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Review

Environmental exposure to endotoxin and its health outcomes: A systematic review

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ABSTRACT

Exposure to endotoxin occurs environmentally and occupationally. There are several differences between them in terms of the variety and severity of health outcomes, possible exposed groups and type and route of exposure. Occupational exposures caused adverse health outcomes in almost all cases, but there is disparity in the incidence of significant health outcomes due to environmental exposure to endotoxin. This study has therefore endeavoured to investigate health outcomes from environmental exposure to endotoxin. A systematic review was conducted of three databases and non-occupational studies reporting the environmental concentration of endotoxin, and observed health outcomes in exposed groups were included in the review (n = 27). The studies showed that first exposure to endotoxin occurs in infancy by the inhalation route. Inhalation is the only exposure route that can induce inflammation as the main symptom of exposure to endotoxin. The studies included were conducted using four approaches: molecular immunology, measurement of lung volumes, clinical sensitisation test and diagnosis of asthmatic and respiratory symptoms such as wheezing. By the immunological approach, all the included studies reported that environmental exposure to endotoxin, especially at a younger age, has a protective effect on the incidence of asthma in adolescence. The main disparity observed was in studies using the approach of diagnosed asthma. Overall, however, they confirm the protective effect of exposure to endotoxin although, in the case of children with non-atopic asthma, the results could be different.

1. Introduction

The outer membrane of gram-negative bacteria is constructed from lipopolysaccharide (LPS) molecules (Bishop, 2005). After the lysis or destruction of bacteria, LPS is distributed into the environment or blood as endotoxin. When the endotoxin molecules enter the blood, the toll-like receptors (TLR4) in innate immune cells such as neutrophils, macrophages and monocytes recognise them and cells begin to phagocytose and secrete cytokines such as IL6, IL12, IL1β and TNFα that can induce fever and inflammation (Biswas and Lopez-Collazo, 2009; Barker et al., 2017). Thus, the main outcome of exposure to endotoxin is inflammation. Endotoxin can induce several side-effects in the body ranging from a slight fever to emergency conditions such as septic shock, which can lead to death (Bottiroli et al., 2017). Other health outcomes such as allergic reaction, fever, lung cancer, atopic asthma and some gastrointestinal disorders have been reported in studies of endotoxin exposure (Iwasaki et al., 2017; Carnes et al., 2017; Hart et al., 2015).

There are two main types of exposure to endotoxin, including occupational and environmental exposure. Several studies have been conducted on endotoxin concentration, uptake rate and its exposure routes in both types of exposure (Thorne et al., 2015; Heutte et al., 2017). Inhalation as the most direct route of immune cell exposure to endotoxin is the main similarity between these types. These molecules

Abbreviations: LPS, Lipopolysaccharide; TLR, Toll-like receptors; IL, Interleukin; TNFα, Tumour necrosis factor α; FEV1, Forced expiratory volume in one second; FVC, Forced vital capacity; PEF, Peak expiratory flow; DV-PEF, Diurnal variation % of peak expiratory flow; RAW, Airway resistance; EU, Endotoxin unit

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can be exposed to the immune cells quickly through the alveolar space and induce immune responses (Skerrett et al., 2004). Inhalation is therefore the most important exposure route for endotoxins, especially in occupational situations. On the other hand, there are some major differences between these two types. The concentration of endotoxin in the occupational matrix (e.g. work place air) is significantly higher than the environmental matrix (Pankhurst et al., 2011). Moreover, the mode of exposure in an occupational situation is periodic or discontinuous, thus environmental exposure is continuous. Another difference is related to exposed groups. Exposed persons in occupational exposures are healthy adults, therefore environmental exposures involve the whole of society, including sensitive groups such as infants and the elderly. However, the main difference between these exposure types is in the observed health outcomes. Almost all studies on occupational exposure to endotoxin have reported the incidence of adverse health outcomes after exposure, including fever, cough, wheezing, dyspnea and asthmatic symptoms (Basinas et al., 2015). Many of these have been conducted on the monitoring of endotoxin concentration in different occupational situations and in different matrices such as bioaerosols at wastewater treatment plant sites, organic dust in livestock farming or dust at composting sites (Sykes et al., 2011; Basinas et al., 2012; Smit et al., 2005). According to observed outcomes, the environmental studies can be divided into two categories. Some have reported significant health outcomes, especially respiratory outcomes, while many did not report any significant outcomes.

A number of studies measured and confirmed existing endotoxin in the environmental matrix such as ambient air, indoor air, drinking water and several kinds of processed foods (Can et al., 2013; Heinrich et al., 2003; Rahman et al., 2013). Thus, this type of exposure to endotoxin is a public health issue and knowledge about its health outcomes is very important and helpful in establishing exposure limits and preventing adverse health outcomes. As regards the cellular aspect, exposure to endotoxins can activate the adaptive immune system and have tolerance effects similar to vaccination, and therefore major agencies such as the World Health Organization (WHO) do not recommended exposure limits for different exposure routes to endotoxin in terms of general exposure from the environment. There are, however, a number of contradictions in observed health outcomes due to environmental exposure to endotoxin.

In this study, therefore, we attempt to review the available evidence on environmental exposure to endotoxin in order to discover when exposure to endotoxins occurs in a person's life. We then aim to determine whether environmental exposure to endotoxin (low dose, continuous exposure) can induce significant health outcomes or not. Finally, we will endeavour to establish whether low-dose environmental exposure to endotoxin can activate the immune system and protect individuals against future acute exposure (like occupational situations) or whether it can induce more sensitivity and a more intense immune response through repeated exposure.

2. Methodology

2.1. Search strategy

This systematic review was conducted in March 2017. Firstly, the main questions were formulated in the following framework: What are the common routes of environmental exposure to endotoxins? What is the common range of endotoxin concentration in the environmental matrix? What are the observed health outcomes of environmental exposure to endotoxins? Occupational exposure was excluded from the study. Based on this assumption, a comprehensive search strategy was framed to find all the related articles on the topic of study. The search for articles was conducted in the three available electronic information resources including *Web of Science*, *Embase* and *Scopus* in the English language and using the same search strategy. Repeated results in the search were removed and all the remaining articles were reviewed by the reviewers.

2.2. Inclusion criteria

In this study, we chose original manuscripts published in peer-reviewed journals on the determination of endotoxin in the environmental matrix and persons exposed to endotoxin, and we observed its health outcomes of various age groups. The articles were chosen without limitation of time, geographic location or study populations.

2.3. Exclusion criteria

In this study, we excluded review articles, books, presentations and letters to editors. In addition, animal studies, occupational exposure such as exposure from compost sites, articles on the diagnosis and treatment of health outcomes induced by endotoxin, and studies on polymorphism and genetic researches were eliminated. In the review process, articles containing only measurement and monitoring of endotoxin concentration without determination of health outcomes in exposed persons, or articles only containing research on the detection of endotoxin health outcomes without measurement of exposure, were omitted. Among the important types of exposure to endotoxin are injection and haemodialysis. They can introduce endotoxin into the circulation rapidly and directly, but we did not include these studies in our study as this route of exposure is not common or continuous. Furthermore, not all injection or haemodialysis cases are contaminated with endotoxin and, if there is contamination, it is accidental.

2.4. Data collection process

The title, abstract and keywords of articles were reviewed by three reviewers independently. In the case of a few obscure articles, a decision was made according to the main text of the article. Next, comprehensive data extraction was performed on the included articles. Information obtained from the articles included the following items: author, year of data collection, matrix containing endotoxin, endotoxin concentration, sampling situation and location, type and age group of exposed persons, sample size, observed health outcomes and applied marker for determination of the health outcome.

3. Results

3.1. Study selection

The search in three databases returned a total of 574 manuscripts. A PRISMA flow diagram of the study selection is presented in Fig. 1. After the removal of duplicates (n = 372), 202 manuscripts remained. After studying manuscript titles, the proceeding and mini reviews were removed. In the next step, some of the available manuscripts that were exclusively monitoring or animal studies were excluded by reading the abstracts. The references of the remaining studies were checked for possible important missed studies and, as a result, one study was manually included. After this, 27 manuscripts remained for systematic review.

3.2. Characteristics of included studies

The included studies are summarised in Table 1. Most of them had a cohort design and were conducted on children and infants (21/27), while the others were conducted on adults. The sources of environmental sampling included settled dust in various location of the house (bedroom, mattress, kitchen), settled dust in schools and indoor suspended particles in classrooms and children's bedrooms. All the included studies looked for health outcomes resulting from respiratory exposure to endotoxin.

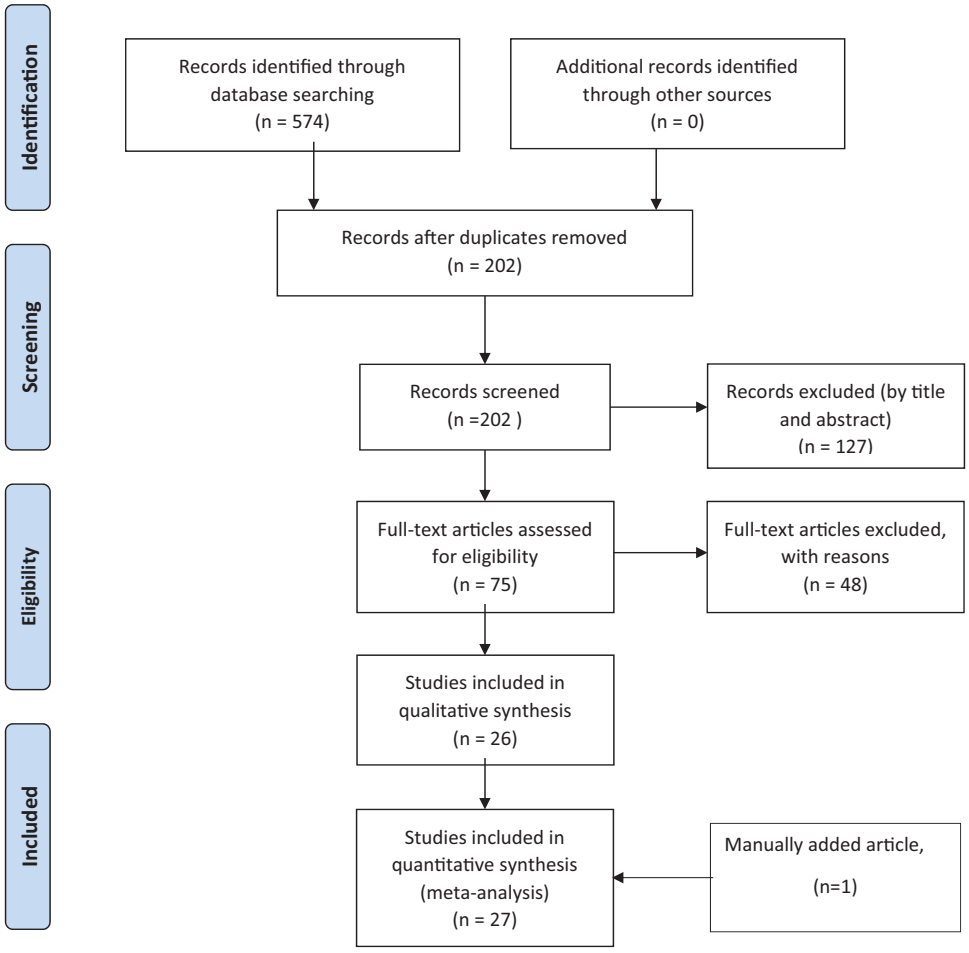

Fig. 1. PRISMA flow diagram.

3.3. Endotoxin sampling and measurement

All the included studies measured the endotoxin content in dust. The dust samples included home settled dust (bedroom, kitchen and other rooms), settled dust in schools and suspended particles in the indoor air of classrooms and children's bedrooms. The sampling adopted two main approaches in the included studies. First, some of them sampled dust from a specific area of the surface, for example 1 m^2, and reported the endotoxin content of collected dust from this area in endotoxin units (EU)/m^2. Another approach was to collect dust in a desired weight, for example 10 g, and report endotoxin content as EU/g. The most frequent technique for endotoxin measurement was to use Limulus Amebocyte Lysate (LAL) assay.

3.4. Reported health outcomes

The included studies used three approaches in determining and reporting health outcomes due to exposure to endotoxin. The first approach was measurement of a change in lung volume after an exposure period such as FEV1, FVC and PEF. The second approach consisted of sensitisation tests such as the skin-prick test, which was, however, rare. The third approach was immunological, based on the measurement of the change in the plasma level of inflammation cytokines such as IL10, IL12, TNFα and specific IgE. The last of these were clinically diagnosed or claimed respiratory and asthmatic symptoms such as wheezing, night cough, asthma attack, hay fever and the frequency of bronchodilator usage. The last approach was the more common and its results also showed the most inconsistency.

4. Discussion

This study reviewed available knowledge about the health outcomes of environmental exposure to endotoxin. We did not find any previous systematic reviews on the health outcomes of non-occupational exposure to endotoxin.

Almost all the included studies measured endotoxin concentration in settled dust in homes or classrooms, and thus focused on indoor air quality. The reason for this focus is that inhaled endotoxin has direct contact with immune cells through the alveolus. The target participants in all of the studies were infants, children and adolescents who spent a significant part of their time at home or at school. It therefore seems unlikely that they have had occupational exposure. Exposure to endotoxin by ingestion is possible (Can et al., 2013; Townsend et al., 2007; Zhang et al., 2016). No study, however, focused on health outcomes due to ingested endotoxin and all of the studies measured induced health outcomes after respiratory exposure.

The respiratory exposure to the endotoxin induces inflammation (Skerrett et al., 2004). Its consequences are respiratory symptoms (Fan and Cook, 2004). The main part of included studies endeavoured to evaluate the prevalence and frequency of respiratory symptoms such as wheezing and cough. Another approach to evaluate induced respiratory inflammation by endotoxin was change in respiratory capacities such a s FEV1% and FEV1/FVC. Finally, some of the included studies attempted to evaluate respiratory inflammation by measurement of inflammation markers, including various types of IL.

According to the findings of the included articles, we can divide the subjects into two main groups, including atopic asthmatic persons and healthy persons. In healthy children, early life exposure to endotoxin at

Table 1
Extracted data from included articles. The data includes participants' features, exposed concentration of endotoxin, clinical or paraclinical test applied for measurement of health outcomes and observed outcomes in participants.

Samples	Participants	Endotoxin concentration*	Markers and values	Statistical analysis	Outcomes	Author(year)
Endotoxin in home settled dust	28 patients with perennial chronic asthma, divided into two groups: low dose exposed (< 5.6 ng/ml) high dose exposed (> 5.6 ng/ml)	2.59 ng/ml house dust (mean)	Markers measured at first and end of a six-month period **FEV1%** (64% in low dose exposed, 55.5% in high dose exposed) **FEV1/FVC** (84.5% in low dose exposed, 67% in high dose exposed) **PEF(l/min)** (280 in low dose exposed, 295 in high dose exposed)	ANOVA analysis between two groups for every marker (P < 0.01 in all of markers)	Significant reduction in FEV1/FVC and more intake of bronchodilator by increase of exposure to endotoxins	(Michel et al., 1991)
Endotoxin in home settled dust	115 Asthmatic children aged 5–18 years	Bedroom floor: (12.4–42.8) Eu/mg Living room floor: (14.8–36.9) Eu/mg	-Number of wheezing attacks during sleep in one-year period in 4 groups: **No attacks/year:** 52 cases **1–3 attacks/year:** 40 cases **4–12 attacks/year:** 19 cases **> 12 attacks/year:**4 cases	ANOVA analysis on endotoxin concentration between4 groups. (p = 0.044)	Endotoxin concentration was associated with frequency of wheezing episodes in asthmatic children	(Leung et al., 2010)
Endotoxin in home settled dust	61 asthma-prone infants 9–24 months old in 2 groups including: Positive/negative skin prick test	104 – 10,000 EU/ml	Proportion of T cells expressing: **Interferon-γ:** (CD4: 3.02%, CD8: 17.37%) **IL4:** (CD4: 0.5%, CD8: 0.17%) **IL5:** (CD4: 0.76%, CD8: 0.56%) **IL13:** (CD4: 0.37%, CD8: 0.1%)	Correlation between endotoxin concentration and proportion of T cells expressing desired markers (p = 0.01)	Increasing exposure to indoor endotoxin can increase protection against allergen sensitisation due to enhanced innate immunity.	(Gereda et al., 2000)
Endotoxin in ambien particulate matters	50 healthy adults, Exposed 130 minutes to: **filtered air, medical air,** **air including fine particles (0.1 – 2.5 μm), air including coarse particles (2.5 − 10 μm)**	0.03 − 21.30 ng/m3	Systolic BP diastolic BP were measured pre-, 0.5-hour post-, and 20-hour post exposure **% variation SBP** 0.5 h post exposure:1.73 20 h post exposure: 0.84% **variation DBP** 0.5 h post exposure: 2.07 20 h post exposure: 1.42	Linear Mixed-Effects Models between blood pressure and endotoxin concentration **0.5 h post exposure:** P < 0.05 for SBP and DBP **20 h post exposure:** P > 0.05 for SBP and DBP	Doubling of endotoxin concentration was associated with 1.73 mm Hg higher systolic BP and 2.07 mm Hg higher diastolic BP short time after exposure	(Zhong et al., 2015)
Endotoxin in home settled dusts	405 adults aged 25–50 years divided into 3 groups according to exposure level: < 1100 ng/g. Dust 1100–4700 > 4700	2,030–2,547 (EU/mg. Dust)	**Number of coughing fits at night:** (35/405) **Number of asthma attacks:** (11/405) **Number of wheezing attacks:** (53/405)	Logistic regression between prevalence of respiratory symptoms and endotoxin concentration (OR = 0.61 to 4.31 for all the symptoms)	No significant respiratory outcome associated with endotoxin exposure was found	(Gehring et al., 2001)
Endotoxin in ambient PM2.5	45 Patients with persistent asthma aged 9–18 years, In 2 groups: *N = 13 followed up in four 10-day periods(G1), *N = 32, followed in eight 10 day periods (G2)	0.002–25.3 EU/m^3	FEV1 during 10-day periods	Linear mixed effects regression model P > 0.05	Any association between increase of exposure to endotoxin and FEV1 decrease, except in children with more severe asthma	(Delfino et al., 2015)

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Table 1 (*continued*)

Samples	Participants	Endotoxin concentration*	Markers and values	Statistical analysis	Outcomes	Author(year)
Endotoxin in home settled dust	678 6-year-old children followed up for 6 years in 2 groups: Germans(n = 346) Dutch(n = 332)	Living-room floor: (10104–32678)	**Rhino-conjunctivitis** Dutch: 28/327 German: 48/343 **Wheezing** Dutch: 48/331 German: 43/341 **Dry cough** Dutch: 80/330 German: 56/343	Logistic regression model between endotoxin concentration outcomes **OR:** (0.78 for rhino-conjunctivitis) (0.82 for wheezing) (0.89 for dry cough)	Inverse associations between domestic exposure to endotoxin and doctor-diagnosed respiratory symptoms	(Tischer et al., 2010)
Endotoxin in home settled dust	2,456 residents of 831 homes in 2 groups: G1:exposure ≤ 16.6(Eu/mg) G2:exposure > 16.6(Eu/mg)	Bedroom floors: 35.3(EU/mg)	**Prevalence of:** diagnosed hay fever, diagnosed asthma symptoms during past month and past year	Logistic regression analysis between endotoxin concentration and symptoms **OR for hay fever:** (G1 = 1, G2 = 1.5) **OR for asthma symptoms:** (G1 = 1, G2 = 2.78)	Household endotoxin exposure is a significant risk factor in increased asthma prevalence	(Thorne et al., 2005)
Endotoxin in home settled dust	308 7-year-old children with a family background of asthma	Geom mean = 60.4 EU/mg	**Recurrent wheeze:**47 cases **Diagnosed asthma**:71 cases **Use of bronchodilator**:49 cases **Use of inhaled steroids**:39 cases	Logistic regression analysis between endotoxin concentration and symptoms. The ORs are: Recurrent wheeze = 0.81 Diagnosed asthma = 0.77 Use of bronchodilator:0.72 Use of inhaled steroids:0.69	Exposure to endotoxin decreased risk of outcomes incidence	(Carlsten et al., 2011)
Endotoxin in dust from children's and parents' mattresses	3,097 neonates (3-months-old) between 1997 to 1999	Mothers' mattress: 3,008EU/g children's mattress: 5,866EU/g	Prevalence of eczema symptoms with and without atopy	Logistic regression model between atopic and non-atopic eczema with endotoxin. The **ORs** are: atopic eczema = 1.2 non-atopic eczema = 0.7	Endotoxin exposure during infancy is unlikely to have a large long-term effect on the development of eczema, especially the atopic form	(Chen et al., 2010)
Endotoxin in school settled and suspended dust - home settled dust	248 students with asthma, from 38 inner-city schools	Geometric mean School air = (0.2–780.0) EU/m^3 School settled dust = (0.7–463.5) EU/mg Home settled dust = (0.1–1,697.7) EU/mg	Max. asthma symptom days in prior 2 weeks IRR for atopic cases = 1 IRR for non-atopic = 1.16	Generalized additive mixed-effects model p = 0.016	Airborne endotoxin levels are associated with increased asthma symptoms in children with nonatopic asthma and can increase incidence rate	(Lai et al., 2015)
Endotoxin in home settled dust	404 children (2–3-months-old)	79.6 (26.2–241.6) EU/mg	Number of wheezing episodes each month for a year **Wheezing prevalence**:42%(n = 360) **Lower respiratory illness:** 28%(n = 360)	Relative risk calculated by endotoxin exposure and prevalence of any wheezing episode (RR = 5.56)	Exposure to endotoxin in the first year of life can increase wheezing incidence	(Horick et al., 2006)
Endotoxin in home settled and mattress dust	126 asthmatic children from 1 to 17 years old	Geometric mean: 218.7 EU/mg dust	Physician visits due to asthma in 12 months divided into 2 groups: **Group 1**: 3.5 ≥ visit /year = 51 cases **Group2**: > 3.5 visit/year = 31 cases	Kruskall–Wallis test P:0.02	Exposure to endotoxins has significant association with asthma symptoms	(Montealegre et al., 2004)
Endotoxin in settled dust of mother's mattress	1,942 infants of 3-months-old over 2 years divided into 4 quartiles according to concentration of exposed endotoxin (Q1,Q2,Q3, Q4)	57 – 1,286,179 EU/gr	**Repeated wheezing:** Q1:16%, Q2: 20%, Q3:19%, Q4: 22% **Symptoms of atopic dermatitis:** Q1:21%, Q2:25%, Q3:22%, Q4: 22%	Multiple logistic regression model, **ORs for repeated wheezing in 4 quartiles:** Q1 = 1, Q2 = 1.31, Q3 = 1.23, Q4 = 1.2 **ORs for symptoms of atopic dermatitis:** Q1 = 1, Q2 = 1.34, Q3 = 1.12, Q4 = 1.52	Early endotoxin exposure increases risk of atopic reaction in 2-year-old infants and has no protective effect against atopy	(Bolte et al., 2003)

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Table 1 (*continued*)

Samples	Participants	Endotoxin concentration*	Markers and values	Statistical analysis	Outcomes	Author(year)
Endotoxin in home settled dust	106 children with wheezing history during the past 12 months. Divided into 2 groups: G1: Low DV-PEF G2: High DV-PEF DV-PEF median = 6.4%	Low DV-PEF = (31.9–61.8) EU/mg High DV-PEF = (45.1–79.9) EU/mg	A 2 weeks monitoring of: **Wheezing** = 22.4%(n = 98) **DV-PEF**	Logistic regression on endotoxin concentration between low and high DV-PEF groups($p = 0.06$) and also wheezing and non-wheezing groups($p < 0.05$)	Exposure to endotoxin can induce significant change in DV-PEF and induce asthma symptoms in asthmatic children	(Lawson et al., 2011)
Dust from endotoxin in dust from children's mattress	812 children in a rural area 319 in a farming family (FF) and 493 in a non-farming family (NFF)	Geometric mean: FARMING = 37.8 EU/mg Non-farming = 22.8 EU/mg	**Atopic asthma(a):** FF = 10(n = 319), NFF = 29(n = 439) **Non-atopic asthma(b):** FF = 5, NFF = 13 **Atopic wheeze(c):** FF = 15, NFF = 29 **Non-atopic wheeze(d):** FF = 5, NFF = 30	ANOVA analysis for comparison prevalence of outcomes between and NFF. **p-values are:** a: 0.07, b:0.31, c:0.47, d:0.002 multivariate logistic regression analyses for outcomes. **ORs are:** a:0.73,b:1.25, c:0.89, d:0.97	Environmental exposure to endotoxin is associated with a significant decrease in the risk of hay fever, atopic sensitisation, atopic asthma, and atopic wheezing in children	(Braun-Fahrländer et al., 2002)
Endotoxin in home settled dust	128 children aged 15–16 (asthmatic and healthy)	8.82EU/mg	Skin prick test	Multivariate logistic regression between prevalence of sensitisation and endotoxin concentration. (OR = 1.58, p = 0.05)	Higher endotoxin exposure was associated with an increased risk of sensitisation	(Nicolaou et al., 2006)
Endotoxin in home settled dust	498 children (2–3 months old) who had a history of allergy or asthma in at least 1 parent	2.14 – 713.2 EU/mg	Prevalence of eczema **First quartile:** Eczema = (39/140), No eczema = (61/358) **Second quartile:** Eczema = (29/140), No eczema = (71/358) **Third quartile:** Eczema = (26/140), No eczema = (75/358) **Fourth quartile:** Eczema = (17/140), No eczema = (83/358)	Logistic regression analyses **ORs**: First quartile: 1 Second quartile:0.64 Third quartile:0.54 Fourth quartile:0.32	Exposure to high levels of endotoxin in home dust in the first 2 to 3 months of life is associated with a decreased risk of eczema in the first year of life among children (OR = 0.76)	(Phipatanakul et al., 2004)
Endotoxin in indoor air and home settled dust	84 smoking adults with moderate to severe COPD	Indoor air = 0.55(± 1.3) EU/m^3 Floor dust = (86.3–236) EU/mg	Wheezing Frequency of Inhaler Use	Multivariate analyses of the association between endotoxin concentration and prevalence of wheezing and Frequency of Inhaler Use **p-values:** Wheezing:0.37 Frequency of Inhaler Use: 0.92	Endotoxin concentrations were not significantly associated with respiratory symptoms, rescue medication use, quality of life, or severe exacerbations	(Bose et al., 2016)
Endotoxin in home settled dust	**50 healthy children** (negative skin prick test) **50 allergic children** (positive skin prick test)	0.05 to 309 EU/mg	**FEV1:** Allergic group = 74 ± 11.9 Healthy group = 89 ± 21.6 **PEF** Allergic group = 71 ± 9.1 Healthy group = 86 ± 11.6	**Wilcoxon rank sum test** for determination differences FEV1 and PEF in two groups: p(FEV1) = 0.032 p(PEF) = 0.025 **Multivariate logistic regression** (OR = 0.98)	Any association between endotoxin exposure and allergic sensitisation	(Yilmaz et al., 2009)

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Table 1 (*continued*)

Samples	Participants	Endotoxin concentration*	Markers and values	Statistical analysis	Outcomes	Author(year)
Endotoxin in home settled dust	1,884 normal-weight neonates followed up to 6 and 12 months	Mother's mattress = 57 to 1,286,197 EU/g dust	**Atopic eczema** *Age 6 months: (169/1868) *Age 12 months: (287/1807) **Wheezing** *Age 6 months:168/1852 *Age 12 months:373/1806 **Bronchitis symptoms** *Age o6 months:862/1866 *Age 12 months:1471/1850	Multivariate logistic regression in 5 quartiles of endotoxin concentration with health outcomes (OR = 1.69 – 2.73 for all symptoms in all of quartiles)	Exposure to high concentrations of endotoxin very early in life might protect against the development of atopic eczema. within the first 6 months of life,	(Gehring et al., 2001)
Endotoxin in home settled dust and mother's mattress	135 2-year-old children of an ongoing birth cohort	Mother's mattress:28 −240,175 EU/m^2	CCR5 expression CCR3 expression	Logistic regression model to determine OR of CCR 3.5 expression in 4 quartiles of endotoxin concentration. **ORs:** Q1 = 4.34, Q2 = 0.34, Q3 = 2.8, Q4 = 3.14	Protective effects of endotoxin	(Bolte et al., 2002)
Endotoxin in home settled dust	226 children younger than 5 were followed for 4 years in 2 endotoxin exposure groups: High level: ≤ 81.3EU/mg Low level: > 81.3 EU/mg	9.4 to 486.0 EU/mg	Prevalence of repeated wheezing in follow-up period **14-months:** Low level = 14% High level = 32% **22-months:** Low level = 19% High level = 22% **46 months:** Low level = 15.5% High level = 10%	Proportional hazards model for calculation of RR. **RRs:** 14 months = 2.7 22months = 1.3 46months = 0.58	Exposure to high levels of endotoxin is associated with increased risk for wheezing early in life. The prevalence of wheezing has reverse relation by exposed endotoxin concentration during lifetime.	(Litonjua et al., 2002)
Endotoxin in home settled dust	881 children followed up from 3 to 15 months old	0.41 − 609,910 EU/g	Repeated wheezing prevalence during 15 months Wheezing = 342/881(38.9%) No-wheeze = 538/881	Logistic regression model between endotoxin concentration and prevalence of wheezing. **Wheezing ORs:** First quartile:1 Second quartile:1.08 Third quartile:1.23 Fourth quartile:1.54	Significant association between higher endotoxin levels and wheezing	(Gillespie et al., 2006)
Endotoxin in home settled dust	6,963 subjects aged 12 to 19 years old and also aged 60 years or older, followed up for 12 months	15.49EU/mg of dust	Prevalence of wheeze-related outcomes in the past 12 months. **Any wheezing:** 974/6960 **Exercise-induced wheeze:** 490/6954	Logistic regression model between endotoxin concentration and prevalence of respiratory outcomes. **ORs including:** Any wheezing: 1.26 Exercise-induced wheeze: 1.3	Higher endotoxin exposure was significantly associated with measures of wheezing	(Thorne et al., 2015)
Endotoxin in home settled dust	10 asthmatic and 10 control children, aged 6–16 years	900 – 100,000 EU/g	**Mite-specific IgE:** Asthmatic children:9/10 Non-asthmatic children:0/10	Spearman correlation analysis between endotoxin level and clinical score of asthma **($r = 0.63$, $p < 0.05$)**	There was a significant correlation between clinical symptom scores and endotoxin exposure	(Cândida Rizzo et al., 1997)
Endotoxin in home settled dust	200 asthmatic and healthy children (control group) aged 4–17 years, followed up for a year	00.02–8,924.6 EU/mg	prevalence of asthma, male children: asthmatic:50/95 females: asthmatic:55/105	ANOVA analysis between concentration of endotoxin in asthmatic and non-asthmatic homes ($p < 0.05$) logistic regression analysis between endotoxin concentration and prevalence of asthma (OR = 1.88, p:0.018)	Endotoxin in home settled dust is a risk factor for development of asthma	(Tavernier et al., 2005)

* Endotoxin concentration is reported in two main forms including concentration per area (EU/m^2), concentration per air volume (EU/m^3) or concentration per gram of collected dust (EU/mg). (1 ng endotoxin = 5EU)

environmental level induces respiratory symptoms including wheezing, cough and respiratory capacity reduction because of air way inflammation. The severity of symptoms show direct relation to endotoxin concentration. Continued and repeated exposure during childhood and adolescence can enhance the adaptive immune system in this group. As result, repeated exposure to endotoxin increases the anti-inflammatory response and suppresses inflammation over their lifetime and, lastly, endotoxin tolerance can be established in these individuals (Biswas and Lopez-Collazo, 2009). Thus, the incidence of endotoxin related wheezing and cough or respiratory capacity reduction in healthy adolescents and adults by environmental endotoxin exposure background is rare. The condition is the same for atopic asthmatic children in early life. Continuous exposure to endotoxin in atopic asthmatic adolescences can, however, gradually reduce respiratory capacity, especially when other allergens such as cat and dog allergens are present with endotoxin.

As defined by the European Respiratory Society (ERS), FEV % < 88% predicted in men and < 89% in women is one of the main criteria for COPD diagnosis and indicates significant obstructive problems in the lungs (Nathell et al., 2007). Endotoxin induced lung obstruction is not dominant as in COPD, but as some studies show that it can affect sensitised individuals such as those with COPD over a short period of time, especially asthmatic individuals (Michel et al., 1991).

The immune response to endotoxin in asthmatic individuals is more complicated than the healthy individuals. Exposure to endotoxin in healthy individuals activates monocytes and macrophages and induces cytokine secretion (Liu, 2002). The upregulation of inflammatory cytokines (IL6,IL12, TNFα) for stronger signalling to other phagocytosis cells can be observed in the first endotoxin challenge in monocytes. Rechallenge with endotoxin induces upregulation of anti-inflammatory cytokines (IL10, TGFβ) and enhances phagocytosis. This mechanism is known as endotoxin tolerance (ET)(Biswas and Lopez-Collazo, 2009). Although some of studies mentioned that repeated exposure to endotoxin cannot induce ET, the endotoxins and concentrations in such studies are not comparable to real situations (Rittig et al., 2015). On the contrary, in asthmatic individuals there are other mechanisms engaged in inflammation. Various have studies indicated that besides endotoxin, several allergens such as cat and dog allergens and mites are present in house or mattress settled dust (Leung et al., 2010). These allergens can induce IgE secretion. The IgE receptors are present on the surface of mast cells, which can secrete histamine following inflammation. In addition to mast cells, monocytes have a high affinity IgE receptor (FcεRI), too (Novak et al., 2001). Several studies have indicated that a dominant IgE level in atopic asthmatic children is significantly higher than in non-atopic asthmatic children (Kukhtinova et al., 2012). Therefore, simultaneous exposure to endotoxin and allergens can produce a synergic effect.

Another important result in the included articles is the significance of respiratory symptoms such as wheezing and cough in respiratory capacity change. Therefore, it is possible that children show wheezing, but the inflammation is not sufficiently dominant to reduce FEV1 and other spirometry capacities. Therefore, the exposure time period is a key factor in determining health outcomes of inhaled endotoxin.

Finally, one of the critical findings of the included articles is the endotoxin concentration range. The maximum observed endotoxin concentration in the included articles was approximately 1287Eu/mg of house settled dust (Gehring et al., 2001b). This concentration is significantly lower than in the occupational situation (Pankhurst et al., 2011). It should be mentioned that none of the included studies reported a significant variation in endotoxin concentration in home settled dust.

This review confirms that continuous exposure to endotoxin can increase the anti-inflammatory response of the immune system and protect people against acute and harmful exposure to endotoxins in the future, but there are some considerations here. First, exposure to high levels of endotoxin in infants and very young children can induce septic shock and be lethal (Sáez-Llorens and McCracken, 1993). Therefore, it seems that monitoring of endotoxin in rural and residential areas near to industrial or occupational sources of endotoxin is necessary. Second, background inflammatory factors such as induced inflammation due to cat allergens can intensify inflammation and lead to hospitalisation, especially in atopic asthmatic children (Sarpong and Karrison, 1997), so monitoring of endotoxin alone, especially in the indoor environment, cannot reflect significant health risk. The monitoring must include common allergens in houses such as cat allergens. A number of monitoring studies have reported that allergens are dominant components in indoor air in houses and schools (Litonjua et al., 2002).

According to these findings, we have some critical questions about endotoxin exposure/dose such as: What is the definition of “high” and “low” for exposure to endotoxin? What is the “safe level” of exposure to endotoxin? What is the “dangerous” dose for exposure to endotoxin? And how much acute exposure to endotoxin is tolerable due to induced ET by environmental exposure to endotoxin? The values that provide the answers to these questions differ from person to person and depend on various factors including: age of first exposure to endotoxin, age and duration of exposure, mode of exposure (continuous or discontinued), endotoxin concentration in the environment, atopy background and synergic effect between endotoxin and present allergen in composition of inhalable dust.

4.1. Limitations

One of the main limitations of this study was the use of various tests and approaches to determine health outcomes. We found three different tests in the included studies. We compared studies that were similar in terms of the health symptom measurement test to minimise the effect of this limitation. Another limitation was that we could not find an association between health outcomes and increasing age. We looked for a study that measured endotoxin concentration in homes with infants (below 1 month old) and followed up their health outcomes and endotoxin concentration in the homes simultaneously for a period of time, but we did not find such studies. We therefore cannot draw a conclusion about endotoxin exposure health outcomes and their correlation to a change in the level of endotoxin in the environment over a period of time (such as home). The third limitation in this systematic review was that, in many of the included studies, especially those focused on diagnosed or claimed respiratory symptoms, the environmentally-collected samples such as home settled dust contained other allergens such as cockroach allergen. The determined respiratory symptoms cannot therefore be attributed merely to endotoxin. Finally, there was a limitation in terms of the quality assessment of the included studies. Some of the published articles were the results of major research projects, and the authors had published the results in numerous articles, so some information is missing in each article. We endeavoured to gather information from these articles and we assumed that they were one article.

4.2. Future perspective

The available studies surveyed the effect of endotoxin exposure on respiratory symptoms. The concentration of endotoxin in the environmental matrix showed no acute change, so it is rare to find acute and direct health outcomes due to environmental exposure. A major question that can, however, be investigated is the strength of the induced protective effect by environmental exposure to endotoxin against the incidence of septic shock induced by accidental therapeutic exposure in high concentration, such as an injection or haemodialysis.

5. Conclusion

The main environmental route of exposure to endotoxin that can cause health outcomes is inhalation. The main source of respirable

endotoxin is settled dust in homes and mattresses. The environmental exposure to endotoxin in early life can induce an inflammation response but continuing exposure induces immunity against endotoxin in healthy individuals. Atopic asthmatic adults are at risk of respiratory symptoms because of endotoxin in the presence of allergens.

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