Lifetime cumulative exposure to rubber dust, fumes and N-nitrosamines and non-cancer mortality: a 49-year follow-up of UK rubber factory workers

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ABSTRACT

Objectives To examine associations between occupational exposures to rubber dust, rubber fumes and N-nitrosamines and non-cancer mortality.

Methods A cohort of 36 441 males aged 35+ years employed in British rubber factories was followed-up to 2015 (94% deceased). Competing risk survival analysis was used to assess risks of dying from non-cancer diseases (respiratory, urinary, cerebrovascular, circulatory and digestive diseases). Occupational exposures to rubber dust, rubber fumes, N-nitrosamines were derived based on a population-specific quantitative job-exposure matrix which in-turn was based on measurements in the EU-EXASRUB database.

Results Exposure–response associations of increased risk with increasing exposure were found for N-nitrosomorpholine with mortality from circulatory diseases (subdistribution hazard ratio (SHR) 1.17; 95% CI 1.12 to 1.23), ischaemic heart disease (IHD) (SHR 1.19; 95% CI 1.13 to 1.26), cerebrovascular disease (SHR 1.19; 95% CI 1.07 to 1.32) and exposures to N-nitrosodimethylamine with respiratory disease mortality (SHR 1.41; 95% CI 1.30 to 1.53). Increased risks for mortality from circulatory disease, IHD and digestive diseases were found with higher levels of exposures to rubber dust, rubber fumes and N-nitrosamines sum, without an exposure-dependent manner. No associations were observed between rubber dust, rubber fumes and N-nitrosamines exposures with mortality from asthma, urinary disease, bronchitis, emphysema, liver disease and some digestive diseases.

Conclusions In a cohort of rubber factory workers with 49 years of follow-up, increased risk for mortality from circulatory, cerebrovascular, respiratory and digestive diseases were found to be associated with cumulative occupational exposures to specific agents.

INTRODUCTION

Occupational exposures in the rubber industry have been linked to increased risks of cancer incidence and mortality, as well as some non-cancer outcomes; particularly respiratory diseases.^{1–7} Analyses of the same British rubber factory workers cohort that the current study is based on documented higher standardised mortality ratios (SMRs) from cancer and non-cancer causes of deaths compared with the general population.³ Further internal analyses of the same cohort observed exposure–response associations between occupational exposures to agents

Key messages

What is already known about this subject?

- Occupational exposures in the rubber industry have been linked to various cancers and non-cancer chronic diseases, including respiratory disease.

What are the new findings?

- Using one of the longest follow-ups of a rubber factory cohort, this study updates assessments of exposure–response associations between occupational exposures and lifetime non-cancer mortality.
- Exposure–response associations of increased risk with increasing exposure were found for exposures to N-nitrosodimethylamine with respiratory disease mortality and N-nitrosomorpholine with cerebrovascular disease mortality.
- Occupational exposures in the rubber industry were not associated with mortality from urinary diseases, liver disease or certain digestive and respiratory diseases.

How might this impact on policy or clinical practice in the foreseeable future?

- This study clarifies that occupational exposures in the rubber industry extend beyond premature mortality risks from cancers to other diseases, and this may have implications for current health and safety practices in the industry in the UK and worldwide.

such as rubber dust, rubber fumes and nitrosamines with cancer mortality. However, these studies did not examine associations between occupational exposures and non-cancer mortality.⁸ The evidence of whether specific exposures encountered in the rubber industry could be associated with higher premature mortality risks from non-cancer diseases is equivocal. Some studies,^{3 9 10} but not all,^{11 12} have found increased mortality from circulatory disease, cerebrovascular disease and respiratory diseases compared with the overall population, as well as within rubber factory worker cohorts; particularly in compounding, milling and vulcanising departments. Studies where no associations were observed^{11 12} had smaller samples and shorter

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follow-ups. A systematic review of non-malignant respiratory disease among rubber factory workers found supporting evidence for higher respiratory-related morbidities, but inconsistent evidence for mortality from non-malignant respiratory disease.¹³

Within the rubber production process, workers perform specific work tasks that are organised by department, where the following operations typically take place: handling raw and synthetic materials, milling, extruding and calendering, component assembly, curing or vulcanising, finishing and storage/dispatch.¹ Tasks within each production operation define workers' interactions with raw materials and chemical additives, leading to variations in the types of agents to which they are exposed and the levels of exposures to these agents. Variations in occupational exposures between different departments in rubber factories may play a role in the development of chronic diseases as they do in cancer incidence and mortality,⁸ and may have consequences on mortality rates from these diseases. In the beginning of the rubber production process, where raw and synthetic materials are handled by workers, rubber dust exposure tends to occur at the highest levels.¹ The milling process involves generating a substantial amount of heat which then generates and exposes workers to rubber fumes, as does the next part of the production process of extrusion and calendering.¹ The vulcanising and curing processes likewise apply heat in addition to mixtures of chemical additives, which in turn generate fumes and N-nitrosamines.¹ In previous research, using expert-estimated exposures based on job titles, workers in compounding, mixing and milling departments were found to have higher mortality from circulatory disease, ischaemic heart disease (IHD), respiratory and digestive diseases while workers in vulcanising departments had higher mortality from circulatory and respiratory diseases compared with the general population.¹⁰ The current study seeks to examine whether occupational exposures to rubber dust, rubber fumes and N-nitrosamines within a cohort of UK rubber workers with 49-year follow-up and nearly complete mortality are associated with mortality from non-cancer causes in an exposure-response fashion.

MATERIALS AND METHODS

Data

This study used data from a UK cohort of male rubber factory workers who were employed in 381 factories and were aged 35–55 in February 1967 (n=36 441). This cohort was followed for mortality until December 2015 when 93.8% (n=34 181) of the cohort had died and 0.4% (n=136) attrited prior to death mainly through emigration, resulting in 880 794 person years for the statistical analyses. Full details of the cohort as well as analyses of cancer mortality and comparisons to the general population have been described elsewhere.^{3,8}

Job title in 1967 for each worker was linked to a quantitative job-exposure matrix (JEM) based on the EU-EXASRUB database which contains personal and stationary measurements of exposure to various agents in rubber factories in Europe.¹⁴ Average exposure was estimated based on a linear (in log-space) mixed effects model with random factory intercept. From these estimates, lifetime cumulative exposures (LCE) were calculated for each person. Similar to the analyses of cancer mortality of the same cohort,⁸ because only job information in 1967 was available, the primary analyses assumed continuous employment in this same department until retirement at age 70 (chosen because there was substantial employment in the rubber industry among men in their 60s), death or emigration. LCEs were

Table 1 International Classification of Diseases (ICD) codes for selected non-cancer causes of deaths

Cause of death	ICD 9	ICD 10	N deaths
Circulatory diseases	390–459	I00–I99	14 627
Ischaemic heart disease	410–414	I20–I25	9349
Cerebrovascular disease	430–438	I60–I69	2795
Respiratory diseases	460–519	J00–J99	4730
Bronchitis	460–491	J40–J42	845
Emphysema	492	J43	163
Asthma	493	J45	63
Digestive diseases	520–577	K00–K93	827
Diseases of the oesophagus, stomach and duodenum	530–537	K20–K31	258
Liver disease	571	K70–K76	93
Urinary diseases	580–599	N00–N39	253
Total deaths from all causes			34 181

calculated separately for exposures to rubber dust, rubber fumes (measured as the cyclohexane soluble fraction of rubber dust), N-nitrosamines sum score (NSS, a sum of exposures to N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine, N-nitrosodibutylamine, N-nitrosopiperidine and N-nitrosomorpholine (NMor)), and NDMA and NMor individually. Full details of the JEM development, LCE construction and distributions have been described elsewhere.⁸ Sensitivity analyses for selected non-cancer causes of death outcomes and employment durations were conducted based on random assignment of employment durations based on the distribution of the employment history of a similar UK cohort of which this study is a part of¹⁵ with the following parameters: 47% of cohort employed for >10 years after 1967 and 12% were employed for >18 years.

Outcomes were mortality from the following non-cancer causes as listed in the death certificate as underlying causes of death (table 1): circulatory disease, IHD, cerebrovascular disease, respiratory diseases, asthma, bronchitis, emphysema, urinary diseases, liver disease, diseases of the oesophagus, stomach and duodenum, and digestive diseases. Respiratory diseases include a broad range of conditions such as acute upper respiratory infections, influenza and pneumonia, and chronic lower respiratory diseases (including bronchitis, asthma and emphysema). Contributing causes of death data were not used because multiple cause of death (MCD) information was not digitised for a large number of death certificates from the early part of the study. Furthermore, historical death certificates would have been sensitive to changes in coding practices, which may not have become consistent across the UK until after 1980s.¹⁶ All models were adjusted for birth year (mean age in 1967 is 50.1 years, SD=8.4) and LCE to rubber dust, rubber fumes and N-nitrosamines (separate models as well as multipollutant models). LCEs are grouped in quartiles of the cumulative exposure distribution in the cohort and analysed separately as continuous variables to assess the linearity of the exposure-response association.

Statistical methods

Competing risk survival analysis was used to model time to death from the selected non-cancer cause, or occurrence of a competing event (death from another cause or censored through attrition or emigration).¹⁷ This method was selected because in analysing specific causes of deaths using a high mortality cohort such as ours (93.8%), the assumptions of random occurrence and independence of censored deaths from other causes in a standard

Cox proportional hazard model would have been violated. Statistical analyses were performed using *stcrreg* in Stata V.15.0,¹⁸ which yielded subdistribution hazard ratios (SHRs) that could be interpreted in a similar manner to HR such as in Cox models.¹⁹ Full details of the statistical method are described elsewhere.⁸

RESULTS

Non-cancer mortality was examined among 36 441 male rubber factory workers who were at least 35 years old in 1967 and followed for mortality until 2015, resulting in 880 794 person-years. The highest proportion of deaths was from circulatory diseases, comprising 40.1% of all deaths ($n=14\,627$), specifically most of which were from IHD ($n=9349$) (table 1). The second highest proportion of deaths was from respiratory diseases, which accounted for 13.0% ($n=4730$), and cerebrovascular disease, accounting for 7.7% ($n=2795$) of all deaths.

Rubber dust exposures (table 2) in the higher LCE quartiles (second to fourth quartiles) were found to be associated with increased risks for mortality from circulatory disease (SHRs up to 1.19; 95% CI 1.13 to 1.24), IHD (SHRs up to 1.22; 95% CI 1.15 to 1.29), cerebrovascular disease (SHRs up to 1.16; 95% CI 1.04 to 1.28), respiratory diseases (SHRs up to 1.1; 95% CI 1.2 to 1.1) and digestive diseases (SHRs up to 1.35; 95% CI 1.12 to 1.64). These results were supported by the sensitivity analyses, which showed in all simulated employment duration models, higher levels of exposures were associated with higher risks of dying from these diseases (online supplementary figures 1–5). Results for mortality from liver disease and diseases of the oesophagus, stomach and duodenum showed increased risks for higher levels of exposures to rubber dust, but with wide CIs and not statistically significant. No evidence was found for excess risks of deaths from asthma, urinary disease, bronchitis and emphysema with higher levels of exposures to rubber dust.

Higher LCE (second to fourth quartiles) to rubber fumes (table 2) were also found to be associated with increased risks of dying from circulatory diseases (SHRs up to 1.22; 95% CI 1.17 to 1.28), IHD (SHRs up to 1.21; 95% CI 1.14 to 1.29), cerebrovascular disease (SHRs up to 1.31; 95% CI 1.18 to 1.46), respiratory diseases (SHRs up to 1.29; 95% CI 1.19 to 1.40) and digestive diseases (SHRs up to 1.67; 95% CI 1.38 to 2.02). Similar to results from rubber dust exposure, increased risks for mortality with higher levels of exposures to rubber fumes were observed in a monotonic exposure–response pattern. These results were not undermined by the sensitivity analyses (online supplementary figures 1–5).

Higher LCEs of NSS (second to fourth quartiles) (table 3) was associated with increased mortality risk from circulatory diseases (SHRs up to 1.28; 95% CI 1.22 to 1.34), IHD (SHRs up to 1.29; 95% CI 1.22 to 1.37), cerebrovascular disease (SHRs up to 1.48; 95% CI 1.33 to 1.64), respiratory diseases (SHRs up to 1.49; 95% CI 1.37 to 1.62) and digestive diseases (SHRs up to 1.60; 95% CI 1.31 to 1.95). Comparable to rubber dust and rubber fumes exposures, exposure–response patterns were not observed, although all higher quartiles of exposures were found to have higher mortality risks compared with the first quartile (reference category). These results were supported by the sensitivity analyses (online supplementary figures 1–5). No evidence of increased risks of mortality from asthma, bronchitis, diseases of the oesophagus, stomach and duodenum, urinary diseases and liver disease associated with NSS exposures were found.

Exposure–response patterns were observed for NDMA and mortality from respiratory diseases (SHRs up to 1.41; 95% CI 1.30 to 1.53) (table 3). Increased risks without linear

associations were found for mortality from circulatory diseases (SHRs up to 1.28; 95% CI 1.22 to 1.34), IHD (SHRs up to 1.43; 95% CI 1.35 to 1.52), cerebrovascular disease (SHRs up to 1.48; 95% CI 1.33 to 1.64) and digestive diseases (SHRs up to 1.60; 95% CI 1.31 to 1.95). These results were supported by the sensitivity analyses (online supplementary figures 1–5). Other diseases where specific quartiles of exposures were associated with increased risks were found for mortality from urinary diseases (third quartile SHR=1.51; 95% CI 1.09 to 2.09) and liver disease (third quartile SHR=2.22; 95% CI 1.24 to 3.99). Exposures to NDMA were not associated with mortality from asthma, bronchitis, emphysema and diseases of the oesophagus, stomach and duodenum.

Increased risks of dying from several non-cancer causes were found to be associated with higher levels of LCEs to NMor (table 3): circulatory diseases (SHRs up to 1.17; 95% CI 1.12 to 1.23), IHD (SHRs up to 1.19; 95% CI 1.13 to 1.26) and cerebrovascular disease (SHRs up to 1.19; 95% CI 1.07 to 1.32). Exposure–response patterns were observed for these associations where mortality risks increase with higher levels of NMor exposures. These results were supported by the sensitivity analyses (online supplementary figures 1–5). Increased mortality risk from respiratory diseases was also found with the second and third quartiles of NMor exposures (SHRs up to 1.17; 95% CI 1.08 to 1.27). Premature risk of mortality from asthma, urinary diseases, bronchitis, digestive diseases, emphysema, liver disease and diseases of the oesophagus, stomach and duodenum was not associated with LCE to NMor.

Multipollutant models with exposures to rubber dust, rubber fumes and NSS were conducted (table 4) for a subset of causes of deaths with the highest proportions. Excess risks of dying from cerebrovascular disease without exposure–response patterns were only found for NSS exposures (SHRs up to 1.44; 95% CI 1.26 to 1.65). For circulatory disease, higher risks of dying were found for rubber dust exposures (SHRs up to 1.12; 95% CI 1.06 to 1.18), rubber fume exposures (SHRs up to 1.09; 95% CI 1.01 to 1.17) and NSS (SHRs up to 1.20; 95% CI 1.13 to 1.27). For IHD, higher risks of dying were found for LCE to rubber dust (SHRs up to 1.16; 95% CI 1.09 to 1.23) and NSS (SHRs up to 1.19; 95% CI 1.10 to 1.28), but risks for higher LCE to rubber fumes were not different from the lowest exposed reference group. For digestive diseases, higher risks of dying were found with higher exposures of rubber fumes (SHRs up to 1.38; 95% CI 1.09 to 1.75) and NSS (SHRs up to 1.40; 95% CI 1.12 to 1.75), and not rubber dust exposures of any level. For respiratory disease, higher risks of dying were found for LCE to rubber dust (SHRs up to 1.11; 95% CI 1.02 to 1.21), rubber fumes (SHRs up to 1.20; 95% CI 1.05 to 1.37) and NSS (SHRs up to 1.44; 95% CI 1.30 to 1.59).

DISCUSSION

We examined associations between occupational exposures to rubber dust, rubber fumes and nitrosamines with non-cancer mortality among a cohort of UK rubber factory workers with a 49-year follow-up. Consistent with previous studies,^{1–7} we observed increased risk for respiratory disease mortality and through examining exposures to specific agents, we were able to link the excess risk to workers with higher levels of exposures to rubber dust, rubber fumes, NDMA and NSS. We also found increased risk for circulatory disease mortality, consistent with previous studies,^{3 9 10} associated with higher levels of occupational exposures to rubber dust, rubber fumes and NSS. Furthermore, this study found that higher occupational exposures to

Table 2 Risk of death from selected non-cancer causes by lifetime cumulative exposure to rubber dust and rubber fumes in a cohort of rubber factory workers in the UK

Disease	N	Cumulative rubber dust (year mg/m ³)			Cumulative rubber fumes (year mg/m ³)		
		Exposure*	SHR†	95% CI	Exposure‡	SHR†	95% CI
Asthma	63	I	1.00		I	1.00	
		II	1.20	0.61 to 2.35	II	1.31	0.62 to 2.76
		III	1.21	0.62 to 2.37	III	1.42	0.67 to 3.02
		IV	0.96	0.46 to 2.00	IV	1.74	0.90 to 3.36
P for trend			0.29			0.18	
Urinary	253	I	1.00		I	1.00	
		II	0.87	0.60 to 1.27	II	1.19	0.85 to 1.65
		III	1.17	0.84 to 1.64	III	1.15	0.81 to 1.63
		IV	1.26	0.91 to 1.73	IV	1.13	0.82 to 1.57
P for trend			0.91			0.65	
Bronchitis	845	I	1.00		I	1.00	
		II	1.11	0.92 to 1.33	II	1.01	0.84 to 1.22
		III	0.85	0.70 to 1.04	III	0.88	0.71 to 1.08
		IV	0.92	0.77 to 1.10	IV	1.04	0.87 to 1.23
P for trend			1.00			0.87	
Cerebrovascular	2795	I	1.00		I	1.00	
		II	1.17	1.05 to 1.30	II	1.27	1.14 to 1.41
		III	1.23	1.11 to 1.37	III	1.31	1.18 to 1.46
		IV	1.16	1.04 to 1.28	IV	1.21	1.09 to 1.34
P for trend			0.57			0.85	
Circulatory	14627	I	1.00		I	1.00	
		II	1.15	1.10 to 1.20	II	1.18	1.12 to 1.23
		III	1.19	1.14 to 1.25	III	1.22	1.17 to 1.28
		IV	1.19	1.13 to 1.24	IV	1.18	1.13 to 1.23
P for trend			0.57			0.48	
Digestive	827	I	1.00		I	1.00	
		II	1.35	1.12 to 1.64	II	1.67	1.38 to 2.02
		III	1.24	1.02 to 1.52	III	1.40	1.14 to 1.71
		IV	1.34	1.10 to 1.63	IV	1.42	1.16 to 1.73
P for trend			0.003			<0.001	
Emphysema	163	I	1.00		I	1.00	
		II	1.05	0.68 to 1.62	II	1.25	0.83 to 1.87
		III	0.86	0.55 to 1.34	III	0.97	0.63 to 1.48
		IV	1.17	0.78 to 1.77	IV	0.91	0.59 to 1.39
P for trend			0.48			0.48	
IHD	9349	I	1.00		I	1.00	
		II	1.18	1.11 to 1.25	II	1.18	1.11 to 1.25
		III	1.23	1.16 to 1.30	III	1.21	1.14 to 1.29
		IV	1.22	1.15 to 1.29	IV	1.17	1.10 to 1.23
P for trend			0.76			0.79	
Liver	93	I	1.00		I	1.00	
		II	1.47	0.85 to 2.53	II	1.33	0.75 to 2.33
		III	1.36	0.77 to 2.40	III	1.45	0.82 to 2.54
		IV	1.00	0.53 to 1.88	IV	1.04	0.57 to 1.90
P for trend			0.62			0.95	
Oesophagus, stomach and duodenum	258	I	1.00		I	1.00	
		II	1.20	0.85 to 1.69	II	1.37	0.98 to 1.92
		III	1.20	0.85 to 1.70	III	1.17	0.81 to 1.69
		IV	1.20	0.85 to 1.68	IV	1.36	0.97 to 1.89
P for trend			0.003			<0.001	
Respiratory	4730	I	1.00		I	1.00	
		II	1.21	1.12 to 1.31	II	1.29	1.19 to 1.40
		III	1.18	1.09 to 1.28	III	1.27	1.17 to 1.38

continued

Table 2 continued

Disease	N	Cumulative rubber dust (year mg/m ³)			Cumulative rubber fumes (year mg/m ³)		
		Exposure*	SHR†	95% CI	Exposure‡	SHR†	95% CI
		IV	1.15	1.06 to 1.24	IV	1.28	1.18 to 1.38
P for trend			0.85			0.91	

*Based on quartiles (I:<14.73 year mg/m³; II: 14.73–21.05 year mg/m³; III: 21.05–31.42 year mg/m³; IV:>31.42 year mg/m³) of the cumulative distribution in the population.

†Subdistribution hazard ratio (SHR) from competing risk survival analysis model adjusted for birth year.

‡Based on quartiles (I:<4.89 year mg/m³; II: 4.89–6.96 year mg/m³; III: 6.96–11.61 year mg/m³; IV:>11.61 year mg/m³) of the cumulative distribution in the population.

IHD, ischaemic heart disease; SHR, subdistribution hazard ratio.

NMor were associated with higher risks for cerebrovascular disease mortality and IHD. A previous analysis of the same cohort as the current study also found higher SMRs among rubber workers compared with the general population for mortality from IHD (SMR=1.08; 95% CI 1.06 to 1.10), circulatory disease (SMR=1.07; 95% CI 1.05 to 1.09), respiratory diseases (SMR=1.14; 95% CI 1.10 to 1.17) and cerebrovascular disease (SMR=1.04; 95% CI 1.00 to 1.08).³ We found increased risks for non-malignant digestive disease mortality with higher levels of exposures to rubber dust, rubber fumes and NSS, unlike several previous studies with shorter follow-up and smaller sample sizes.^{11 12} A Bonferroni correction for multiple comparisons was applied to the results for each cause of death/agent combination, with p-values lower than 0.0009 for 55 distinct analyses to be considered robust. We found that several p-values met these criteria, namely for cardiovascular and IHD mortality for all agents, cerebrovascular disease mortality for rubber fumes, NSS and NDMA LCEs, respiratory disease mortality for all agents except NMor LCEs, and for digestive disease mortality and NDMA LCEs.

In multipollutant models, excess risks of dying from cerebrovascular, circulatory, digestive, respiratory diseases and IHD were only found for NSS exposure, but linear exposure–response associations were not observed. However, the single-pollutant approach has typically been used in previous studies due to issues related to correlations between pollutants and different levels of measurement error for different pollutants.²⁰ No associations were observed between occupational exposures to rubber dust, rubber fumes and N-nitrosamines with premature mortality from asthma, urinary diseases, bronchitis, emphysema, liver disease and diseases of the oesophagus, stomach and duodenum. Previous studies also found no excess risks of mortality from liver and urinary disease in the rubber industry.^{11 12}

Taken together, results from single and multipollutant models suggest a pattern of increased mortality from non-cancer diseases with higher quartiles of lifetime exposures in the rubber industry. Because most previous studies focused on the carcinogenic effects of these exposures, the exact biological mechanism linking these exposures to non-cancer diseases have not been clearly elucidated although excess risks for both heart disease and cancer have been previously reported.^{21 22} Nevertheless, two possible mechanisms have been suggested in previous studies: the inflammatory pathway, which suggests that exposures to rubber dust lead to pulmonary system inflammation which leave workers more susceptible to cardiovascular disease,²³ and the DNA damage pathway, which suggests that increased genotoxic risks faced by rubber factory workers contribute to DNA damage^{24 25} resulting in increased susceptibility to the formation of atherosclerotic plaques,²⁶ further contributing to cardiovascular disease, similar to a mechanism suggested from exposures

to toxic metal contaminants²⁷ and which has also been reported for IHD among asphalt workers.²⁸

The main strength of this study is the 49-year follow-up period, one of the longest follow-ups of rubber factory worker cohorts in the world and the longest in the UK. This allowed for a high cohort mortality rate (94%) with minimal attrition through emigration (0.4%), making it particularly suitable to examine mortality from chronic diseases. Furthermore, given the previous focus on cancer in the rubber industry, this is one of few studies to date to examine non-cancer mortality among rubber factory workers. Finally, through the use of JEMs, this study was able to utilise data from a historical cohort without contemporaneous exposure measurements to quantitatively examine associations between occupational exposures and non-cancer mortality. Sensitivity analyses were conducted with alternative simulated employment durations based on information on employment durations from another, partly overlapping, cohort of British rubber factory workers^{6 15 29} and showed that results of the main analyses are robust. Although exposure estimates from JEMs are generated from mean exposure values and therefore do not allow for individual variabilities, errors that arise from them tend to be attenuated Berkson-type errors, which, unlike random errors, generally do not bias exposure–response associations.^{30–32} Finally, exposure-specific estimates of LCE enabled multipollutant models to explore issues of complex exposure mixtures across the production process.

The main limitations for this study includes a lack of control for lifestyle factors or baseline health status such as smoking, body mass index, physical fitness or blood pressure, which could be related to the development of non-cancer chronic diseases.³³ Because smoking was highly prevalent among all adult males in 1967 (estimated at 54%)³⁴ and a similar smoking prevalence was reported in a more recent cohort of UK rubber factory workers,³⁵ health risks associated with smoking, which has been reported to have the strongest associations with mortality among these lifestyle factors³⁶ could have been distributed similarly across the cohort of rubber factory workers in this analysis. Nevertheless, sensitivity analyses results showed that a small proportion of simulations were affected by the residual confounding of smoking status (full details in online supplementary materials). These results imply that confounding from unmeasured smoking status in this study was unlikely, but cannot be completely excluded. Previous research on occupational status inequalities suggests that workers in supervisory or managerial roles may have better health and have lower risks of dying from chronic diseases.³⁷ This could be applicable to our cohort as workers in these job roles may also have lower exposures to rubber process by-product agents. Second, the study sample included workers who were at least age 35 at baseline, which could possibly be biased towards workers who were healthy enough to sustain

Table 3 Risk of death from selected non-cancer causes by lifetime cumulative exposure to N-nitrosamines sum score (NSS), N-nitrosodimethylamine (NDMA) and N-nitrosomorpholine (NMor) in a cohort of rubber factory workers in the UK

	N	Cumulative N-nitrosamines sum score (NSS)* (year $\mu\text{g}/\text{m}^3$)			Cumulative NDMA (year $\mu\text{g}/\text{m}^3$)			Cumulative NMor (year $\mu\text{g}/\text{m}^3$)		
		Exposure†	SHR‡	95% CI	Exposure§	SHR‡	95% CI	Exposure	SHR‡	95% CI
Asthma	63	I	1.00		I	1.00		I	1.00	
		II	1.38	0.63 to 2.99	II	1.38	0.63 to 2.99	II	1.73	0.85 to 3.53
		III	1.42	0.67 to 3.03	III	1.42	0.67 to 3.03	III	1.50	0.71 to 3.14
		IV	1.71	0.89 to 3.30	IV	1.71	0.89 to 3.30	IV	1.57	0.74 to 3.33
P for trend			0.11			0.11			0.31	
Urinary	253	I	1.00		I	1.00		I	1.00	
		II	1.51	1.09 to 2.09	II	1.51	1.09 to 2.09	II	1.00	0.71 to 1.41
		III	1.24	0.88 to 1.76	III	1.24	0.88 to 1.76	III	1.05	0.74 to 1.48
		IV	0.91	0.64 to 1.29	IV	0.91	0.64 to 1.29	IV	0.98	0.70 to 1.38
P for trend			0.73			0.73			0.58	
Bronchitis	845	I	1.00		I	1.00		I	1.00	
		II	0.94	0.77 to 1.16	II	0.94	0.77 to 1.16	II	1.02	0.85 to 1.22
		III	1.22	1.01 to 1.48	III	1.22	1.01 to 1.48	III	1.06	0.88 to 1.27
		IV	0.96	0.81 to 1.14	IV	0.96	0.81 to 1.14	IV	0.76	0.63 to 0.92
P for trend			0.58			0.58			0.004	
Cerebrovascular	2795	I	1.00		I	1.00		I	1.00	
		II	1.48	1.33 to 1.64	II	1.48	1.33 to 1.64	II	1.17	1.05 to 1.3
		III	1.36	1.21 to 1.51	III	1.36	1.21 to 1.51	III	1.17	1.05 to 1.3
		IV	1.27	1.15 to 1.41	IV	1.27	1.15 to 1.41	IV	1.19	1.07 to 1.32
P for trend			0.69			0.69			0.003	
Circulatory	14627	I	1.00		I	1.00		I	1.00	
		II	1.28	1.22 to 1.34	II	1.28	1.22 to 1.34	II	1.09	1.04 to 1.14
		III	1.18	1.13 to 1.24	III	1.18	1.13 to 1.24	III	1.12	1.07 to 1.18
		IV	1.17	1.12 to 1.22	IV	1.17	1.12 to 1.22	IV	1.17	1.12 to 1.23
P for trend			0.41			0.41			<0.001	
Digestive	827	I	1.00		I	1.00		I	1.00	
		II	1.60	1.31 to 1.95	II	1.60	1.31 to 1.95	II	1.15	0.95 to 1.39
		III	1.54	1.26 to 1.89	III	1.54	1.26 to 1.89	III	0.99	0.81 to 1.21
		IV	1.35	1.11 to 1.65	IV	1.35	1.11 to 1.65	IV	1.20	0.99 to 1.46
P for trend			0.64			0.64			0.17	
Emphysema	163	I	1.00		I	1.00		I	1.00	
		II	1.21	0.81 to 1.78	II	1.34	0.88 to 2.03	II	1.14	0.73 to 1.76
		III	0.84	0.54 to 1.32	III	1.18	0.74 to 1.87	III	1.22	0.79 to 1.88
		IV	0.84	0.55 to 1.27	IV	1.49	0.98 to 2.27	IV	1.06	0.68 to 1.64
P for trend			0.86			0.59			0.49	
IHD	9349	I	1.00		I	1.00		I	1.00	
		II	1.29	1.22 to 1.37	II	1.24	1.18 to 1.32	II	1.10	1.04 to 1.17
		III	1.16	1.09 to 1.23	III	1.43	1.35 to 1.52	III	1.14	1.08 to 1.21
		IV	1.12	1.06 to 1.19	IV	1.28	1.20 to 1.36	IV	1.19	1.13 to 1.26
P for trend			0.40			0.68			<0.001	
Liver	93	I	1.00		I	1.00		I	1.00	
		II	1.55	0.86 to 2.80	II	1.75	0.98 to 3.14	II	0.84	0.48 to 1.49
		III	1.31	0.73 to 2.35	III	2.22	1.24 to 3.99	III	1.03	0.60 to 1.79
		IV	1.34	0.75 to 2.39	IV	1.35	0.73 to 2.49	IV	1.04	0.59 to 1.84
P for trend			0.32			0.34			0.88	
Oesophagus, stomach and duodenum	258	I	1.00		I	1.00		I	1.00	
		II	1.35	0.96 to 1.90	II	1.24	0.89 to 1.74	II	1.06	0.76 to 1.47
		III	1.43	1.01 to 2.03	III	1.40	0.99 to 1.99	III	1.02	0.73 to 1.43
		IV	1.06	0.75 to 1.50	IV	1.27	0.88 to 1.85	IV	0.76	0.53 to 1.09
P for trend			0.79			0.68			0.29	
Respiratory	4730	I	1.00		I	1.00		I	1.00	
		II	1.36	1.25 to 1.47	II	1.17	1.08 to 1.27	II	1.10	1.01 to 1.19
		III	1.49	1.37 to 1.62	III	1.38	1.27 to 1.49	III	1.17	1.08 to 1.27

continued

Table 3 continued

N	Cumulative N-nitrosamines sum score (NSS)* (year µg/m ³)			Cumulative NDMA (year µg/m ³)			Cumulative NMor (year µg/m ³)		
	Exposure†	SHR‡	95% CI	Exposure§	SHR‡	95% CI	Exposure¶	SHR‡	95% CI
	IV	1.28	1.18 to 1.38	IV	1.41	1.30 to 1.53	IV	1.07	0.99 to 1.16
P for trend		0.27			0.92			0.51	

*Sum of lifetime cumulative exposures to N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), N-nitrosodibutylamine, N-nitrosopiperidine (NPIP) and N-nitrosomorpholine (NMor).

†Based on quartiles (I: <17.24 year µg/m³; II: 17.24–26.72 year µg/m³; III: 26.72–546.51 year µg/m³; IV: >546.51 year µg/m³) of the cumulative distribution in the population.

‡Subdistribution hazard ratio (SHR) from competing risk survival analysis model adjusted for birth year.

§Based on quartiles (I: <5.77 year µg/m³; II: 5.77–8.34 year µg/m³; III: 8.34–11.37 year µg/m³; IV: >11.37 year µg/m³) of the cumulative distribution in the population.

¶Based on quartiles (I: <7.70 year µg/m³; II: 7.70–12.31 year µg/m³; III: 12.31–19.01 year µg/m³; IV: >19.01 year µg/m³) of the cumulative distribution in the population.

IHD, ischaemic heart disease; SHR, subdistribution hazard ratio.

employment and had not dropped out of employment due to ill-health, that is, producing a ‘healthy worker effect’.³⁸ However, this is less problematic for this study because it focuses on differences in mortality within the rubber factory worker cohort as opposed to comparing workers to the general population. Third, alternative metrics of exposures such as peak exposure could not be tested because of lack of exposure estimates covering the 49-year follow-up period.

CONCLUSION

This study is to our knowledge the first to examine exposure–response associations between specific occupational exposures in the rubber industry and non-cancer mortality using quantitative exposures through a JEM. The results are consistent with previous studies that similarly found variations in risks of non-cancer mortality by department^{9 10} with elevated risks in

Table 4 Multipollutant model of risk of death from selected causes by lifetime cumulative exposure to rubber dust, rubber fumes and nitrosamines sum score in a cohort of rubber factory workers in the UK

	N	Cumulative rubber dust (year mg/m ³)			Cumulative rubber fumes (year mg/m ³)			Cumulative nitrosamines sum score (NSS)* (year µg/m ³)		
		Exposure†	SHR‡	95% CI	Exposure§	SHR‡	95% CI	Exposure¶	SHR‡	95% CI
Cerebrovascular	2795	I	1.00		I	1.00		I	1.00	
		II	1.07	0.96 to 1.20	II	1.05	0.92 to 1.21	II	1.44	1.26 to 1.65
		III	1.11	0.99 to 1.25	III	1.09	0.94 to 1.27	III	1.35	1.19 to 1.54
		IV	0.94	0.81 to 1.08	IV	1.08	0.91 to 1.28	IV	1.17	1.01 to 1.37
P for trend			0.10			0.11			0.29	
Circulatory	14 627	I	1.00		I	1.00		I	1.00	
		II	1.09	1.04 to 1.15	II	1.04	0.98 to 1.11	II	1.20	1.13 to 1.27
		III	1.12	1.06 to 1.18	III	1.09	1.01 to 1.17	III	1.13	1.06 to 1.20
		IV	1.06	0.99 to 1.12	IV	1.08	1.00 to 1.16	IV	1.07	1.00 to 1.15
P for trend			0.43			0.32			0.25	
Digestive	827	I	1.00		I	1.00		I	1.00	
		II	1.21	0.98 to 1.49	II	1.38	1.09 to 1.75	II	1.31	1.03 to 1.66
		III	1.11	0.90 to 1.38	III	1.13	0.86 to 1.49	III	1.40	1.12 to 1.75
		IV	1.08	0.84 to 1.40	IV	1.17	0.87 to 1.59	IV	1.20	0.91 to 1.57
P for trend			0.56			0.06			0.46	
IHD	9349	I	1.00		I	1.00		I	1.00	
		II	1.13	1.06 to 1.20	II	1.04	0.97 to 1.13	II	1.19	1.10 to 1.28
		III	1.16	1.09 to 1.23	III	1.10	1.00 to 1.20	III	1.10	1.02 to 1.18
		IV	1.08	1.00 to 1.17	IV	1.10	1.00 to 1.21	IV	1.01	0.93 to 1.10
P for trend			0.80			0.73			0.37	
Respiratory	4730	I	1.00		I	1.00		I	1.00	
		II	1.11	1.02 to 1.21	II	1.16	1.04 to 1.29	II	1.27	1.14 to 1.41
		III	1.08	0.99 to 1.18	III	1.13	1.00 to 1.28	III	1.44	1.30 to 1.59
		IV	0.91	0.81 to 1.01	IV	1.20	1.05 to 1.37	IV	1.12	0.99 to 1.27
P for trend			0.80			0.76			0.27	

*Sum of lifetime cumulative exposures to N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), N-nitrosodibutylamine, N-nitrosopiperidine (NPIP) and N-nitrosomorpholine (NMor).

†Based on quartiles (I: <14.73 year mg/m³; II: 14.73–21.05 year mg/m³; III: 21.05–31.42 year mg/m³; IV: >31.42 year mg/m³) of the cumulative distribution in the population.

‡Subdistribution hazard ratio (SHR) from competing risk survival analysis model adjusted for birth year.

§Based on quartiles (I: <4.89 year mg/m³; II: 4.89–6.96 year mg/m³; III: 6.96–11.61 year mg/m³; IV: >11.61 year mg/m³) of the cumulative distribution in the population.

¶Based on quartiles (I: <17.24 year µg/m³; II: 17.24–26.72 year µg/m³; III: 26.72–546.51 year µg/m³; IV: >546.51 year µg/m³) of the cumulative distribution in the population.

IHD, ischaemic heart disease; SHR, subdistribution hazard ratio.

compounding and mixing, milling and vulcanising. Because data on lifestyle factors including smoking were unavailable, effects of residual confounding on our results could not be dismissed. Although this study was based on a cohort employed in the rubber industry in 1967, the results continue to be relevant to the industry today, possibly in terms of worker health litigations and compensation in Europe and North America where rubber production facilities were located in the 20th century. This study adds to the large body of research documenting associations between employment and specific workplace exposures in the rubber industry and chronic disease mortality.

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REFERENCES

- IARC working group. IARC monographs on the evaluation of carcinogenic risks to humans: Chemical agents and related occupations. 2012;100F:599. 2012. Available: <https://monographs.iarc.fr/wp-content/uploads/2018/06/mono100F.pdf> [Accessed 4 Sep 2019].
- Kogevinas M, Sala M, Boffetta P, et al. Cancer risk in the rubber industry: a review of the recent epidemiological evidence. *Occup Environ Med* 1998;55:1–12.
- McElvenny DM, Mueller W, Ritchie P, et al. British rubber and cable industry cohort: 49-year mortality follow-up. *Occup Environ Med* 2018;75:848–55.
- Meijer E, Grobbee DE, Heederik DJ. Health surveillance for occupational chronic obstructive pulmonary disease. *J Occup Environ Med* 2001;43:444–50.
- Peters JM, Monson RR, Burgess WA, et al. Occupational disease in the rubber industry. *Environ Health Perspect* 1976;17:31–4.
- Sorahan T, Parkes HG, Veys CA, et al. Cancer mortality in the British rubber industry: 1946–80. *Occup Environ Med* 1986;43:363–73.
- Tyroler HA, Andjelkovic D, Harris R, et al. Chronic diseases in the rubber industry. *Environ Health Perspect* 1976;17:13–20.
- Hidajat M, McElvenny DM, Ritchie P, et al. Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up. *Occup Environ Med* 2019;76:250–8.
- Gustavsson P, Reuterwall C. Mortality and incidence of cancer among Swedish gas workers. *Occup Environ Med* 1990;47:169–74.
- Wingren G. Mortality in a Swedish rubber tire manufacturing plant: Occupational risks or an "unhealthy worker" effect? *Am J Ind Med* 2006;49:617–23.
- Mirabelli D, Cacciatori AM, Ferrante D, et al. Cohort study of workers employed in an Italian tire manufacturing plant, 1962–2004. *Cancer Causes Control* 2012;23:2023–9.
- Vlaanderen J, Taeger D, Wellman J, et al. Extended cancer mortality follow-up of a German rubber industry cohort. *J Occup Environ Med* 2013;55:966–72.
- Thapa N, Tomasi SE, Cox-Ganser JM, et al. Non-Malignant respiratory disease among workers in the rubber manufacturing industry: a systematic review and meta-analysis. *Am J Ind Med* 2019;62:367–84.
- De Vocht F, Straif K, Szeszenia-Dabrowska N, et al. A database of exposures in the rubber manufacturing industry: design and quality control. *Ann Occup Hyg* 2005;49:691–701.
- Sorahan T, Parkes HG, Veys CA, et al. Mortality in the British rubber industry 1946–85. *Occup Environ Med* 1989;46:1–10.
- Moriyama IM, Loy RM, Robb-Smith AHT, Rosenberg H, Hoyert D, eds. *History of the statistical classification of diseases and causes of death*. Hyattsville, MD: National Center for Health Statistics, 2011. https://www.cdc.gov/nchs/data/misc/classification_diseases2011.pdf
- Fine JP, Gray RJ. A proportional hazards model for the Subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
- StataCorp. *Stata Statistical Software: Release 15*. College Station, TX: StataCo, 2017.
- Ingle SM, May M, Uebel K, et al. Outcomes in patients waiting for antiretroviral treatment in the free state Province, South Africa: prospective linkage study. *AIDS* 2010;24:2717–25.
- Blangiardo M, Pirani M, Kanapka L, et al. A hierarchical modelling approach to assess multi pollutant effects in time-series studies. *PLoS One* 2019;14:e0212565.
- Friesen MC, Demers PA, Spinelli JJ, et al. Chronic and acute effects of coal TAR pitch exposure and cardiopulmonary mortality among aluminum smelter workers. *Am J Epidemiol* 2010;172:790–9.
- Spinelli JJ, Band PR, Svirchev LM, et al. Mortality and cancer incidence in aluminum reduction plant workers. *J Occup Environ Med* 1991;33:1150–5.
- Sjögren B. Occupational exposure to dust: inflammation and ischaemic heart disease. *Occup Environ Med* 1997;54:466–9.
- Peters S, Talaska G, Jönsson BAG, et al. Polycyclic aromatic hydrocarbon exposure, urinary mutagenicity, and DNA adducts in rubber manufacturing workers. *Cancer Epidemiol Biomarkers Prev* 2008;17:1452–9.
- Laffon B, Teixeira P, Silva S, et al. Assessment of occupational genotoxic risk in the production of rubber tyres. *Ann Occup Hyg* 2006;50:583–92.
- Binková B, Strejc P, Boubelik O, et al. Dna adducts and human atherosclerotic lesions. *Int J Hyg Environ Health* 2001;204:49–54.
- Solenkova NV, Newman JD, Berger JS, et al. Metal pollutants and cardiovascular disease: mechanisms and consequences of exposure. *Am Heart J* 2014;168:812–22.
- Burstyn I, Kromhout H, Partanen T, et al. Polycyclic aromatic hydrocarbons and fatal ischemic heart disease. *Epidemiology* 2005;16:744–50.
- Parkes HG, Veys CA, Waterhouse JA, et al. Cancer mortality in the British rubber industry. *Occup Environ Med* 1982;39:209–20.
- Kim HG-MI, Richardson D, Loomis D, et al. Bias in the estimation of exposure effects with individual- or group-based exposure assessment. *J Expo Sci Environ Epidemiol* 2011;21:212–21.
- Kim HM, Yasui Y, Burstyn I. Attenuation in risk estimates in logistic and COX proportional-hazards models due to group-based exposure assessment strategy. *Ann Occup Hyg* 2006;50:623–35.
- Kim H-M, Burstyn I. Bayesian method for improving logistic regression estimates under group-based exposure assessment with additive measurement errors. *Arch Environ Occup Health* 2009;64:261–5.
- Kuh D, Ben Shlomo Y, Ezra S. *A life course approach to chronic disease epidemiology*. Oxford University Press, 2004.
- Wald NJ, Nicolaides-Bouman A. *St. Bartholomew's Hospital. UK Smoking Statistics*. Wolfson Institute of Preventive Medicine, 1991.
- Dost A, Straughan J, Sorahan T. A cohort mortality and cancer incidence survey of recent entrants (1982–91) to the UK rubber industry: findings for 1983–2004. *Occup Med* 2007;57:186–90.
- Lantz PM, House JS, Lepkowski JM, et al. Health behaviors, and mortality: results from a nationally representative prospective study of US adults. *J Am Med Assoc* 1998;279:1703–8.
- Krueger PM, Burgard SA. Work, occupation, income, and mortality. In: Rogers RG, Crimmins EM, eds. *International Handbook of Adult Mortality, International Handbooks of Population* 2. Springer, 2011: 263–88.
- McMichael AJ. Standardized Mortality Ratios and the "Healthy Worker Effect": Scratching Beneath the Surface. *J Occup Environ Med* 1976;18:165–8.