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Risk of lung cancer in relation to contiguous windows of endotoxin exposure among female textile workers in Shanghai

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Abstract

Objective—Exposure to endotoxin has been consistently associated with a reduced risk of lung cancer. However, there is a paucity of information regarding temporal aspects of this relationship. The objective of this study was to investigate the associations between contiguous windows of endotoxin exposure and risk of lung cancer.

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Methods—Data were reanalyzed from a case-cohort study (602 cases, 3,038 subcohort) of female textile workers in Shanghai, China. Cumulative endotoxin exposure was partitioned into two windows: ≥20 and <20 years before risk. Exposure–response relations were examined using categorical and non-linear (semi-parametric) models, accounting for confounding by previous exposure windows.

Results—There was an inverse trend of decreasing risk of lung cancer associated with increasing levels of endotoxin exposure ≥20 years before risk (p trend = 0.02). Women in the highest two categories of cumulative exposures had hazard ratios of 0.78 (95% CI 0.60–1.03) and 0.77 (95% CI 0.58–1.02) for lung cancer, respectively, in comparison with unexposed textile workers. There was, however, a weaker association and not statistically significant between lung cancer and endotoxin exposure accumulated in the more recent window (<20 years before risk).

Conclusion—Results provide further evidence that endotoxin exposure that occurred 20 years or more before risk confers the strongest protection against lung cancer, indicating a possible early anti-carcinogenic effect. Further studies are needed to better understand the underlying biological mechanisms for this effect.

Keywords

Lung cancer; Endotoxin; Exposure windows; Exposure–response models; Latency; Case-cohort analysis; Non-parametric models; Splines

Introduction

Exposure to endotoxin, a component of the external membrane of Gram-negative bacteria, has been associated with reduced risk of lung cancer consistently in occupational studies of agricultural and cotton textile workers [1, 2]. A recently published meta-analysis of 28 occupational studies, of which 11 were conducted in the cotton textile industry, reported an overall 28% reduction in lung cancer risk (95% CI 0.57–0.90) associated with endotoxin exposure in this industry [1]. The relative risk (RR) of lung cancer was even lower (RR = 0.62; 95% CI 0.52–0.75) among agricultural workers exposed to endotoxin in this meta-analysis [1]. Exposure to endotoxin occurs primarily through inhalation of airborne endotoxin present in organic dusts generated in these two industries. The principal active component of endotoxin is lipopolysaccharide (LPS), which has been shown to inhibit tumor initiation and growth through potential immunomodulatory signaling and production of endogenous anti-tumor mediators [3–7]. However, the precise molecular mechanisms that might explain the protective effect of endotoxin exposure on risk of lung cancer remain to be determined.

Astrakianakis et al. [8, 9] examined associations between cumulative exposure to endotoxin and risk of lung cancer in a case-cohort study nested within a large cohort of 267,400 female textile workers in Shanghai, China. Their main findings was an inverse association between cumulative exposure to endotoxin and risk of lung cancer; female textile workers exposed at highest categories of endotoxin had statistically significant 25–30% lower risk of lung cancer in comparison with unexposed workers [8, 9]. In the erratum, the significant inverse exposure–response trends between lung cancer risk and endotoxin were similar when cumulative exposure was lagged by 5, 10, 15, and 20 years [9]. Because of this observation, the investigators concluded that the protection was not amplified in the early stages of lung carcinogenesis.

Lagging of cumulative exposures (e.g., by 10 years) excludes the effects of more recent exposure (<10 years) on cancer risk and is primarily used to account for an exposure-related latency effect [10]. In this approach, recent exposure is assumed to confer zero risk. Even a

sensitivity analysis where the lag period increases from 5 to 20 years does not provide a direct assessment of the contribution of recent exposure on disease risk, since recent exposure is discounted. By contrast, the use of exposure windows offers the opportunity to isolate potential health effects associated with each distinct time period of exposure on risk of a disease [11]. The goal of this study was to estimate the separate effects of past and recent periods of cumulative exposure to endotoxin on risk of lung cancer using contiguous windows of exposures. The shape of the exposure–response relation between cumulative exposure to endotoxin and lung cancer was further explored using smoothing methods to examine possible non-linearity trends.

Materials and methods

Study population and exposure assessment

Detailed descriptions of the study population, case-cohort design, and exposure assessment for the study have been previously reported [8, 12, 13]. Briefly, the study population included 267,400 female textile workers in Shanghai, China, who were followed for cancer incidence from 1989 through 1998. This analysis included 602 incident cases of lung cancer and a comparison subcohort of 3,038 female textile workers, selected to match the year of birth distribution of all cancers in the cohort, for whom occupational endotoxin exposures due to cotton dust were reconstructed from historic cotton dust measurements and use of a jobspecific endotoxin survey [12]. Subjects with potential occupational exposures to endotoxin from other non-cotton-related jobs including machining, wool, and sanitation (26 cases and 150 women in the subcohort) were excluded from this analysis as it was not possible to quantify their endotoxin exposures.

Exposure assessment for endotoxin has been described in detail previously [12–14]. Briefly, jobs with endotoxin exposures were identified by the development of a job-exposure matrix for all textile factory jobs [13]. Historical sampling data for cotton dust from 1975 through 1999, obtained by occupational hygiene surveys conducted by the Chinese government, were compiled and supplemented by measurements taken by Astrakianakis et al. [14]. Differences in historical and contemporary cotton dust sampling methods were reconciled by parallel sampling involving three measurement techniques [14]. These measurements were used to develop a predictive model for cotton dust exposure, which incorporated the following factors: year, factory, major textile process, and minor textile process. Over the period during which historical cotton dust samples were collected, the measurement concentrations fell by approximately 3% per year [12].

Endotoxin contaminant levels in the dust samples were measured by the limulus amoebocyte lysate assay [14]. There were no historical endotoxin measurements available from factory records. Thus, endotoxin concentrations were estimated based on the predicted cotton dust concentrations according to the model described above. Cumulative exposures to endotoxin were estimated by modeling historical trends in cotton dust exposures, based on historical and contemporary measurements, incorporating correlations of cotton dust and endotoxin concentrations [12]. An endotoxin-specific job-exposure matrix was developed and linked to workers detailed occupational history records to construct annual exposure levels for application in dose–response analyses for lung cancer risk.

Risk sets and endotoxin exposure windows

For this analysis, all incident lung cancer cases that occurred in the entire cohort during the follow-up were identified, and a risk set was created for each case by sampling non-cases in the subcohort using incidence-density sampling. The time-axis used in the analysis was time of follow-up from baseline to lung cancer diagnosis or censoring due to death or study end

date on 31 December 1998. Cumulative exposure to endotoxin was accumulated over person-years for each subject, as a time-varying variable, from first exposure until the year(s) at risk. Cumulative exposure to endotoxin was partitioned initially into three contiguous exposure windows: ≥20, 20–10, and <10 years before risk, for all 602 lung cancer cases and person-years at risk. Since the prevalence and range of endotoxin exposure in the last window (<10 years) before risk was very low, we merged the last two windows (20–10 and <10) together and examined the association between only two endotoxin cumulative exposure windows: ≥20 and <20 years before risk.

Data analysis

Associations between risk of lung cancer and cumulative endotoxin exposure in each contiguous exposure window ≥20 and <20 years before risk were examined using Cox proportional hazards models. The analysis was modified for a case-cohort approach using the method described by Langholz and Jiao [15] to calculate the asymptotic variance estimates for an age-stratified subcohort and the 95% confidence intervals (CI) of the hazard ratios (HR).

Initially, we examined dose–response relationships between lung cancer and cumulative endotoxin exposure in each window, separately, ignoring exposure accumulated in the other window. These models were adjusted for age at baseline and smoking status (current and former vs. never smoker), as in the previous analysis of this dataset [8, 9]. We first fit linear dose–response models using continuous exposure measures. Then, exposure in each window was categorized into five groups: unexposed and four quartiles of exposure among the exposed workers. The cut-off points for the categories were based on the distribution of endotoxin exposure in each window among the lung cancer cases. We equalized the number of cases in each exposure category, rather than subcohort participants, to enhance stability and statistical efficiency of exposure–response models [16]. Moreover, in an attempt to better clarify and characterize the exposure–response results, we refined the categorical analysis to provide more overlap in cumulative exposure levels between the two windows. We divided the lowest quartile (Q1) of endotoxin exposure in E1 (≥20 years before risk) and the upper quartile (Q4) of endotoxin exposure in E2 (<20 years before risk) into smaller categories with equal number of cases, and fit exposure–response models.

Tests were computed for linear trend in risk of lung cancer across increasing categories of endotoxin exposure in each window; the median value of cumulative endotoxin exposure among cases in each category of exposure window was used as the value to fit linear trend analysis. Finally, we examined the shape of the exposure–response relations for lung cancer and the 2 time windows of endotoxin using penalized splines in Cox models [17, 18]; Akaike's information criterion (AIC) and biologic plausibility were used to choose the appropriate degrees of freedom (df) for each penalized spline. The choice of df for the splines represented a compromise between over-fitting the data (represented by large df) and biological plausibility [19].

After examining associations between lung cancer risk and each endotoxin exposure window, separately, we then assessed the best approach to adjust each association for the other exposure window. The approach was based on a causal diagram [20] also known as directed acyclic graph (DAG) presented in Fig. 1. The DAG can be used to clarify assumptions and identify structural confounders, defined as common causes of both exposure and outcome [20]. Defining the two windows of endotoxin exposure of ≥20 and <20 years before risk age, as E1 and E2, respectively, we observe in Fig. 1 that E1 is associated with both E2 and lung cancer, whereas E2 is associated with lung cancer, but not with E1. Thus, previous exposure window (E1) may be considered a confounder of the relation between lung cancer and the subsequent exposure window (E2). Thus, to estimate

the unconfounded effect of E2 on lung cancer, we need to adjust for E1 in the model. By contrast, to estimate the unconfounded effect of E1 on lung cancer, we need only that one exposure window in the model [21].

We also fit exposure–response models for both exposure windows among non-smokers and performed stratified analysis according to age at diagnosis (<62 vs. ≥62 years; age 62 was the average age at lung cancer diagnosis in this dataset). SAS version 9.1 (SAS Institute, Cary, NC) was used for all the statistical analyses, with the exception of penalized splines that were fit using the pspline function in R software (R-Development Core Team, Version 2.7.2, Vienna, Austria).

Results

Table 1 provides selected characteristics and distributions of contiguous windows of endotoxin exposure among lung cancer cases and non-cases in the subcohort calculated at the end of follow-up. Lung cancer cases were on average slightly older at baseline compared to non-cases in the subcohort (56.9 vs. 53.3 years), and they were followed for a shorter period of time (4.7 vs. 8.0 years). The majority of both cases and non-cases in the subcohort were non-smokers. In relation to endotoxin exposure, the proportions of exposed cases and non-cases as well as the median endotoxin exposures among the exposed workers were higher in the first window (≥20 years before risk) in comparison with the more recent time window (<20 years before risk). The correlation coefficient between the two contiguous exposure windows ≥20 and <20 years before risk was 0.41 ($p < 0.0001$).

We first examined the association between lung cancer and endotoxin accrued in each window in separate Cox models adjusting for baseline age and smoking status (see models 1 and 2, Table 2). Since the range of cumulative endotoxin exposure was very different in the two windows, we divided the lowest quartile (Q1) of endotoxin exposure in E1 (≥20 years before risk) and the upper quartile (Q4) of endotoxin exposure in E2 (<20 years before risk) into smaller categories with equal number of cases. This approach was intended to provide more overlap in exposure levels between the two windows, and to better clarify and characterize the exposure–response results according to different levels of endotoxin exposure. As observed in Table 2, there was a significant exposure–response trend ($p = 0.02$) between endotoxin exposure >20 years before risk and lung cancer with HRs decreasing from 1.00 to 0.77 over increasing categories of exposure in this window. Women in the highest categories of exposure had HRs of 0.78 (95% CI 0.60–1.03) and 0.77 (95% CI 0.58–1.02) of lung cancer, respectively, in comparison with unexposed textile workers. For the most recent exposure window (<20 years before risk), there was no statistically significant association with risk of lung cancer (p-value for trend = 0.08), although there was a suggestion that women in the highest exposure category had a HR of 0.67 (95% CI 0.42–1.10).

After examining risk of lung cancer separately for each exposure window, we then adjusted each window by the other (these results are shown in model 3, Table 2). As observed, when mutually adjusted for both exposure windows, results were similar to models 1 and 2; however, the linear trend became weaker, and not statistically significant for both exposure windows. However, for the first exposure window E1 (≥20 years before risk), there were no prior windows, and according to the DAG (Fig. 1), no further adjustment for subsequent exposure window (E2) is necessary. Therefore, the results presented in model 1 are the correct one for window E1. By contrast, when estimating the association between lung cancer and exposure window E2 (<20 years before risk), it is necessary to adjust the model for the preceding window E1 (≥20 years before risk). Thus, model 3 (Table 2) provides the best estimate of the association between lung cancer and window E2. The associations did

not change substantially in window E2 after adjustment for window E1, but the *p*-value for linear trend increased to 0.34.

We also fit exposure–response models for endotoxin exposure windows and lung cancer among non-smokers (Table 2b). As observed, the results were similar to those presented for the entire study population, which is not completely unexpected since the majority of the women in this dataset were non-smokers. We also examined risk of lung cancer associated with endotoxin exposure windows in two strata defined by age at diagnosis/risk age (<62 vs. ≥62 years; age 62 was the average age at lung cancer diagnosis in this cohort). There were no differences in risk of lung cancer associated with endotoxin exposure windows in the two strata, although the 95% confidence intervals were larger (data not shown).

Finally, using penalized splines to examine the shape of exposure–response, we observed a linear inverse relationship between lung cancer and endotoxin exposures in both windows: ≥20 and <20 years before risk (Fig. 2a, b). Although the spline for the more recent endotoxin exposure window <20 years before risk was linear, the range of exposure in this window was narrower and the 95% confidence bands were wider.

Discussion

The goal of this analysis was to determine whether a previously observed inverse relation between lung cancer and endotoxin exposure among female textile workers can be further illuminated by examining the temporal course of exposures accumulated in different windows in relation to disease occurrence. An advantage of conducting analyses for exposure windows is that differences in associations among windows may indicate specific periods of greater or lesser susceptibility to disease risk [11]. In the context of occupational cancer epidemiology, the findings may also provide insights into the mechanisms of carcinogenesis. Our results suggested a decreased risk of lung cancer associated with increasing endotoxin exposure more than 20 years before risk (*p*-for trend = 0.02). This finding implies that endotoxin may exert an anti-carcinogenic effect at early stages of lung cancer initiation. By contrast, there was a weaker association, albeit not statistically significant, between lung cancer and endotoxin exposure in the more recent time window <20 years before risk. We observed similar findings when analysis was restricted to non-smokers.

The lack of the association between risk of lung cancer and the more recent endotoxin exposure windows (E2: <20 years and before risk) might be explained by either the absence of a protective effect for lung cancer or a potential threshold for the protective effect. It is important to note that the inverse associations (HRs of 0.77 or 0.78) between risk of lung cancer and endotoxin exposure in the earliest window of >20 years before risk were observed at highest levels of cumulative exposure (>1,900 EU/m^3- years). Thus, it is possible that a threshold cumulative endotoxin exposure must be reached in order to provide a protective effect of lung cancer. In the second exposure window (<20 years before risk), although the average cumulative exposure was lower, women exposed at highest levels of cumulative exposure (>2,950 EU/m^3-years) had a suggestive protective effect for lung cancer (HR = 0.80; 95% CI 0.46–1.40), albeit not statistically significant. This could indicate that highest levels of endotoxin exposure accrued in the more recent window could be protective of lung cancer, but the proportion of women with such high exposures was very low (21 cases and 89 non-cases), and thus there was lack of power to reach statistical significance. As such, the null findings for the more recent time windows should be interpreted with caution.

In this analysis, we used a causal diagram (DAG) to provide the best approach to adjusting for confounding of one exposure window by another. Based on the definition of a confounder as a common cause of exposure and outcome, we were able to clarify appropriate adjustment for contiguous time windows of exposure. Only previous exposure windows can be common causes of subsequent exposures and disease outcome, and thus potential confounders (see Fig. 1). Thus, to estimate the unconfounded effect of an exposure window (e.g., E2) on lung cancer, it is necessary to adjust for previous exposure windows (E1). Although controlling for window E2 is not necessary for estimating an unconfounded estimate of the total effects of endotoxin exposure in window E1, this adjustment might allow the estimation of the direct effect of endotoxin exposure in window E1 on disease risk. However, if the complete DAG includes an unmeasured variable that changes disease risk and also affects E2 exposure, then one cannot necessarily estimate a direct effect in a standard Cox model [21]. For example, unmeasured health status might affect disease as well as future exposure via self-selection out of high-exposure jobs, i.e., healthy worker survivor effect. Subsequent time windows then become colliders and controlling for them can create bias by inducing a spurious association between the exposure and disease [21]. G-estimation, an approach beyond the scope of this analysis, is needed to provide unbiased estimates in such situations [22].

A possible explanation for the inverse association between lung cancer and endotoxin exposure (>20 years before risk) is the fact that the active component of endotoxin LPS has been shown to inhibit tumor initiation and growth through potential immunomodulatory signaling and production of endogenous anti-tumor mediators [3–7]. Animal models have demonstrated that LPS can inhibit tumor size and growth, and in some mice models even increase the survival time. [4, 23–25]. However, corroborative evidence from human studies, apart from the findings presented here, is limited. Endotoxin (LPS) exposure is known to activate the innate immunity through toll-like receptors (TLR) particularly, TLR-4, which in turn induces the release of pro-inflammatory cytokines that are necessary to activate potent immune responses [6, 26–28]. However, genetic variation in *TLR4* has also been associated with endotoxin hyporesponsiveness in humans [29, 30], which may lead to inability of the immune system to eliminate pathogens and chronic inflammation [7]. Chronic inflammation is known to play a role in the development of several cancers including lung cancer, mediated by several mechanisms including increased production of free radicals and other genotoxic compounds that can directly damage DNA, as well as inflammatory cells' release of cytokines that inhibit apoptosis, thus allowing DNA-damaged cells to survive [7, 31, 32]. However, the role of endotoxin exposure and impaired innate immunity on risk of lung cancer is poorly understood and thus potential biological mechanisms responsible for the inverse association between endotoxin and risk of lung cancer remain to be further elucidated.

Our study has several notable strengths. This analysis was based on a very large cohort of female textile workers, with quantitative endotoxin exposure information, and a relatively large number of lung cancer cases ($n = 602$). The large sample size provided adequate power to examine the dose–response relationships. Exposure windows offer a more informative parsing of cumulative exposure than lagged exposure. Rather than assuming no effect of recent exposure, creating time windows allowed us to explore that assumption by examining the distribution of cases and exposure over time. A decline in endotoxin exposure over time was apparent when comparing the distributions of exposure within the original three time windows (>20 years, 10–20, and <10 years prior to risk). Once we combined the two later windows, we had sufficient power to extend the categories at the low end (Q1) of window E1 (≥20 years before risk) and high end (Q4) of window E2 (<20 years before risk) to make meaningful comparisons across exposure categories in two windows. Exposure windows have been rarely applied in occupational studies of cancer [33–37]; however, we encourage

their use when time-dependent exposure data are available. Additionally, the application of semi-parametric modeling using penalized splines to examine the shape of the exposure–response relationship was useful in characterizing a linear exposure– disease relation.

In conclusion, the results of this analysis provide further evidence that exposure to endotoxin is inversely associated with risk of lung cancer, with a 20% reduction in risk for highest cumulative exposures compared to unexposed workers. The findings indicate a possible early-stage anti-carcinogenic effect of endotoxin on lung cancer. Corroboration of findings from time window analyses of lung cancer in other endotoxin-exposed populations will be necessary for reaching more confident etiologic conclusions.

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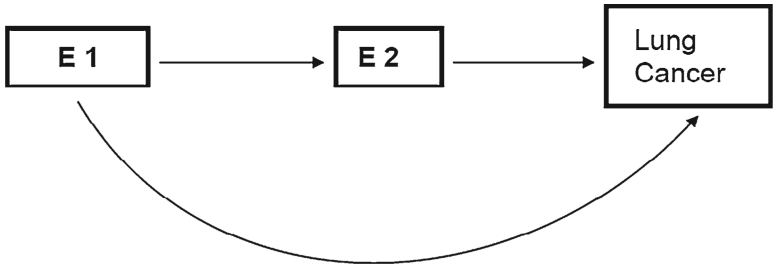

Fig. 1.

Directed acyclic graphs (DAGs) for controlling of confounding effects of windows of cumulative exposure to endotoxin on risk of lung cancer. *E1* endotoxin cumulative exposure in window 1: ≥20 years before risk age, *E2* endotoxin cumulative exposure in window 2: <20 years before risk age

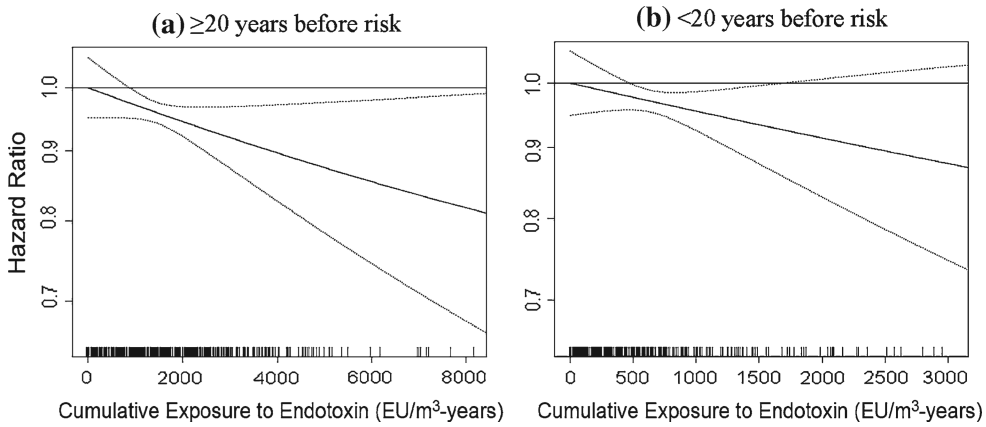

Fig. 2.

Risk of lung cancer associated with cumulative endotoxin exposure in two windows **a** ≥20 years before risk **b**<20 years before risk Legend: The graph of cumulative endotoxin exposure was truncated at 95th percentiles for both windows. *Doted lines* represent 95% pointwise confidence bands. Data rugs are for cases only. Model was adjusted for age at baseline and smoking; degrees of freedom (df) for penalized spline for exposure windows were $df = 3$

Table 1

Selected characteristics and distribution of contiguous windows of endotoxin exposure among lung cancer cases and non-cases in the subcohort of female textile workers

Characteristics	Lung cancer cases (*n* = 602)	Non-cases in subcohort (*n* = 3,035)
Age at hire (y); mean (SD)	23.2 (7.7)	22.4 (7.1)
Age at start of follow-up (y); mean (SD)	56.9 (7.5)	53.3 (9.8)
Duration of follow-up (y); mean (SD)	4.7 (2.4)	8.0 (1.5)
Smoking status at baseline; n (%)		
Non-smoker	535 (88.9)	2,894 (95.4)
Former smoker	61 (10.1)	117 (3.9)
Current smoker	6 (1.0)	24 (0.8)
Cumulative exposure to endotoxin[a] (EU/m^3-years)		
≥20 years before risk (E1)		
Exposed (%)	65.5	64.0
Mean (SD)	5,207.9 (13,110.1)	6,080.3 (15,815.3)
Median	1,917.7	2,098.3
Range	1.4–104,887.0	6.2–144,618.9
<20 years before risk (E2)		
Exposed (%)	56.2	52.0
Mean (SD)	1,796.4 (5,882.2)	1,608.6 (5,515.7)
Median	496.0	419.8
Range	3.0–60,179.3	0.7–74,436.6

[a]Distributions of exposure windows of cumulative endotoxin among exposed subjects in the subcohort are shown at the end of follow-up. Of the entire subcohort (*n* = 3,038), three subjects were diagnosed with lung cancer. Although they contributed person-years to the subcohort, they are included only in the characteristics of cases for simplicity

Table 2

Exposure–response models for lung cancer risk associated with two contiguous endotoxin exposure windows ≥20 and <20 years before risk, among female textile workers

Cumulative exposure[a] (EU/m^3-years)	Cases (n = 602)	Non-cases subcohort[b] (n = 3,035)	Model 1 HR (95% CI)[c]	Model 2 HR (95% CI)[c]	Model 3 HR (95% CI)[d]
All women					
Window 1: ≥20 years before risk					
0	208	1,092	1.00		1.00
≤277.2	24	145	0.86 (0.54–1.37)		0.80 (0.49–1.30)
277.3–604.5	26	122	1.04 (0.66–1.62)		1.02 (0.63–1.62)
604.6–875.6	23	105	0.97 (0.61–1.55)		0.95 (0.58–1.57)
875.7–1050.2	25	90	1.30 (0.82–2.07)		1.25 (0.76–2.07)
1,050.3–1917.7	99	409	0.88 (0.67–1.16)		0.84 (0.59–1.19)
1,917.8–2990.2	99	514	0.78 (0.60–1.03)		0.74 (0.52–1.07)
>2990.2	98	558	0.77 (0.58–1.02)		0.80 (0.55–1.16)
p-value for trend			0.019		0.085
Window 2: <20 years before risk					
0	264	1,458		1.00	1.00
≤221.4	85	611		1.11 (0.85–1.46)	1.26 (0.91–1.74)
221.5–496.0	84	237		1.02 (0.78–1.33)	1.17 (0.84–1.63)
496.1–996.8	84	262		0.84 (0.64–1.10)	0.97 (0.69–1.36)
996.8–1279.0	21	126		0.67 (0.42–1.07)	0.78 (0.47–1.30)
1,279.1–1742.5	22	135		0.74 (0.47–1.18)	0.85 (0.51–1.43)
1,742.6–2952.3	21	117		1.03 (0.63–1.69)	1.18 (0.69–2.02)
>2952.3	21	89		0.67 (0.42–1.10)	0.80 (0.46–1.41)
p-value for trend				0.079	0.344

Cumulative exposure[a] (EU/m^3-years)	Cases (n = 535)	Non-cases subcohort[b] (n = 2,894)	Model 1 HR (95% CI)[c]	Model 2 HR (95% CI)[c]	Model 3 HR (95% CI)[d]
Non-smokers only					
Window 1: ≥20 years before risk					
0	186	1,047	1.00		1.00
≤277.2	21	142	0.81 (0.50–1.33)		0.78 (0.47–1.31)
277.3–604.5	24	120	1.04 (0.66–1.65)		1.02 (0.63–1.66)

Cumulative exposure[a] (EU/m^3-years)	Cases (n = 535)	Non-cases subcohort[b] (n = 2,894)	Model 1 HR (95% CI)[c]	Model 2 HR (95% CI)[c]	Model 3 HR (95% CI)[d]
604.6–875.6	21	99	0.99 (0.61–1.61)		0.97 (0.57–1.63)
875.7–1050.2	23	87	1.39 (0.87–2.23)		1.35 (0.81–2.26)
1,050.3–1917.7	89	392	0.88 (0.66–1.17)		0.84 (0.59–1.22)
1,917.8–2990.2	86	487	0.77 (0.57–1.02)		0.74 (0.50–1.08)
>2990.2	85	520	0.78 (0.58–1.05)		0.78 (0.52–1.16)
p-value for trend			0.033		0.067
Window 2: <20 years before risk					
0	233	1,377		1.00	1.00
≤221.4	68	582		0.97 (0.72–1.31)	1.12 (0.79–1.58)
221.5–496.0	75	227		0.99 (0.75–1.32)	1.14 (0.80–1.62)
496.1–996.8	79	252		0.88 (0.67–1.17)	1.02 (0.72–1.46)
996.8–1279.0	20	121		0.72 (0.45–1.17)	0.84 (0.49–1.43)
1,279.1–1742.5	21	135		0.77 (0.48–1.24)	0.88 (0.52–1.50)
1,742.6–2952.3	20	116		1.02 (0.62–1.69)	1.17 (0.67–2.03)
>2952.3	19	84		0.76 (0.46–1.26)	0.92 (0.51–1.65)
p-value for trend				0.273	0.764

[a] Cut-off points for quartiles were based on the distribution of exposure among all exposed cases

[b] Non-cases in the subcohort are shown at the highest cumulative endotoxin exposure category for each window, although they contributed multiple times in risk sets

[c] HR and 95% CI were adjusted for baseline age

[d] HR and 95% CI were adjusted for baseline age and the other exposure window