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Impact of perinatal environmental tobacco smoke on the development of childhood allergic diseases

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Allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, and food allergy, are most common chronic, noncommunicable diseases in childhood. In the past few decades, the prevalence has increased abruptly worldwide. There are 2 possible explanations for the rising prevalence of allergic diseases worldwide, that an increased disease-awareness of physician, patient, or caregivers, and an abrupt exposure to unknown hazards. Unfortunately, the underlying mechanisms remain largely unknown. Despite the continuing efforts worldwide, the etiologies and rising prevalence remain unclear. Thus, it is important to identify and control risk factors in the susceptible individual for the best prevention and management. Genetic susceptibility or environments may be a potential background for the development of allergic disease, however they alone cannot explain the rising prevalence worldwide. There is growing evidence that epigenetic change depends on the gene, environment, and their interactions, may induce a long-lasting altered gene expression and the consequent development of allergic diseases. In epigenetic mechanisms, environmental tobacco smoke (ETS) exposure during critical period (i.e., during pregnancy and early life) are considered as a potential cause of the development of childhood allergic diseases. However, the causal relationship is still unclear. This review aimed to highlight the impact of ETS exposure during the perinatal period on the development of childhood allergic diseases and to propose a future research direction.

Key words: Asthma, Atopic dermatitis, Child, Allergic rhinitis, Tobacco smoke pollution

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Introduction

Allergic diseases including asthma, allergic rhinitis (AR), atopic dermatitis (AD), and food allergy (FA) are one of the most common chronic diseases in children. In the past few decades, the prevalence has increased abruptly worldwide[1,2]. Currently, there are no overall signs of a declining prevalence of allergic diseases[3]. Rather, they continue to increase in many parts of the world, particularly in Asia[4].

The 2 possible explanations for the rising prevalence of allergic diseases worldwide are an increased disease-awareness of physician, patient, or caregivers[5], and an abrupt exposure to unknown hazards. The etiology of allergic diseases is considered multifactorial, comprising of genetic, epigenetic, developmental and environmental factors, or their complex interactions. Because allergic diseases are earliest onset, chronic noncommunicable diseases (NCDs), it has been proposed that interaction between genetic predisposition and exposure to the various environmental factors influence the fetal functional and developmental programming *in utero* leading to susceptibility for the development of allergic diseases[6]. The fetal origin hypothesis postulates that NCDs in adult, such as

cardiovascular disease, and type 2 diabetes mellitus, originate from growth retardation in the fetal period[7]. Various maternal factors such as maternal disease, diet, and tobacco smoking may influence the fetal development and growth. However, the premature birth or intrauterine growth retardation alone does not explain the abrupt rising prevalence of allergic disease[8], regardless of close-association between low birth-weight and the retarded lung growth in infancy[9]. In addition, maternal exposure to various environments also may pass to the fetus through the transplacental route. Recently, the developmental origins of health and disease (DOHaD) hypothesis was postulated. The DOHaD hypothesized that all organ systems undergo developmental programming *in utero* on the basis of individual genetic background and environmental exposures to shape the physiology and metabolism of the adult[10].

It is well recognized that allergic diseases are more prevalent in a developed than developing country, and also in urban than rural provinces. However, the prevalence of allergic diseases in a metropolis such as Seoul, Singapore, and Hong Kong in Asia is relatively lower than those in the United Kingdom and Australia, and the severity such as severe asthma also seems to be low[3,4]. This discrepancy might stem from genetic differences between different populations or ethnic differences even within a single population. However, genes alone do not explain the rising prevalence worldwide because genetic change in population would be too slow to account for the abrupt rising prevalence. The rising prevalence alongside rapid change in westernized culture and environments in recent decades, together with positive ecologic correlation and international variations, regardless of similarities in highly urbanized environment, indicate that interaction between gene and environment or environment-environment intervene in the critical period (e.g., pre-, postnatal period) rather than genetics or environments alone, are associated with altered gene expression/suppression, and the consequent development of allergic diseases[11].

Despite the continuing efforts worldwide, the etiologies and rising prevalence remain unclear[12]. Thus, it is important to identify and control risk factors in the susceptible individual for the best prevention and management.

Maternal smoking during pregnancy is known to cause a potential hazard to the offspring's public health. This hazard is due to the direct toxic effect on the fetal growth and development and the altered epigenetic mechanisms. The hazard leads to a preterm birth, intrauterine growth retardation, retarded lung growth [13], and various type of birth defects in the perinatal period[14], but also allergic diseases, cardiovascular disease, type II diabetes, and dementia later in life.

This review summarized the basic mechanisms, evidence and limitations of studies for the environmental tobacco smoke (ETS) exposure during perinatal period on the development of childhood allergic disease, and proposed a future research direction.

Mechanism of ETS on the development of childhood allergic diseases

ETS exposure can cause the development of childhood allergic diseases via direct surface damage on the airway and skin, an altered epigenetic mechanisms through histone acetylation, expression of microRNA (miRNA), and DNA methylation[15-18].

Allergen sensitization, particularly in aeroallergen-sensitization, is one of the most potent predisposing factors for the development of allergic disease. The epithelial cells in nose, airway, and skin are the first line defender protecting an invasion of allergen and microorganisms into the human body[19]. The epithelial cells start an innate immune response through activating pattern recognition receptors against the invasion of foreign-materials. Microorganisms, and air pollutants such as ETS, particulate matters and chemicals compounds induce airway or skin barrier damage. Particularly, ETS induces over expression of Toll-like receptor on the airway epithelial-surface, increased oxidative stress, activation of nuclear factor kB pathway, and activation of dendritic cell and innate lymphoid cell-2 through the production of epithelial cytokines such as interleukin (IL)-1, -25, and -33. This consequently leads to easy inside invasion of allergens to cause susceptibility to allergen-sensitization, and further development of asthma[19-22].

The Th2 activation/Th1 silencing for fetal survival during pregnancy, and the reverse balance for adaptation after birth are essential for human survival and adaptation. This epigenetic change depends on the gene, environment, and their interactions, and may induce a long-lasting altered gene expression[18]. Epigenetics can be defined as "the study of heritable changes of a phenotype, such as the gene expression patterns of a specific cell type that are not caused by changes in the nucleotide sequence of the genetic code itself"[23]. In the murine model, these changes may be permanent and even transferred to the second generation offspring through the epigenetic alteration in germ-line[24]. Although many limitations remain, the transgenerational influence of grandmother's smoking is validated in the Norwegian Mother and Child Cohort Study[25].

The evidence of epigenetic mechanism may be obvious in AD, the earliest onset of allergic disease in a life. AD is classified as intrinsic and extrinsic according to the presence of specific Immunoglobulin E[26]. Recently, it is postulated that intrinsic AD may advance to the extrinsic AD through allergic-sensitization[27]. Two hypotheses (e.g., outside-inside and inside-outside) have been proposed to explain the development and exacerbation of AD. The former hypothesizes that primary skin barrier defect and subsequent penetration of allergens through defected skin, known

as loss-of-function mutation, are causes of AD-development, while the later hypothesizes that immune dysregulation induces persistent TH2 polarization, and down regulates the expression of epidermal proteins to cause skin barrier defects after birth. Although it is still an unresolved dilemma, both primary skin barrier defects and immune dysregulation are equally important in the pathogenesis of AD[15,16,28]. A LINA (Lifestyle and environmental factors and their influence on Newborns Allergy risk) cohort, conducted on 622 mother-child pairs birth cohort, showed that maternal smoking during pregnancy increases expression of miRNA-223, reduces regulatory T (Treg)-cell numbers in offspring's cord blood at birth, and increases the subsequent risk for AD and allergic sensitization to food allergen at 1 year of age[29]. Their serial result indicated that this epigenetic effects persists until 3 years of age and is associated with a 2-fold increased risk of AD during the first 3 years or life[30]. Thus, maternal smoking during pregnancy causes epigenetic changes such as up-regulation of miRNA-223, and low Treg cell numbers leading to the atopic tendency and subsequent risk of AD that persists during early infancy.

DNA methylation, an important epigenetic mechanism in AD, is known to be affected by both genetics and various environmental factors. The Taiwan birth panel study reported that the hypomethylation status of the thymic stromal lymphopoietin (TSLP) 5'-CpG island (CGI) in cord blood inversely correlated with the expression of TSLP protein, and strongly associated with ETS in pregnancy (odds ratio [OR], 3.17; 95% confidence interval [CI], 1.63–6.19) and a 2.32-fold increased risk of AD during the first 2 years of life[31].

Tobacco smoking, a known to risk factor that increases the aero-allergen sensitization[32], is likely to be associated with food-allergen sensitization through inhalation food particle attached to the house-dust[33]. The prevalence of FA in infants has increased substantially in recent years. As in wheeze and asthma, ETS exposure may facilitate sensitization to the trace food-allergen in house dust throughout airway-barrier damage, although there is no relevant study to investigate the facilitation of ETS exposure in early life to food-sensitization[33].

Taken together, there is growing evidence that ETS exposure during the perinatal period may induce an immune dysregulation at birth leading to allergic sensitization and development or exacerbation of allergic diseases in early life through epigenetic mechanisms such as expression of miRNA and DNA methylation. At the same time, direct contact-damage from outside to the surface-barrier after birth can induce barrier dysfuction and immune dysregulation.

The impact of ETS exposure during perinatal period on the development of childhood allergic disease: lessons from meta-analysis

The recent evidence for an association between ETS exposure during perinatal period and childhood allergic disease are summarized in Table 1.

Allergic sensitization

There is only one meta-analysis in the medical literature[34] that included any positive result of specific IgE (sIgE) antibodies (when IgE≥0.35 kU/L) or skin prick test (SPT, wheal diameter≥3 mm) to any common food or inhalant allergens. Total 4 studies (6,629 participants) on sIgE and 8 studies (9,033 participants) were involved in the analysis. ETS exposure was associated with the increased the risk of positive sIgE by 12% (OR, 1.12; 95% CI, 1.00–1.25). The observed risk was stronger in the prospective studies (OR, 1.35, 95% CI; 1.10–1.66) and in children <7 years (OR, 1.20; 95% CI, 1.05–1.38). This effect was similarly observed in the increased risk of positive SPT. ETS was associated the increased risk of positive SPT (OR, 1.15; 95% CI, 1.04–1.28), and was stronger in children <7 years (OR, 1.30; 95% CI, 1.05–1.61) and prospective studies (OR, 1.43; 95% CI, 1.01–2.01). However, there are just 2 studies measuring urinary cotinine, and they also measured atopic sensitization at 6 to 12 years of age with inconsistent results[35,36]. Taken together, ETS during perinatal period increases the risk of allergic sensitization in children, particularly in children under the age of 7 years. However, this result is drawn from only 1 meta-analysis, hence, further research is needed.

Childhood asthma and wheeze

One meta-analysis of 79 prospective studies, reported that ETS exposure to the maternal smoking in postnatal period was strongly associated with 70% increased risk of wheeze by the 2 years of age (OR, 1.70; 95% CI, 1.24–2.35), and those in pregnancy was strongly associated with 41% increased risk of wheeze by 2 years of age (OR, 1.41; 95% CI, 1.19–1.67)[37]. The harmful effect of maternal smoking during pregnancy was strongly observed in the early life, while they decreased by the age; a 28% increased risk of wheeze at 3–4 years of age (OR, 1.28; 95% CI, 1.14–1.44); a 30% increased risk of asthma at 3–4 years of age (OR, 1.30; 95% CI, 0.88–1.92) and 23 % at 5–18 years of age (OR, 1.23; 95% CI, 1.12–1.36). It is concluded that ETS exposure increases the risk of wheeze or asthma in children by at least 20%, therefore protection of children's exposure to ETS both during pregnancy and throughout the child's life is important.

Table 1. The effect of environmental tobacco smoke exposure during perinatal period on the development of childhood allergic diseases

Source	Design	Time to ETS exposure	Outcome	Age at outcome measure (yr)	Pooled risk (95% CI)
Feleszko et al.[34]	Meta-analysis	After birth	Allergic sensitization, SPT	Overall	1.15 (1.04–1.28)
				<7	1.30 (1.05–1.61)
				≥7	0.96 (0.79–1.18)
			Allergic sensitization, sIgE	Overall	1.12 (1.00–1.25)
				<7	1.20 (1.05–1.38)
				≥7	1.11 (0.99–1.25)
Burke et al.[37]	Meta-analysis	In utero	Wheeze	≤2	1.41 (1.19–1.67)
				3–4	1.28 (1.14–1.44)
				5–18	1.52 (1.23–1.87)
			Asthma	≤2	1.85 (1.35–2.53)
				3–4	1.30 (0.88–1.92)
				5–18	1.23 (1.12–1.44)
		Maternal smoking, after birth	Wheeze	≤2	1.70 (1.24–2.35)
				3–4	1.65 (1.20–2.28)
				5–18	1.18 (0.99–1.40)
			Asthma	≤2	2.47 (0.65–9.39)
				3–4	1.05 (0.88–1.25)
				5–18	1.20 (0.98–1.44)
Silvestri et al.[38]	Meta-analysis	Perinatal		<6	1.36 (1.19–1.55)
			Wheeze	≥6	1.22 (1.03–1.44)
		In utero only		Overall	1.24 (1.11–1.38)
Saulyte et al.[33]	Meta-analysis	In utero	Allergic rhinitis	Overall	1.07 (0.92–1.28)
Saulyte et al.[33]	Meta-analysis	Perinatal	Atopic dermatitis	Overall	1.07 (0.96–1.19)
Saulyte et al.[33]	Meta-analysis	Postnatal	Food allergy	Overall	1.01 (0.56–1.82)
Henderson et al.[39]	Two birth cohort			<6 Months of age	
	ALSPAC	In utero			1.30 (1.09–1.56)
		After birth	Wheeze		1.11 (0.98–1.25)
	ELSPAC	In utero			0.99 (0.64–1.55)
		After birth			1.66 (1.17–2.36)
Herberth et al.[30]	Birth cohort	In utero	Atopic dermatitis	<1	2.15 (1.05–4.40)
				<2	2.02 (1.08–3.77)
				<3	2.02 (1.12–3.67)
Sariachvili et al.[41]	Birth cohort	In utero, maternal active		<1	0.8 (0.5–1.4)
		In utero, maternal passive	Atopic dermatitis		0.7 (0.5–0.9)
		After birth			1.2 (0.7–2.1)
Linneberg et al.[42]	Birth cohort	In utero	Atopic dermatitis	≤18 months of age	
		Every day			0.87 (0.78–0.98)
		Less than every day			1.07 (0.80–1.44)
Jedrychowski et al.[44]	Birth cohort	Perinatal	Atopic dermatitis	<1	1.13 (0.53–2.42)
		ETS plus PM$_{2.5}$			2.39 (1.10–5.18)

ETS, environmental tobacco smoke; CI, confidence interval; SPT, skin prick test; sIgE, specific IgE; ALSPAC, the Avon Study of Parents and Children; ELSPAC, the United Kingdom and European Longitudinal Study of Pregnancy and Childhood; PM$_{2.5}$, particulate matter 2.5.

A more recent meta-analysis that systematically reviewed 43 studies based on the 29 different birth cohorts, reported that smoking during pregnancy increased risk of wheezing in <6 years of age by 36% (OR, 1.36; 95% CI, 1.19–1.55), and those of asthma in ≥6 years of age by 22% (OR, 1.22; 95% CI, 1.03–1.44)[38]. Thus, maternal smoking during pregnancy increases the risk of childhood wheezing or asthma by at least 20%, and ETS exposure in postnatal period alone does not lead to increased risk. Henderson

et al.[39] compared the cross cultural differences of smoking rate and their association with wheeze and asthma in children between 2 birth cohorts (i.e., the Avon Study of Parents and Children [ALSPAC] cohort in the United Kingdom and European Longitudinal Study of Pregnancy and Childhood [ELSPAC] cohort in the Czech Republic). They used the same protocol to compare 2 cohorts, and demonstrated a higher smoking rate during pregnancy and ETS exposure after birth in the ALSPAC than in the ELSPAC (17.5% vs. 7.1%, 35.5% vs. 9.7%); higher prevalence of wheezing by 6 months of age in the ALSPAC than in the ELSPAC (21.4% vs. 10.3%); inconsistent relationship between ETS exposure and wheezing with age. The ALSPAC cohort showed that infant wheeze was strongly associated with maternal smoking during pregnancy (OR, 1.30; 95% CI, 1.09–1.56), but not with ETS exposure after birth (OR, 1.11; 95% CI, 0.98–1.25), however the ELSPAC cohort showed an significant inverse relationship between infant wheeze and ETS exposure after birth (OR, 1.66; 95% CI, 1.17–2.36), but not with maternal smoking during pregnancy (OR, 0.99; 95% CI, 0.64–1.55). These apparent differences suggest that various factors including population, culture, or smoking rate may be involved in the causal pathway from ETS to the childhood allergic diseases. Taken together, ETS exposure during perinatal period increases the risk of childhood wheezing and asthma. This harmful effect is more clearly observed in the prospective birth cohorts. Among all studies included in these 2 meta-analyses, only 1 study measured cotinine level as objective measure[40].

Childhood AR

Recent meta-analysis published in 2014, identified 196 studies that were conducted in 51 different countries, reported no significant association between passive smoking and AR when restricting the analysis to cohort studies (risk ratio [RR], 1.14; 95% CI, 0.96–1.34), and maternal smoking in pregnancy did not increase the risk of offspring's AR (RR, 1.07; 95% CI, 0.92–1.28)[33]. Most studies included in this meta-analysis, defined AR on the basis of questionnaire, and only 7 studies measured SPT or sIgE for AR definition. Total 11 studies assessed maternal smoking in pregnancy, but no study measured urine cotinine level as an objective measure.

Childhood AD

A meta-analysis of 58 studies on the passive smoking and AD, reported that the association between passive smoking and AD was significant in the general population (RR, 1.07; 95% CI, 1.03–1.12), but not when restricting the analysis to cohort studies (RR

=1.09, 95% CI, 0.96–1.23)[33]. Moreover, only 19 studies assessed maternal smoking during pregnancy, and reported no association with offspring's AD (RR, 1.07; 95% CI, 0.96–1.19). Among the 19 studies that assessed the harmful effect of maternal smoking during pregnancy on the offspring's AD, most studies measured outcome (i.e., AD) after 6 years of age, and only 4 studies measured AD-outcome under 3 years of age[41-44]. The 1,128 mother-child pairs birth cohort in Belgium, reported that both maternal smoking during pregnancy and after birth were not a risk factor (OR, 0.8; 95% CI, 0.5–1.4) for AD development during the first year of life[41]. The Danish National Birth Cohort including 34,793 mother-child pairs measured AD during the first 18 months of life, reported an negative association; every day-maternal smoking during pregnancy (OR, 0.87; 95% CI, 0.78–0.98), and less than every day (OR, 1.07; 95% CI, 0.80–1.44)[42]. Interestingly, an ongoing birth cohort conducted in New York and Krakow demonstrated that perinatal ETS exposure alone was not associated with the increased risk of AD during first year of life (OR, 1.13; 95% CI, 0.53–2.42), but those combined with prenatal exposure to the particulate matter 2.5 increased the risk of AD (OR, 2.39; 95% CI, 1.10–5.18)[44]. Taken together, there is no association between passive smoking and AD, particularly in cohort studies that measured maternal smoking during pregnancy and development of AD during early life. Moreover, none of the cohort studies measure cotinine level as an objective measure.

Childhood FA

There is only 1 meta-analysis to evaluate the maternal smoking during pregnancy and offspring's FA. The study showed that maternal smoking during pregnancy did not increase an offspring's FA (RR, 1.01; 95% CI, 0.56–1.82)[33].

Assessing ETS exposure with questionnaire and biomarkers

The ETS exposure of child could be measured by questionnaire based on the parents report or biomarker such as cotinine in urine, blood, saliva, hair, or toenails[45,46].

The questionnaires are the most widely used method to assess active or passive tobacco smoke because of convenience and cost-effectiveness, as compared to the biomarkers, particularly in the observational studies[45]. However, a valid and reliable measurement of ETS exposure is essential to accurately assess exposure status. If the level of ETS exposure is not accurately assessed, it will lead to biased risk estimates such as misclassification leading to a biased causal relationship. This limitation may derive from recall, false reporting, over/under-reporting issue, or all of

the above. The recall bias may be inherent in the questionnaire based study, particularly in long-memory questions. This will be a potential bias in the retrospective, case-control study. Whereas this randomly occurred in the prospective survey, it may be permitted in the epidemiological studies, and showed modest correlation with biomarker measurements. The recall bias increases with response to the length of the recall period[47], therefore a maximum 7 day recall period in a single assessment is recommended[45].

The false or under/over reporting issue, are also potential limitations of questionnaire by parental report or interview. Because it may depend on the cultural context and legal issue, the responder's confidentiality should be considered, particularly in pregnant women or teenagers.

The smoking rate in pregnant women is approximately 14% in the United States[48], however it is relatively low (0.55%–3%) in Korea[49]. Different smoking rate was observed in the Europe; higher smoking rate during pregnancy and after birth in the United Kingdom than in the Czech Republic[39]. Smoking rate may differ with country, however false, or under/over reporting issue should be considered before accepting the results of questionnaire.

The false reporting issue was proposed in the US 1999–2006 National Health and Nutrition Examination Survey. This study showed that false reporting was observed in 22.9% of pregnant active smokers, and 9.2% of nonpregnant active smokers[50]. It is also observed in the Korean pregnant women study that examined urinary cotinine levels and self-reporting smoking rate among pregnant women in Korea, and reported poor agreement between self-reported smoking status and urinary cotinine >100 ng/mL (0.55% vs. 3.03%, κ=0.20)[49]. It was also observed in the Korean

population-based, 2 teenager's nation-wide survey, the Korea National Health and Nutrition Examination Survey (KNHANESs, face to face interview) with urine-cotinine level and the Korea Youth Risk Behavior (KYRBS, Web-Based Survey)[51]. The overall smoking-experience was higher in the KYRBS (26.74%) than those in the KNHANESs (18.87%), and the current smoking rate was also higher in the KYRBS (12.25%) than those in the KNHANESs (9.63%). Interestingly, 13.5% of participants in the KNHANESs were active current-smokers (i.e., urinary cotinine level >100 ng/mL), and approximately 4% of acute teen-ager smoker reported falsely. This finding showed the importance of confidentiality in the assessment of tobacco smoke.

To overcome the limitation of questionnaire, various biomarkers could be used to assess the ETS exposure[46]. Each biomarker has unique advantages and disadvantages (Table 2). Although urinary or blood cotinine are mostly used in research, investigators should consider the use of appropriate biomarker according to their study population, design and purpose. The first consideration is invasiveness that is classified as non-invasive (e.g., urinary, hair, and toenails), modest (saliva), and invasive (blood) biomarkers. The second consideration is exposure duration and timepoint. Cotinine in the urine, blood, and saliva reflect a recent exposure, and nicotine in hair and toenails reflects a longer exposure. The last consideration is convenience. Urinary and blood cotinine are widely used in clinical research, however they are not suitable in the longitudinal, population-based study because of difficulties in delivering and storing samples for a long-time. Cotinine measurement in dried blood spot (DBS) can be the best alternative in the longitudinal, population-based study because it is easy to deliver and store[52]. However, there are only 7 studies

Table 2. Biomarkers as an objective measurement of exposure to the tobacco smoke, characteristics, and advantage/disadvantage of each biomarkers

Biomarker	Exposure status	Advantages	Disadvantages
Urine	Recent exposure	Noninvasiveness Higher sensitivity Advantage in investigating the recent exposure to tobacco smoking on the human health	Need for creatinine clearance adjustment for hydration
Serum	Recent exposure	No need of adjustment Advantage in investigating the recent exposure to tobacco smoking on the human health	Invasiveness Fast clearance rate in late pregnancy Lower sensitivity
Saliva	Recent exposure	Noninvasiveness Convenience Multiple measurement with short-term interval	Various influencing factors; oral pH, diet, dehydration, drug, age, race, gender Lower sensitivity
Dried blood spot	Recent exposure	Easy to ship and store Advantage in a population-based study	Need for further research
Hair	1 cm of proximal hair reflects the last month's ETS exposure	Noninvasiveness Convenience Advantage in investigating long-term, cumulative hazard of tobacco smoking on the human health	Various influencing factors; hair dyeing, age, gender, or race
Toenails	1 mm of toenails reflects the last month's ETS exposure	Convenience Advantage in investigating long-term, cumulative hazard of tobacco smoking on the human health	Need for further research

ETS, environmental tobacco smoke.

investigating the DBS in the medical literature, hence, further research is required.

Limitations and future research directions

Allergic diseases are a complex disease consisting of hetero-geneous endo-phenotypes[53]. Despite best efforts to find the cause of allergic disease worldwide, the epidemiologic associations between many risk factors and risk of allergic diseases have been inconsistent and are likely to be unresolved in the near future. Although the primary source of this inconsistency may be due to the heterogeneity of allergic disease, much of this inconsistency can result from the heterogeneity of study design, or nonstan-dardized protocols[8]. Therefore, for best understanding of causal relationship between ETS exposure and consequent development of allergic diseases the following should be considered.

First, the quantitative level of ETS exposure should be deter-mined. Most studies that investigated the causal relationship between ETS and allergic diseases, have identified an ETS on the basis of questionnaire or interview and have inherent limitations of questionnaire based design (particularly in smoking yes/no). The exposure status may be affected by personal interest or recall, and it cannot be adjusted by statistics. Moreover, dose-dependent mechanism cannot be measured. To overcome these inherent limitations, objective measurement of ETS such as cotinine in blood or urine as a recent exposure, or hair-cotinine as a chronic exposure, will provide the best representation of ETS-status.

Second, the potential confounder should be well addressed. Various factors including maternal factors, fetal factors, environ-ment exposure *in utero* or after birth, or all of them, are directly or indirectly associated with the ETS exposure and later allergic diseases. Therefore, investigators should appropriately handle the potential confounder at the time of study-design.

Third, the disease-specific sample and objective measure should be used in the defining outcome. Most studies that investigate the impact of ETS during perinatal period on the development of childhood allergic diseases, have been focused on the simple ex-posure and outcome with lack of objective measurements. How-ever, because allergic diseases consist of multiple, heterogeneous phenotypes, blood may be inadequate sample to investigate the epigenetic mechanisms in the development of allergic diseases. Indeed, investigation of epigenetic changes in the disease-specific tissue will be appropriate in nonsystemic type of allergic disease (i.e., some of asthma-phenotypes, intrinsic AD, and local AR) as demonstrated by tissue specific-pattern of DNA methylation in AD[54]. Therefore, adequate tissue should be considered to investi-gate the epigenetic effect on the allergic disease.

Conclusions

Growing evidence supports a strong relationship between ETS in prenatal period and the development of childhood allergic disease. However, it is still unclear for various reasons such as heterogeneous study design, questionnaire-based measurement of ETS level, and nontargeted analysis of disease-specific sample or all of the above.

ETS exposure is a very common and avoidable risk factor. Therefore, it is best to prevent and manage childhood allergic disease if the causal relationship is evident. The objective mea-surement of ETS exposure, standardized definition of allergic diseases, and relationship with specific endo-phenotype of aller-gic disease should be considered in future research. This will help to expand our understanding and establish a better strategy for prevention, management, and policy making. Smoking related intervening clinical trials cannot be conducted due to ethical issues, therefore observational study with smoke-free legislation or smoke-cessation trial are also best alternatives to evaluate the impact of ETS exposure during perinatal period on the develop-ment of childhood allergic diseases.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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