UW Biostatistics Working Paper Series

6-15-2010

Multi-state Life Tables, Equilibrium Prevalence, and Baseline Selection Bias

Paula Diehr
University of Washington, pdiehr@u.washington.edu

David Yanez
University of Washington, yanez@u.washington.edu

Multi-state Life Tables, Equilibrium Prevalence, and Baseline Selection Bias

Paula Diehr [1 2]

David Yanez [1]

From the departments of (1) Biostatistics and (2) Health Services of the University of Washington, Seattle, Washington.

The research reported in this article was supported by contract numbers N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, grant number U01 HL080295 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm

Multi-state Life Tables, Equilibrium Prevalence, and Baseline Selection Bias

Abstract

Consider a 3-state system with one absorbing state, such as Healthy, Sick, and Dead. If the system satisifies the 1-step Markov conditions, the prevalence of the Healthy state will converge to a value that is independent of the initial distribution. This equilibrium prevalence and its variance are known under the assumption of time homogeneity, and provided reasonable estimates in the time non-homogeneous systems studied. Here, we derived the equilibrium prevalence for a system with more than three states. Under time homogeneity, the equilibrium prevalence distribution was shown to be an eigenvector of a partition of the matrix of transition probabilities. The eigenvector worked well for time non-homogeneous examples as well. We developed a test for whether the available sample was at equilibrium, and used it to explore whether there was selection bias in the baseline distribution of a large longitudinal cohort sample.

Key words. Multi-state life table, self-rated health, eigenvalue, eigenvector, equilibrium prevalence, selection bias, cohort sample

Abstract 142 words, text 3977 words, 3 tables, 4 figures, 1 appendix, 1 appendix figure

Multi-state Life Tables, Equilibrium Prevalence, and Baseline Selection Bias

1 Introduction

Longitudinal data enable us to study change over time. If the population can be conceptualized as being Healthy, Sick, or (over time) Dead, the data may be used to estimate the time-specific prevalence of the Healthy state directly from the observed data (**Prev:Obs**). Another approach is to estimate the probabilities of transition among the states. These probabilities are of interest in themselves, and may also be used with multi-state life table (MSLT) methods to project the number of persons in each state at future times, for different hypothetical populations. If the system is a Markov process, the MSLT prevalence of the Healthy state (**Prev:MSLT**) converges to an equililbrium value (**Prev:Equil**), no matter where the system starts out. Prev:Equil can be calculated directly from the pairwise transition probabilities, and its standard error can be calculated in closed form. [1]

In the following we derive Prev:Equil for a system with any number of states, and compare Prev:Equil, Prev:MSLT, and Prev:Obs. We develop a test for whether Prev:Obs is different from Prev:Equil, and argue that this test may be used to explore whether there is selection bias in baseline data from a longitudinal sample. To avoid unnecessary notation, we ground this work in an example using data from the Cardiovascular Health Study (CHS). The analytic results and examples are in the main text, but we present some of "data-specific" arguments in an appendix, in an attempt to improve the flow of the manuscript.

The CHS is a population-based longitudinal study of 5,888 adults aged 65 and older at baseline, designed to identify factors related to the occurrence of coronary heart disease and stroke. [2] Subjects were recruited from a random sample of the Medicare eligibility lists in four

U.S. counties. Persons who did not expect to remain in the area for the next three years, or who were institutionalized, using a wheelchair at home, or receiving treatment for cancer at baseline were ineligible. Extensive baseline data were collected for all subjects, including a home interview and clinic examination. After baseline, subjects had an annual clinic visit, and provided additional information by mail and telephone. Two cohorts were followed, one with 10 annual waves of data (n=5201) and the second (all African American, n=687) with 7 waves. Followup is ongoing for events and a few self-reported measures. [3] Data collection began in about 1990, and follow-up is virtually complete for all surviving subjects in the year 2005. At baseline the mean age was 73 (range 65 to 105), 58% were women, and 84% were white.

2 MSLT and equilibrium prevalence

2.1 Transition probabilities and MSLT calculations

Consider a 6-state system with 5 health states, such as Excellent, Very Good, Good, Fair, or Poor (EVGGFP) and one absorbing state, Death. These states will sometimes be referred to as E, VG, G, F, P, D. Table 1 shows the estimated probabilities of one-year transition among these states, calculated from all waves of the CHS data. For example, the probability that a person whose health state is Excellent at time t is also in Excellent health at time t+1, (P(E|E)), is .396, while the probability of dying, P(D|E), is 0.013.

[Table 1 about here]

For convenience, we assume a first-order Markov process, although this assumption is relaxed later on. Let A^{6x6} be the matrix of transition probabilities, and define a 6x1 vector x_t whose entries are the number of persons in each state at time t. Then the number in each state at t+1 is $x_{t+1} = A*x_t$, and the number at t+5 is A^5*x_t. The transition probabilities are likely to change over time, because of aging.[4] Let A_t be the time- or age-specific transition probabilities

estimated from a crosstabulation of the health data at ages t and t+1. Then, the distribution at age 71, $x_{71} = A_{70} * x_{70}$, and $x_{75} = A_{74} * A_{73} * A_{72} * A_{71} * A_{70} * x_{70}$. These multi-state lifetable (MSLT) results may be used to describe trends over time for a hypothetical initial population.

To simplify the results somewhat, we define being "Healthy" as E+VG+G and being "Sick" as F+P, and summarize the trends by describing the prevalence of the Healthy state (the proportion of living persons who are Healthy). The observed prevalences were similar for men and women (not shown), and all examples here combine men and women. The MSLT prevalence (Prev:MSLT) of the Healthy state for different hypothetical populations is shown in Figure 1. The topmost line shows Prev:MSLT if all were in Excellent health at age 65, and the lowest line if all started in Poor health. At about age 71, a type of equilibrium is reached, in which the prevalence is independent of the initial distribution. This is referred to here as the prevalence at equilibrium, or Prev:Equil. The middle, dotted, line is explained in section 2.4.

[Figure 1 about here]

2.2 Prevalence at equilibrium (Prev:Equil) for a system with 3 states

Diehr and Yanez [1] derived the equilibrium prevalence for a time-homogeneous system with 3 states including one absorbing state. The equilibrium prevalence of the Healthy state is K/(1+K), where

$$K = \frac{P(H \mid H) - P(S \mid S)}{2P(S \mid H)} + \sqrt{\frac{[P(H \mid H) - P(S \mid S)]^2}{[2P(S \mid H)]^2} + \frac{P(H \mid S)}{P(S \mid H)}} . \qquad \{1\}$$

In the overall CHS data, P(H|H)= .822 , P(S|H)= .156, P(H|S)=.238, and P(S|S)= .648. Then K= 1.91, and Prev:Equil is .66. That is, assuming the probabilities are time-homogeneous, after a few years to overcome any initial imbalance, 66% of the living will be Healthy and 34% will be Sick, until eventually all are dead. Once equilibrium is reached, the one-year survival rate is .946

per year (see Appendix). The variance of Prev:Equil for a 3-state system can be calculated in closed form.[1]

The time-homogeneous assumptions were not appropriate for the example data, because of effects of aging, but trajectories of the prevalence from age-specific MSLT calculations were found to agree with the equilibrium prevalence that was calculated from the age-specific transition probabilities. [1] To explore the performance of Prev:Equil further, we calculated Prev:Equil and Prev:MSLT from probabilities estimated in a different dataset, for ages 0-64. [5] As shown in Appendix Figure A, Prev:Equil was close to Prev:MSLT throughout this age range. (Note the larger scale on the Y axis). Thus, Prev:Equil from equation {1} seems to approximate Prev:MSLT even when the probabilities change with age. We next extend the derivation to a system with more states, illustrated using the 6-state system described above.

2.3 Prev:Equil for a system with any number of states

We first assume that the 6-state system for EVGGFP is time-homogeneous. The observed prevalences of the states are shown in column 1 of Table 2. A, the matrix of transition probabilities in Table 1, is stochastic because each column adds to 1, and is singular for the same reason. Now, let $B^{5x5} = A_{11}$, the shaded area in Table 1, which includes only the probabilities of transition among the 5 living states. If z is a 5x1 vector of the number of people in each of the living states Excellent to Poor, then $z_{t+1} = B*z_t$. (Although the number of deaths is not calculated specifically, the number who died between t and t+1 can be calculated from z_t and z_{t+1}).

[Table 2 about here]

Once equilibrium is reached, Prev:MSLT does not change from year to year, by definition. That is,

$$z_{t+1} = B*z_t = \lambda z_t \qquad \{2\},$$

which is the familiar eigenvalue/eigenvector equation. Thus, the equilibrium distribution of the system is an eigenvector of B. The eigenvalue is a number less than 1 that represents the proportion of the original population that survived to the following year (the 1-year survival rate). Mathematica [6] was used to calculate the eigenvectors of B. Because every element of a prevalence vector must be non-negative, the elements of eligible eigenvectors must all have the same sign. We standardized the eigenvector to sum to one.

2.4 Examples

The 3-state model, Healthy, Sick, Dead, was discussed in section 2.2. The results there suggest that the eigenvector is [K/(K+1), 1/(K+1)] = [.657, .343], and that the eigenvalue (survival rate at equilibrium) is .946. This was verified by matrix multiplication. Thus, equation {1} provides the solution for an eigenvector of a 2x2 asymmetric matrix. (For the second eigenvector, the sign of the square root term is negative, resulting in $K \leq 0$).

For the 6-state example, we first assumed time homogeneity. Only one eigenvector of matrix B was a potential equilibrium distribution. The eigenvector, in column 2 of Table 2, suggests that once the population reaches equilibrium, there will be about the same proportion in Excellent as in Poor health, and in Very Good as in Fair health. The eigenvalue associated with the vector is .945, which means that once equilibrium is reached, about 95% of the population survives to the following year.

The transition probabilities change with age, requiring the calculation of a large number of age-specific transition matrices and equilibrium prevalences. Because it was more convenient here to be able to calculate the eigenvectors in closed form, we used an approximate eigenvector, calculated by repeatedly re-defining the "Healthy" state and calculating the equilibrium prevalence from equation {1}. (For example, defining "Healthy" as Excellent, and "Sick" as Very Good to Poor, equation {1} yields the equilibrium prevalence of the Excellent state. Then redefining "Healthy" as E or VG yields the equilibrium prevalence of E+VG, and the equilibrium prevalence of Very Good is obtained by subtracting the prevalence of Excellent). The approximate eigenvector for matrix B is in column 3 of Table 2, and is reasonably close to the exact eigenvector in column 2. (The 3-state probabilities are weighted means of the 6-state probabilities. For the eigenvector, the weights are proportional to the equilibrium distribution, while for the approximate eigenvector the weights are proportional to the observed distribution). This approximation was used to estimate the equilibrium prevalence at each age, from age-specific estimates of B (e.g., from B_{70}). The estimated age-specific equilibrium prevalence of the "Healthy" state for each age is shown as the dotted line in Figure 1. Clearly, the Prev:MSLT lines converge to Prev:Equil, although the effect of the sparseness of data at the oldest ages is evident in the variability of Prev:Equil. Prev-equil decreased about .014 per year of age (calculations not shown).

2.5 Interpretation of Prev:Equil when the system is not time-homogeneous

Prev:Equil was derived as the value of Prev:MSLT that does not change from year to year, once it is reached. This is well-defined for the time-homogeneous system, but the interpretation is less clear when the probabilities, and thus Prev:Equil, change over time. For

example, matrix B_{70} refers to transitions from age 70 to 71. Is Prev:Equil$_{70}$ (the eigenvector of B_{70}) an estimate of Prev:MSLT$_{70}$ or Prev:MSLT$_{71}$ or something else? This cannot be answered in general, but in our case Prev:Equil$_t$ was always closer to Prev:MSLT$_{t+1}$ than to Prev:MSLT $_t$. Prev:MSLT changed slowly with age (see Figure 1 and Appendix Figure A), and so the practical distinction for this example is small.

3 Observed, MSLT, and equilibrium prevalences

At equilibrium, Prev:Equil approximates Prev:MSLT. Ideally, both would approximate the prevalence in the observed data. Figure 2 compares Prev:Equil, Prev:MSLT, and Prev:Obs over time, shown in a larger scale to make small differences easier to observe. Prev:Obs is the observed prevalence, calculated from all persons of a given age, from any survey wave. Prev:MSLT was calculated from a MSLT with initial prevalence .837 (the observed prevalence at age 65). Prev:Equil was calculated from the age-specific transition probabilities. The agreement of the 3 curves is remarkable, given that Prev:Obs$_{t+1}$ is calculated from the raw data at age t+1, while Prev:Equil $_t$ uses the data from both t and t+1, and Prev:MSLT$_{t+1}$ uses all the data from age 65 to t+1**.** (We plotted Prev:Equil$_t$ rather than Prev:Equil$_{t+1}$ to account for the lag identified in section 2.5).

[Figure 2 about here]

The three lines may not agree if the MSLT calculations start out of equilibrium. In Figure 1, the Prev:MSLT lines had converged by age 71. The observed prevalences that correspond approximately to the MSLT prevalences are shown in Figure 3. Prev:Obs for the 5 initial distributions still had not converged by age 81. The MSLT calculations used the (unconditional) age-specific transition probabilities calculated from all the data, but strictly speaking, the (conditional) probability calculations for the top line of Figure 1 should have used

only the data from the top line of Figure 3 (those Excellent at age 65). If the first-order Markov conditions for the system are met, then the conditional and unconditional probabilities are the same, and Prev:MSLT should equal Prev:Obs. Unfortunately, the Markov conditions do not hold in this dataset.[1] When the lifetable is calculated from the equilibrium probabilities, Prev:MSLT is likely to be too pessimistic (with respect to the observed data) for the top three lines, and too optimistic for the bottom two lines. Some methods developed for semi-Markov processes have performed well on these data,[7] but they are not considered here.

We conclude that Prev:MSLT and Prev:Equil agree with Prev:Obs if the system starts out at equilibrium, but that they may not agree if the initial conditions are far from equilibrium, unless the first-order Markov conditions hold. When unconditional probabilities are used to estimate the conditional trajectories, the MSLT trajectories starting "healthier than equilibrium" will be pessimistic, and those starting "sicker than equilibrium" will be optimistic.

4.0 Testing whether a sample is in equilibrium

In Table 2, the observed and the equilibrium prevalences do not agree very well. We next develop a test for whether a sample is "at equilibrium", defined here as the situation where Prev:Obs = Prev:Equil. The test requires reducing the 6-state system to a 3-state system, for which the variance of Prev:Equil can be calculated in closed form. [1] We assume that the transition probabilities for a system at equilibrium are available (see Appendix), and use them to calculate Prev:Equil $_t$, which is compared to Prev:Obs $_t$. The two sample statistics are statistically independent because Prev:Equil$_t$ is calculated from the t to t+1 transition probabilities, which are statistically independent of Prev:Obs $_t$ (see Appendix). The variance of Prev:Obs $_t$ is the variance of a proportion, and the variance of Prev:Equil $_t$ can be calculated in closed form.[1] Therefore, an approximate z-test can be performed:

$$z = \frac{Prev:Obs - Prev:Equil}{\sqrt{\text{var}(Prev:Obs) + \text{var}(Prev:Equil)}} \qquad \{3\}$$

5.0 Example: Test for Selection Bias in CHS Baseline Data

Many longitudinal samples are believed to be biased, in the sense of not being a simple random sample of the population of interest. Eligibility criteria and the sampling design create explicit biases that may be accounted for. Self-selection biases such as healthy volunteer bias are also common, and their effect is usually unknown. Results from samples that are not population-based, such as the American Cancer Society database,[8] may not generalize to the population as a whole. A test for bias in such longitudinal samples would be useful. We will consider bias in the Cardiovascular Health Study, which had the exclusions mentioned above, and which was able to enroll only about 70% of the targeted eligibles, suggesting self-selection bias.

In the following discussion we assume that the original population (Medicare enrollees in 4 counties in 1990) was at equilibrium with respect to the variable of interest (e.g., EVGGFP in the primary example). If the available sample is unbiased, it will also be at equilibrium. If loss to follow-up is low, then the sample transition probabilities will estimate the equilibrium transition probabilities and Prev:Obs will agree with Prev:Equil.

5.1 Apparent baseline bias in 6-state data, in two CHS cohorts

Above, we examined self-rated health (E, VG, G, F, P) using the CHS data. Table 3 shows the observed prevalences in 1990 (baseline) and 1991 as well as Prev:Equil calculated only from the 1990-1991 data. Similar results are given for the second cohort, all African American. Cohort 2 had worse self-rated health that cohort 1. Compared to Prev:Equil, Prev:Obs for Cohort 1 appears to have "too many" Excellent and not enough Very Good or Good

at baseline. In Cohort 2, at baseline there were apparently not enough in Good health, but too many in Fair and Poor. For both cohorts, the second year of data is closer to the equilibrium distribution than the first year of data, suggesting that the bias may have abated over time. Sampling variability is expected, especially for the smaller cohort, and a formal test for bias is needed.

[Table 3 about here]

5.2 Formal test for bias in CHS data

We chose nine health-related variables that were measured every year in CHS and have been described elsewhere. [9] These included self-rating of health as Excellent, Very Good, Good, Fair, or Poor (EVGGFP) [10]; the Modified Mini Mental State Examination score (MMSE) [11]; activities and instrumental activities of daily living (ADL and IADL); the Center for Epidemiologic Studies Depression score (CESD) [12]; whether the person was hospitalized in the prior six months; the time it took to walk 15 feet; whether the person had a flu shot in the previous year; and the number of days spent in bed in the previous 2 weeks. All variables were dichotomized into "Healthy", "Sick", and (over time) Dead, where "healthy" represented a favorable value of the variable under consideration (for example, for ADL, "Healthy" is defined as "no ADL difficulties"). The thresholds defining "healthy" are available elsewhere.[13] Based on the eligibility criteria, and likelihood of volunteer bias, we hypothesized that the CHS sample would be "too healthy" at baseline on all of the variables.

The test for baseline bias compared Prev:Obs_{1990} to Prev:Equil_{1990}. For example, for EVGGFP, Prev:Obs_{1990} = .77, with standard error = .0058. Prev:Equil_{1990} = .82 with standard error .0092. Their difference is .77-.82 = - .05, and z = -.05/.0109 = -4.59, indicating a statistically significant negative bias.

Results are summarized in Figure 4, where the dark bars represent the z-statistic for each variable, with horizontal lines indicating thresholds of +2 and -2. Most of the variables showed some positive bias (Prev:Obs > Prev:Equil). MMSE, ADL, and CESD had significant positive bias ($z > 2$), and IADL, hospitalizations, bed days, and timed walk had no apparent bias. Unexpectedly, EVGGFP and flu shot had significant negative biases. Comparisons for other years, not shown, suggested that any observed bias disappeared in 2 to 3 years. (However, a new analysis found that mortality in CHS from 1993 to 1994 was lower than mortality in Medicare for that period, suggesting that longer-term bias existed).[14]

[Figure 4 about here]

Because CHS had many waves of data, we were able to test for bias in a different way, for comparison. We calculated the age-sex-specific prevalence of the Healthy state for each variable, using all 10 waves of data. Then, we calculated the expected prevalence in 1990 ($\text{Prev:Expected}_{1990}$) if the prevalence at baseline was at its age-sex-expected value. If the observed prevalence equals the expected prevalence, this is evidence against baseline bias. The resulting z-statistics are the clear bars in Figure 4. The test based on Prev:Expected identified the same significant differences as the test based on Prev:Equil.

6 Summary and discussion

The prevalence at equilibrium, Prev:Equil, is defined as the prevalence that is eventually reached in a MSLT calculation, independent of the initial conditions. In a time-homogeneous system, this prevalence is an eigenvector of the partition of the transition probability matrix that involves only the transitions among the living. Even in the more realistic non-homogeneous situation, Prev:Equil was also a good approximation of Prev:MSLT, as seen in Figures 1 and 2

and for a different dataset in Appendix Figure A. It would interesting to test the generalizability of this observation to more datasets.

Prev:Equil and Prev:MSLT agreed with Prev:Obs when the hypothetical population for the MSLT was initially at equilibrium, but Prev:Obs was different if the system started out-of equilibrium, in a perhaps non-intuitive direction (Prev:MSLT is pessimistic for an initial population that is healthier than equilibrium, and optimistic if it starts sicker than equilibrium).

Having evidence about selection bias in a sample could improve the interpretation of results from datasets that are not population based or where selection bias is expected for some other reason. We proposed a test for baseline selection bias by comparing Prev:Obs and Prev:Equil at baseline. In the CHS example, 3 of 9 variables showed significant positive bias, and 2 showed significant negative bias. The test can be performed on large datasets with as few as 2 waves of data. The power of the test needs to be explored in the future.

We were surprised to find negative bias for flu shot and EVGGFP. During the study period, the proportion who received a flu shot increased every year, perhaps due to intensified public health campaigns for older adults to be vaccinated. That is, the underlying population was not at equilibrium with respect to flu shots, violating our assumption. For EVGGFP, there may have been different reasons for this apparent bias. In 1990, EVGGFP was measured as part of a day-long clinical examination, while in 1991 a questionnaire was sent by mail to be filled out at home prior to the clinic visit. This difference in settings suggests that an "instrumentation" effect might have caused the discrepancies.[15] EVGGFP was also elicited at a phone call half way between the two clinic visits, suggesting the potential for learning or "testing" effects that changed the way in which persons evaluated their health over time. These may have contributed

to the observed negative bias. It is important to consider plausible alternative explanations for significant test results, which could be due to something other than baseline selection bias.

The prevalence at equilibrium is easy to calculate, for a system with any number of states, and can be used to approximate the life expectancies from a MSLT. There is an associated standard error if the system has (or can be reduced to) 3 states.[1] The new test for whether a sample is at equilibrium may be useful for evaluating longitudinal data where selection bias at baseline is a possibility. Evaluation of these methods in different settings is needed.

Table 1
6x6 Transition Matrix for all years, ages and both sexes combined
The "A" Matrix. The shaded area is the "B" matrix. (N = 136,816 transition pairs)

	Health Status at time t					
Number of Transition Pairs	8443	31750	54621	33143	8859	
Health at time t+1	**Excellent**	**Very Good**	**Good**	**Fair**	**Poor**	**Dead**
E	.396	.072	.020	.005	.003	0.000
VG	.359	.495	.163	.042	.019	0.000
G	.187	.337	.573	.229	.076	0.000
F	.037	.067	.190	.551	.225	0.000
P	.009	.014	.027	.105	.393	0.000
D	.013	.016	.027	.068	.284	1.000

Entry is the probability of moving from the column health state to the row health state in 1 year. Columns sum to 1.0. The equilibrium eigenvector is in Table 2. The corresponding eigenvalue of = 0.945.

Table 2

Observed, equilibrium, and approximate equilibrium prevalence values

	1 Observed prevalence—all years combined **N=136816**	**2 Equilibrium Prevalence – all data (eigenvector of B matrix)** **N=136816**	**3 Approximate Equilibrium Prevalence (repeated use of equation {1})** **N=136816**
Excellent	.062	.045	.048
Very Good	.232	.208	.214
Good	.399	.396	.394
Fair	.242	.275	.272
Poor	.065	.078	.071

Eigenvalue = .94498

Table 3

Observed and Equilibrium Baseline Prevalence

By cohort.

Cohort	**Cohort 1 (n=5201)**			**Cohort 2 (n=687)**		
Type of prevalence	**Equil from 1990-1991 data**	**Observed 1990**	**Observed 1991**	**Equil from 1993-1994 data**	**Observed 1993**	**Observed 1994**
Excellent	.04	.143	.069	.043	.073	.051
Very Good	.30	.250	.298	.207	.173	.198
Good	.47	.374	.425	.437	.341	.394
Fair	.16	.199	.184	.259	.323	.293
Poor	.02	.034	.024	.054	.090	.064

Figure 1

MSLT calculation of prevalence demonstrating equilibrium

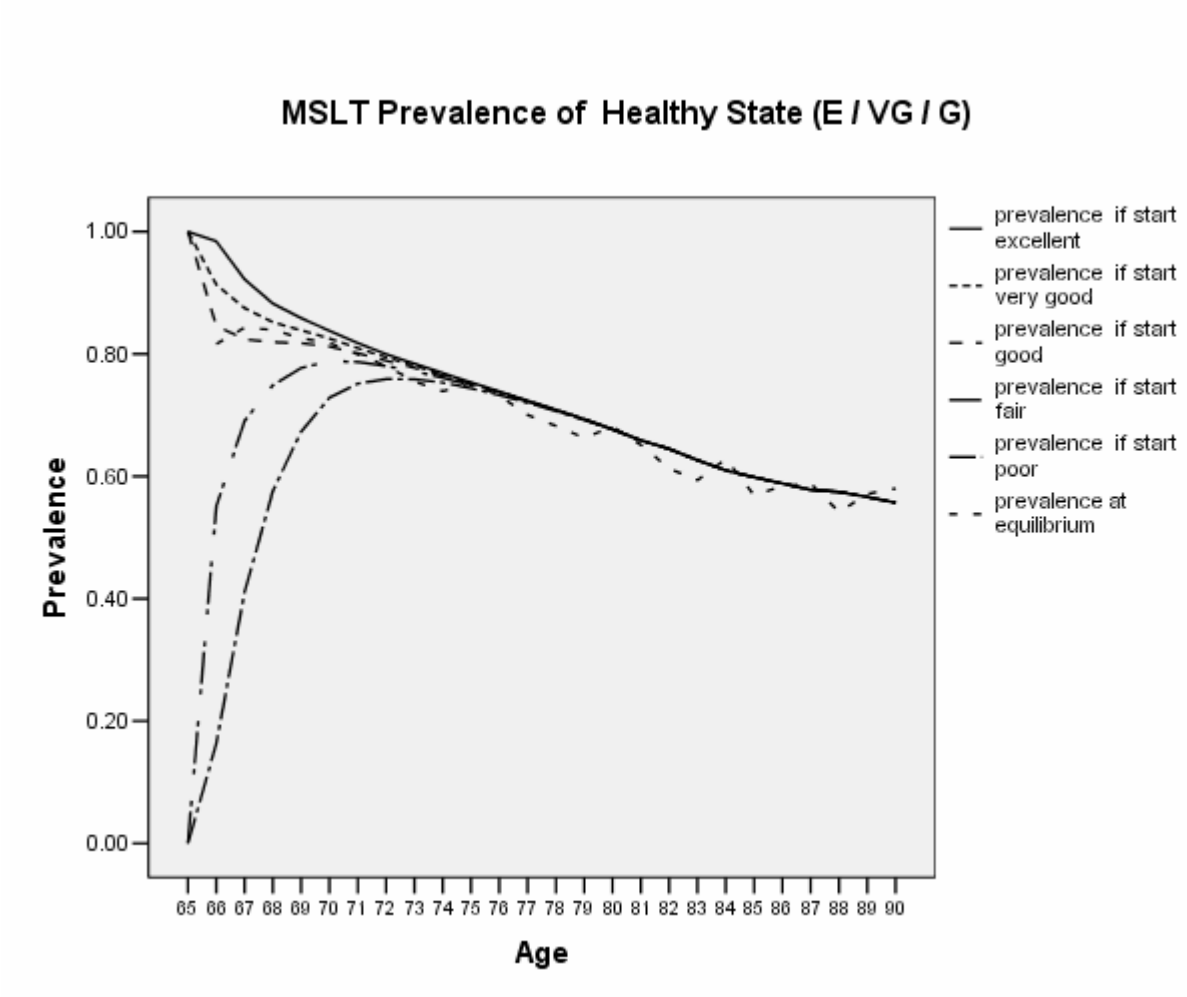


Figure 2

Comparison of Prev:Equil, Prev:Obs, and Prev:MSLT

For a hypothetical population at approximate equilibrium at age 65. The MSLT calculations were started at the observed prevalence.

Figure 3

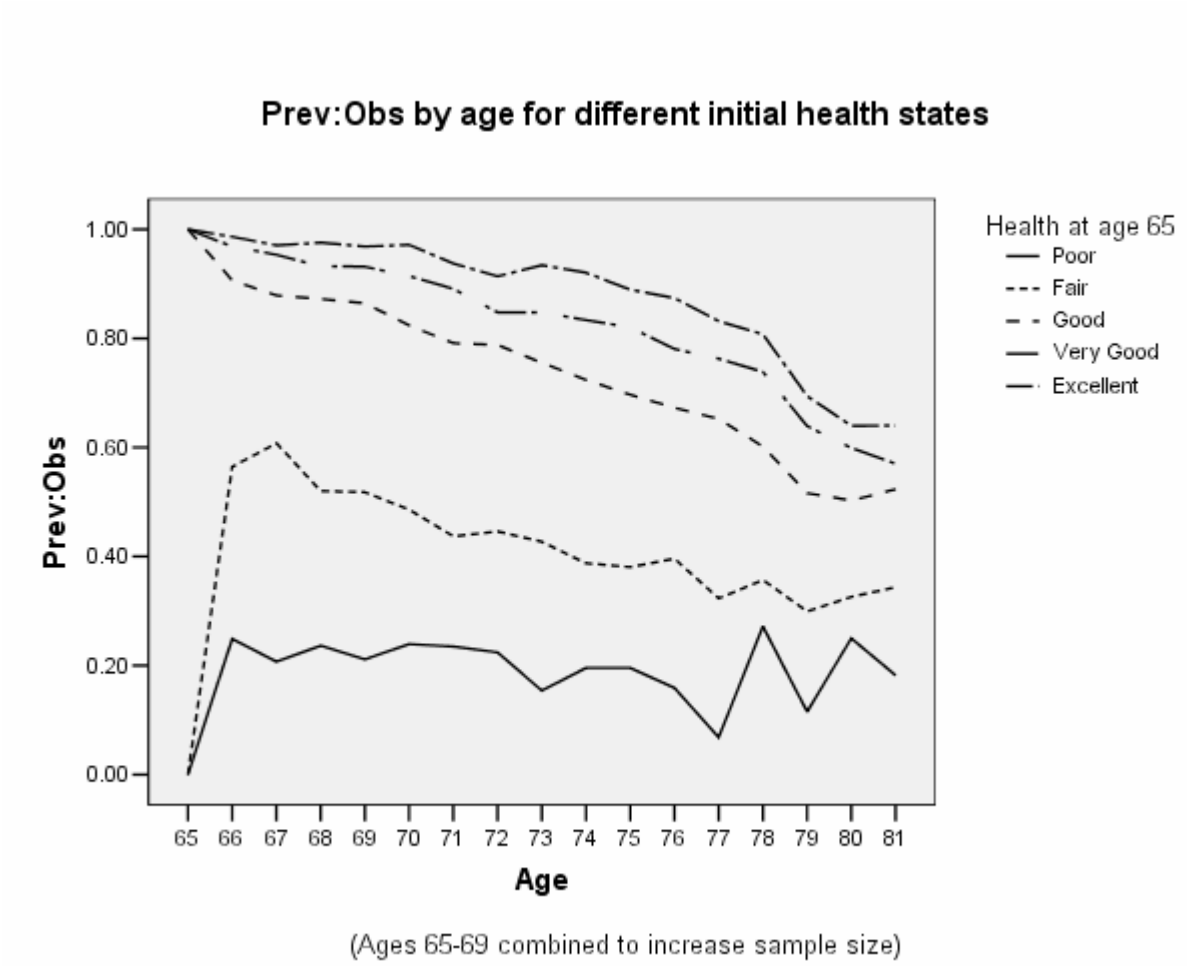
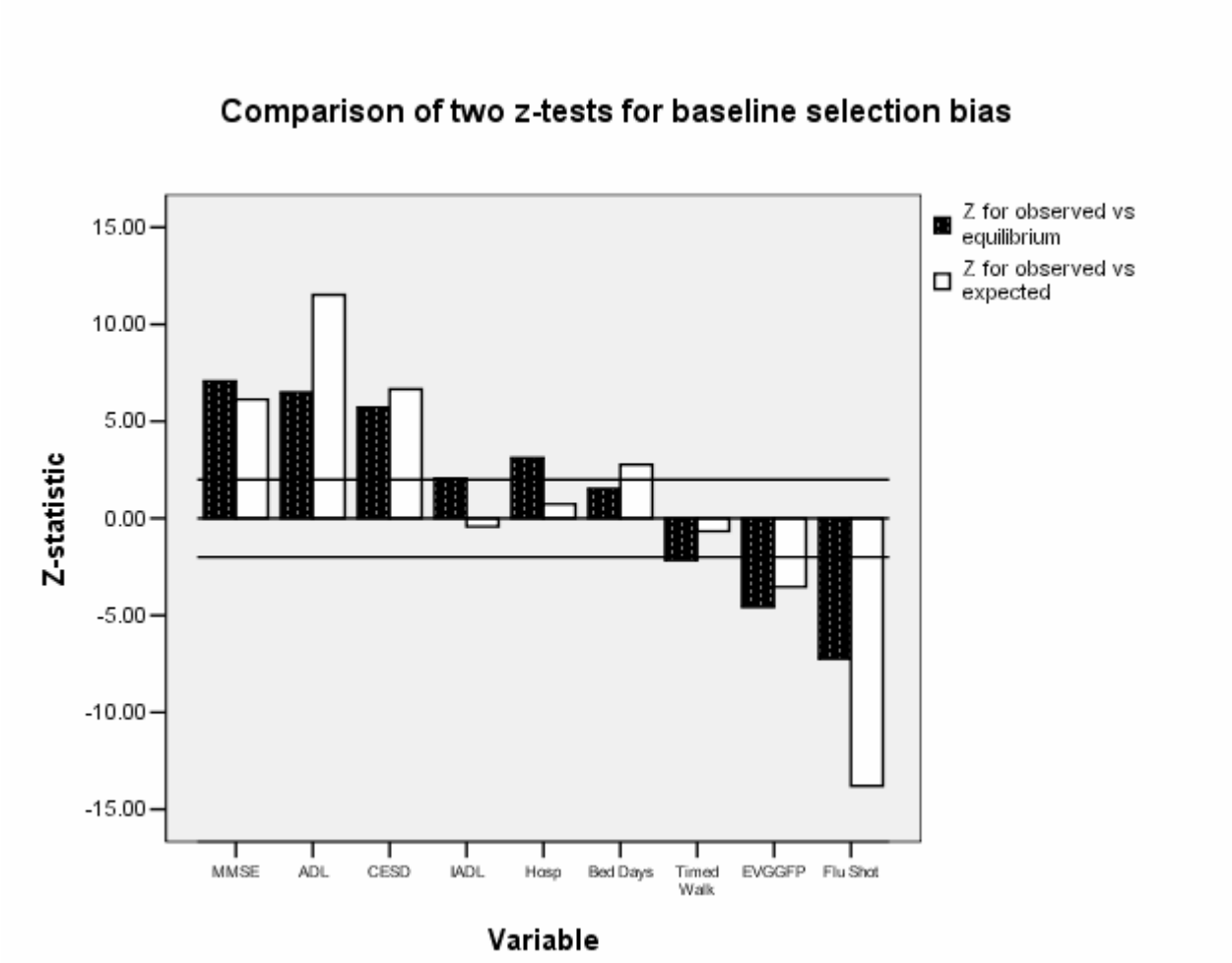


Figure 4

Two "z-tests" for baseline selection bias

(9 different variables)



Appendix

Several assertions made in the main text are discussed in more detail here.

Equation {1} yields an estimate of the eigenvector in the 3-state model.

At equilibrium, by equation {1}, the prevalence vector is $\pi^{2x1} = [K/(1+K), 1/(1+K)]^T$. At that point, the survival fraction is constant, $\sigma = (P(H|H)+P(S|H))* \pi_1 + (P(H|S)+P(S|S))*\pi_2$. If N_t is the number of persons alive at time t, then $N_{t+1} = N_t B \pi = N_t \sigma \pi$, because the system has the same (equilibrium) prevalence at both t and t+1, by definition. Therefore $B \pi = \sigma \pi$, and π is an eigenvector of B, while σ is the corresponding eigenvalue.

Independence of Prev:Equil$_t$ and Prev:Obs$_t$

Transition probabilities are calculated conditional on the current state. For example, $P(H|S)_{70}$ is estimated as the number who are Healthy at age 71 and Sick at 70 divided by the total number Sick at 70. If the sample is biased in some way, such as "too many" Sick persons at age 70, relative to the number who are Healthy, this does not affect the probability calculation because only those Sick at 70 are involved. If the sample had twice as many Healthy persons at age 70, the transition probability estimates would not change. The estimated probabilities of transition from time t to t+1 are thus independent of (Prev:Obs $_t$). Since Prev:Equil $_t$ is calculated from those transition probabilities, it follows that Prev:Equil $_t$ is statistically independent of Prev:Obs$_t$.

When does Prev:Equil = Prev:Obs?

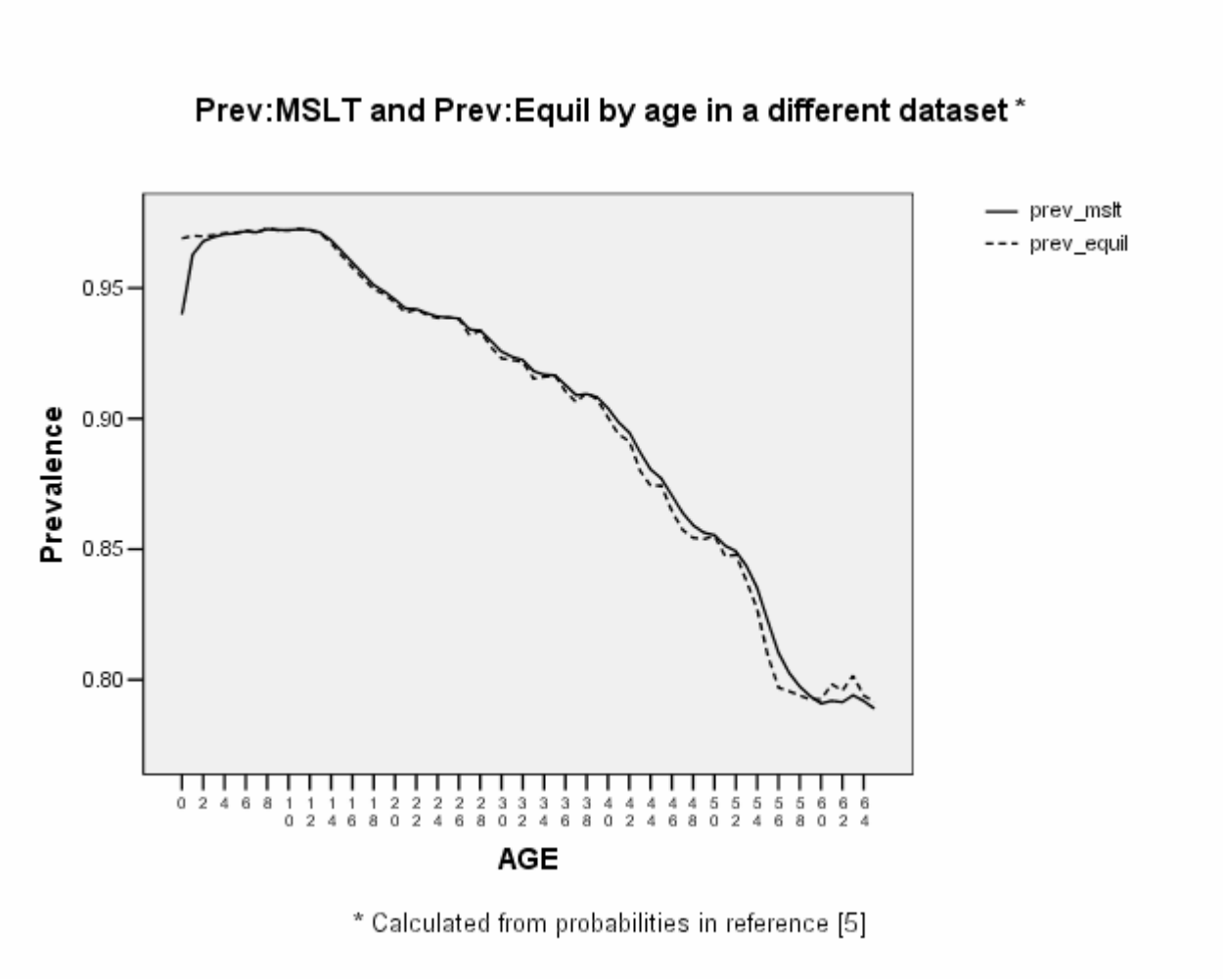
We argue that the original population is likely to be at equilibrium, barring a recent insult that made important changes in the health distribution or the transition probabilities. We will

assume that this is the case. It then follows that a large simple random sample with low loss to follow-up is at equilibrium each year, meaning that the sample prevalence is the same as the population prevalence, and that the sample transition probabilities are estimates of the equilibrium transition probabilities. In this case, observed and equilibrium prevalences will be the same.

If instead the sample is biased among states, such as having too many Healthy persons at baseline, the equilibrium transition probabilities can still be estimated, because the calculation is conditional on the prevalence, and so not affected by the bias. However, we would not expect the observed and equilibrium prevalences to be the same. Finally, if the sample is biased within states, such as having the right number Healthy but too many Excellent within the Healthy group relative to the population, the transition probabilities themselves will be biased estimates of the equilibrium transition probabilities. The expected relationship of Prev:Obs and Prev:Equil would be unclear. The transition probabilities estimated from the wave 1 to wave 2 transitions (1990 and 1991 data in this case) are appropriate for the 1990 sample, whether or not the sample is at equilibrium.

Appendix Figure A

Prev:MSLT and Prev:Equil for ages 0-65, from another dataset *



* Calculated from probabilities in reference [5]

- **References**

1 Diehr P, Yanez D, Derleth A, Newman Anne B. Age-specific prevalence and years of Healthy life in a system with 3 health states. Statistics in Medicine 2008; 27:1371-1386.

2. Fried LP, Borhani NO, Enright PL, et al. The Cardiovascular Health Study: design and rationale. Annals of Epidemiology 1991. 1:263-276.

3. Ives G, Fitzpatrick A, Bild D, et al. Surveillance and ascertainment of cardiovascular events: the cardiovascular health study. Annals of Epidemiology 1995. 5:278-285.

4 Diehr P, Patrick DL. Probabilities of Transition among Health States for Older Adults. *Quality of Life Research* 10:431-422, 2001.

5 Diehr P, Derleth A, Newman AB, Cai L. The number of sick persons in a cohort. Research on aging 2007; 29:555-575.

6 Wolfram Mathematica 7. Wolfram research. 2008. Champaign, IL.

7 Cai L, Schenker N, Lubitz J, Diehr P, Arnold A, Fried LP. Evaluation of a method for fitting a semi-Markov process model in the presence of left-censored spells using the Cardiovascular Health Study. Statistics in Medicine 2008; 27:5509-5524.

8 Calle EE, Thun MJ, Petrelli JM et al. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 1999; 341:1097-105.

9. Diehr P, Williamson J, Burke G, Psaty B. The aging and dying processes and the health of older adults. Journal of Clinical Epidemiology. 2002. 55:269-278.

10. Idler EL, Benyamini Y. Self-rated health and mortality: a review of twenty-seven community studies. J Health Soc Behav 1997; 38:21-37.

11. Teng EL, Shui HC. The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry 1987;48:314-8.

12. Radoff LL. The CESD Scale: a self-report depression scale for research in the general population. Applied Psychological Measurement 1977. 1:385-401.

13 Diehr P, Johnson LL, Patrick DL, Psaty B. Methods for incorporating death into health-related variables in longitudinal studies. Journal of Clinical Epidemiology 2005;58:1115-1124.

14 DiMartino LD, Hammill BG, Curtis LH, Gottdiener JS, Manolio TA, Powe NR, Schulman KA. External validity of the Cardiovascular Health Study: a comparison with the Medicare population. Medical Care 2009; 47:916-923.

15 Campbell D, Stanley J. Experimental and Quasi-experimental designs for research. Rand McNally and Company, Chicago. 1963.