Lifetime cumulative exposure to rubber dust, fumes and N-nitrosamines and non-cancer mortality

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 disease 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 (Sub-hazard ratio (SHR) 1.2; 95%CI 1.1-1.2), ischaemic heart disease (IHD) (SHR 1.2; 95%CI 1.1-1.3), cerebrovascular disease (SHR 1.2; 95%CI 1.1-1.3), and exposures to N-Nitrosodimethylamine with respiratory disease mortality (SHR 1.4; 95%CI 1.3-1.5). 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 chronic circulatory, cerebrovascular, respiratory and digestive diseases were found to be associated with cumulative occupational exposures to specific 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 chronic disease mortality

-Exposure response associations of increased risk with increasing exposure were found for exposures to NDMA with respiratory disease mortality and NMor 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 extends beyond premature mortality risks from cancers to other chronic diseases, and this may have implications for current health and safety practices in the industry in the UK and worldwide.

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 standardized mortality ratios (SMRs) from cancer and non-cancer causes of deaths compared to the general population.[3] Further internal analyses of the same cohort observed exposure-response associations between occupational exposures to agents 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 chronic diseases, however, 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 to the overall population, as well as within rubber factory worker cohorts; particularly in compounding, milling, and vulcanizing departments. Studies where no associations were observed[11,12] had smaller samples and shorter follow-ups. A systematic review of non-malignant respiratory disease amongst 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 organized by department, where the following operations typically take place: handling raw and synthetic materials, milling, extruding and calendering, component assembly, curing or

vulcanizing, 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 vulcanizing 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 vulcanizing departments had higher mortality from circulatory and respiratory diseases compared to 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 chronic diseases 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 60's), death, or emigration. LCEs were calculated separately for exposures to rubber dust, rubber fumes (measured as the cyclohexane soluble fraction of rubber dust), Nitrosamines sum score (a sum of exposures to N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA), N-Nitrosodibutylamine, N-Nitrosopiperidine (NPIP), 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 chronic disease mortality 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 of[15] 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 chronic diseases as listed in the death certificate as underlying causes of death (Table 1): circulatory disease, ischemic heart 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 MCD information was not digitized 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, S.D.=8.4) and LCE to rubber dust, rubber fumes, and N-Nitrosamines (separate models as well as multi-pollutant models). LCEs are grouped in quartiles of the cumulative exposure distribution in the cohort and analyzed 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 chronic disease cause, or occurrence of a competing event (death from another cause or censored through attrition or emigration)[17]. This method was selected because in analyzing

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 15.0[18] which yielded sub-distribution hazard ratios (SHRs) that could be interpreted in a similar manner to hazard ratios such as in Cox models.[19] Full details of the statistical method are described elsewhere.[8]

Results

Non-cancer chronic disease mortality was examined amongst 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 were from circulatory diseases, comprising 40.1% of all deaths (N=14,627), specifically most of which were from IHD (N=9,349) (Table 1). The second highest proportion of deaths were from respiratory diseases, which accounted for 13.0% (N=4,730), and cerebrovascular disease, accounting for 7.7% (N=2,795) of all deaths.

Rubber dust exposures (Table 2) in the higher LCE quartiles (2nd-4th quartiles) were found to be associated with increased risks for mortality from circulatory disease (SHRs up to 1.2; 95%CI 1.1-1.2), IHD (SHRs up to 1.2; 95%CI 1.1-1.3), cerebrovascular disease (SHRs up to 1.2; 95%CI 1.1-1.4), respiratory diseases (SHRs up to 1.2; 95%CI 1.1-1.3) and digestive diseases (SHRs up to 1.4; 95%CI 1.1-1.6). 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 (Supplemental 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 confidence intervals 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 (2nd-4th quartiles) to rubber fumes (Table 2) were also found to be associated with increased risks of dying from circulatory diseases (SHRs up to 1.2; 95% CI 1.2-1.3), IHD (SHRs up to 1.2; 95%CI 1.1-1.3), cerebrovascular disease (SHRs up to 1.3; 95%CI 1.2-1.5), respiratory diseases (SHRs up to 1.3; 95%CI 1.2-1.4), and digestive diseases (SHRs up to 1.7; 95%CI 1.4-2.0). 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 (Supplemental Figures 1-5).

Higher LCEs of N-Nitrosamines sum score (2nd - 4th quartiles) (Table 3) was associated with increased mortality risk from circulatory diseases (SHRs up to 1. 3; 95%CI 1.2-1.3), IHD (SHRs up to 1.3; 95%CI 1.2-1.4), cerebrovascular disease (SHRs up to 1.5; 95%CI 1.3-1.6), respiratory diseases (SHRs up to 1.5; 95%CI 1.4-1.6), and digestive diseases (SHRs up to 1.6; 95%CI 1.3-2.0). 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 to the 1st quartile (reference category). These results were supported by the sensitivity analyses (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 N-Nitrosamines exposures were found.

Exposure-response patterns were observed for NDMA and mortality from respiratory diseases (SHRS up to 1.4; 95%CI 1.3-1.5) (Table 3). Increased risks without linear associations were found for mortality from circulatory diseases (SHRs up to 1.4; 95%CI 1.3-1.4), IHD (SHRs up to 1.4; 95%CI 1.3-1.5), cerebrovascular disease (SHRs up to 1.4; 95%CI 1.2-1.5), and digestive diseases (SHRs up to 1.7; 95%CI 1.4-2.0). These results were supported by the sensitivity analyses (Supplemental Figures 1-5). Other chronic diseases where specific quartiles of exposures were associated with increased risks were found for mortality from urinary diseases (3rd quartile SHR=1.6; 95%CI 1.1-2.3) and liver disease (3rd quartile SHR=2.2; 95%CI 1.2-4.0). 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 chronic diseases were found to be associated with higher levels of LCEs to NMor (Table 3): circulatory diseases (SHRs up to 1.2; 95%CI 1.1-1.2), IHD (SHRs up to 1.2; 95%CI: 1.1-1.3), and cerebrovascular disease (SHRs up to 1.2; 95%CI 1.1-1.3). 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 (Supplemental Figures 1-5). Increased mortality risk from respiratory diseases were also found with the 2nd and 3rd quartiles of NMor exposures (SHRs up to 1.2; 95%CI 1.1-1.3). Premature risk of mortality from asthma, urinary diseases, bronchitis, digestive diseases, emphysema, liver disease, and diseases of the oesophagus, stomach, and duodenum were not associated with LCE to NMor.

Multi-pollutant 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 1.4; 95%CI 1.3-1.7). For circulatory disease, higher risks of dying were found for rubber dust exposures (SHRs up to 1.1; 95%CI 1.1-1.2), rubber fume exposures (SHRs up to 1.1; 95%CI 1.01-1.2), and NSS (SHRs up to 1.2; 95%CI 1.1-1.3). For IHD, higher risks of dying were found for LCE to rubber dust (SHRs up to 1.2; 95%CI 1.1-1.2) and NSS (SHRs up to 1.2; 95% CI 1.1-1.3), 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 1.4; 95%CI 1.1-1.8) and NSS (SHRs up to 1.4; 95%CI 1.1-1.8), 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 1.1; 95%CI 1.02-1.2), rubber fumes (SHRs up to 1.2; 95%CI 1.1-1.4), and NSS (SHRs up to 1.4; 95%CI 1.3-1.6).

Discussion

We examined associations between occupational exposures to rubber dust, rubber fumes, and nitrosamines with non-cancer chronic disease mortality amongst 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 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 amongst rubber workers compared to the general population for mortality from IHD (SMR=1.1; 95%CI 1.06-1.10), circulatory disease (SMR=1.07; 95%CI 1.05 to 1.1), respiratory diseases (SMR=1.1; 95%CI 1.1-1.2), and cerebrovascular disease (SMR=1.04; 95%CI 1.0 to 1.1).[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 multi-pollutant 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 multi-pollutant 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 albeit excess risks for both heart disease and cancer has 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 contaminates[27] and which has also been reported for IHD amongst 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 chronic disease mortality amongst rubber factory workers. Lastly, through the use of job-exposure matrices, this study was able to utilize data from a historical cohort without contemporaneous exposure measurements to quantitatively examine associations between occupational exposures and non-cancer chronic disease 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 job-exposure matrices 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 multi-pollutant 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 (BMI), physical fitness, or blood pressure, which could be related to the development of non-cancer chronic diseases.[33] Because smoking was highly prevalent amongst 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 amongst these lifestyle factors[36] 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 Supplemental 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 non-cancer 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. Secondly, 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 employment and had not dropped out of employment due to ill-health, i.e. 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 chronic disease mortality using quantitative exposures through a job-exposure matrix. The results are consistent with previous studies that similarly found variations in risks of non-cancer chronic disease mortality by department[9,10] with elevated risks in compounding and mixing, milling, and vulcanizing. 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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Table 1. International Classification of Diseases (ICD) codes for selected chronic 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	9,349
Cerebrovascular disease	430-438	I60-I69	2,795
Respiratory diseases	460-519	J00-J99	4,730
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**

Table 2. Risk of death from selected chronic diseases by lifetime cumulative exposure to rubber dust and rubber fumes in a cohort of rubber factory workers in the UK

Chronic Disease	N	Cumulative Rubber Dust (year mg/m^3)			Cumulative Rubber Fumes (year mg/m3)		
		Exposure[a]	SHR[b]	95%CI	Exposure[c]	SHR[b]	95%CI
Asthma	63	I	1.00		I	1.00	
		II	1.20	0.61 – 2.35	II	1.31	0.62 – 2.76
		III	1.21	0.62 – 2.37	III	1.42	0.67 – 3.02
		IV	0.96	0.46 – 2.00	IV	1.74	0.90 – 3.36
P for trend			*0.29*			*0.18*	
Urinary	253	I	1.00		I	1.00	
		II	0.87	0.60 – 1.27	II	1.19	0.85 – 1.65
		III	1.17	0.84 – 1.64	III	1.15	0.81 – 1.63
		IV	1.26	0.91 – 1.73	IV	1.13	0.82 – 1.57
P for trend			*0.91*			*0.65*	
Bronchitis	845	I	1.00		I	1.00	
		II	1.11	0.92 – 1.33	II	1.01	0.84 – 1.22
		III	0.85	0.70 – 1.04	III	0.88	0.71 – 1.08
		IV	0.92	0.77 – 1.10	IV	1.04	0.87 – 1.23
P for trend			*1.00*			*0.87*	
Cerebrovascular	2,795	I	1.00		I	1.00	
		II	1.17	1.05 – 1.30	II	1.27	1.14 – 1.41
		III	1.23	1.11 – 1.37	III	1.31	1.18 – 1.46
		IV	1.16	1.04 – 1.28	IV	1.21	1.09 – 1.34
P for trend			*0.57*			*0.85*	
Circulatory	14,627	I	1.00		I	1.00	
		II	1.15	1.10 – 1.20	II	1.18	1.12 – 1.23
		III	1.19	1.14 – 1.25	III	1.22	1.17 – 1.28
		IV	1.19	1.13 – 1.24	IV	1.18	1.13 – 1.23
P for trend			*0.57*			*0.48*	
Digestive	827	I	1.00		I	1.00	
		II	1.35	1.12 – 1.64	II	1.67	1.38 – 2.02
		III	1.24	1.02 – 1.52	III	1.40	1.14 – 1.71
		IV	1.34	1.10 – 1.63	IV	1.42	1.16 – 1.73
P for trend			*0.003*			*<0.001*	
Emphysema	163	I	1.00		I	1.00	
		II	1.05	0.68 – 1.62	II	1.25	0.83 – 1.87
		III	0.86	0.55 – 1.34	III	0.97	0.63 – 1.48
		IV	1.17	0.78 – 1.77	IV	0.91	0.59 – 1.39
P for trend			*0.48*			*0.48*	
IHD	9,349	I	1.00		I	1.00	
		II	1.18	1.11 – 1.25	II	1.18	1.11 – 1.25
		III	1.23	1.16 – 1.30	III	1.21	1.14 – 1.29
		IV	1.22	1.15 – 1.29	IV	1.17	1.10 – 1.23
P for trend			*0.76*			*0.79*	
Liver	93	I	1.00		I	1.00	

		II	1.47	0.85 – 2.53	II	1.33	0.75 – 2.33
		III	1.36	0.77 – 2.40	III	1.45	0.82 – 2.54
		IV	1.00	0.53 – 1.88	IV	1.04	0.57 – 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 – 1.69	II	1.37	0.98 – 1.92
		III	1.20	0.85 – 1.70	III	1.17	0.81 – 1.69
		IV	1.20	0.85 – 1.68	IV	1.36	0.97 – 1.89
P for trend			*0.003*			*<0.001*	
Respiratory	4,730	I	1.00		I	1.00	
		II	1.21	1.12 – 1.31	II	1.29	1.19 – 1.40
		III	1.18	1.09 – 1.28	III	1.27	1.17 – 1.38
		IV	1.15	1.06 – 1.24	IV	1.28	1.18 – 1.38
P for trend			*0.85*			*0.91*	

[a]Based on quartiles (I: <14.73 year mg/m^3; II: 14.73-21.05 year mg/m^3; III: 21.05-31.42 year mg/m^3; IV:>31.42 year mg/m^3) of the cumulative distribution in the population
[b]Sub-hazard ratio from competing risk survival analysis model adjusted for birth year
[c]Based on quartiles (I: <4.89 year mg/m^3; II: 4.89-6.96 year mg/m^3; III: 6.96-11.61 year mg/m^3; IV:>11.61 year mg/m^3) of the cumulative distribution in the population

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

	N	Cumulative Nitrosamines Sum Score (NSS)[a] (year µg/m^3)			Cumulative NDMA (year µg/m^3)			Cumulative NMor (year µg/m^3)		
		Exposure[b]	SHR[c]	95%CI	Exposure[d]	SHR[c]	95%CI	Exposure[e]	SHR[c]	95%CI
Asthma	63	I	1.00		I	1.00		I	1.00	
		II	1.38	0.63 – 2.99	II	1.38	0.63 – 2.99	II	1.73	0.85 – 3.53
		III	1.42	0.67 – 3.03	III	1.42	0.67 – 3.03	III	1.50	0.71 – 3.14
		IV	1.71	0.89 – 3.30	IV	1.71	0.89 – 3.30	IV	1.57	0.74 – 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 – 2.09	II	1.51	1.09 – 2.09	II	1.00	0.71 – 1.41
		III	1.24	0.88 – 1.76	III	1.24	0.88 – 1.76	III	1.05	0.74 – 1.48
		IV	0.91	0.64 – 1.29	IV	0.91	0.64 – 1.29	IV	0.98	0.7 – 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 – 1.16	II	0.94	0.77 – 1.16	II	1.02	0.85 – 1.22
		III	1.22	1.01 – 1.48	III	1.22	1.01 – 1.48	III	1.06	0.88 – 1.27
		IV	0.96	0.81 – 1.14	IV	0.96	0.81 – 1.14	IV	0.76	0.63 – 0.92
P for trend			*0.58*			*0.58*			*0.004*	
Cerebrovascular	2,795	I	1.00		I	1.00		I	1.00	
		II	1.48	1.33 – 1.64	II	1.48	1.33 – 1.64	II	1.17	1.05 – 1.3
		III	1.36	1.21 – 1.51	III	1.36	1.21 – 1.51	III	1.17	1.05 – 1.3
		IV	1.27	1.15 – 1.41	IV	1.27	1.15 – 1.41	IV	1.19	1.07 – 1.32
P for trend			*0.69*			*0.69*			*0.003*	
Circulatory	14,627	I	1.00		I	1.00		I	1.00	
		II	1.28	1.22 – 1.34	II	1.28	1.22 – 1.34	II	1.09	1.04 – 1.14
		III	1.18	1.13 – 1.24	III	1.18	1.13 – 1.24	III	1.12	1.07 – 1.18
		IV	1.17	1.12 – 1.22	IV	1.17	1.12 – 1.22	IV	1.17	1.12 – 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 – 1.95	II	1.60	1.31 – 1.95	II	1.15	0.95 – 1.39
		III	1.54	1.26 – 1.89	III	1.54	1.26 – 1.89	III	0.99	0.81 – 1.21
		IV	1.35	1.11 – 1.65	IV	1.35	1.11 – 1.65	IV	1.20	0.99 – 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 – 1.78	II	1.34	0.88 – 2.03	II	1.14	0.73 – 1.76
		III	0.84	0.54 – 1.32	III	1.18	0.74 – 1.87	III	1.22	0.79 – 1.88
		IV	0.84	0.55 – 1.27	IV	1.49	0.98 – 2.27	IV	1.06	0.68 – 1.64
P for trend			*0.86*			*0.59*			*0.49*	
IHD	9,349	I	1.00		I	1.00		I	1.00	
		II	1.29	1.22 – 1.37	II	1.24	1.18 – 1.32	II	1.10	1.04 – 1.17
		III	1.16	1.09 – 1.23	III	1.43	1.35 – 1.52	III	1.14	1.08 – 1.21
		IV	1.12	1.06 – 1.19	IV	1.28	1.20 – 1.36	IV	1.19	1.13 – 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 – 2.80	II	1.75	0.98 – 3.14	II	0.84	0.48 – 1.49
		III	1.31	0.73 – 2.35	III	2.22	1.24 – 3.99	III	1.03	0.60 – 1.79
		IV	1.34	0.75 – 2.39	IV	1.35	0.73 – 2.49	IV	1.04	0.59 – 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 – 1.90	II	1.24	0.89 – 1.74	II	1.06	0.76 – 1.47
		III	1.43	1.01 – 2.03	III	1.40	0.99 – 1.99	III	1.02	0.73 – 1.43
		IV	1.06	0.75 – 1.50	IV	1.27	0.88 – 1.85	IV	0.76	0.53 – 1.09
P for trend			*0.79*			*0.68*			*0.29*	
Respiratory	4,730	I	1.00		I	1.00		I	1.00	
		II	1.36	1.25 – 1.47	II	1.17	1.08 – 1.27	II	1.10	1.01 – 1.19
		III	1.49	1.37 – 1.62	III	1.38	1.27 – 1.49	III	1.17	1.08 – 1.27
		IV	1.28	1.18 – 1.38	IV	1.41	1.30 – 1.53	IV	1.07	0.99 – 1.16
P for trend			*0.27*			*0.92*			*0.51*	

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

[b]Based on quartiles (I: <17.24 year μg/m^3; II: 17.24-26.72 year μg/m^3; III: 26.72-546.51 year μg/m^3; IV:>546.51 year μg/m^3) of the cumulative distribution in the population

[c]Sub-hazard ratio from competing risk survival analysis model adjusted for birth year

[d]Based on quartiles (I: <5.77 year μg/m^3; II: 5.77-8.34 year μg/m^3; III: 8.34-11.37 year μg/m^3; IV:>11.37 year μg/m^3) of the cumulative distribution in the population

[e]Based on quartiles (I: <7.70 year μg/m^3; II: 7.70-12.31 year μg/m^3; III: 12.31-19.01 year μg/m^3; IV:>19.01 year μg/m^3) of the cumulative distribution in the population

Table 4. Multi-pollutant model of risk of death from selected chronic diseases 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)[a] (year µg/m^3)		
		Exposure[b]	SHR[c]	95%CI	Exposure[d]	SHR[c]	95%CI	Exposure[e]	SHR[c]	95%CI
Cerebrovascular	2,795	I	1.00		I	1.00		I	1.00	
		II	1.07	0.96 – 1.20	II	1.05	0.92 – 1.21	II	1.44	1.26 – 1.65
		III	1.11	0.99 – 1.25	III	1.09	0.94 – 1.27	III	1.35	1.19 – 1.54
		IV	0.94	0.81 – 1.08	IV	1.08	0.91 – 1.28	IV	1.17	1.01 – 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 – 1.15	II	1.04	0.98 – 1.11	II	1.20	1.13 – 1.27
		III	1.12	1.06 – 1.18	III	1.09	1.01 – 1.17	III	1.13	1.06 – 1.20
		IV	1.06	0.99 – 1.12	IV	1.08	1.00 – 1.16	IV	1.07	1.00 – 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 – 1.49	II	1.38	1.09 – 1.75	II	1.31	1.03 – 1.66
		III	1.11	0.90 – 1.38	III	1.13	0.86 – 1.49	III	1.40	1.12 – 1.75
		IV	1.08	0.84 – 1.40	IV	1.17	0.87 – 1.59	IV	1.20	0.91 – 1.57
P for trend			*0.56*			*0.06*			*0.46*	
IHD	9,349	I	1.00		I	1.00		I	1.00	
		II	1.13	1.06 – 1.20	II	1.04	0.97 – 1.13	II	1.19	1.10 – 1.28
		III	1.16	1.09 – 1.23	III	1.10	1.00 – 1.20	III	1.10	1.02 – 1.18
		IV	1.08	1.00 – 1.17	IV	1.10	1.00 – 1.21	IV	1.01	0.93 – 1.10
P for trend			*0.80*			*0.73*			*0.37*	
Respiratory	4,730	I	1.00		I	1.00		I	1.00	
		II	1.11	1.02 – 1.21	II	1.16	1.04 – 1.29	II	1.27	1.14 – 1.41
		III	1.08	0.99 – 1.18	III	1.13	1.00 – 1.28	III	1.44	1.30 – 1.59
		IV	0.91	0.81 – 1.01	IV	1.20	1.05 – 1.37	IV	1.12	0.99 – 1.27
P for trend			*0.80*			*0.76*			*0.27*	

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

[b]Based on quartiles (I: <14.73 year mg/m^3; II: 14.73-21.05 year mg/m^3; III: 21.05-31.42 year mg/m^3; IV:>31.42 year mg/m^3) of the cumulative distribution in the population
[c]Sub-hazard ratio from competing risk survival analysis model adjusted for birth year
[d]Based on quartiles (I: <4.89 year mg/m^3; II: 4.89-6.96 year mg/m^3; III: 6.96-11.61 year mg/m^3; IV:>11.61 year mg/m^3) of the cumulative distribution in the population
[e]Based on quartiles (I: <17.24 year µg/m^3; II: 17.24-26.72 year µg/m^3; III: 26.72-546.51 year µg/m^3; IV:>546.51 year µg/m^3) of the cumulative distribution in the population

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Competing interests
None declared.

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MH and FdV conceived of the study. FdV, DMME, JC and RA obtained funding for the study. MH conducted the statistical analyses and wrote the first draft version of the manuscript. All authors contributed to interpretation of the results and commented on draft versions of the manuscript. All authors approved the final draft.