A Comparison of Standard Methods With G-estimation of Accelerated Failure-time Models to Address The Healthy-worker Survivor Effect

Application in a Cohort of Autoworkers Exposed to Metalworking Fluids

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Background: Studies of autoworkers exposed to straight metalworking fluids report excess risks of several cancers. These studies, however, have not addressed the healthy-worker survivor effect. Most methods proposed to address this bias do not consider that it may be caused by time-varying confounders affected by prior exposure. G-estimation of accelerated failure-time models was developed to handle this issue but has never been applied to account for the healthy-worker survivor effect.

Methods: We compare results from Cox models and g-estimation in 38,747 autoworkers exposed to straight metalworking fluids. Exposure was defined based on job records and air samples. We examine relationships between duration of exposure and mortality from all causes, cancers, ischemic heart disease, and chronic obstructive pulmonary disease (COPD).

Results: In standard models, hazard ratios were elevated for cancers of the larynx, prostate, and rectum, but below or approximately equal to 1.0 for all other outcomes considered. Adjustment for the healthy-worker survivor effect using time off work, employment status, time since hire, and restriction to inactive workers after 15 years of follow-up did not substantially change the hazard ratios. However, g-estimation yielded higher hazard ratios than standard Cox models for most outcomes. Exposure was related to increased risks of mortality from all causes combined, heart disease, COPD, and all cancers, as well as lung and prostate cancers.

Conclusions: G-estimation may provide a better control for the healthy-worker survivor effect than standard methods.

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Metalworking fluids are complex mixtures used as coolants, lubricants, and anticorrosives in a variety of industrial metal machining operations. Metalworking fluids may be petroleum- or water-based and are generally classified into 3 major categories: straight (mineral oil), soluble, and synthetic. Emulsifiers, antiweld agents, corrosion inhibitors, extreme pressure additives, buffers, and other chemical agents are often added to metalworking fluids to enhance performance characteristics. Exposure to metalworking fluids is widespread throughout the world; updating earlier assessments,[1] Steenland et al estimated that approximately 4.4 million workers alive in 1997 had ever been exposed in the United States.[2] Although dermal exposure from splashes and spills was common in earlier years, exposure now occurs primarily through the respiratory and oral routes, as fluids are aerosolized by modern high-speed machinery. Evidence shows that a large proportion of metalworking fluid particles are in the respirable size range in these environments.[3]

Straight metalworking fluids may contain polycyclic aromatic hydrocarbons (PAHs) such as benzo(a)pyrene, and are classified as human carcinogens (group 1) by the International Agency for Research on Cancer (IARC).[4] Reports from a cohort study with quantitative estimates of exposure suggest that straight metalworking fluids may be more carcinogenic than soluble or synthetic metalworking fluids.[5–11] Cumulative exposure to straight metalworking fluids has been associated with increased risks of laryngeal[5] and rectal[6] cancer mortality, as well as laryngeal,[7] bladder,[8] prostate,[9] skin,[10] and biliary tract[11] cancer incidence. These results were based exclusively on cumulative exposure metrics (mg/m^3-year) using standard conditional regression models such as logistic, Poisson, and Cox proportional hazards. While these studies accounted for the healthy hire effect (eg, the more favorable mortality experience among employed persons relative to the general population) by performing internal dose-response analyses, none accounted for potential bias due to the healthy-worker survivor effect. The healthy-worker survivor effect may bias effect estimates if workers who are less healthy accumulate less exposure. This could occur if these workers take more time off, terminate employ-

ment earlier, have a higher probability of using protective equipment, or are more likely to transfer to a job with lower exposure than healthy workers. Because the healthy-worker survivor effect usually results in a downward bias, earlier studies may have underestimated associations between exposure to straight metalworking fluids and mortality.

Several methods have been proposed to control for the healthy-worker survivor effect. In their landmark article, Fox and Collier[12] proposed restricting analysis to unemployed individuals who were still alive more than 15 years after hire. This restriction was based on the observation that standardized mortality ratios (SMRs) were low shortly after hire, but approached 1.0 after 10 to 15 years of follow-up and among workers who had left the industry.[12,13] Adjustment for time since hire has also been used to address the healthy-worker survivor effect because it is associated with both mortality and cumulative exposure.[12,14] In addition, employment status has been identified as a possible confounder. In a simulation study, Steenland et al[15] found that controlling for this time-dependent variable eliminated bias when cumulative exposure was unrelated to the outcome and the probability of leaving work. However, the method was not effective when exposure and outcome were related. Other approaches such as lagging exposure[16] and adjusting for time since termination[17] have also been proposed.

The aforementioned methods do not account for the possibility that health status may be on the causal pathway between earlier exposure and mortality. Robins[18] has shown that even under the null hypothesis, standard conditional models will provide biased estimates when exposure history predicts future values of a time-dependent risk factor for survival that predicts subsequent exposure. The healthy-worker survivor effect may represent such a scenario. Health status, for instance, may both be affected by past exposure and predict future exposure due to increased time off work, employment termination, use of protective equipment, or job transfer. Because health status is a risk factor for mortality, it would act both as a confounder and as a variable on the causal pathway. Robins proposed methods for such situations, including g-computation[18] and the g-estimation of accelerated failure-time models (referred to as g-estimation hereafter).[19,20] G-estimation, which is less computationally intensive and requires fewer parametric assumptions than g-computation, has been applied effectively in infectious disease epidemiology to evaluate treatment protocols in HIV patients[20,21] and to investigate the effect of smoking cessation,[22] systolic hypertension,[23] and cardiovascular risk factors[24] on mortality. Although g-estimation was originally developed in response to concerns about the healthy-worker survivor effect in occupational epidemiology,[18] the approach has never been used to address this bias. In the present study, we compare results obtained using standard methods to control for the healthy-worker survivor effect with g-estimation of accelerated failure-time models in a mortality study of autoworkers exposed to straight metalworking fluids. While prior reports using g-estimation have focused on scenarios in which populations are continuously exposed throughout follow-up, we provide a blueprint for the application of the method to scenarios in which populations are exposed for a given number of years. This may more realistically reflect the exposure patterns observed when follow-up extends beyond the opportunity for exposure, such as in occupational studies in which subjects are followed after they terminate employment.

METHODS

Study Population

The original study included 46,316 hourly workers employed in 1 of 3 Michigan automobile manufacturing plants and hired before 1 January 1982.[25] Follow-up began 3 years after workers' date of hire or on 1 January 1941 and ended at the time of death or on 31 December 1994.[5] Vital status data were available starting on 1 January 1941. The cohort was therefore restricted to those enrolled after this date (n = 39,400) to minimize survivor bias due to left truncation.[26] We further excluded workers for whom >50% of job data were missing (n = 653), because these data were used to estimate exposure to metalworking fluids (see later in the text). A total of 38,747 workers were thus included in this analysis. Information on age, sex, race, and temporary time off work was obtained through employment records provided by both the employer (General Motors) and the union (United Auto Workers). Missing data on temporary time off work (4% of workers had some missing employment data in their record) were substituted by the closest preceding nonmissing value. Workers with unknown race were classified as white based on the demographics of the industry.[25]

Exposure Assessment

A detailed report of the retrospective methods has been published previously.[27] Briefly, annual exposures to straight, soluble, and synthetic metalworking-fluid particulate matter were estimated based on personal and area air samples collected between 1958 and 1987 by industrial hygienists. Scale factors were developed from a prediction model based on company and research team monitoring data to estimate plant-, department-, and job-specific exposure categories. Although g-estimation methods may be applied to continuous exposures,[28,29] implementation has been described in more detail for dichotomous exposures.[21,23,31] Thus, for the purpose of this study, exposure was categorized as ever versus never exposed to straight metalworking fluids in each calendar year.

Health Outcomes

Data on vital status were obtained through the Social Security Administration, the National Death Index, plant records, and state mortality files. Cause of death was obtained from state vital records, which contained International Clas-

sification of Disease (ICD) codes. Death certificates, coded by an experienced nosologist, were used if vital records could not be located. Examination of ICD codes based on state vital records and death certificates (n~200) revealed little discrepancy.[25] Outcomes of interest included mortality from all causes, ischemic heart disease (ICD-9: 410 to 414), and all cancers (ICD-9: 140 to 209) as well as specific cancers previously reported to be associated with exposure to straight metalworking fluids in quantitative studies (bladder [ICD-9: 188], larynx [ICD-9: 161], prostate [ICD-9: 185] and rectum [ICD-9: 154]). We did not evaluate relationships with biliary and skin cancers due to the small number of cases (n = 20 and 25, respectively). Because exposure is believed to occur primarily through the respiratory and oral routes, we also examined associations with chronic obstructive pulmonary disease (COPD; ICD-9: 490 to 496), and lung (ICD-9: 162), colon (ICD-9: 153), and stomach (ICD-9: 151) cancer mortality.

Data Analysis

We used Cox proportional hazards models to examine associations between duration of exposure to straight metalworking fluids and mortality outcomes. Year of follow-up was set as the time variable. Exposure to straight metalworking fluids was expressed as a dichotomous variable coded as 1 if workers were ever exposed at any time during a calendar year and 0 otherwise. All models also included calendar year to account for secular changes in mortality rates and exposure levels, year of hire, race (white or African American), sex, age and age-squared (in years, continuously), and duration of exposure to synthetic and soluble metalworking fluids (ever- vs. never-exposed in each calendar year). We also adjusted for plant (I, II, or III) to account for unmeasured sociodemographic factors and residential environments. In addition, separate Cox models were applied using previously proposed methods to account for the healthy-worker survivor effect: (1) restricting analyses to unemployed individuals with more than 15 years of follow-up[12]; (2) adjusting for time since hire (years)[12,14]; (3) adjusting for employment status (employed vs. unemployed)[15]; and (4) adjusting for time off work (percent of each year). Time since hire, employment status, and time off work were all expressed as time-varying variables.

We compared results from these standard models with those generated by g-estimation as described by Robins.[20] We followed the procedure described by Hernán et al[21] and Witteman et al[23] with some modifications. A step-by-step description of our application of the method is provided in an eAppendix available online (http://links.lww.com/EDE/A557). In summary, g-estimation simulates nested randomized controlled trials at each time point (calender year of follow-up in the case of this study) within each stratum of previous covariate values. In randomized controlled trials, confounding is addressed by assigning exposure at random (ie, exposure assignment is unrelated to potential for survival when unexposed). By analogy, exposure will be considered randomized in observational studies if it is unrelated to unexposed survival time within each stratum of covariate values (see eAppendix for more details). The correct parameter (ψ) linking observed survival time, exposure, and a counterfactual (ie, contrary to fact) unexposed survival time in an accelerated failure-time model will thus be the one that generates survival times that are unrelated to exposure after adjusting for covariates. Prior applications of g-estimation have compared scenarios in which the entire study population was exposed without interruption throughout follow-up, relative to those in which the population was never exposed. We show how this parameter may be used to compute the ratio of the median survival times under a scenario in which everyone in the study population is exposed for a given number of years, to the median survival time if everyone had been unexposed (ie, the survival ratio).

In addition to the covariates included in the standard models (listed above), g-estimation also adjusted for variables representing the amount of temporary time off work in all prior years of active employment. Time off work was expressed as a proportion in each year. Separate models were run for each method and outcome. Because criteria for inclusion in the study required at least 3 years of employment, workers were considered at risk only after that time interval. Exposure and time off work in the 3 years prior to start of follow-up were used as baseline covariates to adjust for confounding at start of follow-up.

Accelerated failure-time models are used to model survival because there are no unbiased estimating functions for structural nested hazard ratio models.[30] To report measures of association that allow better comparison with standard methods, we transformed survival ratios obtained by g-estimation into hazard ratios by running standard Cox proportional hazards models on counterfactual survival and censoring times. Throughout this article, we report hazard ratios for 5 years of exposure to straight metalworking fluids for both Cox and g-estimation models. Note that the interpretation of the estimates produced by g-estimation and standard Cox models differs. Hazard ratios obtained using g-estimation compare the hazard rates that would have been observed had the entire study population been exposed to straight metalworking fluids for 5 years, relative to hazard rates had everyone been always unexposed. In contrast, hazard ratios estimated by standard methods compare hazards between subsets of workers with various exposure experiences. In addition, g-estimation generates marginal estimates, whereas standard methods are conditional on other covariates. Thus, the magnitude of hazard ratios provided by Cox models and g-estimation may not be strictly comparable, although one may contrast the conclusions that would be drawn when using these methods.

For all models, we adjusted for potential selection bias due to loss to follow-up and competing risk by applying inverse-probability weights determined by multiple logistic regression using the demographic characteristics listed earlier as well as time-varying exposure (to straight, soluble, and synthetic metalworking fluids) and time off work as independent variables.[32] For g-estimation models, administrative censoring was addressed for each worker by considering whether any of the counterfactual survival times would have extended beyond the end of follow-up (see eAppendix, http://links.lww.com/EDE/A557). All statistical analyses were performed with STATA/MP version 11.0 (StataCorp, College Station, TX). Code to perform g-estimation to control for the healthy-worker survivor effect can be found on our Web site at http://ehs.sph.berkeley.edu/eisen/index.html.

RESULTS

Population Characteristics

As shown in Table 1, the cohort was primarily composed of white (82%) men (88%) hired before their mid-30s (81%), with a mean follow-up of 25 years (SD = 11.1). Workers were hired between 1938 and 1981. They were employed for 18 years (SD = 9.5) and died at a mean age of 62 years (SD = 13.6). By the end of follow-up, a total of 971,633 person-years were observed, 9592 (25%) workers had died, and 1514 (4%) were lost to follow-up. Workers were exposed to straight metalworking fluids for an average of 4.1 years (SD = 6.6). Approximately half (52%) of the cohort was ever exposed to straight metalworking fluids, and among those workers, the mean duration of exposure was 7.8 years (SD = 7.4). Ischemic heart disease (n = 2595) and cancer (n = 2386) were the primary causes of death in this cohort. The lung (n = 858), prostate (n = 168), and stomach (n = 116) were the most common cancer sites.

Exposure to Metalworking Fluids and Mortality

Similar to workers who were alive at the end of follow-up, those who died of any cause were exposed to straight metalworking fluids for an average of 4.1 (SD = 6.8) years. Cases of COPD, heart disease, and all cancers combined were exposed for longer periods. Comparing the 8 specific cancers, the average duration of exposure to straight metalworking fluids was highest for workers who died of laryngeal cancer, followed by prostate cancer and rectal cancer. Exposure was lowest for workers with colon cancer and stomach cancer. Consistent with these results, standard Cox proportional hazards models suggested elevated risks for cancers of the larynx, prostate, and rectum, although all confidence intervals included the null (Table 2). However, standard Cox models suggested a protective effect of exposure to straight metalworking fluids for all other causes of death, with hazard ratios (HR) ranging between 0.93 (95% CI = 0.83 to 1.04) and 0.99 (0.83 to 1.20) for every 5 years of exposure. Adjustment for time off work and

TABLE 1. Demographic and Exposure Characteristics by Cause of Death for Autoworkers Participating in the United Auto Workers—General Motors Study

		Cause of Death											
						Site-specific Cancers							
Demographic Characteristics	**Entire Cohort (n = 38,747)**	**All Causes (n = 9592)**	**COPD (n = 306)**	**Heart Disease (n = 2595)**	**All Cancers (n = 2386)**	**Bladder (n = 53)**	**Colon (n = 165)**	**Larynx (n = 41)**	**Lung (n = 858)**	**Prostate (n = 168)**	**Rectum (n = 46)**	**Stomach (n = 116)**
Sex; no. (%)												
Male	33,983 (88)	8829 (93)	282 (92)	2476 (95)	2180 (91)	52 (98)	153 (93)	40 (98)	801 (93)	168 (100)	43 (93)	111 (96)
Female	4764 (12)	632 (7)	24 (8)	119 (5)	206 (9)	1 (2)	12 (7)	1 (2)	57 (7)	(0)	3 (7)	5 (4)
Race; no. (%)												
Caucasian	31,593 (82)	7857 (83)	267 (87)	2316 (89)	1972 (83)	48 (91)	140 (85)	32 (78)	718 (84)	121 (72)	38 (83)	90 (78)
African American	7154 (18)	1604 (17)	39 (13)	279 (11)	414 (17)	5 (9)	25 (15)	9 (22)	140 (16)	47 (28)	8 (17)	26 (22)
Plant; no. (%)												
I	9271 (24)	3098 (33)	92 (30)	776 (30)	759 (32)	15 (28)	54 (33)	16 (39)	275 (32)	68 (40)	13 (28)	41 (35)
II	17,078 (44)	4766 (50)	169 (55)	1370 (53)	1174 (49)	29 (55)	74 (45)	21 (51)	431 (50)	78 (46)	22 (48)	60 (52)
III	12,398 (32)	1597 (17)	45 (15)	449 (17)	453 (19)	9 (17)	37 (22)	4 (10)	152 (18)	22 (13)	11 (24)	15 (13)
Age at death; (years); mean (SD)	62.4 (13.6)	62.4 (13.6)	68.7 (10.1)	64.4 (11.7)	63.4 (11.3)	68.3 (11.7)	67.2 (11.3)	63.3 (9.2)	63.4 (9.9)	71.1 (9.1)	61.0 (11.9)	63.9 (10.7)
Years of follow-up; mean (SD)	25.1 (11.1)	26.1 (11.5)	30.4 (10.6)	26.7 (10.9)	27.3 (11.1)	29.2 (11.9)	29.8 (10.9)	27.0 (9.7)	27.8 (10.5)	30.9 (9.4)	26.3 (12.5)	25.0 (12.0)
Years employed; mean (SD)	18.1 (9.5)	15.7 (9.3)	16.5 (9.1)	16.2 (9.2)	16.8 (9.7)	16.3 (9.0)	18.0 (9.7)	18.7 (9.8)	17.0 (9.9)	18.6 (9.6)	16.0 (10.2)	15.2 (9.1)
Years exposed; mean (SD)	4.1 (6.6)	4.1 (6.8)	4.9 (6.8)	4.5 (7.1)	4.4 (7.2)	4.9 (8.3)	4.1 (7.2)	6.4 (8.5)	4.4 (7.3)	5.7 (8.5)	5.3 (9.3)	4.1 (6.6)

TABLE 2. Hazard Ratios for 5 Years of Exposure to Straight Metalworking Fluids for Site-specific Cancer Mortality (n = 38,747)

	Bladder HR (95% CI)	Colon HR (95% CI)	Larynx HR (95% CI)	Lung HR (95% CI)	Prostate HR (95% CI)	Rectum HR (95% CI)	Stomach HR (95% CI)
Cox models							
Standard	0.99 (0.83 to 1.20)	0.93 (0.83 to 1.04)	1.15 (0.96 to 1.39)	0.96 (0.91 to 1.01)	1.08 (0.98 to 1.19)	1.06 (0.88 to 1.28)	0.96 (0.84 to 1.11)
Adjusted for time off work	1.00 (0.83 to 1.20)	0.93 (0.83 to 1.04)	1.15 (0.96 to 1.39)	0.96 (0.91 to 1.01)	1.08 (0.98 to 1.19)	1.06 (0.88 to 1.28)	0.96 (0.83 to 1.11)
Adjusted for employment status	1.03 (0.86 to 1.25)	0.95 (0.85 to 1.07)	1.21 (1.00 to 1.46)	0.99 (0.94 to 1.04)	1.10 (1.00 to 1.21)	1.10 (0.91 to 1.33)	0.99 (0.86 to 1.14)
Adjusted for time since hire	0.99 (0.83 to 1.20)	0.93 (0.83 to 1.04)	1.15 (0.96 to 1.39)	0.96 (0.91 to 1.01)	1.08 (0.98 to 1.19)	1.06 (0.88 to 1.28)	0.96 (0.84 to 1.11)
Restricted to unemployed workers with >15 year follow up	1.03 (0.84 to 1.25)	0.98 (0.87 to 1.11)	1.19 (0.96 to 1.48)	0.99 (0.94 to 1.04)	1.12 (1.02 to 1.24)	1.18 (0.97 to 1.44)	1.00 (0.86 to 1.17)
G–estimation	1.05 (0.91 to 1.28)	0.97 (0.88 to 1.18)	1.24 (0.97 to 1.69)	1.07 (1.04 to 1.14)	1.21 (1.04 to 1.34)	1.16 (0.92 to 1.76)	1.13 (0.88 to 1.42)

TABLE 3. G-estimation Parameter (ψ), and Survival Ratio (SR) for 5 Years of Exposure to Straight Metalworking Fluids in the UAW-GM Study (n = 38,747)

	ψ (95% CI)	SR (95% CI)
Causes of mortality		
All causes	0.182 (0.133 to 0.231)	0.96 (0.95 to 0.97)
COPD	0.405 (0.223 to 0.595)	0.90 (0.83 to 0.96)
Heart disease	0.325 (0.228 to 0.405)	0.92 (0.90 to 0.94)
All cancers	0.172 (0.105 to 0.244)	0.96 (0.94 to 0.98)
Site–specific cancers		
Bladder	0.100 (−0.205 to 0.588)	0.98 (0.85 to 1.12)
Colon	0.000 (−0.288 to 0.305)	1.00 (0.92 to 1.07)
Larynx	0.431 (−0.043 to 1.435)	0.90 (0.33 to 1.03)
Lung	0.172 (0.069 to 0.282)	0.97 (0.93 to 0.99)
Prostate	0.343 (0.044 to 0.526)	0.92 (0.87 to 1.00)
Rectum	0.405 (−0.241 to 1.610)	0.91 (0.26 to 1.06)
Stomach	0.234 (−0.392 to 0.960)	0.95 (0.68 to 1.10)

SR indicates survival ratio.

time since hire in standard Cox models did not substantially alter results. Restriction to inactive workers after 15 years of follow-up and adjustment for employment status slightly increased hazard ratios for most outcomes. Table 3 shows the estimates of ψ, and corresponding survival ratios demonstrating shorter survival times under 5 years of exposure than under no exposure for all of the outcomes except colon cancer. The largest reductions in survival time were for COPD and laryngeal cancer. The hazard ratios obtained using g-estimation were higher than those from standard methods for most site-specific cancers. The Figure shows that this contrast held for all causes of death combined (HR = 1.07 [95% CI = 1.05 to 1.11]), chronic obstructive pulmonary disease (1.23 [1.13 to 1.38]), ischemic heart disease (1.15 [1.11 to 1.19]), and all cancers combined (1.07 [1.05 to 1.12]). G-estimation results also suggest that longer duration of exposure to straight metalworking fluids was related to increased risks for cancers of the lung (1.07 [1.04 to 1.14]) and prostate (1.21 [1.04 to 1.34]). In addition, results suggest possible increased risk of bladder, laryngeal, rectal, and stomach cancers.

DISCUSSION

Results from this study suggest that after partial adjustment for the healthy-worker survivor effect by g-estimation of accelerated failure-time models, duration of exposure to straight metalworking fluids is related to increased risk of mortality from all causes combined, all cancers combined, COPD, and ischemic heart disease. Relative risks for cancers of the larynx, lung, prostate, rectum, and stomach were also increased in association with duration of exposure, although confidence intervals for some of these outcomes (bladder, larynx, rectum, and stomach) were wide and included the null. Possibly due to the fact that annual exposure was dichotomized, results from this study did not support earlier

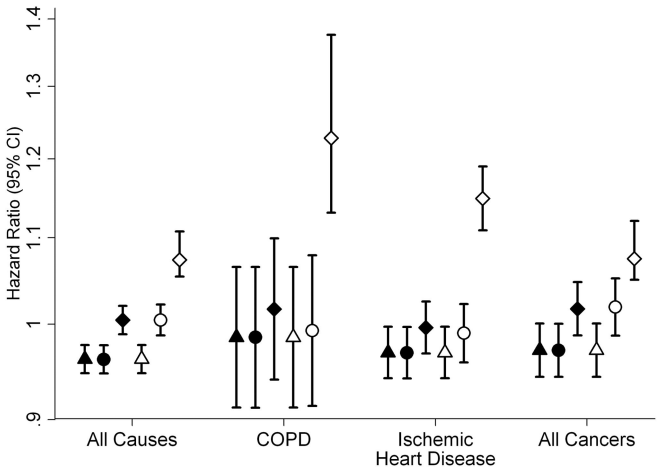

FIGURE. Hazard ratios per 5 years of exposure using various methods to control for the healthy worker survivor effect (n = 38,747). Standard Cox model (▲); Cox model adjusted for time off work (●); Cox model adjusted for employment status (♦); Cox model adjusted for time since hire (△); Cox model restricted to unemployed workers with more than 15 years of follow-up (○); g-estimation (◇).

reports of associations between exposure to straight metalworking fluids based on quantitative measures and cancers of the larynx and rectum in the same cohort. Results, however, provide the first evidence that exposure to straight metalworking fluids may be related to ischemic heart disease and COPD mortality. In contrast with previous null findings,[5,33] this study also provides new evidence that exposure to straight metalworking fluids may be associated with increases in lung cancer mortality. These relationships are supported by a large body of evidence that links long-term exposure to fine particular matter derived from combustion sources to cardiovascular disease[34,35] and malignant and nonmalignant respiratory disease mortality.[36,37] Although metalworking fluid particles do not arise from combustion, the heat generated from these metal machining operations are likely to produce particulate matter with a size distribution similar to combustion products.[38] Furthermore, in our study, the median concentration of metalworking fluid particles, which may contain PAHs and metals, occurred at concentrations that were orders of magnitude higher than National Ambient Air Quality Standards for total particulate matter.[39]

Results from g-estimation contrast with the null or protective effect suggested by standard Cox models, with or without attempting to adjust for the healthy-worker survivor effect. Differences may be due to a better control for the healthy-worker survivor effect by g-estimation models, as Cox-based methods do not consider the possibility that health status (or susceptibility to exposure) may be a time-varying confounder and an intermediate variable between prior exposure and outcome. Thus, traditional conditional methods including logistic, Poisson, and Cox regressions may not appropriately adjust for the healthy-worker survivor effect. Supporting this proposition, Arrighi and Hertz-Picciotto[40] reported in a simulation study that when employment status was a risk factor for mortality, a predictor of exposure, and affected by prior exposure, traditional analyses produced biased results. Moreover, traditional methods suggested a protective effect of exposure that became null after adjusting for employment status when a true adverse association existed. Comparing mortality rates among workers who shared the same employment and exposure history, however, yielded an unbiased estimate. This method (the G-null test[18]) was extended to allow for stratification over fine strata and across a large number of covariates by way of g-estimation of accelerated failure-time models. One prior study of copper smelter workers exposed to arsenic examined standard methods to address the healthy-worker survivor effect and, similar to our results, found no substantial alteration in measures of associations.[41] Other differences between standard methods and g-estimation may also explain the divergent results. For instance, g-estimation yields marginal estimates, comparing the mortality that would have been experienced by the entire population under specific exposure scenarios, whereas standard Cox models provide conditional associations, comparing mortality experiences between subgroups with different exposures. In addition, the Cox and accelerated failure-time models have different forms.

As previously discussed,[40,42] standard methods proposed to adjust for the healthy-worker survivor effect have several limitations. Restricting data analysis to unemployed survivors was based on the observation that SMRs approach 1.0 with time since hire.[12,13] SMRs, however, estimate the magnitude of the healthy-hire effect (ie, the different mortality experiences between occupational cohorts and the general population) rather than that of the healthy-worker survivor effect. Moreover, restricting analysis to unemployed workers may bias measures of associations, as mortality risk is higher in this subgroup. Adjusting for time since hire may also be inappropriate because this variable is not expected to be a risk factor (or ancestor, using the causal diagram terminology) for mortality—a necessary condition for a variable to be considered a confounder.[43] Instead, time since hire may be a proxy for age and reflect a time-related increase in the proportion of workers who retire, in that both factors (age and being unemployed) are related to increased mortality risk. Supporting this hypothesis, Steenland et al[15] showed that controlling for employment status removed associations between time since hire and mortality in pooled data from 10 published mortality studies, and Howe[44] found that SMRs did not increase in analyses restricted to active workers. In addition, a simulation study suggested that controlling for employment status was inadequate when exposure was related to mortality incidence or the probability of leaving work.[15] Finally, if time

off work is affected by health status (as described earlier), then controlling for this variable would be expected to introduce new bias rather than eliminating the healthy-worker survivor effect. This new bias would arise even if exposure does not affect mortality.[20]

A further advantage of g-estimation is that it models survival, which may be of greater interest than hazard ratios.[45] Hernán[46] identified 2 major limitations of the hazard ratio. First, its magnitude depends on length of follow-up, and may vary with time. In addition, period-specific hazard ratios have built-in selection bias, in that the most susceptible individuals die earlier and are eliminated from the at-risk population. Survival is not affected by these issues because the denominator (the number of persons at risk at the beginning of follow-up) does not vary over time. Furthermore, in contrast to both standard methods and marginal structural models, g-estimation yields unbiased estimates even when the positivity assumption is violated.

The rigorous approach to the healthy-worker survivor effect is a compelling feature of g-estimation. However, a few limitations impede a more widespread adoption of the method. First, although the approach has been generalized to continuous exposures,[28,29] implementation details have been published only for dichotomous exposures. Second, the application of the method remains challenging both in terms of the complexity of the theory and the extensive computing time required for application in large datasets. Finally, as for other causal methods, g-estimation yields estimates that may not be directly comparable with those obtained with standard associational methods.

This study has several strengths and a few limitations. Its prospective design precludes recall bias, and its large size and long period of follow-up provide ample statistical power. The limited attrition rate also reduces the potential effect of selection bias due to informative censoring. Although we have not taken full advantage of the quantitative data in this analysis, ours is the only study with estimates of exposure to specific types of metalworking fluids. A major strength of this study is the available data on temporary time off work, which we used as a time-varying health surrogate in the implementation of g-estimation. We, however, had limited data on potential confounders (such as smoking, socioeconomic status, or use of protective equipment).

In summary, this is the first successful application of g-estimation to adjust for the healthy-worker survivor effect in an occupational study. Previously proposed methods to adjust for the healthy-worker survivor effect did not substantially alter measures of associations and suggested that exposure to straight metalworking fluids had a null or protective effect for all outcomes under study. In contrast, results obtained by g-estimation of accelerated failure-time models suggest that exposure increases mortality (and reduces survival) due to all causes of death combined, all cancers combined, ischemic heart disease, and COPD. Analysis of specific cancer sites by g-estimation suggested increased mortality risks for lung and prostate cancers. Different results obtained by standard conditional models and g-estimation are likely due, in part, to a better control for the healthy-worker survivor effect by g-estimation.

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