**Supporting Information**

**SI 1. Descriptive Characteristics of Excluded Sample, Framingham Heart Study.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **N** |  | **Mean (or %)** |  |  | **N** |  | **Mean (or %)** |
| **Original cohort** |  |  |  |  | **Offspring cohort** |  |  |  |
| **Time-invariant variables (N=503)** |  |  |  |  | **Time-invariant variables (N=1,260)** |  |  |  |
| Birth cohorts |  |  |  |  | Birth cohorts |  |  |  |
| 1870 to 1894 | 116 |  | 23.06% |  | 1903 to 1924 | 194 |  | 15.40% |
| 1895 to 1899 | 94 |  | 18.69% |  | 1925 to 1929 | 136 |  | 10.79% |
| 1900 to 1904 | 82 |  | 16.30% |  | 1930 to 1934 | 162 |  | 12.86% |
| 1905 to 1909 | 68 |  | 13.52% |  | 1935 to 1939 | 198 |  | 15.71% |
| 1910 to 1914 | 72 |  | 14.31% |  | 1940 to 1944 | 208 |  | 16.51% |
| 1915 and above | 71 |  | 14.12% |  | 1945 to 1949 | 196 |  | 15.56% |
|  |  |  |  |  | 1950 and above | 166 |  | 13.17% |
| Gender |  |  |  |  | Gender |  |  |  |
| Male | 210 |  | 42.42% |  | Male | 614 |  | 48.73% |
| Female | 285 |  | 57.58% |  | Female | 646 |  | 51.27% |
| Inconsistent gender | 8 |  |  |  |  |  |  |  |
| Educational attainment |  |  |  |  | Years of education |  |  |  |
| Less than high school | 166 |  | 53.90% |  | 0-11 | 2 |  | 12.50% |
| High school graduate | 73 |  | 23.70% |  | 12 | 5 |  | 31.25% |
| Some college | 42 |  | 13.64% |  | 13-15 | 5 |  | 31.25% |
| College graduate | 27 |  | 8.77% |  | 16 and above | 4 |  | 25.00% |
| Unknown | 195 |  |  |  | Unknowna | 1,244 |  |  |
| **Time-variant variables (N=3,024 observations)** |  |  |  |  | **Time-variant variables (N=2,525 observations)** |  |  |  |
| BMI | 2,757 |  | 26.68 |  | BMI | 2,435 |  | 27.77 |
| Body type categories |  |  |  |  | Body type categories |  |  |  |
| Underweightb | 37 |  | 1.34% |  | Underweightb | 18 |  | 0.74% |
| Normal weightc | 959 |  | 34.78% |  | Normal weightc | 812 |  | 33.35% |
| Overweightd | 1,236 |  | 44.83% |  | Overweightd | 931 |  | 38.23% |
| Class I obesitye | 418 |  | 15.16% |  | Class I obesitye | 438 |  | 17.99% |
| Class II/III obesityf | 107 |  | 3.88% |  | Class II/III obesityf | 236 |  | 9.69% |
| Unknown | 267 |  |  |  | Unknown | 90 |  |  |
| Age | 3,024 |  | 58.42 |  | Age | 2,525 |  | 53.83 |
| Smoking behavior |  |  |  |  | Smoking behavior |  |  |  |
| Non-smoker | 875 |  | 61.36% |  | Non-smoker | 1,926 |  | 76.34% |
| Low smoking (1-9 cigarettes) | 121 |  | 8.49% |  | Low smoking (1-9 cigarettes) | 84 |  | 3.33% |
| Moderate smoking (10-19 cigarettes) | 94 |  | 6.59% |  | Moderate smoking (10-19 cigarettes) | 141 |  | 5.59% |
| Heavy smoking (20 or more cigarettes) | 336 |  | 23.56% |  | Heavy smoking (20 or more cigarettes) | 372 |  | 14.74% |
| Unknown | 1,598 |  |  |  | Unknown | 2 |  |  |
| Disease index | 3,024 |  | 48.64% |  | Disease index | 2,525 |  | 77.86% |
| a Missing education is primarily due to individuals not participating in exam 2, which is the only wave to collect the information on years of educational attainment. | | | | | | | | |
| b Underweight was defined as having a BMI less than 18.5 kg/m2 | | | | | | | | |
| c Normal weight was defined as having a BMI between 18.5 and 24.9 kg/m2 | | | | | | | | |
| d Overweight was defined as having a BMI between 25 and 29.9 kg/m2 | | | | | | | | |
| e Class I obesity was defined as having a BMI between 30 and 34. kg/m2 | | | | | | | | |
| f Class II/III obesity was defined as having a BMI greater than or equal to 35 kg/m2 | | | | | | | | |

**SI 2. Technical Details for Latent Class Trajectory Models.**

The group-based trajectory model (i.e., latent class trajectory model) assumes that the population distribution of trajectories arises from a finite mixture of unknown order *J*. Suppose vector represents a longitudinal sequence of an outcome variable for an individual *i* over T periods. Then, the likelihood of each individual *i*, conditional on the number of groups *J*, can be written as

,

where *j* denotes the underlying group *j*, denotes the probability of ,denotes the probability of membership in group *j*, and is the probability of  given membership in group *j*. Group membership probabilities, , *j*=1,…,J, are estimated by a multinomial logit regression. This model assumes that, conditional on membership in group *j*, , t=1,…, T, are independent, thus , where *p*(.) is the distribution of *yit* conditional on membership in group *j* and time *t*. As the outcome variable in this study is log(BMI), is defined by a censored normal distribution. For the censored normal distribution, the linkage between time (age in our study) and the outcome variable is established by means of a latent variable, , that is a function of age. For more detailed explanation of this method, please refer to Nagin (1999, 2005).

Even though latent trajectory model is a straightforward tool to uncover the underlying structure of developmental trajectories in the population, the assignment of individuals to a distinct developmental pattern is based on their highest estimated group-membership probability to the identified pattern; thus, these latent patterns should not be considered as the actual developmental patterns but, rather, as approximations of more complex ones.

Reference:

Nagin DS. Analyzing Developmental Trajectories: A Semiparametric, Group-Based Approach. *Psychol. Methods*. 1999;4:139-157.

Nagin DS. *Group-Based Modeling of Development*. 2005. Cambridge, MA: Harvard University Press.

**SI 3. Population Attributable Mortality Risk Fraction**

After obtaining the hazard ratios associated with BMI trajectories, we calculate the population attributable mortality risk fraction (PAF) using the following formula:

where *j* represents the categories of BMI trajectories, is the proportion of BMI trajectory in the population, and is the relative mortality risk of BMI trajectory relative to the reference category (with the lowest mortality risk), which can be obtained from the hazard ratios in the Cox model. is the counterfactual proportion of the BMI trajectory in the population when all the respondents in this trajectory are assigned to the reference category. We use RRs without adjusting for diseases in the PAF because they can be mechanisms linking BMI trajectories to mortality.

**SI 4. Criteria Used to Determine the Number and Function of BMI Trajectories.**

In terms of criteria used to determine the number and function of BMI trajectories, we use Bayesian Information Criterion (BIC), average posterior probabilities, odds of correct classification of belonging to each identified trajectory, model entropy, and subjective assessment. As suggested by the developer of this method, Nagin et al. (2018: 2019) writes, “model choice cannot be left to mechanical application of fits statistics and model diagnostics. Models must also be evaluated on their substantive interest.” SI 5 displays the model fit statistics for latent trajectory analysis for original cohort and offspring cohort.

Among original cohort, the model with 7 trajectories has a smaller BIC (indicating better model fit) than the 6-trajectory model, but a larger BIC than the 8-trajectory model. We decide to choose 7 trajectories because the model with 8 trajectories does not provide additional information as shown in SI 6. It generated two “normal weight stable” trajectories, adding no trajectories that were substantively different from those identified in the 7-trajectory model. Moreover, no matter which model choice, normal weight upward trajectory has lower mortality risk compared to all other trajectories.

Among offspring cohort, the model with 6 trajectories has a smaller BIC (indicating better model fit) than the 5-trajectory model, but a larger BIC than the 7-trajectory model. We decide to choose 6 trajectories because the model with 7 trajectories does not provide additional information as shown in SI 7. It generated two “overweight obese” trajectories, adding no trajectories that were substantively different from those identified in the 6-trajectory model. Moreover, no matter which model choice, normal weight upward trajectory has lower mortality risk compared to all other trajectories.

In addition to BIC and subjective assessment, we also rely on other important metrics of latent class models such as posterior probabilities and odds of correct classification of belonging to each identified trajectory, as well as model entropy. An “optimal” latent class model must have posterior probabilities of ≥0.7 and odds of correct classification of ≥4.5 for each identified trajectory, and a model entropy of ≥0.7. The 7-trajectory model for the original cohort and 6-trajectory model for the offspring cohort meet all these three additional criteria.

Reference:

Nagin DS, Jones BL, Passos VL, Tremblay RE. Group-based multi-trajectory modeling. *Statistical Methods in Medical Research*. 2018; 27(7):2015-2023.

**SI 5. Model Fit Statistics in Latent Trajectory Analysis (Ages 31 to 80), Framingham Heart Study.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Original Cohort | | 7 trajectories |  | 8 trajectories |  | 6 trajectories |
|  | AIC | -138,968.69 |  | -142,258.79 |  | -134,938.17 |
|  | BIC | -138,785.83 |  | -142,049.81 |  | -134,781.43 |
|  | Model entropy | 0.88 |  | 0.88 |  | 0.87 |
|  | Odds of correct classification |  |  |  |  |  |
|  | Trajectory 1 | 210.38 |  | 308.59 |  | 193.49 |
|  | Trajectory 2 | 37.02 |  | 62.84 |  | 31.73 |
|  | Trajectory 3 | 38.92 |  | 25.79 |  | 17.13 |
|  | Trajectory 4 | 18.90 |  | 50.16 |  | 39.50 |
|  | Trajectory 5 | 49.77 |  | 19.70 |  | 53.10 |
|  | Trajectory 6 | 204.00 |  | 54.90 |  | 579.65 |
|  | Trajectory 7 | 1576.29 |  | 226.16 |  |  |
|  | Trajectory 8 |  |  | 1744.22 |  |  |
|  | Average posterior probabilities |  |  |  |  |  |
|  | Trajectory 1 | 0.96 |  | 0.95 |  | 0.96 |
|  | Trajectory 2 | 0.92 |  | 0.92 |  | 0.92 |
|  | Trajectory 3 | 0.85 |  | 0.88 |  | 0.83 |
|  | Trajectory 4 | 0.84 |  | 0.86 |  | 0.86 |
|  | Trajectory 5 | 0.93 |  | 0.82 |  | 0.93 |
|  | Trajectory 6 | 0.95 |  | 0.92 |  | 0.98 |
|  | Trajectory 7 | 0.97 |  | 0.95 |  |  |
|  | Trajectory 8 |  |  | 0.97 |  |  |
| Offspring Cohort | | 6 trajectories |  | 7 trajectories |  | 5 trajectories |
|  | AIC | -40,768.16 |  | -41,725.49 |  | -39,041.97 |
|  | BIC | -40,614.24 |  | -41,545.91 |  | -38,913.71 |
|  | Model entropy | 0.87 |  | 0.87 |  | 0.88 |
|  | Odds of correct classification |  |  |  |  |  |
|  | Trajectory 1 | 176.23 |  | 29.26 |  | 81.22 |
|  | Trajectory 2 | 25.87 |  | 186.47 |  | 18.58 |
|  | Trajectory 3 | 30.45 |  | 18.20 |  | 20.24 |
|  | Trajectory 4 | 17.43 |  | 72.87 |  | 83.85 |
|  | Trajectory 5 | 96.16 |  | 22.67 |  | 523.23 |
|  | Trajectory 6 | 623.34 |  | 240.64 |  |  |
|  | Trajectory 7 |  |  | 1343.55 |  |  |
|  | Average posterior probabilities |  |  |  |  |  |
|  | Trajectory 1 | 0.94 |  | 0.89 |  | 0.93 |
|  | Trajectory 2 | 0.89 |  | 0.94 |  | 0.90 |
|  | Trajectory 3 | 0.90 |  | 0.87 |  | 0.91 |
|  | Trajectory 4 | 0.88 |  | 0.91 |  | 0.93 |
|  | Trajectory 5 | 0.92 |  | 0.88 |  | 0.96 |
|  | Trajectory 6 | 0.96 |  | 0.93 |  |  |
|  | Trajectory 7 |  |  | 0.96 |  |  |
|  | | | | | | |

**SI 6. Eight latent BMI trajectories from 31 to 80 years of age in the Framingham Heart Study original cohort 1948-2010.**

Chart

Description automatically generated

**SI 7. Seven latent BMI trajectories from 31 to 80 years of age in the Framingham Heart Study offspring cohort 1979-2001.**

Chart, line chart

Description automatically generated

SI 8. Adjusted Hazard Ratios of BMI Trajectories (Ages 31-80) from Cox Hazard Models in Framingham Heart Study Original Cohort 1948-2010.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Model 1 | Model 2 | Model 3 | Model 4 |
|  |  | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| Body mass index trajectories | |  |  |  |  |
|  | Lower level of normal weightᵃ | 1.48 (1.30, 1.68) | 1.49 (1.31, 1.70) | 1.37 (1.20, 1.56) | 1.40 (1.23, 1.60) |
|  | Normal weightᵃ stable | 1.19 (1.07, 1.32) | 1.21 (1.09, 1.34) | 1.17 (1.06, 1.30) | 1.19 (1.07, 1.32) |
|  | Normal weightᵃ upward | 1.00 | 1.00 | 1.00 | 1.00 |
|  | Overweightᵇ downward | 1.37 (1.23, 1.53) | 1.38 (1.24, 1.54) | 1.37 (1.23, 1.53) | 1.38 (1.24, 1.53) |
|  | Overweightᵇ stable | 1.32 (1.18, 1.47) | 1.32 (1.18, 1.46) | 1.34 (1.20, 1.49) | 1.34 (1.20, 1.49) |
|  | Class I obeseᶜ | 1.56 (1.35, 1.80) | 1.53 (1.33, 1.77) | 1.58 (1.36, 1.82) | 1.55 (1.34, 1.79) |
|  | Class II/III obeseᵈ | 2.15 (1.72, 2.69) | 2.11 (1.68, 2.64) | 2.18 (1.69, 2.82) | 2.11 (1.63, 2.73) |
| Birth cohorts | |  |  |  |  |
|  | 1876 to 1894 | 1.00 | 1.00 | 1.00 | 1.00 |
|  | 1895 to 1899 | 0.94 (0.83, 1.06) | 0.94 (0.83, 1.07) | 0.93 (0.82, 1.06) | 0.94 (0.82, 1.07) |
|  | 1900 to 1904 | 0.97 (0.86, 1.10) | 0.98 (0.86, 1.11) | 1.00 (0.88, 1.13) | 1.00 (0.88, 1.13) |
|  | 1905 to 1909 | 0.88 (0.78, 0.99) | 0.89 (0.79, 1.01) | 0.89 (0.79, 1.01) | 0.89 (0.78, 1.01) |
|  | 1910 to 1914 | 0.85 (0.75, 0.95) | 0.86 (0.77, 0.97) | 0.88 (0.78, 1.00) | 0.88 (0.78, 0.99) |
|  | 1915 and Above | 0.77 (0.68, 0.87) | 0.79 (0.70, 0.89) | 0.81 (0.71, 0.91) | 0.80 (0.71, 0.91) |
| Gender | |  |  |  |  |
|  | Male | 1.00 | 1.00 | 1.00 | 1.00 |
|  | Female | 0.60 (0.56, 0.64) | 0.60 (0.56, 0.64) | 0.62 (0.58, 0.66) | 0.61 (0.57, 0.66) |
| Educational attainment | |  |  |  |  |
|  | Less than high school |  | 1.00 | 1.00 | 1.00 |
|  | High school graduate |  | 0.98 (0.91, 1.06) | 0.97 (0.90, 1.05) | 0.98 (0.90, 1.05) |
|  | Some college |  | 0.85 (0.78, 0.94) | 0.87 (0.80, 0.96) | 0.88 (0.80, 0.96) |
|  | College graduate |  | 0.88 (0.80, 0.98) | 0.90 (0.82, 1.00) | 0.90 (0.82, 1.00) |
| Smoking behavior | |  |  |  |  |
|  | Non-smoker |  |  | 1.00 | 1.00 |
|  | Low smoking (1-9 cigarettes) |  |  | 1.41 (1.20, 1.67) | 1.45 (1.23, 1.71) |
|  | Moderate smoking (10-19 cigarettes) |  |  | 1.49 (1.28, 1.74) | 1.54 (1.32, 1.80) |
|  | Heavy smoking (20 or more cigarettes) |  |  | 1.83 (1.65, 2.03) | 1.87 (1.69, 2.07) |
| Disease index | |  |  |  | 1.44 (1.31, 1.58) |
| AIC | | 56,589.88 | 56,581.22 | 56,446.30 | 56,397.36 |
| BIC | | 56,665.15 | 56,675.30 | 56,559.20 | 56,516.53 |
| Number of deaths | | 3,913 | 3,913 | 3,913 | 3,913 |
| N | | 4,576 | 4,576 | 4,576 | 4,576 |
| Observations | | 44,261 | 44,261 | 44,261 | 44,261 |
| ᵃ Normal weight was defined as having a BMI between 18.5 and 24.9 kg/m² | | | | | |
| ᵇ Overweight was defined as having a BMI between 25 and 29.9 kg/m² | | | | | |
| ᶜ Class I obesity was defined as having a BMI between 30 and 34.9 kg/m² | | | | | |
| ᵈ Class II/III obesity was defined as having a BMI greater than or equal to 35 kg/m² | | | | | |

**SI 9: Diseases Profiles by BMI Trajectories in Framingham Heart Study Original and Offspring Cohorts**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Original cohort** | Number of observations | No. of observations with at least one disease reported | % | Number of individuals | No. of individuals with at least one disease reported | % |
| Lower level of normal weightᵃ | 4,298 | 2,587 | 60.19% | 473 | 427 | 90.27% |
| Normal weightᵃ stable | 10,883 | 7,274 | 66.84% | 1,087 | 1,019 | 93.74% |
| Normal weightᵃ upward | 7,080 | 4,906 | 69.29% | 609 | 579 | 95.07% |
| Overweightᵇ downward | 8,765 | 6,222 | 70.99% | 983 | 914 | 92.98% |
| Overweightᵇ stable | 9,110 | 6,722 | 73.79% | 956 | 923 | 96.55% |
| Class I obeseᶜ | 3,468 | 2,792 | 80.51% | 382 | 370 | 96.86% |
| Class II/III obeseᵈ | 657 | 589 | 89.65% | 86 | 85 | 98.84% |
| Total | 44,261 | 31,092 |  | 4,576 | 4,317 |  |
| **Offspring cohort** |  |  |  |  |  |  |
| Lower level of normal weightᵃ | 1,626 | 1,298 | 79.83% | 325 | 325 | 100.00% |
| Normal weightᵃ stable | 4,713 | 3,686 | 78.21% | 927 | 922 | 99.46% |
| Normal weightᵃ upward | 5,701 | 4,574 | 80.23% | 1,113 | 1,109 | 99.64% |
| Overweightᵇ obesity | 4,399 | 3,531 | 80.27% | 867 | 867 | 100.00% |
| Class I obeseᶜ | 2,047 | 1,686 | 82.36% | 402 | 402 | 100.00% |
| Class II/III obeseᵈ | 581 | 510 | 87.78% | 119 | 118 | 99.16% |
| Total | 19,067 | 15,285 |  | 3,753 | 3,743 |  |
| aNormal weight was defined as having a BMI between 18.5 and 24.9 kg/m2 | | | | | | |
| bOverweight was defined as having a BMI between 25 and 29.9 kg/m2 | | | | | | |
| cClass I obesity was defined as having a BMI between 30 and 34.9 kg/m2 | | | | | | |
| dClass II/III obesity was defined as having a BMI greater than or equal to 35 kg/m2 | | | | | | |

**SI 10. Adjusted Hazard Ratios of BMI Trajectories (Ages 31-80) from Cox Hazard Models in Framingham Heart Study Offspring Cohort 1979-2001.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Model 1 | Model 2 | Model 3 | Model 4 |
|  |  | HR (95 % CI) | HR (95 % CI) | HR (95 % CI) | HR (95 % CI) |
| Body mass index trajectories | |  |  |  |  |
|  | Lower level of normal weightᵃ | 1.36 (1.07, 1.73) | 1.43 (1.13, 1.83) | 1.24 (0.97, 1.59) | 1.26 (0.99, 1.61) |
|  | Normal weightᵃ stable | 1.05 (0.89, 1.25) | 1.09 (0.92, 1.30) | 1.04 (0.88, 1.24) | 1.05 (0.89, 1.25) |
|  | Normal weight upward | 1.00 | 1.00 | 1.00 | 1.00 |
|  | Overweightᵇ obesity | 1.01 (0.84, 1.21) | 1.02 (0.85, 1.22) | 1.01 (0.84, 1.21) | 1.00 (0.84, 1.20) |
|  | Class I obeseᶜ | 1.47 (1.19, 1.82) | 1.42 (1.14, 1.76) | 1.43 (1.15, 1.77) | 1.41 (1.14, 1.75) |
|  | Class II/III obeseᵈ | 1.84 (1.24, 2.74) | 1.70 (1.14, 2.55) | 1.79 (1.21, 2.64) | 1.71 (1.16, 2.54) |
| Birth cohorts | |  |  |  |  |
|  | 1903 to 1924 | 1.00 | 1.00 | 1.00 | 1.00 |
|  | 1925 to 1929 | 0.87 (0.73, 1.03) | 0.89 (0.74, 1.05) | 0.88 (0.74, 1.05) | 0.90 (0.75, 1.07) |
|  | 1930 to 1934 | 0.70 (0.57, 0.86) | 0.75 (0.61, 0.92) | 0.76 (0.62, 0.93) | 0.78 (0.64, 0.96) |
|  | 1935 to 1939 | 0.61 (0.48, 0.78) | 0.68 (0.53, 0.87) | 0.70 (0.54, 0.89) | 0.72 (0.57, 0.93) |
|  | 1940 to 1944 | 0.48 (0.36, 0.64) | 0.54 (0.40, 0.73) | 0.55 (0.41, 0.74) | 0.59 (0.44, 0.79) |
|  | 1945 to 1949 | 0.51 (0.35, 0.73) | 0.60 (0.41, 0.86) | 0.62 (0.43, 0.89) | 0.66 (0.46, 0.95) |
|  | 1950 and above | 0.69 (0.42, 1.15) | 0.81 (0.49, 1.35) | 0.86 (0.52, 1.42) | 0.95 (0.57, 1.59) |
| Gender (Reference: Male) | |  |  |  |  |
|  | Female | 0.49 (0.43, 0.56) | 0.47 (0.41, 0.54) | 0.47 (0.41, 0.54) | 0.48 (0.41, 0.55) |
| Educational attainment in years | |  |  |  |  |
|  | 0-11 |  | 1.00 | 1.00 | 1.00 |
|  | 12 |  | 0.77 (0.63, 0.93) | 0.84 (0.69, 1.02) | 0.84 (0.69, 1.02) |
|  | 13-15 |  | 0.65 (0.52, 0.82) | 0.75 (0.61, 0.94) | 0.76 (0.61, 0.94) |
|  | 16 and above |  | 0.53 (0.43, 0.66) | 0.64 (0.52, 0.80) | 0.65 (0.52, 0.81) |
| Smoking behavior | |  |  |  |  |
|  | Non-smoker |  |  | 1.00 | 1.00 |
|  | Low smoking (1-9 cigarettes) |  |  | 1.53 (1.04, 2.25) | 1.51 (1.03, 2.23) |
|  | Moderate smoking (10-19 cigarettes) |  |  | 2.23 (1.63, 3.05) | 2.21 (1.61, 3.04) |
|  | Heavy smoking (20 or more cigarettes) |  |  | 2.65 (2.23, 3.15) | 2.60 (2.18, 3.10) |
| Disease index | |  |  |  | 1.41 (1.15, 1.73) |
| AIC | | 13,858.68 | 13,828.27 | 13,713.75 | 13,703.77 |
| BIC | | 13,917.17 | 13,901.38 | 13,801.49 | 13,796.38 |
| Number of deaths | | 967 | 967 | 967 | 967 |
| N | | 3,753 | 3,753 | 3,753 | 3,753 |
| Observations | | 19,067 | 19,067 | 19,067 | 19,067 |
| ᵃ Normal weight was defined as having a BMI between 18.5 and 24.9 kg/m² | | | | | |
| ᵇ Overweight was defined as having a BMI between 25 and 29.9 kg/m² | | | | | |
| ᶜ Class I obesity was defined as having a BMI between 30 and 34.9 kg/m² | | | | | |
| ᵈ Class II/III obesity was defined as having a BMI greater than or equal to 35 kg/m² | | | | | |

**SI 11. Adjusted Hazard Ratios of Alternative Measures of Body Mass Index Status from Cox Hazard Models in Framingham Heart Study Original Cohort (1948-2010).**

|  | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 | |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | HR (95 % CI) | HR (95 % CI) | HR (95 % CI) | HR (95 % CI) | HR (95 % CI) | HR (95 % CI) | |
| BMI at first exam a |  |  |  |  |  |  | |
| Underweight | 1.42 (1.17, 1.67) |  |  |  |  |  | |
| Normal weight | 1.00 |  |  |  |  |  | |
| Overweight | 1.11 (1.04, 1.18) |  |  |  |  |  | |
| Class I obesity | 1.43 (1.32, 1.53) |  |  |  |  |  | |
| Class II/III obesity | 2.00 (1.79, 2.21) |  |  |  |  |  | |
| Maximum BMI b |  |  |  |  |  |  | |
| Underweight |  | 2.45 (1.95, 2.95) |  |  |  |  | |
| Normal weight |  | 1.00 |  |  |  |  | |
| Overweight |  | 0.87 (0.79, 0.96) |  |  |  |  | |
| Class I obesity |  | 0.88 (0.79, 0.98) |  |  |  |  | |
| Class II/III obesity |  | 1.09 (0.96, 1.22) |  |  |  |  | |
| BMI of highest frequency (Type I) c |  |  |  |  |  |  | |
| Underweight |  |  | 1.86 (1.58, 2.15) |  |  |  | |
| Normal weight |  |  | 1.00 |  |  |  | |
| Overweight |  |  | 0.96 (0.89, 1.03) |  |  |  | |
| Class I obesity |  |  | 1.21 (1.11, 1.32) |  |  |  | |
| Class II/III obesity |  |  | 1.46 (1.27, 1.65) |  |  |  | |
| BMI of highest frequency (Type II)d |  |  |  |  |  |  | |
| Underweight |  |  |  | 1.73 (1.41, 2.05) |  |  | |
| Normal weight |  |  |  | 1.00 |  |  | |
| Overweight |  |  |  | 0.97 (0.90, 1.04) |  |  | |
| Class I obesity |  |  |  | 1.19 (1.08, 1.29) |  |  | |
| Class II/III obesity |  |  |  | 1.54 (1.36, 1.72) |  |  | |
| Proportion of BMI e |  |  |  |  |  |  | |
| Underweight |  |  |  |  | 2.14 (1.86, 2.41) |  | |
| Overweight |  |  |  |  | 0.91 (0.82, 1.00) |  | |
| Class I obesity |  |  |  |  | 1.09 (0.96, 1.22) |  | |
| Class II/III obesity |  |  |  |  | 1.61 (1.38, 1.83) |  | |
| BMI trajectories |  |  |  |  |  |  | |
| Lower level of normal weight |  |  |  |  |  | 1.40 (1.23, 1.60) | |
| Normal weight stable |  |  |  |  |  | 1.19 (1.07, 1.32) | |
| Normal weight upward |  |  |  |  |  | 1.00 | |
| Overweightdownward |  |  |  |  |  | 1.38 (1.24, 1.53) | |
| Overweight stable |  |  |  |  |  | 1.34 (1.20, 1.49) | |
| Class I obese |  |  |  |  |  | 1.55 (1.34, 1.79) | |
| Class II/III obese |  |  |  |  |  | 2.11 (1.63, 2.73) | |
| Birth cohorts |  |  |  |  |  |  | |
| 1876 to 1894 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | |
| 1895 to 1899 | 0.93 (0.83, 1.07) | 0.94 (0.83, 1.07) | 0.95 (0.83, 1.07) | 0.94 (0.82, 1.07) | 0.94 (0.82, 1.07) | 0.94 (0.81, 1.06) | |
| 1900 to 1904 | 1.01 (0.88, 1.13) | 0.99 (0.88, 1.13) | 1.00 (0.89, 1.14) | 1.00 (0.87, 1.12) | 1.01 (0.88, 1.13) | 1.00 (0.88, 1.13) | |
| 1905 to 1909 | 0.89 (0.77, 0.99) | 0.87 (0.78, 1.00) | 0.88 (0.78, 1.00) | 0.88 (0.76, 1.00) | 0.88 (0.76, 1.01) | 0.89 (0.77, 1.01) | |
| 1910 to 1914 | 0.89 (0.76, 0.97) | 0.86 (0.76, 0.97) | 0.86 (0.77, 0.98) | 0.86 (0.74, 0.98) | 0.86 (0.75, 0.98) | 0.88 (0.76, 1.00) | |
| 1915 and Above | 0.83 (0.69, 0.88) | 0.78 (0.70, 0.89) | 0.79 (0.70, 0.89) | 0.79 (0.66, 0.91) | 0.79 (0.67, 0.91) | 0.80 (0.68, 0.93) | |
| Gender |  |  |  |  |  |  | |
| Male | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | |
| Female | 0.60 (0.56, 0.64) | 0.59 (0.56, 0.64) | 0.60 (0.55, 0.63) | 0.60 (0.53, 0.66) | 0.59 (0.52, 0.66) | 0.61 (0.55, 0.68) | |
| Educational attainment |  |  |  |  |  |  | |
| Less than high school | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | |
| High school graduate | 0.99 (0.89, 1.04) | 0.96 (0.90, 1.06) | 0.98 (0.90, 1.05) | 0.98 (0.90, 1.06) | 0.97 (0.89, 1.05) | 0.98 (0.90, 1.05) | |
| Some college | 0.90 (0.78, 0.94) | 0.86 (0.80, 0.97) | 0.88 (0.80, 0.96) | 0.88 (0.79, 0.98) | 0.87 (0.78, 0.97) | 0.88 (0.78, 0.97) | |
| College graduate | 0.92 (0.81, 0.98) | 0.89 (0.82, 1.00) | 0.90 (0.81, 0.99) | 0.90 (0.80, 1.01) | 0.90 (0.79, 1.00) | 0.90 (0.80, 1.01) | |
| Smoking behavior |  |  |  |  |  |  | |
| Non-smoker | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | |
| Low smoking (1-9 cigarettes) | 1.46 (1.23, 1.69) | 1.44 (1.24, 1.72) | 1.46 (1.20, 1.67) | 1.46 (1.31, 1.61) | 1.42 (1.27, 1.56) | 1.45 (1.30, 1.59) | |
| Moderate smoking (10-19 cigarettes) | 1.58 (1.30, 1.77) | 1.52 (1.33, 1.81) | 1.54 (1.30, 1.77) | 1.55 (1.40, 1.70) | 1.51 (1.36, 1.67) | 1.54 (1.39, 1.69) | |
| Heavy smoking (20 or more cigarettes) | 1.92 (1.64, 2.01) | 1.82 (1.69, 2.07) | 1.87 (1.66, 2.04) | 1.87 (1.77, 1.98) | 1.84 (1.74, 1.94) | 1.87 (1.77, 1.97) | |
| Disease index | 1.40 (1.33, 1.61) | 1.46 (1.30, 1.58) | 1.43 (1.31, 1.58) | 1.43 (1.33, 1.54) | 1.44 (1.34, 1.54) | 1.44 (1.33, 1.54) | |
| AIC | 56,395.58 | 56,435.46 | 56,421.08 | 56,424.04 | 56,413.31 | 56,397.36 | |
| BIC | 56,502.20 | 56,542.09 | 56,527.70 | 56,530.67 | 56,519.94 | 56,516.53 | |
| Number of deaths | 3,913 | 3,913 | 3,913 | 3,913 | 3,913 | 3,913 | |
| N | 4,576 | 4,576 | 4,576 | 4,576 | 4,576 | 4,576 | |
| Observations | 44,261 | 44,261 | 44,261 | 44,261 | 44,261 | 44,261 | |
| a BMI at first exam: a categorical variable with information about BMI status reported in the first exam. | | | | | | |
| b Maximum BMI: a categorical variable with information about the maximum BMI status reported throughout the duration of the study. | | | | | | |
| c BMI of highest frequency (Type I): a categorical variable which represents BMI class of the highest frequency reported throughout the duration of the study. If two classes of BMI were with equal highest frequency, we used the lower BMI category. | | | | | | |
| d BMI of highest frequency (Type II): the difference between this categorical variable and BMI of highest frequency (Type I) is that this variable uses the higher BMI category if two classes of BMI were with equal highest frequency. | | | | | | |
| e Proportion of BMI: we created 5 continuous variables to measure the number of times each category of BMI was reported as a proportion of the total number of BMI information provided throughout the duration of the study. | | | | | | |

**SI 12. Adjusted Hazard Ratios of BMI Trajectories from Cox Hazard Models in Framingham Heart Study Original (1948-2010) and Offspring Cohort (1979-2001) Combined Sample.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Model 1 | | Model 2 | | | Model 3 | | | Model 4 | | |
|  |  | HR (95 % CI) | | HR (95 % CI) | | | HR (95 % CI) | | | HR (95 % CI) | | |
| Body mass index trajectories | |  |  | | |  | | |  | | |
|  | Lower level of normal weightᵃ (Original) | 1.49 (1.31, 1.69) | | 1.51 (1.32, 1.71) | | | 1.36 (1.19, 1.54) | | | 1.39 (1.23, 1.59) | | |
|  | Normal weightᵃ stable (Original) | 1.19 (1.07, 1.32) | | 1.21 (1.09, 1.34) | | | 1.17 (1.05, 1.29) | | | 1.19 (1.07, 1.32) | | |
|  | Normal weightᵃ upward (Original) | 1.00 | | 1.00 | | | 1.00 | | | 1.00 | | |
|  | Overweightᵇ downward (Original) | 1.35 (1.22, 1.51) | | 1.36 (1.22, 1.52) | | | 1.35 (1.22, 1.51) | | | 1.36 (1.22, 1.51) | | |
|  | Overweightᵇ stable (Original) | 1.31 (1.18, 1.45) | | 1.30 (1.17, 1.45) | | | 1.33 (1.19, 1.48) | | | 1.33 (1.19, 1.48) | | |
|  | Class I obeseᶜ (Original) | 1.56 (1.35, 1.80) | | 1.52 (1.32, 1.76) | | | 1.57 (1.37, 1.82) | | | 1.55 (1.35, 1.79) | | |
|  | Class II/III obeseᵈ (Original) | 2.16 (1.73, 2.70) | | 2.09 (1.67, 2.62) | | | 2.20 (1.70, 2.85) | | | 2.12 (1.64, 2.75) | | |
|  | Lower level of normal weightᵃ (Offspring) | 1.15 (0.88, 1.49) | | 1.18 (0.91, 1.54) | | | 1.11 (0.86, 1.44) | | | 1.12 (0.86, 1.44) | | |
|  | Normal weightᵃ stable (Offspring) | 0.91 (0.74, 1.13) | | 0.93 (0.75, 1.16) | | | 0.93 (0.75, 1.15) | | | 0.93 (0.75, 1.15) | | |
|  | Normal weightᵃ upward (Offspring) | 0.91 (0.72, 1.15) | | 0.92 (0.73, 1.16) | | | 0.94 (0.74, 1.18) | | | 0.92 (0.73, 1.16) | | |
|  | Overweightᵇ obesity (Offspring) | 0.89 (0.72, 1.09) | | 0.90 (0.73, 1.10) | | | 0.91 (0.74, 1.12) | | | 0.90 (0.73, 1.11) | | |
|  | Class I obeseᶜ (Offspring) | 1.31 (1.01, 1.71) | | 1.31 (1.01, 1.70) | | | 1.34 (1.04, 1.74) | | | 1.30 (1.01, 1.68) | | |
|  | Class II/III obeseᵈ (Offspring) | 1.55 (1.01, 2.37) | | 1.51 (0.99, 2.32) | | | 1.56 (1.03, 2.38) | | | 1.48 (0.98, 2.25) | | |
| Birth cohorts | |  |  | | |  | | |  | | |
|  | 1876 to 1894 | 1.00 | | | 1.00 | | | 1.00 | | | 1.00 | | |
|  | 1895 to 1899 | 0.94 (0.83, 1.06) | | | 0.94 (0.83, 1.07) | | | 0.93 (0.82, 1.06) | | | 0.94 (0.82, 1.07) | | |
|  | 1900 to 1904 | 0.97 (0.86, 1.10) | | | 0.98 (0.87, 1.11) | | | 1.00 (0.88, 1.13) | | | 1.01 (0.89, 1.14) | | |
|  | 1905 to 1909 | 0.88 (0.78, 1.00) | | | 0.90 (0.79, 1.02) | | | 0.90 (0.79, 1.02) | | | 0.90 (0.79, 1.02) | | |
|  | 1910 to 1914 | 0.84 (0.75, 0.94) | | | 0.86 (0.77, 0.97) | | | 0.88 (0.78, 0.99) | | | 0.88 (0.78, 1.00) | | |
|  | 1915 to 1919 | 0.77 (0.68, 0.87) | | | 0.80 (0.70, 0.90) | | | 0.81 (0.72, 0.92) | | | 0.81 (0.72, 0.92) | | |
|  | 1920 to 1924 | 0.80 (0.66, 0.98) | | | 0.84 (0.69, 1.03) | | | 0.88 (0.72, 1.07) | | | 0.88 (0.72, 1.07) | | |
|  | 1925 to 1929 | 0.74 (0.59, 0.94) | | | 0.78 (0.62, 0.99) | | | 0.82 (0.65, 1.04) | | | 0.82 (0.65, 1.04) | | |
|  | 1930 to 1934 | 0.61 (0.47, 0.79) | | | 0.65 (0.50, 0.84) | | | 0.70 (0.54, 0.90) | | | 0.70 (0.54, 0.90) | | |
|  | 1935 to 1939 | 0.54 (0.41, 0.71) | | | 0.59 (0.44, 0.78) | | | 0.65 (0.49, 0.86) | | | 0.65 (0.49, 0.86) | | |
|  | 1940 to 1944 | 0.41 (0.30, 0.57) | | | 0.45 (0.33, 0.62) | | | 0.51 (0.37, 0.70) | | | 0.51 (0.37, 0.70) | | |
|  | 1945 to 1949 | 0.43 (0.29, 0.62) | | | 0.47 (0.32, 0.69) | | | 0.55 (0.38, 0.80) | | | 0.54 (0.37, 0.78) | | |
|  | 1950 and above | 0.56 (0.34, 0.93) | | | 0.62 (0.38, 1.03) | | | 0.75 (0.45, 1.23) | | | 0.75 (0.45, 1.23) | | |
| Gender | |  |  | | |  | | |  | | |
|  | Male | 1.00 | | | 1.00 | | | 1.00 | | | 1.00 | | |
|  | Female | 0.58 (0.54, 0.61) | | | 0.57 (0.54, 0.61) | | | 0.59 (0.56, 0.63) | | | 0.59 (0.55, 0.62) | | |
| Educational attainment | |  |  | | |  | | |  | | |
|  | Less than high school (0-11 yearsᵉ) |  | | | 1.00 | | | 1.00 | | | 1.00 | | |
|  | High school graduate (12 years) |  | | | 0.96 (0.89, 1.04) | | | 0.96 (0.89, 1.03) | | | 0.96 (0.89, 1.03) | | |
|  | Some college (13-15 years) |  | | | 0.83 (0.76, 0.91) | | | 0.86 (0.79, 0.93) | | | 0.86 (0.79, 0.94) | | |
|  | College graduate (16 years and above) |  | | | 0.81 (0.74, 0.89) | | | 0.84 (0.77, 0.92) | | | 0.85 (0.77, 0.92) | | |
| Smoking behavior | |  |  | | |  | | |  | | |
|  | Non-smoker |  | | |  | | | 1.00 | | | 1.00 | | |
|  | Low smoking (1-9 cigarettes) |  | | |  | | | 1.44 (1.23, 1.68) | | | 1.46 (1.25, 1.71) | | |
|  | Moderate smoking (10-19 cigarettes) |  | | |  | | | 1.61 (1.40, 1.85) | | | 1.65 (1.44, 1.91) | | |
|  | Heavy smoking (20 or more cigarettes) |  | | |  | | | 2.01 (1.84, 2.20) | | | 2.04 (1.87, 2.23) | | |
| Disease index | |  |  | | |  | | | 1.44 (1.33, 1.57) | | |
| AIC | | 74,775.02 | 74,748.13 | | | 74,507.03 | | | 74,440.48 | | |
| BIC | | 74,937.34 | 74,929.93 | | | 74,708.31 | | | 74,648.25 | | |
| Number of deaths | | 4,880 | 4,880 | | | 4,880 | | | 4,880 | | |
| N | | 8,329 | 8,329 | | | 8,329 | | | 8,329 | | |
| Observations | | 63,328 | 63,328 | | | 63,328 | | | 63,328 | | |
| ᵃ Normal weight was defined as having a BMI between 18.5 and 24.9 kg/m² | | | | | | | | | | | |
| ᵇ Overweight was defined as having a BMI between 25 and 29.9 kg/m² | | | | | | | | | | | |
| ᶜ Class I obesity was defined as having a BMI between 30 and 34.9 kg/m² | | | | | | | | | | | |
| ᵈ Class II/III obesity was defined as having a BMI greater than or equal to 35 kg/m² | | | | | | | | | | | |
| ᵉEducational attainment for the offspring cohort is measured in number of years. | | | | | | | | | | | |

**SI 13. Adjusted Hazard Ratios of BMI Trajectories from Cox Hazard Models among Those Who were Non-Smokers in All Assessment Time Points, FHS Original Cohort (1948-2010)**



**SI 14. Adjusted Hazard Ratios of BMI Trajectories from Cox Hazard Models among Those Who were Non-Smokers in All Assessment Time Points, FHS Offspring Cohort (1979-2001)**

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**SI 15. Adjusted Cause-Specific Hazard Ratios of BMI Trajectories from Cox Hazard Models, Framingham Heart Study Original Cohort (1948-2010)**

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**SI 16. Adjusted Cause-Specific Hazard Ratios of BMI Trajectories from Cox Hazard Models, Framingham Heart Study Offspring Cohort (1979-2001)**

