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Excess Mortality in Smokeless Tobacco Users Not Meaningful

In a recent study, Bolinder et al. reported that Swedish construction workers aged 35 through 54 who use smokeless tobacco have higher mortality from cardiovascular diseases and from all causes than do workers who use no form of tobacco.[1] Excess deaths from all causes (n = 50) in these smokeless tobacco users are only partly attributable to excess cardiovascular disease deaths (n = 23) and other specific causes. In addition, no excess mortality from any cause was seen in older (aged 55 through 64) smokeless tobacco users. The broad spectrum of fatal "effects" and the striking age specificity do not seem explicable to us in biological terms.

There is a reasonable nonbiological explanation for the apparent excess of cardiovascular and all-cause deaths in young smokeless tobacco users: it is that members of the comparison group, nonusers of tobacco, are exceptionally healthy. We used Swedish population distribution[2] and mortality statistics[3] to estimate the number of deaths that would have occurred in smokeless tobacco users and nonusers aged 35 through 54 if they died at the same rate as the general Swedish male population over the same period.

Nonusers have substantially and identically lower risks of death from cardiovascular diseases and from all other causes (Table 1). In addition, young smokeless tobacco users have essentially no increased mortality when compared with the general population. In further support of this, a recent case–control study from Sweden showed no risk for myocardial infarction in daily snuff users aged 35 through 64.[4]

The question is, which is the appropriate control group for smokeless tobacco users, construction workers who are nonusers of tobacco or the general population? In favor of the first group is the fact that in some respects they are similar to the smokeless tobacco users. However, the nonusers are selected for a major determinant of health, non-smoking. They are thus a health-conscious group that probably practices many health-maintaining behaviors. We suggest that the unselected general population is the appropriate comparison group for smokeless tobacco users. From that perspective smokeless tobacco users have no meaningful excess mortality. □

Brad Rodu, DDS
Philip Cole, MD, DrPH

Brad Rodu is with the Department of Oral Pathology, School of Dentistry, and Philip Cole is with the Department of Epidemiology, School of Public Health, University of Alabama at Birmingham.

Requests for reprints should be sent to Brad Rodu, DDS, SDB 81, University of Alabama at Birmingham, Birmingham, AL 35294-0007.

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TABLE 1—Mortality in Swedish Construction Workers Aged 35 through 54

	Cardiovascular			All Other Causes			All Causes		
	O	E	SMR	O	E	SMR	O	E	SMR
Nonusers	154	315	49	256	520	49	410	835	49
ST users	44	38	116	61	63	97	105	101	104

Note. O = deaths observed by Bolinder et al.; E = deaths expected from general population rates; SMR = standardized mortality ratio; ST = smokeless tobacco.

Bolinder and Alfredsson Respond

When you are performing etiological research to quantitate the relationship between exposure and disease, according to scientific standards you have to study the relationship within a defined study base. After defining the base and assessing the exposure status of the study subjects, you compare the exposed subjects with the unexposed subjects concerning disease outcome. The ideal comparison group should resemble the exposed group in all respects except for the exposure. The validity of the study depends on potential bias due to selection, misclassification of exposure and disease, and/or confounding.

In our study we defined the study base as a group of construction workers examined between 1971 and 1974 and followed for deaths until 1985. Having classified the study population with regard to exposure, we compared the smokeless tobacco users with subjects who had never used tobacco with regard to cardiovascular mortality. In the analysis, adjustments were made for potential confounding factors such as age, residence, body mass index, blood pressure, and previous heart disease. We have discussed and evaluated the possible bias due to selection and misclassification.

Rodu and Cole suggest that a more appropriate group to compare with the smokeless tobacco users would be the general population in Sweden. We find it hard to see a valid argument for this suggestion. From studies within the realm of occupational medicine, it is well known that employed subjects have better health status than the general population, which incorporates healthy as well as unhealthy subjects ("the healthy worker effect"). It is evident that there is a health-related selection in and out of construction work, as illustrated by Rodu and Cole's table.

An important question is whether these selection mechanisms apply equally

to exposed and unexposed construction workers. As discussed in our paper, we suggest that any differences regarding selection mechanisms would probably tend to bias the observed relative risk toward the null value. The reason is that, if there is a cardiovascular effect due to smokeless tobacco use, surviving smokeless tobacco users in the occupational group are likely to be more highly selected for physical fitness than the group of nonusers. This would introduce negative confounding into the study.

On the other hand, the comparisons preferred by Rodu and Cole would suggest that construction work protects against heart disease in nonusers. The question then arises, why is this protective effect not observed among smokeless tobacco users? Might that be an effect of the smokeless tobacco use? □

Gunilla Bolinder, MD
Lars Alfredsson, PhD

Gunilla Bolinder is with the Department of Medicine, Karolinska Hospital, and Lars Alfredsson is with the Department of Epidemiology, Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden.

Requests for reprints should be sent to Gunilla Bolinder, MD, Department of Medicine, Karolinska Hospital, S-171 76 Stockholm, Sweden.

TABLE 1—Selected Characteristics of the Cohort of Out-of-Treatment Injection Drug Users, by Survival Status, Portland, Ore, 1989 through 1991

Characteristic	No. Dead at End of Study	No. Alive at End of Study	Relative Risk	*P*
Age				
>34 y	26	813	4.1	<.001
≤34 y	7	923		
Sex				
Male	27	1270[a]	1.6	.27
Female	6	465		
Race				
Other	16	616	1.7	.12
White	17	1120		
Birthplace				
Oregon	17	587	2.1	.03
Other	16	1149		
Type of major drug used in previous 6 m[b]				
Heroin	14	663	2.2	.07
Other	8	827		
Years of drug use				
>18	28	841	5.8	<.001
≤18	5	895		
Years of injection drug use				
>12	22	843	2.1	<.05
≤12	11	893		
Ever in drug treatment				
Yes	24	973	2.1	.06
No	9	763		
Total	33	1736		

[a]Sex was unknown for one person.
[b]Missing data (question was added during the course of the study).

Mortality among Injection Drug Users Identified as "Out of Treatment"

A number of studies have reported increased mortality among injection drug users enrolled in treatment programs,[1-5] but less is known about the survival of injection drug users not in treatment. Because most injection drug users are not in treatment,[6] such information is important for targeting programs designed to reduce mortality among injection drug users.

Between April 1989 and March 1991, injection drug users who were not currently (i.e., in the past 30 days) enrolled in any treatment program were recruited through outreach workers and public clinics in Portland, Ore. The 1769 participants were interviewed about their demographic characteristics, housing, criminal history, sexual behavior, and drug use and treatment. In 1992, to determine whether any participants had subsequently died, their names, aliases, and demographics were matched with death certificate information for persons who had died in Oregon or were reported to have died out of state between April 1989 and December 1991. The death rate per 100 000 person-years of follow-up was compared with the death rate per 100 000 for the 1990 Oregon population, adjusted to the age distribution of the study population.

The median age of participants was 34 years (range: 15 to 74 years); 1297 (73%) were male, 1137 (64%) were White, and 489 (28%) were Black. The median duration of injection drug use was 12 years (range: <1 to 53 years). Participants were followed for a total of 3149 person-years, until either death or the end of the study.

Thirty-three participants were matched with death certificates, resulting in a crude death rate of 1048 per 100 000 person-years. Compared with the Oregon population, the age-adjusted relative risk for death was 8.3; this risk increased with age. Among participants, major causes of death included narcotic overdose (13 [39%]), trauma (5 [15%]), infection (4 [12%]), and intracranial hemorrhage (4 [12%]). Three death certificates mentioned liver cirrhosis, and none mentioned human immunodeficiency virus (HIV) infection. Participants who died were significantly older, had used drugs for longer periods, and were less likely to have been born out of state than other participants (Table 1).

This excess mortality among Portland injection drug users identified as "out of treatment" is similar to that reported among injection drug users enrolled in drug-treatment programs elsewhere in the United States[3,4,7]; in Rome, Italy[5]; and in Britain.[2] The major causes of death in our study also correspond to those described among injection drug users enrolled in treatment programs,[1,4,5] although other US studies have identified HIV as a prominent cause of death.[6,8,9] The lack of HIV-related deaths in our study reflects the relatively low prevalence of HIV infection among injection drug users in Oregon.[10]

Detecting factors predictive of premature death in this cohort is difficult