SUPPLEMENTAL MATERIAL
Data S1. Supplemental Statistical Methods

For each decade and each cohort, we obtained the numbers of premature CVD events (below age 55, 60, and 65 years) for both sexes separately. We calculated the number of years at risk for each participant for these strata to estimate the incidence rates of premature CVD in each decade. For each stratum, we obtained two average ages, i.e., the average age of the participants at the beginning of the observation period (decade) and the average age at the onset of premature CVD (in that decade). Within each decade (by sex and cohort), we assessed the average systolic and diastolic BP, BMI, average serum cholesterol, and the proportions of participants with diabetes, active smoking, lipid-lowering treatment, and hypertension treatment. For each decade and by FHS cohort within that decade, we report descriptive statistics for all these different variables to assess risk factor patterns across the seven decades.

Our overarching objective was to estimate the sex-specific associations of the calendar period (decade) and the incidence of premature CVD (using three age thresholds to define the early onset of CVD). These analyses are influenced by the well-known conjoint “age-period-cohort effects” that are linearly co-dependent and may be challenging to deconvolute. In the current setting, we considered only cohort effects defined by the three FHS cohorts, i.e., we did not consider specific age-period combinations as separate birth cohorts. This assumption is reasonable because the three FHS cohorts are linked closely to the calendar periods evaluated. Notably, more than one cohort can contribute to observations within some decades based on the time of enrollment of the cohort and the at-risk age group considered; for the highest threshold of 65 years, the original cohort contributed to observations (for incidence of premature CVD) between 1950-1989, the Offspring contributed to the decades 1970-2019, and the Third Generation cohort contributed to observations in the most recent decades (2000-2019).
We conducted three sequential analyses to quantify the temporal trends in incidence of premature CVD over seven decades of observations (1950-2019), to investigate the age-period-cohort effects, and explain potential temporal trends.

The first analysis assumed ‘no cohort effect’ and estimated the sex-specific associations of the calendar period with the incidence of premature CVD. The analysis assumes that the number of premature CVD events has a negative binomial distribution, i.e., an over-dispersed Poisson distribution, to address possible heterogeneity in the incidence of CVD events across periods and cohorts. Incidence rates may show larger variability than expected from a standard Poisson distribution (where variance roughly equals the mean); this additional variability is called over-dispersion. Not addressing the over-dispersion may result in unrealistic small standard errors of associations and, thus, incorrect rejections of the null hypotheses when over-dispersion is present.

We used the canonical log link function and applied the logarithmically-transformed number of years at risk as an offset parameter to model the incidence rate of premature CVD. The calendar period is considered a numerical variable to quantitate the association, i.e., to estimate the effect size per decade (assuming a log-linear effect). We used the asymptotic standard error to construct 95% confidence intervals for the calendar period effect (on the incidence of premature CVD). These aforementioned analyses were both unadjusted and adjusted for the average age of participants at the beginning of the period and at the age of premature CVD. Adjustment for age at entry into a decade and age at onset of premature CVD within that decade (by cohort) is critical because, within a single cohort, the age at entry into a decade will increase serially, as will the age at the onset of premature CVD. Incidence rates calculated from the occurrence of an event below a fixed age threshold cannot distinguish between a rate that occurs when the average age at which this event occurs is close to the
threshold age or much earlier than the threshold age. These essential issues in age differences can confound any calendar period effects.

The second analysis investigated the log-linear sex-specific association of the calendar period with the incidence of premature CVD where the cohort effect is considered random (generalized linear mixed-effects analysis), which is in line with models deemed suitable for analyzing age-period-cohort effects.\textsuperscript{5} We assumed that the number of premature CVD events approximates a Poisson distribution since over-dispersion is addressed by the term in the model for the random effect of the cohort. The association of calendar period with premature CVD is estimated per change in a decade using the canonical log link function with the logarithmically transformed number of years at risk as an offset parameter. We consider the intercept (the incidence rate of premature CVD at the beginning of each decade) to be normally distributed. We performed unadjusted and age-adjusted analyses. Correcting for age at the beginning of the decade or for age at CVD onset may help resolve potential dominant cohort effects in unadjusted analysis. The variability in the incidence rates was quantified on the log scale and determined with maximum likelihood estimation. The interpretation of the variance is that it represents the variability between log incidence rates for the cohorts. More precisely, the conditional distribution of the number of events $Y_{ij}$ for cohort $i$ at period $j$ given the unknown heterogeneity $U_i$ is Poisson distributed with mean parameter $\exp \{U_i\} \lambda_j$. Since it is assumed that $\exp \{U_i\}$ is lognormal, the relative standard deviation (expressed in percentages) is equal to $100\% \sqrt{\exp\{\sigma^2\} - 1}$. Thus, a value of $\sigma^2 = 0.035$ would indicate that the relative standard deviation for incidence rates between cohorts is approximately 18.9%. A value of $\sigma^2 = 0.850$ corresponds to a relative standard deviation in incidence rates across cohorts of 116%.

Then, the third analysis elucidated the role of temporal trends in risk factors that may serve as explanatory variables (confounders) for the association of the calendar period with the incidence of premature CVD. For this purpose, we adjusted individually (one at a time) for
systolic and diastolic BP, total cholesterol, diabetes, smoking, hypertension, hypertension treatment, and lipid-lowering treatment in the second statistical model with a random cohort effect that also corrected for age. Additionally, we performed a Poisson regression analysis with stepwise selection of variables using the Bayesian Information Criteria to identify potential explanatory variables (CVD risk factors listed above) that may contribute to the incidence of premature CVD across the decades (generating a joint analysis of the explanatory variables on incidence of premature CVD).

Additional analyses: Incidence of premature CVD by subtype

We evaluated the sex-specific changes in the relative proportions of various CVD subtypes (CHD, stroke/TIA, heart failure, PAD, and CVD death) among the premature CVD events over the seven-decade observation period. We assessed trends in two major CVD subtypes, i.e., premature CHD and stroke/TIA, using the first two steps of our analysis of premature CVD.

A two-tailed P-values less than 0.05 were considered to be statistically significant in all analyses. All analyses were conducted with software package SAS, version 9.4, by SAS Institute.
Table S1. Characteristics of participants from the three Framingham generations across seven decades: data for participants at risk of premature cardiovascular disease (CVD) below age 65 years

| Variable                        | 1950-59 Gen1 | 1960-69 Gen1 | 1970-79 Gen1 | 1980-89 Gen2 | 1990-99 Gen2 | 2000-09 Gen2 | 2010-2019 Gen2 | 2010-2019 Gen3 |
|---------------------------------|--------------|--------------|--------------|--------------|--------------|--------------|----------------|----------------|
| Number of participants          | 5182         | 3616         | 1927         | 4480         | 4180         | 3158         | 1678           | 3911           |
| Men, %                          | 44.8         | 43.9         | 43.6         | 48.4         | 48.1         | 47.4         | 45.2           | 46.7           |
| Age at start of decade          | 43 (9)       | 50 (7)       | 56 (4)       | 36 (8)       | 42 (9)       | 49 (8)       | 53 (5)         | 38 (8)         |
| Age range                       | 26–62        | 36–64        | 46–64        | 25–64        | 25–64        | 25–64        | 33–64          | 25–64          |
| Body mass index, kg/m²          | 25.7 (4.1)   | 26.1 (4.2)   | 26.7 (4.4)   | 25.4 (4.3)   | 26.2 (4.7)   | 27.7 (5.2)   | 28.5 (5.8)     | 27.3 (5.7)     |
| Systolic blood pressure, mm Hg  | 133 (22)     | 135 (21)     | 135 (19)     | 123 (17)     | 123 (17)     | 124 (17)     | 124 (16)       | 117 (14)       |
| Diastolic blood pressure, mm Hg | 84 (12)      | 83 (11)      | 81 (11)      | 79 (11)      | 79 (10)      | 76 (10)      | 76 (10)        | 75 (10)        |
| Hypertension, %                 | 59.5         | 41.9         | 48.7         | 21.2         | 28.3         | 31.1         | 41.7           | 18.5           |
| Antihypertensive medication, %  | 4.5          | 8.0          | 20.2         | 3.9          | 13.8         | 18.4         | 31.0           | 11.2           |
| Total Cholesterol, mg/dl        | 233 (45)     | 249 (47)     | 231 (42)     | 203 (40)     | 209 (40)     | 203 (38)     | 196 (37)       | 189 (35)       |
| Lipid-lowering medication, %    | 1.5          | 0.7          | 2.5          | 0.6          | 1.3          | 8.5          | 25.6           | 9.8            |
| Diabetes mellitus, %            | 1.6          | 3.1          | 5.1          | 2.2          | 3.6          | 6.3          | 9.5            | 3.6            |
| Smoking, %                      | 52.9         | 46.0         | 34.6         | 44.2         | 31.5         | 19.8         | 16.0           | 13.5           |

Continuous variables are expressed as mean (SD), and binary variables as %. Gen1 refers to the original cohort, Gen2 refers to the Offspring cohort, and Gen3 refers to the Third generation Framingham cohort.
Table S2. Incidence of cardiovascular disease (CVD) events in men and women over seven decades

| Sex   | N of person-observations | Decade     | All CVD events | CVD events before age 65 years, n (%) | CVD events before age 60 years, n (%) | CVD events before age 55 years, n (%) |
|-------|--------------------------|------------|----------------|---------------------------------------|---------------------------------------|---------------------------------------|
| Women | 2862                     | 1950-1959  | 202            | 184 (91.1)                            | 131 (64.9)                           | 83 (41.1)                             |
|       | 2063                     | 1960-1969  | 326            | 161 (49.4)                            | 97 (29.8)                            | 50 (15.3)                             |
|       | 3418                     | 1970-1979  | 455            | 201 (44.2)                            | 130 (28.6)                           | 66 (14.5)                             |
|       | 2200                     | 1980-1989  | 445            | 92 (20.7)                             | 63 (14.2)                            | 34 (7.6)                              |
|       | 1700                     | 1990-1999  | 426            | 71 (16.7)                             | 51 (12.0)                            | 33 (7.7)                              |
|       | 3040                     | 2000-2009  | 388            | 89 (22.9)                             | 53 (13.7)                            | 32 (8.2)                              |
|       | 1981                     | 2010-2019  | 245            | 34 (13.8)                             | 20 (8.2)                             | 14 (5.7)                              |
|       | 7735                     | Total      | 2487           | 832 (33.4)                            | 545 (21.9)                           | 312 (12.5)                            |
| Men   | 2320                     | 1950-1959  | 312            | 296 (94.9)                            | 234 (75.0)                           | 143 (45.8)                            |
|       | 1553                     | 1960-1969  | 398            | 262 (65.8)                            | 188 (47.2)                           | 98 (24.6)                             |
|       | 2989                     | 1970-1979  | 553            | 297 (53.7)                            | 207 (37.4)                           | 131 (23.7)                            |
|       | 1980                     | 1980-1989  | 480            | 212 (44.2)                            | 142 (29.6)                           | 95 (19.8)                             |
|       | 1458                     | 1990-1999  | 396            | 145 (36.6)                            | 88 (22.2)                            | 47 (11.9)                             |
|       | 2549                     | 2000-2009  | 322            | 103 (32.0)                            | 70 (21.7)                            | 42 (13.0)                             |
|       | 1697                     | 2010-2019  | 241            | 76 (31.5)                             | 51 (21.2)                            | 29 (12.0)                             |
|       | 6729                     | Total      | 2702           | 1391 (51.4)                           | 980 (36.3)                           | 585 (21.7)                            |

CVD= cardiovascular disease
Table S3. Association of calendar decade with the incidence of premature cardiovascular disease (CVD) after adjustment for individual potential confounders

| Adjusted for\(^{†}\) | Women | Men | \(95\%\) CI | Men | Men | Men |
|----------------------|-------|-----|-------------|-----|-----|-----|
| Baseline Model\(^{‡}\) | | | | | | |
| CVD before age 55 years | 0.849 | 0.860 | [0.78; 0.93] | 0.816 | 0.805 | 0.787 |
| CVD before age 60 years | 0.851 | 0.860 | [0.78; 0.94] | 0.805 | 0.787 | 0.760 |
| CVD before age 65 years | 0.818 | 0.816 | [0.76; 0.88] | 0.787 | 0.760 | 0.730 |
| Body mass index | 0.866 | 0.868 | [0.76; 0.98] | 0.801 | 0.779 | 0.760 |
| Diabetes | 0.842 | 0.889 | [0.77; 0.92] | 0.799 | 0.760 | 0.720 |
| Systolic blood pressure | 1.008 | 1.053 | [0.75; 1.36] | 0.787 | 0.710 | 0.680 |
| Diastolic blood pressure | 0.927 | 0.780 | [0.71; 1.0] | 0.872 | 0.845 | 0.842 |
| Hypertension | 0.837 | 0.821 | [0.74; 0.94] | 0.804 | 0.771 | 0.754 |
| Antihypertensive medication | 0.813 | 0.792 | [0.73; 0.86] | 0.752 | 0.745 | 0.748 |
| Total Cholesterol | 0.869 | 0.916 | [0.76; 0.99] | 0.834 | 0.861 | 0.845 |
| Lipid-lowering treatment | 0.876 | 0.891 | [0.82; 0.94] | 0.874 | 0.858 | 0.842 |

CVD= cardiovascular disease

\(^{*}\)A multiplication factor of 0.9 indicates that the premature CVD incidence rate reduces by 10% with every decade increase.

\(^{†}\)All models adjust for age at onset of CVD and add a single confounder (one at a time) to the baseline model.

\(^{‡}\)As in Table 2, Model B assumes random cohort effect and adjusting for age at start of decade and age at the onset of premature CVD.

Bold values indicate elimination of decade effect with adjustment of confounder.
Table S4. P-value for a trend in premature CVD incidence rate over decades after correction of different sets of confounders

| Adjustment strategy                                      | Confounders adjusted for*                                                                 | CVD before age 55 years | CVD before age 60 years | CVD before age 65 years |
|----------------------------------------------------------|-------------------------------------------------------------------------------------------|--------------------------|-------------------------|-------------------------|
| Confounders associated with premature CVD for all three age thresholds | Smoking, antihypertensive medication, and lipid-lowering treatment | 0.611                    | 0.596                   | 0.004                   |
| Confounders associated with premature CVD for at least two age thresholds | Smoking, antihypertensive medication, lipid-lowering treatment, male sex, age at CVD, systolic blood pressure, and diabetes | 0.846                    | 0.172                   | 0.456                   |
| Confounders associated with premature CVD for at least one age threshold | Smoking, antihypertensive medication, lipid-lowering treatment, male sex, age at CVD, systolic blood pressure, and diabetes, body mass index | 0.878                    | 0.481                   | 0.912                   |

* The variables were selected based on a model selection approach using stepwise Poisson regression analysis and the Bayesian Information Criteria
Table S5. Type of premature cardiovascular disease (CVD) event across decades by sex

| Decade:       | 1950-1959 | 1960-1969 | 1970-1979 | 1980-1989 | 1990-1999 | 2000-2009 | 2009-2019 | P-trend |
|---------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|---------|
| **CVD type before age 55 years, %** | | | | | | | | |
| **Women N=7735** | | | | | | | | |
| CHD           | 49.4      | 50.0      | 56.1      | 41.2      | 42.4      | 46.9      | 28.6      | 0.329   |
| Stroke/TIA    | 19.3      | 16.0      | 16.7      | 17.6      | 27.3      | 31.2      | 42.8      | 0.976   |
| CHF           | 14.5      | 10.0      | 4.5       | 11.8      | 9.1       | 6.3       | 28.6      | 0.462   |
| PAD           | 8.4       | 10.0      | 22.7      | 29.4      | 18.2      | 12.5      | 0         | 0.062   |
| CVD death     | 8.4       | 14.0      | 0         | 0         | 3.0       | 3.1       | 0         | **0.040**|
| **Men N=6729** | | | | | | | | |
| CHD           | 66.4      | 63.2      | 84        | 71.5      | 61.7      | 64.3      | 51.7      | 0.543   |
| Stroke/TIA    | 9.8       | 9.2       | 5.3       | 9.5       | 10.6      | 19        | 37.9      | 0.383   |
| CHF           | 9.8       | 3.1       | 2.3       | 3.2       | 10.6      | 2.4       | 6.9       | 0.652   |
| PAD           | 7.0       | 13.3      | 7.6       | 8.4       | 14.9      | 7.1       | 0         | **0.006**|
| CVD death     | 7.0       | 11.2      | 0.8       | 7.4       | 2.1       | 7.1       | 3.4       | 0.322   |
| **CVD type before age 60 years, %** | | | | | | | | |
| **Women N=7735** | | | | | | | | |
| CHD           | 56.5      | 53.6      | 56.9      | 55.6      | 49.0      | 47.1      | 30.0      | 0.195   |
| Stroke/TIA    | 14.5      | 15.5      | 14.6      | 12.7      | 29.4      | 30.2      | 35.0      | **0.009**|
| CHF           | 13.0      | 11.3      | 6.2       | 7.9       | 7.8       | 5.7       | 25.0      | 0.575   |
| PAD           | 9.1       | 8.2       | 20.8      | 22.2      | 11.8      | 15.1      | 10.0      | 0.232   |
| CVD death     | 6.9       | 11.3      | 1.5       | 1.6       | 2.0       | 1.9       | 0         | **0.013**|
| **Men N=6729** | | | | | | | | |
| CHD           | 62.8      | 64.4      | 77.3      | 72.5      | 62.5      | 64.3      | 51        | 0.775   |
| Stroke/TIA    | 9.4       | 9         | 6.8       | 9.9       | 12.5      | 17.1      | 35.3      | **0.001**|
| CHF           | 9.4       | 3.2       | 3.4       | 3.5       | 8         | 5.7       | 5.9       | 0.378   |
| PAD           | 9.8       | 11.2      | 10.6      | 7.7       | 10.2      | 7.1       | 3.9       | 0.214   |
| CVD death     | 8.5       | 12.2      | 1.9       | 6.3       | 6.8       | 5.7       | 3.9       | 0.065   |
| **CVD type before age 65 years, %** | | | | | | | | |
| **Women N=7735** | | | | | | | | |
| CHD           | 58.2      | 53.4      | 55.7      | 58.7      | 53.5      | 47.2      | 38.2      | 0.247   |
| Stroke/TIA    | 16.3      | 14.3      | 13.9      | 14.1      | 26.8      | 27.0      | 29.4      | **0.010**|
| CHF           | 10.3      | 10.6      | 6.0       | 7.6       | 7.0       | 11.2      | 20.6      | 0.804   |
| PAD           | 9.2       | 11.8      | 20.9      | 18.5      | 11.3      | 11.2      | 11.8      | 0.570   |
| CVD death     | 6.0       | 9.9       | 3.5       | 1.1       | 1.4       | 3.4       | 0         | **0.007**|
| **Men N=6729** | | | | | | | | |
| CHD           | 65.5      | 61.5      | 71.4      | 70.3      | 63.5      | 60.2      | 48.7      | 0.424   |
| Stroke/TIA    | 9.8       | 10.7      | 7.7       | 10.4      | 13.1      | 18.4      | 30.2      | **<0.001**|
| CHF           | 8.1       | 3.4       | 4.0       | 3.3       | 6.2       | 5.8       | 6.6       | 0.513   |
| PAD           | 9.1       | 11.8      | 13.1      | 10.4      | 11.0      | 7.8       | 6.6       | 0.485   |
| CVD death     | 7.4       | 12.6      | 3.7       | 5.6       | 6.2       | 7.8       | 7.9       | 0.150   |

CHD= coronary heart disease, CHF= congestive heart failure, CVD= cardiovascular disease, PAD= peripheral arterial disease, TIA = transient ischemic attack. Significant P values are bolded
Table S6. Type of first cardiovascular disease (CVD) event (all ages) across decades by sex

|       | Decade | 1950-1959 | 1960-1969 | 1970-1979 | 1980-1989 | 1990-1999 | 2000-2009 | 2009-2019 |
|-------|--------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Women | N=7735 |           |           |           |           |           |           |           |
| CHD   |        | 56.0      | 48.2      | 49.0      | 42.3      | 36.9      | 34.0      | 24.9      |
| Stroke/TIA |    | 17.8      | 18.4      | 19.3      | 28.3      | 33.8      | 29.9      | 33.9      |
| CHF   |        | 10.9      | 11.7      | 9.7       | 12.8      | 16.0      | 25.3      | 34.3      |
| PAD   |        | 8.9       | 10.7      | 13.8      | 10.1      | 8.4       | 6.7       | 2.4       |
| CVD death |     | 6.4       | 11.0      | 8.1       | 6.5       | 4.9       | 4.1       | 4.5       |
| Men   | N=6729 |           |           |           |           |           |           |           |
| CHD   |        | 65.0      | 57.0      | 60.0      | 59.6      | 50.7      | 41.6      | 35.7      |
| Stroke/TIA |    | 10.3      | 12.3      | 15.0      | 15.6      | 20.5      | 25.8      | 31.1      |
| CHF   |        | 8.0       | 6.8       | 5.6       | 7.3       | 11.9      | 18        | 20.3      |
| PAD   |        | 9.0       | 11.3      | 11.9      | 9.2       | 10.1      | 6.5       | 6.2       |
| CVD death |     | 7.7       | 12.6      | 7.4       | 8.3       | 6.8       | 8.1       | 6.6       |

CHD= coronary heart disease, CHF= congestive heart failure, PAD= peripheral arterial disease, TIA = transient ischemic attack
Table S7. Association of calendar decade with the incidence of premature coronary heart disease (CHD)

| Sex          | Uncorrected | Corrected for age at start of decade | Corrected for age at onset of CHD |
|--------------|-------------|--------------------------------------|-----------------------------------|
|              | CHD before age 55 years | CHD before age 60 years | CHD before age 65 years | CHD before age 55 years | CHD before age 60 years | CHD before age 65 years |
| A. Assuming ‘no cohort’ effect |             |                                     |                                  |                         |                         |                         |
| Women        | 0.775 [0.65; 0.92] | 0.738 [0.61; 0.89] | 0.743 [0.59; 0.94] | 0.803 [0.70; 0.92] | 0.761 [0.68; 0.86] | 0.749 [0.68; 0.83] | 0.805 [0.72; 0.90] | 0.785 [0.70; 0.88] | 0.755 [0.68; 0.84] |
| Men          | 0.774 [0.66; 0.91] | 0.769 [0.65; 0.91] | 0.740 [0.59; 0.93] | 0.779 [0.69; 0.88] | 0.763 [0.69; 0.84] | 0.739 [0.67; 0.82] | 0.789 [0.72; 0.86] | 0.762 [0.69; 0.84] | 0.733 [0.67; 0.81] |
| B. Assuming random cohort effect | | | | | | | | | |
| Women        | 1.032 [0.88; 1.21] | 1.095 [0.99; 1.21] | 1.138 [1.05; 1.23] | 0.771 [0.65; 0.92] | 0.757 [0.66; 0.87] | 0.724 [0.63; 0.83] | 0.796 [0.70; 0.90] | 0.808 [0.72; 0.91] | 0.779 [0.70; 0.86] |
| Men          | 1.03 [0.90; 1.19]  | 1.11 [1.02; 1.21]  | 1.159 [1.09; 1.24] | 0.767 [0.65; 0.90] | 0.763 [0.67; 0.87] | 0.740 [0.65; 0.84] | 0.784 [0.71; 0.87] | 0.784 [0.70; 0.88] | 0.761 [0.69; 0.84] |
| Variance of cohort effect† | 0.499 (P<0.001) | 0.859 (P<0.001) | 1.108 (P<0.001) | 0.063 (P<0.001) | 0.052 (P<0.001) | 0.047 (P<0.001) | 0.023 (P=0.007) | 0.044 (P<0.001) | 0.030 (P<0.001) |

CHD = coronary heart disease
*A multiplication factor of 0.9 indicates that the premature CHD incidence rate reduces by 10% with every decade increase.
†Estimated variance in the period trends in premature CHD incidence attributable to the effect of different cohorts contributing to the observations across the decades; a lower variance indicates the cohort effect on premature CHD trends is lower. Correcting for the age of the cohort at the start of the decade and for age at the onset of premature CHD reduces markedly but does not eliminate the contribution of cohorts themselves to the trends in premature CHD.
| Sex            | Uncorrected Stroke before age 55 years | Stroke before age 60 years | Stroke before age 65 years | Corrected for age at start of decade Stroke before age 55 years | Stroke before age 60 years | Stroke before age 65 years | Corrected for age at onset of stroke Stroke before age 55 years | Stroke before age 60 years | Stroke before age 65 years |
|----------------|----------------------------------------|---------------------------|---------------------------|---------------------------------------------------------------|---------------------------|---------------------------|---------------------------------------------------------------|---------------------------|---------------------------|
|                | **Women**                              |                           |                           |                                                              |                           |                           |                                                              |                           |                           |
|                |                                         | 0.867 [0.69; 1.09]         | 0.950 [0.81; 1.11]        | 0.933 [0.79; 1.10]                                             | 0.868 [0.73; 1.04]       | 0.959 [0.87; 1.06]                                             | 0.909 [0.84; 0.99]       | 0.847 [0.71; 1.01]         | 0.983 [0.89; 1.08]         | 0.921 [0.85; 1.00]         |
| Women          |                                         | 0.789 [0.61; 1.02]         | 0.979 [0.85; 1.13]        | 0.960 [0.82; 1.13]                                             | 0.771 [0.63; 0.94]       | 0.974 [0.89; 1.07]                                             | 0.941 [0.87; 1.02]       | 0.745 [0.60; 0.93]         | 0.966 [0.88; 1.06]         | 0.929 [0.86; 1.01]         |
|                | **Men**                                |                           |                           |                                                              |                           |                           |                                                              |                           |                           |
|                |                                         | 0.844 [0.35; 2.01]         | 1.350 [1.10; 1.65]        | 1.367 [1.18; 1.58]                                             | 0.868 [0.71; 1.06]       | 0.959 [0.86; 1.07]                                             | 0.909 [0.83; 0.99]       | 0.844 [0.70; 1.02]         | 0.983 [0.88; 1.09]         | 0.921 [0.84; 1.00]         |
| Men            |                                         | 0.755 [0.29; 2.00]         | 1.375 [1.13; 1.68]        | 1.412 [1.23; 1.63]                                             | 0.771 [0.62; 0.96]       | 0.974 [0.88; 1.08]                                             | 0.941 [0.87; 1.03]       | 0.738 [0.58; 0.93]         | 0.966 [0.87; 1.07]         | 0.929 [0.85; 1.01]         |
|                | **Variance of cohort effect**           |                           |                           |                                                              |                           |                           |                                                              |                           |                           |
|                |                                         | 0.005 (P=0.489)            | 0.687 (P<0.001)           | 0.911 (P<0.001)                                               | 0 (P=1.000)              | 0 (P=1.000)                                                    | 0 (P=1.000)              | 0 (P=1.000)                | 0 (P=1.000)                | 0 (P=1.000)                |

*A multiplication factor of 0.9 indicates that the premature stroke incidence rate reduces by 10% with every decade increase.

†Estimated variance in the period trends in premature stroke incidence attributable to the effect of different cohorts contributing to the observations across the decades; a lower variance indicates the cohort effect on premature stroke trends is lower. Correcting for the age of the cohort at the start of the decade and for age at the onset of premature stroke eliminates the contribution of cohorts themselves to the trends in premature stroke.
### Table S9. Trends in self-reported prevalence of heart disease and stroke between ages 45 and 64 years: National Center for Health Statistics, National Health Interview Survey, Family Core and Sample Adult questionnaires

| CVD Type      | % Prevalence* | Absolute change per decade | Relative change per decade (multiplication factor) |
|---------------|---------------|----------------------------|---------------------------------------------------|
|               | 1997-1998 | 2000-2001 | 2015-2016 | 2017-2018 |                                    |
| **Age 45-54** |               |               |           |           |                                     |
| Heart Disease† | 10.9 | 10.2 | 9.5 | 8.7 | - 0.87 (- 0.37 to -1.37) | - 8.12% (0.919) |
| Stroke‡       | 1.4 | 1.5 | 2.4 | 2.3 | +0.51 (+0.09 to + 0.92) | +36.6% (1.366) |
| **Age 55-64** |               |               |           |           |                                     |
| Heart Disease† | 17.4 | 17.1 | 14.8 | 15.0 | -1.32 (-0.82 to -1.83) | - 7.59% (0.924) |
| Stroke‡       | 3.8 | 3.3 | 3.6 | 4.1 | +0.16 (-0.26 to +0.58) | +4.52% (1.045) |

CVD = cardiovascular disease

**Bold** values are statistically significant.

*source: [https://www.cdc.gov/nchs/hus/contents2019.htm#Table-013](https://www.cdc.gov/nchs/hus/contents2019.htm#Table-013)

†Based on self-reported responses to questions about whether respondents had ever been told by a doctor or other health professional that they had coronary heart disease, angina (angina pectoris), a heart attack (myocardial infarction), or any other kind of heart disease or heart condition.

‡Based on self-reported responses to a question about whether respondents had ever been told by a doctor or other health professional that they had a stroke.
Figure S1. Sample size of each decade by cohort

Framingham Heart Study Participants: N=14,531
- Original cohort (Gen 1): N=5,209
- Offspring cohort (Gen 2): N=5,227
- Third generation cohort (Gen 3): N=4,095

Exclusion N=67
- Prevalent CVD before first examination (N=65)
- CVD before age 25 (N=2)

Eligible participants at-risk with covariates in the following decades (N=14,464):

1950-1959 (N=5,182)
  Gen 1: 5,182
  Gen 2: 0
  Gen 3: 0

1960-1969 (N=3,616)
  Gen 1: 3,616
  Gen 2: 0
  Gen 3: 0

1970-1979 (N=6,407)
  Gen 1: 1,927
  Gen 2: 4,480
  Gen 3: 0

1980-1989 (N=4,180)
  Gen 1: 0
  Gen 2: 4,180
  Gen 3: 0

1990-1999 (N=3,158)
  Gen 1: 0
  Gen 2: 3,158
  Gen 3: 0

2000-2010 (N=5,589)
  Gen 1: 0
  Gen 2: 1,678
  Gen 3: 3,911

2010-2019 (N=3,678)
  Gen 1: 0
  Gen 2: 544
  Gen 3: 3,134
Figure S2. Average ages at entry into a calendar decade (solid lines) and the onset of premature CVD (dotted lines) for women (green) and men (red) per period and cohort

Panel A

Panel B
Panel C

Average ages per period and cohort
Premature CVD before 65 years

Average age (in years)

Decade

1950-1959 1960-1969 1970-1979 1980-1989 1990-1999 2000-2009 2010-2019

Generation 1

Generation 2

Generation 3