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Healthy worker effect in cohort studies on chronic bronchitis

by Katja Radon, PhD,¹ Mark Goldberg, PhD,¹ Margaret Becklake, MD¹

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Objectives Despite the recognition of selection biases arising from the healthy worker effect in occupational mortality studies, the possibility of similar effects in occupational cohort studies on respiratory symptoms is not well known. Two mechanisms are responsible for the healthy worker effect in respiratory cohort studies. One is health-based selection of workers into employment (healthy hire effect), and the other is health-based differential losses to follow-up (healthy worker survivor effect). The aim of the present paper was to estimate the magnitude of the healthy worker survivor effect in cohort studies of symptoms of chronic bronchitis.

Methods A meta-analysis of occupational cohort studies of symptoms of chronic bronchitis was performed that included published articles identified in searches of the Medline bibliographic databases between 1980 and March 2001 and the reference lists of the located articles.

Results Eight cohort studies were identified using an a priori selection criterion. The pooled odds ratio of the prevalence of chronic bronchitis for subjects leaving the cohorts was 1.23 when these subjects were compared with those who remained under study (95% confidence interval 1.04–1.44).

Conclusions The prevalence of respiratory symptoms among exposed workers may be underestimated if the healthy worker survivor effect is not taken into account.

Key terms cohort studies, epidemiology, occupational medicine, selection bias.

The term “healthy worker effect” was first used to describe the lower-than-expected age-standardized mortality rate observed in many occupational studies (1). This phenomenon has been attributed to the use of an inappropriate reference group, namely, the general population (2–4). It has been suggested that membership in the workforce underlies three basic mechanisms (4–7): (i) primary selection at the time of hire (“healthy hire effect”), (ii) secondary selection during employment (“healthy worker survivor effect”), and (iii) changes in life in association with employment. As a result of these mechanisms, the workforce is, on the average, healthier than the general population.

In occupational cohort studies, subjects are selected into the cohort because of their employment in the fa-

cility under consideration. This selection into the workforce might already be differential for those in the group exposed to a potential occupational hazard [eg, hemp workers (8)] as compared with the comparison group [eg, packers working in the same factory as the hemp workers but without exposure to noxious dusts or fumes (8)] because of a pre-employment medical examination and self-selection of the subject (1, 4, 9).

Once employed, workers will eventually leave the workforce, and those who experience symptoms may leave earlier. Therefore, the duration of employment in the job may again differ for those potentially exposed and the comparison group. In addition, workers with symptoms are often transferred to jobs that do not entail the same types of exposures experienced in the

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workers' usual occupations. As a result, the distribution of employees among exposure categories is not random with respect to the outcome (4–7, 10).

While it is difficult to control for the healthy hire effect, one may be able to control appropriately for the healthy worker survivor effect by obtaining a complete follow-up of all the subjects until they leave the cohort or change workplaces when they experience symptoms. If it is not possible to trace subjects after they leave work, the magnitude of the healthy worker survivor effect can be estimated by comparing the prevalence of symptoms at the time of hire among those who left the cohort during the follow-up period to the prevalence of symptoms among those who remained at work.

Only one review of the healthy worker effect has been carried out in respiratory epidemiology (1), and the authors focused on cross-sectional surveys of measurements of lung function. It is of considerable interest to assess the healthy worker effect in occupational cohort studies of respiratory symptoms, and our paper presents an estimate of its magnitude in studies in which chronic bronchitis was assessed.

Subjects and methods

A Medline search was conducted using the key terms "occupational cohort" and "respiratory symptoms", and 163 papers were found. Additional articles were selected from the reference lists of the selected papers.

The following inclusion criteria were used: publication between January 1980 and March 2001 in English or German and report of a longitudinal, prospective occupational cohort study providing information on the baseline prevalence of respiratory symptoms for the exposed subjects who stayed in the cohort over the follow-up period and for those who were lost to follow-up.

For multiple publications of the same cohort, the most recent paper reporting the baseline data on symptoms was used. The meta-analysis was restricted to studies in which symptoms of chronic bronchitis were reported. For each study, the number of subjects who remained in the cohort, the number of subjects who were lost to follow-up over the study period, the industry under study, the duration of follow-up, the country of the survey, and descriptive data of the study population were abstracted from the papers. In addition, the number of workers who were symptomatic at the time of the baseline survey and remained in the cohort and the number of workers who were symptomatic at the time of the baseline survey and who were lost to follow-up were extracted. In order to estimate the health-based selection out of the workforce, we calculated the preva-

lence of chronic bronchitis at the time of the baseline survey for those who stayed in the study population and those who were lost to follow-up. We computed odds ratios (OR) and 95% confidence intervals (95% CI) for the prevalence of chronic bronchitis at the time of entry into the study by comparing the group of workers lost to follow-up with the group of workers who remained under study.

Using the inverse variance of each study as a weight (fixed-effects analysis), we calculated a pooled odds ratio as a weighted mean for the study results (11). In order to estimate the 95% confidence interval for the summary measure, the inverse of the square root of the sum of the weights was used as an estimate of the standard error. The chi-square test for the summary odds ratio was calculated as described by Rothman & Greenland (11). Because of the small number of studies, random effects models could not be used.

Results

Overall, 233 papers were considered for the meta-analysis. (See the appendix; references are available from the authors by request.) The majority of the studies had to be excluded for reasons of design (6 review articles, 4 case reports, 62 cross-sectional studies, 7 case-referent studies, 13 retrospective cohort studies, 4 experimental studies, 4 mortality studies, and 16 population-based surveys). Moreover, 97 studies on respiratory symptoms did not focus on symptoms of chronic bronchitis. Four papers described additional observations on cohorts already included in the analysis. Eight occupational studies of chronic bronchitis did not provide separate baseline characteristics of the dropouts and subjects who were not lost to follow up. Among these latter studies, Westeel et al (12) reported a significantly higher proportion of chronic bronchitis for those excluded or lost to follow-up without giving exact prevalences. Chinn et al (13) found a significantly higher prevalence of chronic phlegm among the dropouts but did not report on chronic bronchitis among those who remained and those who left. Vestbo & Rasmussen (14) found a higher proportion of chronic bronchitis for those who were lost to follow-up but did not report the prevalence of symptoms separately for the exposed subjects. The remaining surveys did not report on the baseline prevalence of symptoms for those who stayed in the cohort (15) or for those who were lost to follow-up (16–19).

Eight studies reporting the prevalence of chronic bronchitis at the beginning of the study were thus included in this analysis (8, 20–26). Two studies (8, 20) provided separate prevalences for the men and women in the cohort, one other study presented separate prevalences

Table 1. Characteristics of the studies included in the meta-analysis. (ATS = questionnaire on respiratory symptoms published by the American Thoracic Society, BMRC = questionnaire published by the British Medical Research Council, CECA = questionnaire pour l'étude de la bronchite chronique et de l'emphyseme pulmonaire)

Study	Occupation	Country	Questionnaire	Duration of follow-up (years)
Zuskin et al, 1991 (20) ^a	Cotton textile workers	Croatia	BMRC	10
Zuskin et al, 1991 (20) ^a	Cotton textile workers	Croatia	BMRC	10
Christiani et al, 2001 (24) ^a	Cotton textile workers	China	ATS	15
Zuskin et al, 1994 (8) ^a	Hemp workers	Croatia	BMRC	3
Zuskin et al, 1994 (8) ^a	Hemp workers	Croatia	BMRC	3
Zuskin et al, 1997 (21) ^a	Food processing	Croatia	BMRC	2
Zuskin et al, 1997 (21) ^a	Food processing	Croatia	BMRC	2
Zejda et al, 1992 (22) ^b	Grain workers	Canada	ATS	4
Pham et al, 1986 (25) ^b	Iron miners	France	BMRC	5
Musk et al, 1982 (23) ^c	Fire fighters	United States	No standard questions	6
Mur et al, 1989 (26) ^c	Arc welders	France	CECA	5

^a Definition of bronchitis: cough and phlegm for at least 3 months for at least 2 consecutive years.^b Definition of bronchitis: ATS criteria.^c Definition of bronchitis: no details given.**Table 2.** Characteristics of the subjects in the studies included in the meta-analysis. (M = male, F = female)

Study	Uncensored (N)	Dropouts (N)	Gender	Mean age (years)		Mean duration of employment		Smokers (%)	
				Uncensored	Dropouts	Uncensored	Dropouts	Uncensored	Dropouts
Zuskin et al, 1991 (20)	31	13	M	.. ^a	.. ^a	..	..	.. ^a	.. ^a
Zuskin et al, 1991 (20)	35	37	F	.. ^a	.. ^a	..	..	.. ^a	.. ^a
Christiani et al, 2001 (24)	346	101	M:F (1:1.1)	36.9	38.9	14.7	16.2	35.5	35.6
Zuskin et al, 1994 (8)	28	1	M	43	..	18	..	93	..
Zuskin et al, 1994 (8)	38	10	F	35	..	12	..	13	..
Zuskin et al, 1997 (21)	39	74	F	31.8	35.3	13.7	13.7	0	0
Zuskin et al, 1997 (21)	10	29	F	25.7	23.6	5.8	3.3	100	100
Zejda et al, 1992 (22)	51	113	M	20	20	0	0	..	..
Pham et al, 1986 (25)	871	308	M	43.7	45	..	..	70.6	75.6
Musk et al, 1982 (23)	951	821	M	40.9	47.6	15.9	22.8	43.4	45.6
Mur et al, 1989 (26)	300	79	M	34.7	36.7	..	..	82 ^b	78.5 ^b

^a Mean age and prevalence of smoking not directly given, statement that variables did not differ between groups.^b Current smokers and ex-smokers.**Table 3.** Prevalence of chronic bronchitis at the time of entry into the studies included in the meta-analysis and the odds ratios (OR) with their 95% confidence intervals (95% CI).

Study	Prevalence of chronic bronchitis ^a (%)		OR	95% CI
	Uncensored	Dropouts		
Zuskin et al, 1991 (20)	19.4	30.8	1.85	0.42–8.11
Zuskin et al, 1991 (20)	8.6	13.5	1.67	0.37–7.57
Christiani et al, 2001 (24)	20.8	23.7	1.19	0.70–2.01
Zuskin et al, 1994 (8)	39.3	100.0	–	..
Zuskin et al, 1994 (8)	26.3	30.0	1.20	0.26–5.56
Zuskin et al, 1997 (21)	10.3	9.5	0.91	0.25–3.34
Zuskin et al, 1997 (21)	20.0	17.2	0.83	0.13–5.17
Zejda et al, 1992 (22)	5.9	9.7	1.73	0.46–6.47
Pham et al, 1986 (25)	23.9	32.5	1.53	1.15–2.04
Musk et al, 1982 (23)	19.4	20.1	1.04	0.82–1.32
Mur et al, 1989 (26)	3.3	5.0	1.55	0.47–5.07

^a At baseline.

for smokers and nonsmokers (21). These groups were considered independently of each other. Table 1 shows a description of the characteristics of these studies, while table 2 presents the characteristics of the subjects under study. The definitions of chronic bronchitis and the instruments used to measure the respiratory symptoms varied across these studies.

For each study, the prevalence of chronic bronchitis at the time of entry and the odds ratios for chronic bronchitis, comparing prevalences of the dropouts to those of the workers who stayed in the cohort, are given in table 3. Figure 1 shows the individual odds ratios for each study and the pooled odds ratio. There was no evidence of heterogeneity in the pooled estimate (chi-square test for homogeneity = 6.25, 9 degrees of freedom). A significantly elevated baseline prevalence of chronic bronchitis was found for the dropouts (pooled OR 1.23, 95% CI 1.04–1.44).

Discussion

The results of this meta-analysis indicate that a survival bias is likely to occur in occupational cohort studies on respiratory health if complete follow-up is not obtained for all workers. Our estimated pooled effect size may be an underestimation, as workers who were symptom-free at baseline may develop symptoms during the follow-up and subsequently quit their job (14). In addition, some persons may already have developed symptoms at an earlier point in time and therefore dropped out of the exposed population before the cohort study was initiated. There may also be a bias towards publishing positive results, although this possibility seems unlikely as the principal objectives of these studies was not related to making comparisons between subjects who left employment and those that did not. Studies with differential losses to follow-up may, however, be less likely to report these differences, especially in nonepidemiologic journals. In addition, these studies are less likely to be published. Therefore, publication bias may lead to an underestimation of the healthy worker survivor effect.

One limitation of our analysis is that we could not control for potential confounding factors such as age, duration of employment, gender, and smoking habits. At the beginning of the studies those who left these cohorts were mostly comparable with respect to these factors with those who stayed (table 2); however, a more-detailed analysis could not be done. In addition, the precise definition of chronic bronchitis was not provided in all the studies, and the questions used to assess chronic bronchitis differed between the studies. Therefore, the assumption of homogeneity with respect to the outcome is not likely to be satisfied. However, as the estimate of relative risk was above unity in most of the studies involving different types of exposures, a wide range of follow-up periods and different age groups, this analysis indicates that the healthy worker survivor effect plays an important role in occupational cohort studies on respiratory health. Moreover, three of the eight studies that had to be excluded from our analyses also gave implications of a higher proportion of symptomatic subjects among those who dropped out of the cohort and thus supported our results (12–14, 27).

In all but two studies (23, 25), all the workers who did not participate in the follow-up survey had left the industry. Nevertheless, in the remaining studies, by Musk et al (23) and Pham et al (25), the dropouts were partly due to nonresponse. In the paper by Musk et al (23) the prevalence of respiratory symptoms was not given stratified for reason of dropout. In contrast, in the study of Pham et al (25), the observed health selection would have been even more pronounced if those who did not respond in the follow-up survey would have been excluded from the analysis.

Figure 1. Odds ratio and 95% confidence intervals for symptoms of chronic bronchitis among workers who were lost to follow-up in comparison to those of workers who stayed in the cohort.

In summary, eight occupational cohort studies were identified that could be used to address the healthy worker survivor effect on chronic bronchitis. The results suggest that workers with symptoms of chronic bronchitis at the start of follow-up have a 23% higher risk of leaving the exposed cohort than persons without such symptoms. This finding, in turn, leads to an underestimation of the risk of disease for exposed workers if the healthy worker survivor effect is not taken into account.

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Appendix

Studies considered for this meta-analysis

	Number of papers
Review articles	6
Case reports	4
Cross-sectional surveys	62
Case-referent studies	7
Retrospective cohort studies	13
Experimental studies	4
Mortality studies	4
Nonoccupational cohorts or population-based studies	16
Studies on respiratory symptoms but not on chronic bronchitis	97
Different paper on the same cohort included	4
Data on baseline prevalence of chronic bronchitis not reported for those lost to follow-up	8
Included	8
Total	233