤ 60 years in the mother); therefore positive paternal history of MI at age < 60 years was not considered premature CVD.

§Participants were asked, “Has either biological parent ever been told by a doctor that he or she had... High blood pressure or stroke before the age of 50? Heart attack or angina before the age of 50?”²⁵ Not compatible with family history definitions for the present analysis due to grouping of endpoints, lack of total (non-premature) family history data, and difference in age thresholds (< 50 years) from those used for premature CVD in the present analysis (≤ 55 or ≤ 60 years in the father or mother, respectively).

|| Participants were asked about the cardiovascular health histories of their siblings but not their parents.⁷ Not compatible with family history definitions for the present analysis, which focused on parental history.

TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; MI, myocardial infarction; CHD, coronary heart disease; CVD, cardiovascular disease.

Supplemental Table 2. Baseline characteristics of the familial hypercholesterolemia phenotype (LDL-C \geq 190 mg/dL) and referent (LDL-C <130 mg/dL) groups, by index age.*

Index Age, Years	Index Age and LDL Cholesterol Category					
	50-59		60-69		70-79	
Category of baseline LDL cholesterol, mg/dL	<130 (referent)	\geq 190 (FH phenotype)	<130 (referent)	\geq 190 (FH phenotype)	<130 (referent)	\geq 190 (FH phenotype)
Baseline person-exams	8,933 (48%)	1,440 (7.8%)	6,673 (47%)	1,135 (7.9%)	3,792 (54%)	364 (5.1%)
Follow-up, person-years	140,335	26,605	96,472	17,848	41,419	4,316
Female	5,062 (57%)	880 (66%) [†]	3,483 (52%)	768 (68%) [†]	1,968 (52%)	267 (73%) [†]
African-American	1,977 (22%)	323 (22%)	1,060 (16%)	248 (22%) [†]	436 (12%)	41 (11%)
Total cholesterol, mg/dL	184 (28)	293 (30) [†]	188 (30)	294 (32) [†]	187 (29)	297 (29) [†]
LDL cholesterol, mg/dL	100 (26)	214 (25) [†]	101 (26)	213 (27) [†]	100 (25)	213 (22) [†]
HDL cholesterol, mg/dL	55 (19)	48 (14) [†]	53 (19)	49 (13) [†]	53 (18)	51 (14)
Non-HDL cholesterol, mg/dL	129 (29)	246 (30) [†]	135 (30)	245 (31) [†]	134 (29)	245 (27) [†]
Systolic blood pressure, mm Hg	122 (18)	126 (20) [†]	129 (20)	133 (22) [†]	136 (21)	143 (22) [†]
Diastolic blood pressure, mm Hg	75 (11)	78 (11) [†]	73 (11)	75 (12) [†]	71 (11)	75 (11) [†]
Body mass index, kg/m ²	27.8 (6.0)	28.1 (5.0)	27.5 (5.3)	27.9 (4.7) [†]	26.9 (4.8)	27.4 (4.8)
Smoking	2,277 (26%)	490 (34%) [†]	1,354 (20%)	260 (23%) [†]	479 (13%)	41 (11%)
Diabetes mellitus	804 (9.0%)	168 (11.7%) [†]	852 (12.9%)	183 (16.2%) [†]	434 (12.1%)	35 (9.9%)

Family history of CVD‡	2,266 (36%)	413 (46%)†	1,634 (40%)	267 (43%)	454 (43%)	17 (34%)
Hypertension treatment at baseline	2,142 (24.0%)	402 (27.9%)†	2,346 (35.2%)	416 (36.7%)	1,577 (42.5%)	126 (35.1%)†
Cholesterol treatment at baseline	478 (5.4%)	85 (5.9%)	482 (7.2%)	89 (7.9%)	325 (9.9%)	25 (7.5%)

*Table 1 shows baseline characteristics for index ages 20-49 years.

†p<0.05 for the comparison between participants at same index age with LDL-C≥190 vs. <130 mg/dL.

‡Estimate among cohorts with family history data available (see Supplemental Table 1).

Continuous data presented as mean (SD), categorical data presented as N(%).

LDL, low-density lipoprotein; LDL-C, LDL cholesterol; FH, familial hypercholesterolemia; CVD, cardiovascular disease; HDL, high-density lipoprotein.

Supplemental Table 3. Baseline characteristics of men and women with the familial hypercholesterolemia phenotype (LDL-C \geq 190 mg/dL), by index age.

	Index Age, Years					
	20-29	30-39	40-49	50-59	60-69	70-79
<i>Men</i>						
Baseline person-exams	49	144	342	560	367	97
Follow-up, person-years	1,145	3,154	6,398	9,775	5,293	1,038
CHD death or nonfatal MI	3 (6.1%)	19 (13.2%)	77 (22.5%)	143 (25.5%)	111 (30.3%)	26 (26.8%)
African-American	23 (47%)	40 (28%)	77 (23%)	115 (21%)	89 (24%)	13 (13%)
Total cholesterol, mg/dL	283 (34)	280 (27)	286 (31)	287 (27)	285 (26)	286 (26)
LDL cholesterol, mg/dL	213 (34)	208 (21)	211 (25)	212 (22)	210 (21)	211 (20)
HDL cholesterol, mg/dL	47 (12)	44 (10)	43 (12)	43 (12)	44 (11)	44 (11)
Non-HDL cholesterol, mg/dL	235 (34)	236 (26)	243 (31)	244 (27)	241 (26)	242 (34)
Systolic blood pressure, mm Hg	120 (11)	120 (13)	123 (16)	125 (18)	132 (20)	140 (21)
Diastolic blood pressure, mm Hg	75 (11)	78 (10)	80 (12)	79 (11)	76 (11)	76 (10)
Body mass index, kg/m ²	26.1 (3.7)	27.4 (3.6)	28.3 (4.1)	28.0 (3.9)	27.7 (4.1)	27.2 (4.2)
Smoking	18 (37%)	84 (59%)	149 (44%)	182 (33%)	96 (26%)	16 (16%)
Diabetes mellitus	1 (2.0%)	4 (2.8%)	12 (3.5%)	57 (10.2%)	65 (17.8%)	13 (13.5%)
Family history of CVD [†]	10 (33%)	18 (35%)	67 (39%)	162 (45%)	100 (45%)	6 (29%)
Hypertension treatment at baseline	1 (2.0%)	6 (4.2%)	37 (10.8%)	146 (26.1%)	122 (33.2%)	28 (29.2%)
Cholesterol treatment at baseline	0	3 (2.5%)	16 (4.7%)	39 (7.0%)	30 (8.2%)	8 (8.9%)

<i>Women</i>						
Baseline person-exams	57	70	249	880	768	267
Follow-up, person-years	1,389	1,522	4,872	16,830	12,555	3,278
CHD death or nonfatal MI	4 (7.0%)	5 (7.1%)	40 (16.1%)	146 (16.6%)*	155 (20.2%)*	47 (17.6%)
African-American	25 (44%)	23 (33%)	77 (31%)*	208 (24%)	159 (21%)	28 (10%)
Total cholesterol, mg/dL	284 (28)	285 (38)	292 (37)*	298 (32)*	298 (33)*	301 (29)*
LDL cholesterol, mg/dL	213 (23)	213 (28)	215 (33)	215 (26)*	214 (30)*	214 (22)
HDL cholesterol, mg/dL	51 (13)	49 (12)*	50 (13)*	51 (14)*	51 (13)*	54 (14)*
Non-HDL cholesterol, mg/dL	233 (26)	237 (34)	242 (35)	247 (32)*	247 (34)*	246 (28)
Systolic blood pressure, mm Hg	110 (11)*	115 (20)*	122 (20)	127 (21)	134 (23)	144 (23)
Diastolic blood pressure, mm Hg	69 (10)*	73 (13)*	78 (12)*	77 (11)*	75 (12)*	75 (12)
Body mass index, kg/m ²	26.3 (5.9)	28.5 (6.8)	28.9 (5.8)	28.2 (5.6)	28.0 (5.0)	27.5 (5.0)
Smoking	28 (49%)	28 (40%)*	110 (44%)	308 (35%)	164 (21%)	25 (9%)
Diabetes mellitus	0	1 (1.4%)	23 (9.2%)*	111 (12.6%)	118 (15.5%)	22 (8.6%)
Family history of CVD†	11 (37%)	8 (29%)	52 (39%)	251 (47%)	167 (43%)	11 (38%)
Hypertension treatment at baseline	2 (3.5%)	4 (5.7%)	65 (26.1%)*	256 (29.1%)	294 (38.3%)	98 (37.3%)
Cholesterol treatment at baseline	0	1 (1.7%)	10 (4.1%)	46 (5.3%)	59 (7.7%)	17 (7.0%)

*p<0.05 for the comparison between men and women at same index age.

†Estimate among cohorts with family history data available (see Supplemental Table 1).

Continuous data are presented as mean (SD), categorical data are presented as N(%).

LDL, low-density lipoprotein; LDL-C, LDL cholesterol; CHD, coronary heart disease; MI, myocardial infarction; HDL, high-density lipoprotein; CVD, cardiovascular disease.

Supplemental Table 4. Race-specific familial hypercholesterolemia phenotype (defined by LDL-C \geq 190 mg/dL) prevalence and coronary heart disease death or nonfatal myocardial infarction at each index age.

Index Age (years)	African American					Non-African American				
	FH Phenotype Prevalence (%)	Observed CHD Events	Unadjusted CHD Rate per 1000 Person-Years for FH Phenotype	Unadjusted CHD Rate per 1000 Person-Years for Referent	Adjusted Hazard Ratio* (95% CI)	FH Phenotype Prevalence (%)	Observed CHD Events	Unadjusted CHD Rate per 1000 Person-Years for FH Phenotype	Unadjusted CHD Rate per 1000 Person-Years for Referent	Adjusted Hazard Ratio* (95% CI)
	20-29	1.7	3	2.8	0.5	3.7 [†] (1.1-13.1)	1.3	4	2.8	0.5
30-39	2.3	5	4.3	0.7	2.5 [†] (0.3-21.2)	2.6	19	5.8	0.9	3.3 (1.9-6.0)
40-49	4.7	19	8.2	2.6	2.3 (1.4-4.0)	4.6	98	11.9	2.2	3.0 (2.3-3.9)
50-59	8.7	70	14.8	6.0	2.1 (1.6-2.8)	7.6	219	10.9	4.7	2.0 (1.7-2.4)
60-69	10.4	67	20.0	10.5	2.0 (1.5-2.7)	7.4	199	14.8	8.3	1.9 (1.6-2.3)
70-79	5.0	10	26.6	14.5	1.5 [†] (0.6-3.7)	5.2	63	16.8	15.0	1.2 (0.9-1.6)

*Adjusted for: age, sex, body mass index, diabetes mellitus, smoking, systolic blood pressure, antihypertensive therapy, and cohort; all except index age 20-29 years also adjusted for high-density lipoprotein cholesterol level and cholesterol medication use. Referent is (race-specific) participants with LDL-C<130mg/dL.

[†]Estimates may be unstable due to small numbers of events.

LDL-C, low-density lipoprotein cholesterol; FH, familial hypercholesterolemia; CHD, coronary heart disease; CI, confidence interval.

Supplemental Table 5. Risk of coronary heart disease death (only) for the familial hypercholesterolemia phenotype, defined by LDL-C \geq 190 mg/dL.

Index Age (years)	Baseline Person-Exams	Person-Years of Follow-Up	Observed CHD Deaths	Unadjusted CHD Death Rate per 1000 Person-Years for FH Phenotype	Unadjusted CHD Death Rate per 1000 Person-Years for Referent	Adjusted Hazard Ratio* (95% CI)		
20-29	106	2,534	2	Men:	1.7	Men:	0.1	6.4 [†]
				Women:	0	Women:	0.03	(1.3-31.6)
30-39	214	4,676	4	Men:	1.3	Men:	0.3	2.4 [†]
				Women:	0	Women:	0.03	(0.8-7.2)
40-49	591	11,270	41	Men:	4.4	Men:	1.5	2.6
				Women:	2.7	Women:	0.2	(1.7-3.8)
50-59	1,440	26,605	135	Men:	7.7	Men:	2.8	2.6
				Women:	3.6	Women:	0.9	(2.0-3.2)
60-69	1,135	17,848	134	Men:	11.1	Men:	5.8	1.8
				Women:	6.0	Women:	2.6	(1.4-2.2)
70-79	364	4,316	45	Men:	14.4	Men:	9.3	1.3
				Women:	9.2	Women:	6.3	(0.9-1.9)

*Adjusted for: age, sex, race, body mass index, diabetes mellitus, smoking, systolic blood pressure, antihypertensive therapy, HDL-C, cholesterol medication use, and cohort. Referent is participants with LDL-C $<$ 130mg/dL.

[†]Calculations based on small numbers of events; therefore, estimates may be unstable, and adjustment is not made for HDL-C or cholesterol medication.

LDL-C, low-density lipoprotein cholesterol; CHD, coronary heart disease; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol.

Supplemental Table 6. Risk of total atherosclerotic cardiovascular disease* for the familial hypercholesterolemia phenotype, defined by LDL-C \geq 190 mg/dL.

Index Age (years)	Baseline Person- Exams	Person-Years of Follow-Up	Observed ASCVD Events	Unadjusted ASCVD Rate per 1000 Person-Years for FH Phenotype	Unadjusted ASCVD Rate per 1000 Person-Years for Referent	Adjusted Hazard Ratio† (95% CI)
20-29	106	2,534	9	3.6	0.8	4.1‡ (1.2-13.4)
30-39	214	4,676	31	7.0	1.4	3.4 (2.1-5.5)
40-49	591	11,270	142	13.8	3.6	2.3 (1.8-2.8)
50-59	1,440	26,605	387	16.0	7.6	1.8 (1.5-2.0)
60-69	1,135	17,848	362	22.6	13.8	1.6 (1.4-1.8)
70-79	364	4,316	103	26.2	24.6	1.0 (0.8-1.3)

*Total atherosclerotic cardiovascular disease: coronary heart disease death, nonfatal myocardial infarction, or ischemic stroke.

†Adjusted for: age, sex, race, body mass index, diabetes mellitus, smoking, systolic blood pressure, antihypertensive therapy, high-density lipoprotein cholesterol, cholesterol medication use, and cohort. Referent is participants with LDL-C<130mg/dL.

‡Estimate may be unstable due to small numbers of events.

LDL-C, low-density lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval.

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