Supplemental Material

Data S1.

Supplemental Methods

Parametric models for time-varying covariates

We estimated the joint density of covariates at each year as the product of conditional densities given the covariate history by fitting parametric models for each covariate in the following order: smoking, BMI, SBP, DBP, antihypertensive treatment, diabetes, heart failure, and myocardial infarction. We fit logistic models for dichotomous covariates and linear models for continuous covariates. We checked the functional form for time and all covariates by assessing the differences between the natural course and observed data, and then fit the model with the most adequate transformation. Our final results included restricted cubic splines for time, BMI, SBP, and DBP.

Pooled logistic models for hazard of atrial fibrillation

We estimated the hazard of AF each year, conditional on the covariate history, with a pooled logistic model.[42-45] For an individual i, the probability of AF at year j is given by

$$logit(p_{ij}) = \beta_0 + Y_i(t_k)^T\boldsymbol{\gamma} + X_i^T\boldsymbol{\alpha} + r(t_k)\boldsymbol{\theta}$$

in which $Y_i(t_j)$ denotes all observed time-varying covariates at year j, X_i denotes time-invariant covariates (sex), and $r(t_j)$ denotes a restricted cubic spline function. The estimated survival probabilities at year k are then given by $\hat{S}(t_k) = \frac{1}{n}\sum_{i=1}^{n}\left(\prod_{j:\, t_j \le t_k}(1 - \widehat{p_{ij}})\right)$, in which p_{ij} denotes the probability of AF for individual i at year j.[41]

In a sensitivity analysis, we estimated the hazard of AF with a pooled negative binomial model instead of a logistic model:

$$log(\mu_{ij}) = \beta_0 + Y_i(t_k)^T\boldsymbol{\gamma} + X_i^T\boldsymbol{\alpha} + r(t_k)\boldsymbol{\theta}$$

where μ_{ij} denotes the expected AF event count for individual i at year j.

Table S1. Body mass index interventions and comparisons assessed with the g-formula.

Intervention	Reference
Non-obese at all times, BMI [18.5, 29.9]	Obese at all times, BMI [30, 40]
Non-obese at all times, BMI [18.5, 29.9]	Natural course
10% decrease in BMI per year when BMI>=25	Natural course

Table S2. Characteristics of participants by Framingham Heart Study cohort (n=4,392).

	Original (n=841)	Offspring (n=3,551)
Age (years)	52.8 ± 1.7	50.3 ± 2
Women	468 (55.6)	1,877 (52.9)
BMI (kg/m^2)	26.3 ± 4.3	27.2 ± 5.1
SBP (mm Hg)	132 ± 19	124 ± 17
DBP (mm Hg)	83 ± 11	79 ± 10
Current smoker	191 (41.4)	993 (28)
Use of hypertension medication	75 (8.9)	504 (14.2)
Diabetes	17 (2.8)	181 (5.5)
Heart failure	3 (0.4)	10 (0.3)
Myocardial infarction	25 (3.0)	70 (2.0)

Values are mean ± SD or n (%).

Table S3. G-formula associations per body mass index intervention group and contrasts between intervention groups by sex at 20 years of follow-up.

Men (n=2,047)	Intervention	Comparator	Measure of Association	
Non-obese vs. obese				
			Hazard ratio	0.81 (0.63, 1.04)
Risk, %	14.81 (12.33, 17.29)	18.11 (14.79, 21.42)	Risk ratio	0.82 (0.66, 1.01)
			Risk difference	-3.30 (-6.89, 0.30)
RMST, years	18.78 (18.41, 19.14)	18.62 (18.25, 18.98)	Difference in RMSTs, mos.	1.89 (-3.67, 7.44)
Non-obese vs. natural course				
			Hazard ratio	0.96 (0.82, 1.14)
Risk, %	14.87 (12.37, 17.37)	15.51 (13.63, 17.39)	Risk ratio	0.96 (0.85, 1.08)
			Risk difference	-0.64 (-2.48, 1.20)
RMST, years	18.77 (18.40, 19.14)	18.82 (18.66, 18.98)	Difference in RMSTs, mos.	-0.61 (-4.70, 3.48)
10% decrease in BMI per year vs. natural course				
			Hazard ratio	0.97 (0.87, 1.07)
Risk, %	14.97 (13.02, 16.93)	15.49 (13.64, 17.34)	Risk ratio	0.97 (0.92, 1.02)
			Risk difference	-0.52 (-1.30, 0.26)
RMST, years	18.84 (18.68, 19.01)	18.82 (18.66, 18.98)	Difference in RMSTs, mos.	0.28 (-0.37, 0.93)
Women (n=2,345)	**Intervention**	**Comparator**	**Measure of Association**	
Non-obese vs. obese				
			Hazard ratio	0.69 (0.48, 1.01)
Risk, %	6.24 (4.52, 7.97)	8.94 (6.45, 11.42)	Risk ratio	0.70 (0.50, 0.98)
			Risk difference	-2.69 (-5.37, -0.02)
RMST, years	19.48 (19.21, 19.76)	19.38 (19.18, 19.59)	Difference in RMSTs, mos.	1.19 (-2.34, 4.71)
Non-obese vs. natural course				
			Hazard ratio	0.93 (0.72, 1.21)
Risk, %	6.24 (4.50, 7.98)	6.63 (5.46, 7.81)	Risk ratio	0.94 (0.76, 1.16)
			Risk difference	-0.39 (-1.80, 1.01)
RMST, years	19.48 (19.20, 19.76)	19.53 (19.44, 19.63)	Difference in RMSTs, mos.	-0.58 (-3.74, 2.58)
10% decrease in BMI per year vs. natural course				
			Hazard ratio	0.97 (0.82, 1.14)
Risk, %	6.37 (5.20, 7.53)	6.63 (5.46, 7.81)	Risk ratio	0.96 (0.91, 1.01)
			Risk difference	-0.27 (-0.62, 0.08)
RMST, years	19.54 (19.45, 19.64)	19.53 (19.44, 19.63)	Difference in RMSTs, mos.	0.11 (-0.13, 0.35)

Numbers are estimates and 95% confidence intervals, obtained with 500 bootstrap samples.

Table S4. G-formula associations per body mass index intervention group and contrasts between intervention groups at 20 years of follow-up in cancer-free participants. (n=3,870).

	Intervention	Comparator	Measure of Association	
Non-obese vs. obese				
			Hazard ratio	0.73 (0.55, 0.97)
Risk, %	10.10 (8.01, 12.19)	13.60 (10.73, 16.46)	Risk ratio	0.74 (0.58, 0.95)
			Risk difference	-3.49 (-6.45, -0.54)
RMST, years	19.22 (18.94, 19.50)	19.05 (18.84, 19.27)	Difference in RMSTs, mos.	1.95 (-2.03, 5.92)
Non-obese vs. natural course				
			Hazard ratio	0.92 (0.76, 1.12)
Risk, %	10.09 (8.00, 12.17)	10.93 (9.24, 12.62)	Risk ratio	0.92 (0.80, 1.07)
			Risk difference	-0.85 (-2.34, 0.65)
RMST, years	19.22 (18.94, 19.49)	19.23 (19.11, 19.34)	Difference in RMSTs, mos.	-0.11 (-3.23, 3.01)
10% decrease in BMI per year vs. natural course				
			Hazard ratio	0.95 (0.85, 1.07)
Risk, %	10.41 (8.72, 12.11)	10.93 (9.25, 12.61)	Risk ratio	0.95 (0.90, 1.00)
			Risk difference	-0.51 (-1.07, 0.04)
RMST, years	19.25 (19.14, 19.36)	19.23 (19.11, 19.34)	Difference in RMSTs, mos.	0.30 (-0.12, 0.71)

Numbers are estimates and 95% confidence intervals, obtained with 500 bootstrap samples.

Table S5. G-formula associations per body mass index intervention group and contrasts between intervention groups at 20 years of follow-up, with complete case data at entry. (n=3,102)

	Intervention	Comparator	Measure of Association	
Non-obese vs. obese				
			Hazard ratio	0.71 (0.51, 0.98)
Risk, %	9.76 (7.64, 11.87)	13.58 (9.81, 17.34)	Risk ratio	0.72 (0.54, 0.96)
			Risk difference	-3.82 (-7.69, 0.05)
RMST, years	19.21 (18.84, 19.57)	19.00 (18.44, 19.55)	Difference in RMSTs, mos.	2.52 (-4.49, 9.54)
Non-obese vs. natural course				
			Hazard ratio	0.97 (0.78, 1.20)
Risk, %	9.77 (7.65, 11.90)	10.15 (8.89, 11.42)	Risk ratio	0.96 (0.81, 1.14)
			Risk difference	-0.38 (-2.15, 1.39)
RMST, years	19.20 (18.84, 19.56)	19.25 (19.15, 19.36)	Difference in RMSTs, mos.	-0.62 (-4.74, 3.49)
10% decrease in BMI per year vs. natural course				
			Hazard ratio	0.96 (0.84, 1.10)
Risk, %	9.64 (8.25, 11.03)	10.14 (8.86, 11.43)	Risk ratio	0.95 (0.88, 1.02)
			Risk difference	-0.51 (-1.19, 0.17)
RMST, years	19.27 (19.16, 19.39)	19.26 (19.15, 19.36)	Difference in RMSTs, mos.	0.23 (-0.32, 0.78)

Numbers are estimates and 95% confidence intervals, obtained with 500 bootstrap samples.

Table S6. G-formula associations per body mass index intervention group and contrasts between intervention groups at 20 years of follow-up, entry at age 60 plus or minus five years (n=6,149).

	Intervention	Comparator	Measure of Association	
Non-obese vs. obese				
			Hazard ratio	0.87 (0.77, 0.99)
Risk, %	19.90 (18.35, 21.45)	22.66 (20.33, 25.00)	Risk ratio	0.88 (0.80, 0.97)
			Risk difference	-2.76 (-4.89, -0.63)
RMST, years	18.35 (18.18, 18.52)	18.22 (18.02, 18.42)	Difference in RMSTs, mos.	1.56 (-0.88, 4.01)
Non-obese vs. natural course				
			Hazard ratio	0.96 (0.87, 1.06)
Risk, %	19.92 (18.36, 21.47)	20.65 (19.21, 22.09)	Risk ratio	0.96 (0.93, 1.00)
			Risk difference	-0.73 (-1.50, 0.03)
RMST, years	18.35 (18.18, 18.51)	18.33 (18.21, 18.46)	Difference in RMSTs, mos.	0.17 (-1.17, 1.52)
10% decrease in BMI per year vs. natural course				
			Hazard ratio	0.99 (0.90, 1.08)
Risk, %	20.44 (18.98, 21.89)	20.64 (19.18, 22.09)	Risk ratio	0.99 (0.97, 1.01)
			Risk difference	-0.20 (-0.62, 0.23)
RMST, years	18.34 (18.21, 18.46)	18.33 (18.21, 18.46)	Difference in RMSTs, mos.	0.01 (-0.35, 0.37)

Numbers are estimates and 95% confidence intervals, obtained with 500 bootstrap samples.

Table S7. G-formula associations per body mass index intervention group and contrasts between intervention groups at 20 years of follow-up, negative binomial model for atrial fibrillation (n=4,392).

	Intervention	Comparator	Measure of Association	
Non-obese vs. obese				
			Hazard ratio	0.72 (0.58, 0.89)
Risk, %	9.78 (8.40, 11.16)	13.18 (11.22, 15.14)	Risk ratio	0.74 (0.63, 0.88)
			Risk difference	-3.40 (-5.45, -1.34)
RMST, years	19.24 (19.05, 19.43)	19.04 (18.87, 19.20)	Difference in RMSTs, mos.	2.39 (-0.28, 5.06)
Non-obese vs. natural course				
			Hazard ratio	0.91 (0.78, 1.07)
Risk, %	9.79 (8.41, 11.17)	10.74 (9.64, 11.84)	Risk ratio	0.91 (0.83, 1.00)
			Risk difference	-0.95 (-1.93, 0.04)
RMST, years	19.24 (19.05, 19.43)	19.20 (19.11, 19.29)	Difference in RMSTs, mos.	0.44 (-1.58, 2.46)
10% decrease in BMI per year vs. natural course				
			Hazard ratio	0.97 (0.86, 1.09)
Risk, %	10.35 (9.15, 11.54)	10.77 (9.59, 11.95)	Risk ratio	0.96 (0.92, 1.00)
			Risk difference	-0.42 (-0.84, -0.01)
RMST, years	19.22 (19.12, 19.32)	19.20 (19.10, 19.30)	Difference in RMSTs, mos.	0.23 (-0.10, 0.56)

Numbers are estimates and 95% confidence intervals, obtained with 500 bootstrap samples.

Figure S1. Diagram of g-formula Monte Carlo simulation.

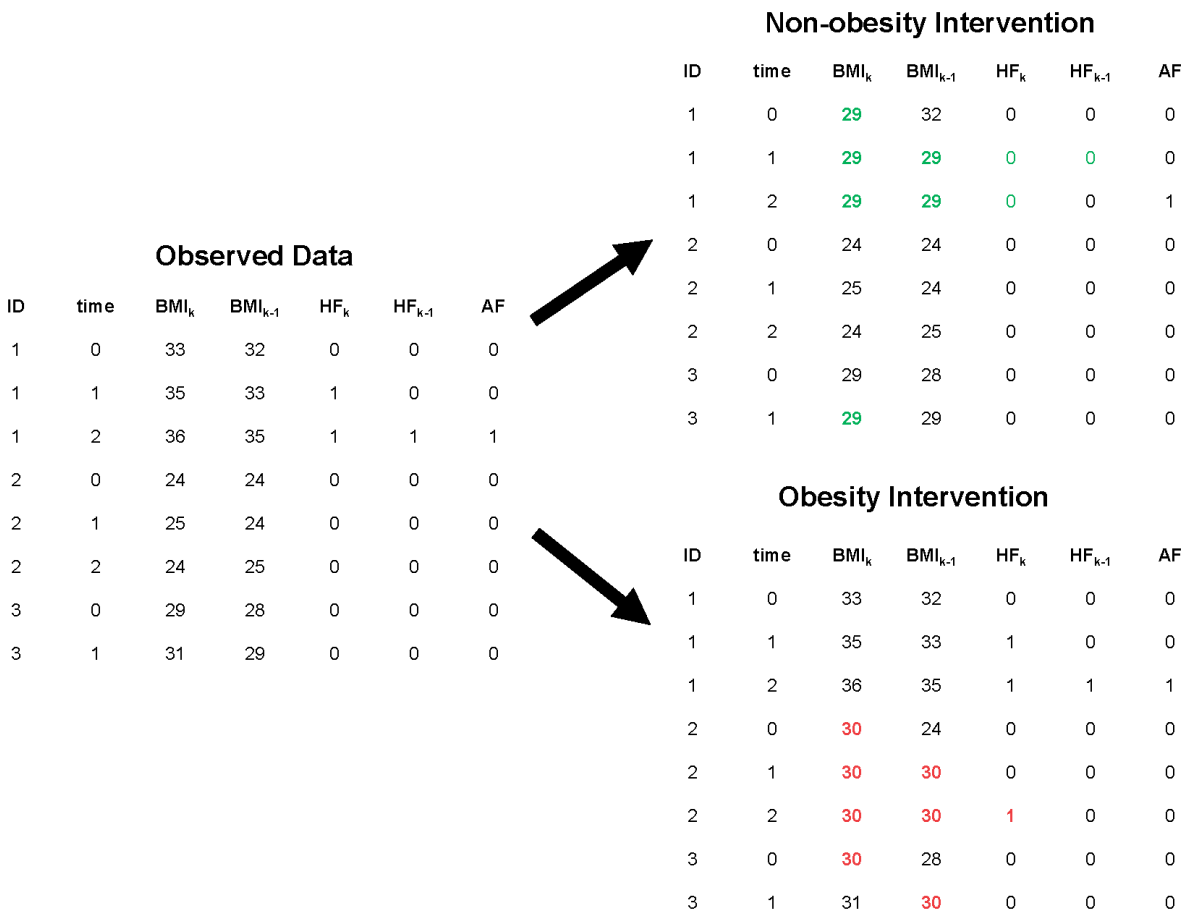

Figure S2. Flow diagram of study participants.

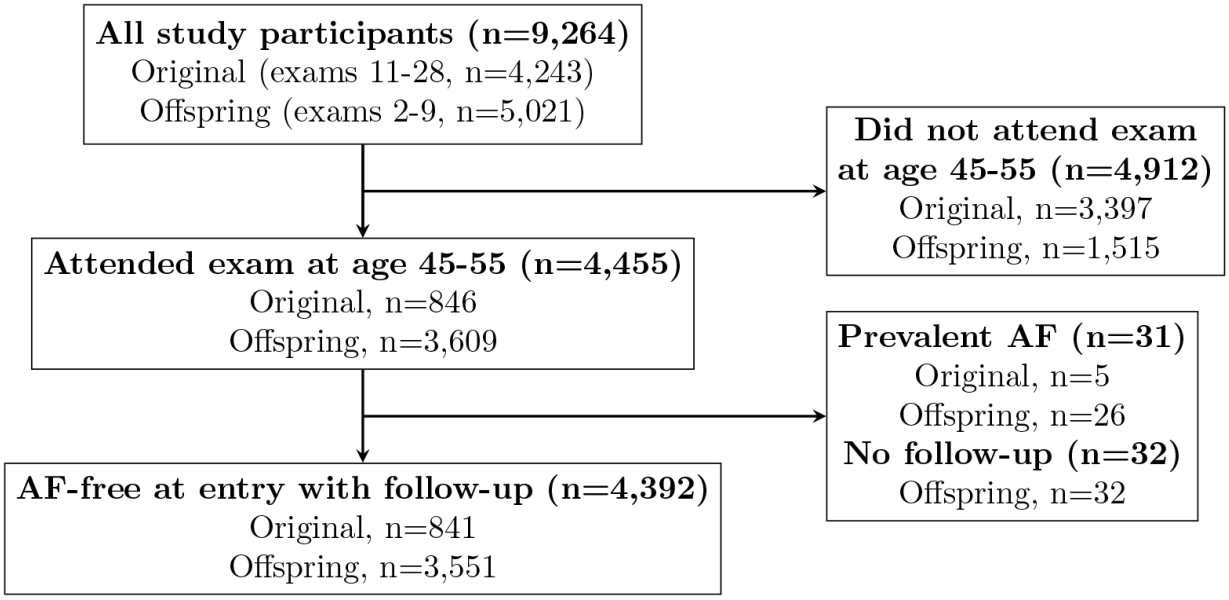

Figure S3. Kaplan Meier curves of g-formula survival probabilities comparing simulated populations under BMI interventions in men and women.