symptoms of gallbladder disease may affect alcohol consumption.

Such (protopathic) bias is not merely speculative. In a case-control study, 16% of gallstone patients reported that they had reduced their alcohol intake because of symptoms; the negative association between alcohol use and risk of gallstone disease disappeared when protopathic bias was controlled.[2] In a review of studies up to 1990, we showed that a negative association was more often found in studies with symptomatic cases than with asymptomatic cases found by screening.[2] More recent studies[3-10] show the same pattern: the studies with asymptomatic gallstone cases found by screening showed no relation.[7-10]

Still, the evidence for a protective effect seems convincing: the pathobiological mechanisms (via high-density lipoprotein cholesterol, bile lithogenicity, and gallbladder motility) are well documented; and alcohol inhibits experimental gallstone formation in the prairie dog.[11,12] Instead of seeking a more precise (but possibly invalid) quantification of a protective effect, we would suggest two other approaches: first, to study specific etiologic hypotheses suggested by new biopathological insights (for example, does alcohol protect against gallstone disease when used as a *digestif*[13] by subjects with a sluggish gallbladder?); second, to evaluate practical applications that can be studied experimentally in high-risk subjects (for example, does alcohol drinking prevent gallstone recurrence after gallstone dissolution therapy?).

Carel Thijs
Pieter Leffers
Paul Knipschild
Department of Epidemiology,
Rijksuniversiteit Limburg, PO Box 616,
NL-6200 MD Maastricht, The Netherlands
(address correspondence to Carel Thijs)

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The Authors Reply:

We agree with Thijs *et al* that early symptoms of gallbladder disease, even before the diagnosis of gallstones, may modify the pattern of alcohol consumption. We also agree that this change in consumption may cause some (hardly estimable) bias in both case-control and cohort studies, as well as in data from population surveys.[1] We further agree that there are plausible biological mechanisms for the possible protective effect of alcohol on gallstone formation, which draws support from descriptive epidemiologic studies.

As suggested by Thijs *et al*, the issue could be resolved in principle through a randomized trial, possibly centered on high-risk subgroups. Ethical considerations aside, for any such trial, the key issues would be (1) duration of follow-up, and (2) compliance. Even apparently reasonable compliance rates (that is, 60–80%) dramatically reduce the efficacy of prevention trials.[2]

Carlo La Vecchia
Adriano Decarli
Monica Ferraroni
Eva Negri
Istituto di Ricerche Farmacologiche "Mario Negri,"
Via Eritrea 62, 20157 Milan, Italy
(address correspondence to Carlo La Vecchia)
and Istituto di Statistica Medica e Biometria,
University of Milan, Milan, Italy

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Healthy Worker Effect and Cumulative Exposure

To the Editor:

Flanders *et al*[1] argue that time-since-hire should be treated as a positive confounder in analyzing exposure-mortality trends in occupational cohort studies. The argument has appeal because mortality is known to increase with time-since-hire as the healthy worker effect wears off, and it is likely that time-since-hire and cumulative exposure will be positively correlated. The authors illustrate their point using simulated data in which follow-up occurs only during employment. They make two assumptions. First, they assume that cumulative exposure is truly unrelated to mortality, and second, that time-since-hire is positively correlated with mortality.

There are flaws in this argument. In fact, mortality does *not* increase with time-since-hire (or follow-up time) for actively employed workers,[2-4] and the well-known wearing off of the healthy worker effect over time for the cohort as a whole is a function of increasing numbers of workers leaving work, some of whom leave owing to health problems. In Table 1, we illustrate this phenomenon using data from 10 large occupational studies (2 million person-years) in which exposure was

TABLE 1. Rate Ratios from Poisson Regression for Mortality (All Causes), Data from 10 Large Cohort Studies (Combined)

	Duration of Exposure/Employment (Years)					
	<1	1–2	2–5	5–10	10–20	≥20
Basic model*	1.00	0.85	0.82	0.77	0.73	0.69
Basic model + employment status	1.00	0.91	0.93	1.00	1.06	1.07
Basic model + time-since-hire	1.00	0.86	0.83	0.78	0.72	0.65

	Time-since-Hire (Years)		
	<10	10–20	≥20
Basic model*	1.00	1.11	1.30
Basic model, active person-time	1.00	1.05	1.01
Basic model, inactive person-time	3.31	3.08	3.37
Basic model + employment status	1.00	0.95	0.99

* Basic model included categorical variables for age (5-year intervals), race, and calendar time (10-year intervals).

judged to have caused no increase in mortality.[3] In the bottom part of Table 1, note that control over active/inactive employment status eliminates the observed positive trend with time-since-hire.

Table 1 (top part) shows that in our data a strong false-*negative* trend with cumulative exposure occurs, rather than the positive one predicted by Flanders *et al*,[1] absent any control over time-since-hire. This negative trend is due to confounding by employment status—those with low cumulative exposure have left work early and have more inactive person-time, and inactive person-time has approximately two to three times the mortality of active person-time. Controlling for time-since-hire has no effect, but the trend is eliminated with stratification by employment status. A note of caution: it is sometimes inappropriate to control for employment status as a confounder, because it may also be an intermediate variable.[5,6] In practice, we suspect that this is a rare occurrence. In the case that employment status is an intermediate variable, more sophisticated analytic methods than usual regression methods may be required.[6]

We have also modified the simulation performed by Flanders *et al*[1] to include inactive workers, assuming a doubling of the mortality rate during inactive person-time (Table 2; details available from the authors). As in our empirical data, a false-negative trend with cumulative exposure occurs, which is unaffected by controlling for time-since-hire, but eliminated by controlling for employment status.

TABLE 2. Simulated Data According to Flanders *et al*[1] but Including Inactive Person-Time

Model	Poisson Regression Results	
	Coefficient	Standard Error
0) Intercept only		
1) Duration of exposure	−0.024	0.024
2) Time-since-hire	0.049	0.008
3) Time-since-hire	0.061	0.009
Duration of exposure	−0.087	0.024
4) Active/inactive status	−0.693	0.067
5) Active/inactive status	−0.693	0.067
Duration of exposure	0.0	0.020

Aside from problems specific to the Flanders *et al*[1] simulation, there arises the general question of whether one should control for time-since-hire as a confounder, especially when employment status is not controlled. There is certainly no biological basis for considering time-since-hire as a confounder. The relation between time-since-hire and disease is artifactual, owing to its correlation with employment status. Its correlation with cumulative exposure exists simply because it is a measure of time (like age). In practice, the correlation between time-since-hire and cumulative exposure may be quite weak—especially if there are few recent hires in the cohort, if average duration of exposure is short relative to the follow-up period, or if exposure intensity is heterogeneous and incorporated into the measure of cumulative dose. Since the correlation between time-since-hire and cumulative exposure may be weak, even when employment status is uncontrolled, the effect of controlling for time-since-hire may be negligible. This situation seems to be the case in our empirical data. In instances in which time-since-hire is strongly correlated with cumulative exposure, adjustment for time-since-hire as a confounder might be appropriate absent control over employment status. On the other hand, controlling for time-since-hire might cause a reduction in the precision of the estimate of cumulative exposure.

Aside from its role as a potential confounder, it is important to consider potential interactions with time-since-hire (or time-since-first-exposure) for diseases requiring a certain latency. In these cases, time-since-hire may act as an effect modifier, with exposure effects observed only after a sufficient latency and varying in magnitude with time after this minimum period of time.

Kyle Steenland
Jim Deddens
Alberto Salvan
(on leave from LADSEB,
National Research Council, Padua, Italy)

Leslie Stayner
National Institute for Occupational Safety
and Health, 4676 Columbia Parkway,
Cincinnati, OH 45226
(address correspondence to Kyle Steenland)

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The Authors Reply:

Steenland *et al* criticize our contention[1] that time-since-hire can confound effect estimates in occupational studies of cumulative exposures. We note the following:

1. Steenland *et al* do not argue that control for time-since-hire is wrong or unnecessary in general, noting times when "adjustment for time-since-hire as a confounder might be ap-