Supplementary Material

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Table S1. Framingham Heart Study examinations

	Original cohort				Offspring cohort				Third Generation cohort		
Exam	Years	Age	N	Exam	Years	Age	N	Exam	Years	Age	N
13	1972-1976	53-85	3133	1	1971-1975	5-70	5124	1	2002-2005	19-72	4095
14	1975-1978	55-88	2871	2	1979-1983	17-77	3863	2	2008-2011	24-78	3411
15	1977-1979	57-89	2632	3	1983-1987	18-77	3873				
16	1979-1982	59-91	2351	4	1987-1991	22-81	4019				
17	1981-1984	61-93	2179	5	1991-1995	26-84	3799				
18	1983-1985	63-94	1825	6	1995-1998	29-86	3532				
19	1985-1988	65-96	1541	7	1998-2001	33-90	3539				
20	1986-1990	67-97	1401	8	2005-2008	40-93	3021				
21	1988-1992	69-99	1319	9	2011-2014	46-98	2430				
22	1990-1994	72-101	1166								
23	1992-1996	73-101	1026								
24	1995-1998	76-103	831								
25	1997-1999	78-104	703								
26	1999-2001	79-103	558								
27	2002-20003	82-104	414								
28	2004-1005	84-104	303								
	New Offspring Spouse cohort				Omni 1 cohort				Omni 2 cohort		
1	2003-2005	47-85	103	1	1994-1998	27-78	506	1	2003-2005	20-80	410
2	2008-2011	53-90	68	2	1999-2001	33-83	405	2	2009-2011	25-85	321
				3	2007-2008	39-89	298				
				4	2011-2014	44-88	301				

Data show the number of FHS participants who attended each exam and their age range. For each epoch, we selected AF-free participants aged 45 years or older at the first exam attended within the epoch, i.e. 1972-1985 for epoch 1, 1986-2000 for epoch 2, and 2001-2015 for epoch 3.

Table S2. Contributions of participants to different age periods across epochs

Epoch 1	Epoch 2	Epoch 3	
✓			N=1862
✓	✓		N=2246
✓		✓	N=17
✓	✓	✓	N=1546
	✓		N=534
	✓	✓	N=1851
		✓	N=2760
N=5671	N=6177	N=6174	

Of 5671 participants contributing to epoch 1, 3792 (67%) contributed to subsequent age periods in epoch 2. Of 6177 participants contributing to epoch 2, 3397 (55%) contributed to subsequent age periods in epoch 3.

Table S3. Characteristics of AF cases ascertained from routine Framingham clinic visits and outside medical records

	AF cases detected during study visit			AF cases detected outside of study visits		
	Epoch 1 1972-1985	Epoch 2 1986-2000	Epoch 3 2001-2015	Epoch 1 1972-1985	Epoch 2 1986-2000	Epoch 3 2001-2015
	n= 66	n=43	n=7	n=239	n=553	n=461
Age, years	73.6 (8.3)	77.2 (10.5)	80.4 (12.8)	74.6 (9.9)	76.5 (10.5)	77.7 (10.7)
Female	43.9	39.5	14.3	49.4	46.3	46.2
Systolic BP, mmHg	141 (21)	136 (22)	129 (15)	146 (23)	142 (22)	136 (20)
Diastolic BP, mmHg	80 (12)	78 (12)	66 (9)	77 (12)	73 (11)	71 (11)
Body mass index, kg/m^2	26.4 (4.2)	29.3 (6.8)	28.1 (7.9)	26.3 (4.6)	27.5 (4.7)	28.8 (5.6)
Total cholesterol	211.7 (42.3)	181.2 (35.5)	165.6 (45.5)	222.7 (50.9)	203.8 (40.6)	176.7 (33.0)
Education						
No high school degree	38.7	23.7	28.6	43.6	29.0	10.2
High school degree only	30.7	34.2	14.3	28.4	33.0	33.0
Some college	16.1	23.7	42.8	16.9	20.3	22.2
College graduate	14.5	18.4	14.3	11.1	17.7	34.6
Statin use	0	7.0	42.9	2.1	8.1	48.6
Current smoker	19.1	7.0	0	20.4	12.9	6.7
Diabetes	11.1	15.2	0	12.7	17.9	22.9
Hypertension treatment	47.7	57.1	42.9	43.5	56.4	65.7
Prior heart failure	6.1	9.3	14.3	9.2	6.5	4.3
Prior myocardial infarction	9.1	4.7	28.6	16.7	15.9	8.5
Prior stroke/TIA, %	10.6	9.3	28.6	13.0	10.7	8.5

'Data are mean (standard deviation) or percentages. BP = blood pressure; TIA = transient ischemic attack

Table S4. Characteristics of AF cases with and without a secondary precipitant

	Secondary AF cases			Non-secondary AF cases		
	Epoch 1 1972-1985	Epoch 2 1986-2000	Epoch 3 2001-2015	Epoch 1 1972-1985	Epoch 2 1986-2000	Epoch 3 2001-2015
	n= 105	n=265	n=201	n=200	n=331	n=267
Age, years	73.6 (9.6)	75.4 (9.9)	78.7 (10.3)	74.8 (9.5)	77.5 (10.8)	77.0 (10.9)
Female	42.9	39.3	42.8	51.0	51.1	47.9
Systolic BP, mmHg	144 (23)	140 (22)	135 (19)	145 (22)	143 (22)	136 (21)
Diastolic BP, mmHg	76 (12)	73 (11)	70 (10)	78 (12)	74 (11)	72 (11)
Body mass index, kg/m^2	26.9 (5.0)	27.4 (4.9)	29.2 (5.9)	26.0 (4.2)	27.9 (5.0)	28.5 (5.4)
Total cholesterol	218.6 (47.5)	208.6 (42.9)	173.6 (33.0)	221.1 (50.2)	196.8 (37.9)	178.7 (33.1)
Education						
No high school degree	44.9	28.9	10.6	41.3	28.4	10.4
High school degree only	26.5	30.8	34.9	30.1	35.0	31.2
Some college	15.3	22.5	19.6	17.5	18.9	24.6
College graduate	13.3	17.8	34.9	11.1	17.7	33.8
Statin use	1.9	9.4	53.2	1.5	7.0	44.9
Current smoker	25.2	18.9	11.0	17.3	7.3	3.4
Diabetes	12.5	20.9	24.6	12.2	14.9	21.1
Hypertension treatment	46.2	57.3	63.3	43.4	55.9	66.8
Prior heart failure	8.6	5.3	4.5	8.5	7.9	4.5
Prior myocardial infarction	19.1	18.9	8.5	13.0	12.1	9.0
Prior stroke/TIA, %	13.3	9.1	10.0	12.0	11.8	7.9

'Data are mean (standard deviation) or percentages. BP = blood pressure; TIA = transient ischemic attack

Table S5. Characteristics of AF cases and matched referents

	Epoch 1 1972-1985		Epoch 2 1986-2000		Epoch 3 2001-2015	
	AF cases n=305	AF controls n=610	AF cases n=589	AF controls n=1170	AF cases n=453	AF controls n=892
Age (years)	73.9 (9.6)	73.9 (9.6)	75.9 (10.3)	75.8 (10.3)	76.6 (10.3)	76.5 (10.3)
Female	48.2	48.2	45.5	45.6	44.6	44.5
Systolic BP (mmHg)	145 (23)	142 (21)	142 (22)	139 (21)	135 (20)	133 (18)
Diastolic BP (mmHg)	77 (12)	76 (10)	74 (11)	73 (11)	71 (11)	70 (11)
BMI (kg/m^2)	26.3 (4.5)	26.2 (4.1)	27.7 (4.9)	27.1 (4.5)	28.9 (5.7)	27.8 (4.9)
Total cholesterol	220.2 (49.2)	224.8 (40.6)	202.0 (40.4)	205.6 (40.6)	176.3 (33.3)	180.1 (35.9)
Education						
No high school degree	42.5	45.0	28.5	27.6	9.9	10.2
High school degree only	28.9	24.9	33.3	33.3	33.2	32.1
Some college	16.7	15.1	20.3	19.4	22.1	26.4
College graduate	11.9	15.0	17.9	19.7	34.8	31.3
Statin use	1.7	1.3	8.2	10.1	48.8	45.3
Current smoker	20.1	19.7	12.6	6.6	6.8	5.4
Diabetes	12.3	8.1	17.8	12.1	22.4	15.0
Hypertension treatment	44.4	34.7	56.5	47.6	64.4	59.9
Prior heart failure	8.5	3.1	6.6	3.4	4.4	3.7
Prior myocardial infarction	15.1	12.1	15.1	11.2	8.6	5.7
Prior stoke/TIA	12.5	6.9	10.5	9.6	8.6	5.9

'Data are mean (standard deviation) or percentages. AF = atrial fibrillation; BP = blood pressure; TIA = transient ischemic attack

Percentages of missing values for each epoch: body mass index = 6.7%, 14.2%, and 14.7%; total cholesterol = 5.8%, 14.8%, and 14.6%; Systolic BP = 0.3%, 2.9%, and 0.2%; Diastolic BP = 0.3%, 3.0%, and 0.2%; education = 3.6%, 4.0%, and 3.1%; statin use = 0.5%, 0.2%, and 0.1%; smoking = 3.4%, 0.2%, and 0.1%; diabetes = 7.2%, 23.1%, and 14.0%; hypertension treatment = 0.8%, 1.5%, and 0.7%, respectively.

Table S6. Association between newly-diagnosed AF and death using the matched cohort design

Epochs	Cases		Referents		Age- and sex-adjusted model	Adjusted for covariates at AF onset
	n	deaths	n	deaths		
1972-1985	305	161	610	133	5.13 (3.67, 7.18)	4.72 (3.29, 6.77)
1986-2000	589	292	1170	286	3.52 (2.81, 4.42)	3.57 (2.79, 4.57)
2001-2015	453	189	892	230	3.55 (2.71, 4.67)	4.05 (2.96, 5.53)

Data are hazard ratios (95% confidence intervals) for the association between AF and death. Models 2 is adjusted for clinical covariates listed in table S1.

Table S7. Ratio of hazard ratios in women versus men

	Age-adjusted model	P	Adjusted for covariates at entry	p	Adjusted for time-varying covariates	p
1972-1985	1.31 (0.92, 1.84)	0.13	1.24 (0.87, 1.77)	0.23	1.30 (0.99, 1.72)	0.06
1986-2000	1.49 (1.15, 194)	0.003	1.54 (1.19, 2.00)	0.001	1.41 (1.16, 1.70)	0.0005
2001-2015	0.83 (0.61, 1.15)	0.26	0.93 (0.67, 1.29)	0.66	0.76 (0.57, 1.02)	0.07

Table S8. Association between newly-diagnosed AF and all-cause mortality, after excluding participants who died within 30 days of AF onset

Epochs	n	deaths	Age-adjusted model	Adjusted for covariates at entry	Adjusted for time-varying covariates
1972-1985	5478	1011	2.61 (2.15, 3.18)	2.42 (1.99, 2.94)	1.66 (1.43, 1.92)
1986-2000	6041	1297	1.85 (1.60, 2.13)	1.78 (1.54, 2.05)	1.26 (1.14, 1.39)
2001-2015	6123	871	1.61 (1.35, 1.92)	1.58 (1.32, 1.89)	1.41 (1.21, 1.65)
Trend P			0.0006	0.002	0.48

Data are hazard ratios (95% confidence intervals) for the association between time-varying AF and death. Models 2 and 3 are adjusted for clinical covariates listed in table S1.

Table S9. Association between new-onset AF detected from outside medical records and all-cause mortality

Epochs	n	deaths	Age-adjusted model	Adjusted for covariates at entry	Adjusted for time-varying covariates
1972-1985	5671	1031	4.71 (3.93, 5.65)	4.11 (3.42, 4.95)	2.36 (2.04, 2.74)
1986-2000	6177	1336	2.49 (2.18, 2.85)	2.39 (2.09, 2.73)	1.45 (1.31, 1.60)
2001-2015	6174	918	2.04 (1.74, 2.39)	2.05 (1.74, 2.41)	1.73 (1.50, 2.00)
Trend P			0.001	0.003	0.42

Data are hazard ratios (95% confidence intervals) for the association between time-varying AF and death. We censored AF cases detected during a Framingham Heart Study visit at the time of diagnosis. Models 2 and 3 are adjusted for clinical covariates listed in table 1. Linear trends across the epochs were tested by using meta-regression models of log hazard ratios.

Table S10. Association between new-onset AF without secondary precipitants and all-cause mortality

Epochs	n	deaths	Age-adjusted model	Adjusted for covariates at entry	Adjusted for time-varying covariates
1972-1985	5671	988	3.68 (2.97, 4.57)	3.18 (2.55, 3.97)	2.02 (1.70, 2.41)
1986-2000	6177	1216	2.25 (1.89, 2.66)	2.19 (1.84, 2.60)	1.54 (1.36, 1.73)
2001-2015	6174	821	1.99 (1.61, 2.46)	2.06 (1.66, 2.55)	1.68 (1.39, 2.04)
Trend P			0.007	0.03	0.40

Data are hazard ratios (95% confidence intervals) for the association between time-varying AF and death. We censored AF cases associated with an acute reversible precipitant at the time of diagnosis. Models 2 and 3 are adjusted for clinical covariates listed in table 1. Linear trends across the epochs were tested by using meta-regression models of log hazard ratios.

Table S11. Association between AF and cause-specific death using the matched cohort design

Epochs	Cardiovascular disease deaths						Non-cardiovascular disease deaths					
	Cases		Referents		Age- and sex-adjusted model	Adjusted for covariates at AF onset	Cases		Referents		Age- and sex-adjusted model	Adjusted for covariates at AF onset
	n	deaths	n	deaths			n	deaths	n	deaths		
1972-1985	305	84	610	56	4.82 (3.07, 7.56)	4.67 (2.73, 7.98)	305	77	610	79	5.54 (3.35, 9.17)	5.76 (3.25, 10.22)
1986-2000	589	102	1170	74	4.48 (2.98, 6.75)	4.66 (2.78, 7.79)	589	190	1170	220	3.15 (2.40, 4.13)	3.40 (2.51, 4.61)
2001-2015	453	69	892	28	9.45 (4.96, 18.01)	10.90 (4.67, 25.41)	453	120	892	179	2.59 (1.90, 3.53)	3.13 (2.18, 4.50)

Hazard ratios (95% confidence interval) from an illness-death model estimated via cause-specific Cox regression. Abbreviation: CVD = cardiovascular disease. Model 2 is adjusted for clinical covariates listed in table S1.

Figure S1. Diagram depicting the cohort study design and contribution of participants to the epochs
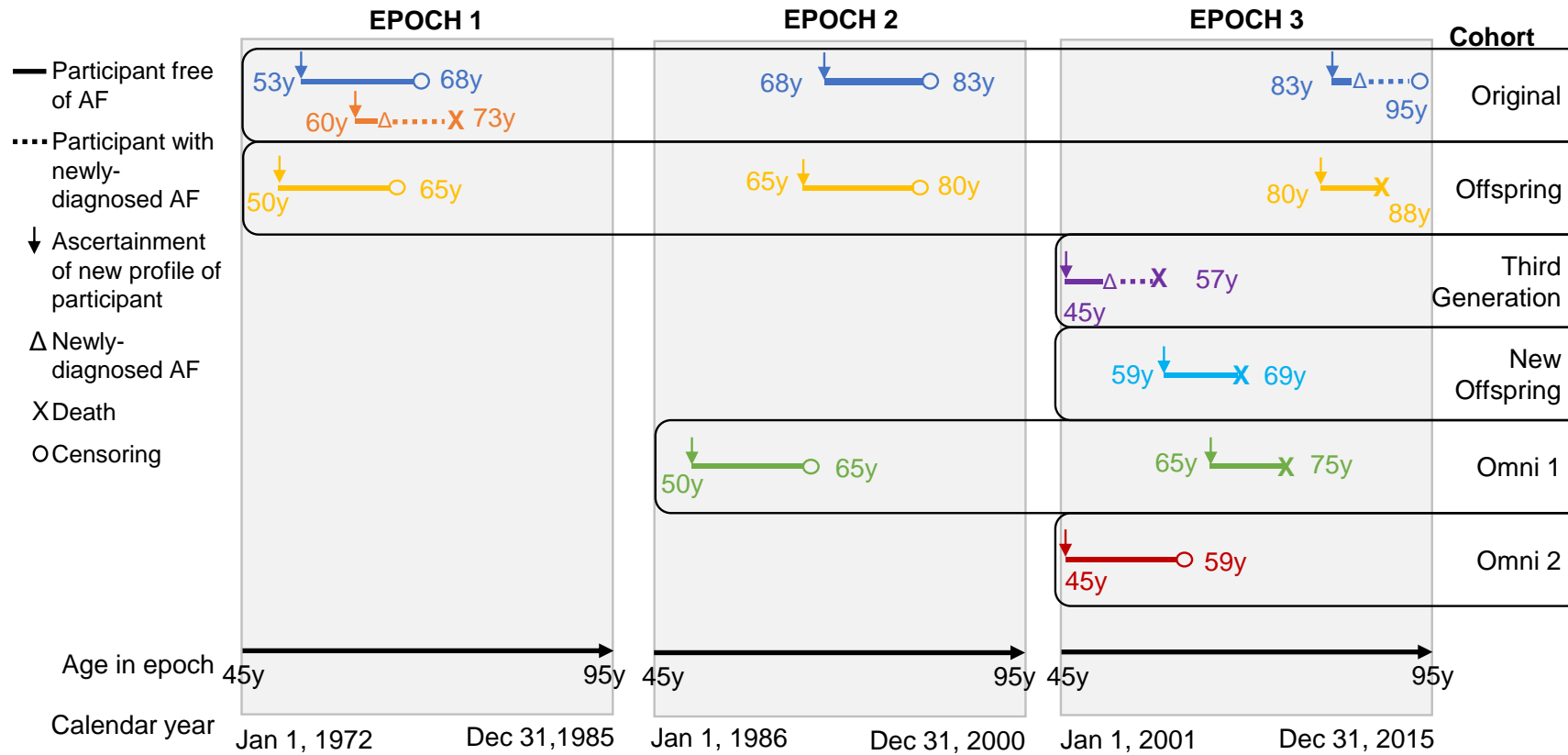
Figure S2. Diagram depicting the matched cohort study design and contribution of participants to the epochs
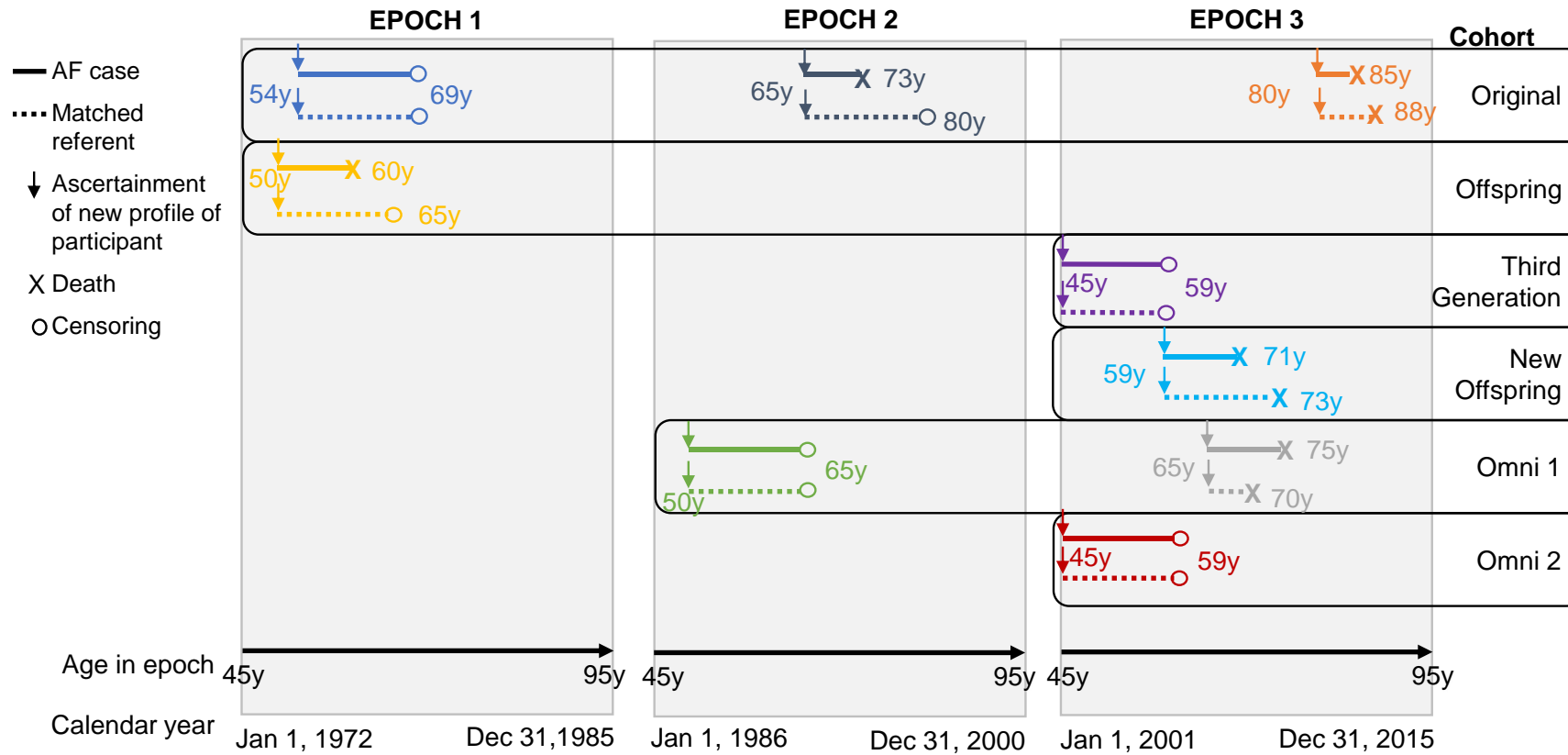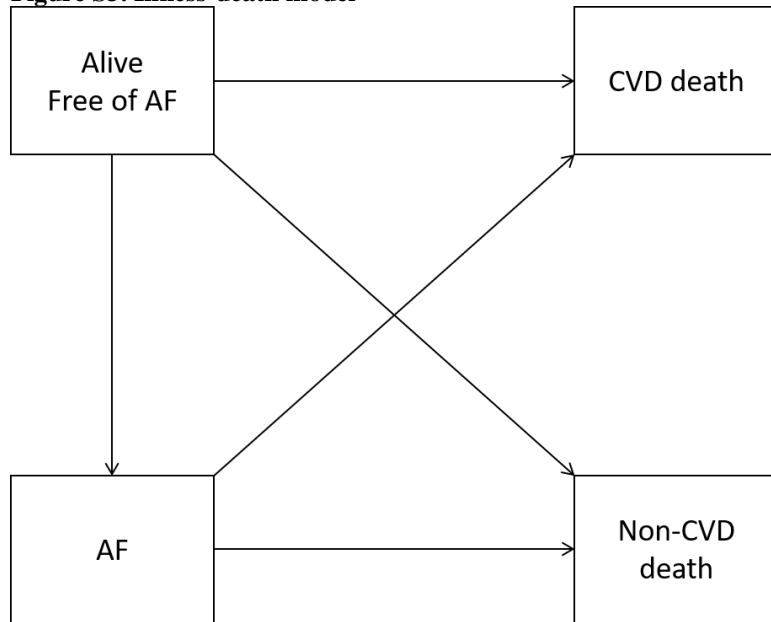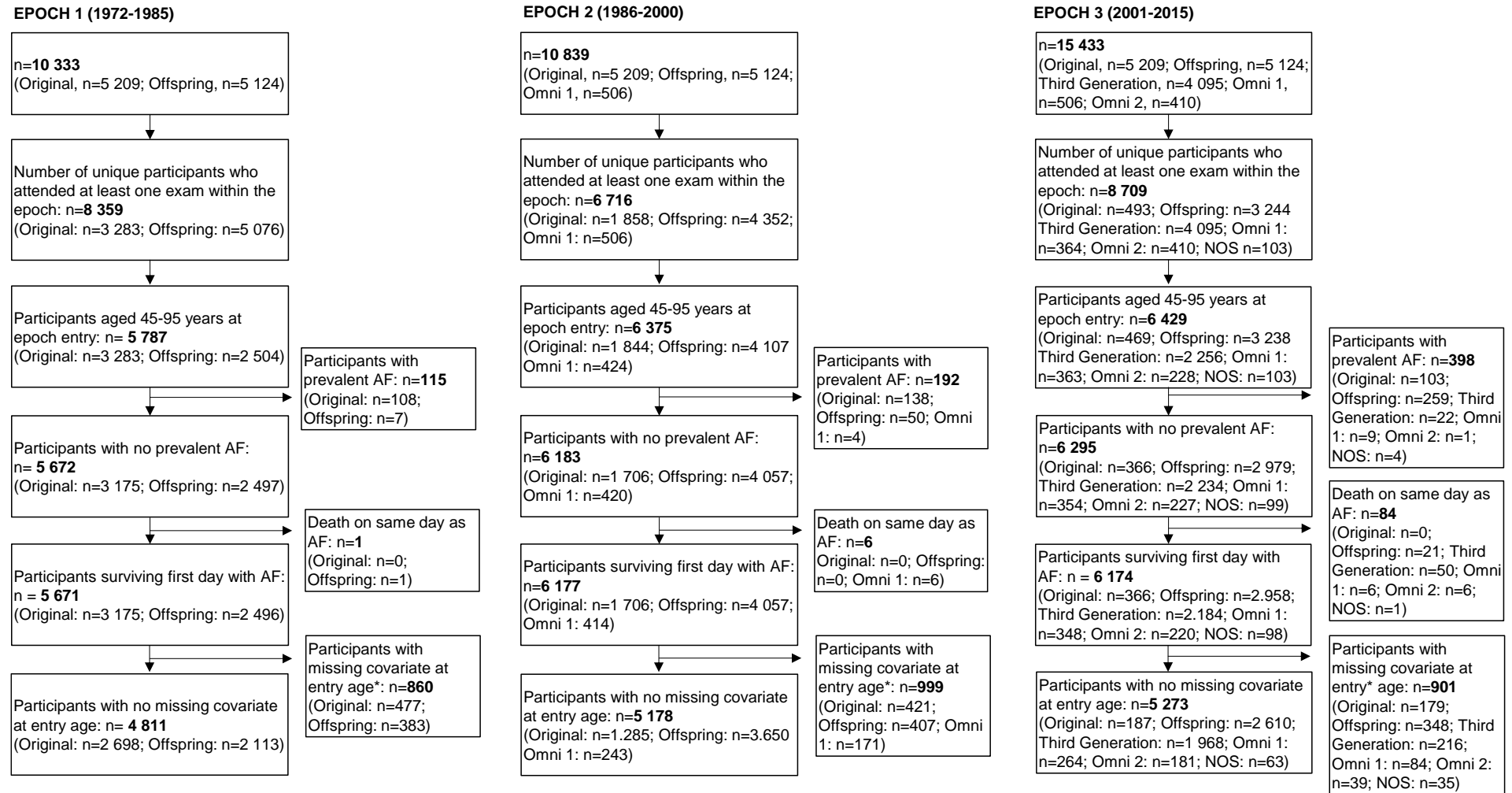
Figure S3. Illness-death model

In the illness-death model, individuals start alive and free of AF; they can eventually develop AF before they transition to CVD death or non-CVD death.

Figure S4. Flow diagrams depicting the selection of participants

EPOCH 1 (1972-1985)

n=**10 333**
(Original, n=5 209; Offspring, n=5 124)

↓

Number of unique participants who attended at least one exam within the epoch: n=**8 359**
(Original: n=3 283; Offspring: n=5 076)

↓

Participants aged 45-95 years at epoch entry: n= **5 787**
(Original: n=3 283; Offspring: n=2 504)

→ Participants with prevalent AF: n=**115**
(Original: n=108; Offspring: n=7)

↓

Participants with no prevalent AF: n= **5 672**
(Original: n=3 175; Offspring: n=2 497)

↓

→ Death on same day as AF: n=**1**
(Original: n=0; Offspring: n=1)

Participants surviving first day with AF: n = **5 671**
(Original: n=3 175; Offspring: n=2 496)

↓

→ Participants with missing covariate at entry age*: n=**860**
(Original: n=477; Offspring: n=383)

Participants with no missing covariate at entry age: n= **4 811**
(Original: n=2 698; Offspring: n=2 113)

EPOCH 2 (1986-2000)

n=**10 839**
(Original, n=5 209; Offspring, n=5 124; Omni 1, n=506)

↓

Number of unique participants who attended at least one exam within the epoch: n=**6 716**
(Original: n=1 858; Offspring: n=4 352; Omni 1: n=506)

↓

Participants aged 45-95 years at epoch entry: n=**6 375**
(Original: n=1 844; Offspring: n=4 107 Omni 1: n=424)

→ Participants with prevalent AF: n=**192**
(Original: n=138; Offspring: n=50; Omni 1: n=4)

↓

Participants with no prevalent AF: n=**6 183**
(Original: n=1 706; Offspring: n=4 057; Omni 1: n=420)

↓

→ Death on same day as AF: n=**6**
Original: n=0; Offspring: n=0; Omni 1: n=6)

Participants surviving first day with AF: n=**6 177**
(Original: n=1 706; Offspring: n=4 057; Omni 1: 414)

↓

→ Participants with missing covariate at entry age*: n=**999**
(Original: n=421; Offspring: n=407; Omni 1: n=171)

Participants with no missing covariate at entry age: n=**5 178**
(Original: n=1.285; Offspring: n=3.650 Omni 1: n=243)

EPOCH 3 (2001-2015)

n=**15 433**
(Original, n=5 209; Offspring, n=5 124; Third Generation, n=4 095; Omni 1, n=506; Omni 2, n=410)

↓

Number of unique participants who attended at least one exam within the epoch: n=**8 709**
(Original: n=493; Offspring: n=3 244 Third Generation: n=4 095; Omni 1: n=364; Omni 2: n=410; NOS n=103)

↓

Participants aged 45-95 years at epoch entry: n=**6 429**
(Original: n=469; Offspring: n=3 238 Third Generation: n=2 256; Omni 1: n=363; Omni 2: n=228; NOS: n=103)

→ Participants with prevalent AF: n=**398**
(Original: n=103; Offspring: n=259; Third Generation: n=22; Omni 1: n=9; Omni 2: n=1; NOS: n=4)

↓

Participants with no prevalent AF: n=**6 295**
(Original: n=366; Offspring: n=2 979; Third Generation: n=2 234; Omni 1: n=354; Omni 2: n=227; NOS: n=99)

↓

→ Death on same day as AF: n=**84**
(Original: n=0; Offspring: n=21; Third Generation: n=50; Omni 1: n=6; Omni 2: n=6; NOS: n=1)

Participants surviving first day with AF: n = **6 174**
(Original: n=366; Offspring: n=2.958; Third Generation: n=2.184; Omni 1: n=348; Omni 2: n=220; NOS: n=98)

↓

→ Participants with missing covariate at entry* age: n=**901**
(Original: n=179; Offspring: n=348; Third Generation: n=216; Omni 1: n=84; Omni 2: n=39; NOS: n=35)

Participants with no missing covariate at entry age: n=**5 273**
(Original: n=187; Offspring: n=2 610; Third Generation: n=1 968; Omni 1: n=264; Omni 2: n=181; NOS: n=63)

At entry age, 15.2%(860/5671) in epoch 1, 16.2% (999/6177) in epoch 2, and 14.6% (901/6174) in epoch 3 had one or more missing covariates. We used multiple imputation analyses to account for missing values.

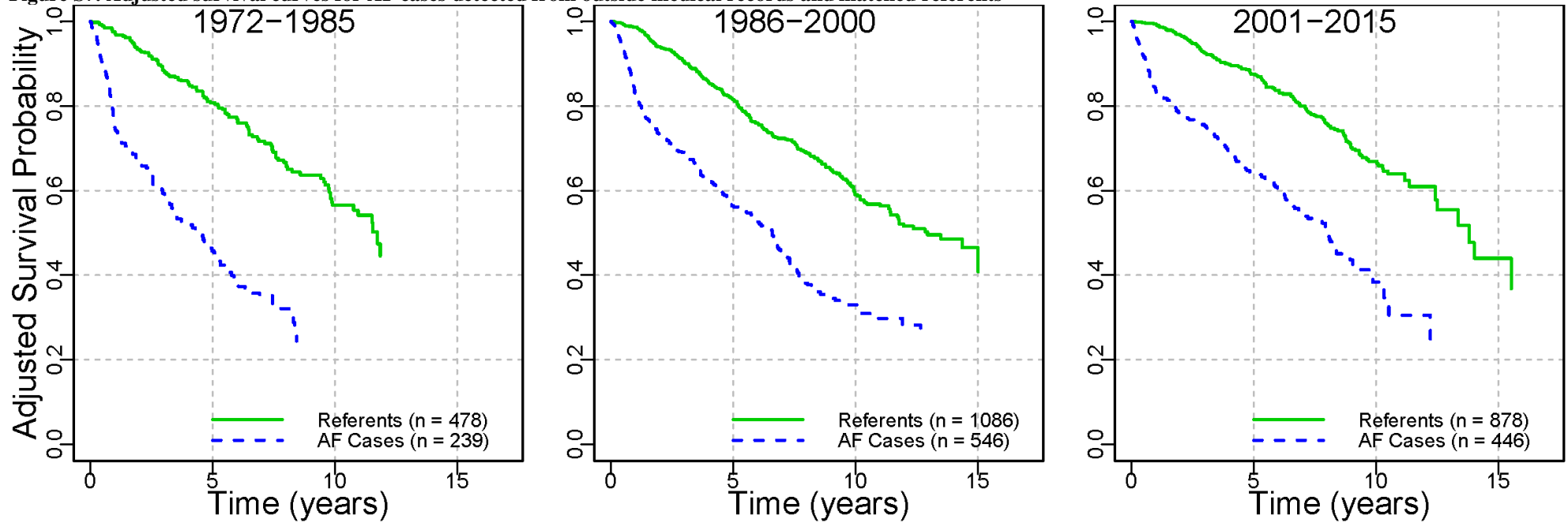**Figure S5. Adjusted survival curves for women with atrial fibrillation and matched referents**
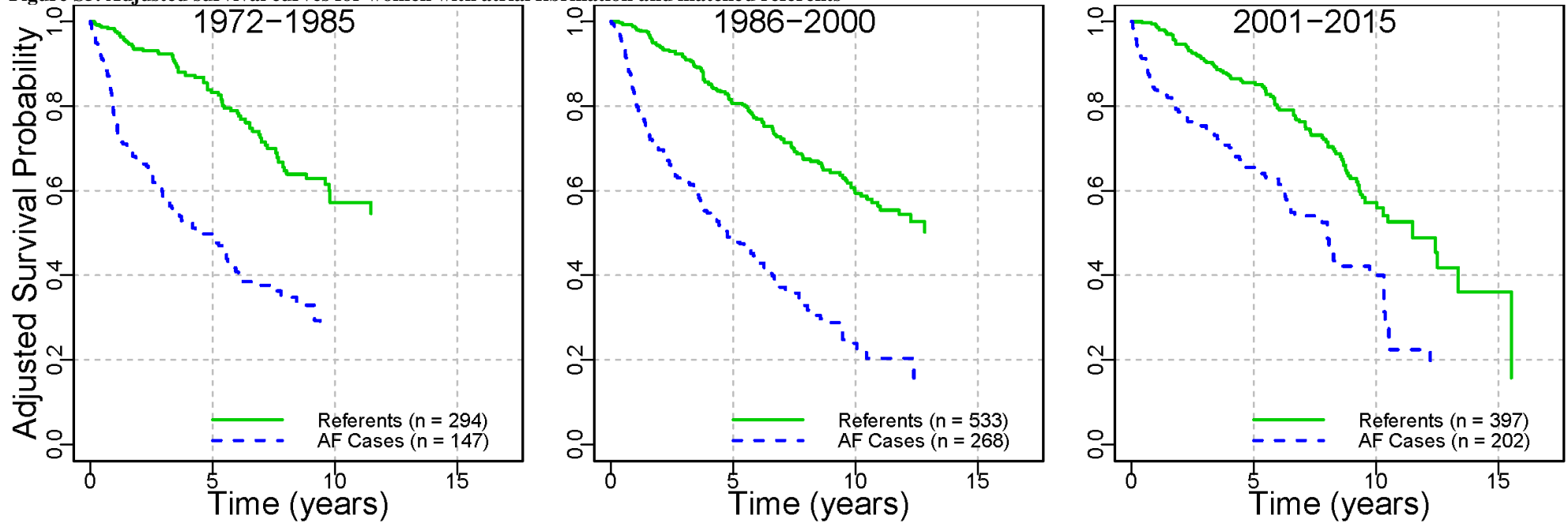
Analyses are adjusted for clinical covariates listed in table 1. Adjusted difference in restricted mean survival times -3.01 years (-3.52, -2.50), -2.91 (-3.28, -2.54), and -1.78 years (-2.20, -1.36) in epoch 1, 2, and 3, respectively (trend p=0.04).

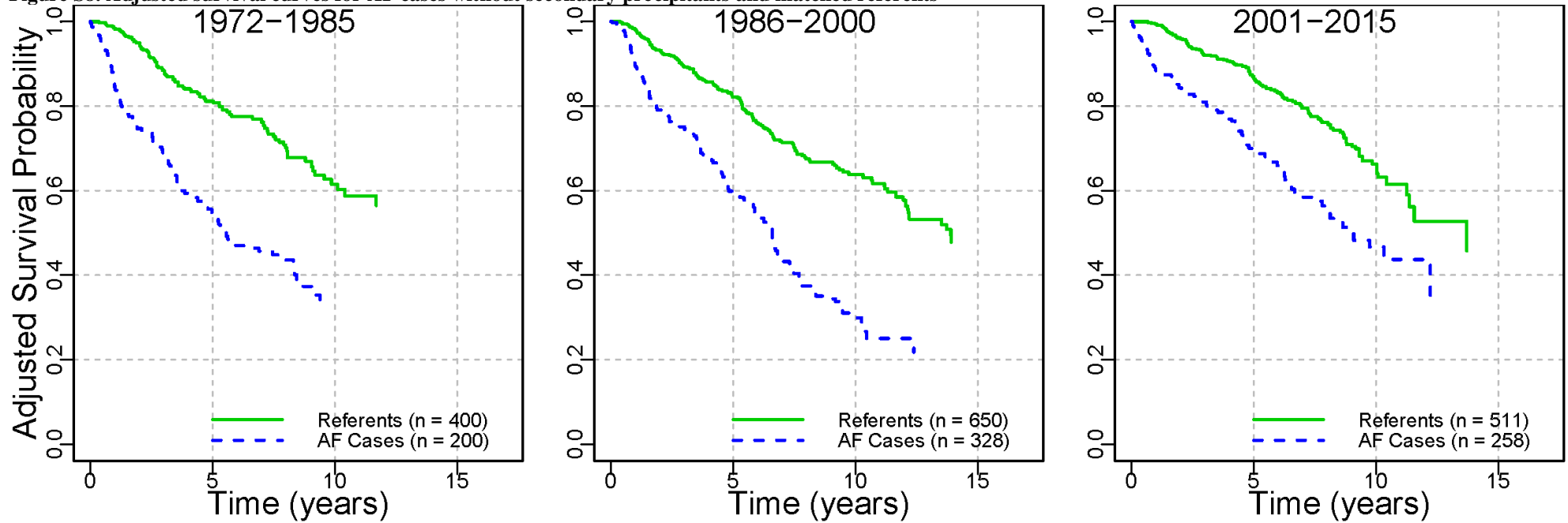**Figure S6. Adjusted survival curves for men with atrial fibrillation and matched referents**
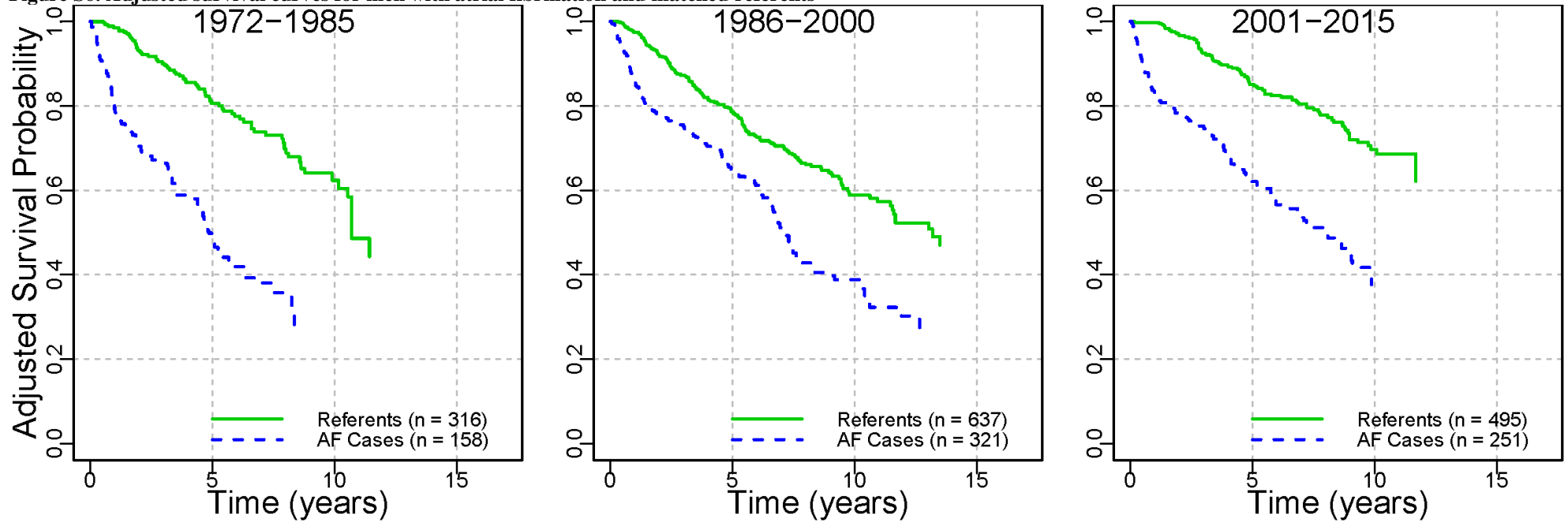
Analyses are adjusted for clinical covariates listed in table 1. Adjusted difference in restricted mean survival times -2.89 years (-3.38, -2.40), -1.52 years (-1.87, -1.18), and -2.23 years (-2.59, -1.86) in epoch 1, 2, and 3, respectively (trend p=0.59)

Figure S7. Adjusted survival curves for AF cases detected from outside medical records and matched referents

We discarded AF cases detected during a Framingham Heart Study visit at the time of diagnosis. Analyses are adjusted for clinical covariates listed in table 1. Adjusted difference in restricted mean survival times -3.13 years (-3.53, -2.73), -2.31 years (-2.57, -2.05), and -2.12 years (-2.39, -1.85) in epoch 1, 2, and 3, respectively (trend p=0.01)

Figure S8. Adjusted survival curves for AF cases without secondary precipitants and matched referents

We discarded AF cases associated with an acute reversible precipitant. Analyses are adjusted for clinical covariates listed in table 1. Adjusted difference in restricted mean survival times -2.34 years (-2.78, -1.90), -2.04 years (-2.37, -1.71), and -1.54 years (-1.89, -1.19) in epoch 1, 2, and 3, respectively (trend p=0.004)

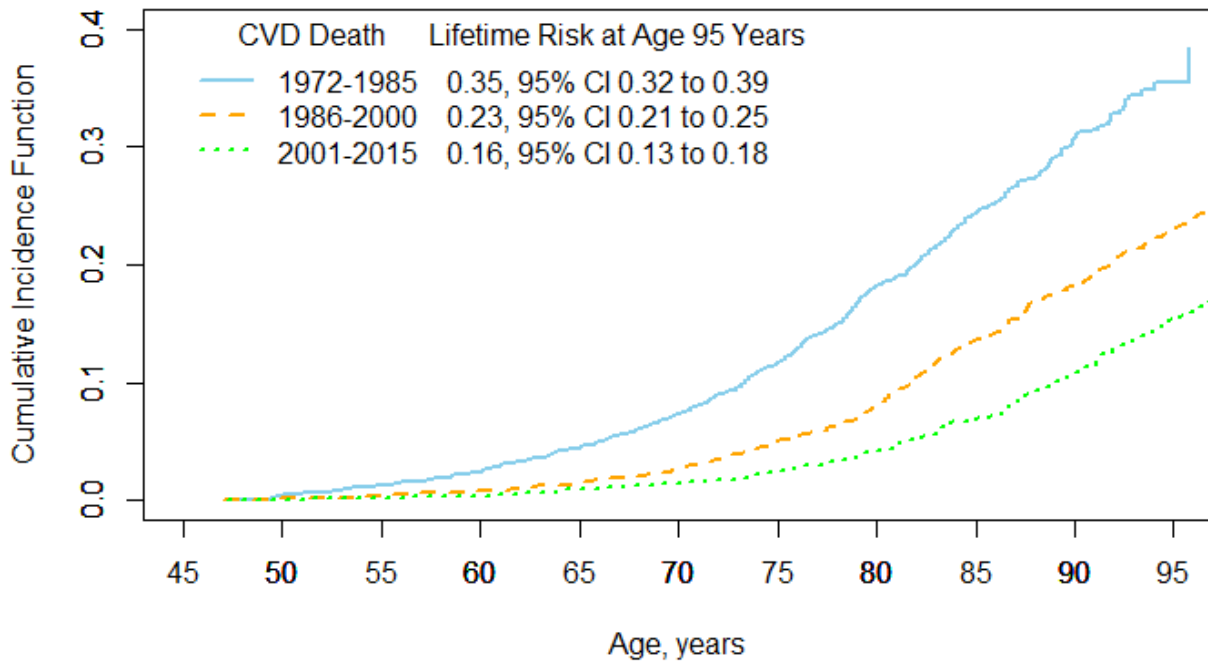**Figure S9. Cumulative incidence function for cardiovascular death**

Figure S10. Cumulative incidence function for non-cardiovascular death