Supporting Information

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SI Materials and Methods

Our main results are obtained by estimating age–period–cohort models, one of the key models used by epidemiologists and social scientists in the quantitative analysis of social change. A large literature going back to the 1970s has examined the problem of identification in these models (1–3) because it is well known that age (years since birth), period (current year), and cohort (YOB) are collinear with each other because age = period − cohort. Intuitively, it would be impossible to observe two individuals at the same point in time that have the same age but were born at different dates. In our analysis, we treated the cohort variable as both continuous and discrete, and we discuss how we achieve identification in both of these specifications of the model below.

Models Treating Birth Year as Continuous. We begin by estimating multivariate regression models using the estimator proposed in ref. 4 that extends the threshold regression to a static panel data structure. The threshold regression determines if there is a unique breakpoint at which there is a permanent structural change in the relationship between the specific genotypes of the *FTO* gene (rs9939609) and BMI. That is, these models can be used to determine the set of threshold YOBs at which there are important changes in the relationships between BMI and *FTO* genotypes. This threshold is chosen based on the minimization of the concentrated sum of squared errors, and we impose the constraint that there must be at least 5% of observations lying on both sides of the breakpoint. Ignoring this constraint did not change our main results identifying the main breakpoint at 1942, but it offers substantial computational advantages by reducing the search over all possible breakpoints. Intuitively, the threshold regression model with a single breakpoint can be viewed as selecting the regression that provided the best fit to the data from the set of all regressions which only differ by the selection of birth year as the breakpoint. That is, we define YOB_Threshold as the birth year that is selected as the breakpoint and estimate the following equation:

$$\begin{aligned}\mathrm{BMI}_{ift} = {} & \beta_0 + \beta_1 \mathrm{age}_{ift} + \beta_2 \mathrm{wave}_t + \beta_3 \mathrm{YOB}_i + \beta_4 \mathrm{gene}_i \\ & + \beta_5 \mathrm{X}_{ift} + \beta_6 (\mathrm{gene}_i \times \mathrm{sex}_i) + \beta_7 (\mathrm{gene}_i \times \mathrm{age}_{ift}) \\ & + \beta_8 (\mathrm{gene}_i \times 1\{\mathrm{YOB}_i \geq \mathrm{YOB\_Threshold}\}) \\ & + \beta_9 (\mathrm{wave}_t \times \mathrm{gene}_i) + \mu_{ift},\end{aligned} \quad \textbf{[S1]}$$

where

- BMI_{ift} is the BMI of person i in family f at time t;
- YOB is the year-of-birth indicator variable if the individual was born during or after the year in which a structural break is determined, henceforth referred to as the threshold year;
- 1{YOB ≥ YOB_Threshold} is an indicator for whether the individual was born following the threshold year.
- wave is a series of indicators for when the measurement occurred (eight waves);
- age is a series of indicators for an individual's age in 5-y intervals;
- gene can represent a vector of discrete indicators for polymorphisms of the gene being investigated (although in this case we are looking at only the *FTO* rs9939609 SNP);
- X is a vector of exogenous attributes including sex; and
- μ_{ift} is random error term with a mean of zero.

This model is run repeatedly because each time the threshold YOB changes, so does 1{YOB ≥ YOB_Threshold}. Because the birth year in the FHS data contains day and month, we use this information for a subset of observations and do not treat birth year as integer valued for all observations in the FHS. This strategy of running a separate regression for each potential breakpoint would have been computationally challenging. The estimator developed in ref. 4 uses grid search techniques to choose the threshold year at which the relationship between the FTO genotype and BMI is significantly modified for individuals born before and after 1942. The threshold year is chosen as the value that minimizes the sum of squared errors. Once the threshold year is identified, OLS is run on Eq. **S1** to obtain the estimates of βs. Note, that although conventional SEs on the coefficients in Eq. **S1**, which treat YOB_Threshold as the true value of the threshold, are asymptotically valid, one needs to be careful in testing the statistical significance of whether there is a nonlinearity in the estimated relationship between cohorts. Standard tests using the Wald statistic have poor finite sample behavior since the asymptotic sampling distribution depends on an unknown parameter (YOB_Threshold) that is not identified under the null hypotheses. We thus adopt the bootstrap F test proposed in ref. 4 when testing if there is a significant threshold effect.

Although this estimator has the advantage of accurately identifying the point at which there are significant changes in the impact of the genotypes based on YOB, it imposes restrictions on how the YOB affects BMI. Although we could add higher-order terms to increase the flexibility, these terms make it more difficult for the test statistics to exhibit dramatic changes as such tests will have no power in many settings. Using different sets of control variables in these models, we consistently identified breakpoints between the years of 1942 and 1945 with decidedly nonlinear changes in the magnitude of the parameter estimates after that time. Estimates of the preferred specification from the breakpoint model are depicted in Fig. 1, where we consider only a single break at 1942, although various models after that time period yield consistent results.

To identify age, period, and cohort (APC) effects in Eq. **S1**, we exploit the fact that we used categorical variable age, irregular period (year of observation) dummies, and mixed continuous–categorical cohort (year born + birth era) in these linear and additive APC models. This empirical strategy has been used widely in the social sciences (5). An alternative approach to identifying the separate effects of APC variables would be to consider nonlinear relationships of a subset of these effects in the specification of the model. To examine the robustness of our results, we followed this strategy and first used small-order polynomials in the YOB to identify and estimate cohort effects. Second, we conducted robustness exercises that estimated specifications allowing for polynomials in period effects. Our main results were robust to these alternative nonlinear treatments of cohort and period effects.

Models Treating Birth Cohort as Discrete. Our preferred method of analysis does not include a continuous birth-year variable for the reasons described above. Instead, we use the 1942 cutoff identified as a breakpoint in our continuous model as a way to compare pre- and postbirth cohorts. By treating the APC variables as dummy variables, identification can be easily achieved by dropping a small number of these variables. Our preferred strategy was to restrict the indicator for individuals under the age of 30 and the indicator for the first medical visit to be equal to zero. Intuitively, we hypothesized that BMI was increasing both over time and as individuals age. Thus, we anticipate that these restrictions would impose the weakest assumption on the model because the reference groups

include the youngest individuals and the earliest time period. Because the selection of which age and period indicators to drop is ad hoc and because prior research (6) demonstrated that the results obtained from APC models can be quite sensitive to which parameter restrictions are made, we investigated the sensitivity of our results to dropping nine different age or period indicators. In each of these nine cases, our main results showed a significant interaction between *FTO* genotype and cohort.

By using indicator variables, we are relaxing the assumptions made on the form and pattern of the relationship between BMI and the explanatory variables, relative to the analysis where birth cohort was modeled as a continuous variable. Estimates of the preferred specification of this model, using discrete birth cohort variables with the earliest age and time period effect restricted to be zero, are presented in Table 1.

In Table S3, we list sample means for BMI within subsamples defined by their rs9939609 genotype and age at examination, with age measured in 5-y intervals. In the bottom two rows of the table for each genotype, we present results from *t* tests of differences in means across cohorts. These results show that, without controlling for other factors, there are numerous significant differences in BMI between those born before and after 1942. Although there is no significant difference in BMI between those born pre-/post-1942 for any age cell for the rs9939609 TT polymorphism, nearly every age cell for the AT polymorphism indicates that BMI is significantly greater for those born after 1942. Similarly, among the sample for those born post-1942 and either aged 35–40 or 45–50, we observe significantly higher BMI among the later cohort.

To more formally examine the importance of birth cohort interactions with genotype, we initially estimated models that allowed for other sources of heterogeneity, shown in Table S3. Specifically we decomposed the error term (μ_{ift}) from Eq. **S1** into two components and estimate

$$\begin{aligned}\mathrm{BMI}_{ift} = {} & \beta_0 + \beta_1 \mathrm{age}_{ift} + \beta_2 \mathrm{wave}_t + \beta_3 \mathrm{post42}_i + \beta_4 \mathrm{gene}_i \\ & + \beta_5 \mathrm{X}_{ift} + \beta_6(\mathrm{gene}_i \times \mathrm{sex}_i) + \beta_7(\mathrm{gene}_i \times \mathrm{age}_{ift}) \\ & + \beta_8(\mathrm{post42}_i \times \mathrm{gene}_i) + \beta_9(\mathrm{wave}_t \times \mathrm{gene}_i) + v_f + \varepsilon_{ift},\end{aligned} \quad \textbf{[S2]}$$

where

- post42 is an indicator variable if the individual was born during or after 1942;
- v_f is a term that controls for family-specific unobserved heterogeneity; and
- ε_{ift} is random error term with a mean of zero.

This model allows for contemporaneous impacts as measured by period of interview, cohort effects, and age effects as well as their interactions with genetic factors. Again, note that family fixed-effect models implicitly include shared genotype as part of shared familial environment. To identify all of these factors, in the main test we imposed restrictions and removed indicators for the first wave, first age interval (27–30), and the TT polymorphism (and their interactions) to ensure there was no multicollinearity.

To evaluate the individual importance of including genetic interactions with sex and APC indicators, we considered specification tests that compared estimates of the unrestricted model in Eq. **S2** to a series of nested models in which only one of these sets of interactions was restricted to be zero. These *F* tests test the joint significance of the set of indicators and help us to identify the regression model that best fits the population from which the data were sampled. Tests of joint significance individually reject both the period interactions ($\beta_9 = 0$, $F = 0.5891$, $P > F = 0.6912$) and the sex interactions ($\beta_6 = 0$, $F = 1.12$, $P > F = 0.3494$) but not the cohort interactions at significance levels below 0.01 ($\beta_8 \neq 0$, $F = 17.51$, $P > F = 2.1 \times 10^{-4}$). Thus, our preferred specification excludes these two sets of interactions and we focus on the following model:

$$\begin{aligned}\mathrm{BMI}_{ift} = {} & \alpha_0 + \alpha_1 \mathrm{age}_{ift} + \alpha_2 \mathrm{wave}_t + \alpha_3 \mathrm{post42}_i + \alpha_4 \mathrm{gene}_i + \alpha_5 \mathrm{X}_{ift} \\ & + \alpha_6(\mathrm{gene}_i \times \mathrm{sex}_i) + \alpha_7(\mathrm{post42}_i \times \mathrm{gene}_i) + v_f + \varepsilon^*_{ift}.\end{aligned} \quad \textbf{[S3]}$$

Note we use different notation for both the coefficients and error term in Eqs. **S2** and **S3** because they may differ due to the omission of the genetic interactions with both sex and wave. We estimate Eq. **S3** using three different estimators that each impose a different assumption regarding v_f . OLS estimates are obtained by assuming $v_f = 0$. The family fixed-effects estimator assumes that v_f is sibling-invariant family-specific unobserved heterogeneity that may be correlated with the explanatory variables. A random-effects estimator assumes that v_f is sibling-invariant family-specific unobserved heterogeneity that is uncorrelated with the explanatory variables. Because these fixed-effect and random-effect models account for family-specific unobserved heterogeneity, more reliable estimates are likely obtained because they adjust for the effects of shared unobserved influences on BMI between biological siblings. The random-effect model yields more precise estimates when part of the effect of genetic factors operates at the level of the family (e.g., there is an independent effect of the extent to which a genotype is present within a family and the mean BMI in the family). However, the family fixed-effects model blocks both genetic factors and parental characteristics/behaviors that are common to family members (e.g., siblings), including unmeasured factors; therefore, from the perspective of confounding, the fixed-effect specification is preferred.

As first noted in ref. 7, estimates of the impacts of genetic factors on outcomes that ignore family fixed effects may also capture dynastic effects because both genetic markers and many phenotypes are transmitted from one generation to the next. OLS and random-effect estimates of Eq. **S3** may not isolate the unique contribution of one's genotype from those arising from intergenerational transmission of genetic and behavioral characteristics. That is, the random-effects model (as with the traditional linear regression estimator) assumes that the family-specific term is uncorrelated with the explanatory variables but makes use of the structure of the error term (μ_{ift}) to provide more reliable and precise estimates. On the other hand, using a family fixed-effects estimator that controls for these unobserved family-specific effects assuming their effects are constant between siblings, allows for correlations with explanatory variables thereby removing a potential source of bias in the resulting estimates, and can (more importantly) isolate the specific contribution of one's genotype.

More generally, we suggest that presenting estimation results that are made with different estimators that each impose different assumptions on how v_f relates to the discrete cohort variables serves as an additional robustness check on the main findings. The results for these three estimators are presented in Table S2. Notice that, irrespective of the estimation method, the interaction term of birth cohort and genotype is significant for AT and AA in the random-effects specification. Because in many age groups BMI was higher for those born before 1942 than after 1942 for those with the TT polymorphism, the negative sign on post42 was expected. Finally, the last two columns of Table S2 indicate the robustness of the main results to different methods of accounting for family unobserved heterogeneity, increasing our confidence in the main findings. Repeated models run on males and females separately further support our findings, as the interactions between genetic polymorphism and being born after 1942 are positive for both sexes and statistically significant, particularly in the random-effects specifications for which the most efficient estimates are obtained.

A final point related to the identification of APC models is that many of the explanatory variables will be highly correlated. For example, in later waves, older individuals will be by definition born in the later cohort. The correlation between the explanatory variables will not bias our estimates but will lead to larger SEs, assuming the model is specified correctly. As such, it is not a surprise that many of the estimated coefficients in our models have wide CIs. Intuitively, large SEs imply that the effects of different variables are highly uncertain, and, when independent variables are highly correlated, high uncertainty is what should be reported. The only solution to reduce the width of CIs would be to collect more data to gain more independent variation to identify the separate effects. Chapter 23 of ref. 8 provides a more detailed discussion of how highly correlated explanatory variables will lead to unbiased estimates but may influence the interpretation of results from linear regression models.

Lastly, in Tables S7 and S8, respectively, we considered estimating models that either ignore both age and cohort effects (as well as their interactions) and models that only ignores cohort effects. Table S7 can be viewed as a model that allows for main genetic effects and contemporaneous g-by-p relationships. Not surprisingly, we find that interaction effects in later waves are larger in magnitude. This is in part capturing the effect of having a larger percentage of older individuals in later time periods and having more people born in the second cohort being interviewed in later time periods. In other words, the g-by-p variable is likely positively correlated with g-by-a and g-by-c variables that correspond to both older individuals and those born in later cohorts. Thus, by omitting both age and cohort effects when estimating a variant of Eq. **S3**, the estimate of the g-by-p effect is biased upwards because it is also capturing part of the effects of these omitted variables that, as described, are correlated with the g-by-p variable. Table S8 shows that many of these biased estimates become smaller once we also allow for age effects. That is, by including age indicators, the coefficients on the g-by-p effect on average become smaller in magnitude, though they continue to exceed the estimates presented in Table 1. The decline in the magnitude of many of the g-by-p effects reinforces the bias from simply omitting relevant information on how genetic factors influence human development over the lifecycle.

However, the estimates in Tables S7 and S8 also omit relevant information on how genetic effects differ across eras in which an individual grows up and, thus, it is not surprising that they differ markedly from those presented in both Table 1 and Tables S1, S2, and S4. In particular, omitting this relevant information allows one to erroneously conclude that several of the g-by-p and g-by-a interactions have a statistically significant impact. Many of these effects become statistically insignificant once we allow for g-by-c effects. Because the specifications presented in Tables S7 and S8 are restricted versions of our more general APC model presented in Eq. **S2**, we conducted a series of model specification tests to examine the validity of these restrictions. Irrespective of the estimator used, the test results reject these restrictions reinforcing that researchers working with the FHS data should both allow for both main cohort effects and g-by-c interactions. This finding has implications for the interpretation of estimates from many g-by-e studies which only use interactions between gene and contemporaneous periods—which, primarily due to data limitations, have collected data on individuals for shorter durations and fewer cohorts. This also reinforces the utility of genotyping large-scale longitudinal databases thereby allowing researchers to examine whether specific g-by-e effects are sensitive to APC effects.

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Table S1. Model estimates of factors influencing BMI, where birth year is treated as continuous variables

	Models that exclude genetic interactions with both age and birth cohort variables			Models that include genetic interactions with both age and birth cohort variables		
Estimation approach	Linear regression	Random effects	Linear regression with controls for family fixed effects	Linear regression	Random effects	Linear regression with controls for family fixed effects
Subject is male	1.805*** (0.152)	1.635*** (0.146)	1.855*** (0.169)	1.804*** (0.152)	1.633*** (0.146)	1.855*** (0.169)
Age 30–34.99	0.195 (0.204)	0.413*** (0.106)	0.0802 (0.165)	0.525* (0.315)	0.437** (0.175)	0.191 (0.263)
Age 35–39.99	0.504* (0.266)	0.648*** (0.126)	0.329* (0.193)	0.497 (0.310)	0.515*** (0.181)	0.247 (0.257)
Age 40–44.99	0.838** (0.375)	1.014*** (0.160)	0.568** (0.266)	0.968** (0.407)	0.860*** (0.204)	0.445 (0.316)
Age 45–49.99	1.023** (0.500)	1.175*** (0.201)	0.564 (0.345)	1.091** (0.525)	0.992*** (0.237)	0.433 (0.395)
Age 50–54.99	1.113* (0.620)	1.193*** (0.243)	0.522 (0.425)	1.105* (0.640)	0.968*** (0.274)	0.26 (0.468)
Age 55–59.99	1.122 (0.743)	1.138*** (0.289)	0.349 (0.505)	1.104 (0.756)	0.954*** (0.316)	0.162 (0.541)
Age 60–63	0.902 (0.858)	0.998*** (0.330)	0.142 (0.589)	0.876 (0.871)	0.859** (0.355)	0.00354 (0.623)
Birth year	−0.039 (0.0265)	−0.0439*** (0.0121)	−0.0733*** (0.0219)	−0.0835*** (0.0288)	−0.0793*** (0.0161)	−0.107*** (0.0266)
Wave 2	0.132 (0.205)	0.259*** (0.0893)	0.367** (0.145)	0.132 (0.205)	0.259*** (0.0893)	0.369** (0.145)
Wave 3	0.608* (0.315)	0.752*** (0.126)	0.974*** (0.221)	0.609* (0.315)	0.753*** (0.126)	0.979*** (0.220)
Wave 4	1.250*** (0.400)	1.338*** (0.156)	1.652*** (0.278)	1.250*** (0.400)	1.339*** (0.156)	1.657*** (0.277)
Wave 5	1.854*** (0.494)	2.007*** (0.190)	2.391*** (0.346)	1.855*** (0.493)	2.008*** (0.190)	2.396*** (0.345)
Wave 6	2.521*** (0.598)	2.667*** (0.228)	3.143*** (0.414)	2.520*** (0.597)	2.667*** (0.228)	3.149*** (0.413)
Wave 7	2.836*** (0.668)	3.054*** (0.256)	3.558*** (0.463)	2.834*** (0.667)	3.053*** (0.256)	3.563*** (0.462)
Wave 8	3.307*** (0.847)	3.713*** (0.318)	4.321*** (0.583)	3.313*** (0.846)	3.718*** (0.318)	4.337*** (0.582)
AA genotype	1.060*** (0.247)	1.035*** (0.226)	0.881*** (0.318)	0.767 (1.267)	−0.953 (0.958)	−0.312 (1.407)
AT genotype	0.421** (0.167)	0.379** (0.161)	0.490** (0.217)	−2.546*** (0.841)	−2.021*** (0.699)	−2.027** (0.943)
Born after 1942 by AA Genotype				0.0632** (0.0286)	0.0538** (0.023)	0.0432 (0.0329)
Born after 1942 by AT Genotype				0.0699*** (0.0187)	0.0537*** (0.0168)	0.0519** (0.0221)
30–34.99 by AA				−1.293** (0.644)	−0.492 (0.311)	−1.142** (0.485)
35–39.99 by AA				0.775 (0.513)	−0.230 (0.290)	−0.746* (0.389)
40–44.99 by AA				−0.991* (0.524)	−0.136 (0.279)	−0.680* (0.404)
45–49.99 by AA				−0.876 (0.544)	−0.167 (0.280)	−0.682 (0.429)
50–54.99 by AA				−0.672 (0.549)	0.0483 (0.279)	−0.368 (0.43)
55–55.99 by AA				−0.6 (0.571)	−0.0159 (0.283)	−0.431 (0.457)
60–63 by AA				−0.378 (0.564)	0.0663 (0.294)	−0.251 (0.454)
30–34.99 by AT				−0.271 (0.393)	0.0883 (0.220)	0.11 (0.338)
35–39.99 by AT				0.227 (0.309)	0.319 (0.204)	0.365 (0.278)
40–44.99 by AT				0.0216 (0.319)	0.334* (0.199)	0.43 (0.296)
45–49.99 by AT				0.114 (0.337)	0.400** (0.199)	0.443 (0.306)
50–54.99 by AT				0.218 (0.336)	0.422** (0.198)	0.612* (0.313)
55–59.99 by AT				0.202 (0.355)	0.356* (0.202)	0.473 (0.325)
60–63 by AT				0.163 (0.344)	0.245 (0.208)	0.326 (0.328)
Constant	24.98*** (1.227)	25.07*** (0.551)	26.42*** (0.987)	26.74*** (1.312)	26.59*** (0.696)	27.89*** (1.172)
Observations	19,617	19,617	19,617	19,617	19,617	19,617
No. of family fixed effects	Not applicable	Not applicable	1,414	Not applicable	Not applicable	1,414
R^2	0.095	0.098	0.479	0.098	0.103	0.48

Presented are estimates of the age–period–cohort model where the cohort variable is treated as continuous. Each entry refers to the effect of the variable listed in the first column on BMI holding all other factors constant. Robust SEs are presented in parentheses. The columns in this table differ based on what factors are accounted for and the method used to estimate the statistical model. See Table S6 for the calendar time corresponding to examinations in each wave. Note that our main results of birth cohort and genotype interactions are not sensitive to the method by which the model was estimated. Estimates from the fifth column were used to generate Fig. 1. The following indicate the statistical significance of an explanatory variable on BMI: *** $P < 0.01$, ** $P < 0.05$, and * $P < 0.1$.

Table S2. Model estimates of factors influencing BMI, where birth year is treated as a discrete variable for pre-/post-1942 as birth year

Estimator → explanatory variables ↓	Linear regression	Random effects	Linear regression with controls for family fixed effects
Subject is male	1.812*** (0.152)	1.641*** (0.146)	1.835*** (0.154)
Age 30–34.99	0.532* (0.306)	0.477*** (0.174)	0.542** (0.254)
Age 35–39.99	0.608** (0.255)	0.608*** (0.174)	0.710*** (0.243)
Age 40–44.99	1.245*** (0.291)	1.011*** (0.188)	1.285*** (0.298)
Age 45–49.99	1.498*** (0.340)	1.199*** (0.212)	1.498*** (0.362)
Age 50–54.99	1.640*** (0.383)	1.231*** (0.238)	1.540*** (0.425)
Age 55–59.99	1.765*** (0.453)	1.272*** (0.269)	1.688*** (0.497)
Age 60–63	1.658*** (0.503)	1.229*** (0.300)	1.635*** (0.567)
Subject was born after 1942	−1.086*** (0.326)	−1.360*** (0.280)	−1.020*** (0.353)
Wave 2	−0.0447 (0.113)	0.173** (0.0774)	0.0239 (0.127)
Wave 3	0.321* (0.166)	0.617*** (0.105)	0.389** (0.192)
Wave 4	0.874*** (0.206)	1.163*** (0.128)	0.888*** (0.241)
Wave 5	1.385*** (0.252)	1.791*** (0.155)	1.434*** (0.299)
Wave 6	1.958*** (0.310)	2.406*** (0.185)	1.984*** (0.365)
Wave 7	2.216*** (0.356)	2.760*** (0.207)	2.223*** (0.416)
Wave 8	2.576*** (0.453)	3.356*** (0.258)	2.703*** (0.526)
AA genotype	1.385** (0.599)	0.708* (0.398)	1.622*** (0.570)
AT genotype	−0.359 (0.389)	−0.412 (0.282)	−0.412 (0.383)
Born after 1942 by AA genotype	0.956* (0.509)	1.041** (0.459)	0.689 (0.563)
Born after 1942 by AT genotype	1.255*** (0.348)	1.135*** (0.326)	1.129*** (0.386)
Age 30–34.99 by AA	−1.236* (0.637)	−0.488 (0.311)	−1.596*** (0.527)
Age 35–39.99 by AA	−0.723 (0.507)	−0.227 (0.290)	−1.241*** (0.404)
Age 40–44.99 by AA	−0.999* (0.517)	−0.135 (0.279)	−1.246*** (0.442)
Age 45–49.99 by AA	−0.921* (0.539)	−0.168 (0.280)	−1.141** (0.460)
Age 50–54.99 by AA	−0.751 (0.543)	0.0459 (0.279)	−0.968** (0.470)
Age 55–59.99 by AA	−0.708 (0.582)	−0.0173 (0.283)	−0.911* (0.493)
Age 60–63 by AA	−0.539 (0.568)	0.0613 (0.294)	−0.710 (0.497)
Age 30–34.99 by AT	−0.171 (0.392)	0.0928 (0.220)	−0.199 (0.332)
Age 35–39.99 by AT	0.343 (0.308)	0.324 (0.204)	0.279 (0.273)
Age 40–44.99 by AT	0.0780 (0.321)	0.338* (0.199)	0.183 (0.293)
Age 45–49.99 by AT	0.155 (0.340)	0.402** (0.199)	0.237 (0.306)
Age 50–54.99 by AT	0.240 (0.338)	0.423** (0.198)	0.455 (0.310)
Age 55–59.99 by AT	0.208 (0.367)	0.357* (0.202)	0.418 (0.326)
Age 60–63 by AT	0.147 (0.360)	0.244 (0.208)	0.272 (0.333)
Constant	23.80*** (0.348)	24.01*** (0.250)	23.75*** (0.335)
Observations	19,617	19,617	19,617
R^2	0.099	0.106	0.397
No. of Individuals	3,720	3,720	3,720
No. of family fixed effects	1,414	1,414	1,414

Presented are estimates of the age–period–cohort model where the cohort variable is treated as discrete as indicated in Eq. **S3**. Each entry refers to the effect of the variable listed in the first column on BMI holding all other factors constant. Robust SEs are presented in parentheses. The columns in this table differ based on what factors are accounted for and the method used to estimate the statistical model. See Table S6 for the calendar time corresponding to examinations in each wave. Note that our main results of birth cohort and genotype interactions are not sensitive to the method by which the model was estimate. The following indicate the statistical significance of each explanatory variable: ***$P < 0.01$, **$P < 0.05$, and *$P < 0.1$.

Table S3. Descriptive statistics of BMI by genotype based on age at examination and between birth cohorts (1942 change point)

			AA genotype			
Age group	30–34.99	35–39.99	40–44.99	45–49.99	50–54.99	55–59.99
Pre-1942	24.679 (0.569)	25.605 (0.370)	26.234 (0.405)	26.526 (0.271)	27.747 (0.253)	28.194 (0.249)
95% CI	23.526–25.832	24.869–26.341	25.433–27.035	25.991–27.060	27.248–28.246	27.704–28.685
Post-1942	25.51027 (0.412)	26.368 (0.391)	27.047 (0.332)	28.155 (0.359)	28.480 (0.385)	29.089 (0.455)
95% CI	24.697–26.323	25.597–27.141	26.395–27.700	27.448–28.861	27.721–29.239	28.192–29.986
Observations by birth cohort sample	38 (pre)	82 (pre)	131 (pre)	222 (pre)	292 (pre)	345 (pre)
	154 (post)	201 (post)	279 (post)	267 (post)	227 (post)	189 (post)
t test of difference in means between cohorts	−0.948	−1.162	−1.457	−3.504	−1.649	−1.879
P value of two-sided *t* test above $P(T < t)$	0.172	0.123	0.073	0.0002	0.050	0.030
			AT genotype			
Age group	30–34.99	35–39.99	40–44.99	45–49.99	50–54.99	55–59.99
Pre-1942	25.134 (0.372)	25.413 (0.233)	25.803 (0.178)	26.269 (0.159)	26.692 (0.135)	27.116 (0.135)
95% CI	24.396–25.872	24.954–25.871	25.453–26.153	25.957–26.581	26.427–26.957	26.851–27.382
Post-1942	24.903 (0.189)	25.822 (0.177)	26.573 (0.180)	27.465 (0.182)	28.283 (0.190)	28.899 (0.244)
95% CI	24.531–25.275	25.474–26.170	26.220–26.925	27.109–27.822	27.910–28.655	28.420–29.377
Observations by birth cohort sample	115 (pre)	290 (pre)	477 (pre)	748 (pre)	1,003 (Pre)	1,116 (pre)
	587 (post)	775 (post)	926 (post)	901 (post)	841 (post)	580 (post)
t test of difference in means between cohorts	0.504	−1.268	−2.739	−4.855	−6.981	−6.933
P value of two-sided *t* test above $P(T < t)$	0.693	0.103	0.003	$P < 0.001$	$P < 0.001$	$P < 0.001$
			TT genotype			
Age group	30–34.99	35–39.99	40–44.99	45–49.99	50–54.99	55–59.99
Pre-1942	24.824 (0.486)	25.392 (0.285)	25.807 (0.245)	26.277 (0.197)	26.878 (0.178)	27.346 (0.170)
95% CI	23.857–25.791	24.829–25.954	25.325–26.288	25.890–26.663	26.528–27.228	27.012–27.680
Post-1942	24.314 (0.233)	24.568 (0.181)	25.687 (0.194)	26.470 (0.191)	27.082 (0.211)	27.611 (0.257)
95% CI	23.855–24.773	24.211–24.924	25.305–26.069	26.096–26.845	26.667–27.497	27.106–28.117
Observations by birth cohort sample	86 (pre)	212 (pre)	373 (pre)	565 (pre)	731 (pre)	876 (pre)
	377 (post)	485 (post)	591 (post)	579 (post)	552 (post)	370 (post)
t test of difference in means between cohorts	0.943	2.475	0.383	−0.708	−0.741	−0.855
P value of two-sided *t* test above $P(T < t)$	0.827	0.993	0.649	0.240	0.230	0.761

The means and SDs are shown in parentheses of BMI for individuals with a specific *FTO* allele type and age range at time of examination. *t* tests test that there are no differences in average BMI conditional on age and *FTO* allele type across the birth cohorts with the 1942 breakpoint are calculated. ***$P < 0.01$, **$P < 0.05$, and *$P < 0.1$. Observation numbers are pre-1942 cohort + post-1942 cohort. The table clearly indicates that there are statistically significant differences for those with the AA and AT genotypes by birth cohort but there are no age ranges for those with the TT genotype where a statistically significant difference in BMI exists between cohorts.

Table S4. Model estimates by sex of factors influencing BMI, where birth year is treated as a discrete variable for pre-/post-1942 as birth year

	Females			Males		
Estimator	Linear regression	Random effects	Linear regression with controls for family fixed effects	Linear regression	Random effects	Linear regression with controls for family fixed effects
Age 35–39.99	0.125 (0.290)	0.0874 (0.171)	0.205 (0.298)	0.364 (0.222)	0.438*** (0.150)	0.438* (0.254)
Age 40–44.99	0.872*** (0.336)	0.676*** (0.191)	0.903*** (0.294)	0.853*** (0.268)	0.617*** (0.166)	0.545** (0.252)
Age 45–49.99	1.117** (0.446)	0.752*** (0.232)	0.973*** (0.315)	1.097*** (0.317)	0.886*** (0.195)	0.714*** (0.266)
Age 50–54.99	1.179** (0.519)	0.780*** (0.279)	1.065*** (0.347)	1.335*** (0.396)	0.895*** (0.230)	0.693** (0.287)
Age 55–59.99	1.387** (0.630)	0.920*** (0.330)	1.264*** (0.387)	1.349*** (0.470)	0.783*** (0.272)	0.539* (0.320)
Age 60–63	1.193 (0.738)	0.793** (0.382)	1.202*** (0.437)	1.373** (0.548)	0.856*** (0.314)	0.566 (0.358)
Subject was born after 1942	−1.764*** (0.485)	−2.067*** (0.427)	−1.89*** (0.227)	−0.313 (0.421)	−0.612* (0.342)	−0.229 (0.204)
Wave 2	0.148 (0.179)	0.427*** (0.116)	0.217 (0.163)	−0.223 (0.136)	−0.0561 (0.0952)	0.00904 (0.132)
Wave 3	0.525** (0.263)	0.926*** (0.157)	0.658*** (0.192)	0.126 (0.198)	0.346*** (0.128)	0.466*** (0.153)
Wave 4	1.147*** (0.329)	1.568*** (0.192)	1.264*** (0.217)	0.592** (0.246)	0.798*** (0.156)	0.980*** (0.172)
Wave 5	1.676*** (0.400)	2.266*** (0.232)	1.869*** (0.249)	1.079*** (0.304)	1.359*** (0.189)	1.577*** (0.198)
Wave 6	2.355*** (0.493)	3.013*** (0.277)	2.591*** (0.289)	1.532*** (0.371)	1.845*** (0.225)	2.140*** (0.230)
Wave 7	2.648*** (0.568)	3.421*** (0.310)	2.913*** (0.320)	1.746*** (0.423)	2.146*** (0.252)	2.478*** (0.255)
Wave8	3.240*** (0.723)	4.164*** (0.384)	3.687*** (0.399)	1.805*** (0.529)	2.574*** (0.315)	2.931*** (0.322)
AA genotype	0.908 (0.838)	0.270 (0.584)	0.982 (0.677)	1.265* (0.744)	0.618 (0.468)	0.982* (0.593)
AT genotype	−1.389*** (0.532)	−1.501*** (0.397)	−0.832* (0.437)	−0.0426 (0.432)	0.0210 (0.310)	0.148 (0.354)
Born after 1942 by AA genotype	0.950 (0.782)	0.917 (0.717)	−0.689* (0.361)	0.925 (0.630)	1.146** (0.552)	1.410*** (0.320)
Born after 1942 by AT genotype	2.043*** (0.524)	1.729*** (0.503)	1.505*** (0.248)	0.362 (0.441)	0.443 (0.398)	−0.0421 (0.219)
Age 30–34.99 by AA	−1.109 (0.741)	−0.0415 (0.383)	−0.823 (0.690)	−0.413 (0.782)	−0.0732 (0.339)	−0.246 (0.599)
Age 35–39.99 by AA	−0.409 (0.684)	0.305 (0.386)	−0.316 (0.708)	−0.418 (0.634)	−0.230 (0.346)	−0.421 (0.617)
Age 40–44.99 by AA	−0.515 (0.707)	0.294 (0.367)	−0.405 (0.676)	−0.876 (0.633)	−0.0224 (0.332)	−0.213 (0.593)
Age 45–49.99 by AA	−0.580 (0.723)	0.483 (0.367)	−0.400 (0.672)	−0.632 (0.685)	−0.268 (0.331)	−0.398 (0.589)
Age 50–54.99 by AA	−0.118 (0.744)	0.744** (0.368)	−0.0716 (0.674)	−0.747 (0.685)	−0.109 (0.331)	−0.183 (0.589)
Age 55–59.99 by AA	−0.185 (0.793)	0.474 (0.373)	−0.0693 (0.681)	−0.567 (0.734)	0.0982 (0.335)	−0.0631 (0.594)
Age 60–63 by AA	−0.0671 (0.788)	0.467 (0.391)	−0.256 (0.718)	−0.403 (0.724)	0.196 (0.352)	0.0746 (0.626)
Age 30–34.99 by AT	0.166 (0.370)	0.838*** (0.214)	0.437 (0.383)	0.614* (0.324)	0.349** (0.176)	0.327 (0.303)
Age 35–39.99 by AT	0.706* (0.397)	1.100*** (0.251)	0.791* (0.462)	0.726** (0.325)	0.230 (0.212)	0.384 (0.374)
Age 40–44.99 by AT	0.550 (0.393)	1.114*** (0.241)	0.767* (0.443)	0.366 (0.343)	0.235 (0.204)	0.315 (0.360)
Age 45–49.99 by AT	0.775* (0.452)	1.349*** (0.238)	1.039** (0.437)	0.296 (0.346)	0.127 (0.203)	0.162 (0.356)
Age 50–54.99 by AT	0.972** (0.437)	1.347*** (0.237)	1.187*** (0.436)	0.248 (0.374)	0.181 (0.201)	0.233 (0.354)
Age 55–59.99 by AT	1.077** (0.484)	1.288*** (0.243)	1.091** (0.444)	0.0747 (0.387)	0.123 (0.206)	0.0603 (0.362)
Age 60–63 by AT	1.130** (0.492)	1.195*** (0.256)	1.086** (0.470)	−0.104 (0.417)	−0.0281 (0.216)	−0.106 (0.380)
Constant	24.29*** (0.420)	24.34*** (0.302)	24.16*** (0.269)	25.85*** (0.335)	26.04*** (0.244)	25.87*** (0.233)
Observations	1,957	1,957	1,957	1,763	1,763	1,763
R^2	0.080	0.87	0.569	0.062	0.073	0.531
No. of Individuals	10,404	10,404	10,404	9,213	9,213	9,213
No. of family fixed effects	Not applicable	Not applicable	983	Not applicable	Not applicable	888

Presented are estimates of the age–period–cohort model where the cohort variable is treated as discrete as indicated in Eq. **S3**. Each entry refers to the effect of the variable listed in the first column on BMI holding all other factors constant. Robust SEs are presented in parentheses. The columns in this table differ based on the sex subsample as indicated row 1 and the method used to estimate the statistical model indicated in row 2. See Table S6 for the calendar time corresponding to examinations in each wave. The following indicate the statistical significance of each explanatory variable: ***$P < 0.01$, **$P < 0.05$, and *$P < 0.1$.

Table S5. Descriptive statistics on genetic characteristics across birth cohorts

Genotype at rs9939609	Individuals born pre-1942	Individuals born post-1942
TT	787 (36.52%)	517 (33.04%)
AT	1,049 (48.68%)	812 (51.77%)
AA	319 (14.85%)	236 (15.08%)
No. of people	2,155	1,565

Presented is the distribution of genetic risk alleles of individuals in the Framingham Offspring Study born pre- and post-1942. A Pearson's χ^2 for the hypothesis that the rows and columns in a two-way table are independent accounting for correlations within families yields $P > X^2 = 0.1550$, $\chi^2(2) = 1.88$. This indicates that the distributions of genetic risk factors do not differ between cohorts born pre- and post-1942.

Table S6. Descriptive statistics

No. of unique subjects	3,720
Total no. of observations in estimation sample	19,617
Subjects that are male, %	52.61
Mean age of subject at data collection (SD)	48.1763 (9.4095)
No. of individuals born before 1920	83
No. of Individuals born between 1920 and 1925	323
No. of Individuals born between 1925 and 1930	481
No. of Individuals born between 1930 and 1935	561
No. of Individuals born between 1935 and 1940	575
No. of Individuals born between 1940 and 1945	715
No. of Individuals born between 1945 and 1950	537
No. of individuals born after 1950	351
Observations collected in wave 1 beginning 30 Aug 1971	3,720
Observations collected in wave 2 beginning 26 Jan 1995	3,581
Observations collected in wave 3 beginning 20 Dec 1983	3,326
Observations collected in wave 4 beginning 22 Apr 1987	2,955
Observations collected in wave 5 beginning 23 Jan 1991	2,488
Observations collected in wave 6 beginning 26 Jan 1995	1,916
Observations collected in wave 7 beginning 11 Sep 1998	1,310
Observations collected in wave 8 beginning 10 Mar 2005	321
No. of Individuals with FTO–AA, %	555 (14.56)
No. of Individuals with FTO–AT, %	1,861 (50.03)
No. of Individuals with FTO–TT, %	1,304 (35.05)
BMI	26.869 (5.013)

Provided are the summary statistics for the measures used in the multivariate regression analysis. We only list the date of the first interview for each wave in the description above because the examinations in each wave were held over several years and the exact time could be inferred by taking the difference between age at examination and YOB.

Table S7. Model estimates of factors influencing BMI, where we ignore cohort effects and interactions of genetic factors with age and birth cohort indicators

Estimator	Linear regression	Random effects	Linear regression with controls for family fixed effects
Wave 2	−0.252** (0.101)	0.0764 (0.0943)	−0.203 (0.169)
Wave 3	0.0669 (0.132)	0.491*** (0.109)	0.146 (0.176)
Wave 4	0.538*** (0.158)	1.023*** (0.122)	0.573*** (0.182)
Wave 5	0.928*** (0.184)	1.530*** (0.139)	0.961*** (0.194)
Wave 6	1.304*** (0.235)	2.146*** (0.161)	1.387*** (0.212)
Wave 7	1.338*** (0.277)	2.337*** (0.178)	1.458*** (0.227)
Wave 8	1.275*** (0.374)	2.831*** (0.220)	1.657*** (0.277)
AA genotype	0.574 (0.357)	0.854*** (0.328)	0.123 (0.254)
AT genotype	0.131 (0.237)	0.336 (0.231)	0.523*** (0.179)
Age 35–39.99	0.595*** (0.101)	0.489*** (0.0718)	0.681*** (0.125)
Age 40–44.99	1.111*** (0.116)	0.954*** (0.0859)	1.244*** (0.126)
Age 45–49.99	1.485*** (0.146)	1.214*** (0.107)	1.570*** (0.134)
Age 50–54.99	1.762*** (0.176)	1.337*** (0.131)	1.856*** (0.147)
Age 55–59.99	1.960*** (0.217)	1.381*** (0.157)	2.015*** (0.163)
Age 60–63	1.912*** (0.251)	1.341*** (0.183)	2.117*** (0.182)
Wave 2 by AA	0.279 (0.182)	0.0714 (0.156)	0.165 (0.305)
Wave 3 by AA	0.225 (0.222)	0.139 (0.157)	0.176 (0.307)
Wave 4 by AA	0.500** (0.235)	0.224 (0.159)	0.396 (0.309)
Wave 5 by AA	0.395 (0.273)	0.254 (0.165)	0.394 (0.319)
Wave 6 by AA	0.620* (0.338)	0.289* (0.175)	0.530 (0.338)
Wave 7 by AA	1.024*** (0.382)	0.553*** (0.182)	0.762** (0.350)
Wave 8 by AA	0.910 (0.590)	0.237 (0.229)	0.561 (0.436)
Wave 2 by AT	0.135 (0.120)	0.0521 (0.110)	0.0905 (0.215)
Wave 3 by AT	0.135 (0.141)	0.00837 (0.111)	0.0159 (0.216)
Wave 4 by AT	0.138 (0.155)	−0.0530 (0.111)	0.00228 (0.217)
Wave 5 by AT	0.314* (0.182)	0.108 (0.116)	0.209 (0.225)
Wave 6 by AT	0.517** (0.230)	0.0139 (0.124)	0.281 (0.239)
Wave 7 by AT	0.724*** (0.267)	0.201 (0.130)	0.502** (0.250)
Wave 8 by AT	1.325*** (0.384)	0.371** (0.160)	0.831*** (0.304)
Constant	23.65*** (0.187)	23.60*** (0.181)	23.41*** (0.150)
Observations	19,617	19,617	19,617
R^2	0.096	0.097	0.480
No. of individuals	3,720	3,720	3,720
No. of family fixed effects	Not applicable	Not applicable	1,414

Presented are estimates of the age–period model where the cohort variable is not included and the only genetic interactions included are those with period effects allowing solely for contemporaneous gene–environment interactions. The age and period variables are treated as discrete as indicated in Eq. **S3**. Each entry refers to the effect of the variable listed in the first column on BMI holding all other factors constant. Robust SEs are presented in parentheses. The columns in this table differ based on what factors are accounted for and the method used to estimate the statistical model. See Table S6 for the calendar time corresponding to examinations in each wave. Note that our main results of birth cohort and genotype interactions are not sensitive to the method by which the model was estimate. The following indicate the statistical significance of each explanatory variable: ***$P < 0.01$, **$P < 0.05$, and *$P < 0.1$.

Table S8. Model estimates of factors influencing BMI, where we ignore cohort effects and interactions of genetic factors with birth cohort indicators

Estimator	Linear regression	Random effects	Linear regression with controls for family fixed effects
Wave 2	−0.411*** (0.121)	−0.0757 (0.112)	−0.337* (0.174)
Wave 3	−0.197 (0.172)	0.244* (0.144)	−0.0737 (0.188)
Wave 4	0.204 (0.215)	0.700*** (0.172)	0.288 (0.200)
Wave 5	0.528** (0.252)	1.124*** (0.204)	0.609*** (0.218)
Wave 6	0.835*** 0.319)	1.646*** 0.242)	0.960*** 0.243)
Wave 7	0.820** (0.378)	1.764*** (0.270)	0.973*** (0.262)
Wave 8	0.654 (0.494)	2.093*** (0.335)	1.032*** (0.319)
AA genotype	1.489** (0.607)	0.954** (0.401)	0.860* (0.465)
AT genotype	0.172 (0.309)	−0.0794 (0.269)	0.213 (0.291)
Age 35–39.99	0.593*** (0.181)	0.498*** (0.123)	0.700*** (0.213)
Age 40–44.99	1.434*** (0.202)	1.068*** (0.146)	1.363*** (0.210)
Age 45–49.99	1.950*** (0.259)	1.438*** (0.183)	1.847*** (0.220)
Age 50–54.99	2.356*** (0.307)	1.657*** (0.224)	2.163*** (0.237)
Age 55–59.99	2.764*** (0.379)	1.886*** (0.269)	2.568*** (0.260)
Age 60–63	2.904*** (0.433)	2.026*** (0.312)	2.870*** (0.288)
Age 30–34.99 by AA	−0.707 (0.570)	0.00615 (0.267)	−0.759 (0.499)
Age 35–39.99 by AA	−0.758 (0.523)	−0.127 (0.304)	−0.782 (0.527)
Age 40–44.99 by AA	−1.255** (0.585)	−0.216 (0.345)	−0.942* (0.521)
Age 45–49.99 by AA	−1.422** (0.648)	−0.434 (0.408)	−1.183** (0.533)
Age 50–54.99 by AA	−1.511** (0.748)	−0.412 (0.478)	−1.091** (0.555)
Age 55–59.99 by AA	−1.710* (0.880)	−0.630 (0.557)	−1.358** (0.585)
Age 60–63 by AA	−1.760* (0.966)	−0.737 (0.632)	−1.378** (0.624)
Age 30–34.99 by AT	0.331 (0.242)	0.577*** (0.142)	0.505* (0.264)
Age 35–39.99 by AT	0.304 (0.277)	0.464** (0.193)	0.393 (0.331)
Age 40–44.99 by AT	−0.186 (0.301)	0.325 (0.224)	0.253 (0.328)
Age 45–49.99 by AT	−0.414 (0.375)	0.215 (0.271)	0.0164 (0.336)
Age 50–54.99 by AT	−0.639 (0.427)	0.0510 (0.322)	−0.0647 (0.351)
Age 55–59.99 by AT	−1.009* (0.516)	−0.208 (0.379)	−0.473 (0.374)
Age 60–63 by AT	−1.367** (0.577)	−0.506 (0.434)	−0.862** (0.401)
Wave 2 by AA	0.547** (0.253)	0.246 (0.209)	0.384 (0.321)
Wave 3 by AA	0.641* (0.354)	0.420 (0.268)	0.506 (0.343)
Wave 4 by AA	0.998** (0.414)	0.589* (0.316)	0.797** (0.361)
Wave 5 by AA	0.967* (0.502)	0.704* (0.377)	0.865** (0.390)
Wave 6 by AA	1.261** (0.629)	0.828* (0.445)	1.073** (0.430)
Wave 7 by AA	1.705** (0.724)	1.159** (0.497)	1.351*** (0.461)
Wave 8 by AA	1.674* (0.991)	1.003 (0.618)	1.276** (0.565)
Wave 2 by AT	0.357** (0.160)	0.221 (0.147)	0.269 (0.226)
Wave 3 by AT	0.522** (0.225)	0.300 (0.189)	0.328 (0.240)
Wave 4 by AT	0.640** (0.278)	0.342 (0.225)	0.419* (0.253)
Wave 5 by AT	0.925*** (0.332)	0.613** (0.268)	0.732*** (0.273)
Wave 6 by AT	1.247*** (0.417)	0.651** (0.318)	0.930*** (0.302)
Wave 7 by AT	1.539*** (0.486)	0.937*** (0.354)	1.249*** (0.323)
Wave 8 by AT	2.338*** (0.645)	1.340*** (0.439)	1.829*** (0.393)
Constant	23.45*** (0.204)	23.58*** (0.190)	23.36*** (0.175)
Observations	19,617	19,617	19,617
R^2	0.098	0.097	0.481
No. of individuals	3,720	3,720	3,720
No. of family fixed effects	Not applicable	Not applicable	1,414

Presented are estimates of an age–period model where the cohort variable and all interactions are not included in the specification. All age and period variables are treated as discrete as indicated in Eq. **S3**. Each entry refers to the effect of the variable listed in the first column on BMI holding all other factors constant. Robust SEs are presented in parentheses. The columns in this table differ based on what factors are accounted for and the method used to estimate the statistical model. See Table S6 for the calendar time corresponding to examinations in each wave. Note that our main results of birth cohort and genotype interactions are not sensitive to the method by which the model was estimated. The following indicate the statistical significance of each explanatory variable: ***$P < 0.01$, **$P < 0.05$, and *$P < 0.1$.