Review Article

Evolving methods for inference in the presence of healthy worker survivor bias

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Running head: Methods for healthy worker survivor bias

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ABSTRACT

Healthy worker survivor bias may occur in occupational studies due to the tendency for unhealthy individuals to leave work earlier, and consequently accrue less exposure, than their healthier counterparts. If occupational data are not analyzed using appropriate methods, this bias can result in attenuation or even reversal of the estimated effects of exposures on health outcomes. Recent advances in computing power, coupled with state-of-the-art statistical methods, have greatly increased the ability of analysts to control healthy worker survivor bias. However, these methods have not been widely adopted by occupational epidemiologists. We update the seminal review by Arrighi and Hertz-Picciotto (1994) of the sources and methods to control healthy worker survivor bias. In our update, we discuss methodologic advances since the publication of that review, notably with a discussion of how directed acyclic graphs can inform the choice of appropriate analytic methods. We summarize and discuss methods for addressing this bias, including recent work applying g-methods to account for employment status as a time-varying covariate affected by prior exposure. In the presence of healthy worker survivor bias, g-methods have advantages for estimating less biased parameters that have direct policy implications and are clearly communicated to decision-makers.

For over a century, occupational epidemiologists have been acutely aware of bias resulting from the relationship between good health and the tendency to gain and maintain employment – termed the healthy worker effect.[1] In that time, a large literature has arisen characterizing the components of the healthy worker effect. One component is a bias that occurs because unhealthy individuals tend to leave work earlier, thus accruing less exposure, than their healthier counterparts. This phenomenon, called healthy worker survivor bias, may present as an apparent reversal of the expected association between cumulative measures of exposure and disease. Much of the research on healthy worker biases describes them in terms of *effects* of employment status on measures of association. However, recent literature re-frames the problem more formally as a *bias* and focuses on identifying the conditions under which an unbiased effect estimate can be obtained. While subtle, the shift in terminology from *effect* to *bias* reflects the evolution of our understanding of this phenomenon and methods for its control.

In their 1994 paper, “The evolving concept of the healthy worker survivor effect”, Arrighi and Hertz-Picciotto defined healthy worker survivor bias and described available methods to address this problem.[2] Since that time, developments in epidemiologic methods have clarified possible mechanisms underlying healthy worker survivor bias and have shown which, if any, analytic techniques can be used to control this bias. Resurgent interest in healthy worker survivor bias[3-13] and recent advances in epidemiologic methods warrants an updated review. We discuss how the understanding of healthy worker survivor bias has evolved since Arrighi and Hertz-Picciotto’s seminal review was published 20 years ago.

Historical views

Healthy worker bias is a form of confounding in occupational studies that occurs because healthy individuals are more likely to become and remain employed. This bias comprises at least two distinct phenomena: healthy hire bias and healthy worker survivor bias.[2,14]

Healthy hire bias exists in comparisons of occupational populations with external reference populations, such as in a standardized mortality ratio (SMR) analysis, due to selection of healthy individuals into the workforce. Workforces under study tend to be healthier than reference populations, either due to unemployed individuals in the reference population or the preferential study of healthy workforces.[15] This phenomenon can lead to bias in analyses comparing occupational cohorts to external reference populations. Healthy hire bias can be controlled, for example, using analyses with an internal referent group of workers. In contrast, healthy worker survivor bias is a continuing selection process whereby workers with poorer health status tend to leave employment. This bias results from differential employment duration by health status *within* an occupational cohort and cannot be addressed by using internal referent groups.

Although a substantial literature on healthy worker biases had been amassed by the 1990s, much of this work pertained to healthy hire bias. A smaller literature focused on healthy worker survivor bias and proposed potential solutions.[16-19] In their 1994 paper reviewing the literature on healthy worker survivor bias, Arrighi and Hertz-Picciotto discussed the proposed underlying mechanisms of this bias and methods for controlling it.[2] We update Arrighi and Hertz-Picciotto's work with advances in the past 20 years.

Conceptualizing healthy worker survivor bias

Since Arrighi and Hertz-Picciotto's review, theoretical and statistical advancements have improved our understanding of healthy worker survivor bias and methods for its control. One such advancement is the application of causal diagrams, such as directed acyclic graphs (DAGs), to identify relationships between variables and determine appropriate analytic methods.[20-22] Healthy worker survivor bias was historically evaluated by examining quantities estimated from the data, such as the change in the SMR with duration of employment. Causal diagrams allow analysts to identify possible biases through application of a simple set of rules, under the assumption that one can posit underlying causal mechanisms for associations between an exposure and an outcome. In Figure 1, we present two DAGs with causal structures that may result in healthy worker survivor bias. In this set of causal diagrams at time k, X_k represents cumulative exposure to an occupational hazard, W_k represents employment status, U_k is an unmeasured variable that may vary with time, and D_k is the occurrence of a health outcome of interest.

Arrighi and Hertz-Picciotto described healthy worker survivor bias as "a continuing selection process such that those who remain employed (that is, are survivors in the workforce) will tend to be healthier than those who leave employment."[2] This essential problem of healthy worker survivor bias is illustrated in the causal diagrams in Figure 1. In both diagrams, the effect of exposure on the outcome is confounded along a backdoor path through an unmeasured factor ($X_k \leftarrow W_k \leftarrow U_k \rightarrow D_k$). The unknown factor ($U_k$) could be a latent form of the disease of interest, an underlying indicator of general health, or a strongly deleterious exposure, such as smoking. Because healthier individuals tend to remain healthy and employed, those who continue working are not exchangeable with individuals who leave work, even under identical prior exposure histories. Under this causal structure, estimates of the effects of cumulative exposures may be biased (usually downward), and deleterious exposures may even appear to be protective against disease outcomes.[14,23,24]

When an occupational exposure of interest has an acute effect on health, it may also affect employment status. This situation is represented in the causal diagram shown in Figure 1B, where there is an additional arrow from $X_{k-1} \rightarrow W_k$. Bias in this situation cannot be controlled using standard analytic techniques such as regression, stratification, or restriction to long-term workers.[19] Adjustment for employment status may control confounding of the cumulative exposure-outcome relationship at time *k* ($X_k \leftarrow W_k \rightarrow D_k$), but it biases the dose-response relationship of prior exposure (X_{k-1}) and the outcome. Conditioning on employment status blocks a causal pathway between exposure and outcome in which employment is a causal intermediate ($X_{k-1} \rightarrow W_k \rightarrow D_k$), introduces collider stratification bias by opening a new confounding pathway ($X_{k-1} \rightarrow W_k \leftarrow U_k \rightarrow D_k$), or both.[21,25,26] Collider stratification bias arises because stratification on employment status induces an association between exposure and health status. For example, in the stratum "unemployed at time *k*," if a worker has low cumulative exposure through time *k-1*, it is more likely that she or he terminated due to underlying health reasons than due to the effects of exposure. Thus, low exposure will be associated with poorer health after adjustment for employment status. While collider stratification bias is distinct from healthy worker survivor bias, it occurs when an investigator attempts to address the latter without accounting for the effects of previous exposure on employment.

Robins[19] proposed the structure of healthy worker survivor bias shown in Figure 2B as a challenge to approaches based on empirical associations or *ad hoc* solutions. He developed a set of methods, known as the g-methods, to control bias in this setting. The extent to which employment status may be a causal intermediate depends on the exposures under study. For example, for occupational exposures that affect only outcomes with long latent periods, this causal path may be less important.[14,23,24] Recent literature on healthy worker survivor bias has focused on quantifying the extent to which employment status might act as an intermediate variable,[8] applying analytic methods for estimating effects under Robins' causal model,[5,9] and quantifying the extent to which regression based methods fail to control healthy worker survivor bias.[11]

To characterize the approaches used by epidemiologists to address this bias, we searched PubMed (5/24/2014) for the term "healthy worker survivor" and identified 39 English language papers describing longitudinal studies that assessed associations between occupational exposures and health. Thirty-seven of the 39 papers estimated adverse effects in a relevant occupational setting. Of these 37 papers, 25 attempted to control for healthy worker survivor bias. The most common approach is regression adjustment for time-since-hire (Table 1). In the past five years, the g-methods have been more frequently applied to address this problem. We discuss each of these methods in the section that follows.

Methods proposed to control healthy worker survivor bias

Although healthy worker survivor bias has been frequently acknowledged in the literature since Arrighi and Hertz-Picciotto's review, there is no consensus on how this bias should be addressed. In practice, suitability of a statistical method depends on the unique context of the exposure-outcome association of interest. We review proposed methods, grouped by the approach used to control confounding (exposure lagging, cohort restriction, stratification, standardization), and use the causal diagrams presented in Figure 1 to link these analytic strategies to subject matter knowledge. A summary of methods is provided in Table 2.

Exposure lagging

Exposure lagging is a form of exposure window analysis that is often used to account for latent periods of disease in observational studies, especially when mortality is considered as an outcome.[27] Exposure lagging can be used to control bias due to exposure misclassification that results when termination caused by undetected, early stage disease leads to lower exposure among those who are eventually diagnosed with the outcome of interest (a form of reverse causality).[28] While lagging does not directly address healthy worker survivor bias, it may be helpful when implemented in concert with other methods (e.g., Garshick et al[29]). Lagged analyses are unbiased when there is no relationship between the exposures during the lag period and the outcome (i.e., for a lag of 1 unit of time, no arrow exists from X_k to D_k in Figure 1A). In practice, latency periods vary across individuals, and lagged exposure analyses are subject to a number of caveats that have been addressed in the context of disease latency.[30]

Cohort restriction

Restriction refers to restricting the study cohort by factors that vary over time. These methods address healthy worker survivor bias as a form of confounding. An early approach developed to control healthy worker survivor bias focused on controlling confounding by time-since-hire. Fox and Collier advocated restricting analysis to cohort members who had been employed at least 15 years.[16] This recommendation was based on the observation that SMRs were below one in the years immediately following hire but increased to unity among workers with at least 15 years of employment.[16] Fox and Collier hypothesized that this attenuation in

SMRs occurred because health related attrition from the workforce ceases after a period of employment.

Stratification

For simplicity, we define stratification as the analysis of exposure effects within strata of confounders, or as a weighted average of the effect measures across strata. This latter approach is used in regression analysis in which confounders are included in the regression model for the outcome of interest.

As shown in Figure 1, healthy worker survivor bias can be conceptualized as a form of confounding by active employment status. Stratifying by employment status[31] and including a term for active employment in a regression model for time varying exposures[28] have been proposed to control healthy worker survivor bias. The latter approach has been recently used to examine the effects of protracted ionizing radiation doses on cancer in nuclear industry workers[32] and flight crews.[33] This method can be problematic because long-term workers will tend to be healthier, and if exposure influences employment status ($X_{k-1} \rightarrow W_k$), stratifying by any function of employment status (e.g. active employment status, employment duration) induces bias.

Another proposed solution to healthy worker survivor bias is adjusting for time-since-hire. This approach reduced bias in a study by Flanders et al[34] that simulated healthy worker survivor bias by gradually lowering the baseline disease rate with time-since-hire. However, the authors did not propose an underlying mechanism for the assumptions of their simulation study.[35] Furthermore, Arrighi and Hertz-Picciotto assessed dose-response associations in two occupational cohorts and demonstrated that estimates adjusted for time-since-hire did not substantially differ from estimates adjusted for other time-related factors.[35] A related literature exists on bias created by including prevalent hires– workers that were employed before the cohort came under observation – in dose response analyses (e.g. Applebaum and colleagues[36,37]). Including prevalent hires is equivalent to a pooled analysis of multiple sub-cohorts with varying restrictions on time-since hire. When exposure influences the rate of leaving work, approaches based on adjustment for time-since-hire suffer the same potential for bias as models that adjust for active employment status.

A related method based on stratifying by employment status is adjustment for time-since-termination to address the change in disease rates immediately following employment termination. In the model of Richardson et al,[23] latent disease processes that cause termination display a strong correlation with mortality that fades over time. In terminated workers, time-since termination is correlated with both mortality and cumulative exposure. This set of correlations may arise because those who work for shorter periods (and are exposed less) will tend to have been off work longer. Because this effect is attributed to employment duration, rather than time-since-termination, *per se*, it is conceptually similar to adjusting for time-since hire. Notably, this model of healthy worker survivor bias acknowledges that, even conditional on current employment status, employment history may be an independent confounder of exposure-disease relationships. This method may be useful when duration of employment is the best available exposure metric, and it has been applied to examine the association between diesel exhaust and lung cancer.[38] However, this approach shares the potential shortcomings of any approach that stratifies on current employment status.

Standardization

Standardization refers to a process in which the outcome distribution in the data is summarized with a weighted average. The weights can be derived from external referent populations, as in the case of SMRs, or derived from an exposure distribution within the cohort. As discussed in the previous sections, methods that address healthy worker survivor bias through stratification or restriction may condition on intermediate variables in analyses with time-varying confounding affected by prior exposure (see Figure 1B), inducing collider stratification bias or blocking the causal effect of prior exposure on the outcome. Standardization is not subject to the same set of caveats and thus may be more useful for estimating unbiased parameters in certain scenarios.[39] Traditional standardization may be difficult, however, when confounders can vary over time or when hypothesized confounders are not measured in the referent population.

As a solution to the shortcomings of traditional standardization, Robins and colleagues developed a set of approaches known as the g-methods,[19] which generalize standardization to complex longitudinal data. Central to these methods is the notion of potential outcomes, or outcomes that would have been observed for an individual under a particular exposure history. These new methods are more flexible and allow the estimation of dose-response metrics as well as potentially more useful metrics, such as the years of life lost due to exposure or the effects of hypothetical interventions to reduce occupational exposures. G-methods have been applied to estimate the effects of occupational exposures in the presence of time-varying confounding by work status. In this section, we briefly describe four g-methods to account for healthy worker survivor bias and summarize examples in which each method has been applied.

G null test

The g-null test is a method developed by Robins[40] to adjust for confounding by time-varying employment status affected by prior exposure without introducing other biases. The g-null test is equivalent to conducting a series of matched case-control studies in which the strata are defined by matching exposure and covariate histories. Because the power of matched case-control studies depends strongly on the number of discordant pairs, this approach can have very low power when exposure takes on many values or when follow-up is over a long period, leading to sparse strata. Hertz-Picciotto and colleagues[41] compared the g-null test to lagging and employment status adjustment in a cohort of copper smelters exposed to arsenic but noted that the g-null test had low power in their study. As discussed below, advances in computing since that time have facilitated the adoption of other methods developed by Robins and colleagues that utilize an approach that is similar approach to the g-null test, but more powerful.

Inverse probability weighted marginal structural models

Inverse probability weighting has been widely adopted to control for time-varying confounding and has been applied to address healthy worker biases.[42,43] This approach uses weights estimated from the covariate conditional exposure distribution in the data to standardize to the exposure distribution in a target population.[44] The weighted "pseudopopulation" can be interpreted as a population in which measured confounders no longer predict exposure. Models comparing outcomes in the inverse probability weighted data are referred to as marginal structural models. Marginal structural models can be fit using g-computation, as well, but inverse probability weighting has proved to be far more popular.

A limitation of this approach is that if unemployed individuals cannot accrue exposure, marginal structural models fit using inverse probability weights cannot control confounding by employment status due to nonpositivity.[12] Nonpositivity occurs when exposure cannot be accrued within all strata of participants defined by confounders at time k, such as in occupational studies when participants who are not at work cannot obtain additional exposure.[45] Weighting methods rely on making copies of observed individuals to eliminate confounding in the observed population. Inverse probability weighted marginal structural models remain confounded because the stratum defined by $X_k = 1$ and $W_k = 0$ contains no individuals to which a weight can be applied.[12] Inverse probability weighting could be used to control healthy worker survivor bias if exposure could be accrued outside the workplace under study since there would no longer be zero probability of exposure when $W_k = 0$. However, this approach would rely on measuring all subsequent occupational and non-occupational exposures.

G-estimation

G-estimation of structural nested models can be used to estimate the effects of occupational exposures in the presence of healthy worker survivor bias. Like inverse probability weighting, g-estimation accounts for confounding by modeling the relationship between the confounders and exposure, in contrast to standard regression techniques that require modeling the relationship between the confounders and the outcome.[46]

Estimating a dose-response parameter using g-estimation consists of two primary steps: 1) calculate the potential outcome under no exposure for each participant as a function of the observed outcome and a hypothesized dose-response relationship between exposure and outcome; and 2) choose the best fitting dose-response estimate using g-estimation, which finds the value of the dose-response parameter for which the potential outcome is unrelated to the actual exposure received. To perform g-estimation with standard software packages, one can regress the observed exposure at each time point on the exposure history, measured covariates, and the potential outcome under no exposure. For binary exposures this could be done with a pooled logistic regression model in which the potential outcome is included as a covariate. In practical terms, this is when the p value for the coefficient for the potential outcome in the pooled logistic model is equal to one.

Unlike marginal structural models fit using inverse probability weighting, g-estimation allows estimation of effects even when unemployed individuals cannot accrue exposure. To avoid nonpositivity, the estimating equation used to determine the value for which observed exposure is unassociated with the potential outcomes can be limited to person-time during which participants are at work.[47]

G-estimation can be used in many types of models to estimate causal effects, though its use in occupational epidemiology has been limited to structural nested mean models, structural nested accelerated failure time models, and structural nested cumulative failure time models. Christiani et al[48] estimated the effect of dust and endotoxin exposure on the average change in subsequent FEV_1 values (a continuous measure of lung function) in cotton textile workers using structural nested mean models. Chevrier et al[11] used g-estimation of structural nested accelerated failure time models to estimate the effect of 5-years of exposure to metal working fluids compared to no exposure on mortality from a variety of causes. In a related analysis, Picciotto et al 2014[3] used g-estimation to estimate the number of years of life lost due to chronic obstructive pulmonary disease that could have been saved if several potential interventions for reducing exposure to metalworking fluids exposure had been in place. Naimi et al used a similar method to estimate the effect of cumulative asbestos exposure in a cohort of textile workers[5] and published simulations to estimate the effect of always being exposed to an occupational exposure versus never being exposed.[7] Picciotto et al[10] describe an alternative model, the structural nested cumulative failure time model, which can estimate risk ratios per unit of exposure under an assumption that the overall hazard is low. Neophytou et al[4] used this this model to compare ischemic heart disease mortality risk and all-cause mortality risk among several possible interventions on employment duration in the trucking industry.

Parametric g-formula

The final g-method used in occupational epidemiology is the parametric g-formula. The standard approach to estimate the effect of an exposure on an outcome using the parametric g-formula is to 1) parametrically model the joint probability density of time-varying confounders, exposures, and outcomes in the observed data; 2) use these regression coefficients to estimate the probability of the outcome for each participant under various exposure scenarios assigned by the investigator; and 3) estimate the parameter of interest in the dataset created in step 2.

The g-formula accounts for confounding through standardization to the distribution of time-fixed and time-varying variables in the study population. This allows the investigator to assign the exposure value for each participant at each time, regardless of covariate information, thus removing time-varying confounding from the final effect estimate. The g-formula may be used in occupational epidemiology to estimate the effects of dynamic treatment regimes such as "when at work, set exposure to *X*; when not at work set exposure to 0." The g-formula can also be used to estimate the effects of more complex interventions, such as threshold interventions in which exposure is estimated, but not allowed to exceed some value.[49,50] Finally, the extended g-formula can be used to incorporate competing events.[9,51]

Cole et al[9] used the parametric g-formula to estimate the effects of several hypothetical regulatory guidelines to limit asbestos exposure on lung cancer mortality in a cohort of textile workers. The investigators compared the observed cumulative incidence of lung cancer mortality to the potential cumulative incidence of lung cancer mortality under four possible interventions to limit exposures. This study estimated the reduction in lung cancer mortality from imposing occupational limits for asbestos exposure, had they been implemented at the time the cohort was formed. This type of effect, which may complement or even be preferred to dose-response analyses, is not possible to estimate using regression models. In a similar analysis, Edwards et al[13] implemented the parametric g-formula to estimate the effects on lung cancer mortality of limiting radon exposure to three historical guidance levels in a cohort of uranium miners.

Discussion of methods

Arrighi and Hertz-Picciotto concluded their review with recommendations for further development in two areas. First, they called for occupational studies to collect information on reasons for employment termination and types of inactive work status (e.g., unemployed versus employed elsewhere) to better characterize and control for underlying health status. While analysis of job-switching may not be possible in the case of cohorts defined by industry records, some progress has been made in characterizing reasons for changing jobs. Lea et al[52] separated unemployed person time by retirement age, inferring that those terminating after retirement age might be leaving work for different reasons from those who terminated at younger ages. Christiani et al[48] found evidence that workers with poor lung function preferentially switched to lower exposure jobs in cotton textile mill workers, suggesting that even within a given industry, there may be job changes related to underlying health status. We extend the original recommendation from Arrighi and Hertz-Picciotto by noting that job changes within a given worksite may also result in healthy worker survivor bias.

Second, Arrighi and Hertz-Picciotto suggested that conditions for time-varying confounding be evaluated in occupational studies, that Robins' methods be applied in studies of cumulative exposures and health, and that estimates from these methods be compared to results using standard approaches. As we have discussed, a rapidly expanding literature on g-methods has evaluated the presence of bias from time-varying confounding by employment status affected by prior exposure and g-methods have been applied in several occupational settings. Furthermore, differences in bias using g-methods and standard approaches have been quantified in occupational studies, suggesting that standard approaches, in some cases, can yield substantially biased results.[5,11] Analyses in non-occupational settings have shown that, when there is time-varying confounding affected by prior exposures, g-methods more accurately estimate the results from clinical trials than do regression models.[46,53,54]

Barriers to implementation of g-methods have been mitigated in recent years. Although g-methods are computationally intensive, rapid advances in computing power have lessened this concern. Lack of understanding of or resources for implementing g-methods may have previously discouraged researchers from using these approaches. Sample code has been published for the parametric g-formula[55,56]and g-estimation of a structural nested accelerated failure time model for binary exposures.[7,11] Further, Naimi et al[8] offer a simple approach to determine when g-methods might be useful in an occupational study by applying standard regression methods to evaluate component associations underlying healthy worker survivor bias.

Future directions

In the preceding sections, we have outlined recent methodological developments to control healthy worker survivor bias. Continued refinements to these methods can improve inference from occupational studies. For example, occupational and environmental epidemiologists have pioneered techniques to account for measurement error of exposures, covariates, and outcomes,[57-59] but these methods are typically tailored to remove bias from a parameter in a standard regression model. Novel methods are needed to extend these techniques to account for measurement error using the g-methods.

Both standard methods to control healthy worker survivor bias and the g-methods include parametric modeling components. Standard methods typically model the outcome using a parametric (or semiparametric) model. In the parametric g-formula, time-varying covariates, exposures, and outcomes are predicted using parametric models, while inverse probability weighting and g-estimation typically use a parametric model only for the exposure process. If these models are misspecified, the estimated dose-response relationship between exposure and outcome could be biased. In addition, inference from these methods assumes the parametric model used is correct, which, at best, is only approximately true. Existing work in machine learning and cross-validated algorithms, such as SuperLearner,[60] has focused on developing accurate models that do not rely on parametric assumptions. As an extension to the methods we discussed to control healthy worker survivor bias, these algorithms could be used to further reduce bias from model misspecification.

Finally, recently proposed methods can be used to estimate different types of parameters to complement the dose-response parameter typically estimated in occupational studies. The g-methods can be easily extended to estimate the effects of potential public health interventions, such as the implementation of new occupational exposure limits.[3,9,51] Other methods capable of controlling healthy worker survivor bias could also be adapted to estimate these effects as well as population burden measures such as the population attributable risk, generalized impact fractions, and disability adjusted life-years to better communicate the results from epidemiological studies to public health practitioners and policy-makers.

There has been a recent resurgence of interest in understanding and controlling healthy worker survivor bias. Advances in methodology and computing speed have enabled researchers to address time-varying confounding by employment status using appropriate methods, and the increasing willingness of investigators to share software to conduct these analyses is a positive step toward broader implementation. Beyond estimating less biased parameters, investigators should consider the policy implications of results estimated from occupational studies. Because the health of workers ultimately relies on technology and standards that limit harmful exposures, the ability of g-methods to examine causal effects that have direct policy implications is an important strength of these approaches. In the presence of healthy worker survivor bias, these methods allow epidemiologists to estimate parameters that can be clearly communicated to decision makers.

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FIGURE 1. Directed acyclic graphs illustrating healthy worker survivor bias in estimates of association between cumulative occupational exposure (X_k) and disease (D_k) in a longitudinal study with time indexed by k. U_k represents an unmeasured variable (e.g., health status). In Figure 1A, employment status (W_k) is a time-varying confounder. In Figure 1B, employment status (W_k) is a time-varying confounder affected by prior exposure (X_{k-1}).

Table 1. Summary of methods used to control for healthy worker survivor bias in epidemiologic studies published during 1994-2014.

Method	Number
Total number of studies	25
Exposure lagging	6
Cohort restriction	4
Regression adjustment for time-since-hire	10
Regression adjustment for active employment status	6
Regression adjustment for time-since-termination	6
G-methods[a]	9

[a]Includes the g-null test, inverse probability weighted marginal structural models, g-estimation of structural nested models, and the parametric g-formula.

Table 2. Summary of proposed methods to address healthy worker survivor bias.

Approach	Confounding approach	Assessment			Key references
		Uses	Strengths	Limitations	
Exposure lagging	NA	When latent disease causes termination; can be used in concert with other methods	Can use standard regression analysis, explicitly solves reverse causality	Does not address confounding by employment status	Gilbert[28]
Cohort restriction to long term workers	Restriction	When interested in inference for healthiest individuals	Can use standard regression analysis	Discards data, inference restricted to healthy subset, may introduce bias	Fox and Collier[16]
Regression adjustment for active employment status	Stratification	When employment status is a risk factor for disease and exposure does not cause termination	Can use standard regression analysis	May introduce bias	Steenland and Stayner[31]
Regression adjustment	Stratification	When time-since-hire or age at hire is a strong predictor of	Can use standard regression analysis	Does not completely control confounding by	Flanders et al[34]

Approach	Confounding approach	Assessment			Key references
		Uses	Strengths	Limitations	
for time-since-hire		mortality		employment status, may introduce bias	Arrighi and Hertz-Picciotto[35]
Regression adjustment for time-since-termination	Stratification	When latent disease causes termination	Can use standard regression analysis	May introduce bias	Richardson et al[23]
G-null test	Standardization	When employment status is a time-varying confounder affected by prior exposure	Not recommended	Low power, not feasible with many confounders or long follow-up	Robins[40] Hertz-Picciotto et al[41]
Inverse probability weighted marginal structural	Standardization	When employment status is a time-varying confounder affected by prior exposure and exposure can occur frequently off work	Can use standard regression analysis	Subject to bias when exposure does not occur off work	Naimi et al[12]

Approach	Confounding approach	Assessment			Key references
		Uses	Strengths	Limitations	
models					
G-estimation of structural nested models	Standardization	When employment status is a time-varying confounder affected by prior exposure and the exposure distribution is well understood	Less modeling intensive than the parametric g-formula	Little available software	Chevrier et al[11] Naimi et al[5]
Parametric G-formula	Standardization	When employment status is a time-varying confounder affected by prior exposure	Can estimate effects of many intervention scenarios	Little available software, requires extensive modeling	Cole et al[9]

Figure 1A

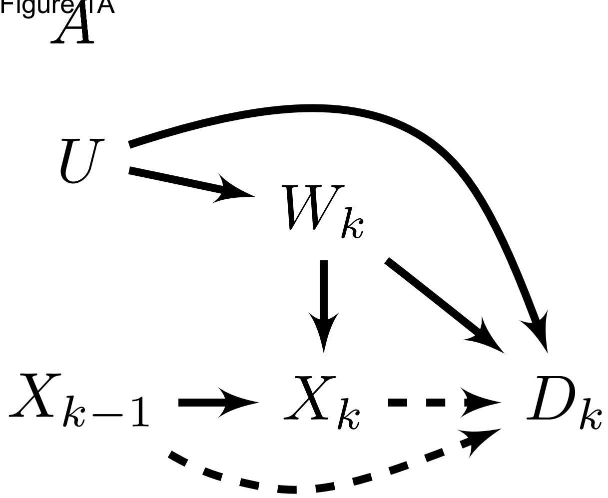

Figure 1B