



## Styrene Exposure and Ischemic Heart Disease: A Case-Cohort Study

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Epidemiologic studies have consistently reported increased daily mortality and hospital admissions for ischemic heart disease related to daily changes in ambient particulate levels. One theory is that substances adhering to particulates might have a cardiovascular effect. Styrene has been found in very low doses in air and has chemical characteristics that would cause adherence to particles. Industrial studies have found an increase in cardiovascular disease among styrene-exposed workers. To explore a possible dose-response relation between styrene exposure and ischemic heart disease, the authors of this case-cohort study included 498 cases that died from ischemic heart disease and a 15% random sample ( $n = 997$ ) of all male workers who were employed during 1943–1984 in two styrene-butadiene rubber-manufacturing plants in the United States. Proportional hazards models showed that recent styrene exposure was significantly associated with acute ischemic heart disease death among active workers. The relative hazard of death from acute ischemic heart disease for exposure during the most recent 2 years among active workers with 2 or more years of employment was 2.95 (95% confidence interval: 1.02, 8.57) at a time-weighted styrene concentration of 0.2–<0.3 ppm and 4.30 (95% confidence interval: 1.56, 11.84) at  $\geq 0.3$  ppm for the same exposure period, respectively.

air pollution; cohort studies; heart diseases; occupational exposure; styrene

Abbreviations: CI, confidence interval; ICD-8, *International Classification of Diseases*, Eighth Revision.

Recent epidemiologic studies have consistently reported increased daily mortality and hospital admissions associated with exposure to particulate air pollution. Ischemic heart disease (*International Classification of Diseases*, Eighth Revision (ICD-8), codes 410–414) has contributed in large measure to this excess mortality (1–7). Despite these observations, it is difficult to see biologically how dust could cause such an immediate effect. However, it may be that some substances appearing with or adhering to particulates could cause acute cardiovascular effects.

Several occupational epidemiologic studies have found that exposure to styrene is probably associated with an increased risk of ischemic heart disease, especially among short-term workers (8, 9), suggesting that styrene might have some acute effects on the human cardiovascular system.

Styrene is widespread in ambient air in most industrialized countries. In addition to industrial sources, styrene is also present in the exhaust gases of various engines, smoke of fossil fuel combustion, and other sources (10–13). The range of instantaneous styrene concentrations varies widely by time and location with possible extreme peak values. Under

special circumstances, styrene concentrations have been reported at levels of 2,934  $\mu\text{g}/\text{m}^3$  in ambient air in communities near some industrial sources (14). In the Total Exposure Assessment Methodology (TEAM) Study conducted for the US Environmental Protection Agency, mean ambient air concentrations of styrene at various locations and times differed by 10-fold, ranging from 0.40 to 3.80  $\mu\text{g}/\text{m}^3$  (0.09–0.89 ppb) (15–17). However, these measured mean concentrations of ambient styrene could understate exposure for the following reasons. 1) Only the vaporous part is measured, and styrene in aerosol form or adhered to suspended particulates is not considered since air samples for styrene usually use charcoal tube collection or passive dosimeters. One experimental study (18) showed that aerosol represented 26–33 percent of the total air concentration of styrene and that 96 percent of the total generated aerosols represented particles that were of respirable size ( $\leq 1 \mu\text{m}$ ). 2) It was also found that styrene aerosols could undergo physical and chemical changes, such as vaporization and/or polymerization. If vaporization occurs after inhalation, the result would be a highly concentrated vaporous dose to the respiratory system.

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3) Styrene is a highly volatile hydrocarbon, which is rapidly transformed in the atmosphere through a reaction with hydroxyl radicals. The half-life for styrene in the atmosphere is 7.3 hours. Thus, styrene is not expected to undergo extensive transportation, suggesting that styrene measured at scattered air-monitoring stations might not represent the high concentrations in restricted areas near styrene-emitting sources (13).

Styrene is highly lipophilic. Inhaled styrene is almost completely absorbed, rapidly dispersed through the body, and subsequently degraded through oxidation of the side chain to soluble metabolites for final excretion. The metabolism of styrene has been well documented (13, 19, 20).

An occupational cohort that has complete job histories and measured levels of styrene would be an excellent resource to determine whether the known exposures to styrene are directly responsible for ischemic heart disease deaths. This would be the first step in establishing a clear association between styrene and ischemic heart disease, which, in turn, may lead to a better understanding of the association between air pollution and ischemic heart disease mortality.

## MATERIALS AND METHODS

### Target cohort population

Eight styrene-butadiene polymer-manufacturing plants have been studied previously to evaluate the health of workers in the rubber industry (21–23). Among the plants from the original studies, two plants, plants 6 and 7, fit the following criteria for inclusion in the current study. They had opened at the inception of the industry in 1943, they had collected styrene and butadiene measurement data, they had relatively large populations, and their records included a complete job history for each worker. All 6,587 male workers, 2,793 in plant 6 and 3,794 in plant 7, employed at any time between 1943 and 1982 were the target cohort population. Females (11.28 percent of the total of 7,453 workers) who had been excluded in previous studies were also excluded in this study because their job histories had not been abstracted. Subjects with unknown sex (0.34 percent) or subjects missing critical date variables (0.29 percent), such as birth date and hire date, were excluded.

### Case definition

The vital status of each male worker between 1943 and 1982 was determined through the death notification system and vital status records of the Social Security Administration and the National Death Index, as well as through follow-up by local plant beneficiary records and motor vehicle administration records. Direct follow-up was conducted for individuals with unknown vital status. All deaths collected during the follow-up period were coded according to ICD-8. Ischemic heart disease cases were defined as those deaths with ICD-8 codes 410–414, including acute myocardial infarction (ICD-8 code 410), other acute and subacute forms of ischemic heart disease (ICD-8 code 411), chronic ischemic heart disease (ICD-8 code 412), angina pectoris (ICD-8 code 413), and asymptomatic ischemic heart disease

(ICD-8 code 414), as either an underlying cause or a contributory cause of death. No case in the target population was recorded as having died from angina pectoris or asymptomatic ischemic heart disease during the follow-up period. In this study, we classified ICD-8 codes 410 and 411 as acute ischemic heart disease and ICD-8 code 412 as chronic ischemic heart disease.

### Case-cohort design

A case-cohort study design (24–26) was used to explore the relation between styrene exposure and ischemic heart disease. The cases included 499 males who died from ischemic heart disease between 1943 and 1982 and a 15 percent random sample of all 6,587 male workers who were ever employed in the same period, representing 997 in the subcohort of the case-cohort study. One case with missing critical dates was excluded. Among 498 cases, 71 were also part of the subcohort. These cases were included as references in the comparison subcohort until the time of death, at which point they were included as cases. The follow-up for each individual began at the time of first hire and ended at the subject's death or at the termination of the study, December 31, 1982.

### Exposure assessment

A job dictionary, which contained 579 unique jobs, was developed for this industry in previous studies (21–23). Each of these 579 jobs was assigned a unique job code, representing a combination of a code for subdivision, work area, subarea, and job title for that particular job. All jobs were reviewed and ranked from 0 to 10 for both styrene and butadiene by a group of expert industrial hygienists and engineers from the industry as well as academia. A detailed job history for each subject was abstracted and coded based on the job dictionary.

Measurement data for styrene and butadiene were collected for many of the jobs from different sources. For any job where there were no measurements, the *z*-score method (27) was used to estimate the exposures. This method assumed that the relative exposure of a job was similar across the industry because tasks associated with the job were similar, but individual plants might have had overall differences in the actual levels of the chemicals. The estimations used the actual measurement values from all other available sources as well as expert rank scores to get the relative exposure by job using the *z*-score method. A proportion represented by the difference between an observed value and the mean of all observed values over the standard deviation is often referred to as a *z* score. A *z* score can be obtained by subtracting the observed value from the mean of all observed values and dividing by the standard deviation. The *z*-score transformation converts data from different sources with different magnitudes, ranges, and units, such as measurement data or industrial hygienist rank scores, into a unitless standard distribution with a constant mean of 0 and a standard deviation of 1. The exposure *z* score of a job shows the relative position of the exposure level for that job among all the jobs in a plant. The *z* score

**TABLE 1. Numbers of cases and noncases in separate analytical models of two rubber plants, United States, 1943–1982\***

Job status at IHD† death	IHD	Ever employed‡		Employed for ≥2 years‡		Employed for ≥5 years‡	
		Cases	Noncases	Cases	Noncases	Cases	Noncases
Active workers	Acute	40	571	36	409	36	325
	Chronic	23	573	23	410	22	326
Left job ≤10 years ago	Acute	61	769	44	244	32	129
	Chronic	38	774	32	246	29	129
Left job >10 years ago	Acute	203	590	53	158	24	67
	Chronic	133	600	36	159	21	67

\* Analyses of cumulative exposure were conducted for active workers and for workers who left the plant. Analyses of intensity exposure for recent years were conducted only for active workers.

† IHD, ischemic heart disease.

‡ Employment duration categories are not exclusive of one another.

can be transferred back to a measurement value given the mean and standard deviation of the underlying measurement distribution among jobs of the plant, by multiplying the  $z$  score by the standard deviation and adding the mean. The available measurements for other jobs in the specific plant were used to determine the measurement distribution parameters. With this method, the unique missing job exposures for a specific plant then could be estimated using the relative value of the job,  $z$  score, and the measurement distribution parameters of the chemical concentrations among jobs in the plant.

The majority of measurements were from the recent past, representing the period from 1976 and forward. We developed a method to take into consideration the change over time, based on a reported decreasing trend of styrene and butadiene in the industry over time from a study that included these two plants (28). A personal exposure matrix was established by matching the detailed job history with styrene and butadiene exposure concentrations by job code, calendar period, and plant.

## Analysis

A Cox proportional hazards model was used for risk analyses with the variance correction based on the published literature using SAS PHREG software (29–32). Age represented the time measure in all the models, so that age became a matching variable when creating risk sets. An adjustment for birth year was included in all models to reduce the influence of secular changes over calendar years. All models were also adjusted for race. Analyses were stratified by plant, because the plant could relate to different control methods and procedures used for chemical measurement, which would bias the result.

Models were fit independently for acute and chronic ischemic heart disease on active workers, workers who left their plants within 10 years, and workers who left their plants more than 10 years previously. To examine the effect of duration of employment, we included all workers and then those with 2 or more and those with 5 or more years of employment. These three employment duration groups were

inclusive of each other. Table 1 shows the numbers of cases and noncases in these separate analytical models.

All styrene and butadiene exposure variables used in risk analyses were time dependent, which meant that the values of the exposure variables changed over time and were calculated at each time point in which an event (ischemic heart disease death) took place. There were two types of time-dependent exposure variables used in the study. The first variable was the cumulative exposure variable, which was a time-dependent variable in parts per million (ppm)-year that accumulated the products of exposure levels in parts per million multiplied by exposure duration in a year for each job held from a defined starting time point to the time of event. This indicator was designed to assess the risk of long-term cumulative exposure. The second variable was the time-weighted average, which was a time-dependent continuous intensity variable calculating the average exposure intensity in parts per million weighted by the exposure time during the time window specified. This indicator was designed to represent instant exposure levels to assess acute effects. For this intensity indicator, it was important to choose an appropriate exposure time window. It was considered that exposure intensity in the most recent period would be a better indicator for assessment of acute risk than intensity for the entire employment period. However, two problems could occur when trying to relate acute heart disease episodes to exposure based on the time of death. The first problem would be that ischemic heart disease onset might occur 1 year or more before death, and the second problem would be that workers could have changed their jobs to cleaner areas after adverse symptoms associated with ischemic heart disease occurred. On the basis of these concerns we believed that the time windows of the most recent 2 years would be reasonable for intensity indicators. Exposure intensities for the most recent 3–5 years were also used as exposure variables in the analysis as a comparison. The risk analysis for the most recent exposure intensity was not done on workers who left the plant, since their most recent exposures were none or unknown. Categorical analysis was used to examine the shape of the possible dose-response relation between styrene exposure and ischemic

**TABLE 2. Risk of ischemic heart disease from cumulative styrene exposure among active workers in two rubber plants, United States, 1943–1982\***

Model	Disease	Styrene exposure variable†	Employed for >0 years		Employed for ≥2 years		Employed for ≥5 years	
			RH‡	95% CI‡	RH	95% CI	RH	95% CI
1	Acute IHD‡	Cumulative ppm-years	1.04	1.00, 1.08	1.04	1.00, 1.09	1.04	1.00, 1.08
2	Acute IHD	Cumulative ppm-years	1.07	1.02, 1.13	1.08	1.02, 1.14	1.07	1.02, 1.13
3	Chronic IHD	Cumulative ppm-years	0.99	0.94, 1.05	0.99	0.93, 1.05	0.99	0.93, 1.05
4	Chronic IHD	Cumulative ppm-years	0.98	0.90, 1.07	0.98	0.90, 1.07	0.98	0.90, 1.07

\* Using age as the timescale, stratified by plant, controlled for race and birth year. Adjustment is made for butadiene in models 2 and 4.

† Time-dependent, cumulative ppm-years prior to the time of event.

‡ RH, relative hazard; CI, confidence interval; IHD, ischemic heart disease.

heart disease deaths for those models with significance in analysis using continuous exposure variables.

Based on the case-cohort design, data were prepared so that cases occurring within the subcohort were coded as “1,” and these cases were considered as noncases and put into the reference group until the last day when they became cases; cases occurring outside the subcohort were coded as “2,” and these cases never served as comparisons with cases but only served as cases on the day they died; and noncase subcohort members were coded as “0,” and they were always in the reference group.

To present the results of each proportional hazards model, we always listed the estimates and confidence intervals for styrene regardless of whether or not they were significant. Other variables were listed only when they were significantly associated with ischemic heart disease.

### Survey on smoking

Smoking could be a potential confounding factor because of its well-known association with ischemic heart disease. However, to be a confounder smoking also would have to be associated with exposure. In the previous eight-plant studies, a survey was conducted for quality control of vital status information on study subjects. The survey included questions on smoking habits. A total of 900 people were randomly selected for follow-up by direct telephone contact (21–23). Of these, 811 people were contacted and agreed to answer the questions. However, only 424 questionnaires were returned. The smoking information, which was collected, was analyzed to estimate variation in smoking histories by job.

## RESULTS

### Risk of ischemic heart disease from cumulative styrene exposures

*Among active workers.* Cumulative time-dependent ppm-years were used in examining the chronic effects of exposure to styrene among active workers with different employment durations. No significant associations between butadiene and acute or chronic ischemic heart disease were found in any models. However, inclusion or exclusion of butadiene in

the models influenced the estimates of styrene. Table 2 shows that, when adjusted for butadiene (models 2 and 4), the cumulative styrene exposures were significantly associated with acute ischemic heart disease in all analyses when both styrene and butadiene were included in the models for acute ischemic heart disease. When butadiene was excluded from the models (models 1 and 3), the cumulative exposures to styrene were found to be significantly associated with acute ischemic heart disease only in one group (workers employed for at least 2 years), suggesting that the association of cumulative styrene exposures with acute ischemic heart disease was of borderline significance in general. No association was found with the cumulative styrene and butadiene exposures and chronic ischemic heart disease. Race was not a significant variable in any of the models.

*Among workers who left the plant.* Using the same analytical models, we examined the risks of acute and chronic ischemic heart disease among workers who left the plants 10 years or less and more than 10 years ago, respectively. Styrene and butadiene showed no association with either acute or chronic ischemic heart disease in any of the models (data not shown). However, chronic ischemic heart disease was significantly associated with the non-White race only among workers who left the plants, with relative hazards ranging from 2.24 to 4.37. The race-chronic ischemic heart disease association seemed independent of the association with styrene and ischemic heart disease.

### Risk of ischemic heart disease in active workers from recent styrene exposure based on continuous intensity measures

Race and birth year were not significant in these models and were not listed in table 3. Butadiene showed no association with acute or chronic ischemic heart disease in any of the models. Styrene was not associated with chronic ischemic heart disease in any of the models. However, the time-weighted average styrene intensity for the most recent 2 years had significant relative hazards of acute ischemic heart disease ranging from 3.26 to 6.60 per ppm increase for the three employment duration categories. For workers employed at least 2 years, the relative hazard was 5.86 (95 percent confidence interval (CI): 1.59, 21.64) per ppm.

**TABLE 3. Risk of ischemic heart disease from recent styrene exposure intensity among active workers in two rubber plants, United States, 1943–1982\***

Model	Disease	Styrene exposure variable (ppm)†	Employed for >0 years		Employed for ≥2 years		Employed for ≥5 years	
			RH‡	95% CI‡	RH	95% CI	RH	95% CI
1	Acute IHD‡	For recent 2 years	3.26	1.09, 9.72	5.86	1.59, 21.64	6.60	1.78, 24.54
		For 2–5 years ago	0.94	0.85, 1.04	0.92	0.82, 1.03	0.90	0.79, 1.01
2	Acute IHD	For recent 2 years	2.34	0.72, 7.57	4.99	1.07, 23.34	4.27	0.84, 21.79
		For 2–5 years ago	0.98	0.87, 1.11	0.95	0.82, 1.09	0.94	0.81, 1.10
3	Chronic IHD	For recent 2 years	1.22	0.08, 18.13	1.45	0.09, 23.93	1.52	0.09, 24.65
		For 2–5 years ago	0.96	0.76, 1.22	0.93	0.72, 1.20	0.93	0.72, 1.20
4	Chronic IHD	For recent 2 years	1.92	0.08, 46.74	2.13	0.07, 62.97	2.18	0.07, 68.27
		For 2–5 years ago	0.89	0.66, 0.70	0.88	0.64, 1.19	0.88	0.65, 1.20

\* Using age as timescale, stratified by plant, controlled for race and birth year. Adjustment is made for butadiene in models 2 and 4.

† Time-dependent, time-weighted average intensity prior to the time of event.

‡ RH, relative hazard; CI, confidence interval; IHD, ischemic heart disease.

### Risk of ischemic heart disease in active workers from recent styrene exposure based on categorical intensity measures

Table 4 shows the results of the categorical analysis for the risks of acute ischemic heart disease at different time-weighted average styrene intensities for the most recent 2 years among active workers for the three employment duration categories. All three employment duration categories show a dose-response relation between styrene intensity for the most recent 2 years and the risk of acute ischemic heart disease. For all active workers, the time-weighted average styrene intensity at 0.30 ppm and above for the most recent 2 years had significant relative hazards for acute ischemic heart disease of 3.10 (95 percent CI: 1.25, 7.67) but no significant risk at less than 0.30 ppm. The relative hazards of acute ischemic heart disease death for exposure during the most recent 2 years among active workers with 2 or more years of employment were 2.95 (95 percent CI: 1.02, 8.57) at a time-weighted styrene concentration from 0.20 to less than 0.30 ppm and 4.30 (95 percent CI: 1.57, 11.84) at 0.30 ppm or above for the same exposure period, respectively. The result for workers who were employed 5 or more years is similar to that for workers who were employed 2 or more years (table 4).

### Smoking data

A total of 424 interviewees were examined for smoking history in relation to the last job held. Table 5 shows the distribution of smoking among the 424 subjects interviewed by subdivision sorted by average styrene concentration levels. The percentage of those never smoking was not correlated with styrene, with a very low correlation coefficient of 0.11 ( $p = 0.41$ ) with styrene. The direction of the correlation by amount smoked differed, with a positive correlation among light smokers (1–9 and 10–19 cigarettes/day) and a negative correlation among heavy smokers (20 or more cigarettes/day). None of the correlations was significant. The data suggest that smoking could not explain or confound the association found between styrene exposure and acute ischemic heart disease death in this study, since smoking was not associated with styrene exposure.

## DISCUSSION

### Study results and previous studies

In previous studies, an interesting phenomenon that occurred was that the risk of ischemic heart disease in workers was associated with short employment periods. A significantly elevated standardized mortality ratio for ischemic heart disease of 1.34 (95 percent CI: 1.04, 1.71)

**TABLE 4. Risk of acute ischemic heart disease at different styrene exposure intensities for the most recent 2 years among active workers in two rubber plants, United States, 1943–1982**

Time-weighted styrene intensity (ppm) for the most recent 2 years	Employed for >0 years		Employed for ≥2 years		Employed for ≥5 years	
	RH*	95% CI*	RH	95% CI	RH	95% CI
<0.10	1.00		1.00		1.00	
0.10–<0.20	0.94	0.29, 3.04	1.24	0.36, 4.33	1.25	0.36, 1.35
0.20–<0.30	2.14	0.80, 5.72	2.95	1.02, 8.57	3.00	1.03, 8.73
≥0.30	3.10	1.25, 7.67	4.30	1.56, 11.84	4.24	1.54, 11.68

\* RH, relative hazard, using age as timescale, stratified by plant, controlled for race and birth year; CI, confidence interval.

**TABLE 5. Smoking distribution among 424 subjects with different styrene levels interviewed by subdivision of two rubber plants, United States, 1943–1982**

Subdivision	Average styrene (ppm)	Cigarette smoking status (%)			
		Never	1–9 cigarettes/day	10–19 cigarettes/day	≥20 cigarettes/day
Warehouse	0.05	34.62	3.85	11.54	50.00
Utilities	0.11	39.39	12.12	9.09	39.39
Administration	0.11	37.78	6.67	13.33	42.22
Services	0.14	21.43	3.97	16.67	57.94
Laboratory	0.21	33.33	11.11	11.11	44.44
Maintenance	0.24	31.58	6.58	12.50	49.34
Production	0.27	41.67	16.67	16.67	25.00
Correlation coefficient ( <i>r</i> )		0.11	0.61	0.37	–0.45
<i>p</i> value		0.41	0.08	0.20	0.16

compared with that of the general US population was found among employees with exposure to styrene and ethylbenzene at time-weighted average concentrations of 5 ppm (21.30 mg/m<sup>3</sup>) or higher in a cohort study. The risk was concentrated primarily among persons with short to moderate (<4 years) duration of exposure (8). The same phenomenon occurred in another occupational study of a cohort of 15,826 workers exposed to styrene and other chemicals in the reinforced plastics and composites industry (9). Standardized mortality ratios decreased with increases in duration of employment. The authors reported standardized mortality ratios for ischemic heart disease among workers with employment durations of <1 year, 1–1.9 years, 2–4.9 years, 5–9.9 years, and ≥10 years as 129.40, 113.80, 108.70, 85.80, and 85.60, respectively. These studies did not separate acute from chronic ischemic heart disease, they provided no information about whether the deaths occurred in active workers or if workers had left the plants many years before death, and they did not explain the phenomenon of inverse risk with duration of employment. Based on the results of this study, however, styrene influenced not only the short-term workers but also the long-term workers. The risk of death from acute ischemic heart disease was actually higher among active workers who were employed 2 or more years (long term) than among all active workers, which included workers who were employed less than 2 years at the same styrene intensity levels (tables 3 and 4). Our explanations for the phenomenon are as follows. 1) Only those who could survive acute heart events in the early years of exposure to styrene would continue to work for a long period. In other words, those individuals with existing compromised blood flow from arteriosclerosis would either die from acute ischemic heart disease, cutting their employment short, or leave the plant because of increased symptoms during the early periods of employment, again resulting in short work histories. 2) Appropriate study designs and methods of analysis are necessary to reveal the risk by employment duration, such as conducting separate analyses on active workers and

on workers who left the plants and conducting analyses in a time-dependent manner.

### Strengths and limitations

There are some particular strengths of this study. 1) This study developed methods to estimate concentrations for unmeasured jobs and to adjust for secular changes in the concentrations. The method enabled us to perform a measurement-based analysis to indicate a dose-response relation between styrene and acute ischemic heart disease. 2) The case-cohort design was used in this study so that the same types of analysis that were possible in a full cohort study would be possible in this case-cohort study. It allowed us to perform the analysis in a time-dependent manner that was very important, especially when follow-up was long and the outcome was an acute event. Comparisons of up-to-date exposures were made at each time point whenever a new case occurred during the 40 years' follow-up. Because the reference group was a random sample of the target population, one could also conduct analyses for different case groups, such as acute or chronic ischemic heart disease, using the same subcohort for comparison. We didn't use a nested case-control study design, because the design was not optimal in dealing with a time-dependent covariate and a long follow-up period of 40 years. 3) The dose-response relation was examined from data on active workers. Analysis of active workers avoided the difficulties of linking a death in later years to a job decades earlier when the outcome was an acute event and of obtaining exposure information for workers after they had left the plants. 4) Analyses of both continuous and categorical exposure indicators supported a positive dose response between recent styrene intensity and death from acute ischemic heart disease, which could not be explained by other factors.

However, there were also some limitations to this study. 1) Ischemic heart disease deaths rather than incident cases were used. We did not know the real onset time of incident ischemic heart disease for each death from this disease. The

exposure status of workers might be changed after the onset of incident ischemic heart disease and before the ischemic heart disease death. Because of the concern of possible exposure misclassification, we did not use the last job as an exposure variable. Intensity exposure for the most recent 2 years was used to try to reduce the possible impact from changing exposure status after diagnosis of incident ischemic heart disease. Using death rather than incident cases would create another problem, which was the competing risk from another cause of death. To deal with this problem, we considered both the underlying and contributory causes of death for the eligible cases in this study. 2) Potential confounders in this study might be smoking, diet, blood pressure, physical activities, and other coexisting chemicals. As mentioned above, to be a confounder, the factor should be associated with both styrene exposure and ischemic heart disease death. Since smoking was not associated with styrene exposures, the association observed in the present study between styrene exposure and acute ischemic heart disease is not likely to be explained by smoking. However, the smoking survey had very low participation, and the subjects might not be representative of the entire cohort, especially when only living workers could be interviewed. Intuitively, there is no reason to believe that diet, blood pressure, or physical activities were associated with styrene exposure. Butadiene was the major coexisting chemical in the synthetic rubber-manufacturing industry. This chemical was related to styrene exposure but not to ischemic heart disease. Other exposures to styrene could have occurred, but these exposures would be very low compared with the occupational sources and should not have differed by job in the industry.

### Implications for ambient styrene exposures

Might a substance like styrene, which was present in very small quantities in urban air on a normal day but could reach higher levels in special circumstances, explain the sudden increase in deaths from acute ischemic heart disease? This study took advantage of an occupational cohort where exposures were high to address this question. This study is important because the data suggest that a chemical found in air and in industrial settings can be associated with an increased risk of heart disease. The risk appears to result in acute events at relatively low industrial exposures. The fact that this chemical is also one that can be adsorbed onto particles provides a possible mechanism to explain why particulates might be related to ischemic heart disease mortality. There may be some other chemicals in the outdoor and indoor environments that may play a role similar to that of styrene and that may contribute to increased ischemic heart disease deaths. This area needs to be investigated.

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