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Ghost-time bias from imperfect mortality ascertainment in aging cohorts

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ABSTRACT

Purpose: Many cohort studies in the United States link with the National Death Index to detect deaths. Although linkage with National Death Index is relatively sensitive, some participant deaths will be missed. These participants continue to contribute person-time to the data set after their death, resulting in bias, which we refer to as ghost-time bias. We sought to evaluate the influence of ghost-time bias on mortality relative risk (RR) estimates.
Methods: Simulations were performed to determine the magnitude of ghost-time bias under a variety of plausible conditions.
Results: Our simulations demonstrate that ghost-time bias can be substantial, particularly among the elderly, where it can reverse the direction of the RR. For example, we conducted a simulation of a cohort of men beginning follow-up at age of 70 years, assuming 5% missed deaths and a true RR of 2.0. In this simulation, observed RRs were 1.89 during the year the cohort was aged 85 years, 1.60 during the year the cohort was aged 90 years, and 0.61 during the year the cohort was aged 95 years. We also provide results from actual cohort data that are consistent with ghost-time bias.
Conclusions: Ghost-time bias may meaningfully affect mortality RR estimates under conditions that can plausibly occur in aging cohorts.

Introduction

Many large cohort studies in the United States, for example, the Cancer Prevention Study II [1], the Multiethnic Cohort [2,3], and the National Health and Nutrition Examination Survey [4] have used computerized linkage with the National Death Index (NDI) as the primary method of follow-up for mortality outcomes. Linkage with NDI allows cohorts to follow up large numbers of study participants for mortality outcomes without the need for personal contact, potentially for several decades.

Linkage with NDI is generally considered to have good sensitivity for detecting deaths, although sensitivity is substantially higher when information on social security number (SSN) is available [5,6]. The largest analysis to date to examine the sensitivity of NDI included over 5000 known deaths in Cancer Prevention Study II participants [1]. In that study, sensitivity was estimated at 97% among participants who had provided a complete SSN and 87% among participants who had not. Reasons that contributed to missed deaths included incomplete information on SSN or date of birth, disagreement between the SSN provided by the participant and that listed on a death certificate, disagreement on birth month or year, the use of informal first names, and misspelled names [1]. In other studies, sensitivities have ranged from 93% to 97% among individuals who provided an SSN and from 88% to 96% among participants who did not [5,6].

From the perspective of a researcher analyzing cohort data, study participants whose deaths are missed by linkage with NDI are "immortal" within the data set. These immortal participants inappropriately contribute person-time accrued after their actual death date. In this report, we refer to person-time inappropriately accrued after a participant's death as "ghost-time" and we refer to bias in mortality relative risk (RR) estimates resulting from ghost-time as "ghost-time bias."

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To our knowledge, the influence of ghost-time bias on mortality RR estimates has not been assessed, although one report documented that ghost-time resulted in overestimated longevity in an elderly study population in Ohio [7]. Ghost-time bias is likely to be negligible during the early years of follow-up of a cohort of young or middle-aged people because nearly all participants are truly alive and therefore only a very small proportion of observed person-time is actually ghost-time. However, ghost-time will inevitably account for a steadily increasing proportion of observed person-time as follow-up continues, and the proportion of participants who are truly alive steadily declines. Ghost-time bias may therefore be an increasingly important concern as cohorts of predominantly middle-aged adults established during the 1980s and 1990s age into their 80s and beyond.

Understanding how and when ghost-time bias can influence results of cohort studies may be useful for researchers who work with data accrued from older study participants. In this report, we describe how ghost-time bias occurs, simulate the magnitude of bias in mortality RR estimates under various conditions, provide an example of actual results consistent with ghost-time bias, and discuss strategies to reduce ghost-time bias.

Material and methods

Simulations

To evaluate ghost-time bias, we simulated observed RRs for mortality, over time, associated with an exposure with a given true RR. For ease of interpretation, we based our simulations on a hypothetical large cohort of people who enrolled at the same age and calendar year and were followed for mortality for many years through linkage with NDI. We assumed that being immortal at enrollment (not being linkable to NDI in the event of death) was unrelated to exposure status and that exposure status and the true RR did not change during cohort follow-up. We describe our calculations as "simulations" because they were based on hypothetical cohorts; we did not conduct Monte Carlo style simulations with repeated iterations.

The end result of our simulations was the observed RR in the cohort in each individual year of follow-up, meaning the RR that would be observed by a researcher conducting analyses without knowledge of which person-time in the data set was actually ghost-time. We refer to the observed RR in the ith year of follow-up as $RR^i_{(obs)}$.

We began each simulation by assigning values to the six "starting" variables shown in Table 1. The values assigned were chosen because they might plausibly occur in a contemporary aging cohort where mortality was ascertained through linkage with the NDI or through another linkage with similar sensitivity. We then used the assigned values from Table 1 to calculate the intermediate variables shown in Table 2. The first four variables shown in Table 2 designated as "*N*" denote the number of people in each of the four possible groups based on exposure status and "immortal" status (exposed immortals, unexposed immortals, exposed mortals, and unexposed mortals). The number of exposed immortals and unexposed immortals never changed during simulations because, being immortal, they never died in the data set. The number of mortals, however, declined due to deaths during each year of follow-up at rates determined by their exposure status, age, and sex.

The fifth variable in Table 2, E^i, the proportion of mortal participants who are exposed, can be calculated in a straightforward way from the four "*N*" variables. It should be noted that E^i is needed to "back calculate" the absolute risk of death among unexposed members of the hypothetical cohort (R^i_U) from published national mortality rates, as national mortality data are not available by exposure status. Once the mortality rate in the unexposed is calculated, the mortality rate in the exposed can be calculated by multiplying by the true RR (RR^T).

Next, we used the variables in Table 2 to calculate $RR^i_{(obs)}$, the end result of interest, using the steps shown below. First, we calculated the observed death rate in the exposed in year i (denoted as $R^i_{E\ (obs)}$) by dividing the observed deaths among the exposed ($D^i_{E\ (obs)}$) by the number of exposed people who were categorized as alive in the data set ($N^i_{E,M} + N_{E,I}$), as shown in Equation 1 below. It is important to note that the denominator in this equation ($N^i_{E,M} + N_{E,I}$) includes both people who are actually alive and people who are dead but whose death was missed by NDI linkage.

$$R^i_{E\ (obs)} = D^i_{E\ (obs)} \Big/ \left(N^i_{E,M} + N_{E,I}\right) \quad 1$$

Then, we used a similar equation, Equation 2, to calculate the observed death rate in the unexposed (denoted as $R^i_{U\ (obs)}$).

$$R^i_{U\ (obs)} = D^i_{U\ (obs)} \Big/ \left(N^i_{U,M} + N_{U,I}\right) \quad 2$$

Finally, using Equation 3, we calculated the observed RR ($RR^i_{(obs)}$) as the ratio of the observed death rates in the exposed and unexposed:

$$RR^i_{(obs)} = R^i_{E\ (obs)} \Big/ R^i_{U\ (obs)} \quad 3$$

Analyses of data from Cancer Prevention Study II

In actual cohort data, in contrast to simulations, ghost-time bias cannot be precisely measured because the exact proportion of immortals at enrollment is unknown. However, we hypothesized that patterns of results consistent with ghost-time bias would be observed in actual data where participants reached advanced ages. We therefore analyzed 30 years of follow-up data (1982–2012) from men and women aged 60–74 years at enrollment into the Cancer Prevention Study II cohort (there were too few people aged 75 years and older at enrollment to analyze). As described in an earlier analysis of diabetes and all-cause and cause-specific mortality in this cohort [9], diabetes was self-reported at baseline in 1982. Exclusions and adjustment variables are the same as those used in the earlier analysis. However, this analysis includes an

Table 1
Assigned values of starting variables for ghost-time bias simulations

Variable	Definition	Assigned values
N	Number of participants in the cohort at study enrollment	100,000
A	Age at cohort enrollment	60, 70, or 80
E	Proportion exposed at enrollment	10%, 50%, or 90%
P	Proportion of participants whose death would not be identifiable through linkage with NDI due to insufficient or inaccurate information (i.e., immortals)	2.5%, 5%, or 10%
RR^T	True RR of exposure	0.5, 0.75, 1.0, 1.5 or 2.0
R^i	True mortality risk during the ith year of follow-up	Age- and sex-specific values from 2011 U.S. vital statistics [8]

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Table 2
Calculation of intermediate variables used in simulations

Variable	Definition	Calculation
Numbers of people		
$N_{E,I}$	Number of exposed "immortals" (constant over time)	$N \times E \times P$
$N_{U,I}$	Number of unexposed "immortals" (constant over time)	$N \times (1\text{-}E) \times P$
$N^i_{E,M}$	Number of exposed "mortals" at start of year i	At start of follow-up (i = 1): $N \times E \times (1-P)$, for subsequent years, calculated by subtracting out cumulative deaths
$N^i_{U,M}$	Number of unexposed "mortals" at start of year i	At start of follow-up (i = 1): $N \times (1\text{-}E) \times (1-P)$, for subsequent years, calculated by subtracting out cumulative deaths
Proportion exposed		
E^i	Proportion of "mortals" exposed in the cohort at start of year i	$N^i_{E,M}/(N^i_{E,M} + N^i_{U,M})$
Risk of death		
R^i_U	True risk of death in year i in the unexposed	Calculated from national age- and sex-specific mortality rates (R^i), prevalence of exposure (E^i), and RR^T. $R^i/(RR^T \times E^i + [1-E^i])$
R^i_E	True risk of death in year i in the exposed	$R^i_U \times RR^T$
Numbers of deaths		
$D^i_{E\ (obs)}$	Observed number of deaths in year i in the exposed	$D^i_{E\ (obs)} = R^i_E \times N^i_{E,M}$
$D^i_{U\ (obs)}$	Observed number of deaths in year i in the unexposed	$D^i_{U\ (obs)} = R^i_U \times N^i_{U,M}$

The equation $R^i_U = R^i/(RR^T \times E^i + [1 - E^i])$ was derived from substituting $(R^i_U \times RR^T)$ for R^i_E into the weighted-average formula $R^i = E^i(R^i_E) + (1 - E^i)(R^i_U)$ then solving for R^i_U.

additional 4 years of data and presents only age-stratified results to focus on results at advanced ages where ghost-time bias is potentially important.

Results

Simulations

Figure 1 shows results from simulations of cohorts of men (left panels) and women (right panels) who enrolled at the same age (their 60th birthday) and calendar date and were followed for mortality over many years through linkage with NDI. Separate curves are shown for the starting percentage of participants in the cohort who were immortal (2.5%, 5%, or 10%), meaning their death (if any) would fail to be detected by linkage with NDI. Each circle on the curves represents the observed RR within an individual year of follow-up. For example, in panel A, the circle above the age of 90 years on the middle curve indicates that the observed RR was about 1.3 during the 1-year period when participants were aged 90 years.

Panel A shows the observed RRs for a cohort of men when the true RR was 1.50. During the early years of follow-up, the observed

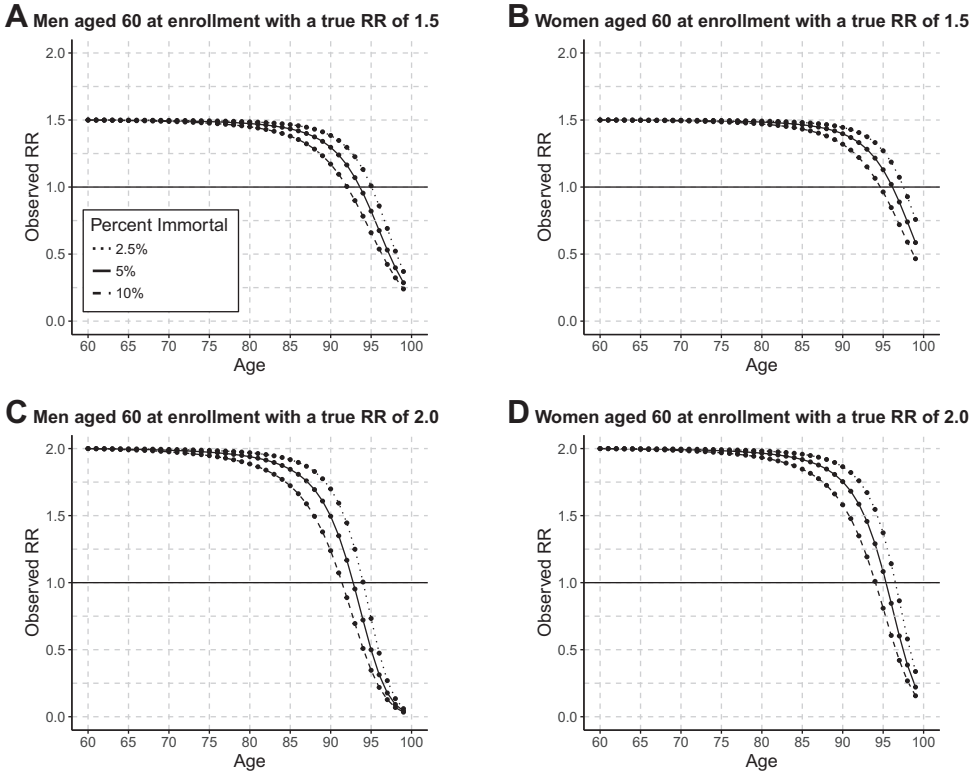

Fig. 1. The panels A and B show changes over time in the observed relative risks (RRs) for mortality resulting from the inability to identify some participant deaths through linkage with the National Death Index (NDI). Simulations were based on hypothetical cohorts of men (A and C) and women (B and D) who were followed for mortality for 40 years, starting at the age of 60 years, by linkage with the NDI. The three curves in each panel are based on differing proportions of participants at enrollment assumed to be "immortal" in the data because of inadequate information to enable detection of their death (if any) through linkage with the NDI (2.5, 5, or 10%). All panels assume an exposure prevalence of 50%. Panels A and B assume a true RR of 1.5 and panels C and D assume a true RR of 2.0. Age- and sex-specific mortality rates used in the simulations were based on 2011 U.S. vital statistics [8].

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RRs remained relatively close to the true RR of 1.50, as expected, because nearly all participants were truly alive and only a very small proportion of total observed person-time was ghost-time. As follow-up continued and the cohort aged, ghost-time bias had a larger influence and the observed RRs declined more rapidly. When the proportion of immortals was 5%, the RR fell below 1.25 by the age of 91 years, fell below 1.0 starting at the age of 94 years, and reached 0.5 by about the age of 97 years.

Panel B shows the observed RRs for a cohort of women, who have somewhat lower mortality rates than men [8]. The shape of the curves is similar to those among men, although the curves are shifted slightly to the right, indicating a specific amount of ghost-time bias will occur a few years later in women than in men.

Panels C and D are similar to Panels A and B but show results for a true RR of 2.0 rather than 1.5. The shapes of the curves are similar to those in Panels A and B, but the decline in the RR is considerably steeper.

Table 3 shows detailed numerical results in individual follow-up years from one of the simulations illustrated in Panel C (men, true RR = 2.0, 5% immortal at enrollment). These results illustrate how ghost-time bias can result in observed RRs <1.0 even when the true RR is >1.0. In both exposed and unexposed participants, mortal participants died off over time while immortal participants remained in the data set, resulting in a steady increase in the proportion of participants who were immortal. However, because of higher death rates in the exposed, the increase in the proportion of participants who were immortal occurred faster in the exposed than in the unexposed. For example, at the age of 90 years, 36% of exposed participants were immortal compared to only 14% of unexposed participants. As a result, death rates were underestimated more in the exposed than in the unexposed, and the observed RR was driven steadily downward, dropping below 1.0 at the age of 93 years. Analogous results for women are shown in eTable 1.

Table 3 also provides cumulative RRs from the beginning of the study through the end of each year of follow-up. It is important to note the difference between the cumulative RR and the RR in an individual year of follow-up. For example, although the RR in Table 3 for the 30th year of follow-up was 1.61, an analysis including the first 30 years of follow-up would have observed the cumulative RR of 1.89. This cumulative RR reflects both the relatively unbiased RRs observed in early years of follow-up and more biased RRs from later years.

Supplemental eFigures 1 and 2 show the influence of age at enrollment (40, 60, 70, or 80 years) on ghost-time bias in men and

Table 3
Observed relative risks and intermediate variables in a simulation of a cohort of men aged 60 years at entry, given a 5% prevalence of immortality at enrollment and a true RR of 2.0

Year of follow-up	Age of cohort	Immortal exposed (N)	Immortal unexposed (N)	Mortal exposed (N)	Deaths in mortal exposed (N)	Mortal unexposed (N)	Deaths in mortal unexposed (N)	Percent immortal among exposed	Percent immortal among unexposed	Observed RR that year	Observed cumulative RR*
1	60	2500	2500	47,500	699	47,500	349	5.0	5.0	2.00	2.00
2	61	2500	2500	46,801	733	47,151	369	5.1	5.0	2.00	2.00
3	62	2500	2500	46,068	769	46,781	391	5.1	5.1	2.00	2.00
4	63	2500	2500	45,299	809	46,391	414	5.2	5.1	2.00	2.00
5	64	2500	2500	44,490	854	45,977	441	5.3	5.2	2.00	2.00
6	65	2500	2500	43,636	907	45,535	473	5.4	5.2	2.00	2.00
7	66	2500	2500	42,729	967	45,062	510	5.5	5.3	1.99	2.00
8	67	2500	2500	41,762	1032	44,552	550	5.6	5.3	1.99	2.00
9	68	2500	2500	40,730	1095	44,002	591	5.8	5.4	1.99	2.00
10	69	2500	2500	39,635	1156	43,410	633	5.9	5.4	1.99	1.99
11	70	2500	2500	38,479	1222	42,777	679	6.1	5.5	1.99	1.99
12	71	2500	2500	37,257	1292	42,098	730	6.3	5.6	1.99	1.99
13	72	2500	2500	35,966	1365	41,368	785	6.5	5.7	1.98	1.99
14	73	2500	2500	34,601	1438	40,584	844	6.7	5.8	1.98	1.99
15	74	2500	2500	33,163	1514	39,740	907	7.0	5.9	1.98	1.99
16	75	2500	2500	31,649	1588	38,833	974	7.3	6.0	1.97	1.99
17	76	2500	2500	30,061	1658	37,859	1044	7.7	6.2	1.97	1.99
18	77	2500	2500	28,403	1730	36,815	1121	8.1	6.4	1.96	1.98
19	78	2500	2500	26,673	1806	35,694	1208	8.6	6.5	1.96	1.98
20	79	2500	2500	24,867	1880	34,485	1304	9.1	6.8	1.95	1.98
21	80	2500	2500	22,987	1943	33,181	1402	9.8	7.0	1.94	1.98
22	81	2500	2500	21,043	1982	31,779	1496	10.6	7.3	1.93	1.97
23	82	2500	2500	19,062	2006	30,282	1594	11.6	7.6	1.91	1.97
24	83	2500	2500	17,055	2006	28,689	1687	12.8	8.0	1.90	1.96
25	84	2500	2500	15,049	1981	27,002	1777	14.2	8.5	1.87	1.95
26	85	2500	2500	13,069	1942	25,225	1874	16.1	9.0	1.85	1.95
27	86	2500	2500	11,127	1866	23,351	1958	18.3	9.7	1.81	1.94
28	87	2500	2500	9261	1752	21,393	2023	21.3	10.5	1.76	1.93
29	88	2500	2500	7509	1601	19,370	2065	25.0	11.4	1.69	1.91
30	89	2500	2500	5908	1419	17,304	2079	29.7	12.6	1.61	1.89
31	90	2500	2500	4488	1214	15,225	2059	35.8	14.1	1.50	1.87
32	91	2500	2500	3274	996	13,166	2002	43.3	16.0	1.35	1.85
33	92	2500	2500	2278	778	11,164	1906	52.3	18.3	1.17	1.83
34	93	2500	2500	1500	574	9258	1770	62.5	21.3	0.95	1.80
35	94	2500	2500	927	395	7488	1598	73.0	25.0	0.72	1.77
36	95	2500	2500	531	252	5890	1396	82.5	29.8	0.50	1.75
37	96	2500	2500	279	146	4494	1176	89.9	35.7	0.31	1.73
38	97	2500	2500	133	76	3318	951	94.9	43.0	0.18	1.72
39	98	2500	2500	57	35	2367	737	97.8	51.4	0.09	1.71
40	99	2500	2500	21	14	1630	547	99.2	60.5	0.04	1.71

* Calculated from a fixed-effects meta-analysis of 1-year interval RRs.

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women. The amount of ghost-time bias observed at any specified attained age decreased slightly with increasing age at enrollment due to the shorter follow-up period in which ghost-time could accumulate within the cohort. For example, in simulations of cohorts of men where the true RR was 2.0 and the proportion immortal was 5%, the observed RRs for a cohort of men enrolling at the age of 40 years were 1.81 at the age of 85 years, 1.42 at the age of 90 years, and 0.43 at the age of 95 years, while the corresponding RRs for enrolling at the age of 70 years were 1.89, 1.60, and 0.61.

Supplemental eFigure 3 shows results from simulations of ghost-time bias when the true RR was 0.5, 0.75, or 1.0, rather than above 1.0. In the simulations where the true RR was <1.0, observed RRs increased with age, rising above 1.0 at advanced ages.

Supplemental eFigure 4 examines the influence of the prevalence of exposure. In our simulation models, increasing exposure prevalence decreased ghost-time bias. However, this trend resulted entirely from the fact that increasing exposure prevalence automatically decreased absolute mortality rates among exposed participants because our simulation model back-calculated mortality rates among exposed and unexposed participants to fit overall national mortality rates. Varying the exposure prevalence had no influence on the magnitude of ghost-time bias in simulations in which absolute mortality rates among exposed and unexposed participants were kept constant.

An interactive Excel spreadsheet including variables shown in Table 3 is provided (Supplementary Material), which allows the input of varying true RRs, immortal proportions, and exposure prevalence. This spreadsheet may be useful to researchers for quantifying potential ghost-time bias under conditions that apply to their own study populations.

Actual results from the Cancer Prevention Study II

Figure 2 shows results from analyses of actual data from the large Cancer Prevention Study II cohort, as described in the methods section. RRs for all-cause mortality associated with diabetes at enrollment are shown by age group at enrollment (60–64, 65–69, or 70–74 years). In both men (panel A) and women (panel B), RRs for diabetes declined toward 1.0 starting at ages where ghost-time bias is unlikely to be meaningful, presumably for other reasons, such as increases in the background mortality rate with age. However, RRs dropped well below 1.0 at the most advanced ages, with statistically significant inverse associations observed in the oldest categories of attained age (90–94 years and 95–99 years). This pattern of results is not biologically plausible but is consistent with ghost-time bias. In panels C and D, results are shown separately for men and women who provided SSNs and those who did not. RRs were below 1.0 at advanced ages in both of these groups but were lower among those who did not provide an SSN than among those who did. This pattern is consistent with ghost-time bias because more ghost-time bias would be expected among those without an SSN because a higher proportion of deaths in this group are missed by the NDI linkage [1].

Discussion

We used simulations to explore the influence of ghost-time bias, defined as bias resulting from the inclusion of person-time accrued after a participant's death. Our simulations demonstrate that ghost-time bias may meaningfully affect mortality RR estimates under conditions that can plausibly occur in aging epidemiologic cohorts.

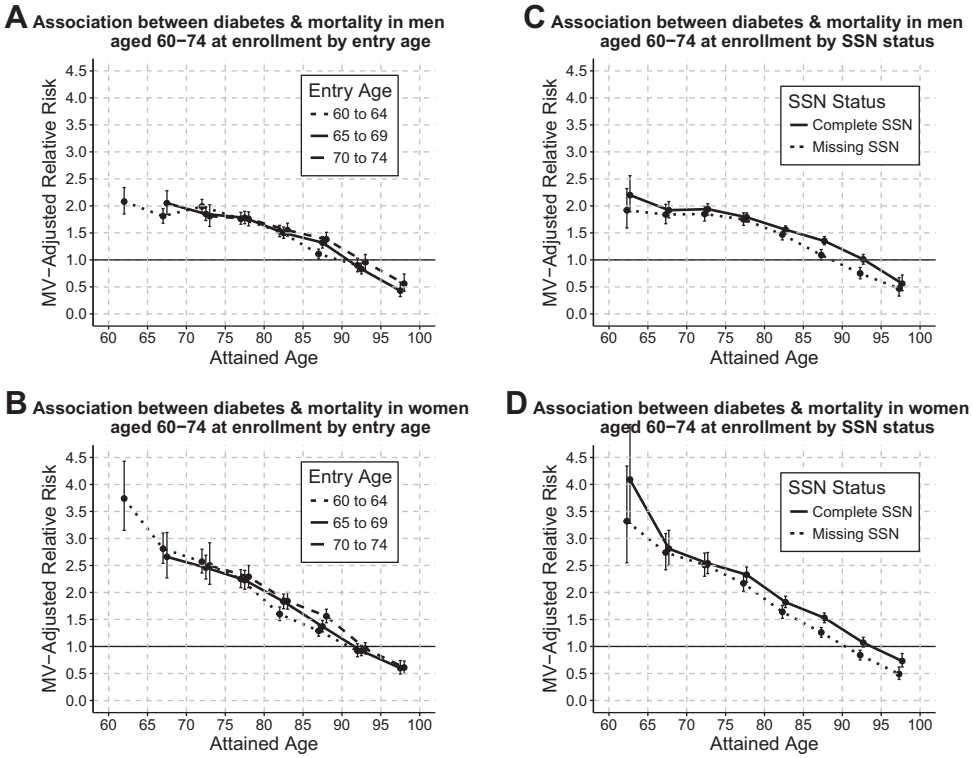

Fig. 2. The figure shows multivariable (MV)-adjusted relative risks (RRs) for mortality associated with diabetes in men and women aged 60–74 years at enrollment in the Cancer Prevention Study II and followed for 30 years (1982–2012). Panels A (men) and B (women) show results by enrollment age in 5-year categories. In panels C (men) and D (women), results are shown separately for those who provided social security numbers (SSNs) and those that did not. Circles and error bars indicate RR estimates for 5-year attained age intervals. For example, the leftmost circle in Panel A indicates the RR among men aged 60–64 years at enrollment during the period when they were aged 60–64 years. Exclusions and adjustment variables are the same as those used in a previous published analysis [9].

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As shown in our simulations, ghost-time bias has a predictable direction in analyses of all-cause mortality, causing underestimation of RRs when the true RR is >1.0 and overestimation of RRs when the true RR is <1.0. Notably, while nondifferential misclassification of outcome is generally expected to result in bias toward the null, ghost-time bias is not limited to bias toward the null. Instead, ghost-time bias can reverse the direction of the association, causing observed RRs to be <1.0 even when the exposure is truly associated with higher risk (i.e., the true RR is >1.0) and causing observed RRs to be >1.0 even when the exposure is truly associated with lower risk (i.e., the true RR is <1.0).

Ghost-time bias results from an increase in the proportion of apparently immortal participants in the cohort data set over time that occurs at different rates among exposed and unexposed participants. Specifically, among both the exposed and unexposed, the proportion of immortals progressively increases as deaths are documented among mortal participants but not among immortal participants. Over time, there is therefore progressively greater underestimation of mortality rates among both the exposed and unexposed. When the exposure is truly associated with higher mortality (i.e., when the true RR is >1.0, particularly when the true RR is large), the increase in the proportion of immortals occurs faster among the exposed than among the unexposed. This difference results in greater underestimation of mortality rates among the exposed than among the unexposed and therefore results in underestimation of the RR. Conversely, when the true RR is <1.0, the increase in the proportion of immortals occurs more slowly among the exposed than among the unexposed, ultimately resulting in overestimation of the RR.

Our simulations focused on the influence of ghost-time bias on RRs for all-cause mortality. It should be noted that ghost-time bias also influences RRs for cause-specific mortality. The direction of bias in cause-specific mortality RRs is still determined, however, by the all-cause mortality RR of the exposure being studied because it is all-cause mortality that drives increases in the proportion of immortal participants over time. For example, because diabetes increases all-cause mortality, ghost-time bias would be expected to result in underestimation of the RRs associated with diabetes for any specific cause of death, particularly at advanced ages.

The magnitude of ghost-time bias is influenced by several factors, notably the proportion of immortals in the cohort at enrollment, mortality rates within the cohort (likely strongly determined by age), length of follow-up, and the size of the true RR. Meaningful ghost-time bias is unlikely when the proportion of participants who are immortal is negligible, when the proportion of participants who have actually died by the end of the follow-up period is small, or when the true all-cause mortality RR is close to 1.

It should be noted that while ghost-time bias is a result of "immortal" participants within the data set, it is not related to "immortal-time bias" [10]. It should also be noted that RRs during 1-year intervals were calculated in our simulations, whereas many cohort analyses calculate hazard ratios. However, the RRs we calculated closely parallel hazard ratios because of the short follow-up time in each interval.

Ghost-time bias has practical implications for epidemiologists who collect or analyze cohort data. First, collecting a complete and correct SSN from as many participants as possible will reduce the number of "immortal" participants and therefore reduce ghost-time bias. Second, epidemiologists analyzing mortality outcomes in cohorts should be aware of the potential for ghost-time bias, particularly in cohorts where many participants are elderly or where mortality rates are high for another reason, such as clinical cohorts of patients with a highly fatal disease.

If there is meaningful potential for ghost-time bias in a cohort, investigators may consider additional efforts to confirm that elderly participants thought to be alive are actually still living. For example, if information on SSN is available for most participants, one approach is to link with Social Security Administration data and censor elderly participants who are not "presumed living" by the Social Security Administration based on information including receipt of social security benefits and reporting of benefits to the Internal Revenue Service [11,12]. This approach has been used by the Southern Community Cohort Study [13]. Alternatively, ghost-time bias can be reduced by simply censoring participants when they reach a maximum age threshold, for example, at the age of 90 or 95 years. In choosing a specific age threshold, investigators need to weigh the benefit of reducing ghost-time bias against the loss of statistical power and precision that will result from prematurely censoring person-time. In a recent analysis of prostate cancer mortality in the Cancer Prevention Study II cohort [14], we chose to censor follow-up at the age of 90 years. Simulations, along the lines of those presented in this analysis, may be helpful in informing decisions about how to address potential ghost-time bias.

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Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.annepidem.2018.06.002.

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eTable 1
Simulation of a cohort of women aged 60 years at entry, given a 5% prevalence of immortality at enrollment and a true RR of 2.0

Year of follow-up	Age of cohort	Immortal exposed	Immortal unexposed	Mortal exposed	Deaths in mortal exposed	Mortal unexposed	Deaths in mortal unexposed	% Immortal among exposed	% Immortal among unexposed	RR that year	Cumulative RR
1	60	2500	2500	47,500	417	47,500	209	5.0	5.0	2.00	2.00
2	61	2500	2500	47,083	446	47,291	224	5.0	5.0	2.00	2.00
3	62	2500	2500	46,636	477	47,067	241	5.1	5.0	2.00	2.00
4	63	2500	2500	46,159	512	46,826	260	5.1	5.1	2.00	2.00
5	64	2500	2500	45,647	553	46,567	282	5.2	5.1	2.00	2.00
6	65	2500	2500	45,094	601	46,285	308	5.3	5.1	2.00	2.00
7	66	2500	2500	44,493	656	45,976	339	5.3	5.2	2.00	2.00
8	67	2500	2500	43,837	713	45,637	371	5.4	5.2	2.00	2.00
9	68	2500	2500	43,123	768	45,266	403	5.5	5.2	1.99	2.00
10	69	2500	2500	42,355	822	44,863	435	5.6	5.3	1.99	2.00
11	70	2500	2500	41,533	880	44,427	471	5.7	5.3	1.99	2.00
12	71	2500	2500	40,653	945	43,956	511	5.8	5.4	1.99	2.00
13	72	2500	2500	39,708	1016	43,446	556	5.9	5.4	1.99	1.99
14	73	2500	2500	38,693	1093	42,890	606	6.1	5.5	1.99	1.99
15	74	2500	2500	37,600	1176	42,284	661	6.2	5.6	1.99	1.99
16	75	2500	2500	36,424	1261	41,623	720	6.4	5.7	1.98	1.99
17	76	2500	2500	35,163	1351	40,903	786	6.6	5.8	1.98	1.99
18	77	2500	2500	33,812	1449	40,117	860	6.9	5.9	1.98	1.99
19	78	2500	2500	32,363	1551	39,258	941	7.2	6.0	1.97	1.99
20	79	2500	2500	30,812	1654	38,317	1028	7.5	6.1	1.97	1.99
21	80	2500	2500	29,159	1747	37,289	1117	7.9	6.3	1.97	1.98
22	81	2500	2500	27,412	1831	36,172	1208	8.4	6.5	1.96	1.98
23	82	2500	2500	25,581	1913	34,963	1307	8.9	6.7	1.95	1.98
24	83	2500	2500	23,668	1989	33,656	1414	9.6	6.9	1.94	1.98
25	84	2500	2500	21,679	2068	32,242	1538	10.3	7.2	1.93	1.97
26	85	2500	2500	19,611	2128	30,705	1666	11.3	7.5	1.92	1.97
27	86	2500	2500	17,484	2154	29,039	1789	12.5	7.9	1.90	1.96
28	87	2500	2500	15,330	2143	27,250	1905	14.0	8.4	1.88	1.96
29	88	2500	2500	13,187	2091	25,345	2010	15.9	9.0	1.85	1.95
30	89	2500	2500	11,095	1995	23,336	2098	18.4	9.7	1.81	1.94
31	90	2500	2500	9101	1854	21,238	2163	21.6	10.5	1.75	1.92
32	91	2500	2500	7247	1671	19,075	2200	25.6	11.6	1.68	1.91
33	92	2500	2500	5576	1455	16,875	2202	31.0	12.9	1.59	1.89
34	93	2500	2500	4121	1215	14,674	2163	37.8	14.6	1.46	1.87
35	94	2500	2500	2906	967	12,510	2081	46.2	16.7	1.29	1.84
36	95	2500	2500	1939	726	10,429	1954	56.3	19.3	1.08	1.81
37	96	2500	2500	1212	510	8475	1782	67.3	22.8	0.85	1.79
38	97	2500	2500	703	330	6693	1572	78.1	27.2	0.60	1.76
39	98	2500	2500	372	194	5121	1336	87.0	32.8	0.39	1.74
40	99	2500	2500	178	102	3785	1088	93.3	39.8	0.22	1.72

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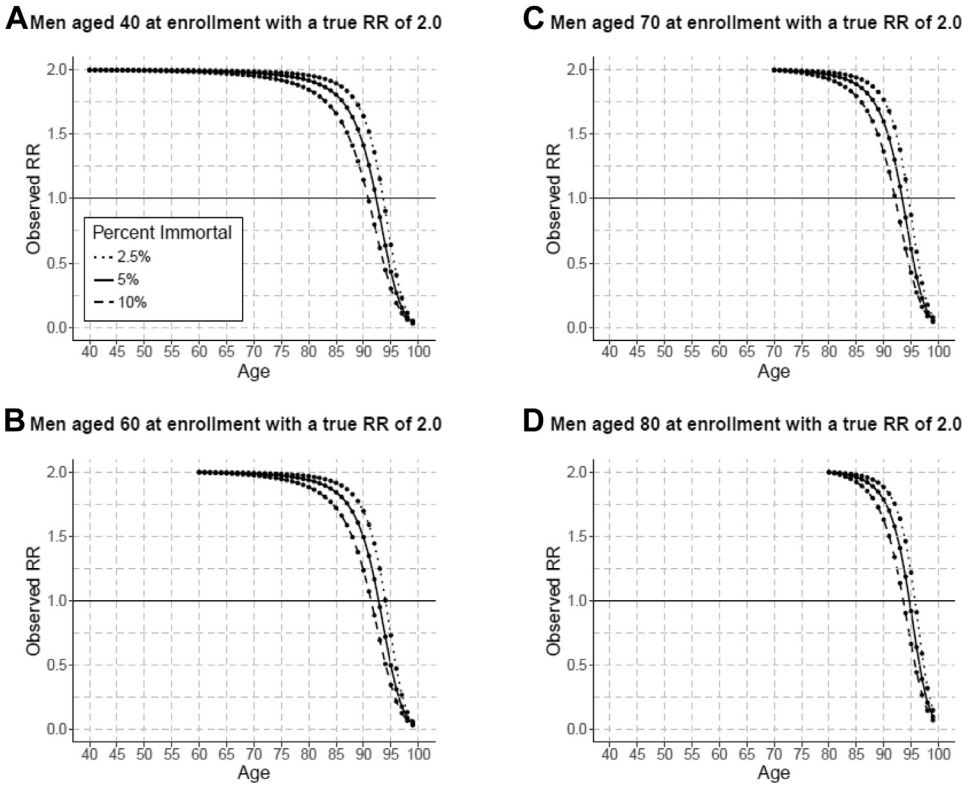
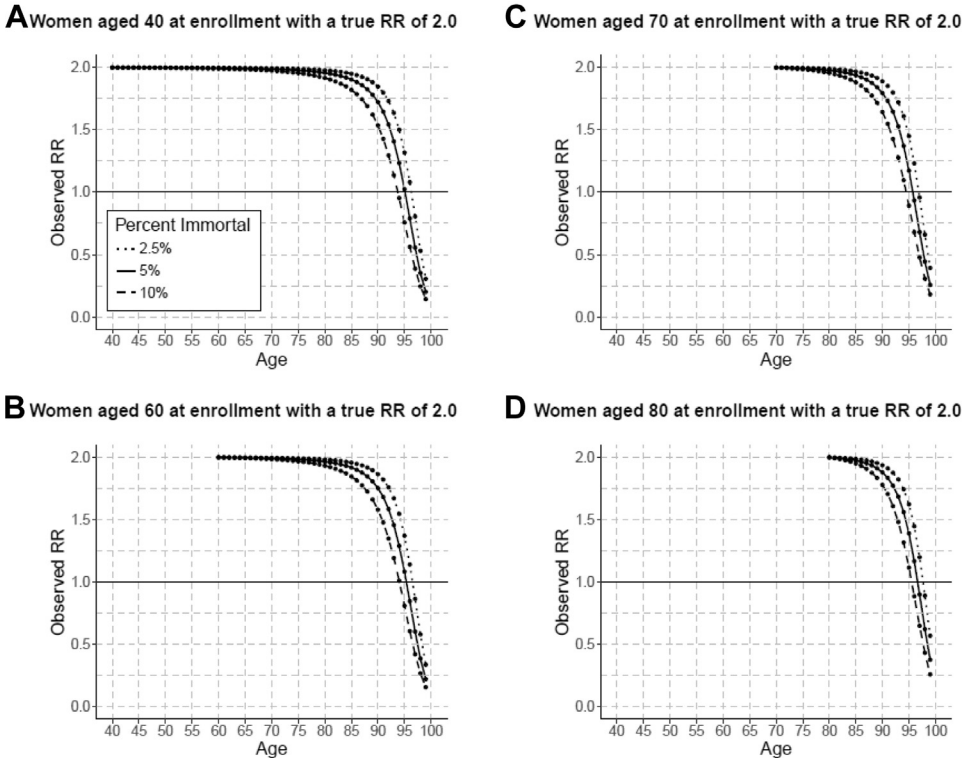


eFig. 1. Observed relative risks (RRs) by age at cohort entry in men given an exposure prevalence of 50%.



eFig. 2. Observed relative risks (RRs) by age at cohort entry in women given an exposure prevalence of 50%.

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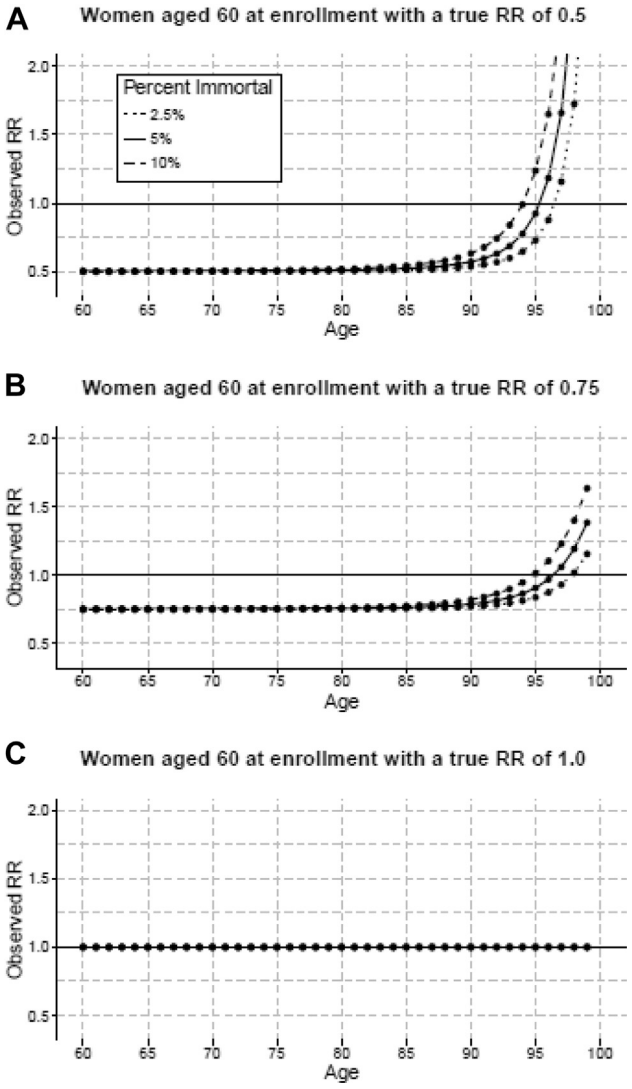
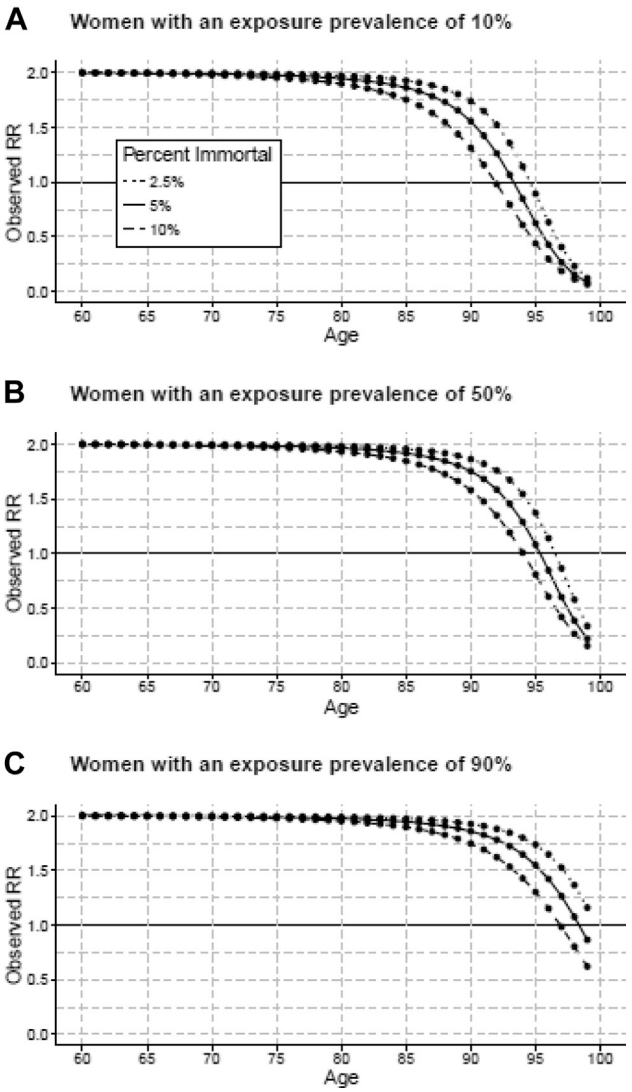


eFig. 3. Observed relative risks (RRs) when the true RR is ≤1.0 given an exposure prevalence of 50%.



eFig. 4. Observed relative risks (RRs) by exposure prevalence in women, assuming the age of 60 years at enrollment and a true RR of 2.0.