How shifts in individual health have changed the nature of mortality risk

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ABSTRACT [150 words]

Public health policy should ideally be built from insights obtained from linking changes in individual-health to changes at the population-level. We investigated how individual health trajectories have shaped the dispersion of mortality over time.

We exactly decomposed changes in population-level health into contributions from the individual-level processes that generate them. We applied this to the Framingham Heart Study. We investigated changes to systolic blood pressure and body mass index in relation to the use of anti-hypertension medication.

Longitudinal changes have driven substantial shifts in population health. This has caused the population-level association between health and mortality to change over time, with shifts among non-medicated individuals having had the greatest influence.

Our findings indicate the success of public health action to reduce systolic blood pressure. However, rising body mass index is shifting the burden of mortality to heavier individuals; this urges further public health action on the social determinants of obesity.

INTRODUCTION

Explaining how changes in health over the individual life course drive changes at the population-level is one of the greatest challenges for epidemiology. The problem is in understand how longitudinal trajectories of individual health interact with mortality to shape health at the population-level. Statistical risk algorithms tell us the likelihood that an individual with a particular pattern of health will develop a disease or die within a

specified period of time. However, whilst these algorithms provide a useful prediction for individuals, they do not tell us about population change. Rose's view of how distributions of health traits, such as blood pressure, shift and morph over time and space is therefore central to understanding the consequent shifts in population health. The risk of mortality varies with the state of current health. Health among survivors may then follow diverse individual trajectories. Coulson and Tuljapurkar's [1] development of Price's [2] early work on trait dynamics provides the mechanism by which these individual-level processes link to population-level trait changes. Their theory of population change has now been applied extensively to explain ecological change in a range of organisms [3-5].

Contemporary human populations have also undergone substantial ecological change and population-level changes in human health depend also on the patterns of mortality and longitudinal changes within individuals. Work on blood pressure and body mass index is a large part of the literature on changes in population health. Investigations have focused on understanding individual health trajectories over the life course and potential influences on the ageing process. For example, we now understand that although distributions of blood pressure shift over time and among populations, blood pressure also follows a characteristic ageing trajectory [6]. This trajectory, of a gradual rise over adulthood, followed by declines in old age also varies widely among individuals. Furthermore, the population changes in blood pressure over time and space are influenced to a large extent by individuals moving in and out of the hypertensive state.

The rapid recent rise of body mass index worldwide has attracted a great deal of attention due to its link with poor health, such as an increased risk of hypertension [7]. However, we still do not fully understand its causes and potential population health consequences. We do know however that body mass index follows a characteristic age-trajectory, rising in middle age with a subsequent later life decline that is apparently associated with increasing frailty. The population mean of BMI is currently shifting upwards as more individuals become overweight and obese. Several investigations have shown that this rise in body mass index has acted to suppress some of the population health gains that would otherwise have come from improvements in public health and medicine over the last decades [8, 9].

A potential solution to the worsening of public health, and an option to drive further public health gains, is to increase the population uptake of preventative medication. Medication given to individuals at risk of hypertension is shown to be effective at reducing or stabilising blood pressure changes over age. However, at the population level there is a close correspondence between public health gains through diet and lifestyle improvements and the rising use of medication. The first use of medication for hypertension was in the 1940s and its usage has gradually risen, creating the situation today where anti-hypertensives are readily prescribed. Has this driven blood pressure decline at the population-level or mitigated rises in blood pressure that would otherwise have occurred? Gaining an insight into this question is particularly important given the ongoing debate about prescribing medication ubiquitously, potentially even to currently healthy individuals.

Thanks to the pioneers who established the first longitudinal biomedical monitoring studies, we have the data to investigate how changes in individuals relate to changes in the population over time. We introduce an analysis method that shows the linkages between the individual and population levels. Using the Framingham Heart Study [10] – the earliest and longest-running longitudinal study – we investigated the changes to systolic blood pressure and body mass index at the individual and population levels, in relation to the use of anti-hypertensive medication.

METHODS

Data

The Framingham Heart Study began in 1948-51 by enrolling around 5,000 participants from the town of Framingham, Massachusetts in the United States (US) [11]. These were adults aged from 28 to 62 (born from 1888 to 1922) who had not yet shown signs of cardiovascular disease. A second wave from 1974-76 enrolled the offspring of the original participants. At enrolment these offspring were aged from 6 to 70 (born from 1906 to 1966). Examinations took place approximately every two years; our sample contained data from 41,312 exams.

Systolic blood pressure

Systolic blood pressure was recorded mostly by a physician at a study clinic, but in some cases during a visit to a participant's home. Measurements were taken after the participant had been seated for some minutes. Where two measurements were available, we used the average, otherwise we used the single reading.

Anti-hypertension medication

We defined a patient as under treatment if medication was being used at the time of exam, or had been used in the period between exams. We defined individuals as not under treatment if medication usage had been coded as uncertain. See the Supporting Information for the specific variable codes used.

Body mass index

Height and weight were recorded to compute body mass index as the weight (kg) divided by the square of height (m).

Trait change over age

Taking systolic blood pressure as an example, we will now describe our adaptation of the analysis method from Coulson and Tuljapurkar [1]. Imagine a set of individuals who are observed at a particular age (a). They have a variety of systolic blood pressure values. Before they are observed again after an interval i, e.g., i = two years, some of the individuals die. If those individuals who have died are a non-random sample with respect to SBP, i.e., if mortality is selective, then the mean value of SBP will change. The direction and magnitude of this change is termed the viability selection differential (V).

It is given by the covariance of SBP at age a (at the start of the interval) with a binary variable (S) indicating whether or not an individual survived (1) or not (0) through the interval to the next observation (see also Rebke et al [12] for an alternative but equivalent formulation). This covariance must then be scaled by the proportion of individuals who survive to the next observation ($\bar{S}$), which is the mean of S.

$$V(a, i) = \frac{\mathrm{Cov}[\mathrm{SBP}(a), S(a, i)]}{\bar{S}(a, i)} \qquad (1)$$

The SBP value of each individual who survives to the next observation is also likely to have changed longitudinally in the intervening time interval. The resulting change to the mean value of SBP is given by the mean value of the longitudinal change among survivors ($\bar{L}$).

$$\bar{L}(a, i) = \overline{\mathrm{SBP}(a+i) - \mathrm{SBP}(a)} \qquad (2)$$

Of course in a real-world study, we can expect that the set of observed individuals will also change due to new enrolments, missed exams and losses of survivors from further follow-up. Considering these additional components allows an exact decomposition of the change in the mean value of SBP over age, and we show that this is so in Appendix 1 and the code supplied as Supporting Information.

Individual trajectories of trait change

For an individual, survival and longitudinal change determine the length and shape of the life course trajectory of the trait under observation. We therefore first investigated the patterns of longitudinal change over the life course in relation to an individual's age at death.

We quantified the individual increments of change L(a, i) for a > 40 and i = 2 for SBP and BMI. To each trait, we fitted a Bayesian hierarchical linear regression to the increments of longitudinal change using the R package MCMCglmm [13] (see Appendix 2 for further details). We fitted random intercepts for individual identity (z) and the year (y) of making the observation at age a. We assumed that the differences among the levels of each random variable had a normal distribution with mean zero and

standard deviation σ. We estimated the longitudinal effects of age (a) by also fitting the age at first exam (f) and age at death (d), such that

$$L(a,i) = f + f^2 + a + a^2 + a^3 + d + d^2 + z + y + \varepsilon \quad (3)$$

We reached a minimum adequate model structure by using the Deviance Information Criterion (DIC) to compare the relative likelihood of alternative nested model structures. Our preliminary analysis indicated no significant effects of gender and so we proceed with a pooled analysis.

Based on DIC, we investigated sequentially if the age at death and the use of anti-hypertension medication modified the effects of age on the longitudinal changes in SBP and BMI. We hypothesised that death would be preceded by a period of senescent decline in both traits. This prediction is supported by evidence from a variety of human and animal studies. We also hypothesised that the use of anti-hypertension medication would have a stronger association with changes in SBP than in BMI, and that its effects on SBP would weaken with increasing age as the prevalence of secondary and resistant hypertension increases.

The components of trait change over time at the population-level

We now use an adaptation of the formula of Coulson and Tuljapurkar to show how viability selection and longitudinal trait changes contribute to population level changes in SBP and BMI. We will represent the mean value of these traits by $\bar{Z}$. Change to the mean trait value ($\Delta\bar{Z}$) between observations in different years (y) is given by the sum of the age-specific components of viability selection (V) and longitudinal change (L). We

consider ages a from the youngest age (α) to the oldest age (ω). The components of change are weighted by the age structure of the population (ϕ), where

$$\sum_{a=\alpha}^{\omega} \phi(y,a) = 1 \tag{4}$$

The proper accounting of change in the population mean between periods also includes effects of changes in the age structure and the entry of new individuals into the population at the youngest age. The formulation is

$$\begin{aligned} \Delta\bar{Z}(y) = & \sum_{a=\alpha}^{\omega-1} \Delta\phi\bar{Z}(y,a) - \phi\bar{Z}(y,\omega) \\ & + \sum_{a=\alpha}^{\omega-1} \phi(y+i,a+i)\left[V+\bar{L}\right](y,a,i) \\ & + \phi\bar{Z}(y+i,\alpha) \end{aligned} \tag{5}$$

Rather than the age structure for each period in the Framingham Heart Study, we used an age structure derived from period life-tables of the US population, obtained from the Human Mortality Database.

We now focus on the age-specific contributions of viability selection and longitudinal change to (5). We further expanded the formulation by the use of anti-hypertension medication at age a. We present this longer formula in Appendix 3. From it we took the contributions of viability selection (V) and longitudinal change (L) for individuals who with certainty were or were not using anti-hypertensives at age a, and who had the same medication status at a+i. From the Framingham Heart Study we quantified the proportion of individuals using anti-hypertensives (p) for each age and year. The

contribution of viability selection to the change in the population mean of a trait Z is then

$$\Delta\bar{Z}_V(y,a,i,m) = \phi(y+i,a+i)\,p(y+i,a+i,m)V(y,a,i,m), \quad (6)$$

and the contribution of longitudinal change is

$$\Delta\bar{Z}_L(y,a,i,m) = \phi(y+i,a+i)\,p(y+i,a+i,m)\bar{L}(y,a,i,m). \quad (7)$$

The consideration of long-term risk

One of the fundamental findings of epidemiology in developed populations is that individuals with relatively high values of SBP and BMI have a higher risk of death in the long-term, e.g., over 10 years. However, over shorter terms we might expect this risk to reduce because, for example, elevated SBP and BMI are upstream factors in the progress of disease pathogenesis. Thus, it may be that viability selection over short intervals, e.g., i = 2 years, contributes little to change in the population mean values of either trait. By contrast, if viability selection is quantified over a longer interval of i = 10 years, we are likely to see the influence that long-term risk has on population change in trait values.

We first investigated the effect on viability selection at each age of setting i = 2, 4, 6, 8, or 10. We then fixed i = 10 to investigate the contribution of changes in long-term risk to population-level changes in the means of SBP and BMI.

Trends over age and time, by medication status

We first described the population-level patterns in SBP, BMI and the uptake of anti-hypertension medication. We then computed the contributions to these population-level patterns of longitudinal change ($i = 2$) and viability selection (for an interval of $i = 10$ years) for individuals using and not using anti-hypertension medication. We analysed each gender separately. For each component of population-level change, we smoothed the trends over age and time using a tensor product spline fitted using the R package mgcv (see Appendix 4 for details).

RESULTS

Individual trajectories of trait change

Figure 1 shows the longitudinal changes in SBP and BMI over two-year intervals of age from age 40 onwards. The general characteristic of these trajectories is an initial increase in trait values that gradually slows before crossing the threshold from increasing to decreasing trait values.

It is clear from Figure 1 that the individual trajectories of each trait also depended strongly on that individual's age at death. The progressive increases in SBP and BMI with age began to slow and subsequently turn to decreasing trait values earlier for individuals who lived for longer.

The use of anti-hypertension medication was associated with significant differences in the longitudinal changes of SBP but not BMI (Table S1). Figure 1(a) shows that the effects of anti-hypertensives on SBP were evident mainly at ages below approximately 65 years. At these ages, medication was successful at stabilising and driving reductions in the trajectory of SBP. Meanwhile, among individuals not on medication, SBP generally increased. However, above around age 65, medication had no detectable

effect. It appeared that the reason for this was that the changes in SBP became influenced increasingly by senescent declines.

Population-level patterns

Figure 2 shows the dramatic shifts that have occurred in SBP, BMI and the uptake of anti-hypertensive medication. Over the 50 year period since the Framingham Heart Study began, SBP has fallen most evidently at around ages 50 to 60, by at least 10 mmHg.

Between 1980 and 2000, the BMI of the average individual aged 30–75 has risen by almost one kg/m^2 each decade. In 1980 the BMI of the average individual aged 30–75 was 26.4 kg/m^2 (standard deviation 4.5 kg/m^2). In 2000, it had reached 28.2 kg/m^2 (standard deviation 5.3 kg/m^2).

However, BMI appears to have remained strikingly constant over time at ages older than 75–80.

The shifts in the uptake of anti-hypertension medication have been the most striking of all. The Framingham Heart Study maps the entire history of anti-hypertensives as a tool to improve population health, from near zero uptake in the 1940s to an uptake of over 50% at ages above 50–60 in 2000.

Individual contributions to population change, by medication status

Figure 3 shows the contribution that longitudinal changes at the individual-level have made to changes in the means of SBP and BMI at the population-level. The most obvious common feature between SBP and BMI is the rapid longitudinal rises in each trait that centred on the 1980s. These rise were of similar magnitude for young adults to ages 70–75.

There are encouraging signs of longitudinal falls in SBP starting just prior to the year 2000. These falls were evident in both individuals using and not using medication for hypertension.

However, in general individuals using anti-hypertensives contributed little to population change. A major reason is that medicated individuals are in the minority; even when uptake at specific ages is high, these ages are generally less populous due to prior mortality.

Mortality risk over age

Figure 4 shows the effect that deaths have on the change in SBP and BMI over age intervals of different length. Our findings for SBP confirm our expectation from the literature that individuals with relatively high SBP values have a higher mortality risk. Having relatively high SBP at ages close to 75 had the strongest association with increased mortality; particularly so when viewed in terms of mortality over the next 10 years. As a result selection acted to decrease the mean value of SBP most strongly around age 75.

However, at ages older than 80–90, selection acted to increase rather than decrease the mean value of SBP. Thus, at these ages having relatively low SBP had the strongest association with increased mortality. This is consistent with the senescent declines noted in Figure 1.

For BMI, selection had no net effect until ages 65–75, when having relatively low BMI associated strongly with increased mortality. This again, is consistent with the senescent declines noted in Figure 1.

The contribution of mortality to population change, by medication status

Figure 5 shows the contribution that changing patterns of mortality made to changes in SBP and BMI. Here we focus on changes in long-term risk, i.e., on deaths within 10 years of an individual being examined.

For SBP there is a clear pattern of decreasing long-term risk over time, such that in later periods viability selection no longer removed individuals with relatively high SBP values from the population. As with longitudinal change in Figure 3, the patterns among individuals not using anti-hypertension medication had most influence at the population-level.

For BMI, the trend for viability selection to remove relatively light individuals tended to weaken at ages where BMI has risen the most over time. This indicates that as BMI has risen, the dispersion of mortality has shifted slightly towards relatively heavier individuals; the pattern is particularly clear among males younger than 75 using anti-hypertensives.

DISCUSSION

To be completed

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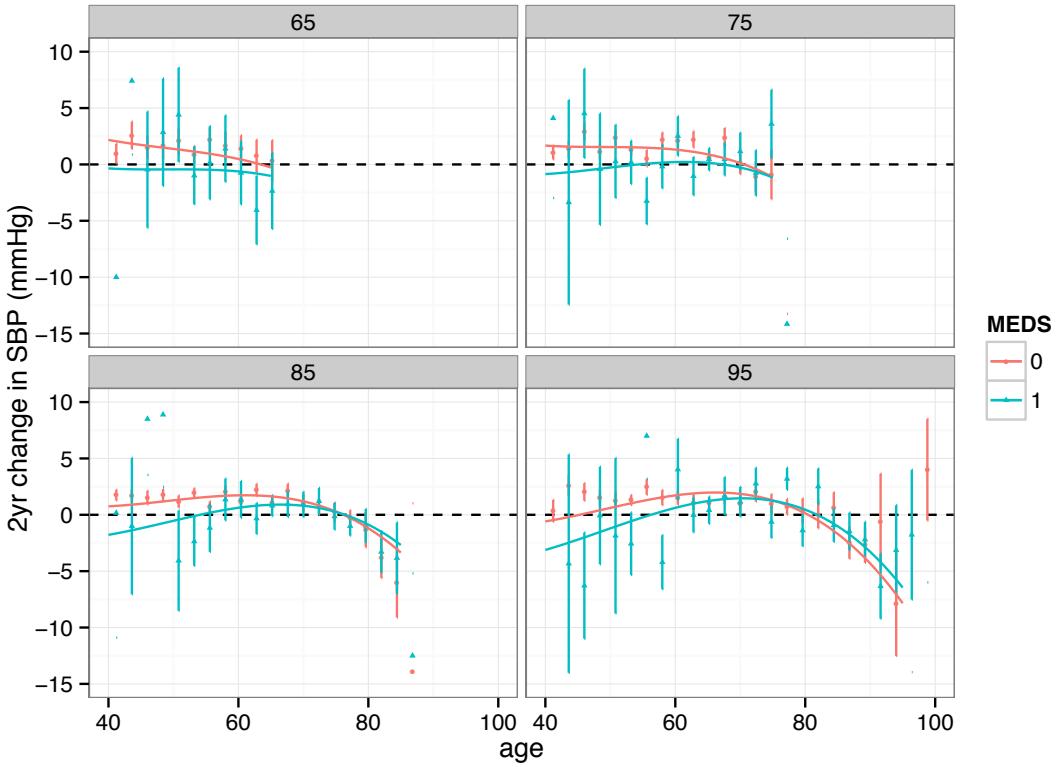
FIGURES

Figure 1. Longitudinal changes over age

The increments of longitudinal change to **(a)** systolic blood pressure (SBP) and **(b)** body mass index (BMI) over two-year age-intervals. The y-axis shows the magnitude and direction of change over the two-year interval, indexed by the age at the start of the interval (x-axis). Data points and error bars show the mean plus or minus one standard error of the changes within 10-year age groups. Lines show the predicted values from a Bayesian hierarchical linear model for the effects of age, age at death and the use of anti-hypertension medication. Panels show the effects of age and medication for four selected ages at death.

(a)



(b)

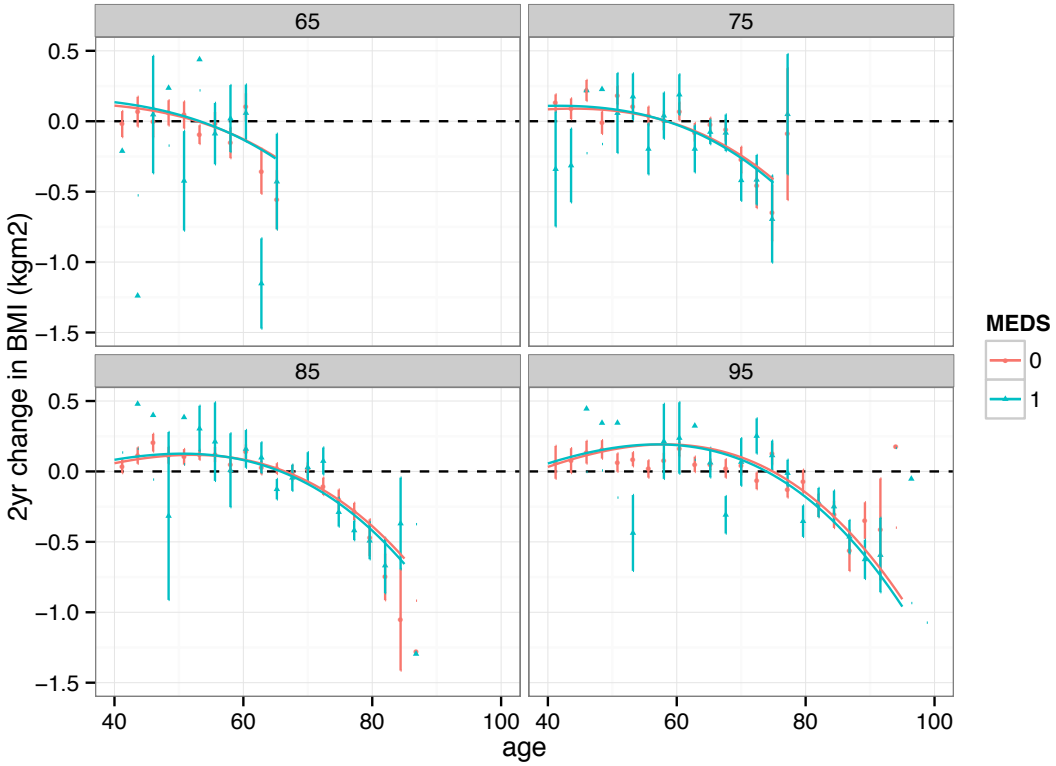


Figure 2. Population-level patterns

Heatmaps that use colours to indicate the trends in the mean values of systolic blood pressure, body mass index and the proportion of individuals using antihypertension medication. The x-axis indicates the year in which individuals were observed and the y-axis indicates their age at observation. Colours closer to the red-end of the spectrum indicate higher values. For each trait the panels show the trends for male and female participants.

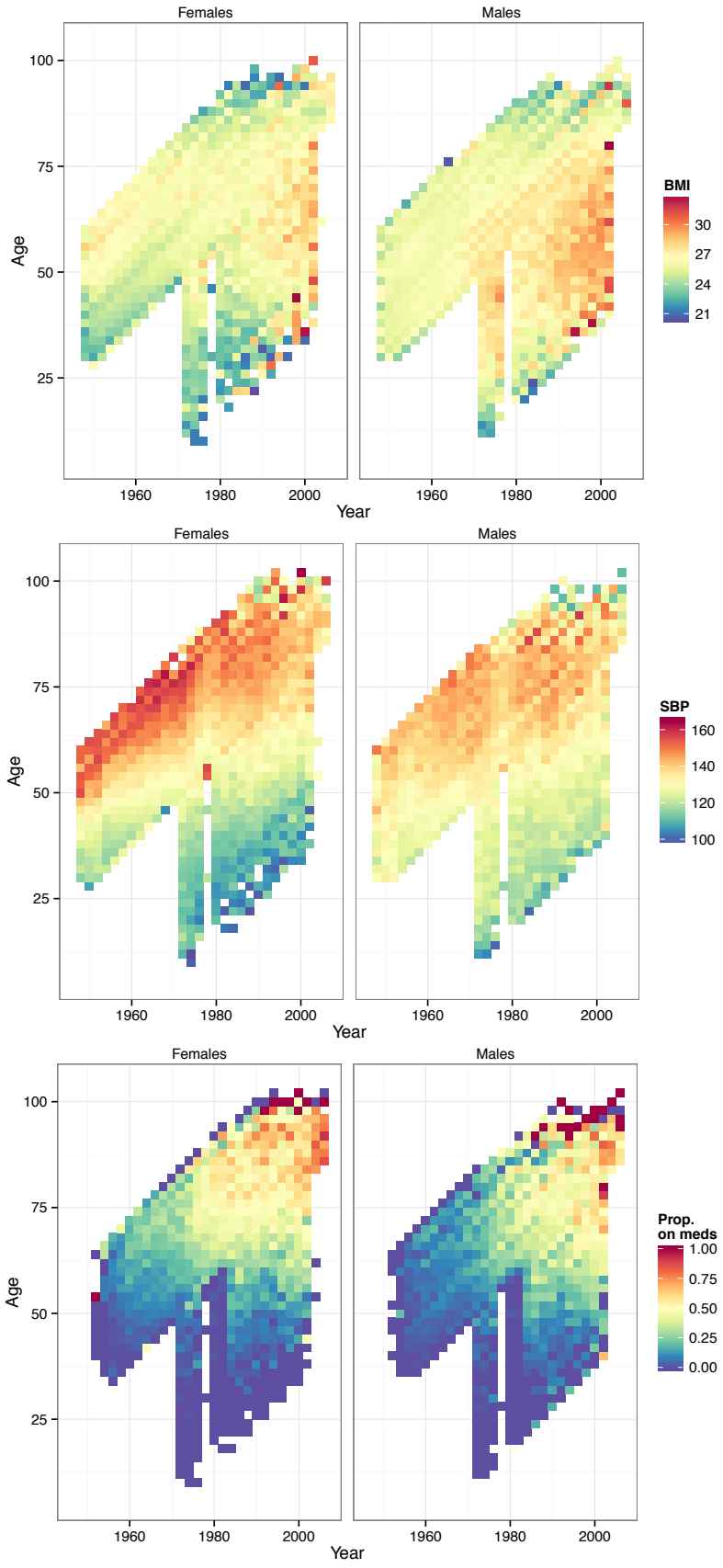
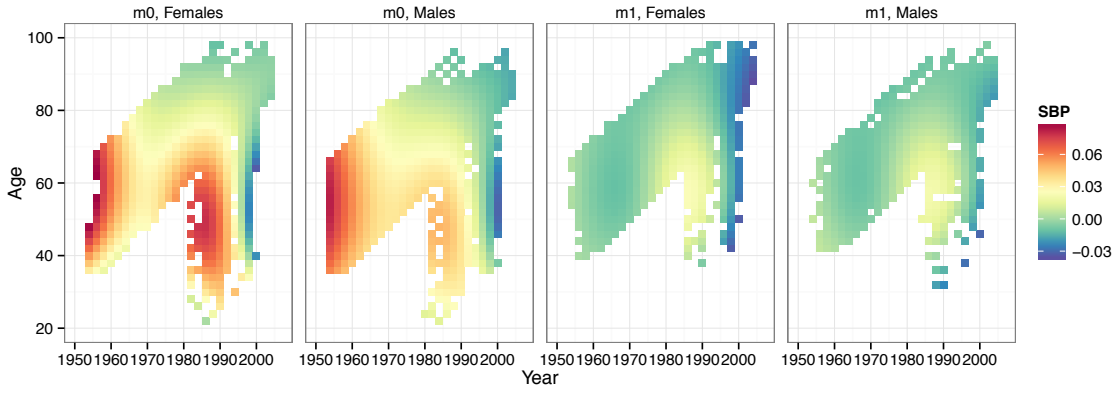

Females
Males
Age
Year
BMI
30
27
24
21
SBP
160
140
120
100
Prop.
on meds
1.00
0.75
0.50
0.25
0.00

Figure 3. Individual contributions to population change

The contributions that longitudinal changes over two-year age-intervals make to change in the mean values of SBP (a) and BMI (b) at the population-level. We quantified these contributions using our formula (7). The weighting by the age-structure of the population in each year is derived from the period life-tables of the United States population. The weighting by medication uptake for each age and year uses the proportion on anti-hypertensive medication from Figure 3. We smoothed the raw data over age and year using a tensor product spline.

(a)



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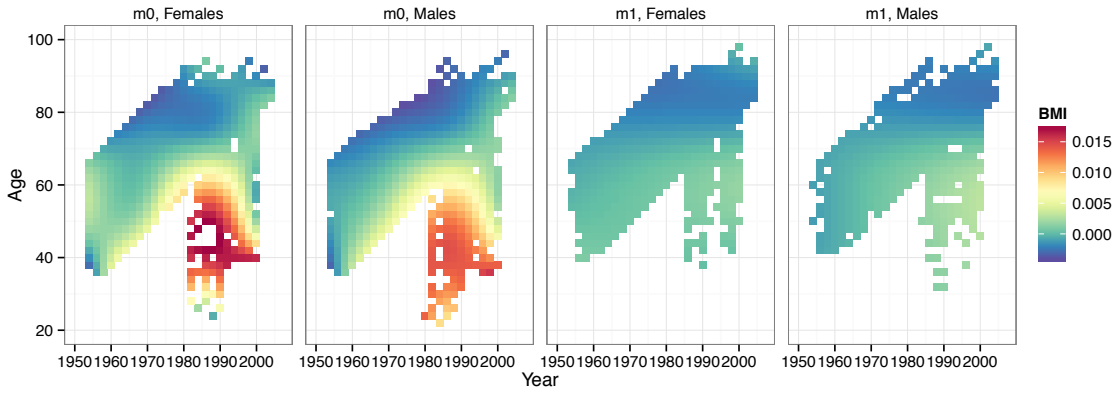
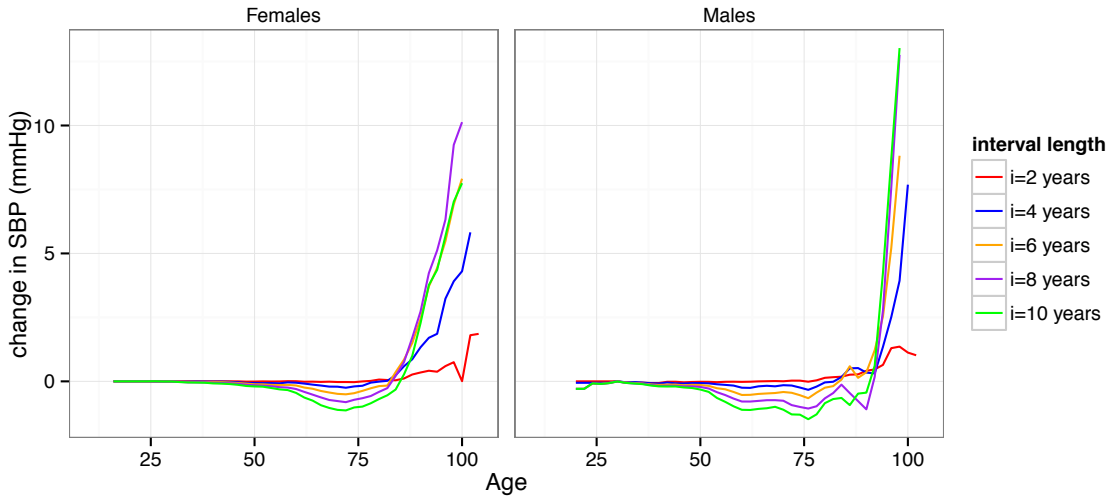


Figure 4. Viability selection over age

The changes over age in the means of SBP **(a)** and BMI **(b)** due to individual deaths. Formally, these changes are the cumulative viability selection differentials. We quantified the effect on the mean trait value at age a of deaths occurring from a to a+i, for i = 2, 4, 6, 8 and 10 years. We then smoothed the results over age a by computing the 5-year moving average.

(a)



(b)

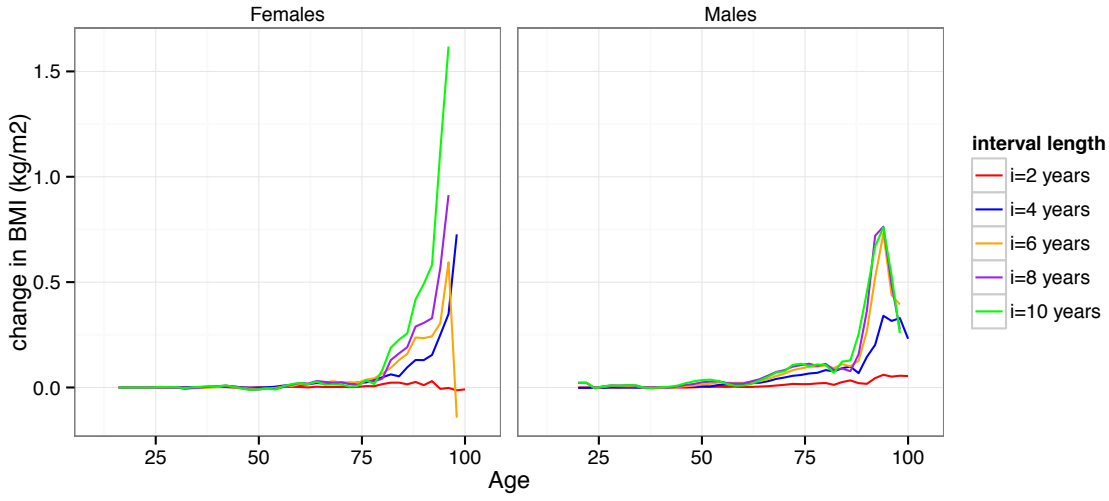
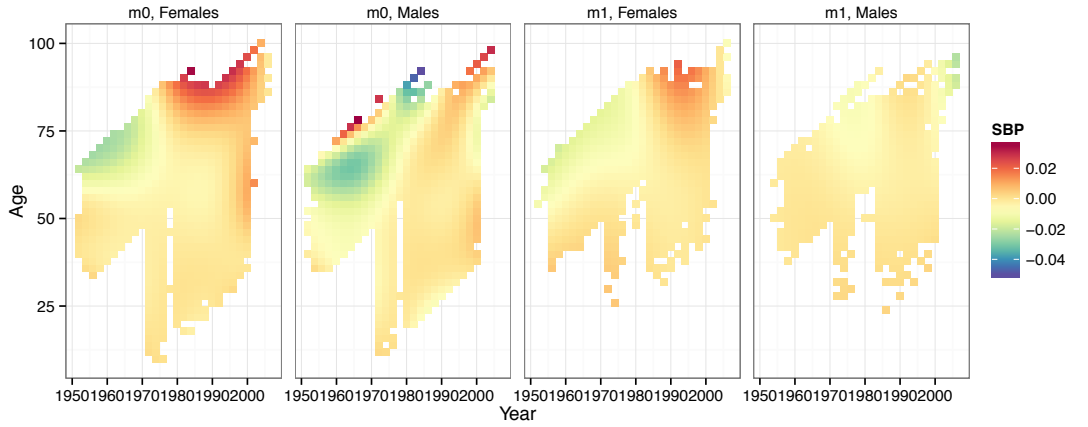


Figure 5. Mortality contributions to population change

The contributions that mortality over ten-year age-intervals make to change in the mean values of SBP (a) and BMI (b) at the population-level, i.e., the cumulative selection differentials over 10 years. We quantified these contributions using our formula (6). The weighting by the age-structure of the population in each year is derived from the period life-tables of the United States population. The weighting by medication uptake for each age and year uses the proportion on anti-hypertensive medication from Figure 3. We smoothed the raw data over age and year using a tensor product spline.

(a)



(b)

APPENDICES

Appendix 1

To be completed

Appendix 2

We analysed the longitudinal changes to SBP and BMI over age-intervals of two years. All analyses were conducted in the R environment [14]. We used the R package MCMCglmm [13], which fits Bayesian generalized linear mixed models (GLMMs). We standardized all continuous explanatory variables by subtracting their mean and dividing by twice their standard deviation before analysis. Thus, the estimated coefficient for each categorical variable corresponds to its effect at the mean value of continuous variables. Estimation of all fixed-effects used the default Gaussian prior (mean=0, variance=10^8); all random-effect variances used inverse-Wishart priors. Coefficient estimates were the means of the posterior distributions for each variable, generated by a Markov Chain Monte Carlo (MCMC) routine. We ran the model for 100,000 iterations, sampling at intervals of 300 after a burn-in of 10 thousand. We confirmed that these MCMC parameters resulted in the convergence of coefficient estimates, minimal autocorrelation, and a consistent DIC ranking of alternative models. Two-tailed 95% intervals of the posterior distributions (95% Credible Intervals, CI) provide a guide to statistical significance.

At each step in our analysis we reached the minimum adequate model structure before proceeding. First, we estimated the model in (3). Second, we added gender to the model and its interaction with the effects of age. Third, we added the interaction between the linear functions of age and age at death. Fourth, we added the usage of anti-hypertension medication at age a, and its interaction with the linear function of age.

The result of this sequential investigation was one model of the longitudinal changes in SBP and one model of the longitudinal changes in BMI. Figures 1 and 2 present the predictions of these models from Table S1.

Table S1. Model estimates

The posterior estimates from a Gaussian hierarchical linear model. We present posterior means and 95% credible intervals. Means and standard deviations of the continuous explanatory variables were: Age at first exam, 43.25 ± 8.14 years; Age, 63.09 ± 12.33 years; Age at death, 81.72 ± 10.42 years.

Dependent variable	Changes in SBP over 2-year age-intervals		Changes in BMI over 2-year age-intervals	
	Mean	95% CI	Mean	95% CI
Fixed-effects				
Age at first exam			-0.069	-0.128 to -0.022
Age	-1.22	-2.23 to -0.35	-0.36	-0.49 to -0.28
Age^2	-3.75	-4.62 to -2.78	-0.41	-0.50 to -0.33
Age^3	-2.06	-3.23 to -0.95	-0.10	-0.23 to 0.00
Age at death	1.12	0.63 to 1.53	0.26	0.21 to 0.31
Age at $death^2$	-0.92	-1.84 to -0.18		
Age x Age at death	3.33	1.72 to 4.68	0.34	0.25 to 0.44
Medication use (not medicated)	1.57	0.69 to 2.47	0.012	-0.051 to 0.065
Medicated	-0.90	-1.35 to -0.42	-0.0089	-0.0465 to 0.0312
Age x Medicated	1.71	0.82 to 2.97	-0.040	-0.136 to 0.055
Random-effects variance				
Individual ID	0.15	0.07 to 0.45	0.0018	0.0004 to 0.0051
Year of exam	3.73	1.72 to 6.05	0.013	0.004 to 0.022
Residual	295	291 to 300	2.19	2.16 to 2.22

Appendix 3

Expanding the decomposition of population change in the mean value of a trait (Z) in (5) to give medication specific values for the change in Z gives

$$\Delta\bar{Z}(y) = \sum_{a=\alpha}^{\omega-1} \Delta\phi\bar{Z}(y,a) - \phi\bar{Z}(y,\omega) + \sum_{a=\alpha}^{\omega-1} \phi(y+i,a+i) \sum_{m=0}^{1} \Delta p\bar{Z}(y,a,m) + \sum_{a=\alpha}^{\omega-1} \phi(y+i,a+i) \sum_{m=0}^{1} p(y+i,a+i,m)\left[V + \bar{L} + E + I\right](y,a,i,m) + \phi\bar{Z}(y+i,\alpha) \quad (1)$$

V is the change to the medication specific mean value of Z due to individual deaths during interval i. $\bar{L}$ is the change to the medication specific mean value of Z due to longitudinal change among individuals who remain at the same medication status from a to a+i.

New components:

E is the change to the medication specific mean value of Z due to individuals leaving medication status m between a and a+i. e is a binary variability indicating whether an individual remained (1) or not (0) at the same medication status

$$E(a,\, i,m) = \frac{\mathrm{Cov}[\mathrm{Z}(a,m),\, e(a,\, i,m)]}{\bar{e}(a,\, i,m)}. \quad (2)$$

I is the change to the medication specific mean value of Z due to individuals entering medication status m between a and a+i. This is the difference between the mean value of Z at a+i and the mean value considering only individuals who stayed at the same medication status from a (Z_+)

$$I(a,\, i,m) = \bar{Z}(a+i,m) - \bar{Z}_{+}(a+i,m). \quad (3)$$

Appendix 4

To be completed