Original Article

Effect of endotoxin exposure on lung cancer risk in cotton textile mills and agriculture: a meta-analysis

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Background: To evaluate the relationship between occupational exposure to endotoxin and the risk of lung cancer among workers in cotton textile mills and agriculture where high levels of endotoxin are contained.

Methods: Relevant studies were searched in PubMed, Embase, the Cochrane library and Chinese databases before March, 2015. Sources of the heterogeneity were identified through Galbraith radial plots and subgroup analyses. We utilized random effects model to estimate the overall risk and 95% confidence interval (CI).

Results: Fourteen cotton textile studies and twenty agricultural studies were finally included in this meta-analysis. The pooled relative risk (RR) between endotoxin exposure and lung cancer was 0.94 (0.79–1.11) for textile workers and 0.70 (95% CI, 0.59–0.84) for agricultural workers. Heterogeneity was existent among agriculture studies (I^2 97.7%, P=0.000). Significant protective effects were showed in several subgroups of cotton textile studies as follows: case-control study, 0.70 (95% CI, 0.58–0.84); adjusted for smoking, 0.79 (95% CI, 0.66–0.95); USA, 0.62 (95% CI, 0.47–0.83); morbidity as outcome, 0.84 (95% CI, 0.73–0.97); follow up 11–20 years, 0.89 (95% CI, 0.80–0.99). For agriculture studies, two subgroups by case-control design (RR 1.42; 95% CI, 1.06–1.91) and Asian region (RR 1.74; 95% CI, 1.25–2.43) significantly altered the protective effect of endotoxin.

Conclusions: This meta-analysis supported that exposure to high concentrations of endotoxin is associated with decreased lung cancer risk in cotton textile mills and agricultural work.

Keywords: Endotoxin; lung neoplasms; textiles; agriculture; meta-analysis

Submitted Feb 16, 2016. Accepted for publication Apr 15, 2016.
doi: 10.21037/tcr.2016.05.06
View this article at: http://dx.doi.org/10.21037/tcr.2016.05.06

Introduction

Endotoxin, usually referred to as lipopolysaccharide, is a component of the outer membrane of Gram-negative bacteria (1). During the period of bacteria dissolution, endotoxin is released to develop its biological functions (1). Endotoxin is widespread in indoor and outdoor environments, especially in various workplaces generated amounts of organic dusts (2,3). High endotoxin concentrations are found in several certain occupational settings, such as cotton textile mills, agriculture work, saw industries and so on (2,3).

Inhaling endotoxin contaminated organic dusts can give rise to numerous acute and chronic respiratory diseases (3-5). In contrast, as early as 1973, Henderson *et al.* noticed that cotton-exposed workers showed a lower than expected mortality of lung cancer, but the exact substances and mechanisms inducing this phenomenon were not clear at that point (6). Subsequently, endotoxin was proven to have the antitumor function in animal models and clinical trials (7-9). To date, many epidemiology researches have reported an inverse association between endotoxin exposure and lung cancer risk (10-13). A meta-analysis incorporated 28 studies also showed a protective effect of endotoxin against lung cancer in cotton textile and agriculture workers (14). However, a promotional lung cancer risk with increasing exposure time or cumulative concentrations have been demonstrated in both an updated case-control study and a large pooled case-cohort study published recently (15,16).

Despite most epidemiological studies suggesting a decreased lung cancer risk exposure to endotoxin, few have measured concentrations quantitatively or adequately adjusted for smoking, which may weaken their conclusions. On account of these inconsistent results, we conducted a meta-analysis to investigate the relationship between endotoxin and lung cancer, focusing on two workplaces, agriculture and cotton textile industries, which highly contaminated by endotoxin (17).

Methods

Search strategies

Relevant articles were searched in PubMed, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Chinese BioMedical Literature database (CBM), WanFang database and VIP database up to March, 2015 by two investigators (LYX and KW). Taking PubMed searches as an example, the strategy was as follows: {"lung cancer" OR "lung neoplasm" OR "pulmonary cancer" OR "pulmonary neoplasm" OR "bronchogenic carcinoma" OR "lung neoplasms [Mesh]"} AND ("endotoxin" OR "organic dust") AND {"cotton" OR "cotton fiber [Mesh]" OR "textile" OR "textile industry [Mesh]" OR "farm" OR "farmers" OR "agriculture" OR "Agricultural Workers' Diseases [Mesh]"}. Moreover, bibliographies of included studies and relevant reviews were scanned to identify additional studies. Meeting's proceedings or abstracts were rejected. Languages were restricted to English and Chinese.

Study selection

Publications were considered to be eligible if they met the following inclusion criteria: (I) they took cotton textile or agricultural workers as participants with the purpose of exploring the effect of occupational endotoxin exposure on lung cancer risk; (II) they provided effect sizes [relative risk (RR) or odds ratio (OR) or hazard ratio (HR) or standardized mortality ratio (SMR) or standardized incidence ratio (SIR)] with the corresponding 95% CIs, or provided enough data to calculate them; (III) research types were limited to cohort, case-control and case-cohort studies. Studies that took other cancer or respiratory disease patients as controls, which may prone to selection bias, were excluded (14,18). When several articles from the same cohort were available, we only included the most recent paper or paper with the most applicable data.

Data collection and quality assessment

Two investigators (LYX and KW) extracted the data independently and discussed to reach a consensus. The following information was recorded: the first author's name, year of publication, country or region, study design, cohort size, number of cases, follow-up period, adjustment for confoundings, exposure assessment and effect size with corresponding 95% CI. Since one cohort study didn't directly provide an overall hazard ratio of lung cancer, we extracted original data from the paper for two-by-two tables and then estimated a crude relative risk (19). If a study didn't report a 95% CI, we utilized the exact Possion confidence intervals or Byar's approximation to calculated it (20). The methodological quality of included studies were assessed through the New-Castle Ottawa Scale (NOS) for observational studies (21). A study scored six or more stars was judged as high-quality (22).

Statistical analysis

As lung cancer incidence was rare in the population, we ignored the distinction among various risk estimates (RR, OR, HR, SMR, SIR) and expressed the pooled effect size as RRs (23,24). If a study separately reported effect sizes classified by gender or different exposure levels, we combined subgroup results into one overall risk by a random-effects model (22). Statistical heterogeneity across studies was quantified using I^2 statistic (25). Heterogeneity was deemed to be statistical significant at P<0.10, in this instance, a random-effects model (DerSimonian and Laird method) should be applied to estimate summary effect size (26). Otherwise, a fixed-effects model (Mantel-Haenszel method) was utilized (27). To identify potential sources of heterogeneity, we performed the Galbraith radial plots (28) and subgroup analyses based on study design, sex, adjustment for smoking, region, outcome, follow-up period

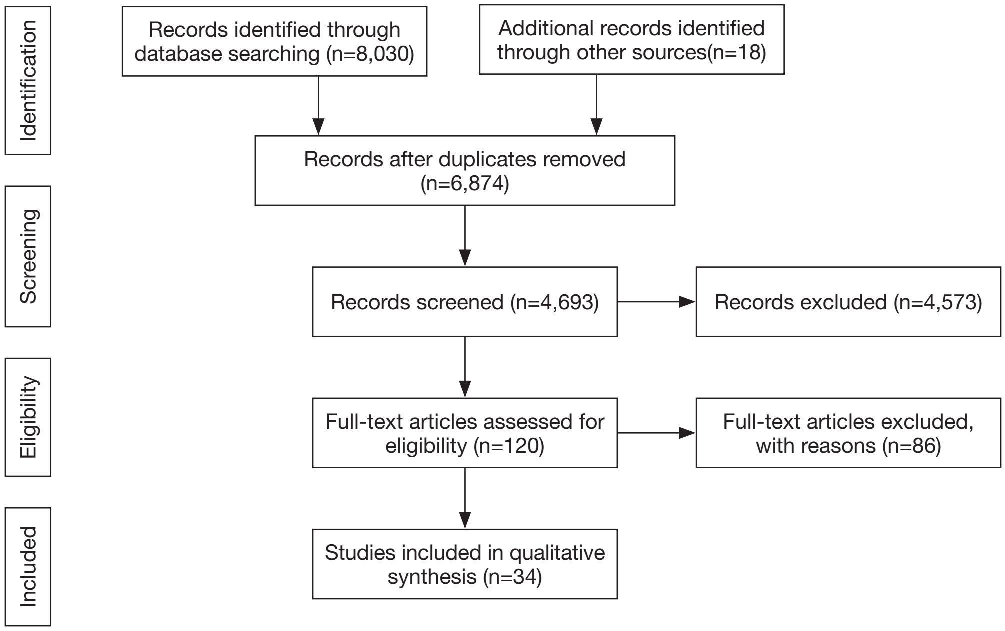

Figure 1 Workflow diagram of study selections.

and farm type. Sensitivity analyses were conducted to assess the influence of each individual study on the summary relative risk. Potential publication bias was evaluated with Egger's test (29) and Begg's funnel plot (30).

All analyses were conducted by STATA, version 12.0 (Stata Corporation, College Station, TX, USA). P<0.05 denoted statistical significance.

Results

Search result and study characteristics

After initial search and removed duplications, a total of 8,202 articles were identified. Eleven cohort (6,11,13,19,31-37), two case-control (12,38), one case-cohort (15) studies for cotton textile workers together with fifteen cohort (39-53), five case-control studies (54-58) for agriculture workers met our criteria and were finally pooled in this meta-analysis. The workflow of study selection was shown (*Figure 1*).

Among the thirty-four accepted study, seven performed in China, seventeen in Europe, seven in USA and three in other countries. All of studies controlled for both age and sex except two (19,54). One study did not provide complete adjusted effect sizes, the other controlled for age and pack-years in their analyses, which did not include lung cancer as an outcome by itself. Therefore, we extracted or calculated crude effect sizes according to original data. Only seven studies adjusted for smoking (12,15,38,41,56-58). Dose-time response were explored in ten studies, of which four quantitatively estimated concentrations of cotton dust or endotoxin exposure (11,15,19,32). Eleven studies stratified according to different exposure duration (11-13,15,19,31,32,38,40,45,58). Detailed characteristics and quality levels of eligible studies were summarized (*Tables 1,2*).

Main, subgroup and sensitive analysis

The overall combined RR and corresponding 95% CI of lung cancer in cotton textile mills showed an insignificant result with 0.94 (0.79–1.11) (*Figure 2*). Substantial heterogeneity was found among studies (I^2 76.5%, P=0.000). A publication from China by Gao was probably a great source of heterogeneity as displayed in the Galbraith radial plot and sensitive analysis (*Figures 3,4*) (36). When we excluded this research and summarized risks of the rest studies, the pooled RR turned out to be a significant result with 0.87 (95% CI, 0.81–0.93), I^2 31.9% (P=0.127) (*Figure 2*). I^2 value indicated no heterogeneity was present. In addition, after removing the literature of Gao, the meta-RR was stable regardless of ruling out any of the 13 studies in sensitive analysis. RRs in most subgroup analyses were less than 1.0 (*Table 3*). The following subgroups showed significant results: case-control study, 0.70 (95% CI,

Table 1 Characteristics of the included 14 studies for cotton textile workers

Author/year	Region	Study design	Follow-up periods	Cohort size	Lung cancer cases	Source of controls	Adjustment for confoundings	Exposure estimate	Effect size (95% CI)	NOS
Checkoway, 2014	Shanghai, China	CCh	1989–2006	F: 267,400	1,456	Randomly select from the cohort	A, S, Sm, Parity	Industry, endotoxin, duration	F: HR 0.88 (0.79–0.98)†	7
Fang, 2013	Shanghai, China	C	1981–2011	444	5	Silk textile workers	A, work year	Industry, endotoxin, cotton dust, duration	RR 1.05 (0.31–3.61)†	8
McElvenny, 2011	UK	C	1966–2007	M: 1,548 F: 1,911	M: 74 F: 54	General population of England and Wales	A, S	Industry, endotoxin, duration	M: SMR 0.89 (0.7–1.11) F: SMR 1.15(0.86–1.48) O: SMR 0.99 (0.82–1.16)	8
Mastrangelo, 2008	Veneto	C	1970–1994	3,961	36	General population of Veneto	A, S	Industry, duration	SMR 1.03(0.72–1.43)	7
Kuzmickiene, 2007	Lithuania	C	1972–2002	M: 5,495 F: 9,155	M: 70 F: 15	General population of Lithuania	A, S	Industry, cotton dust, duration	M: SIR 0.94 (0.73–1.19) F: SIR 1.36 (0.76–2.25) O: SIR 1.00 (0.80–1.25)†	7
Fritschi, 2004	Australia	C	1982–1997	7,679	F: 2	General population of Australia	A, S	Industry	F: SIR 1.06 (0.12–3.81)	7
Szeszenia, 1999	Poland	C	1964–1995	M: 2,852 F: 4,693	M: 85 F: 12	General population of Poland	A, S	Industry, department	M: SMR 0.89 (0.71–1.1) F: SMR 0.55 (0.28–0.96) O: SMR 0.84 (0.69–1.04)†	7
Gao, 1995	Nantong, China	C	1987–1991	M: 6,863 F: 16,711	M: 24 F: 23	General population of Nantong	A,S	Industry	M: SMR 2.368 (1.518–3.505)§ F: SMR 2.19 (1.388–3.285)§ O: SMR 2.28 (1.69–3.08)†	6
Wu-Williams, 1993	Shenyang, Harbin, China	CC	–	F: 966	31	General population of Shenyang and Harbin	A, S, Sm, study area, education	Industry, duration	F: OR 0.7 (0.4–1.1)	6
Li, 1992	China	C	1967–1987	2,915	13	General population	A, S, Sm	Industry	M: SMR 1.369 (0.508–2.32) F: SMR 0.902 (0.428–3.09) O: SMR 1.17 (0.64–2.14)†	6
Koskela, 1990	Finland	C	1950–1985	F: 1,065	3	General female population of Finland	A, S	Industry	F: SMR 1.58 (0.33–4.61)§	7
Levin L, 1987	Shanghai, China	CC	–	1,405	169	General population of Shanghai urban area	A, S, Sm	Industry, duration	M: OR 0.7 (0.5–0.9) F: OR 0.8 (0.6–1.0) O: OR 0.7 (0.6–0.9)	6
Merchant, 1981	North Carolina	C	1940–1975	M: 1,113 F: 393	M: 18	General population of US	A, S, race	Job department	M: SMR 0.74 (0.44–1.17)§	8
Henderson, 1973	Georgia	C	C1: 1938–1963 C2: 1948–1963	C1: 5,822 C2: 6,316	M: 23	General white male population of Georgia	A, S, race	Industry, duration	M: C1 only SMR 0.653 (0.347–0.764)§ C2 only SMR 0.205 (0.042–0.599)§ Both cohorts SMR 0.424 (0.137–0.988)§ O: SMR 0.57 (0.40–0.8†)†	7

†, Both effect size and 95% CI calculated from published data; §, only 95% CI calculated from published data. C, cohort study; CC, case-control study; CCh, case-cohort study; M, male; F, female; SMR, standardized mortality ratios; SIR, standardized incidence ratios; HR, hazard ratio; RR, relative risk; OR, odds ratio; overall effect size; A, age; S, sex; Sm, smoking.

Table 2 Characteristics of the included 20 studies for agriculture workers

Author/year	Region	Study design	Follow-up periods	Cohort size	Lung cancer (cases)	Source of controls	Adjustment for confoundings	Exposure estimate	Effect size (95% CI)	NOS
Salerno, 2015	Vercelli	CC	–	–	19	Residents of Vercelli suburban area	–	Occupation	OR: 2.165 (1.222–3.669)	7
Baser, 2013	Turkey	CC	–	–	80	Relatives of the patients	A, S	Occupation	OR: 1.89 (1.17–2.98)	7
Corbin, 2011	New Zealand	CC	–	–	99	General population of New Zealand	A, S, Sm, race, socio-economic status	Occupation	OR: 1.03 (0.75–1.04)	7
Koutros, 2010	Iowa and North Carolina, USA	C	1993–2006	M: 52,394 Spouses: 32,346	M: 436 F: 133	General population of the two states	A, S, race, state	Occupation	M: SIR 0.48 (0.43–0.53) F: SIR 0.42 (0.35–0.50) O: SIR 0.46 (0.42–0.51)†	8
Laakkonen, 2008	Finland	C	1995–2005	M: 87,534 F: 75,552	Continue: 352 Quit: 1,443	General population of Finland	A, S	Occupation, farm type, duration	Continue: SIR 0.60 (0.54–0.66) Quit: SIR 0.73 (0.69–0.76) O: SIR 0.70 (0.67–0.73)†	7
Lee, 2006	USA	C	1986–2002	3,540	34	Other occupational categories	A, S, Sm	Occupation	Farm and other agricultural workers: M: HR 1.2 (0.63–2.29) F: HR 1.14 (0.28–4.71) M/F: HR 1.19 (0.79–1.89) Farm operators and managers: M: HR 0.92 (0.59–1.44) M/F: HR 0.83 (0.51–1.35) M: HR 1.0 (0.69–1.45)† O: HR 1.01 (0.73–1.40)†	7
Mastrangelo, 2005	Vicenza	C	1970–1998	M: 2,916	75	General population of Veneto	A, S	No. of dairy cattle, farmlands, termination of farm work	M: SMR 0.64 (0.51–0.81)	6
Wang, 2002	New York	C	1980–1993	F: 6,310	21	Women aged 30–64 of New York rural area	A, S	Occupation	F: SIR 0.33 (0.20–0.51)	6
Sperati, 1999	Viterbo	C	1971–1996	M: 2,978 F: 2,586	46	General population of Lazio region	A, S	Occupation	M: SMR 0.54 (0.39–0.74) F: SMR 0.67 (0.22–1.57) O: SMR 0.55 (0.41–0.75)†	6
Jahn, 1999	Germany	CC	–	–	128	All German women	A, S, Sm, region	Occupation	F: OR 1.20 (0.88–1.72)	8
Mastrangelo, 1996	Padova	C	1970–1992	M: 2,283	39	General male population of Veneto	A,S	Occupation, duration, farm size, farm type	Dairy: SMR 0.49 (0.31–0.74) Crop/orchard: SMR 0.81 (0.46–1.31) M: O: SMR 0.6 (0.43–0.84)†	6

Table 2 (*continued*)

Table 2 (*continued*)

Author/year	Region	Study design	Follow-up periods	Cohort size	Lung cancer (cases)	Source of controls	Adjustment for confoundings	Exposure estimate	Effect size (95% CI)	NOS
Wiklund, 1994	Sweden	C	1971–1987	F: 50,682	94	General female population of Sweden	A, S	Occupation	F: SIR 0.46 (0.37–0.57)	5
Faustini, 1993	Aprilia	C	1970–1980	M: 1,701 F: 426	42	General population of Italy	A, S	Occupation	M: SMR 1.02 (0.73–1.38) F: one case	6
Ronco, 1992	Denmark	C	1970–1980	–	810	All persons economically active in 1970	A, S	Occupation	M: SIR 0.45 (0.42–0.48)¶ F: SIR 0.46 (0.35–0.60)¶ O: SIR 0.45 (0.42–0.48)†	6
Gunnarsdottir, 1991	Iceland	C	1977–1987	M: 5,922	20	General male population of Iceland	A, S	Occupation	M: SIR 0.41 (0.27–0.59)	7
Alberghini, 1991	Italy	C	1974–1987	M: 4,580	65	General male population of Italy	A, S	Occupation	M: SMR 0.68 (0.52–0.87)	7
Stark, 1990	New York	C	1973–1983	M: 18,811	103	Men aged more than 25 of New York rural areas	A, S	Occupation	M: SIR 0.524 (0.428–0.636)§	6
Wiklund, 1988	Sweden	C	1961–1979	M: 254,417	1,155	The 1,725,845 man working in other than agriculture, horticulture, or silviculture	A, S	Occupation	M: RR 0.36 (0.34–0.38)	5
Levin, 1988	Shanghai, China	CC	–	–	M: 57	General male population aged 35–64 of Shanghai urban area	A, S, Sm	Occupation, duration	M: OR 1.6 (1.0–2.6)	8
Burmeister, 1981	Iowa	C	1971–1978	M: 21,101	1,466	White male population of Iowa	A, S, race	Occupation	M: SMR 0.84 (0.80–0.88)§	7

† Both effect size and 95% CI calculated from published data; §, only 95% CI calculated from published data; ¶, combined employees self-employed and family workers. C, cohort study; CC, case-control study; CCh, case-cohort study; M, male; F, female; SMR, standardized mortality ratios; SIR, standardized incidence ratios; HR, hazard ratio; RR, relative risk; OR, odds ratio; overall effect size; A, age; S, sex; Sm, smoking.

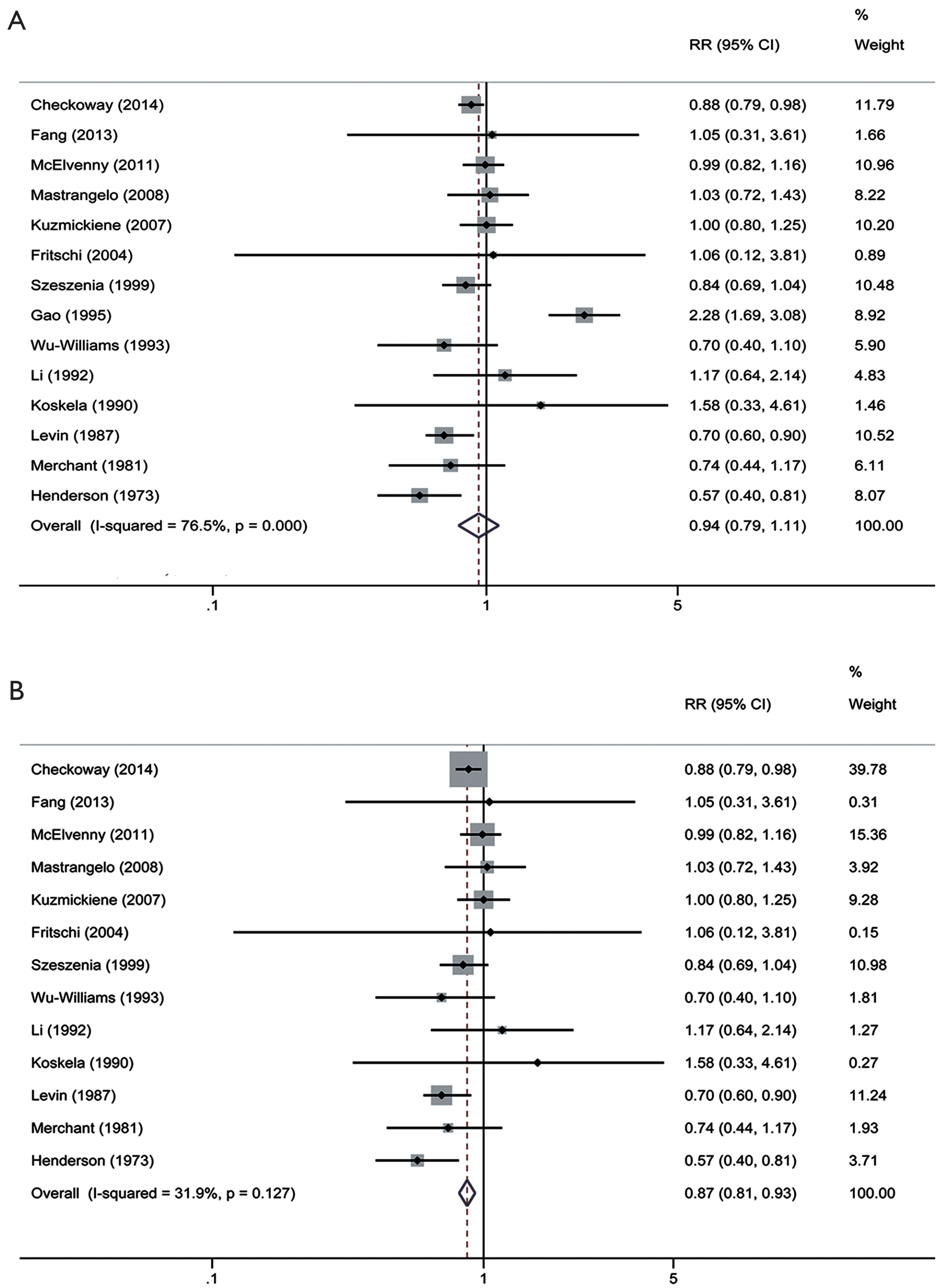

Figure 2 Forest plots of endotoxin exposure and lung cancer risk for 14 cotton textile studies (A) and for 13 studies which removing heterogeneity (B).

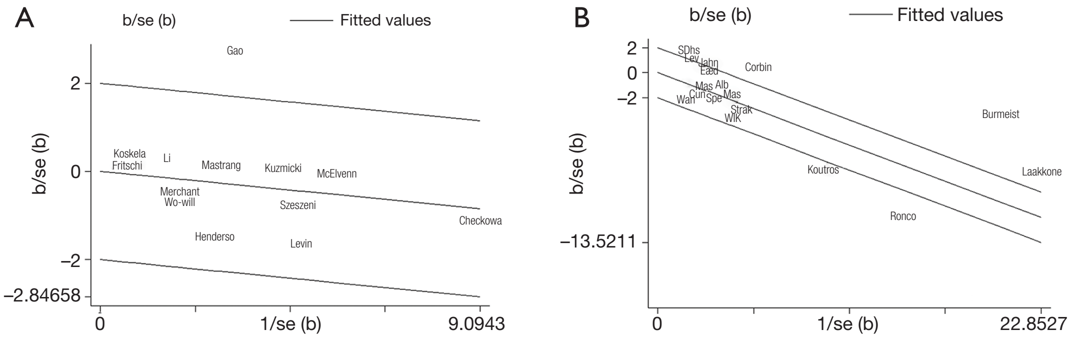

Figure 3 Galbraith radial plots of involved studies for cotton textile mills (A) and agriculture (B).

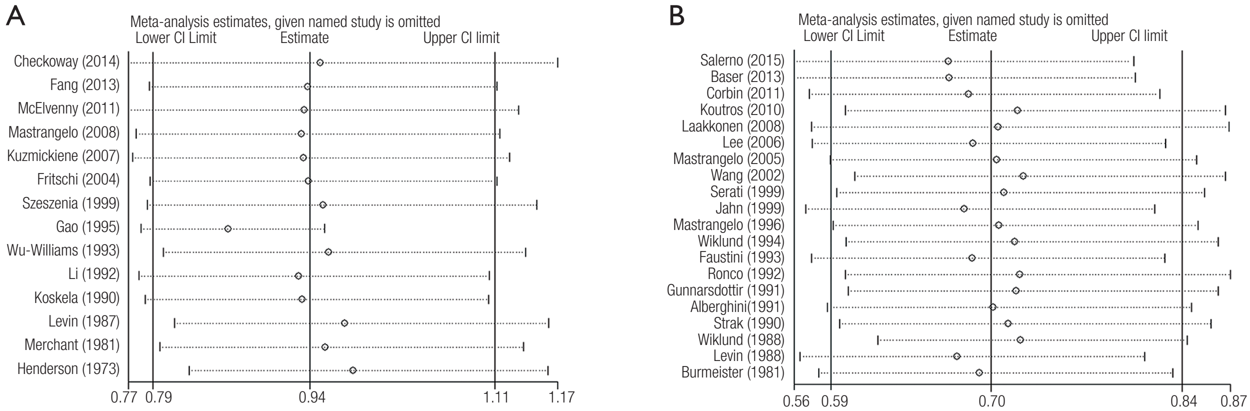

Figure 4 Sensitive analyses of the 14 cotton textile studies (A) and 20 agricultural studies (B).

0.58–0.84); adjusted for smoking, 0.79 (95% CI, 0.66–0.95); USA, 0.62 (95% CI, 0.47–0.83); morbidity as outcome, 0.84 (95% CI, 0.73–0.97); follow up 11–20 years, 0.89 (95% CI, 0.80–0.99).

In agricultural investigations, the pooled RR of lung cancer was 0.70 (95% CI, 0.59–0.84) (*Figure 5*). I^2 value exhibited a huge heterogeneity (I^2 97.7%, P=0.000). Eight studies deviated slope of the Galbraith radial plot (*Figure 3*), it was difficult to confirm which studies produced this heterogeneity. According to subgroup analysis (*Table 4*), heterogeneity was disappeared in four subgroups (adjustment for smoking, Asian countries, follow up over 20 years and farm types), while still presented great in others. Three subgroups showed inverse or insignificant results of reducing lung cancer risk as follows: case-control studies, 1.42 (95% CI, 1.06–1.91); adjusted for smoking, 1.10 (95% CI, 0.95–1.27); Asia region, 1.74 (95% CI, 1.25–2.43). Studies from Europe and USA region had similar meta-RRs with 0.64 (95% CI, 0.51–0.81) and 0.59 (95% CI, 0.41–0.86). Different from the cotton textile studies, the reduction of lung cancer risk was obvious and significant in both male and female subgroups (RR, 0.63, 95% CI, 0.50–0.80 and 0.54, 95% CI, 0.39–0.74, respectively). The lowest risk was found in the follow-up time between 11 to 20 years (RR, 0.50, 95% CI, 0.40–0.64) compared to other two periods. The sensitive analysis was robust (*Figure 4*).

Publication bias

There was no evidence of publication bias in either cotton textile studies or agricultural studies according to both Egger's test (P>0.60) and Begg's test (P>0.30). Begg's funnel plots were displayed (*Figure 6*).

Discussion

This updated meta-analysis indicated that exposure to endotoxin is associated with a 6.0% decreased risk of lung

Table 3 Subgroup analysis of lung cancer risk among the 14 studies in cotton textile mills

Subgroup	No. of studies	RR (95% CI)	I^2 (P value)	References
Study design				
Cohort	12	0.99 (0.82–1.20)	76.5% (0.000)	(6,11,13,15,19,31-37)
Case-control	2	0.70 (0.58–0.84)	0.0% (1.000)	(12,38)
Sex				
Male	8	0.93 (0.73–1.18)	77.9% (0.000)	(6,11-13,32,33,36,37)
Female	10	1.01 (0.80–1.26)	65.9% (0.002)	(11,12,15,32-38)
Smoke				
Adjusted	3	0.79 (0.66–0.95)	53.3% (0.118)	(12,15,38)
Unadjusted	11	1.01 (0.80–1.28)	77.1% (0.000)	(6,11,13,19,31-37)
Region				
China	6	1.03 (0.71–1.49)	88.8% (0.000)	(12,15,19,36-38)
Europe	5	0.96 (0.86–1.06)	0.0% (0.631)	(11,31-33,35)
USA	2	0.62 (0.47–0.83)	0.0% (0.396)	(6,13)
Australia	1	1.06 (0.19–5.97)	_	(34)
Outcome				
Mortality	9	1.02 (0.76–1.36)	81.7% (0.000)	(6,13,19,31-33,35-37)
Morbidity	5	0.84 (0.73–0.97)	31.9% (0.161)	(11,12,15,34,38)
Follow-up periods				
0–10 years	1	2.28 (1.69–3.08)	_	(36)
11–20 years	3	0.89 (0.80–0.99)	0.0% (0.647)	(15,34,37)
21–30 years	5	0.86 (0.70–1.05)	50.9% (0.086)	(6,11,19,31,33)
31–40 years	3	0.97 (0.82–1.14)	0.0% (0.416)	(13,32,35)

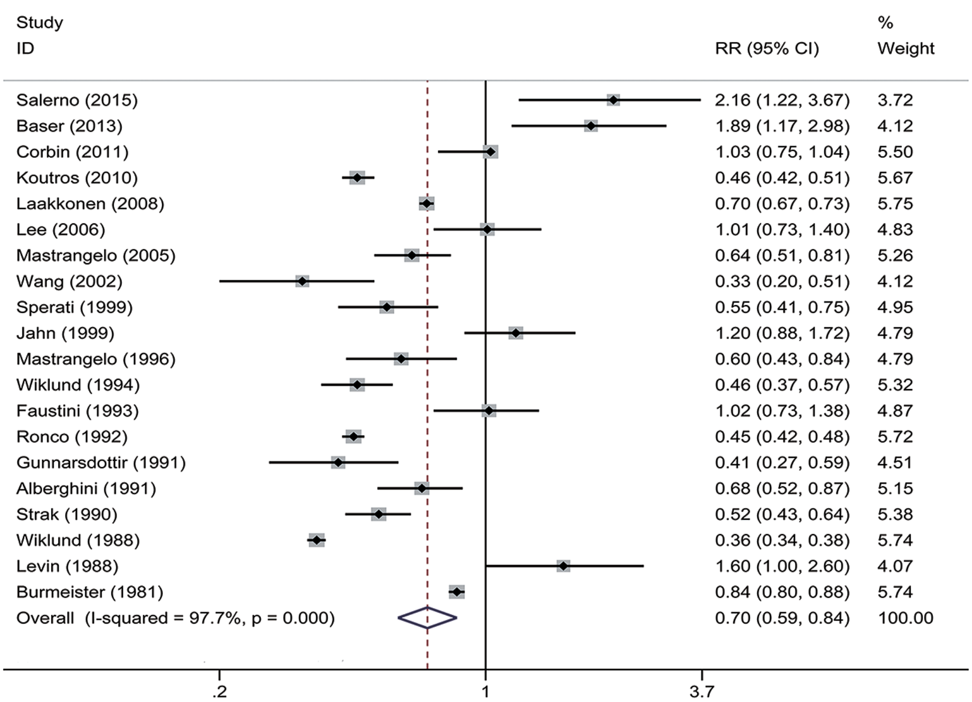

Figure 5 Forest plot of endotoxin exposure and lung cancer risk for agricultural studies.

Table 4 Subgroup analysis of lung cancer risk among the 20 agricultural studies

Subgroup	No. of studies	RR (95% CI)	I^2 (P value)	References
Study design				
Cohort	15	0.57 (0.47–0.69)	98.0% (0.000)	(39-53)
Case-control	5	1.42 (1.06–1.91)	68.7% (0.012)	(54-58)
Sex				
Male	13	0.63 (0.50–0.80)	98.1% (0.000)	(39,41,42,44,45,47-53,58)
Female	7	0.54 (0.39–0.74)	88.0% (0.000)	(39,41,43,44,46,48,57)
Smoke				
Adjusted	4	1.10 (0.95–1.27)	13.3% (0.326)	(41,56-58)
Unadjusted	16	0.62 (0.51–0.75)	98.0% (0.000)	(39,40,42-55)
Region				
Asia	2	1.74 (1.25–2.43)	0.0% (0.625)	(55,58)
Europe	12	0.64 (0.51–0.81)	97.5% (0.000)	(40,42,44-50,52,54,57)
USA	5	0.59 (0.41–0.86)	97.3% (0.000)	(39,41,43,51,53)
New Zealand	1	1.03 (0.87–1.21)	–	(56)
Outcome				
Mortality	8	0.70 (0.59–0.84)	78.7% (0.000)	(41,42,44,45,47,49,50,53)
Morbidity	12	0.71 (0.56–0.89)	98.0% (0.000)	(39,40,43,46-48,51,52,54-58)
Follow-up periods				
0–10 years	6	0.63 (0.50–0.79)	97.9% (0.000)	(40,47-49,51,53)
11–20 years	6	0.50 (0.40–0.64)	93.0% (0.000)	(39,41,43,46,50,52)
21–30 years	3	0.60 (0.51–0.71)	0.0% (0.736)	(42,44,45)
Farm types				
Dairy	3	0.55 (0.47–0.65)	19.8% (0.287)	(40,42,45)
Crop/orchard	2	0.62(0.42–0.92)	46.2% (0.173)	(40,45)

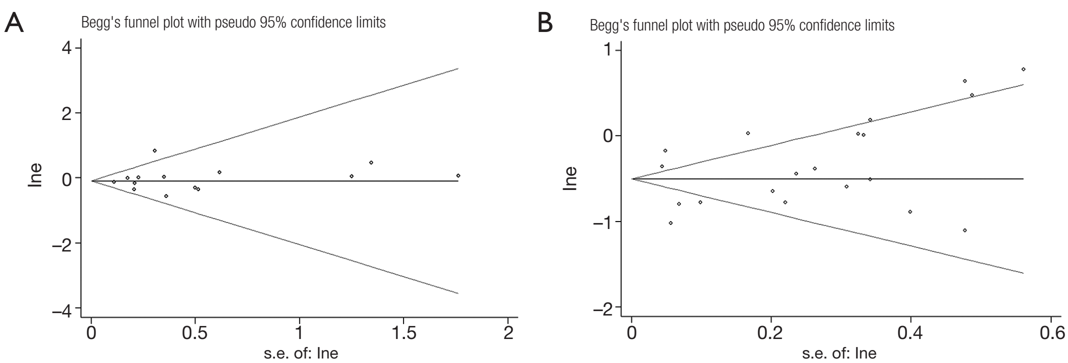

Figure 6 Begg's funnel plots of cotton textile studies (A) and agricultural studies (B).

cancer for cotton textile workers, while decreased 30% risk for agriculture workers.

For cotton textile industries, heterogeneity was substantial among the initial 14 studies. A study on Nantong cotton textile workers was the source of heterogeneity (36). This investigation was suggestive of greater lung cancer risks with SMR 2.37 for male and SMR 2.19 for female textile workers. However, these results were based on a 5-year follow-up periods which was much shorter than other investigations. Since exposure to endotoxin was a chronic process, the protective effect of endotoxin was considered to be time dependent. More obvious decreased lung cancer risk has been found in longer durations of employment lasted at least 10 years, even 20 years or more (11,59).

Workers at 20–39 age took majority in the Nantong cohort, these young people probably had short durations since first exposure. As follow-up time extended, work years and cumulative endotoxin concentrations would increase correspondingly, the risk of lung cancer among Nantong textile workers perhaps represented a declined trend. Moreover, the cause of death of a few workers were not documented and just speculated according to descriptions of family members, which perhaps led to misclassifications.

A dose-dependent antitumor effect of LPS have been demonstrated in an animal experiment by Morita back in 1996 (60). Several epidemiological researches measured concentrations of endotoxin, showed a wide variation range in cotton mills. Endotoxin levels reduced from early to late stages, ranged from the lowest value 5.8 EU/m^3 at packing sit to the highest 10,836 EU/m^3 at carding sit in Taiwan textile plants (61). Astrakianakis *et al.* quantitatively assessed cotton dust and endotoxin concentrations of seven manufacturing processes in three Shanghai textile factories, the geometric mean of endotoxin with the highest levels 1,871 EU/m^3 obtained in drawing department and decreased obviously in spinning and weaving departments (17). In our meta-analysis, two of thirteen studies took subgroup discussions according to job departments (13,33). Merchant found a lower lung cancer mortality in yarn processing (SMR 0.3) than in weaving (SMR 0.79). No distinct trends of lung cancer risk among different work sections were observed in Szeszenia's investigation, perhaps due to mix other synthetic fibers which might increase lung cancer risk (62). Four studies directly measured the concentrations of endotoxin or cotton dust exposure (11,15,19,32). One study by Checkoway showed a modest raised RR in the subgroup of exposure more than 15 years. Compared to the other three, this study with more recent cohort had lower endotoxin concentrations. It was possible that pervasive application of automation equipment and better working environment diminished the exposure, which resulted in greater lung cancer risk. Nearly 70% female workers of Checkoway's cohort aged over 55 when follow-up began. While this inverse dose-response effect continued more than 10 years but dismissed after 15 years since cessation of exposure (32,63,64). With time went on, workers had more chance to leave industries and stopped exposing. Just as the subgroup of follow-up more than 20 years in our meta-analysis exhibited a protective effect with RR 0.86 (95% CI, 0.73–1.03) and slightly raised in the 31–40 years subgroup. The dose of endotoxin exposure in agriculture work is partly dependent on the types of farming and farm size (65). Many studies have revealed that dairy farmers had more reduction of lung cancer risk compared to the orchard or crop farmers, because of the latter exposed only in the harvested season which less frequent than livestock farmers (40,45). However, similar deficits of lung cancer by farm types or farm size were found in other investigations (66). Compared to crop or orchard farmers, dairy farmers showed a lower cancer risk in the farm types subgroup. Unfortunately, most studies included in our meta-analysis did not classified by type of farming which might be a potential source of heterogeneity.

Smoking is an important confounding factor deserves to be paid more attention in any studies about lung cancer. Smoking in cotton textile industries was prohibited because of an explosion hazard (67). For this reason, previous researches often attributed decreased lung cancer risks to low rate of tobacco smoking. However, after adjusting for smoking, the risk estimate of lung cancer still presented reduction (RR 0.79; 95% CI, 0.66–0.95) for cotton textile workers, but raised in unadjusted group (RR 1.01; 95% CI, 0.80–1.28). Compared to former meta-analysis (18), the reason for this increasing risk had the possibility of insufficient adjustment for residual confounding. It was noteworthy that textile workers in the adjusted group were all from China. Populations in the same region were more likely to have common lifestyle, diet habit, air quality and tobacco varieties. These potential unbalanced baseline could also affect the overall effect sizes, likewise, resulted in heterogeneity. Furthermore, the strongest evidence of increased cancer risk comes from the study conducted by Gao which lack of information about smoking rate. It was still hard to affirm whether death-rates varied little between smokers and nonsmokers exposed to endotoxin.

Relative risk between agricultural work and lung cancer insignificantly elevated with 1.10 (95% CI, 0.95–1.27) in adjustment for smoking subgroup based on four studies. To a degree, farmers in this meta-analysis smoked less than the general population (40,41,47,49,52,54,58,59). A raised meta-RR after controlling for smoking could be predicted. Of note, three of the four studies were case-control studies. Therefore, this slightly elevated RR might emerge from the interaction of adjustment for smoking and study design. A recently published large pooled case-control investigation by Peters *et al.* demonstrated an increased lung cancer risk with OR 1.13 (95% CI, 1.04–1.22) among farmers (16). Compared with Peters, the pooled relative risk based on five case-control studies was even higher (RR 1.42; 95% CI; 1.06–1.92) in our meta-analysis, which contrary to the cohort subgroup. For a case-control study, memory bias is difficult to avoid. This kind of information bias is influenced by education level and socio-economic status. The insufficient exposure measurement such as farm types perhaps has a degree of misclassification, while the sequence of exposure experience and lung cancer is also hard to judge. Moreover, selection bias is more likely to occur among hospital-based case-control studies. Whether the inadequate correction for smoking in cohort studies or the case-control study design resulted in these inverse outcomes were not clear.

Our research also did not detected large variations of lung cancer risks in different sex for agriculture workers like former meta-analysis demonstrated (18). While for cotton textile workers, we observed that women had more raised summary risk of lung cancer than men. One possible reason was that lung cancer risk connected with endotoxin exposure was considered to be gender differences. Male workers have more chance than female to work in departments involved in high levels of endotoxin (68). The healthy-worker effect, meaning that workers with acute health impairments or severe respiratory syndrome associated with exposure to endotoxin and cotton dust, had intense trend to leave the industry or change job tasks prematurely (69). This effect reduced 10% to 40% mortality rates of workers compared to general populations and then underestimated overall risk ratios (70). It was supposed to have greater influence on male workers than female workers (2,71,72), but was weak in farmers. Since farming was the sole source of incomes, farmers had low rate to quit their work (73). In addition, agriculture workers usually involved in high intensity of physical activities on farm, which were related to the decreased lung cancer risk (74,75).

There were several limitations in our study. First, endotoxin exposure assessment was deficient. Only three studies in our meta-analysis directly measured concentrations of endotoxin, two of them did not provide enough information to draw a dose-response curve, which limited us to identify further association between endotoxin exposure and lung cancer risk. Second, there were still great heterogeneity in agriculture studies, we did not find out source of the heterogeneity. However, the different study design was noteworthy, all of the case-control studies showed obvious increased lung cancer risks, it seems to be inappropriate to explain by exposure misclassification or other biases. Third, because of rare lung cancer incidence and mortality, we took different risk estimates (RR, OR, HR, SMR, SIR) as RR. However, only when the age-specific mortality rates of interest in comparison population are small, the age interval and rang is not too broad can SMR approximate RR. Almost all studies in this meta-analysis have 5-year short age bands, but the age rang has uncontrollability. Some studies involved the elder which might underestimate the RR. Furthermore, SMR is higher than RR in general, the difference usually increases with mortality. Therefore, SMR >1 doesn't mean the RR is definitely raised (76). Fourth, because of deficient information about smoking histories for participants in most studies, it was still hard to state whether adjustment for smoking would create great influence on the overall risk. Future investigations have the necessary of focusing on the relationship between the dose-time response and lung cancer risk on the basis of sufficient adjustment for smoking and homogeneity.

Conclusions

In conclusion, our findings were consistent with the previous meta-analysis (18). Our investigation added weight to the viewpoint that occupational exposure to endotoxin is inversely associated with lung cancer risk in cotton textile mills and agricultural work.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.05.06). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Xu LY, Wang K, Li WJ, Guo YL, Kong JL. Effect of endotoxin exposure on lung cancer risk in cotton textile mills and agriculture: a meta-analysis. Transl Cancer Res 2016;5(3):250-264. doi: 10.21037/tcr.2016.05.06